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#### Asymptomatic Bacteriuria in Pregnancy: Systematic Reviews of Screening and Treatment Effectiveness and Patient Preferences

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SCHOLARONE<sup>™</sup> Manuscripts

# Asymptomatic Bacteriuria in Pregnancy: Systematic Reviews of Screening and Treatment Effectiveness and Patient Preferences

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#### ABSTRACT (word count=300)

**Objective:** To systematically review screening and treatment effectiveness, and patient preferences, to inform recommendations by the Canadian Task Force on Preventive Health Care on screening for asymptomatic bacteriuria in pregnancy.

**Design:** We searched multiple databases (inception – September 2017) and grey literature sources for studies on screening effectiveness and patient preferences. For treatment with antibiotics, we searched three databases for systematic reviews and obtained search results of the Cochrane Pregnancy and Childbirth Group's Trials Register to update a Cochrane review. Study selection, risk of bias assessment, and evaluation of the quality for each outcome using Grading Recommendations Assessment and Development Evidence (GRADE) was completed independently by two reviewers with consensus. Meta-analysis was conducted when appropriate as were analyses based on planned sub-group variables.

**Outcomes:** For screening and treatment effectiveness: maternal and perinatal mortality, maternal and neonatal sepsis, pyelonephritis, spontaneous abortion, preterm delivery, low birth weight, and serious adverse events. Valuation of outcomes for patient preferences.

**Results:** Four studies compared outcomes before and after the introduction of a screening program or between different screening programs. All evidence on screening effectiveness was considered very low quality. Women have conflicting opinions about antibiotic use during pregnancy. Fifteen trials compared antibiotic treatment with no treatment or placebo in women with confirmed bacteriuria. Low quality evidence found that treatment lowered rates of pyelonephritis (12 trials, RR 0.24; 95% CI 0.13, 0.42; ARR 17.6%; NNT 6, 95% CI 5, 7) and low birth weight (7 trials, RR 0.63; 95% CI 0.45, 0.90; ARR 4.4%; NNT 23, 95% CI 15, 85).

**Conclusions:** Antibiotic treatment for women having significant bacteriuria likely reduces the incidence of pyelonephritis and low birth weight, but we are uncertain about the magnitude of the effect and about the extent to which we can apply these results to asymptomatic populations and the screening scenario.

#### Protocol registration number: CRD42016045263

**Keywords:** asymptomatic infections, bacteriuria, pregnancy, mass screening, anti-bacterial agents, systematic review, meta-analysis

#### Strengths and limitations of this study

- Comprehensive search, risk of bias and quality assessments were conducted for all studies.
- Methodological limitations were common across many studies.
- Applicability of results to routine, prenatal care for women is limited by scant and inconsistent reporting of population and screening characteristics among included studies.
- The quality of the body of evidence was low to very low for reported outcomes.
- No direct evidence was available on how women weigh benefits and harms of screening.

#### BACKGROUND

Asymptomatic bacteriuria (ASB) signifies a significant quantitative count of bacteria in the urine without symptoms of a lower (acute cystitis) or upper urinary tract/kidney (acute pyelonephritis) infection.<sup>1, 2</sup> Prevalence of ASB in premenopausal, ambulatory women is 2-10%,<sup>1</sup> but due to anatomical and physiological changes (e.g., displaced bladder) to the urinary tract in pregnancy there are theoretical reasons to suspect higher rates of ASB during pregnancy and consequently a greater chance of progression to symptomatic UTI and other pregnancy complications (e.g., pyelonephritis, preterm delivery).<sup>1,3</sup> Numerous risk factors for ASB in pregnancy have been identified (e.g., low socioeconomic status, higher parity, a history of recurrent UTI, diabetes, and anatomical abnormalities of the urinary tract<sup>1, 2, 4</sup>).

Controversy exists over the mechanism linking ASB, pyelonephritis, and adverse perinatal outcomes (i.e., whether ASB affects pregnancy and neonatal outcomes solely through pyelonephritis or also other mechanisms such as prostaglandin activation),<sup>2, 4</sup> and therefore also about whether treatment of ASB with antibiotics will reduce the risk of such adverse outcomes. Additionally, some sources have outlined concerns with incidence and reporting on adverse effects of antibiotic treatment for ASB, UTIs, or antibiotic use in general during pregnancy.<sup>2, 4, 5</sup>

Reports of reduced incidence of pyelonephritis in pregnant women after introduction of routine screening (e.g., 0.3 to 0.57% vs. 1-2%<sup>6</sup>) suggest that these programs have been beneficial. Practices of urine testing may be used to detect conditions in pregnancy other than ASB. There appears to be diversity in screening for ASB with variations in urine testing methods, timing, and collection, as well as treatment protocols (duration, test-for-cure, threshold of bacteria for treatment).

Our reviews examined the following questions:

- 1) What are the benefits and harms of screening compared with no screening, or different screening methods or algorithms, for ASB in pregnancy?
- 2) How do women weigh the benefits and harms of screening and treatment of ASB in pregnancy, and how does this outcome valuation inform their decisions to undergo screening?
- 3) What are the benefits and harms of antibiotic treatment compared with placebo or no treatment for ASB in pregnancy?

#### METHODS

This series of systematic reviews (SRs) follow methods of the Canadian Task Force on Preventive Health Care (CTFPHC); the protocol was registered with PROSPERO (CRD42016045623) and is available online (Supplement 1).

#### Search strategy

Preliminary searches for SRs and primary studies in PubMed found one SR on treatment effectiveness, but no relevant studies on screening effectiveness. Comprehensive searches were developed and conducted by our research librarian in bibliographic databases for each question (details in Supplement 2). For screening effectiveness, the following databases were searched (inception to September 2017): MEDLINE (1946-) via Ovid; Embase (1974-) via Ovid; Cochrane Library; CINAHL (1937-present) via EBSCOhost; and PubMed via NCBI Entrez. For women's outcome valuation, we also searched PsycINFO. Limits were applied for language (English and French) but not study design or publication date. For treatment effectiveness, SRs were searched on October 14, 2016 in PubMed (1946-) via NCBI Entrez, the Cochrane Database of Systematic Reviews (inception-) and the Database of Abstracts of Reviews of Effects (DARE) (inception-2013) via Wiley Cochrane Library. Authors of the SR on treatment<sup>4</sup> provided results of their recent search update (Cochrane Pregnancy and Childbirth Group's Trials Register) in October 2017. Additional studies were identified through contact with experts and grey literature.<sup>7</sup>

#### Study selection and eligibility criteria

Two reviewers independently screened titles and abstracts, followed by full-text review, using a standard eligibility criteria form and DistillerSR software (Evidence Partners, Ottawa, Canada).<sup>8</sup> The flow of screening and decisions were recorded in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart.

The criteria for inclusion (populations, interventions, comparators, outcomes, timing and setting [PICOTS]) for screening and treatment effectiveness, and women's outcome valuation are summarized in Supplement 3.

For treatment effectiveness, existing SRs were eligible based on a) searching more than one database, b) reporting selection criteria, and c) using PICOTS criteria that closely match the current review. The included studies were assessed for eligibility to meet our inclusion criteria, incorporating existing data and extracting additional data as necessary, conducting quality assessments, and performing new meta-analyses and GRADE quality assessments.

#### Data extraction and risk of bias assessment

One reviewer independently extracted data and another verified data from each included study on study details and relevant PICOTS, including information for patient and intervention subgroups. Authors of included studies were contacted for clarification of study details and outcome data with follow-up as necessary. Intention-to-treat results were recorded whenever possible. For all outcomes, including harms, counts or proportions, and sample size by study arm, were recorded.

Two reviewers independently assessed the risk of bias (ROB) of each included study with disagreements resolved via consensus or third-reviewer consultation. For observational studies on screening effectiveness, the Newcastle-Ottawa Quality Assessment Scale was used; a separate assessment for reporting bias was included due to suspected selective outcome reporting. For cross-sectional studies on women's outcome valuation, the tool developed by the Center for Evidence-based Management<sup>32</sup> was used. For treatment effectiveness, all controlled trials were appraised using the Cochrane Risk of Bias tool.<sup>9</sup>

## Data synthesis and analysis

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Relative risks (RR) were reported using the DerSimonian and Laird random effects model with Mantel-Haenszel method and corresponding 95% confidence intervals (CI). Sensitivity (for ROB and study design) and subgroup (for pre-defined population and screening characteristic variables) analyses were conducted when possible and appropriate. We report values for statistical heterogeneity ( $I^2$ ) but did not rely on this for decisions about meta-analysis or subgroup analysis. A minimum of two of the following criteria determined credibility of subgroup investigations: a) visual inspection of forest plot showing a meaningful difference between effect estimates (e.g., clinical decision making on the intervention would differ for each subgroup), b) a reduction in the heterogeneity ( $I^2$ ) for each subgroup from the original meta-analysis, and c) a statistically significant Chi<sup>2</sup> test for subgroup effects.

Analyses were performed using Review Manager Version 5.3. For outcomes that demonstrated significant effects, absolute risk reduction (ARR) and number needed to screen (NNS) or number needed to treat (NNT), were calculated. The values for NNS or NNT were calculated using absolute numbers from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables estimated using the control group event rate and RR with the 95% CI obtained from the meta-analysis.<sup>10</sup>

Small-study bias (for meta-analyses with eight or more studies) was assessed using the funnel plot and Egger's test.<sup>11</sup>

#### Quality assessment

Two reviewers independently assessed the quality of the body of evidence for each outcome using GRADE methodology<sup>12, 13</sup> with disagreements resolved through discussion or consultation with a third reviewer. For evidence on benefits and harms of screening and treatment, quality was assigned initially as high for evidence from RCTs and low for evidence from observational studies. Thereafter, quality was potentially downgraded based on five core domains: study limitations/ROB, inconsistency, indirectness, imprecision, and publication/reporting bias. We did not consider upgrading because of serious concerns with the main domains.<sup>14</sup> Assessments were entered into the GRADEpro software<sup>15</sup> and summarized in GRADE Summary of Findings (SOF) and Evidence Profiles (EP) tables.<sup>16</sup>

#### RESULTS

#### Study selection and characteristics

Study flow and selection is in Figure 1. Characteristics of included studies for screening and treatment effectiveness is in Table 1; detailed study information is in Supplement 4.

Screening effectiveness: Four studies (7,611 women)<sup>17-20</sup> were included. One study<sup>17</sup> was published in French. All were non-concurrent cohort studies, comparing outcomes before and after introduction of a screening program.

Women's outcome valuation: No studies were identified that examined how women weigh the benefits and harms of screening and/or treatment of ASB in pregnancy or how their valuation of benefits and harms inform their decisions to undergo screening and treatment. Six surveys and one cross-sectional

study were included: three studies provide information on drug utilization opinions,<sup>21-23</sup> while four studies provide information on perceptions of teratogenic risk.<sup>24-28</sup> One study was a multicenter screening cohort of pregnant women with an embedded RCT of antibiotic treatment for women with significant bacteriuria; cross-sectional findings from the women eligible for treatment are used for information on treatment preference.<sup>22</sup>

Treatment effectiveness: One SR<sup>4</sup> met our inclusion criteria. Contact with the information specialist of the Cochrane Pregnancy and Childbirth Group's Trials Register confirmed one study (Kazemier et al<sup>22</sup>) identified from their ongoing search updates (to October 2017) relevant for treatment effectiveness. Fifteen primary studies<sup>22, 29-42</sup> (2,869 women), mostly published in the 1960s, examined treatment effectiveness for bacteriuria. One study<sup>30</sup> included in the Cochrane review<sup>4</sup> only reported on persistent bacteriuria and therefore was excluded from analysis and the overall body of evidence relevant to our fore was ... outcomes of interest.

| Study design;<br>ROB<br>no. of studies)                            | Setting<br>(no. of studies)  | Sample<br>(no. of<br>participants)   | Population characteristics<br>(no. of studies)  | Screening details<br>(no. of studies)  | Treatment details<br>(no. of studies)  | Follow-up details<br>(no. of studies)   | Outcomes reported<br>(no. of studies)  |
|--|--|--|---|--|--|---|--|
| Studi  | ies of screening effe  | ctiveness  |   |  | L  |   |  |
| Inclear ROB (3)  | Countries:<br>France (1)<br>Spain (1)<br>Turkey (1)<br>USA (1)<br>Clinical setting:<br>Hospital (1)<br>Hospital-based<br>midwifery<br>practice (1)<br>Obstetrics clinic,<br>academic (2) | Total=7,611<br>Screening (2,008)<br>vs.<br>no screening<br>(3,651);<br>Frequent<br>screening (933)<br>vs.<br>one-time<br>screening (1,019) | <ul> <li>&lt;25wks GA (1)</li> <li>&lt;32wks GA (1)</li> <li>Predominantly medically<br/>underserved and Hispanic women<br/>(1)</li> <li>GDM, range 3-9% (2)</li> </ul>   | Screened at first visit:<br>• Mean 20wks GA (1)<br>• <32wks GA (1)<br>• Urine culture (4)<br>• $\geq 10^5$ CFU/mL ( $\geq 10^8$<br>CFU/L) (2)  | Treatment after sensitivity<br>testing (3)   | Follow-up culture, at least<br>once (2)   | Pyelonephritis (4)<br>Perinatal mortality (2)<br>Spontaneous abortion (1)<br>Preterm delivery (3)<br>Fetal abnormalities (1)   |
| tudies of treatme  |  |  |   |  |  |   |  |
| CT (11)<br>CT (4)<br>igh ROB (11)<br>Inclear ROB (3)<br>ow ROB (1) | Australia (3)<br>Denmark (1)<br>Ireland (1)<br>Jamaica (1)<br>Netherlands (1)<br>UK (3)<br>USA (5)<br>Hospital-based<br>clinics (15)   | Total=2,869<br>Treatment (1,357)<br>vs.<br>no<br>treatment/placebo<br>(1,262)  | <ul> <li>First prenatal visit (9)</li> <li>Second prenatal visit (1)</li> <li>≤32 wks GA (9)</li> <li>≥50% non-Caucasian ethnicity (3)</li> <li>100% Caucasian ethnicity (1)</li> <li>Low education, range 10-15% (1)</li> <li>All from lowest income category (1)</li> <li>Previous UTI, ~40% (1)</li> <li>Past history of UTI, 10-15% (2)</li> <li>No urogenital anomalies (2)</li> <li>No chronic renal insufficiency (1)</li> <li>~20% with renal-tract disease or abnormalities (2)</li> <li>&gt;50% with renal abnormalities (1)</li> <li>Asymptomatic patients only (4)</li> </ul> | <ul> <li>Clean-catch/MSU (13)</li> <li>1 urine sample (5)</li> <li>≥2 urine samples (10)</li> <li>Routine urine culture (13)</li> <li>Urine dipslide device (2)</li> <li>≥10<sup>5</sup> CFU/mL in at least one sample (11)</li> <li>10<sup>2</sup>-10<sup>6</sup> CFU/mL, group B streptococci (1)</li> </ul> | Antibiotic treatment:<br><ul> <li>&gt;1 dose (14)</li> <li>Up to 1wk (5)</li> <li>Up to 3wks (1)</li> <li>Up to 30d (1)</li> <li>Up to delivery (6)</li> </ul> Tested for persistent bacteriuria: <ul> <li>during pregnancy, retreatment as warranted (7)</li> <li>after delivery only (1)</li> <li>during pregnancy and after delivery (3)</li> </ul> | Follow-up until:<br>• delivery or postpartum<br>(5)<br>• 10d post-delivery (1)<br>• 6wks post-delivery (4)<br>• >6wks post-delivery (2) | Pyelonephritis (12)<br>Perinatal mortality (6)<br>Spontaneous abortion (2)<br>Neonatal sepsis (1)<br>Preterm delivery (4)<br>Low birth weight (7)<br>Fetal abnormalities (4)<br>Hemolytic anemia (1) |
| CCT:   | controlled clinical tr   | ial; d: day(s); GA: gesta  | tional age; GDM: gestational diabetes m   | ellitus; no: number; RCT: randor   | nized controlled trial; ROB: risk  | of bias; UTI: urinary tract infect  | ion; wks: weeks  |
|  |  |  |   |  |  |   | 7  |
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#### **ROB** and quality assessments

Overall ROB assessments for screening and treatment effectiveness are in Table 1, and reported with quality assessments below; detailed ROB assessments are in Supplement 5.

For women's outcome valuation, all seven studies addressed a focused research question and used a sample representative of this study question, their reported sampling methods could potentially introduce bias and only one of the studies<sup>24</sup> fully accounted for confounding factors through statistical analysis. None of the papers reported that their sample size was based on pre-study considerations while only two papers<sup>23, 28</sup> used survey questions that were considered valid and reliable.

Quality of evidence assessments for screening and treatment effectiveness are in Table 2; detailed GRADE SOF and EP tables and forest plots are in Supplement 6.

#### **Screening effectiveness**

Three studies<sup>17, 18, 20</sup> of unclear ROB (5,659 women) found a statistically significant difference for *screening compared with no screening* on the outcome of **pyelonephritis** (RR 0.28; 95% CI 0.15, 0.54;  $I^2$ =0%; ARR 1.3%; NNS 77, 95% CI 65, 121; very low quality). One study<sup>19</sup> (1,952 women) with low ROB comparing *screening at all prenatal visits with screening at first prenatal visit only*, found no significant difference for pyelonephritis (RR 1.09; 95% CI 0.27, 4.35; very low quality).

Two studies<sup>17, 20</sup> (724 women) with unclear ROB and suspected reporting bias<sup>43</sup> found no significant difference (RR 1.21, 95% CI 0.01, 102.93,  $I^2=84\%$ ; very low quality) in **perinatal mortality**. One study of 370 women<sup>17</sup> with unclear ROB but suspected reporting bias found no significant difference (RR 0.96, 95% CI 0.41, 2.27; very low quality) in **spontaneous abortion** at  $\leq 28$  weeks of gestation.

Two studies<sup>17, 20</sup> (722 women) with unclear ROB but suspected reporting bias<sup>43</sup> compared *screening with no screening* and found no significant difference (RR 8.70, 95% CI 0.32, 240.07; I<sup>2</sup>=80%; very low quality) in **preterm delivery**. The study<sup>19</sup> comparing *different screening algorithms* found a significant difference for preterm delivery (RR 1.57; 95% CI 1.11, 2.23; very low quality) with more preterm deliveries among the group that was screened at all prenatal visits. The study authors did not present a possible hypothesis to explain this result.

One study<sup>20</sup> (372 women) with unclear ROB found no significant difference (RR 1.50, 95% CI 0.25, 8.87; very low quality) in **fetal abnormalities**.

No study reported on maternal mortality, maternal sepsis, neonatal sepsis or low birthweight.

Subgroup analyses were not performed due to insufficient number of studies per category comprising *a priori* subgroups.

#### Women's outcome valuation

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Studies demonstrated varied opinions on antibiotic use during pregnancy, with nearly half of participants from two studies (47-48%) expressing that antibiotics should not be used during pregnancy.<sup>21, 23</sup> Cross-sectional analysis of patients recruited for an RCT of treatment for ASB found similar results, with 61% of 255 women with ASB not wanting to be treated for an asymptomatic condition.<sup>22</sup> Some evidence suggested that women thought penicillin posed a teratogenic risk<sup>24, 26</sup> and that antibiotics were unsafe during pregnancy particularly for the fetus.<sup>25, 27</sup> How these attitudes may inform the women's decisions on whether to screen for ASB was not reported, nor were details on accuracy or understanding of information regarding potential risks and benefits.

#### Treatment effectiveness

Twelve studies<sup>22, 29, 31-39, 41</sup> (2,017 women) examined the effects of antibiotic treatment and found a significant difference in development of **pyelonephritis** (RR 0.24; 95% CI 0.13, 0.41; I<sup>2</sup>=60%; ARR 17.6%; NNT 6, 95% CI 5, 7; low quality) (Figure 2). Three trials explicitly included women without symptoms at baseline (other trials may have included some symptomatic women); sensitivity analysis did not affect the results (3 trials,<sup>22, 38, 41</sup> RR 0.22; 95% CI 0.10, 0.49; I<sup>2</sup>=0%). Sensitivity analysis for ROB (removing studies with overall high risk) and study design (removing CCTs) did not change the results.

Subgroup analysis for the number of urine samples—studies using one or more additional cultures to confirm ASB compared with just one culture—appeared to explain the heterogeneity among all studies combined (I<sup>2</sup>=60%) for pyelonephritis (RR 0.19, 95% CI 0.11, 0.31; I<sup>2</sup>=31% versus RR 0.50, 95% CI 0.19, 1.35; I<sup>2</sup>=41%). The test for subgroup differences was not statistically significant (p=0.08), but the heterogeneity in each subgroup was reduced and visual inspection of the forest plots suggests a meaningful difference in effect. There was a statistically significant subgroup difference (Chi<sup>2</sup> p=0.001) when testing for persistent bacteriuria was done during pregnancy and after delivery (RR 0.11, 95% CI 0.05, 0.25; I<sup>2</sup>=0%) compared with testing during pregnancy only (RR 0.24, 95% CI 0.13, 0.41; I<sup>2</sup>=30%) or with testing only after delivery (RR 0.65, 95% CI 0.37, 1.14). Studies that followed women beyond six weeks after delivery (RR 0.11, 95% CI 0.05, 0.25; I<sup>2</sup>=0%) found greater reduction in pyelonephritis than those only following women until delivery or six weeks post-delivery (RR 0.31, 95% CI 0.18, 0.54; I<sup>2</sup>=53%; Chi<sup>2</sup> p=0.04).

The funnel plot (Supplement 7) appeared symmetrical; however, Egger's test was inconclusive (p=0.065). The twelve studies with small sample sizes limit the ability to detect or exclude the possibility of small-study bias.

Six studies (1,104 women) examined **perinatal mortality**; one study<sup>22</sup> was at low ROB, three studies<sup>31, 35, 42</sup> were at high ROB, and two studies<sup>36, 37</sup> were unclear. No significant difference was found between groups on perinatal mortality (RR 0.96, 95% CI 0.27, 3.39; I<sup>2</sup>=56%; very low quality).

Two studies<sup>33, 42</sup> (379 women) with high ROB reported on **spontaneous abortion** and found no significant difference between groups (RR 0.60, 95% CI 0.11, 3.10;  $I^2=17\%$ ; very low quality). Two studies<sup>22, 40</sup> (154 women) with low ROB reported on **neonatal sepsis** with no statistically significant difference (very low quality) between groups.

Two studies<sup>22, 40</sup> with low risk of bias and two studies<sup>33, 42</sup> with high ROB (total 533 women) showed no significant difference between groups on **preterm delivery** (RR 0.57, 95% CI 0.21, 1.56;  $I^2=70\%$ ; very low quality).

Seven studies (1,522 women) with two studies<sup>22, 37</sup> at low, three<sup>29, 31, 35</sup> at high and one<sup>36</sup> at unclear ROB examined the effect of treatment on **low birth weight** (Figure 3). There was a statistically significant difference favoring antibiotics (RR 0.63; 95% CI 0.45, 0.90;  $I^2$ =20%; ARR 4.4%; NNT 23, 95% CI 15, 85; low quality).

Four studies (821 women; 2 low  $ROB^{22, 37}$ , two high  $ROB^{31, 33}$ ) examined the effect of treatment on **fetal abnormalities**, and found no statistically significant difference between groups (RR 0.49, 95% CI 0.17, 1.43; I<sup>2</sup>=0%; very low quality).

One study<sup>31</sup> (265 women) with high ROB (very low quality) reported no cases of **hemolytic anemia** in infants.

No study reported on maternal mortality, maternal sepsis, or maternal harms.

| U  | creening                             |                        |  |                        |                        |  |
|--|--------------------------------------|------------------------|--|------------------------|------------------------|--|
| Outcomes No. of<br>participants<br>(no. of<br>studies)   |                                      | Absolute o             | Absolute difference per 1,000              |                        |                        |  |
|  |                                      | Risk with no screening | (95% CI)<br>Risk with screening            | (95% CI)               | evidence<br>(GRADE)    |  |
| Pyelonepł  | ritis 5,659<br>(3)                   | 18                     | NS*  | 0.28 (0.15 to 0        | 0.54) Ve               |  |
| Perinatal mortality 724<br>(2)<br>Spontaneous 370<br>abortion (1)  |                                      | 19                     | NS*  | 1.21 (0.01 to 1        | 102.93) Ve             |  |
|  |                                      | 55                     | NS*  | 0.96 (0.41 to 2        | 2.27) Ve               |  |
| Preterm d  | elivery 722<br>(2)                   | 13                     | NS*  | 8.70 (0.32 to 2        | 240.07) Ver            |  |
| Neonatal<br>harm:  | (1)                                  | 11                     | NS*  | 1.50 (0.25 to 8.87)    |                        |  |
| fetal abno   | rmalities<br>creening vs. one-ti     | me screening           |  |                        |                        |  |
| Trequent   | screening vs. one-ti                 | ine sereening          |  |                        |                        |  |
| Outcomes   | No. of                               | Absolute o             | Absolute difference per 1,000              |                        |                        |  |
|  | participants<br>(no. of              | Risk with one-time     | (95% CI)<br>Risk with frequent             | (95% CI)               | evidence<br>(GRADE)    |  |
| Pyelonephritis 1,952<br>(1)  |                                      | screening<br>4         | screening<br>NS*                           | 1.09 (0.27 to 4.35)    | Very Low               |  |
| Perinatal mortalit   |                                      | 49                     | NS*  | 1.57 (1.11 to 2.23)    | Very Low               |  |
| Treatment vs. no   | treatment/placebo                    |                        |  |                        |                        |  |
| Outcomes   | No. of<br>participants               | Absolute o             | difference per 1,000<br>(95% CI)           | Risk ratio<br>(95% CI) | Quality of<br>evidence |  |
|  | (no. of<br>studies)                  | Risk with no treatment | Risk with treatment                        |                        | (GRADE)                |  |
| Pyelonephritis   | 2,017<br>(12)                        | 232                    | 176 fewer<br>(from 137 fewer to 202 fewer) | 0.24 (0.13 to 0.41)    | Low                    |  |
| Perinatal mortalit   | (6)                                  | 40                     | NS*  | 0.96 (0.27 to 3.39)    | Very Low               |  |
| Spontaneous<br>abortion  | 379<br>(2)                           | 33                     | NS*  | 0.60 (0.11 to 3.10)    | Very Low               |  |
| Neonatal sepsis  | 154<br>(2)                           | 22                     | NS*  | 0.22 (0.01 to 4.54)    | Very Low               |  |
| Dustance I. II   | 533<br>(4)                           | 158                    | NS*  | 0.22 (0.21 to 1.56)    | Very Low               |  |
|  |                                      | 118                    | 44 fewer<br>(from 12 fewer to 65 more)     | 0.63 (0.45 to 0.90)    | Low                    |  |
| Low birth weight   | 1,522<br>(7)                         |                        |  | 0.49 (0.17 to 1.43)    | Very Low               |  |
| Low birth weight<br>Neonatal serious<br>harm:  | (7)<br>821<br>(4)                    | 19                     | NS*  |                        |                        |  |
| Low birth weight<br>Neonatal serious<br>harm:<br>fetal abnormalitie<br>Neonatal serious<br>harm:   | (7)<br>821<br>(4)                    | 19<br>0                |  | Not estimable          | Very Low               |  |
| Preterm delivery<br>Low birth weight<br>Neonatal serious<br>harm:<br>fetal abnormalitie<br>Neonatal serious<br>harm:<br>hemolytic anemia<br>Cl: confider<br>versus | (7)<br>821<br>(4)<br>5<br>265<br>(1) | 0                      | NS*  |                        |                        |  |

#### **CONCLUSIONS & DISCUSSION**

This paper reports on three SRs to inform recommendations on screening for ASB in pregnancy. Using the GRADE approach, very low quality was found for most outcomes from studies of screening programs using urine culture, including evidence from one study comparing frequent screening with one-time screening. No direct evidence was found on how women weigh the benefits and harms of screening and/or treatment for ASB and how this valuation might affect their decisions to undergo screening. Low quality evidence for women with significant bacteriuria provides limited confidence that antibiotic treatment reduces the incidence of pyelonephritis and the number of babies born at low birth weight.

#### Limitations of evidence base and review

Many patient and intervention characteristics were inconsistently reported or unreported, making it difficult to infer direct associations between specific risk or intervention factors and outcomes, as well as limiting potential subgroup analyses. Outcomes were defined variably among studies.

Much of the evidence came from trials on treatment of bacteriuric women (2-10% of screening population), therefore the results fail to incorporate several effects that would be captured in studies of screening effectiveness (e.g. effects on non-screened women who develop symptoms, or on ASB-negative women; effects from non-adherence to screening protocol). Only three studies explicitly reported patients as exclusively asymptomatic pregnant women; among treated patients, the beneficial effects may be larger among symptomatic women compared with asymptomatic women. Early stopping due to low incidence of primary outcomes in one study<sup>22</sup> may have biased effects of treatment.

#### Comparison with other reviews

Similar to findings of the current review, a recent systematic review by Angelescu et al<sup>43</sup> that examined benefits and harms of screening for ASB in pregnancy found no trials on screening effectiveness. The review authors included four RCTs focused on treatment of ASB.<sup>22 30 38 41</sup> These authors limited inclusion to studies reporting exclusively on treatment in asymptomatic women. We included studies that likely included some women with symptoms, and found no meaningful difference for this variable in subgroup analysis. Angelescu et al<sup>43</sup> examined some intervention characteristics (e.g., treatment regimen and adjunct treatments) and outcomes (e.g., lower urinary tract infection (UTI), very low birth weight <1500g) that were not included in our review. They concluded that there was no reliable evidence on the benefits and harms of screening to support routine screening for ASB using urine culture in pregnant women.<sup>43</sup>

#### **Future research**

Although the anticipation of a large RR reduction for pyelonephritis appears to limit the clinical equipoise necessary to conduct RCTs on screening for ASB, such trials may be considered based on: (1) very low quality evidence from screening studies and the linked nature of treatment evidence, particularly concerns about the methodological quality and the applicability of dated trials to current practice, and (2) some evidence suggesting that the incidence of pyelonephritis in untreated ASB (e.g., 2.5% in recent screening

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cohort study<sup>22</sup>) may be substantially lower than that reported in historical literature and most of the available treatment trials (median control group incidence of 23%), such that the absolute number of women who benefit from screening may be relatively low. Studies evaluating screening programs should aim to capture data accurately on harms and include a cost-effectiveness analysis, in clearly defined populations, using modern definitions for outcomes.

Better information is needed to determine whether there are important moderating factors for ASB screening, as we attempted to examine in comparing different screening methods/algorithms. Subgroup analyses of studies using one urine culture versus at least one additional confirmatory culture, had some credibility but were limited to reliance on between-study effects. Studies directly examining this, and other factors such as different thresholds for treatment, could provide high-quality data and be informative for how to maximize benefit. Enhanced culture protocols (e.g. expanded spectrum) for detecting the most clinically relevant uropathogens are emerging,<sup>44, 45</sup> and if found to consistently provide better detection of these microorganisms than standard urine culture, studies comparing screening programs differing by these methods are encouraged to determine if they also predict how well treatment reduces the risk for pyelonephritis and other pregnancy complications in asymptomatic women.

More evidence or information about how women weigh the benefits and harms of screening and treatment for ASB in pregnancy would be valuable. It may be useful to use deliberative processes or focus groups to facilitate patients' understanding of results on such benefits and harms; this may be informative to determine whether it is critical to better engage patients in shared decision-making.

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#### Figures

- Figure 1. PRISMA flow diagram of study selection
- Figure 2. Forest plot of the effect of antibiotic treatment on incidence of pyelonephritis
- Figure 3. Forest plot of the effect of antibiotic treatment on incidence of babies born at low birth weight

#### Supplementary data

This paper is based on a full report conducted by the Edmonton Evidence Review and Synthesis Centre "Screening for Asymptomatic Bacteriuria in Pregnancy: Systematic Review & Meta-analysis", available at [CTFPHC website link when available].

Supplement 1 – Protocol Supplement 2 – Search strategy Supplement 3 – Eligibility criteria Supplement 4 – Characteristics of included studies Supplement 5 – Risk of bias assessments for included studies Supplement 6 – GRADE Summary of Findings & Evidence Profiles tables & forest plots Supplement 7 – Funnel plot

**Contributors:** LH, AW, JP, MS, MG, RF, KS and BV critically reviewed and contributed to drafts of the report. AW, JP, MS, MG, KS and BV conducted screening, quality assessments, data extraction and analysis. AW, JP, LH, MS, KS and BV contributed to interpretation of results. All of the authors approved the final version of this report.

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## REFERENCES

- 1. Glaser AP, Schaeffer AJ. Urinary tract infection and bacteriuria in pregnancy. The Urologic Clinics of North America 2015;42(4);547-60. PMID:26475951.
- 2. Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. European Journal of Clinical Investigation 2008;38(Suppl 2);50-7. PMID:18826482.
- Ipe DS, Sundac L, Benjamin WH, Jr., Moore KH, Ulett GC. Asymptomatic bacteriuria: Prevalence rates of causal microorganisms, etiology of infection in different patient populations, and recent advances in molecular detection. FEMS Microbiology Letters 2013;346(1);1-10. PMID:23808987.
- 4. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. The Cochrane Database of Systematic Reviews 2015;8(CD000490). PMID:26252501.
- Guinto VT, De Guia B, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. The Cochrane Database of Systematic Reviews 2010;9(CD007855). PMID:20824868.
- 6. Patterson TF, Andriole VT. Bacteriuria in pregnancy. Infectious Disease Clinics of North America 1987;1(4);807-22. PMID:3333660.
- 7. Canadian Agency for Drugs and Technologies in Health. Grey matters: A practical tool for searching health-related grey literature. Ottawa, ON; 2015.
- 8. Evidence Partners Inc. [Internet]. Distiller (DistillerSR systematic review software program). [cited: December 20, 2017]. Available from: <u>http://systematic-review.net/</u>.
- 9. Higgins JP, Green S. [Internet]. Section 8. Assessing risk of bias in included studies. [cited: December 20, 2017]. Available from: http://handbook.cochrane.org
- 10. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables—binary outcomes. Journal of Clinical Epidemiology 2013;66(2);158-72.
- 11. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical Research Ed) 1997;315(7109);629-34. PMID:9310563.
- 12. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: A new series of articles in the Journal of Clinical Epidemiology. Journal of Clinical Epidemiology 2011;64(4);380-2. PMID:21185693.
- Hsu J, Brozek JL, Terracciano L, et al. Application of grade: Making evidence-based recommendations about diagnostic tests in clinical practice guidelines. Implementation Science 2011;6;62. PMID:21663655.
- 14. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidenceimprecision. Journal of Clinical Epidemiology 2011;64(12);1283-93. PMID:21839614.
- 15. McMaster University. [Internet]. GRADEpro (GRADEpro GDT computer software). [cited: December 20, 2017]. Available from:https://gradepro.org.

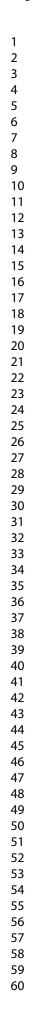
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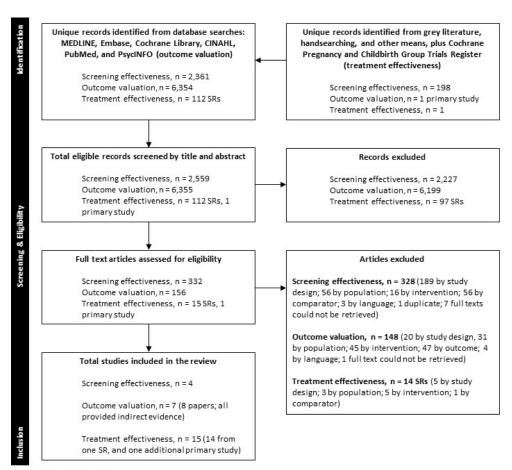
| 16. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-grade evidence profiles and |
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| summary of findings tables. Journal of Clinical Epidemiology 2011;64(4);383-94.                      |
| PMID:21195583.   |

- 17. Gérard J, Blazquez G, Mounac M. [Importance of systematic research of urinary infection in pregnant women and the cost of its detection. Proposal for a practical approach]. Journal de Gynécologie, Obstétrique et Biologie de la Reproduction (Paris) 1983;12(3);243-51. PMID:6886322.
- Gratacós E, Torres PJ, Vila J, Alonso PL, Cararach V. Screening and treatment of asymptomatic bacteriuria in pregnancy prevent pyelonephritis. Journal of Infectious Diseases 1994;169(6);1390-2. PMID:8195624.
- 19. Rhode MA, Shapiro H, Jones OW, 3rd. Indicated vs. routine prenatal urine chemical reagent strip testing. Journal of Reproductive Medicine 2007;52(3);214-9. PMID:17465289.
- 20. Uncu Y, Uncu G, Esmer A, Bilgel N. Should asymptomatic bacteriuria be screened in pregnancy? Cliniccal and Experimental Obstetrics and Gynecology 2002;29(4);281-5. PMID:12635746.
- 21. Butters L, Howie CA. Awareness among pregnant women of the effect on the fetus of commonly used drugs. Midwifery 1990;6(3);146-54. PMID:2233396.
- 22. Kazemier BM, Koningstein FN, Schneeberger C, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: A prospective cohort study with an embedded randomised controlled trial. The Lancet Infectious Diseases 2015;15(11);1324-33. PMID:26255208.
- 23. Sharma R, Kapoor B, Verma U. Drug utilization pattern during pregnancy in north india. Indian Journal of Medical Sciences 2006;60(7);277-87. PMID:2006369645.
- 24. Lupattelli A, Picinardi M, Einarson A, Nordeng H. Health literacy and its association with perception of teratogenic risks and health behavior during pregnancy. Patient Education and Counseling 2014;96(2);171-8. PMID:24862909.
- 25. Mashayekhi SO, Dilmaghanizadeh M, Fardiazar Z, Bamdad-Moghadam R, Ghandforoush-Sattari F. Study of awareness among pregnant women of the effects of drugs on the fetus and mother in iran. Health Policy 2009;91(1);89-93. PMID:2009210441.
- 26. Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. European Journal of Clinical Pharmacology 2010;66(2);207-14. PMID:19841915.
- 27. Sanz E, Gomez-Lopez T, Martinez-Quintas MJ. Perception of teratogenic risk of common medicines. European Journal of Obstetrics Gynecology and Reproductive Biology 2001;95(1);127-31. PMID:2001099054.
- 28. Twigg MJL, A.; Nordeng, H. Women's beliefs about medication use during their pregnancy: A UK perspective. International Journal of Clinical Pharmacy 2016;38);968-76.
- 29. Brumfitt W. The effects of bacteriuria in pregnancy on maternal and fetal health. Kidney International 1975;4(Supp 4);113.

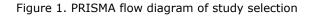
30. Elder H, Santamarina B, Smith S, Kass E. Use of sulfasymazine in the treatment of bacteriuria of pregnancy. Antimicrobial Agents and Chemotherapy 1966;6;142-8.

- 31. Elder H, Santamarina B, Smith S, Kass E. The natural history of asymptomatic bacteriuria during pregnancy: The effect of tetracycline on the clinical course and the outcome of pregnancy. American Journal of Obstetrics and Gynecology 1971;111(3);441-62.
- 32. Foley M, Farquharson R, Stronge J. Is screening for bacteriuria in pregnancy worthwhile? British Medical Journal (Clinical Research ed) 1987;295(6592);270.
- 33. Furness E, McDonald P, Beasley N. Urinary antiseptics in asymptomatic bacteriuria of pregnancy. The New Zealand Medical Journal 1975;81(539);417-9.
- 34. Gold EM, Traub FB, Daichman I, Terris M. Asymptomatic bacteriuria during pregnancy. Obstetrics and Gynecology 1966;27(2);206-9.
- 35. Kass E. The role of asymptomatic bacteriuria in the pathogenesis of pyelonephritis. In Quinn EL, Kass EH (editors). Biology of pyelonephritis. Boston: Little Brown and Company 1960;399-412.
- 36. Kincaid-Smith P BM. Bacteriuria in pregnancy. The Lancet 1965;1;1382-7.
- 37. Little P. The incidence of urinary infection in 5000 pregnant women. The Lancet 1966;288(7470);925-8.
- 38. Mulla N. Bacteriuria in pregnancy. Obstetrics & Gynecology 1960;16(1);89-92.
- 39. Pathak U, Tang K, Wifflams L, Stuart K. Bacteriuria of pregnancy: Results of treatment. The Journal of Infectious Diseases 1969;120(1);91-103.
- 40. Thomsen A, Mo/rup L, Hansen KB. Antibiotic elimination of group-b streptococci in urine in prevention of preterm labour. The Lancet 1987;329(8533);591-3.
- 41. Williams G, Campbell H, Davies K. Urinary concentrating ability in women with asymptomatic bacteriuria in pregnancy. British Medical Journal 1969;3(5664);212-5.
- 42. Wren B. Subclinical renal infection and prematurity. The Medical Journal of Australia 1969;2(12);596-600.
- 43. Angelescu K, Nussbaumer-Streit B, Sieben W, Scheibler F, Gartlehner G. Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: A systematic review. BMC Pregnancy and Childbirth 2016;16(1);336. PMID:27806709.
- 44. Hilt EE, McKinley K, Pearce MM, et al. Urine is not sterile: Use of enhanced urine culture techniques to detect resident bacterial flora in the adult female bladder. Journal of Clinical Microbiology 2014;52(3);871-6. PMID:PMC3957746.
- 45. Price TK, Dune T, Hilt EE, et al. The clinical urine culture: Enhanced techniques improve detection of clinically relevant microorganisms. Journal of Clinical Microbiology 2016;54(5);1216-22.





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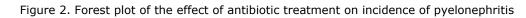


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|                                   | Treatm    | ent    | No treatment or p     | lacebo         |        | <b>Risk Ratio</b>   | Risk Ratio   |
|-----------------------------------|-----------|--------|-----------------------|----------------|--------|---------------------|--|
| Study or Subgroup                 | Events    | Total  | Events                | Total          | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl  |
| Brumfitt 1975                     | 9         | 87     | 20                    | 86             | 12.8%  | 0.44 [0.21, 0.92]   |  |
| Elder 1971                        | 4         | 133    | 27                    | 148            | 10.6%  | 0.16 [0.06, 0.46]   |  |
| Foley 1987                        | 3         | 100    | 3                     | 120            | 7.1%   | 1.20 [0.25, 5.82]   | •  |
| Furness 1975                      | 23        | 139    | 17                    | 67             | 14.1%  | 0.65 [0.37, 1.14]   |  |
| Gold 1966                         | 0         | 35     | 2                     | 30             | 2.9%   | 0.17 [0.01, 3.45]   | •  |
| Kass 1960                         | 1         | 93     | 26                    | 98             | 5.4%   | 0.04 [0.01, 0.29]   | ·  |
| Kazemier 2015                     | 0         | 40     | 1                     | 45             | 2.6%   | 0.37 [0.02, 8.93]   |  |
| Kincaid-Smith 1965                | 2         | 61     | 20                    | 55             | 8.0%   | 0.09 [0.02, 0.37]   |  |
| Little 1966                       | 4         | 124    | 35                    | 141            | 10.7%  | 0.13 [0.05, 0.36]   |  |
| Mulla 1960                        | 1         | 50     | 12                    | 50             | 5.3%   | 0.08 [0.01, 0.62]   |  |
| Pathak 1969                       | 3         | 76     | 17                    | 76             | 9.4%   | 0.18 [0.05, 0.58]   |  |
| Williams 1969                     | 5         | 85     | 18                    | 78             | 11.2%  | 0.25 [0.10, 0.65]   |  |
| Total (95% CI)                    |           | 1023   |                       | 994            | 100.0% | 0.24 [0.13, 0.41]   | •  |
| Total events                      | 55        |        | 198                   |                |        |                     |  |
| Heterogeneity: Tau <sup>2</sup> = | 0.49; Chi | = 27.8 | i9, df = 11 (P = 0.00 | 4); $ ^2 = 60$ | %      |                     |  |
| Test for overall effect:          |           |        |                       |                |        |                     | 0.01 0.1 1 10 10<br>Favours treatment Favours no treatment |



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|                                   | Treatn     | nent                | No treatment or p                   | lacebo |        | Risk Ratio          | Risk Ratio  |
|-----------------------------------|------------|---------------------|-------------------------------------|--------|--------|---------------------|---|
| Study or Subgroup                 | Events     | Total               | Events                              | Total  | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl   |
| Brumfitt 1975                     | 18         | 235                 | 21                                  | 178    | 23.0%  | 0.65 [0.36, 1.18]   |   |
| Elder 1971                        | 15         | 133                 | 15                                  | 145    | 19.4%  | 1.09 [0.55, 2.14]   | <b>_</b>  |
| Kass 1960                         | 7          | 93                  | 21                                  | 98     | 14.8%  | 0.35 [0.16, 0.79]   |   |
| Kazemier 2015                     | 1          | 40                  | 4                                   | 45     | 2.5%   | 0.28 [0.03, 2.41]   |   |
| Kincaid-Smith 1965                | 9          | 61                  | 12                                  | 56     | 15.5%  | 0.69 [0.31, 1.51]   |   |
| Little 1966                       | 10         | 124                 | 13                                  | 141    | 15.4%  | 0.87 [0.40, 1.92]   |   |
| Wren 1969                         | 4          | 83                  | 14                                  | 90     | 9.3%   | 0.31 [0.11, 0.90]   |   |
| Total (95% CI)                    |            | 769                 |                                     | 753    | 100.0% | 0.63 [0.45, 0.90]   | •   |
| Total events                      | 64         |                     | 100                                 |        |        |                     |   |
| Heterogeneity: Tau <sup>2</sup> = | 0.04; Chi  | <sup>2</sup> = 7.52 | , df = 6 (P = 0.28); I <sup>≉</sup> | = 20%  |        |                     |   |
| Test for overall effect:          | Z = 2.57 ( | (P = 0.0            | 1)                                  |        |        |                     | 0.01 0.1 1 10 100<br>Favours treatment Favours no treatment |

Figure 3. Forest plot of the effect of antibiotic treatment on incidence of babies born at low birth weight

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# Supplement 1. Protocol: Screening for asymptomatic bacteriuria in pregnancy

December 1, 2016

ERSC Project Lead Investigator: Lisa Hartling ERSC Project Staff: Aireen Wingert, Jennifer Pillay, Robin Featherstone (MLIS), and Ben Vandermeer (Statistician)

Suggested citation: Wingert A, Pillay J, Featherstone R, Vandermeer B, and Hartling L. Screening for asymptomatic bacteriuria in pregnancy: protocol for evidence review. Edmonton, AB; Evidence Review Synthesis Centre. Available at: <u>http://canadiantaskforce.ca/ctfphc-guidelines/overview/</u>

#### **Author Contributions**

AW and JP drafted the protocol and RF developed the search strategy and provided text for the protocol. AW, JP, and LH contributed to discussions with the CTFPHC and PHAC on the scope for this work. LH and BV critically reviewed the protocol. All of the authors approved the final version of this protocol.

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<u>CTFPHC Asymptomatic Bacteriuria Working Group</u>: Ainsley Moore (Chair), Roland Grad, Stéphane Groulx, Kevin Pottie, Brett Thombs, and Marcello Tonelli

<u>PHAC Global Health & Guidance Division Staff:</u> Marion Doull, Alejandra Jaramillo Garcia, Susan Courage, Nicki Sims-Jones

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ASB Protocol - Page 1

# Section I. Background and Purpose

# Asymptomatic Bacteriuria in Pregnancy

Asymptomatic bacteriuria (ASB) - synonymous with asymptomatic urinary tract infection (UTI) - signifies a significant quantitative count of bacteria in the urine without symptoms of a lower (acute cystitis) or upper urinary tract (acute pyelonephritis) infection (1, 2). There is a 2-10% prevalence of ASB in premenopausal, ambulatory women (1), but due to anatomical and physiological changes (e.g., urinary stasis - difficulty emptying the bladder due to extended accumulation of urine) to the urinary tract in pregnancy there are theoretical reasons to suspect a greater chance of progression to symptomatic UTI and other pregnancy complications (e.g., maternal kidney infection, preterm delivery) (1, 3). Numerous risk factors for ASB in pregnancy have been identified, with low socioeconomic status, parity, a history of recurrent UTI, diabetes, and anatomical abnormalities of the urinary tract most cited (1, 2, 4).

# Consequences of Untreated Bacteriuria in Pregnancy and Rationale for Review of Screening

There is a potentially greater risk in pregnant women compared to other populations for ASB developing into pyelonephritis (upper urinary tract infection) (3) with its associated inflammation of the renal parenchyma, calices and pelvis (5), although controversy exists. There is significant heterogeneity in reports of the incidence of pyelonephritis in untreated ASB during pregnancy. Some reports suggest low incidences of 1% or less after the introduction of screening and treatment for ASB and 4% or higher before the era of screening and treatment of ASB in pregnancy. Historical reports prior to 1966 indicated up to 40% of pregnant women with ASB developed pyelonephritis. These higher rates were before modern obstetrical care; however, these numbers continue to be cited in current systematic reviews (4) and guidelines (6) of ASB in pregnancy (1, 7). Furthermore, whether there is evidence to support a causal link between ASB and pyelonephritis in contemporary practice is uncertain.

There is an association between clinical signs of pyelonephritis and maternal respiratory insufficiency, septicemia, renal dysfunction and anemia, as well as evidence of a 20 to 50% higher incidence of preterm birth and low birth weight (4, 8). However, controversy exists over the direct link between ASB, pyelonephritis, and adverse perinatal outcomes (e.g., whether ASB affects pregnancy and neonatal outcomes solely through pyelonephritis or also other mechanisms) (2, 4), and also about whether treatment of ASB will reduce the risk of such adverse outcomes. A 2015 Cochrane review (4) found that antibiotic treatment for ASB in pregnancy may greatly reduce the incidence of pyelonephritis, preterm birth, and low birth weight babies. However, the authors' confidence in the findings were low due to poor quality evidence. A preliminary search identified a recent cohort study (9) with an embedded RCT, which found no statistically significant difference between ASB-positive women who were untreated or placebo-treated compared to ASB-negative women in terms of both pyelonephritis and preterm birth (6/208 [2.9%] vs 77/4035 [1.9%]; adjusted odds ratio [OR] 1.5, 95% CI 0.6–3.5).

Although the direct link between pyelonephritis and adverse perinatal outcomes may not be easily resolved (4), some main issues to examine include: 1) which, if any, screening tests and methods (e.g., collection methods, timing) are most accurate, and; 2) whether screening of all pregnant women and treatment for positive cases is effective (9). The effectiveness of screening for reducing risk of pyelonephritis and neonatal and maternal complications need to be examined in an era of modern obstetrical care.

#### **Issues to Consider for Screening Tests**

Significant bacteriuria is usually defined by the presence of at least 10<sup>5</sup> colony-forming units (CFU) per mL of urine of a single uropathogen, in two consecutive clean-catch specimens (4, 7). Acceptable thresholds and repetitions considered positive for bacteriuria in pregnancy may vary in practice. The quantitative urine culture is considered to be the gold standard for accurate detection of ASB. However, it is costlier, more labor intensive and more time-consuming compared with other rapid urine screening tests (urinalysis, dipstick nitrite tests) which reportedly have lower sensitivity<sup>1</sup> (1, 2). A preliminary search for recent literature identified a systematic review of onsite tests (point-of-care tests that are widely available in resource-limited settings) compared with urine culture that concluded specificity<sup>2</sup> was high overall but sensitivity was low and therefore onsite tests were not reliable in detecting pregnant women with ASB (10). There is no consistent recommendation for urine specimen collection in pregnancy (clean-catch with or without perineal cleansing) or optimal timing and frequency of screening tests or followup cultures (2). It is unclear whether universal screening (with subsequent treatment) for ASB confers benefits, and whether available screening tests for ASB are comparable to the current gold standard (urine culture) for identifying bacteriuric patients. The standard urine culture protocol is evolving with the testing of emerging techniques that may improve the detection of uropathogens (11, 12). However, at this time, urine culture is considered the reference standard. Resource needs for screening may be an important factor to consider. For example, an economic analysis indicated that screening with a dipstick and providing screen positive women treatment with antibiotics remained cost-beneficial for reducing pyelonephritis when prevalence of ASB is <2% or when the proportion of patients with ASB who develop pyelonephritis dropped to 10%, but the cost-benefit was not seen for culture diagnostics where the absolute clinical benefit was shown to be reduced (13).

<sup>1</sup>Sensitivity is a diagnostic test accuracy outcome that refers to how well a test correctly identifies individuals with a disease/condition; <sup>2</sup>Specificity is a diagnostic test accuracy outcome that refers to how well a test correctly identifies individuals without a disease/condition.

#### Issues to Consider for Harms of Screening

Patients may have preferences for avoiding harms due to screening and treatment in asymptomatic conditions (e.g., test anxiety/distress). Although the harms from screening tests may be considered minimal, harms from antibiotic treatment need to be considered when making decisions about screening practices for ASB in pregnancy. Some sources have outlined concerns with incidence and reporting on adverse effects of antibiotic treatment for ASB, UTIs, or antibiotic use in general during pregnancy (2, 4, 14). Some trials evaluating treatment versus no treatment/placebo of ASB in pregnancy have been critiqued for poorly reporting harms (4), such that making judgments on the net balance of benefits and harms may be difficult. The significance of the expected side effects from a short course of antibiotics may be small although increasingly there are concerns about the effect of antibiotics on the human microbiome and the

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immune system. Antimicrobial resistance has certainly made the selection of an antibiotic for an individual woman more difficult (4). Additionally, patients may have preferences for avoiding treatment harms in asymptomatic conditions that need to be considered.

The goal of this review is to determine the effectiveness of screening for ASB among pregnant women. This evidence synthesis will inform recommendations on screening for ASB made by the Canadian Task Force for Preventive Healthcare (CTFPHC). As part of the guideline development process, the CTFPHC will also engage organizational stakeholders and peer-reviewers to gather information on key implementation considerations, such as strategies to help address potential health inequities and any concerns about the acceptability and feasibility of the guideline.

# Section II. Recommendations in Other Guidelines and Current Practice

# **Canadian Organizations**

The Society of Obstetricians and Gynecologists of Canada (SOGC), concerned over maternal and perinatal risks associated with ASB, recommends to treat single-strain colony counts of 10<sup>5</sup> CFU/mL (or 10<sup>8</sup> CFU/L) or greater with appropriate antibiotics during pregnancy to prevent adverse outcomes such as pyelonephritis and pretern birth (15). They support a single quantitative culture in any trimester as sufficient and recommend re-treatment with sensitivities for women with recurrent bacteriuria although they do not make recommendations for timing or frequency of re-testing. Similar recommendations apply when group B streptococcal (GBS) bacteria is detected in the urine during screening in pregnancy; separate recommendations (not relevant for this review) are made for screening and treating GBS (at any colony counts) at time of labour or rupture of membranes for prevention of early-onset neonatal GBS disease.

# **Guidelines from International Organizations**

The U.S. Preventive Services Task Force 2008 guideline (16) on screening of ASB in adults recommends all pregnant women be screened at 12 to 16 weeks' gestation (or first prenatal visit) for ASB using a urine culture, and that treatment with antibiotics significantly reduces the incidence of symptomatic maternal urinary tract infections. The evidence informing this reaffirmation of the original recommendation from 2004 is mainly drawn from a Cochrane review of treatment effectiveness (17). The American Academy of Family Physicians (AAFP) (18) endorses the recommendations of the USPSTF. The Infectious Diseases Society of America (6) recommends screening for bacteriuria by urine culture for pregnant women in early pregnancy, and treatment if results are positive, with periodic re-testing for recurrent bacteriuria after therapy. The American Academy of Pediatrics (AAP), jointly with the American College of Obstetricians and Gynecologists (ACOG) recommend to treat ASB and then to test for cure (19).

The UK's National Institute for Health and Care Excellence (NICE) states that women should be offered routine screening for ASB by midstream urine culture early in pregnancy to reduce the risk of developing pyelonephritis (20).

The Scottish Intercollegiate Guidelines Network (SIGN) recommends that pregnant women be tested for ASB by urine culture at the first antenatal visit and culture-positive patients be treated with an antibiotic (21).

#### **Current Practice**

Several major healthcare organizations in North America (USPSTF, IDSA, ACOG, AAP, AAFP) advocate screening of pregnant women, and nearly all recommend treating patients who have been confirmed with ASB using antibiotics. In Canada, the current usual practice is to obtain a urine sample at each prenatal visit, where testing may typically be done by culture early in pregnancy and then followed with subsequent testing if indicated. It is clear there is diversity in which of these samples are collected for the presence of significant bacteriuria, how the sample is collected, how presence of bacteriuria is determined, and when sample(s) for ASB is/are collected in pregnancy. It is unclear whether and to what degree practices use screening methods incorporating tests other than urine culture.

# Section III. Review Approach and Scope

This review will be completed by the Evidence Review and Synthesis Centre (ERSC) at the University of Alberta. The review will be developed, conducted, and prepared according to the CTFPHC methods (http://canadiantaskforce.ca/methods/methods-manual/). A working group of CTFPHC members was formed for development of the topic, refinement of the key questions and scope, and rating of patient-important outcomes considered most important for creating a recommendation. The CTFPHC will not be involved in the conduct of the review including selection of studies and data analysis, but will comment on the draft report and provide input on the interpretations of findings. The Global Health and Guidelines Division science team at the Public Health Agency of Canada provided assistance and input on CTFPHC methodological considerations during the topic refinement and development of the protocol. Perspectives of patients, and members of the public have been be incorporated regarding prioritization of outcomes (benefits and harms), as well as other aspects of guideline development. A draft version of this protocol was reviewed by nine external topic experts and stakeholders and all comments were considered when finalizing this protocol. This final version of the protocol has been approved by the entire CTFPHC and will be posted on the CTFPHC website and registered with the International Prospective Registry of Systematic Reviews (PROSPERO) database.

# **Analytical Framework and Staged Approach**

Figure 1 is an analytical framework that depicts the structure used to address the Key Questions (KQs) for evaluating the benefits and harms of screening asymptomatic women during pregnancy for bacteriuria.

A staged approach will be followed based on the availability and quality of the body of evidence. Quality of evidence (classified as high, moderate, low, very low) will be assessed using methods developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (<u>http://www.gradeworkinggroup.org/</u>), whereby high quality evidence relies on precise and consistent effect estimates from studies having few limitations on internal validity (i.e., low bias) and examining directly relevant populations, interventions, comparators, and outcomes (i.e., PICOs) (see Section IV for more details). The staging approach of the

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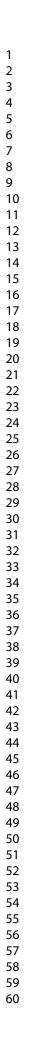
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CTFPHC relies on choices made when considering, primarily, the GRADE domains of study limitations and indirectness. Moreover, decisions made during the evidence review are based on the information needs of the CTFPHC for making a screening recommendation based on the balance of critical patient-important benefits and harms.

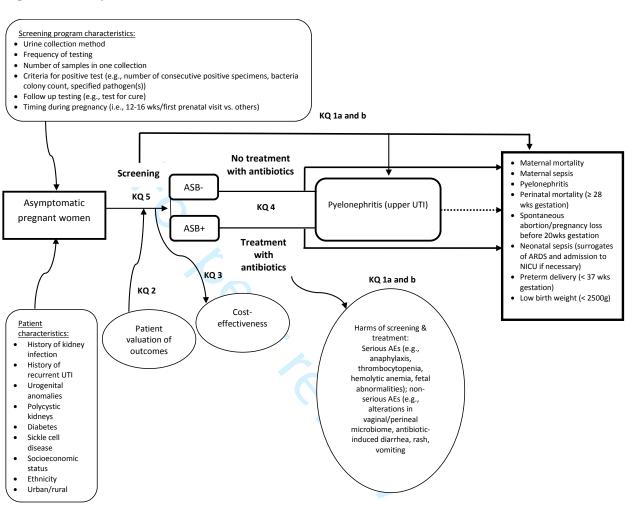
The most direct and least biased evidence for the effectiveness of screening for ASB will be prioritized. This review will start by examining evidence from randomized-controlled trials (RCTs) on the clinical effectiveness of screening on patient-important outcomes. Staging beyond this point will require careful deliberation with documentation of rationale. If data from the initial stage is scarce for critical benefits or harms the CTFPHC will consider searching for data from (potentially) more biased study designs or indirect evidence (e.g., evidence from observational studies treatment RCTs, test accuracy studies. In cases where evidence on test accuracy and treatment effects will be used to provide indirect evidence on screening effectiveness, the limitations of such an indirect approach will be described. Examining both accuracy and treatment data may not be useful in all cases; for example, if the CTFPHC becomes confident that treatment is ineffective there would be no need to further examine test accuracy. In general, subsequent stages will only be conducted when the evidence from the previous stage(s) is non-existent or of too poor quality (e.g., very low quality based on GRADE tables) for the Task Force to make a screening recommendation based on the balance of patient-important benefits and harms.

For this review, the first stage will focus on identifying and using data from studies directly linking screening for ASB to patient-important benefits and harms (KQ1). Study designs providing the highest internal validity (e.g., RCTs) for this KQ will be preferred with a hierarchy of evidence used after this point if necessary. After RCTs we will consider controlled clinical trials (CCTs; defined for this review as *experimental trials without random allocation but where intervention(s) are introduced, standardized, and allocated objectively [e.g., by date of birth, but not using subjective means such as patient or clinician preferences] by investigators and blinding of participants is typically possible)* and then prospective and retrospective controlled observational studies. This stage will also include examination of KQ2 on women's valuation of benefit and harm outcomes of screening for ASB (and more broadly/indirectly treatment with antibiotics) in pregnancy. The cost-effectiveness of screening for ASB (KQ3) will also be considered only if there is evidence from KQ1 indicating a favorable benefit-harm ratio such that screening may be recommended.

If this first stage does not provide high enough quality of evidence for making a recommendation, the CTFPHC will carefully consider pursuing stage two with documentation of rationale before proceeding. Stage two will commence with examination of effectiveness of treatment of ASB in pregnancy (KQ4). If there is sufficient quality evidence indicating favorable treatment effectiveness from KQ4, an examination of KQ5 on diagnostic test accuracy will be considered in stage 3. Due to the indirectness of evidence provided by KQs 4 and 5 for making recommendations for the clinical effectiveness of screening, we will only seek data from study designs offering the greatest potential for high internal validity. That is, for KQ4 (treatment) we will focus on RCTs, and for KQ5 (test accuracy) we will exclude case-control designs. Where high quality systematic reviews exist examining these indirect evidence links, we will utilize these when possible.



#### Figure 1. Analytical Framework



AEs: adverse events; ARDS: acute respiratory distress syndrome; ASB: asymptomatic bacteriuria; d: day; g: grams; KQ: key question; NICU: neonatal intensive care unit; UTI: urinary tract infection; wks: weeks

## Key Questions (KQs)\*

#### Stage 1:

#### Benefits and harms of screening

**KQ1a:** What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy? Are there subgroup differences with SES or other patient characteristics?

**KQ1b:** What are the comparative benefits and harms of screening with different screening tests/algorithms for asymptomatic bacteriuria in pregnancy?

## **Outcome valuation**

**KQ2a:** How do women weigh the benefits and harms of screening and treatment of asymptomatic bacteriuria in pregnancy?

**KQ2b:** How do women's valuation of benefits and harms of screening and treatment inform their decisions to undergo screening?

#### **Resource use\*\***

**KQ3:** What is the cost-effectiveness of screening for asymptomatic bacteriuria in pregnancy?

#### Stage 2:

#### Treatment

**KQ4:** What are the benefits and harms of antibiotic treatment compared with no treatment for asymptomatic bacteriuria in pregnancy?

#### Stage 3:

#### **Diagnostic accuracy of screening tests**

**KQ5:** What is the diagnostic accuracy of screening tests for asymptomatic bacteriuria in pregnancy?

\*Decision process for staging outlined in section on Analytical Framework and Staged Approach \*\*Conducted if benefit-harm ratio deemed beneficial based on KQ1

# **Section IV. Review Methods**

# **Literature Search**

The literature search strategy will be developed and implemented by a research librarian. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords, and will be peer-reviewed. Methodological filters will not be applied to limit retrieval by study design; study designs included for each KQ are identified in the section on inclusion and exclusion criteria. Searches will be restricted by language to include full texts published in English and French, without a publication date restriction.

We will conduct comprehensive searches in bibliographic databases most relevant for each KQ. For evidence informing stage 1 of our review we will perform comprehensive searches for studies meeting our inclusion criteria as described below. For KQ1, we will search MEDLINE (1946-) via Ovid; Embase (1974-) via Ovid; Cochrane Library; CINAHL (1937-present) via EBSCOhost; and PubMed via NCBI Entrez. The detailed search strategy for MEDLINE is reported in Appendix 1 and will be adapted to accommodate the controlled vocabularies of each database. For KQs 2 (women's outcome valuation) and 3 (cost-effectiveness of screening), we will modify the search to include relevant terms and will add suitable databases (e.g. PsycINFO for patient preferences, NHS Economic Evaluation Database [EED] for cost effectiveness). Full search strategies for all databases will be included in the final report.

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For evidence used in stages 2 and 3, we are aware of at least one high-quality systematic review for KQs 4 (4) and 5 (10) which we may rely on. For KQ4 on effectiveness of antibiotic treatment compared with no treatment, we anticipate updating a recent Cochrane review of treatment for asymptomatic bacteriuria in pregnancy (4); if an update is not possible, we will follow methods adopted by the CTFPHC for integrating systematic reviews (see Appendix 2). If we update this review, the original search will be updated. For KQ5 (test accuracy), we anticipate using a recent review of screening tests for asymptomatic bacteriuria in pregnancy (10) and any additional reviews that may be identified as similar in scope. While multiple reviews may be considered for KO5 (test accuracy) if found, we will not attempt to update the search(es) to identify more recent studies. If the scope of any review is narrower (e.g., does not include all interventions applicable to our topic), we may screen the excluded studies list(s) to identify potentially relevant studies for inclusion. To ensure we have identified all potentially relevant systematic reviews relevant to KQs 4 and 5, we will conduct a database search for systematic reviews. We will search PubMed (1946-) via NCBI Entrez, the Cochrane Database of Systematic Reviews (inception-) and the Database of Abstracts of Reviews of Effects (DARE) (inception-2013) via Wiley Cochrane Library to identify systematic reviews, meta-analyses and health technology assessments. Our PubMed search will utilize a search filter from CADTH (https://www.cadth.ca/resources/findingevidence).

Grey literature will be searched and documented according to CTFPHC methods and will include internet-based searches (via adapted Canadian Agency for Drugs and Therapeutics in Health [CADTH] checklists; <u>https://www.cadth.ca/resources/finding-evidence/grey-matters</u>), electronic libraries (e.g., Health Canada Library, Canadian Electronic Library), and trial registries (ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform). Based on consultation with clinical experts, the following highly relevant conference proceedings will be hand-searched for recent studies not yet published (2014-present): Society of Obstetricians and Gynaecologists of Canada, Association of Medical Microbiology and Infectious Disease Canada, ID Week, and American Society for Microbiology meeting (ICAAC). Clinical and content experts identified by the CTFPHC will be contacted and invited to identify relevant research reports for consideration; websites of relevant Canadian stakeholder organizations will be searched.

# **Eligibility Criteria**

Table 1 outlines the inclusion and exclusion criteria for all KQs, and details are provided below.

## Population

Studies will be considered for inclusion in all KQs if they examine pregnant women at any stage of pregnancy where the population represents a "routine screening" scenario (e.g., the majority of patients do not have a degree of signs or symptoms prompting diagnostic testing and/or treatment for upper or lower UTI). It is recognized that many women experience nocturnal and increased frequency of urination, or other symptoms, which do not necessarily indicate bacteriuria or infections. We will include studies where a proportion of, but not all, women have risk factors for UTIs or other outcomes of the review. KQ2 on women's outcome valuation, we will include studies of women of child-bearing age if no evidence is found from studies with pregnant women; studies will still be required to examine screening or antibiotic treatment during pregnancy.

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We will exclude studies *exclusively* including women with conditions that place them at substantially higher than average risk for bacteriuria (i.e., kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infections [UTI], diabetes, sickle-cell disease), or with symptoms of UTI.

*Population subgroups of interest*: history of kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection (UTI), diabetes, sickle cell disease, socioeconomic status (i.e., education, income), ethnicity (i.e., percent South Asian versus others), and urban/rural setting.

# **Interventions & Comparators**

For clinical effectiveness of screening (KQ1), any screening test/algorithm for ASB will be eligible for inclusion and the comparator is absence of screening (1a) or a different urine test or screening algorithm (1b). Studies that compare urine cultures of differing criteria (e.g., threshold 10<sup>3</sup> CFU/mL versus 10<sup>5</sup> CFU/mL) will also be eligible for inclusion. For women's outcome valuation (KQ2), any screening test for ASB during pregnancy will be eligible for inclusion; indirect evidence about antibiotic treatment during pregnancy broadly will be used if needed. For cost-effectiveness (KQ3), any screening test compared with no screening or another screening test (i.e., urine culture) will be eligible for inclusion; costs must be compared with outcomes/effects such that studies examining costs only will be excluded. For treatment effectiveness (KQ4), any antibiotic treatment for ASB compared to no treatment or placebo will be eligible for inclusion. For diagnostic accuracy (KQ5), any index test compared with a urine culture for detecting ASB will be eligible for inclusion. For all KQs, studies that include screening or treatment for group B streptococcus (GBS) at any time of pregnancy for any of the outcomes of interest will be included.

We will exclude studies exclusively examining urine tests used for screening for other conditions (e.g., proteinuria, glycosuria), and non-urine screening tests (e.g., vaginal/rectal swab culture for GBS testing).

*Screening subgroups of interest*: urine collection methods (e.g., clean-catch and/or midstream; excluding catheter methods/samples), frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified pathogen(s)), follow-up testing during pregnancy, and timing during pregnancy.

# Outcomes

As with the KQs, the outcomes for inclusion for KQ1 (screening effectiveness) and KQ4 (treatment) will be staged to some extent, if necessary. Each outcome has been rated independently by members of the CTFPHC and by women, as per the patient engagement activities of an independent group with expertise in knowledge translation from St. Michael's Hospital in Toronto, Ontario. All patient-important outcomes rated as critical (7 to 9 out of 9) or important (4 to 6 out of 9) for decision making were considered for inclusion. From these ratings, the eight outcomes were rated as critical will be included in stage 1; of three outcomes rated as important, low birth weight (but not hypertension or acute kidney injury) will be included

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because in the past (i.e. older studies) this was conceptually considered the same as "pre-term birth", which both the CTFPHC members and patients rated as critical. Considering harms separately, if no evidence is found for any of the outcomes (serious adverse events [AEs]) in stage 1, there will be inclusion of the outcomes (non-serious AEs) from stage 2. This grouped and staged approach to harms will address infrequent reporting, reporting of different harms across studies, and also uncertainty regarding all the potential harms that may be reported. Nonserious AEs, particularly if frequent or severe, are considered important but not critical for decision making by the CTFPHC. This approach acknowledges guidance to limit the number of total outcomes (maximum 7) to those which can be successfully managed cognitively by guideline panels when balancing multiple benefits and harms.

Outcomes for KQs 1 and 4 with ratings:

#### Benefits (reduced incidence for all):

- 1. maternal mortality (9)
- 2. maternal sepsis (8)
- 3. pyelonephritis (7)
- 4. perinatal mortality ( $\geq$  28 weeks of gestation (e.g., intrauterine demise, stillbirth, early neonatal death)) (9)
- 5. spontaneous abortion/pregnancy loss before 20 weeks of gestation (8)
- 6. neonatal sepsis (if not reported will include surrogate outcomes of acute respiratory distress syndrome [ARDS] or admission to neonatal intensive care unit [NICU]) (8)
- 7. preterm delivery (live fetus passed < 37 weeks of gestation) (7)
- 8. low birth weight (< 2500g) (6)

#### Harms:

- 1. serious adverse event(s)<sup>a</sup> associated with antibiotic treatment, *including but not limited to*: (7)
  - a. anaphylaxis,
  - b. thrombocytopenia,
  - c. hemolytic anemia,
  - d. fetal abnormalities; and,
- 2. non-serious adverse event(s) associated with treatment, *including but not limited to*: (4)
  - a. alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis),
  - b. antibiotic-induced diarrhea,
  - c. rash,
  - d. vomiting

<sup>a</sup>Serious adverse event (experience) or reaction is any untoward medical occurrence that: a) results in death, b) is lifethreatening, c) requires in-patient hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect (Health Canada, 2011);

We will exclude studies that screen pregnant women for group B streptococcus near delivery or at time of rupture of membranes for the prevention or treatment of chorioamnionitis or neonatal GBS (without other outcomes of interest listed above).

Women's outcome valuation (KQ2) include several possible outcomes related to the weighing of benefits and harms of screening and treatment (KQs 1 and 4) and how this may affect their decisions to undergo screening (e.g., relative weight/utilities of benefit and harms; willingness to be screened based on relative value placed on benefits and harms of screening programs or treatment); these outcomes will be based on considerations of the possibility or perceived/expected magnitude of effects for the outcomes identified for KQs 1 and 4.

During focus groups, women identified an additional outcome - psychological distress/anxiety and rated this as critical (7 out of 9), although it was interpreted differently by some women as either a benefit (e.g., reduction in psychological distress/anxiety by knowing the health status of themselves and their baby) or a harm (e.g., another of many tests and potential worries during pregnancy). Anxiety as a critical outcome will be sought and synthesized within findings from KQ2 on women's valuation of benefits and harms of screening and treatment, as well as within interpretation of test accuracy outcomes from KQ5 (TP, TN, FP, FN) which will be *interpreted based on the CTFPHC judgments* on the magnitude of potential consequences of each (e.g., unnecessary anxiety from high FP, loss of potential benefit in FN) as identified in the section below "Assessment of the Overall Quality of the Evidence using GRADE".

Cost-effectiveness (KQ3) outcomes include cost per quality-adjusted life year (QALYs), incremental cost-effectiveness ratios (ICERs), and net benefit (in dollars from cost-benefit studies.

Diagnostic test accuracy (KQ5) outcomes include: sensitivity, specificity, false positives, false negatives, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio.

# Setting, Study Design & Timing

Studies conducted in primary care, or relevant clinical settings (e.g., prisons, remote stations, community health centers, midwifery practice) will be included. For KQ3 on cost-effectiveness we will limit studies to those conducted using data relevant to Canada, thus within countries having a very high Human Development Index (22).

For KQ1 (screening effectiveness), we will include RCTs initially and then, if needed based on the GRADE assessment of overall quality of the evidence, we will search for CCTs (defined in Section III) and then controlled observational studies (i.e., prospective and retrospective cohort, case-control, controlled before-after). For KQ2 (outcome valuation), we will include any study where women are asked to balance the benefits and harms of screening and treatment for ASB and state/choose their willingness to be screened and treated; surveys, experimental designs (e.g., contingent valuation), and qualitative research are examples. Cost-effectiveness (KQ3) will look at any study comparing effects and costs (e.g., cost-effectiveness, cost-utility, cost-benefit) and may include modelling of effects and/or costs. For KQ4 (treatment), we will rely on RCTs. For KQ5 (test accuracy), we will rely on prospective and retrospective studies where a consecutive or random sample of participants receive both the index test(s) and reference standard, or where participants are randomized to different index tests but all receive the reference standard, and

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assessment in a cross-sectional manner. We will exclude case-control studies and studies with longitudinal assessment of the reference standard.

For all KQs, case reports and case series (i.e., group of patients selected based on particular outcome) will be excluded as will papers not reporting primary research (e.g. editorials, commentaries, opinion pieces). Conference abstracts will not be eligible for inclusion, but will be captured and serve to help identify full study reports and assess the quality of evidence in relation to potential publication and reporting biases. No limits will be applied to publication year.

# Additional considerations

We do not have a minimum sample size for inclusion, nor do we have a minimum threshold for extent of incomplete follow-up or participant attrition; these factors will be considered during assessment of the quality of evidence (e.g., precision domain accounts for sample size across studies), and during sensitivity analyses in cases of substantial heterogeneity in findings at the data synthesis stage (see relevant sections).

# Tables 1 to 5. Inclusion and Exclusion Criteria for Key Questions

| Population    | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria.   |
|---------------|---|
|               | Patient subgroups: women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI]), diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural   |
|               | Exclude: studies <i>exclusively</i> including women with conditions that place them at substantially higher than average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI], diabetes, and sickle cell disease), or with symptoms of UTI  |
| Interventions | Any screening program or test   |
|               | <u>Screening subgroups/algorithms, including</u> : urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy  |
|               | Exclude: urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for group B streptococcus (GBS) testing)  |
| Comparator    | KQ1a: No screening (but may include indicated/targeted testing and/or treatment upon development of symptoms or for high-risk groups)         KQ1b: A different screening test or algorithm (see intervention subgroups)  |
| Outcomes      | Benefits (reduced incidence for all):         1. maternal mortality (9)         2. maternal sepsis (8)\         3. pyelonephritis (7)         4. perinatal mortality (≥ 28 week's gestation (e.g., intrauterine demise, stillbirth, early neonatal death)) (9)         5. spontaneous abortion/pregnancy loss before 20 week's gestation (8)         6. neonatal sepsis (if not reported will include surrogate outcomes of acute respiratory distress syndrome [ARDS] or admission to neonatal intensive care unit [NICU]) (8)         7. preterm delivery (live fetus passed < 37 week's gestation) (7) |
|               | <ol> <li>serious adverse event(s)<sup>a</sup> associated with antibiotic treatment, <i>including but not limited to</i>: (7)</li> <li>a. anaphylaxis,</li> </ol>  |

# Table 1. KQ1a, b: Benefits and harms of screening

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| Timeframe     | No publication date limits  |
|---------------|---|
| Setting       | Primary care and clinical settings (e.g., prisons, remote stations, community centers, midwifery practices)   |
| Language      | English and French  |
| Study Designs | Staged: RCTs, CCTs, controlled observational (i.e., prospective and retrospective cohorts, case-control, controlled before-after)   |
|               | Exclude: screening for GBS near delivery or at time of rupture of membranes for the prevention or treatment of chorioamnionitis or neonatal GBS (without other outcomes of interest in list above)  |
|               | c. rash,<br>d. vomiting   |
|               | <ul> <li>2. non-serious adverse event(s) associated with treatment, <i>including but not limited to</i>: (4)</li> <li>a. alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis),</li> <li>b. antibiotic-induced diarrhea,</li> </ul> |
|               | d. fetal abnormalities; and,  |
|               | b. thrombocytopenia,<br>c. hemolytic anemia,  |

CCT: controlled clinical trial; KQ: key question; RCT: randomized controlled trial

<sup>a</sup>Serious adverse event (experience) or reaction is any untoward medical occurrence that: a) results in death, b) is life-threatening, c) requires in-patient hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect (Health Canada, 2011)

### Table 2. KQ2: Outcome valuation

| Population            | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria; will also accept asymptomatic women who are not pregnant if necessary  |
|-----------------------|--|
|                       | <u>Patient subgroups</u> : women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI]), diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural  |
|                       | Exclude: studies <i>exclusively</i> including women with conditions that place them at substantially higher than   |
|                       | average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary   |
|                       | tract infection [UTI], diabetes, and sickle cell disease), or with symptoms of UTI   |
| Interventions/Index   | Any screening program or test, and any antibiotic; will accept studies on treatment for any bacterial  |
| Test                  | condition in pregnancy   |
|                       | <u>Screening subgroups/algorithms, including</u> : urine collection method, frequency of testing, criteria for a positive test (including number of consecutive positive specimens, bacteria colony count, and specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy |
|                       | <u>Exclude</u> : urine <i>screening</i> is done for other conditions (e.g., proteinuria, glycosuria), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing)   |
| Comparator/Reference  | Not applicable   |
| Standard              |  |
| Outcomes <sup>§</sup> | Several possible outcomes (e.g., relative weight/utilities of benefit and harms; willingness to be screened based on relative value placed on benefits and harms of screening programs or treatment)   |
| Study Designs         | Qualitative, mixed methods, surveys/cross-sectional  |
| Language              | English and French   |
| Setting               | Primary care and clinical settings (e.g., prisons, remote stations, community centers, midwifery practices)  |
| Time frame            | No publication date limits   |

KQ: key question

<sup>§</sup>If there is a very limited quality of evidence base for KQ2 (i.e., in terms of quantity/sample size, methodological quality, inconsistency between studies, or applicability to our population or setting) we will consider including studies examining women's valuation of harms *or* benefits rather than the trade-off between the two. For example, studies examining women's acceptance of screening and/or treatment for ASB when only considering their perspectives on the potential

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risks of antibiotic treatment to their baby, or the importance placed on reassurance about the potential to prevent preterm delivery et cetera, could offer some indirect evidence to help the CTFPHC in their deliberations. Likewise, the relative value placed on different benefit or harm outcomes (e.g., serious versus non-serious AEs) could be informative.

Table 3. KQ3: Cost-effectiveness of screening

| Population                          | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria.  |
|-------------------------------------|--|
|                                     | Patient subgroups: women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI], diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural   |
| •                                   | <u>Exclude</u> : studies <i>exclusively</i> including women with conditions that place them at substantially higher than average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI], diabetes, and sickle cell disease), or with symptoms of UTI               |
| Interventions/Index<br>Test         | Any screening program or test  |
|                                     | <u>Screening subgroups/algorithms, including</u> : urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy |
|                                     | <u>Exclude</u> : urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing)   |
| Comparator/Reference<br>Standard    | No screening (but may include indicated/targeted testing and/or treatment upon development of symptoms or for high-risk groups), or a different screening test or algorithm (see intervention subgroups)   |
| Outcomes                            | Cost per quality-adjusted life-years (cost per QALY), incremental cost-effectiveness ratio (ICER), net benefit/cost  |
| Study Designs                       | Economic evaluations   |
| Language                            | English and French   |
| Setting                             | Primary care and clinical settings (e.g., prisons, remote stations, community centers, midwifery practices); limited to countries rated as having very high Human Development Index (22)   |
| Time frame                          | No publication date limits   |
| KQ: key question Table 4. KO4: Trea | tmont  |

### **Table 4. KQ4: Treatment**

| Population           | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria.  |
|----------------------|--|
|                      | <u>Patient subgroups</u> : women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI]), diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural  |
|                      | Exclude: studies <i>exclusively</i> including women with conditions that place them at substantially higher than   |
|                      | average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary   |
|                      | tract infection [UTI], diabetes, and sickle cell disease), or with symptoms of UTI   |
| Interventions/Index  | Any antibiotic   |
| Test                 |  |
|                      | <u>Screening subgroups/algorithms, including</u> : urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy |
|                      | Exclude: urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia,), non-urine   |
|                      | screening test (e.g., vaginal/rectal swab culture for GBS testing)   |
| Comparator/Reference | No treatment or placebo  |
| Standard             |  |
| Outcomes*            | Benefits (reduced incidence for all):  |
|                      | 1. maternal mortality (9)  |

|                            | 2. maternal sepsis (8)   |
|----------------------------|--|
|                            | 3. pyelonephritis (7)  |
|                            | 4. perinatal mortality ( $\geq$ 28 week's gestation (e.g., intrauterine demise, stillbirth, early neonatal               |
|                            | death)) (9)  |
|                            | 5. spontaneous abortion/pregnancy loss before 20 week's gestation (8)  |
|                            | 6. neonatal sepsis (if not reported will include surrogate outcomes of acute respiratory distress                        |
|                            | syndrome [ARDS] or admission to neonatal intensive care unit [NICU]) (8)   |
|                            | 7. preterm delivery (live fetus passed < 37 week's gestation) (7)  |
|                            | 8. low birth weight ( $< 2500$ g) (6)  |
|                            | Harms:   |
|                            | 1. serious adverse event(s) <sup>a</sup> associated with antibiotic treatment, <i>including but not limited to</i> : (7) |
|                            | a. anaphylaxis,  |
|                            | b. thrombocytopenia,   |
|                            | c. hemolytic anemia,   |
|                            | d. fetal abnormalities; and,   |
|                            | 2. non-serious adverse event(s) associated with treatment, <i>including but not limited to</i> : (4)                     |
|                            | a. alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis),  |
|                            | b. antibiotic-induced diarrhea,  |
|                            | c. rash,   |
|                            | d. vomiting  |
|                            |  |
|                            | Exclude: screening for group B streptococcus near delivery or at time of rupture of membranes for the                    |
|                            | prevention or treatment of chorioamnionitis or neonatal GBS (without other outcomes of interest listed                   |
| Gt I D :                   | above)   |
| Study Designs              | RCTs   |
| Language                   | English and French   |
| Setting                    | Primary care and clinical settings (e.g., prisons, remote stations, community centers, midwifery practices)              |
| Time frame                 | No publication date limits   |
| KO: key question: RCT: rar | adomized controlled trial  |

KQ: key question; RCT: randomized controlled trial

<sup>a</sup>Serious adverse event (experience) or reaction is any untoward medical occurrence that: a) results in death, b) is life-threatening, c) requires in-patient hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect (Health Canada, 2011)

## Table 5. KQ5: Diagnostic accuracy of screening tests

| Population                  | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria.   |
|-----------------------------|---|
|                             | Patient subgroups: women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI]), diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural   |
|                             | Exclude: studies exclusively including women with conditions that place them at substantially higher than   |
|                             | average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary  |
|                             | tract infection [UTI], diabetes, and sickle cell disease), or with symptoms of UTI  |
| Interventions/Index         | Any index test  |
| Test                        | <u>Screening subgroups/algorithm, including</u> : urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy<br><u>Exclude</u> : urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing) |
| <b>Comparator/Reference</b> | A urine culture   |
| Standard                    | Screening subgroups/algorithm, including: urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy   |

| -             | · · · · · · · · · · · · · · · · · · ·  |
|---------------|--|
|               | Exclude: urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine  |
|               | screening test (e.g., vaginal/rectal swab culture for GBS testing)   |
| Outcomes      | Sensitivity, specificity, false positives, true positive, false negatives, true negatives, positive and negative   |
|               | likelihood ratios, prevalence/pre-test probability (true positive + false positive)/total number of people)  |
| Study Designs | Prospective and retrospective studies where a consecutive or random sample of participants receive both the index test(s) and the reference standard, or where participants are randomized to different index tests but all receive the reference standard, and assessment in a cross-sectional manner |
|               | Exclude: case-control studies and studies with longitudinal assessment of the reference standard   |
| Language      | English and French   |

### Screening and Selecting Studies for Inclusion

For the database searches, two reviewers will independently screen the titles and abstracts (when available) using broad inclusion/exclusion criteria. Citations will be classified as "include/unsure," "exclude," or "reference" (i.e., conference abstracts, protocols, and systematic reviews). One reviewer will review the "reference" group and will conduct all other searching as outlined in the above section. The full text of all studies classified as "include/unsure" or identified after reviewing the reference citations will be retrieved for full review; two reviewers will independently assess eligibility using a standard form that outlines the inclusion and exclusion criteria. Disagreements on final inclusion of all studies will be resolved through consensus or third party adjudication. For KOs 4 and 5, any existing systematic review(s) identified as relevant will be assessed for eligibility based on whether the authors: i) searched more than one database, ii) report their selection criteria, and iii) use PICOTS criteria that are a close match to that for the relevant KQ. In cases where there is more than one possible review providing results for the same intervention-outcome pair, we will choose one based on: AMSTAR (23) rating (score 8 or higher preferred), comprehensiveness of search (i.e., reports on most or more papers included by other existing reviews), closest match to our PICOTS, most recent date of study inclusion/search, and the quality and extent of reporting on individual study characteristics, data, and quality assessments. All decisions to exclude a study at full text review will be provided. The title/abstract screening and full-text selection processes will be conducted and documented in DistillerSR. The flow of literature and reasons for full text exclusions will be recorded in a PRISMA Flow Chart.

### **Data Extraction & Reporting**

One reviewer will independently extract data from each included study or systematic review into DistillerSR; a second reviewer will verify all data. Disagreements will be resolved through discussion or third-party consultation until consensus is reached.

When using individual studies for a KQ, a narrative summary (with accompanying tables) will be provided to report on all studies by design, country of origin, sample sizes, population(s) (including subgroups), intervention(s)/index tests (including data on thresholds and for subgroup questions), comparator(s)/reference test, setting, and outcome measures, as reported by studies. When there are multiple publications associated with a study we will consider the earliest report of the main (primary) outcome data to be the primary data source. We will extract data from the primary source first and then add outcome data reported in the secondary/associated publications and data sources. We will reference the primary source throughout the evidence report; all associated literature will be tabulated for reference.

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When relying on systematic reviews for KQs 4 (treatment) and 5 (test accuracy), we will extract data on the characteristics of the systematic review (PICOTS), the included studies with specifics related to the population (size and characteristics), outcomes evaluated (including definitions and timing of assessment), quality/risk of bias (by domain/construct if available), the methods of analysis (meta-analytical approach and its findings in relation to heterogeneity, if applicable), findings from their syntheses including subgroup analysis and GRADE or other quality assessments if performed across studies, and any limitations noted by the systematic review authors. For KQs 4 and 5, data verification will be completed on 5 to 10% of included studies in any existing systematic review(s), and if satisfied with concordance, we will consider incorporating the reported data on study and participant characteristics without returning to the primary studies. If additional studies are included (e.g., new studies from updated search [KQ4] or excluded studies in the identified systematic review that is subsequently included for current review to ensure coverage of scope [KQ5]), these will be clearly identified and presented.

When using individual studies, we will record intention-to-treat results, if possible. For continuous outcomes measures, we will extract (by arm) the mean baseline and endpoint or change scores, standard deviations (SD) or other measure of variability, and number analyzed. We will not include outcome data from studies that did not provide a follow up change or endpoint mean or data that could be used to calculate follow up scores. If necessary, we will approximate means by medians. If standard deviations are not given, they will be computed from p-values, 95% confidence intervals (95% CIs), standard errors, z-statistics, or t-statistics. If computation is not possible they will be estimated from upper bound p-values, ranges, interquartile ranges, or (as a last resort) by imputation using the largest reported SD from the other studies in the same meta-analysis. When computing SDs for change from baseline values, we will assume a correlation of 0.5, unless other information is present in the study that allows us to compute it more precisely. For dichotomous outcomes, we will report counts or proportions, and sample size, by study arm.

For dichotomous data on harms, each adverse event (AE) will be counted as if it represents a unique individual; because a single individual might experience more than one AE, this assumption may overestimate the number of people having an AE. Only numerical data for AEs will be extracted; that is, we will make no assumptions on lack or presence of an AE if this is not reported; authors that report only p-values or that one arm had fewer events than another (but where it is explicit that the outcome was captured in the study) will be contacted (3 times via email) to provide the data.

Data on within-study subgroup analysis will be collected, including: subgroups (independent variables), the type of analysis (e.g., subgroup/stratified or regression analysis), the outcomes assessed (dependent variables), and the authors' conclusions. We will collect data suitable for all patient and intervention subgroups (see Table 1) for performing our own subgroup analyses (e.g., stratified analysis, meta-regression) based on study-level data.

### Risk of Bias/Methodological Quality Assessment

Two reviewers will independently assess the risk of bias (ROB) of each included study (KQs 1-3), with disagreements resolved through discussion or third-party consultation to reach consensus. The results for each study and across studies will be reported by each domain and for the overall ROB score. The ROB for each study will be assessed on an outcome basis where needed, particularly when different outcomes are assumed to have different susceptibilities to bias; for example, subjective outcomes and expected harms are more prone to bias from non-blinding than objective outcomes and unexpected/rare harms.

RCTs and CCTs (theoretically only differing from RCTs by lack of random sequence generation and not by other ROB domains) will be appraised using the Cochrane Risk of Bias tool (24). This tool consists of six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other" sources of bias) and a categorization of the overall risk of bias. Blinding will be assessed separately for patients/providers and outcome assessors taking into account the type of outcome that may be affected (e.g. subjective vs. objective). To assist with outcome reporting bias assessments, we will seek study protocols and studies/data from registries. The overall assessment is based on the responses to individual domains. If one or more individual domains are assessed as having a high risk of bias, the overall score will be rated as high risk of bias. If at least one domain is assessed as unclear, and no domains are assessed as high, the overall score will be rated as unclear risk of bias. The overall risk of bias will be considered low only if all components are rated as having a low risk of bias.

Controlled observational studies will be appraised using the Newcastle-Ottawa Quality Assessment Scale (25); three domains (sample selection, comparability of cohorts, and assessment of outcomes) are evaluated. Each item that is adequately addressed is awarded one star, except for the "comparability of cohorts" item, for which a maximum of two stars can be given. The overall score is calculated by tallying the stars. We will consider a total score of 6 to 8 stars to indicate low ROB, 4 or 5 stars to indicate moderate ROB, and 3 or fewer stars to indicate high ROB.

For diagnostic accuracy studies (KQ5), we will rely on the Quality of Diagnostic Accuracy Studies (QUADAS-2) (26) used to assess ROB. This tool assesses concerns of risk of bias among four domains (patient selection, index test, reference standard, and flow and timing) and concerns of applicability across the first three domains.

If one or more systematic review(s) is used to provide evidence for KQ4 (treatment) or KQ5 (accuracy), we will assess if the review used an explicit tool (e.g., Cochrane ROB [KQ4], QUADAS [KQ5]) for assessing the main sources of potential bias. If so, we will complete assessments on 5 to 10% of included studies to establish concordance before considering the use of assessments reported by each review.

Studies answering KQ2 (outcome valuation) will be evaluated by tools appropriate to their study design: for surveys and qualitative studies we will use tools developed by the Center for Evidence-based Management (<u>http://www.cebma.org/resources-and-tools/what-is-critical-appraisal/</u>). The quality of economic evaluation studies (KQ3) will be assessed using Drummond's checklist for economic evaluation studies (27).

### Data Analysis & Synthesis

We will provide summaries of intervention effects for each study by calculating the appropriate statistics based on types of outcomes.

## Key Question 1

For pair-wise meta-analysis in KQ1 (screening effectiveness), we will employ a random effects model. For continuous outcomes, we will report a pooled mean difference (MD) when one measurement tool is used, or other options that exist for communicating results when combining two or more outcome scales measuring similar constructs (28, 29). For dichotomous outcomes, we will report relative risks (RR) and risk differences (RD) between groups with corresponding 95% CIs. For those outcomes (e.g. serious adverse events) where at least one intervention group contains zero events, only the risk difference will be used. For calculating the RD, we will use the median baseline risk for the control group in the included studies, although may perform sensitivity analysis using differing baseline risks if thought suitable (30, 31). The decision to pool studies will not be based on the statistical heterogeneity (I<sup>2</sup> statistic will be reported), but rather on interpretation of the clinical and methodological differences between studies. When substantial heterogeneity is suspected, we will conduct sensitivity analyses if appropriate (e.g., in the presence of studies with outlying effect sizes, for studies rated as high risk of bias in some domains such as incomplete outcome data [<80 percent] or lack of allocation concealment, parallel versus cross-over designs). Heterogeneity will also be examined during our planned subgroup analyses for important patient and intervention variables (see Table 1). Where there are at least eight studies in a meta-analysis, we will analyze publication bias both visually using the funnel plot and quantitatively using Egger's test (32). We will not combine results from RCTs with CCTs or controlled observational studies (if used via staging approach for KQ on screening); rather, the latter two will be used to support or provide context for the evidence from RCTs.

## Key Questions 2 & 3

For KQs 2 (outcome valuation) and 3 (cost-effectiveness), results will be narratively described in most cases. If more than one study is identified providing numerical values for ranking benefits and/or harms (KQ2) or similar outcomes (KQ3) these will be summarized descriptively and results across studies compared. Thematic analysis may be undertaken for KQ2, including coding data (meaning and context) into descriptive themes that accurately reflect the data and then summarizing this in a narrative format.

## Key Questions 4 and 5

When using systematic reviews for stages 2 and 3, any meta-analysis will be reconstructed if possible to provide graphical representation of the findings to support our interpretations. Meta-analysis may be recalculated, if possible, when new studies are found in search updates (KQ4), analysis methods are not thought appropriate (e.g., use of random rather than fixed effects models, ability but no use of HSROC models [see below]) or if further analysis (e.g. between-study stratification) may be possible for subgroups of interest. When substantial methodological heterogeneity was found, we may conduct sensitivity analyses if appropriate and able (e.g., for studies rated as high risk of bias, different study designs) or decide to not use the pooled/combined estimate. If not conducted by the authors and when there are at least eight studies in a meta-analysis, we will if possible analyze publication bias both visually using the

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funnel plot and quantitatively using Egger's test (32). If meta-analysis was not performed, we will summarize the findings of the systematic review authors.

For KQ5 (diagnostic accuracy), if individual studies are incorporated we will construct 2 x 2 tables and calculate sensitivity, specificity, and positive and negative likelihood ratios (LR+, LR-). Sensitivity and specificity are measures of test accuracy. Likelihood ratios are used to estimate the increased or decreased probability of disease (i.e., ASB) for a patient and can be used to refine clinical judgement based on varying pre-test probabilities. The larger the LR+, the more accurate the test is and the greater the likelihood of disease following a positive test; the smaller the LR-, the more accurate the test is, the lesser the likelihood of disease following a negative test (33). A LR+ that is >10 indicates a large and often conclusive probability that the condition is present; a LR- that is <0.10 suggests a large and often conclusive probability that the condition probable in a patient with and without the disease/condition.

If there are more than three studies and they are clinically homogenous (i.e., timing in pregnancy, thresholds, diagnostic criteria), we will pool data using a hierarchical summary receiver-operator curve (HSROC) and bivariate analysis of sensitivity and specificity (34). The HSROC simultaneously compares the sensitivity and specificity (taking their correlation into account) for all studies comparing a particular screening test with ASB diagnostic criteria. We will use Review Manager Version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark) to perform meta-analyses, and Stata 11.0 (metandi program; StataCorp LP, College Station, TX, USA) to fit the bivariate and HSROC models and produce the pooled estimates of sensitivity, specificity, and likelihood ratios.

The results will be organized by type of screening test. If possible, we will examine the impact of screening before and after 12-16 weeks' gestation and in relation to other intervention subgroups described in Table 5. Sensitivities, specificities, and likelihood ratios and their 95% confidence intervals (CI) will be presented in summary tables that include all screening tests and diagnostic criteria. Based on the findings for sensitivity and specificity and estimates of one or more relevant baseline prevalence, an evidence profile will be generated for the outcomes FN, FP, TN, and TP (30).

### **Subgroup Analyses**

Our primary approach for evaluating differential effect for subgroups will be to record any within-study subgroup analyses performed by study investigators using individual patient data; these results preserve the within-study randomization. Because these results are often based on diverse methodology and may be difficult to interpret across the body of evidence, we will also perform our own subgroup analyses using study-level data, as possible, using formal statistical approaches (e.g., meta-regressions) or by stratifying the results of the pairwise meta-analyses by subgroup variables. When determining whether entire studies fall into a particular subgroup category (e.g., recurrent UTI), we will consider  $\geq$ 80 percent of the study population meeting the criteria as sufficient. We will employ regression analyses when: for continuous variables (e.g., timing during pregnancy) there are at least six to ten studies reporting on the outcome within a specific subgroup, and for categorical variables (e.g., history of recurrent UTI) there are at least three studies for each category level. The number of sufficient studies serves as a rule of thumb

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for the lower bound that investigators can consider for a meta-regression, but power will vary according to the size and variability of the effect. These analyses would rely on study-level data, such that the results would be considered observational in nature.

# Assessment of the Overall Quality of the Evidence using GRADE

Two reviewers will independently assess the quality of the body of evidence or confidence in the effect for each outcome of interest (see Table 1) using the GRADE methodology. Discrepancies will be resolved through discussion or third-party consultation to reach consensus. Assessments will be entered into the GRADEPro software and summarized in GRADE evidence profiles, Summary of Findings tables and Evidence to Decision Tables. Footnotes to the tables will explain all decisions. The CTFPHC will then use this evidence on each outcome, to assess the net benefits and harms of each service, consider patient preferences and values, and other elements of the GRADE methodology to develop the recommendations on screening for bacteriuria (feasibility, acceptability and equity).

The general approach is outlined here although methods will align with GRADE guidance (30, 35). When using systematic reviews, GRADE assessments will be based on the individual studies and reporting by review authors (e.g., on ROB assessments and PICOTS characteristics) and upon validation of a sample by the review team. For evidence on the benefits and harms of screening (KQ1), as a starting point the quality is assigned as high for evidence from RCTs and low for evidence from observational studies, when used. For accuracy studies, cross-sectional or cohort studies in patients with diagnostic uncertainty and direct comparison of test results with an appropriate reference standard will be considered high quality. Thereafter, we will examine and potentially downgrade the quality based on five core domains: study limitations/ROB, inconsistency, indirectness, imprecision, and publication/reporting bias. For outcomes where there is evidence from observational studies and no other reason to downgrade the evidence, we will also consider the additional domains of dose-response association, plausible confounding, and strength of association (i.e., large magnitude of effect [i.e., large  $\leq 0.5$  or  $\geq 2.0$  or very large RR  $\leq 0.2$  or  $\geq 5.0$ ]), to potentially upgrade the quality (36).

For the *study limitations (risk of bias)* domain RCTs and CCTs may be downgraded one or two levels depending on the proportion of trials (e.g., one very large trial may outweigh two very small trials) assessed as having high ROB for the particular outcome under consideration (37). Evidence from observational studies will be downgraded when most studies have moderate or high ROB. For *inconsistency* (consistent, inconsistent) we will assess the magnitude of the effects of the included studies (e.g., inconsistent when lack of overlap in 95% CIs for some studies) (38). *Indirectness* of the evidence (direct or indirect) is based on evaluating the relevance of the study's PICOs compared to ours for our primary KQ1 (effectiveness of screening); when relying on test accuracy and treatment studies there will be downgrading by at least one level for this domain (36). We will assess *imprecision* (precise or imprecise) on the basis of clinical thresholds and Optimal Information Size (39). For outcomes where clinical thresholds are used/determined, we will typically downgrade this domain once if the entire pooled 95% CI crosses the threshold (i.e. only one limit of the CI crosses), and downgrade twice if the 95% CI crosses the threshold and no difference (0 MD or 1.0 RR) or does not cross

the threshold at all. Thresholds may be determined a priori (prior to viewing results from studies) but may also be revised post hoc based on careful benefit-harm considerations when considering all outcomes together (e.g., lower benefit threshold in cases of few and minor harms). A precise estimate is one that allows for a clinically useful conclusion. *Reporting bias* (suspected or undetected) will be evaluated with respect to publication bias.

Interpreting these domains when relying on evidence from diagnostic test (KQ5) data has certain considerations, including how certain the CTFPHC is about the consequences of each outcome (FP, FN, TP, TN) in relation to the main outcomes of interest for KQs 1, 2 & 4 (30).

# **External Review**

The evidence review will be peer-reviewed by external content experts (minimum 3) and invited stakeholder organizations (minimum 10), with response to all comments shared with all reviewers approximately two months after posting of the final review.

# **Planned Schedule and Timeline**

Draft protocol approved by CTFPHC members: July 29, 2016 External peer review: August 1-10, 2016 Final protocol: November 30, 2016 Draft evidence review: January 31, 2017 Final evidence review: March 31, 2017

# **Conflict of Interest Statement**

None of the study team members have any known actual or perceived conflicts of interest related to this review.

# References

1. Glaser AP, Schaeffer AJ. Urinary Tract Infection and Bacteriuria in Pregnancy. The Urologic clinics of North America. 2015;42(4):547-60.

2. Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. European journal of clinical investigation. 2008;38 Suppl 2:50-7.

3. Ipe DS, Sundac L, Benjamin WH, Jr., Moore KH, Ulett GC. Asymptomatic bacteriuria: prevalence rates of causal microorganisms, etiology of infection in different patient populations, and recent advances in molecular detection. FEMS microbiology letters. 2013;346(1):1-10.

4. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. The Cochrane database of systematic reviews. 2015;8:CD000490.

5. Connolly A, Thorp JM, Jr. Urinary tract infections in pregnancy. The Urologic clinics of North America. 1999;26(4):779-87.

6. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2005;40(5):643-54.

7. Kass EH. Bacteriuria and the pathogenesis of pyelonephritis. Laboratory investigation; a journal of technical methods and pathology. 1960;9:110-6.

8. Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. American journal of obstetrics and gynecology. 2014;210(3):219 e1-6.

9. Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, de Miranda E, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. The Lancet Infectious diseases. 2015;15(11):1324-33.

10. Rogozinska E, Formina S, Zamora J, Mignini L, Khan KS. Accuracy of Onsite Tests to Detect Asymptomatic Bacteriuria in Pregnancy: A Systematic Review and Meta-analysis. Obstet Gynecol. 2016;128(3):495-503. Epub 2016/08/09.

11. Hilt EE, McKinley K, Pearce MM, Rosenfeld AB, Zilliox MJ, Mueller ER, et al. Urine Is Not Sterile: Use of Enhanced Urine Culture Techniques To Detect Resident Bacterial Flora in the Adult Female Bladder. Journal of Clinical Microbiology. 2014;52(3):871-6.

12. Price TK, Dune T, Hilt EE, Thomas-White KJ, Kliethermes S, Brincat C, et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. Journal of Clinical Microbiology. 2016;54(5):1216-22.

ASB Protocol - Page 24

13. Rouse DJ, Andrews WW, Goldenber RL, Owen J. Screening and Treatment of Asymptomatic Bacteriuria of Pregnancy to Prevent Pyelonephritis - a Cost-Effectiveness and Cost-Benefit-Analysis. Obstet Gynecol. 1995;86(1):119-23.

14. Guinto VT, De Guia B, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. The Cochrane database of systematic reviews. 2010(9):CD007855.

15. Allen VM, Yudin MH, Bouchard C, Boucher M, Caddy S, Castillo E, et al. Management of group B streptococcal bacteriuria in pregnancy. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC. 2012;34(5):482-6.

16. United States Preventive Services Task Force. Screening for asymptomatic bacteriuria in adults: U.S. Preventive Services Task Force reaffirmation recommendation statement. Annals of internal medicine. 2008;149(1):43-7.

17. Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. The Cochrane database of systematic reviews. 2007(2):CD000490.

18. American Academy of Family Physicians. Summary of Recommendations for Clinical Preventive Services. Leawood, KS: 2015.

19. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Guidelines for perinatal care. 7 ed: Amer Academy of Pediatrics; 2012.

20. NICE (National Institute for Health and Care Excellence). Antenatal care for uncomplicated pregnancies. Clincial guideline 62. United Kingdom: NICE; 2016. Available from: https://www.nice.org.uk/guidance/cg62.

21. SIGN (Scottish Intercollegiate Guidelines Network). SIGN 88. Management of suspected bacterial urinary tract infections in adults. Edinburgh, Scotland: SIGN; 2012. Available from: <u>http://www.sign.ac.uk/guidelines/fulltext/88/index.html</u>.

22. Malik K, Human Development Report 2013 Team. Human Development Report 2013. The Rise of the South: Human Progress in a Diverse World. N.Y., New York. : United Nations Development Programme, 2013.

23. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 2007;7(1):10.

24. Higgins JP, Green S. Section 8. Assessing risk of bias in included studies.: The Cochrane Collaboration; 2011. Available from: <u>http://handbook.cochrane.org</u>

25. Wells GA, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.

ASB Protocol - Page 25

### BMJ Open

26. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-36.

27. Drummond MF SM, Torrance G, O'Brien B, Stoddart G. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. Oxford, UK: Oxford University Press; 2005.

28. Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. Journal of clinical epidemiology. 2013;66(2):173-83.

29. Johnston BC, Patrick DL, Thorlund K, Busse JW, da Costa BR, Schunemann HJ, et al. Patient-reported outcomes in meta-analyses-part 2: methods for improving interpretability for decision-makers. Health and quality of life outcomes. 2013;11:211.

30. Hsu J, Brozek JL, Terracciano L, Kreis J, Compalati E, Stein AT, et al. Application of GRADE: making evidence-based recommendations about diagnostic tests in clinical practice guidelines. Implementation science : IS. 2011;6:62.

31. Spencer FA, Iorio A, You J, Murad MH, Schunemann HJ, Vandvik PO, et al. Uncertainties in baseline risk estimates and confidence in treatment effects. BMJ. 2012;345:e7401.

32. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed). 1997;315(7109):629-34.

33. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. Jama. 1994;271(9):703-7.

34. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. Journal of clinical epidemiology. 2005;58(10):982-90.

35. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology. 2011;64(4):380-2.

36. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. Journal of clinical epidemiology. 2011;64(12):1311-6.

37. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). Journal of clinical epidemiology. 2011;64(4):407-15.

**BMJ** Open

38. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. Journal of clinical epidemiology. 2011;64(12):1294-302.

39. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. Journal of clinical epidemiology. 2011;64(12):1283-93.

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| 1        |  |
|----------|--|
| 2        |  |
| 3        | Appendix 1. MEDLINE Search Strategy (KQ1 [screening effectiveness])  |
| 4        | rippendix it (independent Strategy (inder Estreming enteent entess))   |
| 5<br>6   | Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R)   |
| 7        | Daily and Ovid MEDLINE(R) 1946 to Present  |
| 8<br>9   | Search Title: PHTF Bacteriuria Screening in Pregnancy  |
| 10       |  |
| 11<br>12 | Strategy:  |
| 13       | 1. Asymptomatic Infections/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-  |
| 14       | cystiti* or pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.   |
| 15       | 2. Bacteriuria/  |
| 16       | 3. exp Cystitis/   |
| 17       | 4. Dysuria/  |
| 18       | 5. Pyelonephritis/   |
| 19       |  |
| 20       | 6. Urinary Tract Infections/   |
| 21       | 7. bacilluria*.tw,kf.  |
| 22       | 8. bacteriuria*.tw,kf.   |
| 23       | 9. cystiti <sup>*</sup> .tw,kf.  |
| 24       | 10. (cysto-pyeliti* or cystopyeliti*).tw,kf.   |
| 25       | 11. dysuria*.tw,kf.  |
| 26       | 12. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw,kf.   |
| 27       | 13. (pyelo-cystiti* or pyelocystiti*).tw,kf.   |
| 28       |  |
| 29       | 14. (pyelo-nephriti* or pyelonephriti*).tw,kf.   |
| 30       | 15. (UTI or UTIs).tw,kf.   |
| 31       | 16. or/1-15 [Combined MeSH & text words for bacteriuria]   |
| 32       | 17. Antibody-Coated Bacteria Test, Urinary/  |
| 33       | 18. *Bacteriuria/di, pc, mi, ur  |
| 34       | 19. exp *Cystitis/di, pc, mi, ur   |
| 35<br>36 | 20. Mass Screening/  |
| 37       | 21. Microbial Sensitivity Tests/   |
| 38       |  |
| 39       | 22. Microscopy/  |
| 40       | 23. Predictive Value of Tests/   |
| 41       | 24. *Pyelonephritis/di, pc, mi, ur   |
| 42       | <ul> <li>22. Microscopy/</li> <li>23. Predictive Value of Tests/</li> <li>24. *Pyelonephritis/di, pc, mi, ur</li> <li>25. Reagent Kits, Diagnostic/</li> </ul> |
| 43       | 26. Reagent Strips/  |
| 44       | 27. "Sensitivity and Specificity"/   |
| 45       | 28. Urinalysis/  |
| 46       | 29. *Urinary Tract Infections/di, pc, mi, ur   |
| 47       | 30. ((accurac* or diagnostic) adj5 (algorithm* or test*)).tw,kf.   |
| 48       |  |
| 49       | 31. diagnostic accurac*.tw,kf.   |
| 50       | 32. culture*.tw,kf.  |
| 51       | 33. (detect* or predict* or screen*).tw,kf.  |
| 52       | 34. (dip slide* or dipslide* or dip stick* or dipstick*).tw,kf.  |
| 53       | 35. (micro-scopy or microscopy).tw,kf.   |
| 54       | 36. (microb* adj2 test*).tw,kf.  |
| 55       | 37. ((re-agent* or reagent) adj3 (strip* or test*)).tw,kf.   |
| 56       |  |
| 57       |  |
| 58       | ASB Proposal - Appendix Page <b>1</b>  |
| 59       | For poor roviow only, http://bmionon.hmi.com/site/shout/suidalines.yhtml   |
| 60       | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml  |

- 38. strip\* test\*.tw,kf.
- 39. urine test\*.tw,kf.
- 40. (urinalys\* or urine analys\*).tw,kf.
- 41. uriscreen.tw,kf.
- 42. or/17-41 [Combined MeSH & text words for screening]
- 43. exp Pregnancy/
- 44. Pregnancy Complications, Infectious/
- 45. Pregnant Women/
- 46. Prenatal Care/
- 47. Prenatal Diagnosis/
- 48. (antenatal\* or pre-natal\* or prenatal\*).mp.
- 49. (expect\* adj (female? or mother? or wom#n)).tw,kf.
- 50. pregnan\*.mp.
- 51. or/43-50 [Combined MeSH & text words for pregnancy]
- 52. and/16,42,51 [Combined searches for bacteriuria, screening & pregnancy]
- 53. Male/ not (Female/ and Male/)
- 54. 52 not 53 [Male only records excluded]
- 55. exp Animals/ not (exp Animals/ and Humans/)
- 56. 54 not 55 [Animal only records excluded]
  - 57. (comment or editorial or news or newspaper article).pt.
  - 58. (letter not (letter and randomized controlled trial)).pt.
  - 59. 56 not (57 or 58) [Opinion pieces excluded]
  - 60. case reports.pt.
  - 61. 59 not 60 [Case reports excluded]
  - 62. limit 61 to (english or french)
  - 63. remove duplicates from 62

## Appendix 2. Methods for Integrating Existing Systematic Reviews into New Reviews

One or more systematic reviews may exist that align with one or more key questions (KQs) of the reviews undertaken to inform CTFPHC guidelines. The CTFPHC and ERSCs have considered the manner in which new reviews conducted for CTFPHC guidelines can benefit from efficiencies by incorporating existing systematic reviews, while maintaining methodological rigor in their own systematic review conduct, closely aligning existing reviews within their review scope (i.e., inclusion/exclusion criteria), and maintaining consistency with other CTFPHC Methods. They have based their approach on work conducted by a methods working group composed of investigators from the Evidence-based Practice Center Program funded by the U.S. Agency for Healthcare Research and Quality.<sup>1,2</sup> A summary of the way the ERSCs will operationalize the 12 AHRQ recommendations (Box 1) to meet their needs is outlined below. This approach differs from situations when "updating" a single existing systematic review is deemed suitable, that is, in some cases a high-quality review will be used to answer one or more of the CTFPHC KQs in entirety, usually without revisions to the review's scope, search for evidence (apart from updating to present), methodological quality/risk of bias assessments, data extraction, or data analysis.

### Summary of CTFPHC Approach

The recommendations developed by AHRQ (Box 1) will serve as an overall framework for ERSC reviews, although in most cases existing systematic reviews will be used to build efficiencies in discrete steps within the review process—mainly search and selection of literature, and data extraction—which will not generally include refinement of the scope or data analysis and interpretation. Moreover, we will not in most circumstances include a systematic review itself as a study design for inclusion (unless the intention is to specifically conduct an overview of reviews). The ability to use any given systematic review will largely depend on how it aligns with the CTFPHC review's scope (PICOTS). A further primary consideration will be the comprehensiveness of its search strategy and reporting of literature flow. It is important to note that some CTFPHC reviews need to be complex with multiple stages (e.g., a review of screening effectiveness for patient-important benefits and harms may require including evidence on indirect evidence of test accuracy and treatment) such that existing systematic reviews may exist for one or more discrete stages but not for others. Some key points on the operationalization, and minor revision, by the ERSCs of these recommendations are provided below.

1. **Choosing systematic reviews**: Following the identification of relevant reviews (a search for systematic reviews may be undertaken for some topics), the evidence for each will be mapped to the PICOTS elements and the quality of the review will be assessed (e.g., using the AMSTAR tool which has been evaluated and found effective to discriminate reviews with high and low quality of methods and reporting).<sup>3</sup> Some of the CTFPHC KQs may only have a single existing systematic review for possible incorporation, while others may have more than one; if suitable, a decision between systematic reviews will be based on methodological quality, comprehensiveness and quality of its literature search and reporting (e.g., assessed using PRESS checklist), comprehensiveness of reporting on included studies, and the best fit within the CTFPHC scope and methods. In some cases two or more reviews may be integrated because, together, they capture the full scope of the CTFPHC KQ(s). Rationale will be provided for choices made.

**Note:** If no review is deemed a good fit for purpose for integration (i.e., de novo process all together appears to be best option) we will at minimum examine available reviews for their search strategies (to ensure that our search strategies are comprehensive) and review their reference lists for identification of studies.

- 2. Searching: Various strategies will be considered. If one or more reviews are fit for purpose (but do not meet criteria for classification as a systematic review update) and cover a scope that is very similar or broader than the CTFPHC topic, we may update the search(es) if the last search date was prior to 6 months before commencing our review. When there are multiple reviews being considered, updating the literature to present may involve a new comprehensive search strategy to identify studies published after the date of the earliest existing review; this may reduce complexities when trying to implement, document, and remove duplicates from multiple searches. Alternatively, if the scope of the existing review(s) is *narrower* (e.g., missing an element in PICOTS) or the search deemed sub-optimal in some manner (e.g., missing key terms, additional database viewed as highly relevant) we may re-run the existing review's search concurrent with an original (e.g., broader) search and remove the citations previously screened for the other review. If more appropriate, we may update the other review's search and use a new search for the missing PICO element(s) (e.g., one additional intervention) for a longer time period to meet our timeframe. In cases where we feel screening excluded studies lists is appropriate we will also undertake this. Careful consideration will be used to ensure a comprehensive search is conducted regardless of approach taken; moreover, the ERSC librarians will help determine on a case-by-case basis what approach would be feasible for implementation to ensure aims of building efficiencies are possible.
- 3. Screening and selection: We will assess articles included in all relevant reviews (based on full text if necessary) to determine if they meet our inclusion criteria.
- 4. **Data extraction and methodological quality assessments**: We will consider incorporating the data on study and participant characteristics rather than extracting these data anew; we may also use the review author's risk of bias assessments if the tools/methods are consistent with CTFPHC methods. These steps will create efficiencies but because they are dependent on the quality of the systematic review and extent of reporting, the ERSC staff will verify the data on at least 5 to 10% of studies.<sup>1</sup>
- 5. **Data analysis**: We will consider using quantitative outcome data from reviews (with verification), but will not typically use meta-analyses or quality (GRADE) assessments of existing reviews.
- 6. **Reporting**: Transparent reporting of all integration steps used will be included in the evidence review report.

## Box 1. Recommendations developed by AHRQ EPCs\*1,2

\*Strength of evidence refers to AHRQ's slightly modified approach to the GRADE quality of evidence approach

| 1.  | Existing reviews should be confirmed as systematic reviews through the application of a minimum set of eligibility criteria. We propose that the minimum eligibility criteria for systematic reviews include an explicit and adequate search, application of predefined eligibility criteria to select studies, risk of bias assessment for included studies, and synthesis of results.  |
|-----|--|
| 2.  | Criteria to assess the relevance, in terms of question elements and currency, and quality of existing systematic reviews under consideration for inclusion in reviews should be predefined.  |
| 3.  | The quality of relevant existing systematic reviews should be assessed in an explicit manner with a minimum set of quality criteria that include search of multiple sources, use of a generally accepted tool for risk of bias assessment, and sufficient information to assess the strength of the body of evidence that includes the major domains of risk of bias, directness, consistency, precision, and reporting bias.                          |
| 4.  | The risk of bias assessments from the existing systematic review may be used when the review described an explicit process, including the use of a tool or method that is compatible with the approach of the current review and that assessed the key sources of potential bias.  |
| 5.  | We suggest that risk of bias assessment be repeated in a sample of studies from an existing review under consideration for inclusion in a new review to confirm concordance with current review team approach.   |
| 6.  | We recommend that at a minimum, reviews should narratively describe findings of the prior review(s), including the number and types of studies included, and the overall findings.   |
| 7.  | We recommend that newly identified studies be clearly distinguished from studies in the existing review(s) when presented in the narrative and any tables (eg, separate tables).   |
| 8.  | Summary tables should include sufficient information to support ratings for overall strength of evidence, including ratings for individual strength of evidence domains (study limitations, consistency, precision, directness, reporting bias). The strength of evidence ratings should be based on the underlying primary evidence, not the number or quality of existing systematic reviews.  |
| 9.  | Using strength of evidence domains as a framework (study limitations, consistency, precision, directness, and reporting bias), review authors should consider how new evidence would change estimates of effect or ratings for strength of evidence. A new quantitative synthesis (ie, pooled estimate) is needed if new studies would change conclusions or strength of evidence judgements, or to obtain a more precise or more up-to-date estimate. |
| 10. | In cases where the existing systematic review(s) did not complete strength of evidence grading for a comparison<br>and outcome of interest, the strength of evidence should be assessed for the body of evidence, considering primary<br>studies from prior review(s) and any new studies identified.  |
| 11. | In cases where no new studies are added to the body of evidence, the strength of evidence assessment from the existing systematic review may be used if conducted using an acceptable grading approach consistent with current review context. In these cases, we suggest that the overall strength of evidence assessment be reviewed, considering the strength of evidence domains, to confirm consistency with current review team assessments.     |
| 12. | In cases where new studies are added to the body of evidence, the strength of evidence may need to be reassessed<br>on the basis of all studies/evidence.  |

### **Appendix 2 References**

- 1. Robinson KA, Chou R, Berkman ND, et al. Integrating bodies of evidence: existing systematic reviews and primary studies. Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 Feb.
- 2. Robinson KA, Chou R, Berkman ND, et al. Twelve recommendations for integrating existing systematic reviews into new reviews: EPC guidance. J Clin Epidemiol. 2016 Feb;70:38-44. PMID: 26261004.
- 3. Foisy M, Hartling L. Challenges and considerations involved in using AMSTAR in overviews of reviews. 22<sup>nd</sup> Cochrane Colloquium. Hyderabad (India); 2014 Sept 21-26.

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| 2        |  |
|----------|--|
| 3        | Supplement 2. Search Strategy  |
| 4        | Supprement 2. Search Strategy  |
| 5        | KQ1: Screening Effectiveness   |
| 6        | Database: Ovid Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R)          |
| 7        | Daily and Ovid MEDLINE(R) 1946 to Present  |
| 8        | Date Searched: 13 June 2016  |
| 9        |  |
| 10<br>11 | Records Retrieved: 1437  |
| 12       | م م · · · ۲ · · / · / · · · ب · · · · · · · · · · ·  |
| 13       | 1. Asymptomatic Infections/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or |
| 14       | pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.                               |
| 15       | 2. Bacteriuria/  |
| 16       | 3. exp Cystitis/   |
| 17       | 4. Dysuria/  |
| 18       | 5. Pyelonephritis/   |
| 19       | 6. Urinary Tract Infections/   |
| 20       | 7. bacilluria*.tw,kf.  |
| 21       | 8. bacteriuria*.tw,kf.   |
| 22       | 9. cystiti*.tw,kf.   |
| 23       | 10. (cysto-pyeliti* or cystopyeliti*).tw,kf.   |
| 24<br>25 | 11. dysuria*.tw,kf.  |
| 26       | 12. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw,kf.               |
| 27       | 13. (pyelo-cystiti* or pyelocystiti*).tw,kf.   |
| 28       | 14. (pyelo-nephriti* or pyelonephriti*).tw,kf.   |
| 29       | 15. (UTI or UTIs).tw,kf.   |
| 30       | 16. or/1-15 [Combined MeSH & text words for bacteriuria]   |
| 31       | 17. Antibody-Coated Bacteria Test, Urinary/  |
| 32       | 18. *Bacteriuria/di, pc, mi, ur  |
| 33       | 19. exp *Cystitis/di, pc, mi, ur   |
| 34       | 20. Mass Screening/  |
| 35       | 21. Microbial Sensitivity Tests/   |
| 36<br>37 | 22. Microscopy/  |
| 38       | 23. Predictive Value of Tests/   |
| 39       | 24. *Pyelonephritis/di, pc, mi, ur   |
| 40       | 25. Reagent Kits, Diagnostic/  |
| 41       | 26. Reagent Strips/  |
| 42       | 27. "Sensitivity and Specificity"/   |
| 43       | 28. Urinalysis/  |
| 44       | •  |
| 45       | 29. *Urinary Tract Infections/di, pc, mi, ur   |
| 46       | 30. ((accurac* or diagnostic) adj5 (algorithm* or test*)).tw,kf.                                       |
| 47       | 31. diagnostic accurac*.tw,kf.   |
| 48<br>49 | 32. culture*.tw,kf.  |
| 49<br>50 | 33. (detect* or predict* or screen*).tw,kf.  |
| 51       | 34. (dip slide* or dipslide* or dip stick* or dipstick*).tw,kf.  |
| 52       | 35. (micro-scopy or microscopy).tw,kf.   |
| 53       | 36. (microb* adj2 test*).tw,kf.  |
| 54       | 37. ((re-agent* or reagent) adj3 (strip* or test*)).tw,kf.   |
| 55       | 38. strip* test*.tw,kf.  |
| 56       | 39. urine test*.tw,kf.   |
| 57       |  |
| 58       |  |
| 59       | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                              |
| 60       | rol peer review only inteps/binjopen.binj.com/site/about/guidelines.kittin                             |

| 1        |   |
|----------|---|
| 2<br>3   |   |
| 4        | 40. (urinalys* or urine analys*).tw,kf.   |
| 5        | 41. uriscreen.tw,kf.  |
| 6        | 42. or/17-41 [Combined MeSH & text words for screening]   |
| 7        | 43. exp Pregnancy/  |
| 8        | 44. Pregnancy Complications, Infectious/  |
| 9        | 45. Pregnant Women/   |
| 10       | 46. Prenatal Care/  |
| 11       | 47. Prenatal Diagnosis/   |
| 12       | 48. (antenatal* or pre-natal* or prenatal*).mp.   |
| 13       | 49. (expect* adj (female? or mother? or wom#n)).tw,kf.  |
| 14<br>15 | 50. pregnan*.mp.  |
| 16       | 51. or/43-50 [Combined MeSH & text words for pregnancy]   |
| 17       | 52. and/16,42,51 [Combined searches for bacteriuria, screening & pregnancy]                           |
| 18       | 53. Male/ not (Female/ and Male/)   |
| 19       | 54. 52 not 53 [Male only records excluded]  |
| 20       | 55. exp Animals/ not (exp Animals/ and Humans/)   |
| 21       | 56. 54 not 55 [Animal only records excluded]  |
| 22       | 57. (comment or editorial or news or newspaper article).pt.   |
| 23       | 58. (letter not (letter and randomized controlled trial)).pt.   |
| 24       | 59. 56 not (57 or 58) [Opinion pieces excluded]   |
| 25<br>26 | 60. case reports.pt.  |
| 20       | 61. 59 not 60 [Case reports excluded]   |
| 28       | 62. limit 61 to (english or french)   |
| 29       | 63. remove duplicates from 62   |
| 30       |   |
| 31       |   |
| 32       | KQ1: Screening Effectiveness  |
| 33       | Database: Ovid Embase 1974 to 2016 Week 24  |
| 34       | Date Searched: 13 June 2016   |
| 35       | Records Retrieved: 1613   |
| 36<br>37 |   |
| 38       | 1 acuta nucleananhritic/  |
| 39       | 1. acute pyelonephritis/<br>2. asymptomatic bacteriuria/  |
| 40       | 3. asymptomatic infection/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or |
| 41       |   |
| 42       | pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.                              |
| 43       | 4. bacteriuria/   |
| 44       | 5. exp cystitis/  |
| 45       | 6. dysuria/   |
| 46       | 7. kidney infection/  |
| 47<br>48 | 8. pyelonephritis/  |
| 48       | 9. urinary tract infections/  |
| 50       | 10. bacilluria*.tw.   |
| 51       | 11. bacteriuria*.tw.  |
| 52       | 12. cystiti*.tw.  |
| 53       | 13. (cysto-pyeliti* or cystopyeliti*).tw.   |
| 54       | 14. dysuria*.tw.  |
| 55       | 15. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw.                 |
| 56       | 16 (pyolo cystiti* or pyolocystiti*) tw   |
|          | 16. (pyelo-cystiti* or pyelocystiti*).tw.   |
| 57       | 10. (pyelo-cystiti ol pyelocystiti ).tw.  |
| 57<br>58 |   |
| 57       | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                             |

| 2        |   |
|----------|---|
| 3        | 17. (pyelo-nephriti* or pyelonephriti*).tw.                               |
| 4        | 18. (UTI or UTIs).tw.   |
| 5        | 19. or/1-18 [Combined Emtree & text words for bacteriuria]                |
| 6        | 20. *asymptomatic bacteriuria/di, pc                                      |
| 7        | 21. *acute pyelonephritis/di, pc  |
| 8<br>9   | 22. *bacteriuria/di, pc   |
| 9<br>10  | 23. $exp * cystitis/di, pc$   |
| 11       | 24. diagnostic kit/   |
| 12       | 25. fluorescent antibody technique/                                       |
| 13       |   |
| 14       | 26. *kidney infection/di, pc  |
| 15       | 27. mass screening/   |
| 16       | 28. microbial sensitivity test/   |
| 17       | 29. microscopy/   |
| 18       | 30. predictive value/   |
| 19       | 31. *pyelonephritis/di, pc  |
| 20       | 32. "sensitivity and specificity"/  |
| 21       | 33. screening/  |
| 22<br>23 | 34. test strip/   |
| 23       | 35. exp urinalysis/   |
| 25       | 36. *urinary tract infection/di, pc                                       |
| 26       | 37. ((accurac* or diagnostic) adj5 (algorithm* or test*)).tw.             |
| 27       | 38. diagnostic accurac*.tw.   |
| 28       | 39. culture*.tw.  |
| 29       | 40. (detect* or predict* or screen*).tw.                                  |
| 30       | 41. (dip slide* or dipslide* or dip stick* or dipstick*).tw.              |
| 31       | 42. (micro-scopy or microscopy).tw.                                       |
| 32       | 43. (microb* adj2 test*).tw.  |
| 33       | 44. ((re-agent* or reagent) adj3 (strip* or test*)).tw.                   |
| 34<br>35 | 45. strip* test*.tw.  |
| 36       | 46. urine test*.tw.   |
| 37       | 47. (urinalys* or urine analys*).tw.                                      |
| 38       | 48. uriscreen.tw.   |
| 39       | 49. or/20-48 [Combined Emtree & text words for screening]                 |
| 40       | 50. exp pregnancy/  |
| 41       | 51. pregnancy complication/   |
| 42       | 52. pregnant woman/   |
| 43       | 53. prenatal care/  |
| 44       | 54. prenatal diagnosis/   |
| 45       | 55. prenatal screening/   |
| 46<br>47 | 56. (antenatal* or pre-natal* or prenatal*).mp.                           |
| 47<br>48 | 57. (expect* adj (female? or mother? or wom#n)).tw.                       |
| 49       | 57. (expect add (ienale? of mother? of wom#n)).tw.<br>58. pregnan*.mp.    |
| 50       |   |
| 51       | 59. or/50-58 [Combined Emtree & text words for pregnancy]                 |
| 52       | 60. and/19,49,59 [Combined Emtree & text words for pregnancy]             |
| 53       | 61. Male/ not (Female/ and Male/)   |
| 54       | 62. 60 not 61 [Male only records excluded]                                |
| 55       | 63. animals/ not (animals/ and humans/)                                   |
| 56       | 64. 62 not 63 [Animal only records excluded]                              |
| 57       |   |
| 58<br>50 |   |
| 59<br>60 | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml |
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|        | 65. (c   | onference* or editorial or letter).pt.  |
|--------|----------|---|
|        | -        | 1 not 65 [Excluded publication types – RF note: will search conference proceedings separately |
|        |          | different strategy]   |
|        |          | ise report/ or case report*.ti.   |
|        |          | 5 not 67 [Case reports excluded]  |
|        |          | nit 68 to (english or french)   |
| C      |          | move duplicates from 69   |
| 1      |          |   |
| 2      |          |   |
| 3      | KO1:     | Screening Effectiveness   |
| 4      |          | base: Wiley Cochrane Library  |
| 5      |          | Searched: 13 June 2016  |
| כ<br>ז |          | ds Retrieved: 11 in Cochrane Database of Systematic Reviews                                   |
| /<br>2 |          | ds Retrieved: 1 in Database of Abstracts of Reviews of Effects (DARE)                         |
| 9      |          | ds Retrieved: 111 Database of Abstracts of Reviews of Effects (DARE)                          |
| )      |          |   |
| 1      | Recor    | ds Retrieved: 1 in Health Technology Assessment Database                                      |
| 2      | #1       | [mb A"Asymptomatic Infections"] and (basteriuria* or bladder* or excitic* or kidney* or       |
| 3      | #1       | [mh ^"Asymptomatic Infections"] and (bacteriuria* or bladder* or cystitis* or kidney* or      |
| 4      | #2       | -cystiti* or pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*):ti,ab,kw    |
| 5      |          | [mh ^Bacteriuria]   |
| כ<br>ז | #3       | [mh Cystitis]   |
| ,<br>2 | #4<br>#F | [mh ^Dysuria]   |
| 9      | #5       | [mh ^Pyelonephritis]  |
| )      | #6       | [mh ^"Urinary Tract Infections"]  |
| 1      | #7       | bacilluria*:ti,ab,kw  |
| 2      | #8       | bacteriuria*:ti,ab,kw   |
| 3      | #9       | cystiti*:ti,ab,kw   |
| 4      | #10      | (cysto-pyeliti* or cystopyeliti*):ti,ab,kw  |
| 5      | #11      | dysuria*:ti,ab,kw   |
| כ<br>ד | #12      | (infection* near/2 (bladder* or genitourin* or kidney* or urin* or urogenita*)):ti,ab,kw      |
| /<br>2 | #13      | (pyelo-cystiti* or pyelocystiti*):ti,ab,kw  |
| 9      | #14      | (pyelo-nephriti* or pyelonephriti*):ti,ab,kw  |
| )      | #15      | (UTI or UTIs):ti,ab,kw  |
| 1      | #16      | {or #1-#15}   |
| 2      | #17      | [mh ^"Antibody-Coated Bacteria Test, Urinary"]  |
| 3      | #18      | [mh ^Bacteriuria [mj]/DI,PC,MI,UR]  |
| 4      | #19      | [mh Cystitis [mj]/DI,PC,MI,UR]  |
| 5      | #20      | [mh ^"Mass Screening"]  |
| כ<br>ז | #21      | [mh ^"Microbial Sensitivity Tests"]   |
| ,<br>2 | #22      | [mh ^Microscopy]  |
| 9      | #23      | [mh ^"Predictive Value of Tests"]   |
| )      | #24      | [mh ^Pyelonephritis [mj]/DI,PC,MI,UR]   |
| 1      | #25      | [mh "Reagent Kits, Diagnostic"]   |
| 2      | #26      | [mh "Reagent Strips"]   |
| 3      | #27      | [mh ^"Sensitivity and Specificity"]   |
| 4      | #28      | [mh ^Urinalysis]  |
| 5      | #29      | [mh ^"Urinary Tract Infections" [mj]/DI,PC,MI,UR]   |
| 5<br>7 |          |   |
| 3      |          |   |
| 9      |          |   |
| n      |          | For peer review only - http://bmiopen.bmi.com/site/about/guidelines.xhtml                     |

| 1  |  |   |  |  |
|--|--|---|--|--|
| 2  |  |   |  |  |
| 3  | #30  | ((accurac* or diagnostic) near/5 (algorithm* or test*)):ti,ab,kw  |  |  |
| 4<br>5   | #31  | "diagnostic accurac*":ti,ab,kw  |  |  |
| 6  | #32 culture*:ti,ab,kw  |   |  |  |
| 7  | #33 (detect* or predict* or screen*):ti,ab,kw  |   |  |  |
| 8  | #34  | ("dip slide*" or dipslide* or "dip stick*" or dipstick*):ti,ab,kw   |  |  |
| 9  | #35  | (micro-scopy or microscopy):ti,ab,kw  |  |  |
| 10   | #36  | (microb* near/2 test*):ti,ab,kw   |  |  |
| 11   | #37  | ((re-agent* or reagent) near/3 (strip* or test*)):ti,ab,kw  |  |  |
| 12   | #38  | "strip* test*":ti,ab,kw   |  |  |
| 13   | #39  | "urine test*":ti,ab,kw  |  |  |
| 14   | #40  | (urinalys* or "urine analys*"):ti,ab,kw   |  |  |
| 15<br>16   | #41  | uriscreen:ti,ab,kw  |  |  |
| 17   | #42  | {or #17-#41}  |  |  |
| 18   | #43  | [mh Pregnancy]  |  |  |
| 19   | #44  | [mh ^"Pregnancy Complications, Infectious"]   |  |  |
| 20   | #45  | [mh ^"Pregnant Women"]  |  |  |
| 21   | #46  | [mh ^"Prenatal Care"]   |  |  |
| 22   | #47  | [mh ^"Prenatal Diagnosis"]  |  |  |
| 23   | #48  | (antenatal* or pre-natal* or prenatal*):ti,ab,kw  |  |  |
| 24   | #49  | (expect* near/1 (female* or mother* or wom?n)):ti,ab,kw   |  |  |
| 25   | #50  | pregnan*:ti,ab,kw   |  |  |
| 26   | #50<br>#51   | {or #43-#50}  |  |  |
| 27   | #51<br>#52   | {and #16, #42, #51}   |  |  |
| 28<br>29   | #32  |   |  |  |
| 30   |  |   |  |  |
|  |  |   |  |  |
| 31   | KU1. C   | crooning Effectiveness  |  |  |
| 31<br>32   |  | creening Effectiveness  |  |  |
|  | Databa   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost   |  |  |
| 32<br>33<br>34   | <b>Datab</b> a<br>Date S   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016  |  |  |
| 32<br>33<br>34<br>35   | <b>Datab</b> a<br>Date S   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost   |  |  |
| 32<br>33<br>34<br>35<br>36   | <b>Datab</b> a<br>Date S<br>Recorc   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249   |  |  |
| 32<br>33<br>34<br>35<br>36<br>37   | Databa<br>Date S<br>Recorc<br>S1. (M   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")   |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38   | Databa<br>Date S<br>Recorc<br>S1. (M<br>S2. (M   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")   |  |  |
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| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")   |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")  |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S6. bad  | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*  |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S6. bad<br>S7. bad   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*  |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S6. bad<br>S7. bad<br>S8. cys  | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*   |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. cys<br>S7. bad<br>S8. cys<br>S9. "cy   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>cteriuria*  |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. cys<br>S7. bad<br>S8. cys<br>S9. "cy   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*   |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S6. bad<br>S7. bad<br>S7. bad<br>S8. cys<br>S9. "cy<br>S10. dy   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>cteriuria*  |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48<br>49   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S6. bad<br>S7. bad<br>S7. bad<br>S8. cys<br>S9. "cy<br>S10. dv<br>S11. (in   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Vrinary Tract Infections")<br>cilluria*<br>cteriuria*<br>stiti*<br>rsto-pyeliti*" or cystopyeliti*<br>ysuria*  |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48<br>49<br>50   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S6. bac<br>S7. bac<br>S8. cys<br>S9. "cy<br>S10. dy<br>S11. (ii<br>S12. "g   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>cteriuria*<br>cteriuria*<br>hfection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))   |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48<br>49<br>50<br>51   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S6. bac<br>S7. bac<br>S7. bac<br>S7. bac<br>S8. cys<br>S9. "cy<br>S10. dy<br>S11. (ii<br>S12. "p<br>S13. "p<br>S14. U  | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>cteriuria*<br>titi*<br>rsto-pyeliti*" or cystopyeliti*<br>ysuria*<br>nfection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))<br>oyelo-cystiti*" or pyelocystiti*<br>oyelo-nephriti*" or pyelonephriti*<br>TI or UTIs  |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48<br>49<br>50<br>51<br>52   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S6. bac<br>S7. bac<br>S7. bac<br>S7. bac<br>S8. cys<br>S9. "cy<br>S10. dy<br>S11. (ii<br>S12. "p<br>S13. "p<br>S14. U  | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>cteriuria*<br>stot:<br>titi*<br>rsto-pyeliti*" or cystopyeliti*<br>ysuria*<br>nfection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))<br>oyelo-cystiti*" or pyelocystiti*<br>oyelo-nephriti*" or pyelonephriti*   |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48<br>49<br>50<br>51   | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5 | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>cteriuria*<br>titi*<br>rsto-pyeliti*" or cystopyeliti*<br>ysuria*<br>nfection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))<br>oyelo-cystiti*" or pyelocystiti*<br>oyelo-nephriti*" or pyelonephriti*<br>TI or UTIs  |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48<br>49<br>50<br>51<br>52<br>53                                     | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S6. bad<br>S7. bad<br>S7. bad<br>S7. bad<br>S7. bad<br>S9. "cy<br>S10. dy<br>S11. (iii<br>S12. "¢<br>S13. "¢<br>S14. U<br>S15. S2<br>S16. (M   | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>cteriuria*<br>cteriuria*<br>dtiti*<br>rsto-pyeliti*" or cystopyeliti*<br>ysuria*<br>nfection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))<br>oyelo-cystiti*" or pyelocystiti*<br>oyelonephriti*" or pyelonephriti*<br>TI or UTIs<br>1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14                                      |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48<br>49<br>50<br>51<br>52<br>53<br>54                               | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. cys<br>S9. "cy<br>S10. dy<br>S11. (iii<br>S12. "p<br>S13. "p<br>S14. U<br>S15. S2<br>S16. (M<br>S17. (M  | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>cteriuria*<br>dtiti*<br>rsto-pyeliti*" or cystopyeliti*<br>ysuria*<br>nfection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))<br>oyelo-cystiti*" or pyelocystiti*<br>oyelonephriti*" or pyelonephriti*<br>TI or UTIs<br>1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14<br>AM "Bacteriuria/DI/PC/MI/UR")                   |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48<br>49<br>50<br>51<br>52<br>53<br>54<br>55<br>56<br>57             | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. cys<br>S9. "cy<br>S10. dy<br>S11. (iii<br>S12. "p<br>S13. "p<br>S14. U<br>S15. S2<br>S16. (M<br>S17. (M  | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>dtiti*<br>rsto-pyeliti*" or cystopyeliti*<br>ysuria*<br>nfection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))<br>oyelo-cystiti*" or pyelonephriti*<br>Ti or UTIs<br>L OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14<br>AM "Bacteriuria/DI/PC/MI/UR")   |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48<br>49<br>50<br>51<br>51<br>52<br>53<br>54<br>55<br>56<br>57<br>58 | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. cys<br>S9. "cy<br>S10. dy<br>S11. (iii<br>S12. "p<br>S13. "p<br>S14. U<br>S15. S2<br>S16. (M<br>S17. (M  | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>dtiti*<br>rsto-pyeliti*" or cystopyeliti*<br>ysuria*<br>nfection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))<br>oyelo-cystiti*" or pyelonephriti*<br>Ti or UTIs<br>L OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14<br>AM "Bacteriuria/DI/PC/MI/UR")<br>AM "Cystitis+/DI/MI/PC/UR")                                      |  |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47<br>48<br>49<br>50<br>51<br>52<br>53<br>54<br>55<br>56<br>57             | Databa<br>Date S<br>Record<br>S1. (M<br>S2. (M<br>S3. (M<br>S4. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. (M<br>S5. cys<br>S9. "cy<br>S10. dy<br>S11. (iii<br>S12. "p<br>S13. "p<br>S14. U<br>S15. S2<br>S16. (M<br>S17. (M  | ase: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost<br>earched: 13 June 2016<br>ds Retrieved: 249<br>H "Bacteriuria")<br>H "Cystitis+")<br>H "Dysuria")<br>H "Pyelonephritis")<br>H "Urinary Tract Infections")<br>cilluria*<br>cteriuria*<br>dtiti*<br>rsto-pyeliti*" or cystopyeliti*<br>ysuria*<br>infection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))<br>oyelo-cystiti*" or pyelocystiti*<br>oyelonephriti*" or pyelonephriti*<br>TI or UTIs<br>L OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14<br>AM "Bacteriuria/DI/PC/MI/UR")<br>AM "Cystitis+/DI/MI/PC/UR") |  |  |

|        | S19. (MH "Health Screening")   |
|--------|--|
|        | S20. (MH "Microbial Culture and Sensitivity Tests")  |
|        | S21. (MH "Microscopy")   |
|        | S22. (MH "Predictive Value of Tests")  |
|        | S23. (MM "Pyelonephritis/DI/PC/MI/UR")   |
|        | S24. (MH "Reagent Kits, Diagnostic+")  |
| )      | S25. (MH "Sensitivity and Specificity")  |
|        | S26. (MH "Urinalysis")   |
| 2      | S27. (MM "Urinary Tract Infections/DI/PC/MI/UR")   |
| 5      | S28. (accurac* or diagnostic) N5 (algorithm* or test*)                                       |
| +      | S29. "diagnostic accurac*"   |
| 5      | S30. culture*  |
| 7      | S31. detect* or predict* or screen*  |
| 3      | S32. "dip slide*" or dipslide* or "dip stick*" or dipstick*                                  |
| )      | S33. "micro-scopy" or microscopy   |
| )      | S34. microb* N2 test*  |
| l      | S35. ("re-agent*" or reagent) N3 (strip* or test*)   |
| 2      | S36. "strip* test*"  |
| 3      | S37. "urine test*"   |
| +      | S38. urinalys* or "urine analys*"  |
| 5      | S39. uriscreen   |
| 7      | S40. S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 |
| 3      | OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39                 |
| )      | S41. (MH "Expectant Mothers")  |
| )      | S42. (MH "Pregnancy+")   |
| l      | S43. (MH "Pregnancy Complications, Infectious")  |
| 2      | S44. (MH "Prenatal Care")  |
| 3      | S45. (MH "Prenatal Diagnosis")   |
| 1<br>- | S46. antenatal* or "pre-natal*" or prenatal*   |
| )<br>: | S47. expect* N1 (female? or mother? or wom?n)  |
| )<br>7 | S48. pregnan*  |
| 3      | S49. S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48                                    |
| )      | S50. S15 AND S40 AND S49   |
| )      | S51. MH "Male" NOT ((MH "Female") AND (MH "Male"))   |
| l      | S52. S50 NOT S51   |
| 2      | S53. ((MH "Vertebrates+") NOT MH Human)  |
| 3      | S54. S52 NOT S53   |
| 1      | S55. Limiters - Publication Type: Anecdote, Case Study, Commentary, Editorial, Letter        |
| )<br>- | S56. S54 NOT S55   |
| 7      | S57. S56 Narrow by Language: - english [RF: No French records in results to include]         |
| 2      |  |
| )      |  |
| )      | KQ1: Screening Effectiveness   |
| l      | Database: PubMed via NCBI Entrez (1946 to Present)   |
| 2      | Date Searched: 14 June 2016  |
| 3      |  |
| 1      | Records Retrieved: 1246  |
| )<br>- |  |
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| -<br>) |  |
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#### **BMJ** Open

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((((("asymptomatic infections"[mh] AND (("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields]) OR ("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields] OR "bacteriurias"[All Fields]) OR ("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields]) OR ("cystitis"[MeSH Terms] OR "cystitis"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields]) OR ("pyelocystitis"[MeSH Terms] OR "pyelocystitis"[All Fields]) OR ("pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]) OR ("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR ("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) OR UTI[all] OR ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections" [All Fields] OR "utis" [All Fields]))) OR "bacteriuria" [MeSH Terms: no exp] OR "cystitis"[MeSH Terms] OR "dysuria"[MeSH Terms:noexp] OR "pyelonephritis"[MeSH Terms:noexp] OR "Urinary Tract Infections" [mh:noexp] OR bacilluria[tiab] OR bacteriuria[tiab] OR bacteriurias[tiab] OR "bladder infection"[tiab] OR "bladder infections"[tiab] OR cystitis[tiab] OR cystopyelitis[tiab] OR dysuria[tiab] OR "genito-urinary infection"[tiab] OR "genitourinary infection"[tiab] OR "genito-urinary infections"[tiab] OR "genitourinary infections"[tiab] OR "kidney infection"[tiab] OR "kidney infections"[tiab] OR "pyelo-nephritis"[tiab] OR pyelocystitis[tiab] OR pyelonephritis[tiab] OR "urinary infection"[tiab] OR "urinary infections"[tiab] OR "urogenital infection"[tiab] OR "urogenital infections"[tiab] OR UTI[tiab] OR UTIs[tiab]) AND ("Antibody-Coated Bacteria Test, Urinary"[mh] OR "Bacteriuria/diagnosis"[Majr] OR "Bacteriuria/prevention and control"[Majr] OR ("bacteriuria/microbiology"[Mesh Terms] AND Majr[All Fields]) OR "Bacteriuria/urine"[Majr] OR "Cystitis/diagnosis"[Majr] OR "Cystitis/prevention and control"[Majr] OR "Cystitis/microbiology"[Majr] OR "Cystitis/urine"[Majr] OR "Mass Screening"[mh:noexp] OR "Microbial Sensitivity Tests"[mh:noexp] OR "Microscopy"[mh:noexp] OR "Predictive Value of Tests"[mh:noexp] OR "Pyelonephritis/diagnosis"[Majr] OR "Pyelonephritis/prevention and control" [Majr] OR "Pyelonephritis/microbiology" [Majr] OR "Pyelonephritis/urine" [Majr] OR "Reagent Kits, Diagnostic"[mh:noexp] OR "Reagent Strips"[mh:noexp] OR "Sensitivity and Specificity"[mh:noexp] OR "Urinalysis"[mh:noexp] OR "Urinary Tract Infections/diagnosis"[Majr] OR "Urinary Tract Infections/prevention and control"[Majr] OR "Urinary Tract Infections/microbiology"[Mair] OR "Urinary Tract Infections/urine"[Mair] OR detect[tiab] OR detected[tiab] OR detection[tiab] OR detecting[tiab] OR detects[tiab] OR "diagnostic accuracy"[tiab] OR "diagnostic algorithm"[tiab] OR "dip slide"[tiab] OR "dip slides"[tiab] OR "dip stick"[tiab] OR "dip sticks"[tiab] OR dipslide[tiab] OR dipslides[tiab] OR dipstick[tiab] OR dipsticks[tiab] OR culture[tiab] OR cultures[tiab] OR "diagnostic test"[tiab] OR "diagnostic tests"[tiab] OR "microbial test"[tiab] OR "microbial tests"[tiab] OR microscopy[tiab] OR predict[tiab] OR predicted[tiab] OR prediction[tiab] OR predicting[tiab] OR predicts[tiab] OR "reagent strip"[tiab] OR "reagent strips"[tiab] OR "reagent test"[tiab] OR "reagent testing"[tiab] OR "reagent tests"[tiab] OR screen[tiab] OR screened[tiab] OR screening[tiab] OR screens[tiab] OR "strip test"[tiab] OR "strip tests"[tiab] OR "strip testing"[tiab] OR "test accuracy"[tiab] OR urinalyses[tiab] OR urinalysis[tiab] OR "urine analyses"[tiab] OR "urine analysis"[tiab] OR "urine test"[tiab] OR "urine tested"[tiab] OR "urine testing"[tiab] OR "urine tests"[tiab] OR uriscreen[tiab]) AND ("Pregnancy"[mh] OR "Pregnancy Complications, Infectious"[mh:noexp] OR "Pregnant Women"[mh:noexp] OR "Prenatal Care"[mh:noexp] OR "Prenatal Diagnosis"[mh:noexp] OR antenatal[tiab] OR "pre-natal"[tiab] OR prenatal[tiab] OR "expectant mother"[tiab] OR "expectant mothers"[tiab] OR "expecting mothers"[tiab] OR "expecting mothers"[tiab] OR "expectant woman"[tiab] OR "expectant women"[tiab] OR "expecting women"[tiab] OR pregnancies[tiab] OR pregnancy[tiab] OR pregnant[tiab])) NOT ("Male"[mh] NOT ("Female"[mh] AND "Male"[mh]))) NOT (((Animals[MESH] OR Animal Experimentation[MESH] OR "Models, Animal"[MESH] OR Vertebrates[MESH]) NOT (Humans[MESH] OR Human

experimentation[MESH])) OR (((animals[tiab] OR animal model[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR rabbit[tiab] OR rabbits[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR swine[tiab] OR dog[tiab] OR dogs[tiab] OR hamster[tiab] OR hamsters[tiab] OR chicken[tiab] OR chickens[tiab] OR sheep[tiab]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])) NOT (human[ti] OR humans[ti] OR people[ti] OR children[ti] OR adults[ti] OR seniors[ti] OR patient[ti] OR patients[ti])))) NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR newspaper article[pt])

> limit to English or French

#### KQ2: Women's Outcome Valuation Database: Ovid Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date Searched: 4 July 2016

Records Retrieved: 2965

1. Asymptomatic Infections/ and (bacteriuria\* or bladder\* or cystitis\* or kidney\* or pyelo-cystiti\* or pyelo-cystiti\* or pyelo-nephriti\* or pyelonephriti\* or urin\* or UTI\*).mp.

- 2. Bacteriuria/
- 3. exp Cystitis/
- 4. Dysuria/
- 5. Pyelonephritis/
- 6. Urinary Tract Infections/
- 7. bacilluria\*.tw,kf.
- 8. bacteriuria\*.tw,kf.
- 9. cystiti\*.tw,kf.
- 10. (cysto-pyeliti\* or cystopyeliti\*).tw,kf.
- 11. dysuria\*.tw,kf.
- 12. (infection\* adj2 (bladder\* or genitourin\* or kidney\* or urin\* or urogenita\*)).tw,kf.
- 13. (pyelo-cystiti\* or pyelocystiti\*).tw,kf.
- 14. (pyelo-nephriti\* or pyelonephriti\*).tw,kf.
- 15. (UTI or UTIs).tw,kf.
- 16. or/1-15 [Combined MeSH & text words for bacteriuria]
- 17. Antibody-Coated Bacteria Test, Urinary/
- 18. \*Bacteriuria/di, pc, mi, ur
- 19. exp \*Cystitis/di, pc, mi, ur
- 20. Mass Screening/
  - 21. Microbial Sensitivity Tests/
    - 22. Microscopy/
  - 23. Predictive Value of Tests/
  - 24. \*Pyelonephritis/di, pc, mi, ur
  - 25. Reagent Kits, Diagnostic/
  - 26. Reagent Strips/
  - 27. "Sensitivity and Specificity"/
  - 28. Urinalysis/
  - 29. \*Urinary Tract Infections/di, pc, mi, ur
- 30. ((accurac\* or diagnostic) adj5 (algorithm\* or test\*)).tw,kf.
- 56 31. diagnostic accurac\*.tw,kf.
- 57 58

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| 3        |  |
| 4        | 32. culture*.tw,kf.  |
| 5        | <ol> <li>33. (detect* or predict* or screen*).tw,kf.</li> <li>34. (dip slide* or dipslide* or dip stick* or dipstick*).tw,kf.</li> </ol> |
| 6        |  |
| 7        | 35. (micro-scopy or microscopy).tw,kf.   |
| 8        | 36. (microb* adj2 test*).tw,kf.  |
| 9        | 37. ((re-agent* or reagent) adj3 (strip* or test*)).tw,kf.   |
| 10<br>11 | 38. strip* test*.tw,kf.  |
| 12       | 39. urine test*.tw,kf.   |
| 12       | 40. (urinalys* or urine analys*).tw,kf.  |
| 14       | 41. uriscreen.tw,kf.   |
| 15       | 42. or/17-41 [Combined MeSH & text words for screening]  |
| 16       | 43. and/16,42 [Combined searches for ASB and screening]  |
| 17       | 44. Anti-Bacterial Agents/   |
| 18       | 45. Antibiotic Prophylaxis/  |
| 19       | 46. Anti-Infective Agents, Urinary/  |
| 20       | 47. Asymptomatic Infections/dt, th   |
| 21       | 48. *Bacteriuria/dt, th  |
| 22<br>23 | 49. Drug Therapy, Combination/   |
| 23<br>24 | 50. Norfloxacin/   |
| 25       | 51. exp Penicillins/   |
| 26       | 52. exp Sulfonamides/  |
| 27       | 53. *Urinary Tract Infections/dt, th   |
| 28       | 54. amoxicillin*.mp.   |
| 29       | 55. ampicillin*.mp.  |
| 30       | 56. (anti-bacteria* or antibacteria*).tw,kf.   |
| 31       | 57. (anti-biotic* or antibiotic*).tw,kf.   |
| 32       | 58. aztreonam*.mp.   |
| 33       | 59. cefadroxil*.mp.  |
| 34<br>35 | 60. cefepime*.mp.  |
| 36       | 61. ceftibuten*.mp.  |
| 37       | 62. ceftri?xone*.mp.   |
| 38       | 63. cefuroxime*.mp.  |
| 39       | 64. cephalexin*.mp.  |
| 40       | 65. cephalosporin <sup>*</sup> .mp.  |
| 41       | 66. cephradine*.mp.  |
| 42       | 67. clindamycin*.mp.   |
| 43       | 68. (co-trimoxazole* or cotrimoxazole*).mp.  |
| 44<br>45 | 69. cycloserine*.mp.   |
| 45<br>46 | 70. fosfomycin*.mp.  |
| 40<br>47 | 71. gentam#cin*.mp.  |
| 48       | 72. nalidixic acid*.mp.  |
| 49       | 73. nitrofurantoin*.mp.  |
| 50       | 74. penicillin*.mp.  |
| 51       | 75. piperacillin*.mp.  |
| 52       | 76. pivampicillin*.mp.   |
| 53       | 77. pivmecillinam*.mp.   |
| 54       | 78. sulfadimethoxine*.mp.  |
| 55       | •  |
| 56<br>57 | 79. sulfadiazine*.mp.  |
| 57<br>58 |  |
| 58<br>59 |  |
|          | For neer review only - http://hmionen.hmi.com/site/about/gui   |

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| 2        |  |
| 3        | 80. sulfamethizole*.mp.  |
| 4        | 81. sulfamethoxazole*.mp.  |
| 5        | 82. sulfamethoxypyridazine*.mp.  |
| 6        | 83. sulfonamide*.mp.   |
| 7        | 84. sulphadimidine*.mp.  |
| 8<br>9   | 85. sulphonamide*.mp.  |
| 10       | 86. tetracycline*.mp.  |
| 11       | 87. vancomycin*.mp.  |
| 12       | 88. or/44-87 [Combined MeSH & text words for antibiotic treatment]                                     |
| 13       | 89. exp Pregnancy/   |
| 14       | 90. Pregnancy Complications, Infectious/   |
| 15       | 91. Pregnant Women/  |
| 16       | 92. Prenatal Care/   |
| 17       | 93. Prenatal Diagnosis/  |
| 18<br>19 | 94. (antenatal* or pre-natal* or prenatal*).mp.  |
| 20       | 95. (expect* adj (female? or mother? or wom#n)).tw,kf.   |
| 21       | 96. pregnan*.mp.   |
| 22       | 96. pregnant .mp.<br>97. or/89-96 [Combined MeSH & text words for pregnancy]                           |
| 23       | 98. and/88,97 [Combined searches for antibiotic treatment and pregnancy]                               |
| 24       | 99. Choice Behavior/   |
| 25       | 100. *Consumer Behavior/   |
| 26       |  |
| 27       | 101. exp Consumer Participation/   |
| 28<br>29 | 102. Cooperative Behavior/<br>103. exp Decision Making/  |
| 30       | 104. Focus Groups/   |
| 31       | 104. Focus Groups/<br>105. Health Care Surveys/  |
| 32       | 106. exp Informed Consent/   |
| 33       | 107. Interviews as Topic/  |
| 34       | 108. Patient Acceptance of Health Care/  |
| 35       | 109. exp Patient Education as Topic/   |
| 36       | 110. Patient Participation/  |
| 37<br>38 | 110. Patient Patient Preference/   |
| 39       | 112. Social Values/  |
| 40       | 113. "Surveys and Questionnaires"/   |
| 41       | 113. Sulveys and Questionnaires 7<br>114. Treatment Refusal/   |
| 42       | 114. Treatment Kerusal/<br>115. (15D* and (HRQoL or QoL or "quality of life")).mp.                     |
| 43       | 116. ((accept* or consider* or choice? or choos* or chose? or decid* or decis* or input* or involv* or |
| 44       | opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or refus* or respons* or   |
| 45       | valuation or value? or valuing or view*) adj3 (citizen? or client? or consumer? or female? or male? or |
| 46<br>47 | men or patient? or public or stake?holder* or user? or wom#n)).tw,kf.                                  |
| 47<br>48 | 117. ((analys#s or valuation? or value? or valuing) adj3 (conjoint or contingent)).tw,kf.              |
| 49       | 118. (choice? adj2 (behavio?r* or discrete or experiment*)).tw,kf.                                     |
| 50       | 119. ((choice? or choos* or consent* or decision*) adj1 informed).tw,kf.                               |
| 51       | 120. ((choice? or choos* or decision*) adj2 (made or make or makes or making or shar* or               |
| 52       | support*)).tw,kf.  |
| 53       | 121. (EQ 5D or EQ5D or EuroQoL 5D or EuroQoL5D).mp.  |
| 54       | 122. (focus group? or interview* or questionnaire? or survey*).tw,kf.                                  |
| 55<br>56 | 123. gambl*.tw,kf.   |
| 57       |  |
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| 60       | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                              |
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| 2        |  |
| 3        | 124. health utilit*.tw,kf.   |
| 4        | 125. HUI.tw,kf.  |
| 5<br>6   | 126. (multi?attribute or multi?criteria).tw,kf.  |
| 7        | 127. (preference? adj1 (elicit* or scor* or state*)).tw,kf.  |
| 8        | 128. prospect theor*.tw,kf.  |
| 9        | 129. (SF 12 or SF 36 or SF 6D or SF12 or SF36 or SF6D).mp.   |
| 10       | 130. (trade off? or tradeoff?).tw,kf.  |
| 11       | 131. (willing* adj2 pay*).tw,kf.   |
| 12       | 132. or/99-131 [Combined MeSH & text words for patient preferences & values]                             |
| 13       | 133. and/43,132 [Combined searches for patient preferences & ASB screening]                              |
| 14       | 134. and/98,132 [Combined searches for patient preferences & antibiotic treatment and pregnancy]         |
| 15       | 135. or/133-134 [Combined sets of patient preferences for ASB screening & patient preferences for        |
| 16<br>17 | antibiotic treatment in pregnancy]   |
| 17       | 136. Male/ not Female/   |
| 19       | 137. 135 not 136 [Male only records excluded]  |
| 20       | 138. exp Animals/ not (exp Animals/ and Humans/)   |
| 21       | 139. 137 not 138 [Animal only records excluded]  |
| 22       | 140. (comment or editorial or news or newspaper article).pt.   |
| 23       | 141. (letter not (letter and randomized controlled trial)).pt.   |
| 24       | 142. 139 not (140 or 141) [Opinion pieces excluded]  |
| 25       | 143. case reports.pt.  |
| 26<br>27 | 144. 142 not 143 [Case reports excluded]   |
| 27       | 145. limit 144 to (english or french)  |
| 29       | 146. remove duplicates from 145  |
| 30       |  |
| 31       |  |
| 32       | KQ2: Women's Outcome Valuation   |
| 33       | Database: Ovid Embase 1974 to 2016 Week 27   |
| 34       | Date Searched: 4 July 2016   |
| 35<br>36 | Records Retrieved: 3922  |
| 30<br>37 |  |
| 38       | 1. acute pyelonephritis/   |
| 39       | 2. asymptomatic bacteriuria/   |
| 40       | 3. asymptomatic infection/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or    |
| 41       | pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.                                 |
| 42       | 4. bacteriuria/  |
| 43       | 5. exp cystitis/   |
| 44       | 6. dysuria/  |
| 45<br>46 | 7. kidney infection/   |
| 40<br>47 | 8. pyelonephritis/   |
| 48       | 9. urinary tract infections/   |
| 49       | 10. bacilluria*.tw.  |
| 50       | 11. bacteriuria*.tw.   |
| 51       |  |
| 52       | 12. cystiti*.tw.   |
| 53       | 13. (cysto-pyeliti* or cystopyeliti*).tw.  |
| 54       | 14. dysuria*.tw.<br>15. (infaction* adi2 (bladder* or gonitourin* or kidnov* or urin* or urogonita*)) tw |
| 55<br>56 | 15. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw.                    |
| 56<br>57 | 16. (pyelo-cystiti* or pyelocystiti*).tw.  |
| 57       |  |
| 59       |  |
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| 2<br>3   |   |
| 3<br>4   | 17. (pyelo-nephriti* or pyelonephriti*).tw.                   |
| 5        | 18. (UTI or UTIs).tw.   |
| 6        | 19. or/1-18 [Combined Emtree & text words for bacteriuria]    |
| 7        | 20. *asymptomatic bacteriuria/di, pc                          |
| 8        | 21. *acute pyelonephritis/di, pc                              |
| 9        | 22. *bacteriuria/di, pc                                       |
| 10       | 23. exp *cystitis/di, pc                                      |
| 11       | 24. diagnostic kit/   |
| 12       | 25. fluorescent antibody technique/                           |
| 13       | 26. *kidney infection/di, pc                                  |
| 14       | 27. mass screening/   |
| 15       | 28. microbial sensitivity test/                               |
| 16<br>17 | 29. microscopy/   |
| 17       | 30. predictive value/   |
| 18       | 31. *pyelonephritis/di, pc                                    |
| 20       | 32. "sensitivity and specificity"/                            |
| 21       | 33. screening/  |
| 22       | 34. test strip/   |
| 23       |   |
| 24       | 35. exp urinalysis/   |
| 25       | 36. *urinary tract infection/di, pc                           |
| 26       | 37. ((accurac* or diagnostic) adj5 (algorithm* or test*)).tw. |
| 27       | 38. culture*.tw.  |
| 28       | 39. (detect* or predict* or screen*).tw.                      |
| 29       | 40. diagnostic accurac*.tw.                                   |
| 30<br>31 | 41. (dip slide* or dipslide* or dip stick* or dipstick*).tw.  |
| 32       | 42. (micro-scopy or microscopy).tw.                           |
| 33       | 43. (microb* adj2 test*).tw.                                  |
| 34       | 44. ((re-agent* or reagent) adj3 (strip* or test*)).tw.       |
| 35       | 45. strip* test*.tw.  |
| 36       | 46. urine test*.tw.   |
| 37       | 47. (urinalys* or urine analys*).tw.                          |
| 38       | 48. uriscreen.tw.   |
| 39       | 49. or/20-48 [Combined Emtree & text words for screening]     |
| 40       | 50. and/19,49 [Combined searches for ASB and screening]       |
| 41       | 51. antibiotic agent/   |
| 42<br>43 | 52. antibiotic prophylaxis/                                   |
| 43       | 53. antiinfective agent/                                      |
| 45       | 54. *asymptomatic bacteriuria/dt, th                          |
| 46       | 55. *asymptomatic infection/dt, th                            |
| 47       | 56. *bacteriuria/dt, th                                       |
| 48       | 57. exp *cystitis/dt, th                                      |
| 49       | 58. drug combination/   |
| 50       | 59. *kidney infection/dt, th                                  |
| 51       | 60. norfloxacin/  |
| 52       | 61. penicillin derivative/                                    |
| 53<br>54 | 62. *pyelonephritis/dt, th                                    |
| 54<br>55 | 63. sulfonamide/  |
| 56       | 64. urinary tract antiinfective agent/                        |
| 57       |   |
| 58       |   |
| 59       |   |
| 60       | For peer review only - http://bmiopen.bmi.com/s               |

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2 3 65. \*urinary tract infection/dt, th 4 66. amoxicillin\*.mp. 5 67. ampicillin\*.mp. 6 68. (anti-bacteria\* or antibacteria\*).tw. 7 69. (anti-biotic\* or antibiotic\*).tw. 8 70. aztreonam\*.mp. 9 10 71. cefadroxil\*.mp. 11 72. cefepime\*.mp. 12 73. ceftibuten\*.mp. 13 74. ceftri?xone\*.mp. 14 75. cefuroxime\*.mp. 15 76. cephalexin\*.mp. 16 77. cephalosporin\*.mp. 17 , mp. 78. cephradine\*.mp. 18 19 79. clindamycin\*.mp. 20 80. (co-trimoxazole\* or cotrimoxazole\*).mp. 21 81. cycloserine\*.mp. 22 82. fosfomycin\*.mp. 23 83. gentam#cin\*.mp. 24 84. nalidixic acid\*.mp. 25 85. nitrofurantoin\*.mp. 26 86. penicillin\*.mp. 27 87. piperacillin\*.mp. 28 29 88. pivampicillin\*.mp. 30 89. pivmecillinam\*.mp. 31 90. sulfadimethoxine\*.mp. 32 91. sulfadiazine\*.mp. 33 92. sulfamethizole\*.mp. 34 93. sulfamethoxazole\*.mp. 35 94. sulfamethoxypyridazine\*.mp. 36 95. sulfonamide\*.mp. 37 38 96. sulphadimidine\*.mp. 39 97. sulphonamide\*.mp. 40 98. tetracycline\*.mp. 41 99. vancomycin\*.mp. 42 100. or/51-99 [Combined Emtree & text words for antibiotic treatment] 43 101. exp pregnancy/ 44 102. pregnancy complication/ 45 103. pregnant woman/ 46 47 104. prenatal care/ 48 105. prenatal diagnosis/ 49 106. prenatal screening/ 50 107. (antenatal\* or pre-natal\* or prenatal\*).mp. 51 108. (expect\* adj (female? or mother? or wom#n)).tw. 52 109. pregnan\*.mp. 53 110. or/101-109 [Combined Emtree & text words for pregnancy] 54 111. and/100,110 [Combined searches for antibiotic treatment and pregnancy] 55 112. cooperation/ 56 57 58 59

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| 2        |  |
| 3        | 113. *consumer attitude/   |
| 4<br>5   | 114. exp decision making/  |
| 5<br>6   | 115. health care survey/   |
| 0<br>7   | 116. informed consent/   |
| 8        | 117. exp interview/  |
| 9        | 118. exp patient attitude/   |
| 10       | 119. patient education/  |
| 11       | 120. exp questionnaire/  |
| 12       | 121. social psychology/  |
| 13       | 122. treatment refusal/  |
| 14       | 123. (15D* and (HRQoL or QoL or "quality of life")).mp.  |
| 15       | 124. ((accept* or consider* or choice? or choos* or chose? or decid* or decis* or input* or involv* or                                     |
| 16<br>17 | opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or refus* or respons* or                                       |
| 18       | valuation or value? or valuing or view*) adj3 (citizen? or client? or consumer? or female? or male? or                                     |
| 19       | men or patient? or public or stake?holder* or user? or wom#n)).tw,kw.  |
| 20       | 125. (choice? adj2 (behavio?r* or discrete or experiment*)).tw,kw.   |
| 21       | 126. ((choice? or choos* or consent* or decision*) adj1 informed).tw,kw.   |
| 22       | 127. ((choice? or choos* or decision*) adj2 (made or make or makes or making or shar* or   |
| 23       | support*)).tw,kw.  |
| 24       | 128. (EQ 5D or EQ5D or EuroQoL 5D or EuroQoL5D).mp.  |
| 25       | 129. (focus group? or interview* or questionnaire? or survey*).tw,kw.  |
| 26<br>27 | 130. gambl*.tw,kw.   |
| 27       | 131. health utilit*.tw,kw.   |
| 29       | 132. HUI.tw,kw.  |
| 30       | 133. (multi?attribute or multi?criteria).tw,kw.  |
| 31       | 134. (preference? adj1 (elicit* or scor* or state*)).tw,kw.  |
| 32       | 135. prospect theor*.tw,kw.  |
| 33       | 136. (SF 12 or SF 36 or SF 6D or SF12 or SF36 or SF6D).mp.   |
| 34       | 137. (trade off? or tradeoff?).tw,kw.  |
| 35       | 138. (willing* adj2 pay*).tw,kw.   |
| 36<br>37 | 139. or/112-138 [Combined Emtree & text words for patient preferences & values]  |
| 38       | 140. and/50,139 [Combined searches for patient preferences & ASB screening]  |
| 39       | 141. and/111,139 [Combined searches for patient preferences & antibiotic treatment and pregnancy]  |
| 40       | 142. or/140-141 [Combined sets of patient preferences for ASB screening & patient preferences for  |
| 41       | antibiotic treatment in pregnancy]   |
| 42       | 143. Male/ not (Female/ and Male/)   |
| 43       | 144. 142 not 143 [Male only records excluded]  |
| 44       | 145. animals/ not (animals/ and humans/)   |
| 45       | 145. 144 not 145 [Animal only records excluded]  |
| 46<br>47 | 140. 144 not 145 [Annual only records excluded]<br>147. (conference* or editorial or letter).pt.   |
| 47<br>48 | 147. (conference of editorial of fetter).pt.<br>148. 146 not 147 [Excluded publication types – RF note: will search conference proceedings |
| 49       |  |
| 50       | separately with different strategy]  |
| 51       | 149. case report/ or case report*.ti.  |
| 52       | 150. 148 not 149 [Case reports excluded]   |
| 53       | 151. limit 150 to (english or french)  |
| 54       | 152. remove duplicates from 151  |
| 55       |  |
| 56       |  |
| 57<br>59 |  |
| 58<br>59 |  |
| 59<br>60 | For peer review only - http://bmiopen.bmi.com/site/about/guidelines.xhtml  |

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| 2        |                                |   |  |  |  |
| 3        | KQ2: Women's Outcome Valuation |   |  |  |  |
| 4        | -                              | Database: Wiley Cochrane Library  |  |  |  |
| 5        |                                | Searched: 5 July 2016   |  |  |  |
| 6<br>7   |                                | ds Retrieved: 45 in Cochrane Database of Systematic Reviews   |  |  |  |
| 8        |                                | ds Retrieved: 1 in Database of Abstracts of Reviews of Effects (DARE)   |  |  |  |
| 9        |                                | ds Retrieved: 321 in Cochrane Central Register of Controlled Trials (CENTRAL)   |  |  |  |
| 10       |                                | Records Retrieved: 4 in Cochrane Methodology Register   |  |  |  |
| 11       |                                | ds Retrieved: 14 in Economic Evaluations Database   |  |  |  |
| 12       | neccor                         |   |  |  |  |
| 13<br>14 | #1                             | [mh ^"Asymptomatic Infections"] and (bacteriuria* or bladder* or cystitis* or kidney* or  |  |  |  |
| 14       |                                | cystiti* or pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*):ti,ab,kw   |  |  |  |
| 16       | #2                             | [mh ^Bacteriuria]   |  |  |  |
| 17       | #3                             | [mh Cystitis]   |  |  |  |
| 18       | #4                             | [mh ^Dysuria]   |  |  |  |
| 19       | #5                             | [mh ^Pyelonephritis]  |  |  |  |
| 20       | #6                             | [mh ^"Urinary Tract Infections"]  |  |  |  |
| 21<br>22 | #7                             | bacilluria*:ti,ab,kw  |  |  |  |
| 23       | #8                             | bacteriuria*:ti,ab,kw   |  |  |  |
| 24       | #9                             | cystiti*:ti,ab,kw   |  |  |  |
| 25       | #10                            | (cysto-pyeliti* or cystopyeliti*):ti,ab,kw  |  |  |  |
| 26       | #11                            | dysuria*:ti,ab,kw   |  |  |  |
| 27       | #12                            | (infection* near/2 (bladder* or genitourin* or kidney* or urin* or urogenita*)):ti,ab,kw  |  |  |  |
| 28<br>29 | #13                            | (pyelo-cystiti* or pyelocystiti*):ti,ab,kw  |  |  |  |
| 30       | #14                            | (pyelo-nephriti* or pyelonephriti*):ti,ab,kw  |  |  |  |
| 31       | #15                            | (UTI or UTIs):ti,ab,kw  |  |  |  |
| 32       | #16                            | {or #1-#15}   |  |  |  |
| 33       | #17                            | [mh ^"Antibody-Coated Bacteria Test, Urinary"]  |  |  |  |
| 34       | #18                            | [mh ^Bacteriuria [mj]/DI,PC,MI,UR]  |  |  |  |
| 35       | #19                            | [mh Cystitis [mj]/DI,PC,MI,UR]  |  |  |  |
| 36<br>37 | #20                            | [mh ^"Mass Screening"]  |  |  |  |
| 38       | #21<br>#22                     | [mh ^"Microbial Sensitivity Tests"]   |  |  |  |
| 39       | #22<br>#23                     | [mh ^Microscopy]<br>[mh ^"Predictive Value of Tests"]<br>[mh ^Pyelonephritis [mj]/DI,PC,MI,UR]<br>[mh "Reagent Kits, Diagnostic"] |  |  |  |
| 40       | #23<br>#24                     | [mh ^Pyelonephritis [mj]/DI,PC,MI,UR]   |  |  |  |
| 41       | #24<br>#25                     | [mh "Reagent Kits, Diagnostic"]   |  |  |  |
| 42<br>43 | #23<br>#26                     | [mh "Reagent Strips"]   |  |  |  |
| 43<br>44 | #20                            | [mh ^"Sensitivity and Specificity"]   |  |  |  |
| 44       | #28                            | [mh ^Urinalysis]  |  |  |  |
| 46       | #29                            | [mh ^"Urinary Tract Infections" [mj]/DI,PC,MI,UR]   |  |  |  |
| 47       | #30                            | ((accurac* or diagnostic) near/5 (algorithm* or test*)):ti,ab,kw  |  |  |  |
| 48       | #31                            | "diagnostic accurac*":ti,ab,kw  |  |  |  |
| 49       | #32                            | culture*:ti,ab,kw   |  |  |  |
| 50<br>51 | #33                            | (detect* or predict* or screen*):ti,ab,kw   |  |  |  |
| 52       | #34                            | ("dip slide*" or dipslide* or "dip stick*" or dipstick*):ti,ab,kw   |  |  |  |
| 53       | #35                            | (micro-scopy or microscopy):ti,ab,kw  |  |  |  |
| 54       | #36                            | (microb* near/2 test*):ti,ab,kw   |  |  |  |
| 55       | #37                            | ((re-agent* or reagent) near/3 (strip* or test*)):ti,ab,kw  |  |  |  |
| 56       |                                |   |  |  |  |
| 57<br>58 |                                |   |  |  |  |
| 58<br>59 |                                |   |  |  |  |
| 60       |                                | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml   |  |  |  |
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| 2        |            |  |
| 3<br>4   | #38        | "strip* test*":ti,ab,kw                        |
| 5        | #39        | "urine test*":ti,ab,kw                         |
| 6        | #40        | (urinalys* or "urine analys*"):ti,ab,kw        |
| 7        | #41        | uriscreen:ti,ab,kw                             |
| 8        | #42        | {or #17-#41}                                   |
| 9        | #43        | #16 and #42                                    |
| 10       | #44        | [mh ^"Anti-Bacterial Agents"]                  |
| 11       | #45        | [mh ^"Antibiotic Prophylaxis"]                 |
| 12       | #46        | [mh ^"Anti-Infective Agents, Urinary"]         |
| 13       | #47        | [mh ^"Asymptomatic Infections"/DT,TH]          |
| 14       | #48        | [mh ^Bacteriuria [mj]/DT,TH]                   |
| 15       | #49        | [mh ^"Drug Therapy, Combination"]              |
| 16       | #50        | [mh ^Norfloxacin]                              |
| 17       | #51        | [mh Penicillins]                               |
| 18<br>19 | #52        | [mh Sulfonamides]                              |
| 20       | #52<br>#53 | -  |
| 20       |            | [mh ^"Urinary Tract Infections" [mj]/DT,TH]    |
| 22       | #54<br>#55 | amoxicillin*:ti,ab,kw                          |
| 23       | #55        | ampicillin*:ti,ab,kw                           |
| 24       | #56        | ("anti-bacteria*" or antibacteria*):ti,ab,kw   |
| 25       | #57        | ("anti-biotic*" or antibiotic*):ti,ab,kw       |
| 26       | #58        | aztreonam*:ti,ab,kw                            |
| 27       | #59        | cefadroxil*:ti,ab,kw                           |
| 28       | #60        | cefepime*:ti,ab,kw                             |
| 29       | #61        | ceftibuten*:ti,ab,kw                           |
| 30       | #62        | ceftri?xone*:ti,ab,kw                          |
| 31       | #63        | cefuroxime*:ti,ab,kw                           |
| 32       | #64        | cephalexin*:ti,ab,kw                           |
| 33<br>34 | #65        | cephalosporin*:ti,ab,kw                        |
| 35       | #66        | cephradine*:ti,ab,kw                           |
| 36       | #67        | clindamycin*:ti,ab,kw                          |
| 37       | #68        | ("co-trimoxazole*" or cotrimoxazole*):ti,ab,kw |
| 38       | #69        | cycloserine*:ti,ab,kw                          |
| 39       | #70        | fosfomycin*:ti,ab,kw                           |
| 40       | #71        | gentam?cin*:ti,ab,kw                           |
| 41       | #72        | "nalidixic acid*":ti,ab,kw                     |
| 42       | #73        | nitrofurantoin*:ti,ab,kw                       |
| 43       | #74        | penicillin*:ti,ab,kw                           |
| 44       | #75        | piperacillin*:ti,ab,kw                         |
| 45       | #76        | pivampicillin*:ti,ab,kw                        |
| 46<br>47 | #70<br>#77 | pivmecillinam*:ti,ab,kw                        |
| 47<br>48 |            | sulfadimethoxine*:ti,ab,kw                     |
| 48       | #78<br>#70 |  |
| 50       | #79<br>#00 | sulfadiazine*:ti,ab,kw                         |
| 51       | #80<br>#81 | sulfamethizole*:ti,ab,kw                       |
| 52       | #81        | sulfamethoxazole*:ti,ab,kw                     |
| 53       | #82        | sulfamethoxypyridazine*:ti,ab,kw               |
| 54       | #83        | sulfonamide*:ti,ab,kw                          |
| 55       | #84        | sulphadimidine*:ti,ab,kw                       |
| 56       | #85        | sulphonamide*:ti,ab,kw                         |
| 57       |            |  |
| 58       |            |  |

| 2        |            |   |
|----------|------------|---|
| 3        | #86        | tetracycline*:ti,ab,kw  |
| 4        | #80<br>#87 | vancomycin*:ti,ab,kw  |
| 5        | #88        | {or #44-#87}  |
| 6        | #89        | [mh Pregnancy]  |
| 7<br>8   | #90        | [mh ^"Pregnancy Complications, Infectious"]   |
| 9        | #91        | [mh ^"Pregnant Women"]  |
| 10       | #92        | [mh ^"Prenatal Care"]   |
| 11       | #93        | [mh ^"Prenatal Diagnosis"]  |
| 12       | #94        | (antenatal* or "pre-natal*" or prenatal*):ti,ab,kw  |
| 13       | #95        | (expect* near/1 (female* or mother* or wom?n)):ti,ab,kw   |
| 14       | #96        | pregnan*:ti,ab,kw   |
| 15       | #97        | {or #89-#96}  |
| 16<br>17 | #98        | #88 and #97   |
| 18       | #99        | [mh ^"Choice Behavior"]   |
| 19       | #100       | [mh ^"Consumer Behavior" [mj]]  |
| 20       | #101       | [mh "Consumer Participation"]   |
| 21       | #102       | [mh ^"Cooperative Behavior"]  |
| 22       | #103       | [mh "Decision Making"]  |
| 23       | #104       | [mh ^"Focus Groups"]  |
| 24       | #105       | [mh ^"Health Care Surveys"]   |
| 25<br>26 | #106       | [mh "Informed Consent"]   |
| 20       | #107       | [mh ^"Interviews as Topic"]   |
| 28       | #108       | [mh ^"Patient Acceptance of Health Care"]   |
| 29       | #109       | [mh "Patient Education as Topic"]   |
| 30       | #110       | [mh ^"Patient Participation"]   |
| 31       | #111       | [mh ^"Patient Preference"]  |
| 32       | #112       | [mh ^"Social Values"]   |
| 33<br>34 | #113       | [mh ^"Surveys and Questionnaires"]  |
| 35       | #114       | [mh ^"Treatment Refusal"]   |
| 36       | #115       | (15D* and (HRQoL or QoL or "quality of life")):ti,ab,kw   |
| 37       | #116       | ((accept* or consider* or choice? or choos* or chose? or decid* or decis* or input* or involv*    |
| 38       | or opir    | nion* or participat* or perceiv* or percepti* or perspective? or prefer* or refus* or respons* or |
| 39       | valuati    | ion or value? or valuing or view*) near/3 (citizen? or client? or consumer? or female? or male?   |
| 40       | or mer     | n or patient? or public or stake?holder* or user? or wom?n)):ti,ab,kw                             |
| 41       | #117       | ((analys?s or valuation? or value? or valuing) near/3 (conjoint or contingent)):ti,ab,kw          |
| 42<br>43 | #118       | (choice? near/2 (behavio?r* or discrete or experiment*)):ti,ab,kw                                 |
| 44       | #119       | ((choice? or choos* or consent* or decision*) near/1 informed):ti,ab,kw                           |
| 45       | #120       | ((choice? or choos* or decision*) near/2 (made or make or makes or making or shar* or             |
| 46       | suppor     | rt*)):ti,ab,kw  |
| 47       | #121       | ("EQ 5D" or EQ5D or "EuroQoL 5D" or EuroQoL5D):ti,ab,kw   |
| 48       | #122       | ("focus group?" or interview* or questionnaire? or survey*):ti,ab,kw                              |
| 49       | #123       | gambl*:ti,ab,kw   |
| 50<br>51 | #124       | "health utilit*":ti,ab,kw   |
| 51<br>52 | #125       | HUI:ti,ab,kw  |
| 53       | #126       | ("multi-attribute" or "multi-criteria" or multiattribute or multicriteria):ti,ab,kw               |
| 54       | #127       | (preference? near/1 (elicit* or scor* or state*)):ti,ab,kw  |
| 55       | #128       | "prospect theor*":ti,ab,kw  |
| 56       | #129       | ("SF 12" or "SF 36" or "SF 6D" or SF12 or SF36 or SF6D):ti,ab,kw                                  |
| 57       |            |   |
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| 59<br>60 |            | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                         |
| 00       |            |   |

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> 57 58 59

> 60

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#130

#131

#132

#133

#134

#135

("trade off?" or tradeoff?):ti,ab,kw

(willing\* near/2 pay\*):ti,ab,kw

{or #99-#131}

#43 and #132

#98 and #132

#133 or #134

**KQ2: Women's Outcome Valuation** Database: Ovid PsycINFO 1806 to June Week 5 2016 Date Searched: 5 July 2016 **Records Retrieved: 113** 1. Bacterial Disorders/ and (bladder\* or genitourin\* or kidney\* or urin\* or urogenita\*).mp. 2. Infectious Disorders/ and (bladder\* or genitourin\* or kidney\* or urin\* or urogenita\*).mp. 3. Urinary Function Disorders/ and infection\*.mp. 4. Urogenital Disorders/ and infection\*.mp. 5. bacilluria\*.mp. 6. bacteriuria\*.mp. 7. cystiti\*.mp. 8. (cysto-pyeliti\* or cystopyeliti\*).mp. 9. dysuria\*.mp. 10. (infection\* adj2 (bladder\* or genitourin\* or kidney\* or urin\* or urogenita\*)).mp. 11. (pyelo-cystiti\* or pyelocystiti\*).mp. 12. (pyelo-nephriti\* or pyelonephriti\*).mp. 13. (UTI or UTIs).mp. 14. or/1-13 [Combined subject headings & text words for bacteriuria] 15. Health Screening/ 207/ 16. Screening/ 17. Screening Tests/ 18. Test Reliability/ 19. exp Test Validity/ 20. Urinalysis/ 21. ((accurac\* or diagnostic) adj5 (algorithm\* or test\*)).ti,ab. 22. diagnostic accurac\*.ti,ab. 23. culture\*.ti,ab. 24. (detect\* or predict\* or screen\*).ti,ab. 25. (dip slide\* or dipslide\* or dip stick\* or dipstick\*).ti,ab. 26. (micro-scopy or microscopy).ti,ab. 27. (microb\* adj2 test\*).ti,ab. 28. ((re-agent\* or reagent) adj3 (strip\* or test\*)).ti,ab. 29. strip\* test\*.ti,ab. 30. urine test\*.ti,ab. 31. (urinalys\* or urine analys\*).ti,ab. 32. uriscreen.ti,ab. 33. or/15-32 [Combined subject headings & text words for screening] 34. and/14,33 [Combined searches for ASB and screening] 35. antibiotics/

| 1  |  |
|----|--|
| 2  |  |
| 3  | 36. penicillins/   |
| 4  | 37. amoxicillin*.mp.   |
| 5  |  |
| 6  | 38. ampicillin*.mp.  |
| 7  | 39. (anti-bacteria* or antibacteria*).mp.  |
| 8  | 40. (anti-biotic* or antibiotic*).mp.  |
| 9  | 41. aztreonam <sup>*</sup> .mp.  |
| 10 | 42. cefadroxil*.mp.  |
| 11 | 43. cefepime*.mp.  |
| 12 | 44. ceftibuten*.mp.  |
| 13 |  |
| 14 | 45. ceftri?xone*.mp.   |
| 15 | 46. cefuroxime*.mp.  |
| 16 | 47. cephalexin*.mp.  |
| 17 | 48. cephalosporin*.mp.   |
| 18 | 49. cephradine*.mp.  |
| 19 | 50. clindamycin*.mp.   |
| 20 | 51. (co-trimoxazole <sup>*</sup> or cotrimoxazole <sup>*</sup> ).mp.   |
| 21 | 52. cycloserine*.mp.   |
| 22 | 53. fosfomycin*.mp.  |
| 23 |  |
| 24 | 54. gentam#cin*.mp.  |
| 25 | 55. nalidixic acid*.mp.  |
| 26 | 56. nitrofurantoin*.mp.  |
| 27 | 57. penicillin*.mp.  |
| 28 | 58. piperacillin*.mp.  |
| 29 | 59. pivampicillin*.mp.   |
| 30 | 60. pivmecillinam*.mp.   |
| 31 | 61. sulfadimethoxine*.mp.  |
| 32 |  |
| 33 | 62. sulfadiazine*.mp.  |
| 34 | 63. sulfamethizole*.mp.  |
| 35 | 64. sulfamethoxazole*.mp.  |
| 36 | 65. sulfamethoxypyridazine*.mp.  |
| 37 | 66. sulfonamide*.mp.   |
| 38 | 67. sulphadimidine*.mp.  |
| 39 | 68. sulphonamide*.mp.  |
| 40 | 69. tetracycline*.mp.  |
| 41 | 70. vancomycin*.mp.  |
| 42 | 71. or/35-70 [Combined subject headings & text words for antibiotic treatment]   |
| 43 |  |
| 44 | 72. adolescent pregnancy/  |
| 45 | 73. pregnancy/   |
| 46 | 74. prenatal care/   |
| 47 | 75. (antenatal* or pre-natal* or prenatal*).ti,ab.   |
| 48 | 76. (expect* adj (female? or mother? or wom#n)).ti,ab.   |
| 49 | 77. pregnan*.mp.   |
| 50 | 78. or/72-77 [Combined subject headings & text words for pregnancy]  |
| 51 | 79. and/71,78 [Combined searches for antibiotic treatment and pregnancy]   |
| 52 | 80. Choice Behavior/   |
| 53 |  |
| 54 | 81. Client Attitudes/  |
| 55 | 82. Client Participation/  |
| 56 | 83. Client Rights/   |
| 57 |  |
| 58 |  |
| 59 | For poor routing only there is a set of the late of th |
| 60 | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.   |
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| 1        |   |
|----------|---|
| 2        |   |
| 3        | 84. Cooperation/  |
| 4<br>5   | 85. Decision Making/  |
| 5<br>6   | 86. *Consumer Behavior/   |
| 7        | 87. Informed Consent/   |
| 8        | 88. Interviews/   |
| 9        | 89. Preferences/  |
| 10       | 90. Questionnaires/   |
| 11       | 91. Social Values/  |
| 12       | 92. Surveys/  |
| 13       | 93. Treatment Barriers/   |
| 14       | •   |
| 15       | 94. Treatment Refusal/  |
| 16       | 95. (15D* and (HRQoL or QoL or "quality of life")).mp.  |
| 17       | 96. ((accept* or consider* or choice? or choos* or chose? or decid* or decis* or input* or involv* or   |
| 18       | opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or respons* or valuation or |
| 19       | value? or valuing or view*) adj3 (citizen? or client? or consumer? or female? or male? or men or        |
| 20       | patient? or public or stake?holder* or user? or wom#n)).ti,ab.  |
| 21       | 97. ((analys#s or valuation? or value? or valuing) adj3 (conjoint or contingent)).ti,ab.                |
| 22       | 98. (choice? adj2 (behavio?r* or discrete or experiment*)).mp.  |
| 23       | 99. ((choice? or choos* or consent* or decision*) adj1 informed).ti,ab.                                 |
| 24<br>25 | 100. ((choice? or choos* or decision*) adj2 (made or make or makes or making or shar* or                |
| 25<br>26 | support*)).ti,ab.   |
| 20       | 101. (EQ 5D or EQ5D or EuroQoL 5D or EuroQoL5D).mp.   |
| 28       | 102. (focus group? or interview* or questionnaire? or survey*).ti,ab.                                   |
| 29       | 103. gambl*.ti,ab.  |
| 30       | 104. health utilit*.ti,ab.  |
| 31       | 105. HUI.mp.  |
| 32       | 106. (multi?attribute or multi?criteria).mp.  |
| 33       |   |
| 34       | 107. (preference? adj1 (elicit* or scor* or state*)).mp.  |
| 35       | 108. prospect theor*.ti,ab.   |
| 36       | 109. (SF 12 or SF 36 or SF 6D or SF12 or SF36 or SF6D).mp.  |
| 37       | 110. (trade off? or tradeoff?).ti,ab.   |
| 38       | 111. (willing* adj2 pay*).ti,ab.  |
| 39       | 112. or/80-111 [Combined subject & text words for patient preferences & values]                         |
| 40       | 113. and/34,112 [Combined searches for patient preferences & ASB screening]                             |
| 41<br>42 | 114. and/79,112 [Combined searches for patient preferences & antibiotic treatment and pregnancy]        |
| 42       | 115. or/113-114 [Combined sets of patient preferences for ASB screening & patient preferences for       |
| 44       | antibiotic treatment in pregnancy]  |
| 45       | 116. (boy* or male* or men).ti.   |
| 46       | 117. 115 not 116 [Male records excluded]  |
| 47       | 118. (case report* or comment* or editorial or letter).ti.  |
| 48       | 119. 117 not 118 [Opinion pieces & case reports excluded]   |
| 49       | 120. limit 119 to (english or french)   |
| 50       | 121. remove duplicates from 120   |
| 51       |   |
| 52       |   |
| 53       | KQ2: Women's Outcome Valuation  |
| 54       |   |
| 55       | Database: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost                                |
| 56<br>57 | Date Searched: 5 July 2016  |
| 57       |   |
| 58<br>50 |   |
| 59       | For peer review only - http://bmiopen.hmi.com/site/about/quidelines.yhtml                               |

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| 1        |  |
|----------|--|
| 2        |  |
| 3        | Records Retrieved: 872   |
| 4        |  |
| 5        | S1. (MH "Bacteriuria")   |
| 6        | S2. (MH "Cystitis+")   |
| 7        | S3. (MH "Dysuria")   |
| 8        |  |
| 9        | S4. (MH "Pyelonephritis")  |
| 10<br>11 | S5. (MH "Urinary Tract Infections")  |
| 12       | S6. bacilluria*  |
| 13       | S7. bacteriuria*   |
| 14       | S8. cystiti*   |
| 15       | S9. "cysto-pyeliti*" or cystopyeliti*  |
| 16       | S10. dysuria*  |
| 17       | S11. (infection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))   |
| 18       | S12. "pyelo-cystiti*" or pyelocystiti*   |
| 19       | S13. "pyelo-nephriti*" or pyelonephriti*   |
| 20       | S14. UTI or UTIs   |
| 21       | S15. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14   |
| 22       | S16. (MM "Bacteriuria/DI/PC/MI/UR")  |
| 23       | S17. (MM "Cystitis+/DI/MI/PC/UR")  |
| 24       | S18. (MH "Fluorescent Antibody Technique")   |
| 25       | S19. (MH "Health Screening")   |
| 26       |  |
| 27       | S20. (MH "Microbial Culture and Sensitivity Tests")  |
| 28       | S21. (MH "Microscopy")   |
| 29       | S22. (MH "Predictive Value of Tests")  |
| 30<br>31 | S23. (MM "Pyelonephritis/DI/PC/MI/UR")   |
| 32       | S24. (MH "Reagent Kits, Diagnostic+")  |
| 33       | S25. (MH "Sensitivity and Specificity")  |
| 34       | S26. (MH "Urinalysis")   |
| 35       | S27. (MM "Urinary Tract Infections/DI/PC/MI/UR")   |
| 36       | S28. (accurac* or diagnostic) N5 (algorithm* or test*)   |
| 37       | S29. "diagnostic accurac*"   |
| 38       | S30. culture*  |
| 39       | S30. culture*<br>S31. detect* or predict* or screen*<br>S32. "dip slide*" or dipslide* or "dip stick*" or dipstick*<br>S33. "micro-scopy" or microscopy<br>S24. microb* N2 test* |
| 40       | S32. "dip slide*" or dipslide* or "dip stick*" or dipstick*  |
| 41       | S33. "micro-scopy" or microscopy   |
| 42       | S34. microb* N2 test*  |
| 43       | S35. ("re-agent*" or reagent) N3 (strip* or test*)   |
| 44       | S36. "strip* test*"  |
| 45       | ·  |
| 46       | S37. "urine test*"   |
| 47       | S38. urinalys* or "urine analys*"  |
| 48       | S39. uriscreen   |
| 49<br>50 | S40. S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28   |
| 51       | OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39   |
| 52       | S41. S15 AND S40 [Combined searches for ASB and screening]   |
| 53       | S42. (MH "Antibiotic Prophylaxis")   |
| 54       | S43. (MH "Antibiotics")  |
| 55       | S44. (MH "Antibiotics, Combined")  |
| 56       | S45. (MH "Antiinfective Agents, Urinary+")   |
| 57       |  |
| 58       |  |
| 59       |  |

|               | S46. (MM "Bacteriuria/DT/TH")  |
|---------------|--|
|               | S47. (MH "Penicillins")  |
|               | S48. (MH "Sulfonamides")   |
|               | S49. (MM "Urinary Tract Infections/DT/TH")   |
|               | S50. amoxicillin*  |
|               | S51. ampicillin*   |
| )             | S52. ("anti-bacteria*" or antibacteria*)   |
|               | S53. ("anti-biotic*" or antibiotic*)   |
| 2             | S54. aztreonam*  |
| ,<br>1        | S55. cefadroxil*   |
| 5             | S56. cefepime*   |
| 5             | S57. ceftibuten*   |
| 7             | S58. ceftri?xone*  |
| 3             | S59. cefuroxime*   |
| )             | S60. cephalexin*   |
| )             | S61. cephalosporin*  |
| )             | S62. cephradine*   |
| -<br>}        | S63. clindamycin*  |
| ŀ             | S64. ("co-trimoxazole*" or cotrimoxazole*)   |
| 5             | S65. cycloserine*  |
| 5             | S66. fosfomycin*   |
| 7             | S67. gentam?cin*<br>S68. "nalidixic acid*"   |
| 3             |  |
| ,<br>)        | S69. nitrofurantoin*   |
| ,<br>         | S70. penicillin*   |
| <u>2</u>      | S71. piperacillin*<br>S72. pivampicillin*  |
| 3             | S72. pivmpcillinam*  |
| ł             | S74. sulfadimethoxine*   |
| 5             | S75. sulfadiazine*   |
| )<br>7        | S76. sulfamethizole*   |
| 3             | S77. sulfamethoxazole*   |
| )             | S78. sulfamethoxypyridazine*   |
| )             | S79. sulfonamide*  |
|               | S80. sulphadimidine*   |
| 2             | S81. sulphonamide*   |
| 5             | S82. tetracycline*   |
| +             | S83. vancomycin*   |
| 5             | S84. S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 |
| 7             | OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67   |
| 3             | OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80   |
| )             | OR S81 OR S82 OR S83   |
| )             | S85. (MH "Expectant Mothers")  |
|               | S86. (MH "Pregnancy+")   |
| <u>-</u><br>} | S87. (MH "Pregnancy Complications, Infectious")  |
| ,<br>         | S88. (MH "Prenatal Care")  |
| 5             | S89. (MH "Prenatal Diagnosis")   |
| 5             | S90. antenatal* or "pre-natal*" or prenatal*   |
| 7             |  |

| 1        |   |
|----------|---|
| 2        |   |
| 3        | S91. expect* N1 (female? or mother? or wom?n)   |
| 4        | S92. pregnan*   |
| 5        | S93. S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92   |
| 6        | S94. S84 AND S93  |
| 7<br>8   | S95. (MH "Consumer Participation")  |
| 9        | S96. (MH "Consensus")   |
| 10       | S97. (MH "Consent+")  |
| 11       | S98. (MH "Cooperative Behavior")  |
| 12       | S99. (MH "Decision Making")   |
| 13       |   |
| 14       | S100. (MH "Decision Making, Patient")   |
| 15       | S101. (MH "Dissent and Disputes+")  |
| 16       | S102. (MH "Focus Groups")   |
| 17       | S103. (MH "Interviews+")  |
| 18       | S104. (MH "Patient Education")  |
| 19       | S105. (MH "Quality of Health Care")   |
| 20       | S106. (MH "Questionnaires+")  |
| 21       | S107. (MH "Self Report")  |
| 22<br>23 | S108. (MH "Social Values+")   |
| 23<br>24 | S109. (MH "Surveys")  |
| 25       | S110. (MH "Treatment Refusal")  |
| 26       | S111. (15D* and (HRQoL or QoL or "quality of life"))  |
| 27       | S112. ((accept* or consider* or choice* or choos* or chose* or decid* or decis* or input* or involv*    |
| 28       | or opinion* or participat* or perceiv* or percepti* or perspective* or prefer* or refus* or respons* or |
| 29       | valuation or value* or valuing or view*) N3 (citizen* or client* or consumer* or female* or male* or    |
| 30       | men or patient* or public or "stake-holder*" or stakeholder* or user* or wom?n))                        |
| 31       | S113. ((analys?s or valuation* or value* or valuing) N3 (conjoint or contingent))                       |
| 32       | S114. (choice* N2 (behavio* or discrete or experiment*))  |
| 33       | S115. ((choice* or choos* or consent* or decision*) N1 informed)  |
| 34       | S116. ((choice* or choos* or decision*) N2 (made or make or makes or making or shar* or support*))      |
| 35       | S117. ("EQ 5D" or EQ5D or "EuroQoL 5D" or EuroQoL5D)  |
| 36<br>37 | S118. ("focus group*" or interview* or questionnaire* or survey*)                                       |
| 38       | S119. gambl*  |
| 39       | S120. "health utilit*"  |
| 40       | S120. Health duint  |
| 41       |   |
| 42       | S122. ("multi-attribute" or "multi-criteria" or multiattribute or multicriteria)                        |
| 43       | S123. (preference* N1 (elicit* or scor* or state*))<br>S124. "prospect theor*"                          |
| 44       |   |
| 45       | S125. ("SF 12" or "SF 36" or "SF 6D" or SF12 or SF36 or SF6D)   |
| 46       | S126. ("trade off*" or tradeoff*)   |
| 47       | S127. (willing* N2 pay*)  |
| 48       | S128. S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR                |
| 49<br>50 | S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR                 |
| 50<br>51 | S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127                    |
| 52       | S129. S41 AND S128  |
| 53       | S130. S94 AND S128  |
| 54       | S131. S129 OR S130  |
| 55       | S132. MH "Male" NOT ((MH "Female") AND (MH "Male"))   |
| 56       | S133. S131 NOT S132   |
| 57       |   |
| 58       |   |
| 59       |   |

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S134. ((MH "Vertebrates+") NOT MH Human)
S135. S133 NOT S134
S136. Limiters - Publication Type: Anecdote, Case Study, Commentary, Editorial, Letter
S137. S135 NOT S136
S138. S135 NOT S136 Narrow by Language: - english [RF: No French records in results to include]

# KQ2: Women's Outcome Valuation Database: PubMed via NCBI Entrez (1946 to Present) Date Searched: 5 July 2016 Records Retrieved: 65

(((((("asymptomatic infections"[mh] AND (("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields]) OR ("bacteriuria" [MeSH Terms] OR "bacteriuria" [All Fields] OR "bacteriurias" [All Fields]) OR ("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields]) OR ("cystitis"[MeSH Terms] OR "cystitis"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields]) OR ("pyelocystitis"[MeSH Terms] OR "pyelocystitis"[All Fields]) OR ("pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]) OR ("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR ("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) OR UTI[all] OR ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections" [All Fields] OR "utis" [All Fields]))) OR "bacteriuria" [MeSH Terms: no exp] OR "cystitis" [MeSH Terms] OR "dysuria" [MeSH Terms: noexp] OR "pyelonephritis" [MeSH Terms:noexp] OR "Urinary Tract Infections" [mh:noexp] OR bacilluria[tiab] OR bacteriuria[tiab] OR bacteriurias[tiab] OR "bladder infection"[tiab] OR "bladder infections"[tiab] OR cystitis[tiab] OR cystopyelitis[tiab] OR dysuria[tiab] OR "genito-urinary infection"[tiab] OR "genitourinary infection"[tiab] OR "genito-urinary infections"[tiab] OR "genitourinary infections"[tiab] OR "kidney infection"[tiab] OR "kidney infections"[tiab] OR "pyelo-nephritis"[tiab] OR pyelocystitis[tiab] OR pyelonephritis[tiab] OR "urinary infection"[tiab] OR "urinary infections"[tiab] OR "urogenital infection"[tiab] OR "urogenital infections"[tiab] OR UTI[tiab] OR UTIs[tiab]) AND ("Antibody-Coated Bacteria Test, Urinary"[mh] OR "Bacteriuria/diagnosis"[Majr] OR "Bacteriuria/prevention and control"[Majr] OR ("bacteriuria/microbiology"[Mesh Terms] AND Majr[All Fields]) OR "Bacteriuria/urine"[Majr] OR "Cystitis/diagnosis"[Majr] OR "Cystitis/prevention and control"[Majr] OR "Cystitis/microbiology"[Majr] OR "Cystitis/urine"[Majr] OR "Mass Screening"[mh:noexp] OR "Microbial Sensitivity Tests"[mh:noexp] OR "Microscopy"[mh:noexp] OR "Predictive Value of Tests"[mh:noexp] OR "Pyelonephritis/diagnosis"[Majr] OR "Pyelonephritis/prevention and control" [Majr] OR "Pyelonephritis/microbiology" [Majr] OR "Pyelonephritis/urine" [Majr] OR "Reagent Kits, Diagnostic"[mh:noexp] OR "Reagent Strips"[mh:noexp] OR "Sensitivity and Specificity"[mh:noexp] OR "Urinalysis"[mh:noexp] OR "Urinary Tract Infections/diagnosis"[Majr] OR "Urinary Tract Infections/prevention and control"[Majr] OR "Urinary Tract Infections/microbiology" [Majr] OR "Urinary Tract Infections/urine" [Majr] OR detect[tiab] OR detected[tiab] OR detection[tiab] OR detecting[tiab] OR detects[tiab] OR "diagnostic accuracy"[tiab] OR "diagnostic algorithm"[tiab] OR "dip slide"[tiab] OR "dip slides"[tiab] OR "dip stick"[tiab] OR "dip sticks"[tiab] OR dipslide[tiab] OR dipslides[tiab] OR dipstick[tiab] OR dipsticks[tiab] OR culture[tiab] OR cultures[tiab] OR "diagnostic test"[tiab] OR "diagnostic tests"[tiab] OR "microbial test"[tiab] OR "microbial tests"[tiab] OR microscopy[tiab] OR predict[tiab] OR predicted[tiab] OR prediction[tiab] OR predicting[tiab] OR predicts[tiab] OR "reagent strip"[tiab] OR "reagent strips"[tiab] OR "reagent

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#### **BMJ** Open

3 test"[tiab] OR "reagent testing"[tiab] OR "reagent tests"[tiab] OR screen[tiab] OR screened[tiab] OR 4 screening[tiab] OR screens[tiab] OR "strip test"[tiab] OR "strip tests"[tiab] OR "strip testing"[tiab] OR 5 "test accuracy"[tiab] OR urinalyses[tiab] OR urinalysis[tiab] OR "urine analyses"[tiab] OR "urine 6 analysis"[tiab] OR "urine test"[tiab] OR "urine tested"[tiab] OR "urine testing"[tiab] OR "urine 7 tests"[tiab] OR uriscreen[tiab])) AND ("Choice Behavior"[mh:noexp] OR "Consumer 8 Behavior"[majr:noexp] OR "Consumer Participation"[mh] OR "Cooperative Behavior"[mh:noexp] OR 9 10 "Decision Making"[mh] OR "Focus Groups"[mh:noexp] OR "Health Care Surveys"[mh:noexp] OR 11 "Informed Consent"[mh] OR "Interviews as Topic"[mh:noexp] OR "Patient Acceptance of Health 12 Care"[mh:noexp] OR "Patient Education as Topic"[mh] OR "Patient Participation"[mh] OR "Patient 13 Preference"[mh:noexp] OR "Social Values"[mh:noexp] OR "Surveys and Questionnaires"[mh:noexp] 14 OR "Treatment Refusal" [mh:noexp] OR (15D[tiab] AND (HRQoL[tiab] OR QoL[tiab] OR "quality of 15 life"[tiab])) OR ((accept[tiab] OR accepted[tiab] OR accepting[tiab] OR accepts[tiab] OR consider[tiab] 16 OR consideration[tiab] OR considerations[tiab] OR considered[tiab] OR considering[tiab] OR 17 considers[tiab] OR choice[tiab] OR choices[tiab] OR choose[tiab] OR choosing[tiab] 18 OR chose[tiab] OR chosen[tiab] OR decide[tiab] OR decided[tiab] OR deciding[tiab] OR decides[tiab] 19 20 OR decision[tiab] OR decisionmaker[tiab] OR decisionmaking[tiab] OR decisions[tiab] OR 21 decisive[tiab] OR input[tiab] OR involve[tiab] OR involved[tiab] OR involving[tiab] OR 22 involvement[tiab] OR involves[tiab] OR opinion[tiab] OR opinionated[tiab] OR opinions[tiab] OR 23 participate[tiab] OR participated[tiab] OR participating[tiab] OR participation[tiab] OR 24 participates[tiab] OR perceive[tiab] OR perceived[tiab] OR perceiving[tiab] OR perceives[tiab] OR 25 perception[tiab] OR perceptions[tiab] OR perceptive[tiab] OR perspective[tiab] OR perspectives[tiab] 26 OR prefer[tiab] OR preference[tiab] OR preferences[tiab] OR preferred[tiab] OR preferring[tiab] OR 27 refusal[tiab] OR refuse[tiab] OR refused[tiab] OR refusing[tiab] OR refuses[tiab] OR response[tiab] OR 28 29 responses[tiab] OR valuation[tiab] OR value[tiab] OR valued[tiab] OR values[tiab] OR valuing[tiab] OR 30 view[tiab] OR viewed[tiab] OR viewing[tiab] OR viewpoint[tiab] OR viewpoints[tiab] OR views[tiab]) 31 AND (citizen[tiab] OR citizens[tiab] OR client[tiab] OR clients[tiab] OR consumer[tiab] OR 32 consumers[tiab] OR female[tiab] OR females[tiab] OR male[tiab] OR males[tiab] OR men[tiab] OR 33 patient[tiab] OR patients[tiab] OR public[tiab] OR "stake-holder"[tiab] OR "stake-holders"[tiab] OR 34 stakeholder[tiab] OR stakeholders[tiab] OR user[tiab] OR users[tiab] OR woman[tiab] OR 35 women[tiab])) OR ((analyses[tiab] OR analysis[tiab] OR valuation[tiab] OR valuations[tiab] OR 36 value[tiab] OR values[tiab] OR valuing[tiab]) AND (conjoint[tiab] OR contingent[tiab])) OR "choice 37 behavior"[tiab] OR "choice behaviour"[tiab] OR "choice experiment"[tiab] OR "choice 38 39 experiments"[tiab] OR "discrete choice"[tiab] OR "EQ 5D"[tiab] OR EQ5D[tiab] OR "EuroQoL 5D"[tiab] 40 OR EuroQoL5D[tiab] OR "focus group"[tiab] OR "focus groups"[tiab] OR gamble[tiab] OR 41 gambled[tiab] OR gambling[tiab] OR gambles[tiab] OR "health utilities"[tiab] OR "health utility"[tiab] 42 OR HUI[tiab] OR "informed choice"[tiab] OR "informed choices"[tiab] OR "informed consent"[tiab] OR 43 "informed decision"[tiab] OR interview[tiab] OR interviewed[tiab] OR interviewing[tiab] OR 44 interviews[tiab] OR "multi-attribute"[tiab] OR "multi-criteria"[tiab] OR multiattribute[tiab] OR 45 multicriteria[tiab] OR "preference score"[tiab] OR "preference scores"[tiab] OR "preference 46 47 scoring"[tiab] OR "prospect theory"[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR "SF 48 12"[tiab] OR "SF 36"[tiab] OR "SF 6D"[tiab] OR SF12[tiab] OR SF36[tiab] OR SF6D[tiab] OR "stated 49 preference"[tiab] OR survey[tiab] OR surveyed[tiab] OR surveys[tiab] OR "trade off"[tiab] OR "trade 50 offs"[tiab] OR tradeoff[tiab] OR tradeoffs[tiab] OR "willing to pay"[tiab] OR "willingness to pay"[tiab])) 51 OR ((("Anti-Bacterial Agents"[mh:noexp] OR "Antibiotic Prophylaxis"[mh:noexp] OR "Anti-Infective 52 Agents, Urinary"[mh] OR "Asymptomatic Infections/therapy"[mh] OR "Bacteriuria/drug 53 therapy"[Majr] OR "Bacteriuria/therapy"[Majr] OR "Drug Therapy, Combination"[mh:noexp] OR 54 "Norfloxacin"[mh:noexp] OR "Penicillins"[mh] OR "Sulfonamides"[mh] OR "Urinary Tract 55 Infections/drug therapy"[Majr] OR "Urinary Tract Infections/therapy"[Majr] OR amoxicillin[tiab] OR 56 57 58

#### **BMJ** Open

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> amoxicillins[tiab] OR ampicillin[tiab] OR ampicillins[tiab] OR "anti-bacteria"[tiab] OR "antibacterial"[tiab] OR "anti-bacterials"[tiab] AND "anti-biotic"[tiab] OR "anti-biotics"[tiab] OR antibacteria[tiab] OR antibacterial[tiab] OR antibacterials[tiab] OR antibiotic[tiab] OR antibiotics[tiab] OR aztreonam[tiab] OR cefadroxil[tiab] OR cefepime[tiab] OR ceftibuten[tiab] OR ceftriaxone[tiab] OR cefuroxime[tiab] OR cephalexin[tiab] OR cephalosporin[tiab] OR cephalosporins[tiab] OR cephradine[tiab] OR clindamycin[tiab] OR "co-trimoxazole"[tiab] OR cotrimoxazole[tiab] OR cycloserine[tiab] OR cycloserines[tiab] OR fosfomycin[tiab] OR gentamicin[tiab] OR gentamycin[tiab] OR "nalidixic acid"[tiab] OR nitrofurantoin[tiab] OR penicillin[tiab] OR penicillins[tiab] OR piperacillin[tiab] OR pivampicillin[tiab] OR pivmecillinam[tiab] OR sulfadimethoxine[tiab] OR sulfadiazine[tiab] OR sulfamethizole[tiab] OR sulfamethoxazole[tiab] OR sulfamethoxypyridazine[tiab] OR sulfonamide[tiab] OR sulfonamides[tiab] OR sulphadimidine[tiab] OR sulphonamide[tiab] OR tetracycline[tiab] OR tetracyclines[tiab] OR vancomycin[tiab]) AND ("Pregnancy"[mh] OR "Pregnancy Complications, Infectious" [mh:noexp] OR "Pregnant Women" [mh:noexp] OR "Prenatal Care"[mh:noexp] OR "Prenatal Diagnosis"[mh:noexp] OR antenatal[tiab] OR "pre-natal"[tiab] OR prenatal[tiab] OR "expectant mother"[tiab] OR "expectant mothers"[tiab] OR "expecting mothers"[tiab] OR "expecting mothers"[tiab] OR "expectant woman"[tiab] OR "expectant women"[tiab] OR "expecting women"[tiab] OR pregnancies[tiab] OR pregnancy[tiab] OR pregnant[tiab])) AND ("Choice Behavior"[mh:noexp] OR "Consumer Behavior"[majr:noexp] OR "Consumer Participation"[mh] OR "Cooperative Behavior"[mh:noexp] OR "Decision Making"[mh] OR "Focus Groups"[mh:noexp] OR "Health Care Surveys"[mh:noexp] OR "Informed Consent"[mh] OR "Interviews as Topic"[mh:noexp] OR "Patient Acceptance of Health Care"[mh:noexp] OR "Patient Education as Topic"[mh] OR "Patient Participation"[mh] OR "Patient Preference"[mh:noexp] OR "Social Values"[mh:noexp] OR "Surveys and Questionnaires"[mh:noexp] OR "Treatment Refusal"[mh:noexp] OR (15D[tiab] AND (HRQoL[tiab] OR QoL[tiab] OR "quality of life"[tiab])) OR ((accept[tiab] OR accepted[tiab] OR accepting[tiab] OR accepts[tiab] OR consider[tiab] OR consideration[tiab] OR considerations[tiab] OR considered[tiab] OR considering[tiab] OR considers[tiab] OR choice[tiab] OR choices[tiab] OR choose[tiab] OR chooses[tiab] OR choosing[tiab] OR chose[tiab] OR chosen[tiab] OR decide[tiab] OR decided[tiab] OR deciding[tiab] OR decides[tiab] OR decision[tiab] OR decisionmaker[tiab] OR decisionmaking[tiab] OR decisions[tiab] OR decisive[tiab] OR input[tiab] OR involve[tiab] OR involved[tiab] OR involving[tiab] OR involvement[tiab] OR involves[tiab] OR opinion[tiab] OR opinionated[tiab] OR opinions[tiab] OR participate[tiab] OR participated[tiab] OR participating[tiab] OR participation[tiab] OR participates[tiab] OR perceive[tiab] OR perceived[tiab] OR perceiving[tiab] OR perceives[tiab] OR perception[tiab] OR perceptions[tiab] OR perceptive[tiab] OR perspective[tiab] OR perspectives[tiab] OR prefer[tiab] OR preference[tiab] OR preferences[tiab] OR preferred[tiab] OR preferring[tiab] OR refusal[tiab] OR refuse[tiab] OR refused[tiab] OR refusing[tiab] OR refuses[tiab] OR response[tiab] OR responses[tiab] OR valuation[tiab] OR value[tiab] OR valued[tiab] OR values[tiab] OR valuing[tiab] OR view[tiab] OR viewed[tiab] OR viewing[tiab] OR viewpoint[tiab] OR viewpoints[tiab] OR views[tiab]) AND (citizen[tiab] OR citizens[tiab] OR client[tiab] OR clients[tiab] OR consumer[tiab] OR consumers[tiab] OR female[tiab] OR females[tiab] OR male[tiab] OR males[tiab] OR men[tiab] OR patient[tiab] OR patients[tiab] OR public[tiab] OR "stake-holder"[tiab] OR "stake-holders"[tiab] OR stakeholder[tiab] OR stakeholders[tiab] OR user[tiab] OR users[tiab] OR woman[tiab] OR women[tiab])) OR ((analyses[tiab] OR analysis[tiab] OR valuation[tiab] OR valuations[tiab] OR value[tiab] OR values[tiab] OR valuing[tiab]) AND (conjoint[tiab] OR contingent[tiab])) OR "choice behavior"[tiab] OR "choice behaviour"[tiab] OR "choice experiment"[tiab] OR "choice experiments"[tiab] OR "discrete choice"[tiab] OR "EQ 5D"[tiab] OR EQ5D[tiab] OR "EuroQoL 5D"[tiab] OR EuroQoL5D[tiab] OR "focus group"[tiab] OR "focus groups"[tiab] OR gamble[tiab] OR gambled[tiab] OR gambling[tiab] OR gambles[tiab] OR "health utilities"[tiab] OR "health utility"[tiab]

OR HUI[tiab] OR "informed choice"[tiab] OR "informed choices"[tiab] OR "informed consent"[tiab] OR "informed decision"[tiab] OR interview[tiab] OR interviewed[tiab] OR interviewing[tiab] OR interviews[tiab] OR "multi-attribute"[tiab] OR "multi-criteria"[tiab] OR multiattribute[tiab] OR multicriteria[tiab] OR "preference score"[tiab] OR "preference scores"[tiab] OR "preference scoring"[tiab] OR "prospect theory"[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR "SF 12"[tiab] OR "SF 36"[tiab] OR "SF 6D"[tiab] OR SF12[tiab] OR SF36[tiab] OR SF6D[tiab] OR "stated preference"[tiab] OR survey[tiab] OR surveyed[tiab] OR surveys[tiab] OR "trade off"[tiab] OR "trade offs"[tiab] OR tradeoff[tiab] OR tradeoffs[tiab] OR "willing to pay"[tiab] OR "willingness to pay"[tiab]))) NOT ("Male"[mh] NOT ("Female"[mh] AND "Male"[mh]))) NOT (((Animals[MESH] OR Animal Experimentation[MESH] OR "Models, Animal"[MESH] OR Vertebrates[MESH]) NOT (Humans[MESH] OR Human experimentation[MESH])) OR (((animals[tiab] OR animal model[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR rabbit[tiab] OR rabbits[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR swine[tiab] OR dog[tiab] OR dogs[tiab] OR hamster[tiab] OR hamsters[tiab] OR chicken[tiab] OR chickens[tiab] OR sheep[tiab]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])) NOT (human[ti] OR humans[ti] OR people[ti] OR children[ti] OR adults[ti] OR seniors[ti] OR patient[ti] OR patients[ti]))) NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR newspaper article[pt])) AND ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)) > limit to English or French

# KQs4,5: Systematic Review & HTA Search

#### Database: PubMed via NCBI Entrez (1946 to Present) Date Searched: 14 October 2016

Records Retrieved: 104

((((((("asymptomatic infections"[mh] AND (("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields]) OR ("bacteriuria" [MeSH Terms] OR "bacteriuria" [All Fields] OR "bacteriurias" [All Fields]) OR ("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields]) OR ("cystitis"[MeSH Terms] OR "cystitis"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields]) OR ("pyelocystitis"[MeSH Terms] OR "pyelocystitis"[All Fields]) OR ("pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]) OR ("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR ("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) OR UTI[all] OR ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections" [All Fields] OR "utis" [All Fields]))) OR "bacteriuria" [MeSH Terms: noexp] OR "cystitis"[MeSH Terms] OR "dysuria"[MeSH Terms:noexp] OR "pyelonephritis"[MeSH Terms:noexp] OR "Urinary Tract Infections"[mh:noexp] OR bacilluria[tiab] OR bacteriuria[tiab] OR bacteriurias[tiab] OR "bladder infection"[tiab] OR "bladder infections"[tiab] OR cystitis[tiab] OR cystopyelitis[tiab] OR dysuria[tiab] OR "genito-urinary infection"[tiab] OR "genitourinary infection"[tiab] OR "genito-urinary infections"[tiab] OR "genitourinary infections"[tiab] OR "kidney infection"[tiab] OR "kidney infections"[tiab] OR "pyelo-nephritis"[tiab] OR pyelocystitis[tiab] OR pyelonephritis[tiab] OR "urinary infection"[tiab] OR "urinary infections"[tiab] OR "urogenital infection"[tiab] OR "urogenital infections"[tiab] OR UTI[tiab] OR UTIs[tiab]) AND (("Antibody-Coated Bacteria Test, Urinary"[mh] OR "Bacteriuria/diagnosis"[Majr] OR "Bacteriuria/prevention and control"[Majr] OR ("bacteriuria/microbiology"[Mesh Terms] AND Majr[All Fields]) OR "Bacteriuria/urine"[Majr] OR "Cystitis/diagnosis"[Majr] OR "Cystitis/prevention and control"[Majr] OR

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"Cystitis/microbiology"[Majr] OR "Cystitis/urine"[Majr] OR "Mass Screening"[mh:noexp] OR "Microbial Sensitivity Tests"[mh:noexp] OR "Microscopy"[mh:noexp] OR "Predictive Value of Tests"[mh:noexp] OR "Pyelonephritis/diagnosis"[Majr] OR "Pyelonephritis/prevention and control" [Majr] OR "Pyelonephritis/microbiology" [Majr] OR "Pyelonephritis/urine" [Majr] OR "Reagent Kits, Diagnostic"[mh:noexp] OR "Reagent Strips"[mh:noexp] OR "Sensitivity and Specificity"[mh:noexp] OR "Urinalysis"[mh:noexp] OR "Urinary Tract Infections/diagnosis"[Majr] OR "Urinary Tract Infections/prevention and control"[Majr] OR "Urinary Tract Infections/microbiology"[Majr] OR "Urinary Tract Infections/urine"[Majr] OR detect[tiab] OR detected[tiab] OR detection[tiab] OR detecting[tiab] OR detects[tiab] OR "diagnostic accuracy"[tiab] OR "diagnostic algorithm"[tiab] OR "dip slide"[tiab] OR "dip slides"[tiab] OR "dip stick"[tiab] OR "dip sticks"[tiab] OR dipslide[tiab] OR dipslides[tiab] OR dipstick[tiab] OR dipsticks[tiab] OR culture[tiab] OR cultures[tiab] OR "diagnostic test"[tiab] OR "diagnostic tests"[tiab] OR "microbial test"[tiab] OR "microbial tests"[tiab] OR microscopy[tiab] OR predict[tiab] OR predicted[tiab] OR prediction[tiab] OR predicting[tiab] OR predicts[tiab] OR "reagent strip"[tiab] OR "reagent strips"[tiab] OR "reagent test"[tiab] OR "reagent testing"[tiab] OR "reagent tests"[tiab] OR screen[tiab] OR screened[tiab] OR screening[tiab] OR screens[tiab] OR "strip test"[tiab] OR "strip tests"[tiab] OR "strip testing"[tiab] OR "test accuracy"[tiab] OR urinalyses[tiab] OR urinalysis[tiab] OR "urine analyses"[tiab] OR "urine analysis"[tiab] OR "urine test"[tiab] OR "urine tested"[tiab] OR "urine testing"[tiab] OR "urine tests"[tiab] OR uriscreen[tiab]) OR ("Anti-Bacterial Agents"[mh:noexp] OR "Antibiotic Prophylaxis"[mh:noexp] OR "Anti-Infective Agents, Urinary"[mh] OR "Asymptomatic Infections/therapy"[mh] OR "Bacteriuria/drug therapy"[Majr] OR "Bacteriuria/therapy"[Majr] OR "Drug Therapy, Combination"[mh:noexp] OR "Norfloxacin"[mh:noexp] OR "Penicillins"[mh] OR "Sulfonamides"[mh] OR "Urinary Tract Infections/drug therapy"[Majr] OR "Urinary Tract Infections/therapy"[Majr] OR amoxicillin[tiab] OR amoxicillins[tiab] OR ampicillin[tiab] OR ampicillins[tiab] OR "anti-bacteria"[tiab] OR "anti-bacterial"[tiab] OR "anti-bacterials"[tiab] AND "antibiotic"[tiab] OR "anti-biotics"[tiab] OR antibacteria[tiab] OR antibacterial[tiab] OR antibacterials[tiab] OR antibiotic[tiab] OR antibiotics[tiab] OR aztreonam[tiab] OR cefadroxil[tiab] OR cefepime[tiab] OR ceftibuten[tiab] OR ceftriaxone[tiab] OR cefuroxime[tiab] OR cephalexin[tiab] OR cephalosporin[tiab] OR cephalosporins[tiab] OR cephradine[tiab] OR clindamycin[tiab] OR "co-trimoxazole"[tiab] OR cotrimoxazole[tiab] OR cycloserine[tiab] OR cycloserines[tiab] OR fosfomycin[tiab] OR gentamicin[tiab] OR gentamycin[tiab] OR "nalidixic acid"[tiab] OR nitrofurantoin[tiab] OR penicillin[tiab] OR penicillins[tiab] OR piperacillin[tiab] OR pivampicillin[tiab] OR pivmecillinam[tiab] OR sulfadimethoxine[tiab] OR sulfadiazine[tiab] OR sulfamethizole[tiab] OR sulfamethoxazole[tiab] OR sulfamethoxypyridazine[tiab] OR sulfonamide[tiab] OR sulfonamides[tiab] OR sulphadimidine[tiab] OR sulphonamide[tiab] OR tetracycline[tiab] OR tetracyclines[tiab] OR vancomycin[tiab]))) AND ("Pregnancy"[mh] OR "Pregnancy Complications, Infectious"[mh:noexp] OR "Pregnant Women"[mh:noexp] OR "Prenatal Care"[mh:noexp] OR "Prenatal Diagnosis"[mh:noexp] OR antenatal[tiab] OR "pre-natal"[tiab] OR prenatal[tiab] OR "expectant mother"[tiab] OR "expectant mothers"[tiab] OR "expecting mothers"[tiab] OR "expecting mothers"[tiab] OR "expectant woman"[tiab] OR "expectant women"[tiab] OR "expecting women"[tiab] OR pregnancies[tiab] OR pregnancy[tiab] OR pregnant[tiab])) AND (systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tiab] OR integrative review\*[tiab] OR integrative overview\*[tiab] OR research integration\*[tiab] OR research overview\*[tiab] OR collaborative review\*[tiab] OR collaborative overview\*[tiab] OR systematic review\*[tiab] OR technology assessment\*[tiab] OR technology overview\*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison\*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab])

AND comparison\*[tiab]) OR Embase\*[tiab] OR Cinahl\*[tiab] OR systematic overview\*[tiab] OR methodological overview\*[tiab] OR methodologic overview\*[tiab] OR methodological review\*[tiab] OR methodologic review\*[tiab] OR quantitative review\*[tiab] OR quantitative overview\*[tiab] OR quantitative synthes\*[tiab] OR pooled analy\*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch\*[tiab] OR hand search\*[tiab] OR metaregression\*[tiab] OR metaregression\*[tiab] OR data synthes\*[tiab] OR data extraction[tiab] OR data abstraction\*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect\*[tiab] OR "Cochrane Database Syst Rev"[Journal] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal])) NOT ("Male"[mh] NOT ("Female"[mh] AND "Male"[mh]))) NOT (((Animals[MESH] OR Animal Experimentation[MESH] OR "Models, Animal"[MESH] OR Vertebrates[MESH]) NOT (Humans[MESH] OR Human experimentation[MESH])) OR (((animals[tiab] OR animal model[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR rabbit[tiab] OR rabbits[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR swine[tiab] OR dog[tiab] OR dogs[tiab] OR hamster[tiab] OR hamsters[tiab] OR chicken[tiab] OR chickens[tiab] OR sheep[tiab]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])) NOT (human[ti] OR humans[ti] OR people[ti] OR children[ti] OR adults[ti] OR seniors[ti] OR patient[ti] OR patients[ti]))) NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR newspaper article[pt])

## KQs4,5: Systematic Review & HTA Search Database: Wiley Cochrane Library

Date Searched: 14 October 2016

Records Retrieved: 19 in Cochrane Database of Systematic Reviews Records Retrieved: 4 in Database of Abstracts of Reviews of Effects (DARE) Records Retrieved: 1 in Health Technology Assessment Database Records Retrieved: 3 in Economic Evaluations Database

#1 [mh ^"Asymptomatic Infections"] and (bacteriuria\* or bladder\* or cystitis\* or kidney\* or pyelo-cystiti\* or pyelo-nephriti\* or pyelonephriti\* or urin\* or UTI\*):ti,ab,kw

- #2 [mh ^Bacteriuria]
- #3 [mh Cystitis]
- #4 [mh ^Dysuria]
- #5 [mh ^Pyelonephritis]
- #6 [mh ^"Urinary Tract Infections"]
- #7 bacilluria\*:ti,ab,kw
  - #8 bacteriuria\*:ti,ab,kw
  - #9 cystiti\*:ti,ab,kw
  - #10 (cysto-pyeliti\* or cystopyeliti\*):ti,ab,kw
  - #11 dysuria\*:ti,ab,kw
  - #12 (infection\* near/2 (bladder\* or genitourin\* or kidney\* or urin\* or urogenita\*)):ti,ab,kw

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- #13 (pyelo-cystiti\* or pyelocystiti\*):ti,ab,kw
- #14 (pyelo-nephriti\* or pyelonephriti\*):ti,ab,kw
- #15 (UTI or UTIs):ti,ab,kw
- #16 {or #1-#15}

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| 4        | #17        | [mh ^"Antibody-Coated Bacteria Test, Urinary"]                    |
| 5        | #18        | [mh ^Bacteriuria [mj]/DI,PC,MI,UR]                                |
| 6        | #19        | [mh Cystitis [mj]/DI,PC,MI,UR]                                    |
| 7        | #20        | [mh ^"Mass Screening"]  |
| 8        | #21        | [mh ^"Microbial Sensitivity Tests"]                               |
| 9        | #22        | [mh ^Microscopy]  |
| 10       | #23        | [mh ^"Predictive Value of Tests"]                                 |
| 11       | #24        | [mh ^Pyelonephritis [mj]/DI,PC,MI,UR]                             |
| 12       | #25        | [mh "Reagent Kits, Diagnostic"]                                   |
| 13       | #26        | [mh "Reagent Strips"]   |
| 14       | #27        | [mh ^"Sensitivity and Specificity"]                               |
| 15       | #27        | [mh ^Urinalysis]  |
| 16       |            |   |
| 17       | #29        | [mh ^"Urinary Tract Infections" [mj]/DI,PC,MI,UR]                 |
| 18       | #30        | ((accurac* or diagnostic) near/5 (algorithm* or test*)):ti,ab,kw  |
| 19       | #31        | "diagnostic accurac*":ti,ab,kw                                    |
| 20       | #32        | culture*:ti,ab,kw   |
| 21       | #33        | (detect* or predict* or screen*):ti,ab,kw                         |
| 22       | #34        | ("dip slide*" or dipslide* or "dip stick*" or dipstick*):ti,ab,kw |
| 23<br>24 | #35        | (micro-scopy or microscopy):ti,ab,kw                              |
| 24<br>25 | #36        | (microb* near/2 test*):ti,ab,kw 🕥                                 |
| 26       | #37        | ((re-agent* or reagent) near/3 (strip* or test*)):ti,ab,kw        |
| 27       | #38        | "strip* test*":ti,ab,kw   |
| 28       | #39        | "urine test*":ti,ab,kw  |
| 29       | #40        | (urinalys* or "urine analys*"):ti,ab,kw                           |
| 30       | #41        | uriscreen:ti,ab,kw  |
| 31       | #42        | {or #17-#41}  |
| 32       | #43        | [mh ^"Anti-Bacterial Agents"]                                     |
| 33       | #43<br>#44 | [mh ^"Anti-bacterial Agents ]                                     |
| 34       |            |   |
| 35       | #45        | [mh ^"Anti-Infective Agents, Urinary"]                            |
| 36       | #46        | [mh ^"Asymptomatic Infections"/DT,TH]                             |
| 37       | #47        | [mh ^Bacteriuria [mj]/DT,TH]                                      |
| 38       | #48        | [mh ^"Drug Therapy, Combination"]                                 |
| 39       | #49        | [mh ^Norfloxacin]   |
| 40       | #50        | [mh Penicillins]  |
| 41<br>42 | #51        | [mh Sulfonamides]   |
| 43       | #52        | [mh ^"Urinary Tract Infections" [mj]/DT,TH]                       |
| 44       | #53        | amoxicillin*:ti,ab,kw   |
| 45       | #54        | ampicillin*:ti,ab,kw  |
| 46       | #55        | ("anti-bacteria*" or antibacteria*):ti,ab,kw                      |
| 47       | #56        | ("anti-biotic*" or antibiotic*):ti,ab,kw                          |
| 48       | #57        | aztreonam*:ti,ab,kw   |
| 49       | #58        | cefadroxil*:ti,ab,kw  |
| 50       | #59        | cefepime*:ti,ab,kw  |
| 51       | #60        | ceftibuten*:ti,ab,kw  |
| 52       | #00<br>#61 | ceftri?xone*:ti,ab,kw   |
| 53       | #61<br>#62 | cefuroxime*:ti,ab,kw  |
| 54       |            |   |
| 55       | #63        | cephalexin*:ti,ab,kw  |
| 56       | #64        | cephalosporin*:ti,ab,kw   |
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| 5        | #66        | clindamycin*:ti,ab,kw                                   |
| 6        | #67        | ("co-trimoxazole*" or cotrimoxazole*):ti,ab,kw          |
| 7        | #68        | cycloserine*:ti,ab,kw                                   |
| 8        | #69        | fosfomycin*:ti,ab,kw                                    |
| 9        | #70        | gentam?cin*:ti,ab,kw                                    |
| 10       | #71        | "nalidixic acid*":ti,ab,kw                              |
| 11       | #72        | nitrofurantoin*:ti,ab,kw                                |
| 12       | #73        | penicillin*:ti,ab,kw                                    |
| 13       | #74        | piperacillin*:ti,ab,kw                                  |
| 14       | #75        | pivampicillin*:ti,ab,kw                                 |
| 15       | #76        | pivmecillinam*:ti,ab,kw                                 |
| 16<br>17 | #77        | sulfadimethoxine*:ti,ab,kw                              |
| 18       | #78        | sulfadiazine*:ti,ab,kw                                  |
| 19       | #79        | sulfamethizole*:ti,ab,kw                                |
| 20       | #80        | sulfamethoxazole*:ti,ab,kw                              |
| 21       | #81        | sulfamethoxypyridazine*:ti,ab,kw                        |
| 22       | #81        | sulfonamide*:ti,ab,kw                                   |
| 23       | #82<br>#83 | sulphadimidine*:ti,ab,kw                                |
| 24       | #85<br>#84 |   |
| 25       |            | sulphonamide*:ti,ab,kw                                  |
| 26       | #85<br>#86 | tetracycline*:ti,ab,kw                                  |
| 27       | #86        | vancomycin*:ti,ab,kw                                    |
| 28       | #87        | {or #43-#86}  |
| 29       | #88        | #16 and (#42 or #87)                                    |
| 30<br>31 | #89        | [mh Pregnancy]  |
| 32       | #90        | [mh ^"Pregnancy Complications, Infectious"]             |
| 33       | #91        | [mh ^"Pregnant Women"]                                  |
| 34       | #92        | [mh ^"Prenatal Care"]                                   |
| 35       | #93        | [mh ^"Prenatal Diagnosis"]                              |
| 36       | #94        | (antenatal* or "pre-natal*" or prenatal*):ti,ab,kw      |
| 37       | #95        | (expect* near/1 (female* or mother* or wom?n)):ti,ab,kw |
| 38       | #96        | pregnan*:ti,ab,kw                                       |
| 39       | #97        | {or #89-#96}  |
| 40       | #98        | #88 and #97   |
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# Supplement 3. Eligibility criteria for screening effectiveness, women's outcome valuation, and treatment effectiveness

|                                 | PICOTS  | Study designs;<br>Language  |
|---------------------------------|---|---|
| Benefits and harms of screening | P: Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria   | RCTs, CCTs, controlled<br>observational designs (i.e.,                        |
|                                 | I: Any screening program, whereby there is an intent (i.e., clinical algorithm) for all pregnant women to receive a screening test with follow-up of screen-positive cases  | prospective and<br>retrospective cohort, case-<br>control, controlled before- |
|                                 | C: No screening program (but may include indicated testing and/or treatment upon development of symptoms), or a different screening test or algorithm   | after)  |
|                                 | O*: Maternal mortality (9), maternal sepsis (8), pyelonephritis (7), perinatal mortality ≥20 weeks' gestation (9), spontaneous abortion/pregnancy loss before 20 weeks' gestation (8), neonatal sepsis (8), preterm delivery <37 weeks' gestation (7), low birth weight <2500g (6), serious maternal and neonatal harms (7) | English and French  |
|                                 | T: Any timing   |   |
|                                 | S: Any primary care or clinical setting providing antenatal care to pregnant women  |   |
| Outcome valuation               | <b>P:</b> Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria; will also accept asymptomatic women who are not pregnant if necessary   | Qualitative, mixed methods<br>surveys/cross-sectional<br>designs              |
|                                 | I: Any screening program or test, and any antibiotic; will accept studies on treatment for any bacterial condition in pregnancy   | English and French  |
|                                 | C: Not applicable   |   |
|                                 | <b>O</b> : Several possible outcomes (e.g., relative weight/utilities of benefits and harms; willingness to be screened based on relative value placed on benefits and harms of screening programs or treatment)  |   |
|                                 | T: Any timing   |   |
|                                 | S: Any primary care or clinical setting providing antenatal care to pregnant women  |   |
| Benefits and harms of treatment | P: Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria   | RCTs (or systematic review(s))  |
|                                 | I: Any antibiotic   | English and French  |
|                                 | C: No treatment or placebo  |   |
|                                 | O*: Maternal mortality (9), maternal sepsis (8), pyelonephritis (7), perinatal mortality ≥20 weeks' gestation (9), spontaneous abortion/pregnancy loss before 20 weeks' gestation (8), neonatal sepsis (8), preterm delivery <37 weeks' gestation (7), low birth weight <2500g (6), serious maternal and neonatal harms (7) |   |

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|                          | T: Any timing   |
|--------------------------|---|
|                          | S: Any primary care or clinical setting providing antenatal care to pregnant women  |
| * Outcomes ratings inclu | Is Any timing Star primary care or clinical setting providing antenatal care to pregnant women lal; grams: PICOTS: populations, interventions, comparators, outcomes, timing, and setting; RCT: randomized clinical trial ded in brackets; these were rated as critical/important for decision-making by CTFPHC members and by women recruited for patient engagement |
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# Supplement 4. Characteristics of included studies on screening effectiveness, outcome valuation, and treatment effectiveness

## Characteristics of included studies on screening effectiveness

| Objective     | To determine if a routine screening program for ASB can reduce the incidence of   |
|---------------|---|
| ,             | pyelonephritis and other adverse pregnancy outcomes, and if such a program would be   |
|               | economically feasible   |
| Methods       | Design: Non-concurrent cohort   |
|               |   |
|               | Inclusion criteria: All pregnant women followed at the Centre Hospitalier de Corbeil-   |
|               | Essonnes (prospective). Controls were all women who were not involved in the screening program (retrospective).   |
|               | Exclusion criteria: NR  |
| Participants  | Setting: Centre Hospitalier de Corbeil-Essonnes (a Hospital)  |
|               | Study period: January-October 1979 (and 10 previous months for the control group)   |
|               | Sample: n=370 pregnant women; n=170 in study group; n=200 in control group  |
|               | Mean age, y (SD): NR  |
|               | Risk factors: NR  |
|               | Length of follow-up: until delivery, and for 3-6 months after in those with $\geq$ 2 instances of ASB; loss to follow-up: n=0.  |
| Interventions | Implementation of a routine screening and treatment program for ASB:  |
|               | <ol> <li>Screening of all women at 3, 5, 7 and 9 months of pregnancy, and treatment of those<br/>diagnosed with ASB</li> </ol>  |
|               | 2) Controls only screened after presenting with clinical signs  |
|               | Urine testing characteristics:  |
|               | Urine collection: Midstream urine sample with cleansing of the vulva before micturition   |
|               | Urine testing: Microscopy, urine culture and Gram staining<br>Criteria for positive test: ≥10 <sup>5</sup> CFU/mL   |
|               | Gestational age (weeks) at first prenatal visit: ~3 months for the treatment group; NR for  |
|               | the control group   |
|               | Number of prenatal visits: at least 4 (every 2 months) for the treatment group; NR for  |
|               | control group   |
|               | Treatment: Treatment based on antibiotic sensitivity and at the discretion of the prescribin  |
|               | physician (figure 1) and the second |
| Outcomes      | Acute pyelonephritis: Clinical signs (fever, lumbar pain, dysuria, pollakiuria (urinary   |
|               | frequency)) and positive urine culture of 10 <sup>5</sup> CFU/mL  |
|               | Spontaneous abortion: ≤28 wks GA  |
|               | Preterm delivery: Delivery at <37 wks GA  |
|               | Birth weight: Reported means for ASB vs. non-ASB in study group; symptomatic + positive culture vs. asymptomatic in controls  |
|               | Perinatal mortality: "stillbirth" as either death in utero or during delivery, all $\geq$ 31 wks GA   |

|                | Adverse event(s): NR   |
|----------------|--|
| Notes          | Study is descriptive, no between-group associations tested   |
|                | atic bacteriuria; CFU/mL: colony-forming units per millilitre; GA: gestational age; n: number; N<br>D: standard deviation; wks: weeks; y: year   |
| Gratacós et al | ., 1994  |
| Objective      | To determine the incidence of pyelonephritis in pregnant women before and after the introduction of a screening program for ASB  |
| Methods        | Design: Non-concurrent cohort  |
|                | Inclusion criteria: Study group were women who were seen at the clinic at <25 wks GA wh<br>subsequently delivered January 1991-December 1992. Controls were women who were<br>seen at the clinic at <25 wks GA and delivered January 1987-December 1990. |
|                | Exclusion criteria: NR   |
| Participants   | Setting: An obstetrics clinic in Barcelona, Spain  |
|                | Study period: January 1987-December 1992 (study group: January 1991-December 1992; controls: January 1987-December 1990)   |
|                | Sample: n=4,917 pregnant women; n=1,652 in study group, n=3,265 in control group   |
|                | Mean age, y (SD): NR   |
|                | Risk factors: NR   |
|                | Length of follow-up: until delivery; loss to follow-up: n=10   |
| Interventions  | Implementation of a routine screening and treatment program for ASB:<br>1) Screening of all women <25 wks pregnant and treatment of those diagnosed with<br>ASB  |
|                | 2) Controls: no routine screening  |
|                | Urine testing characteristics:<br>Urine collection: Midstream morning urine sample. Women with positive culture returne<br>within 1-2 wks for a second midstream urine culture, after stressing the importance of  |
|                | cleansing the vulva before micturition.<br>Urine testing: Urine culture following the guidelines of the National Committee for Clinica   |
|                | Laboratory Standards<br>Criteria for positive test: Two consecutive positive urine cultures (number of organisms N   |
|                | with growth of the same species  |
|                | Gestational age (wks), at first prenatal visit: <25<br>Number of prenatal visits: study group: NR; controls: NR  |
|                | Treatment: 7-day course of antibiotics based on antibiotic sensitivity testing, started 1-2  |
|                | wks after the second culture. At 1-4 wks after treatment and at least once more before delivery, additional midstream urine samples were obtained. If repeat cultures were   |
|                | positive, antibacterial therapy was repeated until cultures were negative for ASB.   |
| Outcomes       | Pyelonephritis: fever, flank pain, tenderness in costovertebral angle, ≥1 positive culture   |

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|       | Adverse event(s): NR   |
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| Notes | Also investigated prevalence of ASB and response to treatment in the study group, but this |
|       | was not compared to the controls who did not receive routine screening                     |

ASB: asymptomatic bacteriuria; n: number; ND: not defined; NR: not reported; SD: standard deviation; wks: weeks; y: year(s)

| Rhode, 2007   |   |
|---------------|---|
| Objective     | To determine if urinary tract infection, high blood pressure, and gestational diabetes mellitus are underdiagnosed when prenatal urine testing is done on a clinically indicated  |
|               | basis versus a routine basis  |
| Methods       | Design: Non-concurrent cohort   |
|               |   |
|               | Inclusion criteria: Routine screening group were all pregnant women who enrolled for care<br>and delivered before August 15, 2002. Indicated screening group were all women who<br>enrolled for care and delivered after August 15, 2002.   |
|               | Exclusion criteria: Women who were in the transitional urine screening group (enrollment  |
|               | prior to and delivery after August 15, 2002), who received both screening techniques (n=570)  |
| Participants  | Setting: Hospital-based nurse-midwifery practice, Aurora, Colorado; provides care to predominantly medically underserved and Hispanic women   |
|               | Study period: Charts of patients enrolled for care and delivered November 2000-March 2004   |
|               | Sample: n= 1,952 pregnant women; n=933 in routine screening group; n=1019 in indicated screening group  |
|               | Mean age, y (SD): Routine screening= 24.4 (5.6); Indicated screening= 24.9 (5.1)  |
|               | Risk factors:   |
|               | Gestational diabetes: routine screening=81 (9.3%), indicated screening=42 (4.2%)<br>Race (ethnicity): Hispanic; routine screening=669 (72.1%), indicated screening=783 (76.9%)  |
|               | Length of follow-up: until delivery or patient left the practice; loss to follow-up (n=112; 4.6%); total ineligible=459 (19%), due to: spontaneous abortion (n=58), transfer of care (n=218), transfer to high risk care (n=71)   |
| Interventions | Routine urine screening (enrollment and delivery before August 15, 2002): first visit with chemical reagent strips, lab urinalysis and culture; subsequent visits with chemical reagent strips, culture or urinalysis as indicated <sup>1</sup>   |
|               | Indicated urine screening (enrollment on and delivery after August 15, 2002): first visit with chemical reagent strips, lab urinalysis and culture; subsequent visits with chemical reagent strip only if one of the criteria was present (risk factors for UTI, GDM). Follow-up of culture |
|               | or lab urinalysis as indicated <sup>1</sup>   |
|               | Urine testing characteristics:  |
|               | Urine collection: midstream morning urine sample, first visit   |
|               | Urine testing: chemical reagent strip test, lab urinalysis and culture;   |

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|          | Mean number of strip tests performed (SD): Routine screening= 7.8 (3.4), range 0-19;                        |
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|          | Indicated screening= 1.4 (1.3), range 0-16  |
|          | Criteria for positive test: NR  |
|          | Gestational age (wks) at start of care (SD): Routine screening= 20.5 (9.4); Indicated screening= 20.3 (8.9) |
|          | Number of prenatal visits: NR   |
|          | Treatment: NR   |
| Outcomes | Pyelonephritis: ND; however, clearly differentiated from ASB, cystitis and undetermined UTI                 |
|          | Preterm delivery: <37 wks GA <sup>2</sup>   |
|          |   |
|          | Adverse event(s): NR  |
| Notes    | Authors compared eligible participants to those who became ineligible during the study                      |
|          | period. In the routine screening group, eligible and ineligible women differed in terms of                  |
|          | marital status, race, payment source, # preterm deliveries, and # weeks gestation at start of               |
|          | care. In the indicated screening group, eligible and ineligible women differed in terms of                  |
|          | race, # of abortions, and # weeks of gestation at start of care.  |
| L        | The second sections, and in weeks of gestation at start of care.  |

ASB: asymptomatic bacteriuria; n: number; ND: not defined; NR: not reported; SD: standard deviation; UTI: urinary tract infection; GDM: gestational diabetes mellitus; wks: weeks; y: year(s)

<sup>1</sup> lab urinalysis may be used instead of culture due to presence of blood in urine; culture typically done to confirm reagent strip, unless reagent strip was used to test for elevated blood pressure (information provided by study author)

<sup>2</sup> Criteria for outcomes were confirmed by study author(s)

| Uncu, 2001   |   |
|--------------|---|
| Objective    | To determine the incidence of asymptomatic bacteriuria during pregnancy and its relation to pregnancy complications   |
| Methods      | Design: Non-concurrent cohort   |
|              | Inclusion criteria: Screened group were pregnant women ≤32 wks GA seen at the antenatal outpatient clinic. Controls were women who delivered in clinic before study and were not screened for ASB; formed in retrospective manner from first day of study |
|              | Exclusion criteria: Patients who were followed-up at clinic due to prior renal disease, positive for ASB or were taking antibiotics   |
| Participants | Setting: Antenatal outpatient clinic, Uludag University Faculty of Medicine, Department of Obstetrics and Gynecology, Turkey  |
|              | Study period: June 1998-January 1999  |
|              | Sample: Screened= 186; Controls= 186  |
|              | Mean age, y (SD): Screened= 27.7 (5.1); Controls= 27.7 (4.6)  |
|              | Risk factors:   |
|              | Gestational diabetes mellitus: Screened=7 (3.8%); Controls= 5 (2.7%)<br>Socioeconomic status: lower SES correlated with high prevalence of ASB*   |
|              | Length of follow-up: NR; loss to follow-up: NR  |

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| Interventions        | Determine incidence of asymptomatic bacteriuria during pregnancy and relation to   |
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|                      | <ul> <li>pregnancy complications:</li> <li>1) Screening group: All pregnant women routinely screened at first visit with whole blood count, total urine analysis and urine culture.</li> </ul> |
|                      | 2) Controls: Formed in a retrospective manner from the first day of the study with pregnant women who delivered in the clinic and who were not routinely screened.                             |
|                      | Urine testing characteristics:   |
|                      | Urine collection: midstream morning urine sample, first visit  |
|                      | Urine testing: whole blood count, total urine analysis, and urine culture  |
|                      | Criteria for positive test: >10 <sup>5</sup> CFU/mL of the same organism   |
|                      | Gestational age (wks), at time of urine culture: beginning of pregnancy  |
|                      | Number of prenatal visits: NR  |
|                      | Treatment: n=23 [7-10 days of antibiotics, Follow-up 7-days of antibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)   |
| Outcomes             | Pyelonephritis: ND   |
|                      | Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation  |
|                      | Prematurity <sup>2</sup> : <37 wks of gestation  |
|                      | Adverse event(s): NR   |
|                      | Fetal abnormalities: ND  |
| Notes                | Total screened for ASB=270 $\rightarrow$ with urine cultures=247 $\rightarrow$ sufficient delivery records=186 (61 excluded)   |
| statistically signif | icant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: gestation   |
| ge; ND: not defin    | ed; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrasonograph   |
| vks: weeks; y: yea   |  |
|                      | mes were confirmed by study author(s)  |

2 (5)

| Butters, 1990  |  |
|----------------|--|
| Objective      | To determine the level of knowledge of the effects of commonly used drugs on a fetus   |
| Methods        | Design: Cross-sectional (self-completed questionnaire)   |
|                | Recruitment: Participants were recruited from postnatal wards of the hospitals on a weekly basis   |
| Participants   | Setting: Two maternity hospitals: one serves a white urban and semirural population, the other serves a wi population mix from rural to urban and includes ethnic minorities. Both are located in Glasgow, Scotland. |
|                | Inclusion criteria: Postnatal women who were still in hospital after delivering. They had to be given the  |
|                | questionnaire in person (i.e. they were either in their bed or in the sitting room when the questionnaire was distributed).  |
|                | Exclusion criteria: Women who had vaginal delivery on the day of the study, women one or two days post-<br>delivery by caesarean section, and women who were unable to read English.                                 |
|                | Study period: October 1, 1987 and March 31, 1988.  |
|                | Sample: n=514  |
|                | Age range: 15 to 40 years; 66 (13%) between 15 and 20 years, 141 (27%) between 21 and 25 years, 176 (34 between 26 and 30 years, and 127 (25%) aged over 30 years.   |
|                | Gestational age: NA  |
|                | Parity: First pregnancy (53%)  |
|                | Race/ethnicity: Multiple ethnicities, mainly Scottish.   |
|                | Education level: NR  |
| Interventions  | Anonymous short questionnaire with mostly tick boxes.  |
| Outcomes       | -254 (49%) said they would take an antibiotic prescribed by their doctor, 246 (48%) said they would not, an  |
|                | 14 (3%) did not respond.   |
|                | <ul> <li>The responses were similar for all ages and social class groups.</li> <li>There was a strong relationship between the women that would avoid taking an analgesic (n=80, 74%)) and</li> </ul>                |
|                | those that would avoid taking an antibiotic (187, 45%), p<0.0001.  |
| NA: not a      | applicable; NR: not reported   |
|                |  |
| Kazemier, 2015 |  |
| Objective      | To investigate the consequences of treated and untreated ASB in pregnancy  |

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Methods

1

| Methods          | Design: Prospective cohort (screening vs. no screening) with embedded RCT (decision on entry into the study considered cross-sectional)  |
|------------------|--|
|                  | Recruitment: Pregnant women attending antenatal clinics offering screening (not routinely available)   |
| Participants     | Setting: 8 hospitals and 5 ultrasound centres, the Netherlands   |
|                  | Inclusion criteria: Pregnant women aged ≥18 years with a singleton pregnancy who were between 16 and 22 wks GA, tested positive for ASB, and did not have symptoms of UTI.   |
|                  | Exclusion criteria: History of preterm delivery <34 wks GA, warning signs of imminent preterm delivery, fetal congenital malformations, antibiotic use within 2 weeks of screening, known glucose-6-phosphate dehydrogenase deficiency, hypersensitivity to nitrofurantoin, risk factors for complicated UTI (e.g., pre-gestational DM, use of immunosuppressive medication or functional or structural abnormalities of the urinary tract). |
|                  | Study period: October 11, 2011-August 22, 2014   |
|                  | Sample: n=248  |
|                  | Mean age (SE), years: treated=29 (0.74), placebo or untreated=31 (0.33)  |
|                  | Gestational age (wks + days at screening (SE)): treated=20+2 (19+6 to 20+5), placebo or untreated=20+0 (19+3 to 20+3)  |
|                  | Parity (% nulliparous): treated=50%, placebo or untreated=42%  |
|                  | Ethnicity (non-white): treated n=3 (8%), placebo or untreated n=36 (17%)   |
|                  | Low education (≤pre-vocational level): treated n=6 (15%), placebo or untreated n=21 (10%)  |
| Interventions    | Women who were positive for ASB were invited to participate in a treatment RCT. Reasons for declining participation were recorded.   |
| Outcomes         | Most women (155/163 positive for ASB, 94%) who did not want to participate made this choice because they did not want to receive antibiotics during pregnancy for an asymptomatic condition.   |
|                  | mptomatic bacteriuria; DM: diabetes mellitus; GA: gestational age; NA: not applicable; NR: not reported;<br>domized controlled trial; SE: standard error; UTI: urinary tract infection; wks: weeks   |
| Lupattelli, 2014 |  |
| Objective        | To investigate the association between health literacy and perception of medication risk, beliefs about medications, use and non-adherence to prescribed pharmacotherapy during pregnancy.   |
|                  |  |

| Recruitment: Banners announcing the study were placed on one to four websites per country and/or social |
|---|
| networks commonly visited by pregnant women that had a high number of daily users.                      |

Design: Cross-sectional internet-based questionnaire

| Participants                                      | Setting: Anonymous internet questionnaire with participants from 18 countries: Australia, Austria, Canada  |
|---|--|
| • • •   | Croatia, Finland, France, Iceland, Italy, The Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweder  |
|   | Switzerland, United Kingdom and United Sates as well as some South American countries.   |
|   | Inclusion criteria: Pregnant women at any stage of gestation.  |
|   | Exclusion criteria: Women who were not currently pregnant.   |
|   | Study period: October 1 2011 to February 29, 2012  |
|   | Sample: n=4999   |
|   |  |
|   | Mean age (SD): NR overall  |
|   | Costational again wasks maan (SD): 22.4 (10.2)   |
|   | Gestational age in weeks, mean (SD): 22.4 (10.3)   |
|   | Race/ethnicity: Multinational  |
| Interventions                                     | Health literacy was measured using a self-assessment scale of 0 to 4 for three questions.  |
|   | Perceived risk of medications was measured using 13 agents on a scale of 0 to 10.  |
|   | Beliefs about medications were measured using a 5-point agreement scale for three questions.   |
|   |  |
|   | Participants were asked standardized questions about medication use for specific illnesses, non-adherence  |
|   | Participants were asked standardized questions about medication use for specific illnesses, non-adherence over-the-counter medication use with free text entry.  |
|   | -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.<br>reported; SD: standard deviation   |
|   | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation  |
| NR: not<br>Mashayekhi, 20                         | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation  |
| NR: not   | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation  |
| NR: not<br>Mashayekhi, 20<br>Objective            | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire   |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         009         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.   |
| NR: not<br>Mashayekhi, 20<br>Objective            | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire   |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         009         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.   |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.         Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.  |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.         Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.         Inclusion criteria: Antenatal and postnatal women.   |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.         Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.         Inclusion criteria: Antenatal and postnatal women.         Exclusion criteria: Women who had a complicated labor.  |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.         Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.         Inclusion criteria: Antenatal and postnatal women.         Exclusion criteria: Women who had a complicated labor.         Study period: August 2006 and May 2007               |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation <b>109</b> To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.         Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.         Inclusion criteria: Antenatal and postnatal women.         Exclusion criteria: Women who had a complicated labor.         Study period: August 2006 and May 2007         Sample: n=400 |

|                                       | Parity: None – 200 (50.0%), one – 127 (31.8%), two (54, 13.5%), more than two – 19 (4.8%)  |
|---------------------------------------|--|
|                                       | Race/ethnicity: Iranian  |
|                                       | Education level: High school or lower – 184 (46.0%), diploma – 147 (36.8%), University education – 69 (17.3%)  |
| Interventions                         | Face-to-face questionnaire divided into three sections: demographic information, drug use before and during pregnancy including drug safety, source of information regarding drugs safety during pregnancy. Majority of response options were tick boxes.  |
| Outcomes                              | <ul> <li>-Specific antibiotics the women felt were safe: penicillin – 51 (12.8%), ampicillin – 36 (9.0%), amoxicillin – 66 (16.5%), metronidazole - 20 (5.0%), cephalosporin - 10 (2.5%), other antibiotics - 6 (1.5%).</li> <li>-For penicillin use none felt it was unsafe for the mother, 143 (35.8%) felt it was unsafe for the fetus, 40 (10.0%) felt it was unsafe for both.</li> <li>-For ampicillin use 4 (1.0%) felt it was unsafe for the mother, 145 (36.3%) felt it was unsafe for the fetus, 28 (7.0%) felt it was unsafe for both.</li> <li>-For amoxicillin use 5 (1.3%) felt it was unsafe for the mother, 147 (36.8%) felt it was unsafe for the fetus, 18 (4.5%) felt it was unsafe for both.</li> <li>-For metronidazole use none felt it was unsafe for the mother, 129 (32.3%) felt it was unsafe for the fetus, 21 (5.3%) felt it was unsafe for both.</li> <li>-For cephalosporin use none felt it was unsafe for the mother, 127 (31.8%) felt it was unsafe for the fetus, 18 (4.5%) felt it was unsafe for both.</li> <li>-For other antibiotic use none felt it was unsafe for the mother, 125 (31.3%) felt it was unsafe for the fetus, 28 (7.0%) felt it was unsafe for both.</li> </ul> |
| NA: not a Nordeng, 2010               | applicable; SE: standard error; SD: standard deviation   |
|                                       | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most   |
| Nordeng, 2010                         |  |
| Nordeng, 2010<br>Objective            | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used   |
| Nordeng, 2010<br>Objective            | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by  |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.  |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.         Setting: Internet  |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.         Setting: Internet         Inclusion criteria: Pregnant woman or a mother of a child less than 5 years old.   |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.         Setting: Internet         Inclusion criteria: Pregnant woman or a mother of a child less than 5 years old.         Exclusion criteria: NR  |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.         Setting: Internet         Inclusion criteria: Pregnant woman or a mother of a child less than 5 years old.         Exclusion criteria: NR         Study period: September 16, 2008 to October 25, 2008   |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.         Setting: Internet         Inclusion criteria: Pregnant woman or a mother of a child less than 5 years old.         Exclusion criteria: NR         Study period: September 16, 2008 to October 25, 2008         Sample: n=1793; 866 (48.3%) pregnant, 927 (51.7%) mothers   |

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| <ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>40</li> </ul> |  |
| 48<br>49<br>50<br>51<br>52<br>53<br>54<br>55<br>56<br>57<br>58<br>59<br>60   |  |

|               | Race/ethnicity: Norwegian   |
|---------------|---|
|               | Education level: Basic school level – 88 (4.9%), upper secondary education – 390 (21.8%), tertiary education (<4 years) – 810 (45.2%), tertiary education (>4 years) – 421 (23.5%), other education – 84 (4.7%) |
| Interventions | Questionnaire consisted of open-ended questions and numeric rating scales from 0 to 10 relating to teratogenic risk of 17 drugs, foods, chemicals and radiation.  |
| Outcomes      | -There was a significant difference in mean risk perception scores between non-users of the indicated drugs<br>and users of 4.3 vs. 3.0 (p<0.001) with a ratio between non-users/users of 1.4.                  |

NR: not reported

| Objective     | To assess the perception of the teratogenic risk of common medication by professionals and the public             |
|---------------|---|
| Methods       | Design: Cross-sectional   |
|               | Recruitment: Pregnant women attending a regular obstetric follow up in an out-patient clinic at a University      |
|               | hospital; non-pregnant women from an obstetric and gynecological out-patient clinic in the hospital and in a      |
|               | randomized manner from four different neighborhoods. Medical staff (general physicians, gynecologists and         |
|               | medical students were also recruited and interviewed, their data are not included here).                          |
| Participants  | Setting: Outpatient clinic at a University hospital, home setting   |
|               |   |
|               | Inclusion criteria:   |
|               | Currently pregnant for the pregnant women group, not pregnant for the comparison group                            |
|               | Exclusion criteria: NR  |
|               | Study period: NR  |
|               | Sample: n=81 pregnant women, n=63 non-pregnant women  |
|               | Median age: NR  |
|               | Gestational age: NR   |
|               | Gravidity: NR   |
|               | Parity: NR  |
|               | Race/ethnicity: Spanish   |
|               | Education level: NR   |
| Interventions | A visual analogue scale with a 10 cm horizontal line with a short vertical line at each end, with a scale of 0 to |
|               | 100%. Participants were asked to mark on the scale what they thought was the potential risk for fetal             |
|               | malformations and malformations in non-pregnant women given exposure to a particular drug.                        |

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| Outcomes     | -The mean value of the perceived teratogenic risk by non-pregnant women was higher than that perceived by  |
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|              | pregnant women for erythromycin (55.6 vs. 38.7) but not amoxicillin (49.3 vs. 40.4) (Mann-Whitney U Test).   |
|              | -The median value of the perceived teratogenic risk by non-pregnant women was higher than that perceived   |
|              | by pregnant women for erythromycin (50.0 vs. 30.0) but not amoxicillin (50.5 vs. 34.0) (Mann-Whitney U Test).  |
|              | -In comparison to the "true" limits, risk from antibiotics was rated higher by pregnant women (erythromycin  |
|              | chi-square: 3.99, p=0.045; amoxicillin chi-square: 17.21, p=0.0001).   |
| cm: cen      | timeter(s); NR: not reported   |
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|              |  |
| Sharma, 2006 |  |
|              |  |
| Objective    | To evaluate the drug utilization pattern in pregnant women and the effect of education and economic status.  |
|              |  |
| Methods      | Design: Retrospective cross-sectional study  |
|              | Descriptment: Medical students interviewed program women visiting the enterestal clinic  |
| Participants | Recruitment: Medical students interviewed pregnant women visiting the antenatal clinic.Setting: Antenatal clinic of a medical college in North India |
| Participants | Setting. Antenatal clinic of a medical conege in North India   |
|              | Inclusion criteria: Pregnant women   |
|              | inclusion enteria. Pregnant women  |
|              | Exclusion criteria: NR   |
|              |  |
|              | Study period: June 2005 to December 2005   |
|              |  |
|              | Sample: n=405  |
|              |  |
|              | Age range: Less than 20 years – 25 (6.17%), 20 to 35 years – 240 (59.26%), more than 35 years – 90 (22.22%)  |
|              |  |
|              | Gestational age: First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.90%)                                       |
|              |  |

| Gravidity: 243 primigravida; 152 multigravida               |              |
|---|--------------|
| Race/ethnicity: Indian                                      |              |
| Education level: Undergraduates – 220 (54.32%), graduates - | 185 (45.68%) |

|               | Education level: Undergraduates – 220 (54.32%), graduates - 185 (45.68%)  |
|---------------|---|
| Interventions | 98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed a written questionnaire after interviewing each participant. The participants' statements were confirmed by their records if available. |
| Outcomes      | -190 (46.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should be used.   |
| ND: not r     |   |

NR: not reported

| Twigg, 2016 |   |
|-------------|---|
| Objective   | To describe beliefs and risk perception associated with medicines for treatment of common acute conditions. |
| Methods     | Design: Cross-sectional internet-based questionnaire  |

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|               | Recruitment: Advertisements announcing the study were placed on two commonly visited by pregnant wome          |
|---------------|--|
|               | or new mothers   |
| Participants  | Setting: Anonymous internet questionnaire with participants from across the United Kingdom (England,           |
| •             | Scotland, Wales and Northern Ireland).   |
|               |  |
|               | Inclusion criteria: Women who were pregnant or within one year of giving birth.                                |
|               |  |
|               | Exclusion criteria: NR   |
|               |  |
|               | Study period: November 15, 2011 to January 15, 2012  |
|               |  |
|               | Sample: n=1120   |
|               |  |
|               | Mean age (SD): 30.5 (5.2) years  |
|               |  |
|               | Gestational age: 442 (39.5%) were currently pregnant   |
|               |  |
|               | Parity (95% Cl): No previous children – 48.0% (45.1-50.9%)   |
|               |  |
|               | Race/ethnicity: NR   |
|               |  |
|               | Education level (95% CI): Less than high school – 0.6% (0.14-1.05), high school – 27.9% (25.3-30.5), more than |
|               | high school – 52.1% (49.2 – 55.0), other – 19.3% (17.0-21.6).  |
| Interventions | Health literacy was measured using a self-assessment scale of 0 to 4 for three questions.                      |
|               | General beliefs about medicine were obtained using the validated Beliefs about Medicines Questionnaire         |
| 0             | (BMQ-General) with an additional four questions regarding the benefit of medications on a scale of 1 to 5.     |
| Outcomes      | -Women with a UTI using medication for treatment had lower mean risk perception scores relating to the         |
|               | overuse and harm of medication and a higher mean risk score relating to the benefits of medication compare     |
|               | to women with a UTI who did not undergo treatment with medication.   |
|               | Overuse [mean(SD)]: 11.5 (2.8) vs. 12.6 (2.7), p=0.006<br>Harm [mean(SD)]: 9.3 (2.7) vs. 10.4 (2.9), p=0.014   |
|               | Benefit [mean(SD)]: 16.3 (2.2) vs. 14.9 (2.3), p<0.001   |
| Notes         | Sub-study of the Multinational Medication Use in Pregnancy Study which was reported by Lupattelli et al. and   |
| NOLES         | another paper from that study is included in this review.  |
| CI: confi     | dence interval; NR: not reported; SD: standard deviation; UK: United Kingdom; UTI: urinary tract infection     |
| CI. COIIII    | dence interval, NK. not reported, 3D. standard deviation, OK. Onited Kingdoni, OT. drinary tract infection     |
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## Characteristics of included studies on treatment effectiveness

| Brumfitt, 1975 |   |  |
|----------------|---|--|
| Objective      | To assess the impact of screening and treatment for ASB on maternal and fetal health  |  |
| Methods        | Design: RCT (randomization ND); placebo controlled  |  |
|                | Recruitment: Pregnant women attending one of three antenatal clinics for the first time   |  |
|                | Inclusion criteria: Pregnant women who were screened and found to be positive for<br>'significant bacteriuria' at their first antenatal visit and 7-10 days later                       |  |
|                | Exclusion criteria: Home delivery, abortions, treatment before confirmation of bacteriuria and other complicating factors   |  |
| Participants   | Setting: Birmingham (1 clinic) and London (2 clinics), UK; urban  |  |
|                | Study period: NR; ~1967-1968  |  |
|                | Sample: n=426; treated (n=235), placebo (n=179)   |  |
|                | Mean age (SD), years: Treated=26.5 (6.8); Placebo=26.2 (6.9)  |  |
|                | Risk factors:   |  |
|                | Ethnicity (Asian and West Indian): Treated n=49 (20.8%); Placebo n=35 (14.1%)   |  |
|                | Length of follow-up: until delivery and the postpartum period for perinatal mortality   |  |
|                | Loss to follow-up: NR; outcome of pyelonephritis reported only for a subset (n=173); n=413 for outcome of low birth weight.   |  |
| Interventions  | Screening characteristics:  |  |
|                | Timing: First antenatal visit<br>Urine collection: Clean-catch urine sample   |  |
|                | Urine testing method: Urine culture   |  |
|                | Criteria for positive test: Two positive tests; women with one positive test were recalled for a second test 7-10 days later and 'detailed documentation'. Microbiological criteria NR. |  |
|                | Treatment characteristics (Williams, 1968):   |  |
|                | Type of antibiotic and length of treatment: 2g sulphonamide in a single dose; additional  |  |
|                | courses of treatment for persistent bacteriuria   |  |
|                | Control group: Received placebo under 'double-blind conditions'<br>Follow-up testing: Subset of treated women (n=87) retested after 1 and 2 courses of                                  |  |
|                | treatment (as applicable)   |  |
| Outcomes       | Benefits:   |  |
|                | Pyelonephritis: Presence of loin pain and tenderness together with a temperature of ≥100°F  |  |
|                | and >10 <sup>5</sup> CFU/mL (Condie, 1968)  |  |
|                | Low birth weight (reported as prematurity): ≤2500g  |  |
|                | Harms: NR   |  |
| Notes          | Study also included a non-bacteriuric control group. There are two preliminary reports  |  |
|                | associated with this study (Condie, 1968; Williams, 1968). Brumfitt, 1975 reported outcome  |  |
|                | of pyelonephritis for the placebo group only (55/179), comparison between groups only   |  |

|   | available for a subset of treatment group (Condie, 1968). No explanation for variation in     |  |
|---|---|--|
|   | number of participants across reports for this study, nor for the various outcomes.           |  |
| ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millilitre; F: Fahrenheit; g: gram(s); n: number; |   |  |
| ND: not defined; N  | R: not reported; RCT: randomized controlled trial; SD: standard deviation; UK: United Kingdom |  |

| Ohiostivo     | To avaluate the effectiveness of sulfacturesing for the treatment of ACD in program turns  |
|---------------|--|
| Objective     | To evaluate the effectiveness of sulfasymazine for the treatment of ASB in pregnant wome   |
| Methods       | Design: RCT; placebo-controlled  |
|               | Recruitment: Pregnant women registering for prenatal care  |
|               | Inclusion criteria: Pregnant women ≤32 wks GA with bacteriuria at registration confirmed i two additional samples  |
|               |  |
|               | Exclusion criteria: >32 wks GA, included in other bacteriuria studies, given treatment in error, moved away  |
| Participants  | Setting: Boston City Hospital, Boston, US; urban   |
|               | Study period: June 9, 1965-March 9, 1966   |
|               | Sample: n=106; treated (n=54); placebo (n=52)  |
|               | Mean age (SD): NR  |
|               | Risk factors: NR   |
|               | Length of follow-up: Until delivery  |
|               | Loss to follow-up: 5 (5%) lost; 2(4%) treated patients left the community, 3 (6%) placebo-<br>treated patients dropped out of the study  |
| Interventions | Screening characteristics:   |
|               | Timing: At registration for prenatal care  |
|               | Urine collection: Clean-voided urine sample  |
|               | Urine testing method: Urine culture  |
|               | Criteria for a positive test: Three uncontaminated urine specimens containing the same species of bacteria with $\geq 10^4$ CFU/mL in one and $\geq 10^5$ CFU/mL in the other two. |
|               | Treatment characteristics  |
|               | Type of antibiotic and length of treatment: 0.5g sulfasymazine once daily until delivery; if   |
|               | there was evidence of persistent bacteriuria, another treatment was given according to   |
|               | clinical judgment (usually nitrofurantoin)   |
|               | Control group: Received placebo  |
|               | Follow-up testing: Retested after one week of treatment, and at each clinic visit (at least  |
| <u> </u>      | weekly for the first 3 wks, then at least biweekly until 36 wks GA, then weekly until deliver  |
| Outcomes      | Benefits: NR   |
|               | Harms: NR  |

| Notes | There are no relevant results reported in this study. Study also included non-bacteriuric |
|-------|---|
|       | control patients. 7/52 (13%) of women in the placebo group developed 'asymptomatic        |
|       | pyelonephritis', but not information provided for the treated group.                      |

ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millilitre; g: gram(s); GA: gestational age; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; US: United States; wks: weeks

| Objective     | To assess the effect of treatment of ASB on pregnancy outcomes  |
|---------------|---|
| Methods       | Design: Quasi-RCT; placebo-controlled   |
|               |   |
|               | Recruitment: Patients registering for prenatal care   |
|               |   |
|               | Inclusion criteria: Pregnant women ≤32 wks GA, with confirmed bacteriuria at the first  |
|               | prenatal visit  |
|               | Evaluation exite via Tracted for LITI during the surgery and perform the first  |
|               | Exclusion criteria: Treated for UTI during the current pregnancy and before the first   |
|               | obstetric appointment, >32 wks GA, delivered or had aborted before the first obstetric visi went elsewhere for prenatal care, delivered twins |
| Participants  | Setting: Boston City Hospital, Boston, US; urban  |
| Participants  | Setting. Boston City Hospital, Boston, OS, urban  |
|               | Study period: January 28, 1963-July 2, 1965   |
|               |   |
|               | Sample: n=281; treated (n=133), placebo (n=148)   |
|               |   |
|               | Mean age (SE), years: Treated=24.8 (0.60); Placebo=25.3 (0.46)  |
|               |   |
|               | Risk factors:   |
|               | Ethnicity (non-white): Treated=66.2%; Placebo=54.7%   |
|               | Previous UTI: Treated=35.9%; Placebo=40.1%  |
|               | Length of follow-up: Until delivery, and postpartum (time frame ND) for complications   |
|               | Loss to follow-up: Of original n=289, 8 (3%) were excluded because they moved away. No  |
|               | loss to follow-up for pyelonephritis; 3 (1%) patients in the placebo group lost for low   |
|               | birthweight because they were treated for reasons other than UTI; 8 (3%) lost for perinata  |
|               | mortality, 11 (4%) for neonatal sepsis, and 16 (6%) fetal abnormalities and hemolytic   |
|               | anemia, reasons NR.   |
| Interventions | Screening characteristics:  |
|               | Timing: Upon registration at the clinic   |
|               | Urine collection: Clean-voided urine sample   |
|               | Urine testing method: Urine culture   |
|               | Criteria for a positive test: Three samples (two at registration and one at the first obstetric   |
|               | visit); colony count from 2 of 3 specimens $\geq 10^5$ CFU/mL and no specimens with $< 10^4$  |
|               | CFU/mL, with the same species predominating in all 3 specimens  |
|               | Treatment characteristics:  |
|               | Type of antibiotic and length of treatment: 250mg tetracycline, 4 times daily for 6 wks; if   |
|               | infection did not clear in 2 wks, another antibiotic (usually nitrofurantoin) was given until in  |
|               | cleared   |
|               | Control group: Given identically appearing placebo to be taken similarly  |

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|          | Follow-up testing: Retested at each clinic visit until delivery (includes recurrence and       |
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|          | excludes those who became symptomatic); colony count <10 <sup>3</sup> CFU/mL on two successive |
|          | cultures considered cleared  |
| Outcomes | Benefits:  |
|          | Pyelonephritis: Temperature of ≥100°F with signs and symptoms localized to the urinary         |
|          | tract and not otherwise explained  |
|          | Perinatal mortality: Stillbirth or neonatal death prior to hospital discharge                  |
|          | Respiratory distress: Respiratory distress syndrome and other causes of 'respiratory           |
|          | embarrassment'   |
|          | Low birth weight (defined as prematurity): ≤2500g  |
|          | Harms:   |
|          | Serious adverse events: Congenital malformations of bone, genitourinary system, other;         |
|          | hemolytic anemia (erythroblastosis fetalis)  |
| Notes    | Study also included a non-bacteriuric control group. Some patients may have participated       |
|          | more than once if they had more than one pregnancy during the study period (treatment          |
|          | assigned by alternation regardless of assignment for previous pregnancy). Outcomes of low      |
|          | birth weight, fetal abnormalities and hemolytic anemia reported for live births only. 4        |
|          | bacteriuric women delivered twins and are not included.  |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; °F: degrees Fahrenheit; g: gram(s); GA: gestational age; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SE: standard error; US: United States; UTI: urinary tract infection; wks: weeks

| Foley, 1987   | Foley, 1987   |  |
|---------------|---|--|
| Objective     | Test of treatment vs. non-treatment of ASB for the prevention of symptomatic UTI in pregnancy   |  |
| Methods       | Design: RCT   |  |
|               | Recruitment: Pregnant women attending an antenatal clinic for the first time  |  |
|               | Inclusion criteria: Pregnant women with bacteriuria at the first prenatal visit   |  |
|               | Exclusion criteria: NR  |  |
| Participants  | Setting: National Maternity Hospital, Dublin, Ireland; urban  |  |
|               | Study period: 1985  |  |
|               | Sample: n=220; treated (n=100); not treated (n=120)   |  |
|               | Mean age (SD), years: NR  |  |
|               | Risk factors: NR  |  |
|               | Length of follow-up: Until delivery (patients interviewed post-delivery)  |  |
|               | Loss to follow-up: Reported follow-up rate of 81%, unclear if these were from treatment or control groups (total n used in analysis). |  |
| Interventions | Screening characteristics:  |  |
|               | Timing: First antenatal visit   |  |
|               | Urine collection: Midstream urine sample  |  |

|          | Urine testing method: NR  |
|----------|---|
|          | Criteria for a positive test: One urine sample with $>10^5$ CFU/mL                              |
|          | Treatment characteristics:  |
|          | Type of antibiotic and length of treatment: 300mg sulphamethizole or 150mg nitrofurantoin       |
|          | daily for 3 days, on the basis of sensitivity testing; further treatment, including maintenance |
|          | treatment, provided if needed to render urine sterile   |
|          | Control group: Received no treatment  |
|          | Follow-up testing: Retested 'at follow-up'; not further defined                                 |
| Outcomes | Benefits:   |
|          | Pyelonephritis: ND; 'admitted with pyelonephritis'  |
|          | Harms: NR   |
| Notes    | Reported as a letter to the editor, not a full publication.                                     |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; mg: milligram(s); ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; UTI: urinary tract infection

| Furness, 1975 |  |
|---------------|--|
| Objective     | To examine the effectiveness of urinary antiseptics in preventing pyelonephritis and adverse among pregnant women with ASB                   |
| Methods       | Design: RCT  |
|               | Recruitment: Pregnant women attending their initial prenatal visit   |
|               | Inclusion criteria: Pregnant women with 'significant' bacteriuria at the second prenatal visit   |
|               | Exclusion criteria: NR   |
| Participants  | Setting: Queen Victoria Hospital, Adelaide, Australia; urban   |
|               | Study period: NR   |
|               | Sample: n=206; treated (n=139); not treated (n=67)   |
|               | Mean age (SD), years: NR<br>Risk factors: NR   |
|               | Risk factors: NR   |
|               | Length of follow-up: Until 6 wks postpartum  |
|               | Loss to follow-up: None reported   |
| Interventions | Screening characteristics:   |
|               | Timing: At the second antenatal visit  |
|               | Urine collection: Midstream urine sample   |
|               | Urine testing method: Dipslide   |
|               | Criteria for a positive test: One specimen with >10 <sup>5</sup> CFU/mL or two specimens each with 10 <sup>4</sup> to 10 <sup>5</sup> CFU/mL |
|               | Treatment characteristics  |

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|          | Type of antibiotic and length of treatment: 1g methenamine mandelate 4 times daily or 1g methenamine hippurate twice daily until delivery; if pyelonephritis developed the patient |
|----------|--|
|          | was treated with the appropriate antibiotic and no further antiseptics were given  |
|          | Control group: Received no treatment   |
|          | Follow-up testing: A postnatal urine specimen was obtained at the 6-week postnatal visit   |
|          | from women who did not develop clinical pyelonephritis during pregnancy or the   |
|          | puerperium   |
| Outcomes | Benefits:  |
|          | Pyelonephritis: Frequency and burning on micturition accompanied by pyrexia or loin  |
|          | tenderness, with presence of a significant number of bacteria in urine   |
|          | Spontaneous abortion: ND; 'abortions'  |
|          | Preterm delivery: <38 wks GA   |
|          |  |
|          | Harms:   |
|          | Serious adverse events: Major fetal abnormality (anencephaly)  |
| Notes    | The treatment group received one of two antiseptics, the two groups were combined for  |
|          | reporting of outcomes. Outcome of pyelonephritis includes both during pregnancy and the  |
|          | puerperium. Three intrauterine deaths reported but it is unclear which group the patients  |
|          | belonged to. GA at delivery reported for 118 treated and 52 placebo untreated patients   |
|          | with no explanation given, total n used as denominator in analysis.  |
|          | atic bactoriuria: CEU/mL: colony forming units nor millilitro; g: gram/s); CA: gostational ago; n:   |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; wks: weeks

| Gold, 1966   |   |
|--------------|---|
| Objective    | To determine whether chemotherapy for ASB, continued throughout the rest of the prenatal period, reduces the incidence of prematurity |
| Methods      | Design: Quasi-RCT; placebo-controlled   |
|              | Recruitment: Pregnant women registering at a prenatal clinic  |
|              | Inclusion criteria: Pregnant women with two consecutive positive tests for bacteriuria at any prenatal visit                          |
|              | Exclusion criteria: Failed to return to the clinic, aborted, delivered at other hospitals, found                                      |
|              | to not be pregnant, ectopic pregnancy, transferred to other care, delivered by a private physician                                    |
| Participants | Setting: Prenatal clinic at a hospital in New York, NY, US; urban   |
|              | Study period: February 2, 1962-December 21, 1964  |
|              | Sample: n=65; treated (n=35); placebo (n=30)  |
|              | Mean age (SD), years: NR  |
|              | Risk factors:<br>Ethnicity: 85% non-white, 6% Puerto-Rican, 9% other white (distribution among groups NR)                             |
|              | Length of follow-up: Until the 'postpartum period' (exact time NR)  |
|              | Loss to follow-up: None reported  |

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| Interventions | Screening characteristics:  |
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|               | Timing: First prenatal visit and each visit thereafter  |
|               | Urine collection: Clean-voided midstream urine sample   |
|               | Urine testing method: Urine culture   |
|               | Criteria for a positive test: Two consecutive laboratory reports with >10 <sup>5</sup> CFU/mL of the same species                                       |
|               | Treatment characteristics:  |
|               | Type of antibiotic and length of treatment: 0.5g sulfadimethoxine once per day until 36 wks GA, 1g sulfadiazine 3 times daily thereafter until delivery |
|               | Control group: Received placebo tablets taken in the same manner  |
|               | Follow-up testing: Each patient had repeat tests at each antenatal visit until delivery (either   |
|               | for diagnosis or persistent bacteriuria); data presented for persistent bacteriuria at delivery.  |
| Outcomes      | Benefits:   |
|               | Pyelonephritis: ND  |
|               | Harms: NR   |
| Notes         | Also reported delivery data for non-bacteriuric patients. Only antepartum pyelonephritis  |
|               | included in the analysis (postpartum excluded). 'Preterm delivery' reported for 2/35 treated  |
|               | and 0/30 placebo patients, but this is not further defined.   |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; n: number; ND: not defined; NR: not reported; NY: New York; RCT: randomized controlled trial; SD: standard deviation; US: United States; wks: weeks

| Kass, 1960   |   |
|--------------|---|
| Objective    | To assess the effect of early detection and eradication of bacteriuria on excessive morbidity   |
|              | in pregnant women   |
| Methods      | Design: Quasi-RCT; placebo controlled   |
|              | Recruitment: Pregnant women ≤32 wks GA registering for a prenatal clinic  |
|              | Inclusion criteria: Pregnant women with bacteriuria at the first prenatal visit and confirmed on two repeat cultures  |
|              | Exclusion criteria: >32 wks GA, chronic renal insufficiency, given treatment in error, did not have further prenatal care, records were inadequate or unobtainable, urine samples were contaminated, unable to void, found to not be pregnant |
| Participants | Setting: Boston City Hospital, Boston, US; urban  |
|              | Study period: October 1956-April 1960   |
|              | Sample: n=214 (n=11 recruited via renal clinic); treatment (n=93); placebo (n=98)   |
|              | Mean age (SD), years: NR; similar distribution between treated and placebo groups   |
|              | Risk factors:<br>Ethnicity (black): Treated (~50%); placebo (slightly <50%)   |
|              | History of UTI: ~15% (distribution by group NR)<br>Diabetes: n=2 (distribution by group NR)   |

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|  | ne abnormalities: reported for n=2 bacteriuric women with cesarean section;<br>lence in rest of population NR   |
|--|---|
|  | h of follow-up: Until the post-delivery period and up to 12 months postpartum;<br>ds reviewed 3-4 years later   |
| befor  | o follow-up: n=23 (11%) lost; 13 (12%) in the treatment group (7 not seen in last 4 wks<br>e delivery, 5 delivered out of state, 1 incorrectly assigned), 10 (9%) in the placebo<br>9 (8 cleared spontaneously or false positive, 2 lost)   |
|  | ning characteristics:   |
| Timin  | g: At the time of registration for the clinic   |
| Urine  | collection: Clean-voided urine sample   |
| Urine  | testing method: Urine culture   |
|  | ia for a positive test: 10 <sup>3</sup> -10 <sup>5</sup> CFU/mL at registration, then two additional cultures with CFU/mL of the same species   |
| Treat  | ment characteristics:   |
|  | of antibiotic and length of treatment: 0.5g sulfamethoxypyridazine daily until delivery;  |
| if infe                                      | ction did not clear in one week, the patient was given 100mg nitrofurantoin 3 times<br>until delivery   |
| -  | ol group: Received a placebo tablet supplied by the same manufacturer   |
| Follow                                       | v-up testing: Treated patients were retested within the 4 wks preceding delivery. Data 12 months postpartum bacteriuria presented for a subset of women (n=91) (Kass,   |
| Outcomes Benef                               |   |
| Pyelo<br>inflam<br>and fe<br>depar<br>Perina | nephritis: dysuria, frequency, and flank pain or other localizing evidence of<br>mation, with either documented temperature of 100°F or above or a history of chills<br>ever. When patients were seen outside the clinic (e.g., accident floor or emergency<br>tment), it was not always clear that patients were indeed febrile.<br>atal mortality: ND; 'perinatal death' and fetal loss >20 wks GA<br>wirth weight (defined as prematurity): <2500g |
| Harm   | s: NR   |
| Notes Kass,<br>1967<br>patier<br>receiv      | 1960 is a preliminary report, updated and more complete data retrieved from Savage, are presented. The study also includes a group of non-bacteriuric women. Some nts participated for >1 pregnancy, and were reassigned to the same treatment they yed in the first pregnancy. Outcome of pyelonephritis reported only for the antenatal d, postpartum excluded. Outcome of low birth weight given for the total number of                           |
|  | ries (3 twin deliveries in the placebo group and none in the treated group).  |
|  | iuria; CFU/mL: colony forming units per millilitre; F: Fahrenheit; g: gram(s); GA:  |
| estational age mg millig                     | ram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled tria   |
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| Kazemier, 2015 |  |
|----------------|--|
| Objective      | To investigate the consequences of treated and untreated ASB in pregnancy                            |
| Methods        | Design: Prospective cohort (screening vs. no screening) with embedded RCT                            |
|                | Recruitment: Pregnant women attending antenatal clinics offering screening (not routinely available) |

|               | Inclusion criteria: Pregnant women aged ≥18 years with a singleton pregnancy who were between 16 and 22 wks GA, tested positive for ASB, and did not have symptoms of UTI  |
|---------------|--|
|               | Exclusion criteria: History of preterm delivery <34 wks, warning signs of imminent pretern<br>delivery, fetal congenital malformations, antibiotic use within 2 wks of screening, known<br>glucose-6-phosphate dehydrogenase deficiency, hypersensitivity to nitrofurantoin, risk<br>factors for complicated UTI (e.g., pre-gestational DM, use of immunosuppressive<br>medication or functional or structural abnormalities of the urinary tract) |
| Participants  | Setting: 8 hospitals and 5 ultrasound centres, the Netherlands   |
|               | Study period: October 11, 2011-August 22, 2014   |
|               | Sample: n=248; treated (n=40); placebo (n=45), untreated (n=163)   |
|               | Mean age (SE), years: treated=29 (0.74), placebo or untreated=31 (0.33)  |
|               | Risk factors:  |
|               | Ethnicity (non-white): treated n=3 (8%), placebo or untreated n=36 (17%)<br>Low education (≤pre-vocational level): treated n=6 (15%), placebo or untreated n=21 (109   |
|               | Length of follow-up: Until 6 wks postpartum  |
|               | Loss to follow-up: n=12 (5%) lost, all from the untreated or placebo group; 5 women could not be contacted for outcomes because of errors in their contact information. Missing dat were imputed (see notes).  |
| Interventions | <ul> <li>Screening characteristics:</li> <li>Timing, median (IQR) wks + days GA: treated=20+2 (19+6 to 20+5), placebo or untreated=20+0 (19+3 to 20+3)</li> <li>Urine collection: Midstream urine sample</li> <li>Urine testing method: Dipslide</li> <li>Criteria for a positive test: ≥10<sup>5</sup> CFU/mL of a single microorganism or when two different</li> </ul>  |
|               | colony types were present but one had a concentration of $\geq 10^5$ CFU/mL  |
|               | Treatment characteristics:   |
|               | Type of antibiotic and length of treatment: 100mg nitrofurantoin twice daily for 5 days; if<br>bacteriuria did not clear the treatment was repeated for a maximum of two rounds<br>Control group: Received identical placebo capsules on the same dose and schedule as<br>treated patients, or no treatment  |
|               | Follow-up testing: All participants provided a follow-up dipslide 1 week after the end of treatment; those who remained positive were retested after each new round of treatmer for a maximum of two rounds  |
| Outcomes      | Benefits:<br>Pyelonephritis: Hospital admission with ≥2 of the following: fever (body temperature  |
|               | <ul> <li>≥38°C), symptoms of pyelonephritis (nausea, vomiting, chills, and costovertebral tenderness), and a positive urine culture indicating the presence of bacteria in the urine.</li> <li>Perinatal mortality: neonatal death before discharge from the neonatal ward</li> <li>Preterm delivery: spontaneous birth between 32 and 37 wks GA</li> <li>Low birth weight: &lt;10<sup>th</sup> or 5<sup>th</sup> percentile</li> </ul>            |
|               | Neonatal sepsis: Confirmed with culture, includes group B streptococcal sepsis   |
|               | Harms:   |
|               | Serious adverse events: Congenital abnormalities (ND)  |

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| Notes | Cohort study addressed screening, results reported here for treatment RCT only. Study        |
|-------|--|
|       | included both placebo and untreated groups who were combined in the analysis. When           |
|       | data were missing, these were imputed taking into account patient characteristics and        |
|       | outcomes. Differences in outcomes between groups were controlled for potential               |
|       | confounders (smoking, low education, conception through in-vitro fertilization or            |
|       | intracytoplasmic sperm injection, pre-existing hypertension). 5 women originally assigned to |
|       | treatment group were later found to not have ASB, but remained in their assigned group       |
|       | (intention-to-treat analysis).   |

ASB: asymptomatic bacteriuria; C: Celsius; CFU/mL: colony forming units per millilitre; DM: diabetes mellitus; g: gram(s); GA: gestational age; IQR: interquartile range; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SE: standard error; UTI: urinary tract infection; wks: weeks

| Objective     | To assess the effectiveness of antibacterial drugs for pregnant women with bacteriuria in preventing pyelonephritis, perinatal mortality, and low birth weight   |
|---------------|--|
| Methods       | Design: RCT; placebo-controlled  |
|               | Recruitment: Pregnant women attending their first antenatal visit before 26 wks GA   |
|               | Inclusion criteria: Pregnant women <26 wks GA with ASB at the first antenatal visit and confirmed by a subsequent positive test  |
|               | Exclusion criteria: NR   |
| Participants  | Setting: Queen Victoria Hospital, Melbourne, Australia; urban  |
|               | Study period: 1964-1965  |
|               | Sample: n=145; treated (n=61), placebo (n=56) (see notes)  |
|               | Mean age (SD), years: NR   |
|               | Risk factors: (see notes)<br>Socioeconomic status: All from lowest income category in community, but the community<br>has a high standard of living<br>Urogenital anomalies: At post-delivery testing, 51.4% of patients had an abnormal<br>intravenous pyelogram and 5 patients had poorly functioning or non-functioning kidneys of<br>one side due to ureteric obstruction.       |
|               | Length of follow-up: Until 6 months postpartum   |
|               | Loss to follow-up: Of initial 240 women with completed pregnancies, no outcomes reported<br>for 95 women for various reasons (6 aborted before treatment, 20 developed symptoms<br>before treatment, 22 attended infrequently, 33 failed to take tablets continuously, 14 had<br>coagulase-negative staphylococcal bacteriuria); further information on non-compliant<br>patients NR |
| Interventions | Screening characteristics:<br>Timing: First antenatal visit  |
|               | Urine collection: Midstream urine sample; the second test was clean-voided (first was not)<br>Urine testing method: Urine culture<br>Criteria for a positive test: >10 <sup>5</sup> CFU/mL on two occasions  |

| Outcomes          | Treatment characteristics:<br>Type of antibiotic and length of treatment: 0.5g sulphamexydiazine daily, changing to 1g<br>sulphadimidine 3 times daily in the 13 <sup>th</sup> week of gestation, continuing until delivery; if<br>resistance to sulphonamides was indicated by sensitivity tests, 500mg ampicillin 3 times<br>daily or 50mg nitrofurantoin 4 times daily was prescribed instead.<br>Control group: Received identical placebo capsules and tablets<br>Follow-up testing: Patients re-examined at monthly intervals, on any hospital admission,<br>and at delivery. Retesting at 6 wks-3 months and 6 months postpartum ongoing at the time<br>of publication. These subsequent samples involved cleansing of the periurethral area and<br>insertion of a vaginal tampon to avoid contamination.<br>Benefits:<br>Pyelonephritis: Loin pain and tenderness, with or without pyrexia, and rigors, with or<br>without symptoms of dysuria and frequency |
|-------------------|--|
|                   | Perinatal mortality: >28 wks GA<br>Low birth weight (reported as preterm delivery): <2500g   |
|                   |  |
|                   | Harms: NR  |
| Notes             | Study also included a non-bacteriuric group. 29/145 (20%) patients were given treatment or   |
|                   | placebo prior to confirmation of ASB (before the second culture was analyzed); outcomes  |
|                   | for these patients were reported separately, leaving 116 in the current analysis. 11 fetal   |
|                   | losses reported but group assignment NR.   |
| ASB: asymptomatic | chacteriuria: CEU/mL: colony forming units per millilitre; g: gram(s): GA: gestational age; mg:  |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; mg: milligram(s); NR: not reported; RCT: randomized controlled trial; SD: standard deviation; wks: weeks

| Little, 1966 |  |
|--------------|--|
| Objective    | To assess the effect of antibiotic treatment for pregnant women with ASB on incidence of                                 |
|              | pyelonephritis and adverse pregnancy outcomes  |
| Methods      | Design: RCT; placebo-controlled  |
|              | Recruitment: Pregnant women attending their first antenatal visit  |
|              | Inclusion criteria: Pregnant women with bacteriuria at the first antenatal visit and confirmed with a subsequent culture |
|              | Exclusion criteria: NR   |
| Participants | Setting: Charing Cross Hospital and Fulham Maternity Hospital, London, England; urban                                    |
|              | Study period: 1962-1965  |
|              | Sample: n=265; treated (n=124), placebo (n=141)  |
|              | Mean age (SD), years: NR; 6.89% 10-20, 4.99% 21-30, 4.62% 31-40, 4.25% ≥40   |
|              | Risk factors:<br>Past history of urinary tract disease: 62 (23.4%) recalled a past episode (both groups<br>combined)     |
|              | Length of follow-up: Until 6 wks postpartum  |

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|               | Loss to follow-up: None reported.  |
|---------------|--|
| Interventions | Screening characteristics:   |
|               | Timing: First antenatal visit, usually ~12 <sup>th</sup> week of gestation   |
|               | Urine collection: Clean-voided midstream urine sample  |
|               | Urine testing method: Urine culture  |
|               | Criteria for a positive test: Two consecutive urine cultures with >10 <sup>5</sup> CFU/mL  |
|               | Treatment characteristics:   |
|               | Type of antibiotic and length of treatment: At start of trial, patients were given 0.5g sulphamethoxypyridazine daily for 30 days; if bacteriuria did not clear, 1.5g ampicillin daily was given for 1 week, then a maintenance dose of 1g daily until delivery. Because treatment |
|               | with ampicillin was generally not successful, later in the trial, a single dose of 100mg   |
|               | nitrofurantoin became the first form of treatment.   |
|               | Control group: Received placebo tablets<br>Follow-up testing: Retested monthly throughout pregnancy  |
| Outcomes      | Benefits:  |
| Outcomes      | Pyelonephritis: Loin pain and tenderness, a fever >100°F, >10 <sup>5</sup> CFU/mL. Usually there was also frequency and dysuria, and sometimes rigors and hematuria Perinatal mortality: ND  |
|               | Low birth weight (reported as prematurity): <2500g   |
|               | Harms:   |
|               | Serious adverse events: fetal abnormalities, ND  |
| Notes         | No additional notes  |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; F: Fahrenheit; g: gram(s); mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation

| Mulla, 1960  |   |
|--------------|---|
| Objective    | To evaluate the clinical results of treatment of bacteriuria in pregnant women with long- |
|              | acting sulfonamide  |
| Methods      | Design: RCT   |
|              | Recruitment: Pregnant women attending the obstetrical clinic                              |
|              | Inclusion criteria: Pregnant women with ASB at their 30-32 wks GA obstetric visit         |
|              | Exclusion criteria: NR  |
| Participants | Setting: St. Elizabeth Hospital, Ohio, US; urban  |
|              | Study period: NR  |
|              | Sample: n=100; treated (n=50), not treated (n=50)   |
|              | Mean age (SD), years: NR  |
|              | Risk factors: NR  |
|              | Length of follow-up: Until delivery and immediately after                                 |

|               | Loss to follow up: None reported   |  |  |  |  |  |  |  |
|---------------|--|--|--|--|--|--|--|--|
|               | Loss to follow-up: None reported.  |  |  |  |  |  |  |  |
| Interventions | Screening characteristics:   |  |  |  |  |  |  |  |
|               | Timing: Obstetric visit at 30-32 wks GA  |  |  |  |  |  |  |  |
|               | Urine collection: Catheter urinalysis (antimicrobial jelly used on the catheter)             |  |  |  |  |  |  |  |
|               | Urine testing method: Urine culture  |  |  |  |  |  |  |  |
|               | Criteria for a positive test: NR   |  |  |  |  |  |  |  |
|               | Treatment characteristics:   |  |  |  |  |  |  |  |
|               | Type of antibiotic and length of treatment: 250mg sulfadimethoxine twice daily for 1 week    |  |  |  |  |  |  |  |
|               | the regimen was repeated if bacteriuria persisted  |  |  |  |  |  |  |  |
|               | Control group: Received no medication until symptoms appeared                                |  |  |  |  |  |  |  |
|               | Follow-up testing: Followed at weekly intervals until delivery; were re-tested at least once |  |  |  |  |  |  |  |
|               | after the first course of treatment.   |  |  |  |  |  |  |  |
| Outcomes      | Benefits:  |  |  |  |  |  |  |  |
|               | Pyelonephritis: Clinical evidence of active infection, including acute symptoms of           |  |  |  |  |  |  |  |
|               | cystopyelitis; urine was tested at the time of the episode                                   |  |  |  |  |  |  |  |
|               |  |  |  |  |  |  |  |  |
|               | Harms: NR  |  |  |  |  |  |  |  |
| Notes         | Pyelonephritis after delivery was reported, but this was excluded from the present analysi   |  |  |  |  |  |  |  |

randomized controlled trial; SD: standard deviation; US: United States; wks: weeks

| Pathak, 1969 |   |  |  |  |  |  |  |  |  |
|--------------|---|--|--|--|--|--|--|--|--|
| Objective    | To determine the effect of short-term antibacterial therapy on eradication of bacteriuria   |  |  |  |  |  |  |  |  |
|              | during pregnancy, and its effects on pregnancy outcomes   |  |  |  |  |  |  |  |  |
| Methods      | Design: RCT; placebo-controlled   |  |  |  |  |  |  |  |  |
|              | Recruitment: Pregnant women attending antenatal clinics   |  |  |  |  |  |  |  |  |
|              | Inclusion criteria: Pregnant women ≤24 wks GA with confirmed bacteriuria on two   |  |  |  |  |  |  |  |  |
|              | consecutive tests   |  |  |  |  |  |  |  |  |
|              | Exclusion criteria: Confirmation of bacteriuria at >24 wks GA, blood pressure >130/90mmH  |  |  |  |  |  |  |  |  |
|              | at the initial antenatal visit, did not re-attend after first examination (wrong dates or could<br>not be traced), early abortions, clinical pyelonephritis, 'mentally defective' |  |  |  |  |  |  |  |  |
| Participants | Setting: University College Hospital and Kingston Public Hospital, Jamaica; urban   |  |  |  |  |  |  |  |  |
|              | Study period: NR  |  |  |  |  |  |  |  |  |
|              | Sample: n=178; treated (n=76); placebo (n=76)   |  |  |  |  |  |  |  |  |
|              | Mean age (SD), years: NR  |  |  |  |  |  |  |  |  |
|              | Risk factors:   |  |  |  |  |  |  |  |  |
|              | Sickle-cell trait: 18/24 (21.4%) in bacteriuric patients, incidence by group NR   |  |  |  |  |  |  |  |  |
|              | Urogenital anomalies: 9/50 (18%) of bacteriurics had abnormalities on postpartum  |  |  |  |  |  |  |  |  |
|              | intravenous pyelogram (1 bilateral hydroureter with hydronephrosis, 1 localized calyceal  |  |  |  |  |  |  |  |  |
|              | clubbing, 1 bifid pelvis, 2 had changes consistent with papillary necrosis, 4 showed evidence   |  |  |  |  |  |  |  |  |
|              | of chronic pyelonephritis).   |  |  |  |  |  |  |  |  |

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|              | Length of follow-up: Until delivery (all) and 3-9 months postpartum for a subset  |
|--------------|---|
|              | Loss to follow-up: n=26 (15%) lost; 12 (14%) treated (9 antibiotic received for positive  |
|              | serology, 3 defaulted from the clinic and could not be traced), 14 (16%) placebo (12 antibiotic received, 3 defaulted from the clinic)  |
| nterventions | Screening characteristics:  |
|              | Timing: NR; ≤24 wks GA  |
|              | Urine collection: clean-voided urine sample   |
|              | Urine testing method: NR  |
|              | Criteria for a positive test: >10 <sup>5</sup> CFU/mL on two consecutive specimens  |
|              | Treatment characteristics:  |
|              | Type of antibiotic and length of treatment: 100mg nitrofurantoin twice daily for 3 wks;<br>patients who did not respond received 400mg nitrofurantoin daily for a further 4 days<br>Control group: Received placebo identical in appearance |
|              | Follow-up testing: Retested at weekly intervals during treatment (or placebo), then every 2 wks until delivery, and a subset (n=69, 24 treated and 45 placebo) at 3-9 months postpartum   |
| Outcomes     | Benefits:<br>Pyelonephritis: ND   |
|              | Harms: NR   |
| Notes        | Reported preterm birth/fetal loss only by bacteriuric status, not by treatment group.   |

ASB: asymptomatic bacteriuria; CFU: colony forming units per millilitre; GA: gestational age; mg: milligram; mmHg: millimetre of mercury; n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; wks: weeks

| Thomsen, 1987 |   |  |  |  |  |  |  |  |
|---------------|---|--|--|--|--|--|--|--|
| Objective     | To assess the effect of treatment for group-B streptococcal bacteriuria in pregnant women<br>on the incidence of preterm labour |  |  |  |  |  |  |  |
| Methods       | Design: RCT; placebo-controlled   |  |  |  |  |  |  |  |
|               | Recruitment: Pregnant women attending Statens Seruminstitut   |  |  |  |  |  |  |  |
|               | Inclusion criteria: Pregnant women 27-31 wks GA who were positive for group-B streptococcal bacteriuria                         |  |  |  |  |  |  |  |
|               | Exclusion criteria: NR; <27 or >31 wks GA   |  |  |  |  |  |  |  |
| Participants  | Setting: University Hospital, Denmark; urban  |  |  |  |  |  |  |  |
|               | Study period: October 1, 1984-October 1, 1986   |  |  |  |  |  |  |  |
|               | Sample: n=69; treated (n=37), placebo (n=32)  |  |  |  |  |  |  |  |
|               | Mean age, years: 28.1, similar for both groups  |  |  |  |  |  |  |  |
|               | Risk factors:   |  |  |  |  |  |  |  |
|               | Ethnicity: All patients were white  |  |  |  |  |  |  |  |
|               | Socioeconomic status: Similar for both groups   |  |  |  |  |  |  |  |

|  | Length of follow-up: Until delivery (see notes)   |  |  |  |  |  |  |  |  |
|--|---|--|--|--|--|--|--|--|--|
|  | Loss to follow-up: None reported.   |  |  |  |  |  |  |  |  |
| Interventions  | Screening characteristics:  |  |  |  |  |  |  |  |  |
|  | Timing: NR; 27-31 wks GA  |  |  |  |  |  |  |  |  |
|  | Urine collection: Midstream urine sample  |  |  |  |  |  |  |  |  |
|  | Urine testing method: Urine culture<br>Criteria for a positive test: $10^2$ - $10^6$ CEU/mL of group-B streptococci bacteria  |  |  |  |  |  |  |  |  |
|  | Criteria for a positive test: 10 <sup>2</sup> -10 <sup>6</sup> CFU/mL of group-B streptococci bacteria  |  |  |  |  |  |  |  |  |
|  | Treatment characteristics:  |  |  |  |  |  |  |  |  |
|  | Type of antibiotic and length of treatment: 10 <sup>6</sup> IU penicillin 3 times daily for 6 days;   |  |  |  |  |  |  |  |  |
|  | treatment was repeated if bacteriuria persisted   |  |  |  |  |  |  |  |  |
|  | Control group: Received placebo tablets   |  |  |  |  |  |  |  |  |
|  | Follow-up testing: Retested weekly until delivery for persistent bacteriuria or recurr  |  |  |  |  |  |  |  |  |
| Outcomes   | Benefits:   |  |  |  |  |  |  |  |  |
|  | Preterm delivery: <37 wks GA (mean wks GA for treated: 39.6, placebo: 36.2)   |  |  |  |  |  |  |  |  |
|  | Neonatal sepsis: ND   |  |  |  |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
|  | Harms: NR   |  |  |  |  |  |  |  |  |
| Notes  | Patients positive for streptococci at delivery were treated with 2g ampicillin intrave  |  |  |  |  |  |  |  |  |
|  | followed by 1g intravenously every 4 hours from the start of labour. Infants were given   |  |  |  |  |  |  |  |  |
|  | ampicillin (50mg/kg) intramuscularly every 12 hours to avoid sepsis. Umbilical cord   |  |  |  |  |  |  |  |  |
|  | was tested from group-B streptococci and babies with positive cultures were treate  |  |  |  |  |  |  |  |  |
|  |   |  |  |  |  |  |  |  |  |
|  | days. One infant tested positive for sepsis at 6 wks post-delivery.<br>tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age<br>t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra   |  |  |  |  |  |  |  |  |
| nternational uni<br>ontrolled trial; v                   | days. One infant tested positive for sepsis at 6 wks post-delivery.<br>tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age<br>t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra   |  |  |  |  |  |  |  |  |
| iternational uni   | days. One infant tested positive for sepsis at 6 wks post-delivery.<br>tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age<br>t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra   |  |  |  |  |  |  |  |  |
| nternational uni<br>ontrolled trial; v                   | days. One infant tested positive for sepsis at 6 wks post-delivery.<br>tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age<br>t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra<br>wks: weeks   |  |  |  |  |  |  |  |  |
| nternational uni<br>ontrolled trial; v<br>Williams, 1969 | days. One infant tested positive for sepsis at 6 wks post-delivery.<br>tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age<br>t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra<br>wks: weeks   |  |  |  |  |  |  |  |  |
| nternational uni<br>ontrolled trial; v<br>Williams, 1969 | days. One infant tested positive for sepsis at 6 wks post-delivery.<br>tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age<br>t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra<br>wks: weeks<br>To investigate the effect of treatment of ASB in pregnancy on urine concentrating a  |  |  |  |  |  |  |  |  |
| ontrolled trial; w<br>Williams, 1969<br>Objective        | days. One infant tested positive for sepsis at 6 wks post-delivery.         tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age         t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra         wks: weeks         To investigate the effect of treatment of ASB in pregnancy on urine concentrating a and the development of symptomatic UTI         Design: RCT   |  |  |  |  |  |  |  |  |
| ontrolled trial; w<br>Williams, 1969<br>Objective        | days. One infant tested positive for sepsis at 6 wks post-delivery.         tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age         t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra         wks: weeks         To investigate the effect of treatment of ASB in pregnancy on urine concentrating a and the development of symptomatic UTI         Design: RCT         Recruitment: Pregnant women attending their first antenatal visit   |  |  |  |  |  |  |  |  |
| ontrolled trial; w<br>Williams, 1969<br>Objective        | days. One infant tested positive for sepsis at 6 wks post-delivery.         tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age         t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra         wks: weeks         To investigate the effect of treatment of ASB in pregnancy on urine concentrating a and the development of symptomatic UTI         Design: RCT         Recruitment: Pregnant women attending their first antenatal visit         Inclusion criteria: Pregnant women <30 wks GA with significant ASB at the first antenatal   |  |  |  |  |  |  |  |  |
| ontrolled trial; w<br>Williams, 1969<br>Objective        | days. One infant tested positive for sepsis at 6 wks post-delivery.         tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age         t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra         wks: weeks         To investigate the effect of treatment of ASB in pregnancy on urine concentrating a and the development of symptomatic UTI         Design: RCT         Recruitment: Pregnant women attending their first antenatal visit   |  |  |  |  |  |  |  |  |
| ontrolled trial; w<br>Williams, 1969<br>Objective        | days. One infant tested positive for sepsis at 6 wks post-delivery.         tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age         t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra         wks: weeks         To investigate the effect of treatment of ASB in pregnancy on urine concentrating a and the development of symptomatic UTI         Design: RCT         Recruitment: Pregnant women attending their first antenatal visit         Inclusion criteria: Pregnant women <30 wks GA with significant ASB at the first antenatal   |  |  |  |  |  |  |  |  |
| ontrolled trial; w<br>Williams, 1969<br>Objective        | days. One infant tested positive for sepsis at 6 wks post-delivery.         tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age         t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra         wks: weeks         To investigate the effect of treatment of ASB in pregnancy on urine concentrating a and the development of symptomatic UTI         Design: RCT         Recruitment: Pregnant women attending their first antenatal visit         Inclusion criteria: Pregnant women <30 wks GA with significant ASB at the first anter visit, confirmed by a second positive test within 10 days |  |  |  |  |  |  |  |  |
| williams, 1969<br>Objective<br>Methods                   | days. One infant tested positive for sepsis at 6 wks post-delivery.         tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age         t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: ra         wks: weeks         To investigate the effect of treatment of ASB in pregnancy on urine concentrating a and the development of symptomatic UTI         Design: RCT         Recruitment: Pregnant women attending their first antenatal visit         Inclusion criteria: Pregnant women <30 wks GA with significant ASB at the first anten visit, confirmed by a second positive test within 10 days |  |  |  |  |  |  |  |  |
| williams, 1969<br>Objective<br>Methods                   | days. One infant tested positive for sepsis at 6 wks post-delivery.         tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age         t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: rawks: weeks         To investigate the effect of treatment of ASB in pregnancy on urine concentrating a and the development of symptomatic UTI         Design: RCT         Recruitment: Pregnant women attending their first antenatal visit         Inclusion criteria: Pregnant women <30 wks GA with significant ASB at the first anter visit, confirmed by a second positive test within 10 days          |  |  |  |  |  |  |  |  |
| williams, 1969<br>Objective<br>Methods                   | days. One infant tested positive for sepsis at 6 wks post-delivery.         tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age         t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: rawks: weeks         To investigate the effect of treatment of ASB in pregnancy on urine concentrating a and the development of symptomatic UTI         Design: RCT         Recruitment: Pregnant women attending their first antenatal visit         Inclusion criteria: Pregnant women <30 wks GA with significant ASB at the first anten visit, confirmed by a second positive test within 10 days          |  |  |  |  |  |  |  |  |
| williams, 1969<br>Objective<br>Methods                   | days. One infant tested positive for sepsis at 6 wks post-delivery.         tic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age         t; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: rawks: weeks         To investigate the effect of treatment of ASB in pregnancy on urine concentrating a and the development of symptomatic UTI         Design: RCT         Recruitment: Pregnant women attending their first antenatal visit         Inclusion criteria: Pregnant women <30 wks GA with significant ASB at the first anter visit, confirmed by a second positive test within 10 days          |  |  |  |  |  |  |  |  |

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|               | Length of follow-up: Until 10 days postpartum  |  |  |  |  |  |  |  |  |
|---------------|--|--|--|--|--|--|--|--|--|
|               | Loss to follow-up: None reported   |  |  |  |  |  |  |  |  |
| Interventions | Screening characteristics:   |  |  |  |  |  |  |  |  |
|               | Timing: First antenatal visit; mean (SE) 20.78 (0.45) wks GA   |  |  |  |  |  |  |  |  |
|               | Urine collection: Clean-voided midstream urine sample  |  |  |  |  |  |  |  |  |
|               | Urine testing method: Urine culture  |  |  |  |  |  |  |  |  |
|               | Criteria for a positive test: >10 <sup>5</sup> gram-negative CFU/mL in at least two consecutive urine  |  |  |  |  |  |  |  |  |
|               | specimens; if the first specimen was positive, patients were recalled for a second specimen within 10 days   |  |  |  |  |  |  |  |  |
|               | Treatment characteristics:   |  |  |  |  |  |  |  |  |
|               | Type of antibiotic: 1g sulphadimidine 3 times daily for 7 days; if bacteriuria persisted, patients received 100mg nitrofurantoin twice daily for 7 days; if bacteriuria still persisted, |  |  |  |  |  |  |  |  |
|               | patients received 250mg ampicillin 3 times daily for 7 days (ampicillin repeated as necessary)   |  |  |  |  |  |  |  |  |
|               | Control group: received no treatment until symptoms presented  |  |  |  |  |  |  |  |  |
|               | Follow-up testing: Retested 2-3 wks after the first course of treatment, and each subsequent course of treatment   |  |  |  |  |  |  |  |  |
| Outcomes      | Benefits:  |  |  |  |  |  |  |  |  |
|               | Pyelonephritis: loin pain and tenderness with or without fever (no record of fever in  |  |  |  |  |  |  |  |  |
|               | antenatal patients)  |  |  |  |  |  |  |  |  |
|               | Harms: NR  |  |  |  |  |  |  |  |  |
| Notes         | The study also included a non-bacteriuric and a non-pregnant group. Data for pyelonephriti   |  |  |  |  |  |  |  |  |
|               | includes postpartum infections (n=6) because group assignment NR.  |  |  |  |  |  |  |  |  |

| nfection; wks: w | reeks  |  |  |  |  |  |  |  |  |
|------------------|--|--|--|--|--|--|--|--|--|
| Wren, 1969       |  |  |  |  |  |  |  |  |  |
| Objective        | To evaluate the effect of treatment of pregnant women with ASB on the incidence of premature deliveries and other adverse pregnancy outcomes |  |  |  |  |  |  |  |  |
| Methods          | Design: Quasi-RCT<br>Recruitment: Pregnant women booking at an antenatal clinic  |  |  |  |  |  |  |  |  |
|                  | Inclusion criteria: Pregnant women with ASB at their first antenatal visit   |  |  |  |  |  |  |  |  |
|                  | Exclusion criteria: NR   |  |  |  |  |  |  |  |  |
| Participants     | Setting: Royal Hospital for Women, New South Wales, Australia; urban<br>Study period: November 1968-December 1968                            |  |  |  |  |  |  |  |  |
|                  | Sample: n=183; treated (n=83), untreated (n=90)  |  |  |  |  |  |  |  |  |
|                  | Mean age (SD): NR  |  |  |  |  |  |  |  |  |
|                  | Risk factors: NR   |  |  |  |  |  |  |  |  |

|               | Length of follow-up: Until 6 wks postpartum  |  |  |  |  |  |  |  |  |
|---------------|--|--|--|--|--|--|--|--|--|
|               | Loss to follow-up: Of original n=183, 10 (5%) women lost; 2 sets of twins, 4 moved away and could not be traced, 3 received antibiotics before the trial started, 1 refused to take the    |  |  |  |  |  |  |  |  |
|               | treatment  |  |  |  |  |  |  |  |  |
| Interventions | Screening characteristics:   |  |  |  |  |  |  |  |  |
|               | Timing: First antenatal visit  |  |  |  |  |  |  |  |  |
|               | Urine collection: Midstream urine sample   |  |  |  |  |  |  |  |  |
|               | Urine testing method: NR   |  |  |  |  |  |  |  |  |
|               | Criteria for a positive test: NR   |  |  |  |  |  |  |  |  |
|               | Treatment characteristics:   |  |  |  |  |  |  |  |  |
|               | Type of antibiotic and length of treatment: Rotational therapy with 100mg nitrofurantoin   |  |  |  |  |  |  |  |  |
|               | twice daily for 2 wks, 250mg ampicillin 4 times daily for 1 week, 500mg sulphurazole 4 time  |  |  |  |  |  |  |  |  |
|               | daily for 4 wks, and nalidixic acid 4 times daily for 2 wks. Each new patient started with one of the four drugs, then rotated through the remaining drugs in order. Every 9 wks, patients |  |  |  |  |  |  |  |  |
|               | began a new course of rotational therapy until 1-6 wks after delivery.   |  |  |  |  |  |  |  |  |
|               | Control group: Untreated until clinical evidence of UTI developed  |  |  |  |  |  |  |  |  |
|               | Follow-up testing: Patients were retested one per month when possible, until the last  |  |  |  |  |  |  |  |  |
|               | month of pregnancy   |  |  |  |  |  |  |  |  |
| Outcomes      | Benefits:  |  |  |  |  |  |  |  |  |
|               | Spontaneous abortion: ND; 'abortion'   |  |  |  |  |  |  |  |  |
|               | Perinatal mortality: Stillbirth and neonatal death   |  |  |  |  |  |  |  |  |
|               | Preterm delivery: <37 wks GA   |  |  |  |  |  |  |  |  |
|               | Low birth weight (reported as prematurity): <2501g   |  |  |  |  |  |  |  |  |
|               |  |  |  |  |  |  |  |  |  |
|               | Harms: NR  |  |  |  |  |  |  |  |  |
| Notes         | The study also included a control group of non-bacteriuric women.  |  |  |  |  |  |  |  |  |

ASB: asymptomatic bacteriuria; g: gram(s); GA: gestational age; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; UTI: urinary tract infection; wks: weeks

4 5

# Supplement 5. Risk of bias (ROB) assessments for included studies

| 5        | Summary of ROB for studies of screening effectiveness |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
|----------|---|---|------------------------------------|---------------------------|--|------------|--------------------------|-----------------------|-----------------------|-------------------------------------|-------------------------------------|-----------|------------|------------------------------|
| 6<br>7   | First Author,   |   |                                    | Selection                 |  |            |                          | Comparability Outcome |                       |                                     |                                     |           | Total      | Selective                    |
| 8        | Year  |   |                                    |                           |  |            |                          |                       |                       |                                     | Score <sup>a</sup>                  | Outcome   |            |                              |
| 9        |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           | (max       | <b>Reporting<sup>b</sup></b> |
| 10       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           | 9)         |                              |
| 11       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 12       |   |   | σ                                  | e                         | /  |            | Ś                        |                       | a)                    | Ň                                   | 4                                   |           |            |                              |
| 13       |   | of                                      | ose                                | nso                       | it si<br>itis  |            | ort                      |                       | and a                 | lo                                  | d                                   |           |            |                              |
| 14       |   | Representativeness of<br>exposed cohort | Selection of non-exposed<br>cohort | Ascertainment of exposure | Outcome not present at start<br>of study (pyelonephritis/<br>other outcomes) |            | Comparability of cohorts |                       | Assessment of outcome | Adequacy of length of follow-<br>up | Adequacy of follow-up of<br>cohorts |           |            |                              |
| 15       |   | oh d                                    | t h                                | ofe                       | ser<br>nel   |            | ofo                      |                       | no                    | ÷                                   | llo<br>S                            |           |            |                              |
| 16       |   | ativ<br>d c                             | of non<br>cohort                   | Ť                         | elo<br>Ltc   | Total      | ₹                        | Total                 | tof                   | eng<br>up                           | f fo                                | Total     |            |                              |
| 17       |   | ente                                    | of                                 | nei                       | r by   | Ĕ          | pil                      | Ĕ                     | ent                   | lf le                               | y of foll<br>cohorts                | Ĕ         |            |                              |
| 18       |   | resentativeness<br>exposed cohort       | u                                  | in in i                   | he n<br>he n   |            | ara                      |                       | sm                    | 20                                  | ac                                  |           |            |                              |
| 19       |   | epr                                     | ect                                | erte                      |  |            | dr                       |                       | ses                   | nac                                 | nba                                 |           |            |                              |
| 20       |   | Å                                       | Sele                               | SCE                       | utco<br>of s   |            | CO                       |                       | As                    | ed                                  | Ade                                 |           |            |                              |
| 21       |   |   | •,                                 | A                         | ō  |            | _                        |                       |                       | Ad                                  |                                     |           |            |                              |
| 22       | Gérard, 1983  | 1                                       | 1                                  | 0                         | 0/1  | 3          | 0                        | 0                     | 1                     | 1                                   | 1                                   | 3         | 6          | Suspected <sup>c</sup>       |
| 23       | Gratacós, 1994  | 1                                       | 1                                  | 0                         | 0/1  | 3          | 0                        | 0                     | 1                     | 1                                   | 1                                   | 3         | 6          | Suspected <sup>d</sup>       |
| 24       | Rhode, 2007   | 1                                       | 1                                  | 1                         | 0/1  | 4          | 1                        | 1                     | 1                     | 1                                   | 1                                   | 3         | 8          | Suspected <sup>e</sup>       |
| 25       | Uncu, 2002  | 1                                       | 1                                  | 1                         | 0/1  | 4          | 0                        | 0                     | 1                     | 1                                   | 0                                   | 2         | 6          | Not                          |
| 26       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            | suspected <sup>f</sup>       |
| 27<br>28 | aAssesse  | ed using t                              | the Newo                           | castle-Ot                 | tawa Qual  | ity Asses  | ssment S                 | cale <sup>31</sup>    |                       |                                     |                                     |           |            |                              |
| 28<br>29 | <sup>b</sup> Assesse                                  | ed due to                               | concerr                            | n regardi                 | ng reportir  | ng bias ir | h the stu                | dies, but             | assessm               | ent not i                           | included                            | in the to | otal score | 2                            |
| 30       | <sup>c</sup> Did not                                  | report o                                | on fetal a                         | bnormal                   | ities  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 31       | <sup>d</sup> Did not                                  | report o                                | on sponta                          | aneous a                  | bortion, p   | erinatal ı | mortality                | , pretern             | n deliver             | y or feta                           | l abnorn                            | nalities  |            |                              |
| 32       | <sup>e</sup> Did not                                  | report o                                | on sponta                          | aneous a                  | bortion, pe  | erinatal ı | mortality                | , or fetal            | abnorm                | alities                             |                                     |           |            |                              |
| 33       | <sup>f</sup> Reporte                                  | d on all                                | outcome                            | s, includ                 | ing fetal d  | eath >20   | weeks o                  | of gestati            | on (eligil            | ble for p                           | erinatal                            | mortality | /)         |                              |
| 34       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 35       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 36       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 37       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 38       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 39       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 40       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 41       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 42       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 43<br>44 |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 44       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 46       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 47       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 48       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 49       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 50       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 51       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 52       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 53       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 54       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 55       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 56       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 57       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 58       |   |   |                                    |                           |  |            |                          |                       |                       |                                     |                                     |           |            |                              |
| 59       |   |   | Farmer                             | or route                  | با باعما   | to.//k*    | onen l-                  | oi com- / -           | +0/04-                | +/~                                 | in an aire                          |           |            |                              |
| 60       |   |   | For pe                             | er reviel                 | w only - ht  | rb://pm]   | open.br                  | ij.com/s              | ie/abou               | it/guidel                           | mes.xnt                             | 111       |            |                              |

| Domain   | Author's<br>judgement | Support for judgement  |
|--|-----------------------|--|
| Gérard, 1983 (cohort)  | J                     |  |
| Representativeness of the exposed cohort                                       | 1                     | Included all pregnant women who visited the clinic at <25 wks GA.  |
| Selection of the non-<br>exposed cohort  | 1                     | Formed retrospectively, pregnant women attending the clinic in th 10 previous months (before implementation of screening). |
| Ascertainment of exposure  | 0                     | Not reported.  |
| Outcome not present at<br>start of study<br>(pyelonephritis/other<br>outcomes) | 0/1                   | Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.                  |
| Comparability of the cohorts   | 0                     | No evidence of comparability.  |
| Assessment of outcome  | 1                     | Appear to have used a chart review.  |
| Adequacy of length of follow-up  | 1                     | Follow-up until delivery and for 3-6 months post-partum for those with ≥2 instances of asymptomatic bacteriuria.           |
| Adequacy of follow-up of cohorts   | 1                     | No loss to follow-up.  |
| Selective outcome<br>reporting <sup>b</sup>                                    | suspected             | Did not report on fetal abnormalities.   |
| Total score (maximum 10)   | 6                     | 4  |
| Gratacós, 1944 (cohort)  |                       |  |
| Representativeness of the<br>exposed cohort                                    | 1                     | All pregnant women presenting to the clinic at <25 wks GA betwee<br>January 1991 and December 1992.                        |
| Selection of the non-<br>exposed cohort  | 1                     | Women who visited the same clinic in years (January 1987 to December 1990) before implementation of the screening program  |
| Ascertainment of exposure  | 0                     | Not reported.  |
| Outcome not present at<br>start of study<br>(pyelonephritis/other<br>outcomes) | 0/1                   | Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.                  |
| Comparability of the<br>cohorts  | 0                     | No evidence of comparability.  |
| Assessment of outcome  | 1                     | Used a chart review – 'was recorded for 6 years'.  |
| Adequacy of length of follow-up  | 1                     | Followed-up until delivery.  |
| Adequacy of follow-up of<br>cohorts  | 1                     | 10 (6.9%) lost to follow-up.   |
| Selective outcome reporting <sup>b</sup>                                       | suspected             | Did not report on spontaneous abortion, perinatal mortality, prete<br>delivery or fetal abnormalities.                     |
| Total score (maximum 10)   | 6                     |  |
| Rhode, 2007 (cohort)   |                       |  |
| Representativeness of the<br>exposed cohort                                    | 1                     | All pregnant women who enrolled for care and delivered after Aug 15, 2002.   |
| Selection of the non-<br>exposed cohort  | 1                     | All pregnant women who enrolled for care at the same practice an delivered before August 15, 2002.                         |

| Domain   | Author's<br>judgement | Support for judgement  |
|--|-----------------------|--|
| Ascertainment of exposure  | 1                     | Used delivery records.   |
| Outcome not present at<br>start of study<br>(pyelonephritis/other<br>outcomes) | 0/1                   | Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.    |
| Comparability of the<br>cohorts  | 1                     | Compared 10 demographic factors, showing that groups were simila   |
| Assessment of outcome  | 1                     | Used a chart review.   |
| Adequacy of length of follow-up  | 1                     | Followed-up until delivery of the patient left the practice.   |
| Adequacy of follow-up of cohorts   | 1                     | 112 (4.6%) lost to follow-up.  |
| Selective outcome reporting <sup>b</sup>                                       | suspected             | Did not report on spontaneous abortion, perinatal mortality or fetal abnormalities.                          |
| Total score (maximum 10)   | 8                     |  |
| Uncu, 2002 (cohort)  |                       |  |
| Representativeness of the<br>exposed cohort                                    | 1                     | All pregnant women <32 wks GA seen at an antenatal outpatient clinic.  |
| Selection of the non-<br>exposed cohort  | 1                     | Women who visited the clinic prior to the start of the screening stud  |
| Ascertainment of exposure  | 1                     | Used delivery records.   |
| Outcome not present at<br>start of study<br>(pyelonephritis/other<br>outcomes) | 0/1                   | Not ascertained for pyelonephritis, other outcomes could not have<br>been present at the start of the study. |
| Comparability of the cohorts   | 0                     | No evidence of comparability.  |
| Assessment of outcome  | 1                     | Used delivery records.   |
| Adequacy of length of follow-up  | 1                     | Follow-up until post-delivery.   |
| Adequacy of follow-up of<br>cohorts  | 0                     | Not reported.  |
| Selective outcome  | not                   | Reported on all outcomes, including fetal death >20 wks GA (eligible   |
| reporting <sup>b</sup>   | suspected             | for perinatal mortality).  |
|  |                       |  |

<sup>a</sup>Assessed using the Newcastle-Ottawa Quality Assessment Scale

<sup>b</sup>Assessed due to concern regarding reporting bias in the studies, but assessment not included in the total score

| First<br>Author,<br>Year | Did the study address a clearly focused question /<br>issue? | Is the research method (study design) appropriate<br>for answering the research question? | Is the method of selection of the subjects clearly described? | Could the way the sample was obtained introduce<br>bias? | Was the sample of subjects representative of the population to which the findings will be referred? | Was the sample size based on pre-study<br>considerations of | Was a satisfactory response rate achieved? | Are the measurements (questionnaires) likely to be valid and reliable? | Was the statistical significance assessed? | Are confidence intervals given for the main results? | Could there be confounding factors that haven't<br>been<br>accounted for? | Can the results be applied to your organization? |
|--------------------------|--|---|---|--|---|---|--|--|--|--|---|--|
| Butters, 1990            | 1  | 1   | 1   | 2  | 1   | 2   | 1  | 2  | 1  | 3  | 1   | 1  |
| Kazemier, 2015           | 2  | 2   | 1   | 3  | 1   | 2   | 2  | 2  | 3  | 3  | 2   | 3  |
| Lupattelli, 2014         | 1  | 1   | 1   | 1  | 1   | 2   | 2  | 2  | 1  | 1  | 3   | 1  |
| Mashayekhi, 2009         | 1  | 1   | 1   | 1  | 1   | 2   | 2  | 2  | 1  | 3  | 1   | 1  |
| Nordeng, 2010            | 1  | 1   | 1   | 1  | 1   | 2   | 2  | 2  | 1  | 3  | 2   | 1  |
| Sanz, 2000               | 1  | 1   | 3   | 2  | 1   | 2   | 2  | 2  | 1  | 3  | 1   | 1  |
| Sharma, 2006             | 1  | 1   | 3   | 2  | 1   | 2   | 2  | 1  | 1  | 3  | 1   | 1  |
| Twigg, 2016              | 1  | 1   | 1   | 1  | 1   | 2   | 2  | 1  | 1  | 3  | 1   | 1  |

<sup>a</sup>Assessed using a tool developed by the Center for Evidence-based Management<sup>32</sup> for cross-sectional studies (surveys)

1=Yes, 2=Can't Tell, 3=No

| Domain  | Author's<br>judgement* | Support for judgement  |
|---|------------------------|--|
| Butters, 1990 (cross-sectional survey                                 | y)                     |  |
| Clearly focused question/issue  | 1                      | Awareness of the effects of commonly used drugs, cigarettes and alcohol on the fetus   |
| Appropriate research method<br>(study design)                         | 1                      | Cross-sectional survey of women in postnatal ware  |
| Selection of subjects clearly described                               | 1                      | Provides inclusion and exclusion criteria, outlines selection methods  |
| Sampling method introduces bias                                       | 2                      | Sampling was not random, may be consecutive  |
| Sample of subjects representative of the population                   | 1                      | Included women who were recently post-partum   |
| Sample size based on pre-study considerations of statistical power    | 2                      | Not reported   |
| Satisfactory response rate  | 1                      | Response rate was 87%  |
| Questionnaires are likely to be valid and reliable                    | 2                      | Validation of survey questions was not reported  |
| Statistical significance assessed 🥂                                   | 1                      | Chi-square analysis  |
| Confidence intervals for main results                                 | 3                      | No confidence intervals reported   |
| Confounding factors not accounted for                                 | 1                      | Confounders were not addressed with study desigor or analysis  |
| Applicability of the results  | 1                      | Identifies areas for further education in this population  |
| outcomes obtained/reported in cross<br>Clearly focused question/issue | 2                      | To assess maternal and neonatal consequences of  |
|   |                        | treating and not treating asymptomatic bacteriuri<br>in pregnancy; however, no direct examination of<br>outcome valuation set out in protocol or study<br>methods  |
| Appropriate research method<br>(study design)                         | 2                      | Appears to be cross-sectional for information<br>regarding why eligible women did not consent to<br>participate in treatment trial   |
| Selection of subjects clearly described                               | 1                      | Clear inclusion and exclusion criteria for screening<br>cohort and treatment RCT, with study flow<br>documented  |
| Sampling method introduces bias                                       | 3                      | Various clinics, hospitals and ultrasound centres in the Netherlands   |
| Sample of subjects representative of the population                   | 1                      | Women 18 years or older with singleton pregnand without symptoms of urinary tract infection.   |
| Sample size based on pre-study considerations of statistical power    | 2                      | Sample size estimates reported in statistical analy<br>but none specified for cross-section of women for<br>outcome valuation  |
| Satisfactory response rate  | 2                      | Authors did not report response rate specifically f<br>cross-section of women who declined treatment.<br>255 ASB-positive women, 163 received no treatm<br>(of whom 155 did not want treatment for specifie<br>reason), but authors do not report if those who |

| Questionnaires are likely to be valid and reliable | 2      | Validation of reason(s) for dissenting not reported   |
|--|--------|---|
| Statistical significance assessed                  | 3      | Fisher's exact test for outcomes from screening cohort and treatment trial; no significance for   |
|  |        | outcome valuation data  |
| Confidence intervals for main                      | 3      | Cl's reported for outcomes from screening cohort  |
| results  |        | and treatment trial; no Cl's for outcome valuation data   |
| Confounding factors not accounted for              | 2      | Assessed confounders for outcomes from screening cohort and treatment trial, but not for outcome valuation data   |
| Applicability of the results                       | 3      | Medication avoidance for asymptomatic conditions<br>in pregnancy among Dutch women acknowledged b<br>study authors to align with Dutch guidelines (not<br>routinely screening and treating women with ASB);<br>may be more applicable for the Netherlands but not |
|  | 6      | for Canada where routine screening and treatment is standing practice   |
| Lupattelli, 2014 (cross-sectional surv             | /ey)   |   |
| Clearly focused question/issue                     | 1      | Association of health literacy and risk perception  |
| Appropriate research method<br>(study design)      | 1      | Cross-sectional survey of pregnant women  |
| Selection of subjects clearly described            | 1      | Self-selection, voluntary internet survey   |
| Sampling method introduces bias                    | 1      | Informal sampling method – self-selection was not random or consecutive   |
| Sample of subjects representative                  | 1      | Pregnant women with internet access   |
| of the population                                  |        |   |
| Sample size based on pre-study                     | 2      | Not reported  |
| considerations of statistical power                |        |   |
| Satisfactory response rate                         | 2      | Large n, no response rate reported  |
| Questionnaires are likely to be                    | 2      | Validation of survey questions was not reported   |
| valid and reliable                                 |        |   |
| Statistical significance assessed                  | 1      | Mann-Whitney U test, Spearman's rank correlation  |
| Confidence internals for main                      | 4      | coefficient, logistic regression  |
| Confidence intervals for main results              | 1      | Reported in Table 3   |
| Confounding factors not accounted for              | 3      | Adjusted for confounders in statistical analysis  |
| Applicability of the results                       | 1      | Health literacy is significantly associated with<br>adherence to pharmacotherapy in pregnant womer  |
| Mashayekhi, 2009 (cross-sectional s                | urvey) |   |
| Clearly focused question/issue                     | 1      | Awareness of pregnant women on the effects of<br>drugs during pregnancy   |
| Appropriate research method<br>(study design)      | 1      | Cross-sectional survey of pre and postnatal women   |
| Selection of subjects clearly described            | 1      | Reports selection methods   |
| Sampling method introduces bias                    | 1      | Sampling was not random or consecutive  |
| Sample of subjects representative                  | 1      | Included pre and postnatal women in hospital ward   |

| Sample size based on pre-study considerations of statistical power    | 2   | Not reported  |
|---|-----|---|
| Satisfactory response rate  | 2   | Large n, no response rate reported  |
| Questionnaires are likely to be<br>valid and reliable                 | 2   | Validation of survey questions was not reported                               |
| Statistical significance assessed                                     | 1   | Chi-square, Student's t-test, Pearson correlation<br>ANOVA                    |
| Confidence intervals for main results                                 | 3   | Not reported  |
| Confounding factors not accounted for                                 | 1   | Confounders were not addressed with study de<br>or analysis                   |
| Applicability of the results  | 1   | Identifies roles for pharmacists in education of t population                 |
| Nordeng, 2010 (cross-sectional surve                                  | ey) | ·   |
| Clearly focused question/issue  | 1   | Women's perception of risk during pregnancy                                   |
| Appropriate research method (study design)                            | 1   | Cross-sectional survey of pregnant women and mothers                          |
| Selection of subjects clearly described                               | 1   | Self-selection, voluntary internet survey                                     |
| Sampling method introduces bias                                       | 1   | Informal sampling method – self-selection was random or consecutive           |
| Sample of subjects representative of the population                   | 1   | Pregnant women and young mothers (child less<br>5 years) with internet access |
| Sample size based on pre-study<br>considerations of statistical power | 2   | Not reported  |
| Satisfactory response rate  | 2   | Large n, no response rate reported  |
| Questionnaires are likely to be valid and reliable                    | 2   | Validation of survey questions was not reported                               |
| Statistical significance assessed                                     | 1   | Linear regression, ANOVA, Student's t-test                                    |
| Confidence intervals for main results                                 | 3   | Confidence intervals were available in graph for only                         |
| Confounding factors not accounted for                                 | 2   | Addressed in limitations  |
| Applicability of the results  | 1   | Indicates women overestimate risks and more education in this area is needed. |
| Sanz, 2000 (cross-sectional)  | •   | ·   |
| Clearly focused question/issue  | 1   | Drug utilization in pregnant women  |
| Appropriate research method<br>(study design)                         | 1   | Cross sectional, visual analogue scale  |
| Selection of subjects clearly<br>described                            | 3   | Selection methods are not reported for all populations                        |
| Sampling method introduces bias                                       | 2   | Not reported for all populations  |
| Sample of subjects representative of the population                   | 1   | Pregnant women attending out-patient clinic at<br>hospital                    |
| Sample size based on pre-study considerations of statistical power    | 2   | Not reported  |
| Satisfactory response rate  | 2   | Small n, no response rate reported  |
| Questionnaires are likely to be valid and reliable                    | 2   | Validation of VAS questions was not reported                                  |
| Statistical significance assessed                                     | 1   | Mann-Whitney U, Kruskal Wallis, Chi-squared                                   |

| Confidence intervals for main results                              | 3  | Only in graph format  |
|--|----|---|
| Confounding factors not accounted                                  | 1  | Confounders were not addressed with study desig   |
| for  |    | or analysis   |
| Applicability of the results                                       | 1  | Pregnant women have high perceptions of<br>teratogenic risk   |
| Sharma, 2006 (cross-sectional survey                               | y) |   |
| Clearly focused question/issue                                     | 1  | Drug utilization in pregnant women  |
| Appropriate research method<br>(study design)                      | 1  | Cross-sectional survey of pregnant women  |
| Selection of subjects clearly                                      | 3  | Selected from an antenatal clinic but no sampling   |
| described  |    | methods   |
| Sampling method introduces bias                                    | 2  | Not reported  |
| Sample of subjects representative of the population                | 1  | Pregnant women  |
| Sample size based on pre-study considerations of statistical power | 2  | Not reported  |
| Satisfactory response rate   | 2  | Large n, no response rate reported  |
| Questionnaires are likely to be                                    | 1  | Women's statements were confirmed through   |
| valid and reliable   |    | medical records when available  |
| Statistical significance assessed                                  | 1  | Chi-squared test  |
| Confidence intervals for main<br>results provided                  | 3  | Not reported  |
| Confounding factors not accounted                                  | 1  | Confounders were not addressed with study desig   |
| for  |    | or analysis   |
| Applicability of the results                                       | 1  | Education of women of child-bearing age regarding<br>benefits and harms of drug use during pregnancy in<br>needed |
| Twigg, 2016 (cross-sectional survey)                               |    | licedeu   |
| Clearly focused question/issue                                     | 1  | Risk perception of medications in pregnant women  |
| , , ,  |    | and relationship with use   |
| Appropriate research method<br>(study design)                      | 1  | Cross-sectional survey of pregnant women and ne mothers   |
| Selection of subjects clearly described                            | 1  | Self-selection, voluntary internet survey   |
| Sampling method introduces bias                                    | 1  | Informal sampling method – self-selection was not random or consecutive   |
| Sample of subjects representative                                  | 1  | Pregnant women or women <1 year post-natal wit  |
| of the population  |    | internet access   |
| Sample size based on pre-study                                     | 2  | Not reported  |
| considerations of statistical power                                |    |   |
| Satisfactory response rate   | 2  | Large n, no response rate reported  |
| Questionnaires are likely to be valid and reliable                 | 1  | Used validated BMQ-General questionnaire  |
| Statistical significance assessed                                  | 1  | Chi-square, Fisher's exact test, Mann-Whitney U,<br>Independent t-test  |
| Confidence intervals for main results                              | 3  | No confidence intervals for the main results, descriptive statistics only   |
| Confounding factors not accounted                                  | 1  | Adjustment for confounding not reported in design<br>or analysis  |

| Applicability of the results   | 1                         | Medication use by pregnant women is impacted by<br>beliefs about risk |
|--|---------------------------|---|
| <sup>a</sup> Assessed using a tool develo<br>* 1=Yes, 2=Can't Tell, 3=No | oed by the Center for     | Evidence-based Management for cross-sectional studies                 |
| ANOVA: analysis of variance;   |                           | acteriuria; BMQ: beliefs about medicine questionnaire; n:             |
| sample size; RCT:randomized  | clinical trial; VAS: visu | al analogue scale   |
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|                         | Sequence Generation | Allocation Concealment | Blinding of Participants<br>and Personnel <sup>1</sup> | Blinding of Outcome<br>Assessors <sup>1</sup> | Incomplete Reporting <sup>2</sup> | Selective Reporting <sup>3</sup> | Other Bias <sup>4</sup> | Ov<br>I R<br>of<br>Bia |
|-------------------------|---------------------|------------------------|--|---|-----------------------------------|----------------------------------|-------------------------|------------------------|
| Brumfitt 1975           | 0)                  | ~                      | ш (ў   |   | -                                 | 0)                               | 0                       |                        |
| Elder 1966              |                     |                        |  |   |                                   |                                  |                         |                        |
| Elder 1971              |                     |                        |  |   |                                   |                                  |                         |                        |
| Foley 1987              |                     |                        |  |   |                                   |                                  |                         |                        |
| Furness 1975            |                     |                        |  |   |                                   |                                  |                         |                        |
| Gold 1966               |                     |                        |  |   |                                   |                                  |                         |                        |
| Kass 1960               |                     |                        |  |   |                                   |                                  |                         |                        |
| Kazemier 2015           |                     |                        |  |   |                                   |                                  |                         |                        |
| Kincaid-Smith 1965      |                     |                        |  |   |                                   |                                  |                         | -                      |
| Little 1966             |                     |                        |  |   |                                   |                                  |                         |                        |
| Mulla 1960              |                     |                        |  |   |                                   |                                  |                         |                        |
| Pathak 1969             |                     |                        |  |   |                                   |                                  |                         |                        |
| Thomsen 1987            |                     |                        |  |   |                                   |                                  |                         |                        |
| Williams 1969           |                     |                        |  |   |                                   |                                  |                         |                        |
| Wren 1969               |                     |                        |  |   |                                   |                                  |                         | -                      |
| $\sim$ FOL TOO COLOCTIV | e reporting d       |                        |  |   | r selective rep                   |                                  | thickers                |                        |

| Domain                   | Author's<br>judgement | Support for judgement  |
|--------------------------|-----------------------|--|
| Brumfitt, 1975 (RCT)     | , ,                   |  |
| Random sequence          | Unclear               | No description of the sequence generation process, how women       |
| generation               |                       | were assigned to treatment or placebo, unequal numbers in          |
| 0                        |                       | treatment and placebo groups.                                      |
| Allocation               | Unclear               | No information provided to judge.                                  |
| concealment              |                       |  |
| Blinding of participants | Low                   | "were given placebo under double-blind conditions". Method not     |
| and personnel            |                       | described in sufficient detail. Objective outcomes.                |
| Blinding of outcome      | Low                   | "were given placebo under double-blind conditions". Method not     |
| assessment               | 2011                  | described in sufficient detail. Objective outcomes.                |
| Incomplete outcome       | High                  | Inconsistencies in total number of women not explained (number of  |
| data                     | Tingin                | <2500g babies provided for 413/326 bacteriuric women); results no  |
| uata                     |                       | provided for pyelonephritis for all women in treated group (only   |
|                          |                       |  |
| Colostino non entire e   | Llink                 | subset).   |
| Selective reporting      | High                  | Results not provided for pyelonephritis for all women allocated to |
|                          |                       | treatment.   |
| Other bias               | Low                   | Insufficient information to judge.                                 |
| Overall risk of bias     | High                  |  |
| Elder, 1966 (RCT)        | 1                     |  |
| Random sequence          | Unclear               | "a random sequence". Insufficient information to judge.            |
| generation               |                       |  |
| Allocation               | Unclear               | No information provided to judge.                                  |
| concealment              |                       | $\sim$   |
| Blinding of participants | Low                   | "double-blind trial"; no information provided to judge. Objective  |
| and personnel            |                       | outcomes.  |
| Blinding of outcome      | Low                   | "double-blind trial"; no information provided to judge. Objective  |
| assessment               |                       | outcomes.  |
| Incomplete outcome       | Low                   | Information provided on women lost to follow-up, reasonably        |
| data                     | -                     | balanced between groups.   |
| Selective reporting      | High                  | Result not provided for pyelonephritis for all participants; no    |
|                          |                       | pregnancy outcomes (GA, birthweight).                              |
| Other bias               | Low                   | Insufficient information to judge.                                 |
| Overall risk of bias     | High                  |  |
| Elder, 1971 (CCT)        | 111611                |  |
|                          | High                  | "alternate bacteriuricwere assigned."                              |
| Random sequence          | High                  | aiternate batteriuntwere assigned.                                 |
| generation               | Lliab                 | Derticipants were allocated by alternation                         |
| Allocation               | High                  | Participants were allocated by alternation.                        |
| concealment              | the el                |  |
| Blinding of participants | Unclear               | "identical-appearing placebo"; insufficient information to judge.  |
| and personnel            |                       |  |
| Blinding of outcome      | Unclear               | "identical-appearing placebo"; insufficient information to judge.  |
| assessment               |                       |  |
| Incomplete outcome       | Unclear               | Insufficient information to judge.                                 |
| data                     |                       |  |
| Selective reporting      | Unclear               | Unable to judge; twin deliveries were excluded.                    |
| Other bias               | Low                   | Insufficient information to judge.                                 |
| Overall risk of bias     | High                  |  |
| Foley, 1987              |                       | 1  |

| Domain                   | Author's<br>judgement | Support for judgement   |
|--------------------------|-----------------------|---|
| Random sequence          | Low                   | Allocated to treatment or no treatment by "toss of a coin".         |
| generation               |                       |   |
| Allocation               | Unclear               | No information to judge.  |
| concealment              |                       |   |
| Blinding of participants | Unclear               | No description of any attempt at blinding; not placebo-controlled.  |
| and personnel            |                       | Objective outcomes.   |
| Blinding of outcome      | Unclear               | No description of any attempt at blinding; not placebo-controlled.  |
| assessment               |                       | Objective outcomes.   |
| Incomplete outcome       | Unclear               | Loss to follow-up: 19%; no reasons provided for missing outcome     |
| data                     |                       | data.   |
| Selective reporting      | High                  | No pregnancy outcomes (GA, birthweight).                            |
| Other bias               | Low                   | Insufficient information to judge.                                  |
| Overall risk of bias     | High                  |   |
| Furness, 1975 (RCT)      | 0                     |   |
| Random sequence          | Unclear               | "by random allocation"; no additional information to judge.         |
| generation               |                       | ,                             |
| Allocation               | Unclear               | No information to judge.  |
| concealment              |                       |   |
| Blinding of participants | Unclear               | Not placebo-controlled. Objective outcomes.                         |
| and personnel            | •                     |   |
| Blinding of outcome      | Unclear               | No information to judge.  |
| assessment               | Uncical               |   |
| Incomplete outcome       | High                  | 20/226 women withdrawn from trial, no details provided. All wome    |
| data                     |                       | included in outcome of pyelonephritis, 17% loss to follow-up or low |
|                          |                       | birthweight and GA at delivery.                                     |
| Selective reporting      | Unclear               | Unable to separate incidence of pyelonephritis during pregnancy an  |
|                          |                       | puerperium; results combined.                                       |
| Other bias               | Low                   | Insufficient information to judge.                                  |
| Overall risk of bias     | High                  |   |
| Gold, 1966 (CCT)         |                       |   |
| Random sequence          | High                  | Women allocated to treatment based on study number: odd numbe       |
| generation               | i iigii               | treatment, even number control.                                     |
| Allocation               | High                  | Allocated to treatment based on study number.                       |
| concealment              |                       | Anotated to treatment based on study humber.                        |
| Blinding of participants | Unclear               | Placebo-controlled; no further details provided. Objective outcomes |
| and personnel            | Chelcal               | . acces controlled, no farther actails provided, objective outcome. |
| Blinding of outcome      | Unclear               | No information to judge. Objective outcomes.                        |
| assessment               | Uncicul               |   |
| Incomplete outcome       | Low                   | Does not appear to be any loss to follow-up.                        |
| data                     |                       |   |
| Selective reporting      | Unclear               | No definition provided for prematurity.                             |
| Other bias               | Low                   | Insufficient information to judge.                                  |
| Overall risk of bias     | High                  |   |
| Kass, 1960 (CCT)         | 1 1 6 1               |   |
|                          | High                  | "alternate women received a placebe"                                |
| Random sequence          | High                  | "alternate women received a placebo".                               |
| generation               | Lliab                 | Allocation based on alternation, "alternate warran reasing da       |
| Allocation               | High                  | Allocation based on alternation: "alternate women received a        |
| concealment              |                       | placebo".   |

| Domain                    | Author's<br>judgement | Support for judgement  |
|---------------------------|-----------------------|--|
| Blinding of participants  | Low                   | Placebo was used and "the nature of the treatment was not known to   |
| and personnel             |                       | the patient or to the attending obstetrical staff".  |
| Blinding of outcome       | Unclear               | Although a placebo was used, no further details are provided on  |
| assessment                |                       | blinding of outcome assessment. Objective outcomes.  |
| Incomplete outcome        | Unclear               | 40 (21%) women were not enrolled either because they were >32  |
| data                      |                       | weeks GA before treatment could be started (n=30), or already  |
|                           |                       | received treatment for symptomatic infection (n=10). Loss to follow-   |
|                           |                       | up: 23 (11%) for pyelonephritis and low birthweight, no details  |
|                           |                       | provided; 69 (34%) for long-term persistent bacteriuria.   |
| Selective reporting       | Unclear               | 3 women had subsequent pregnancy and were reassigned to their  |
|                           |                       | original treatment group included in the analysis. In 5 placebo  |
|                           |                       | patients, symptomatic disease was assumed but no symptoms were   |
|                           |                       | documented. Not all women in symptomatic group were confirmed  |
|                           |                       | to have fever. Women treated for infections other than that in the   |
|                           |                       | urinary tract were included in the symptomatic group if they had   |
| 0.1                       |                       | cleared their bacteriuria.   |
| Other bias                | Low                   | Insufficient information to judge.   |
| Overall risk of bias      | High                  |  |
| Kazemier, 2015 (RCT)      |                       |  |
| Random sequence           | Low                   | Random assignment in 1:1 ratio; computer-generated list with   |
| generation                | 1.000                 | random block sizes of 2/4/6 participants.  |
| Allocation<br>concealment | Low                   | Women, treating physicians and researchers remained unaware of bacteriuria status and treatment allocation. Central allocation - |
| conceannent               |                       | unmasking of treatment allocation was possible by 24h telephone  |
|                           |                       | service.   |
| Blinding of participants  | Low                   | Double-blinded. Women, treating physicians and researchers   |
| and personnel             | 2011                  | remained unaware of bacteriuria status and treatment allocation.   |
| P                         |                       | Objective outcomes.  |
| Blinding of outcome       | Low                   | Outcomes recorded by participants on questionnaires, and from data   |
| assessment                | -                     | provided by hospitals and midwives up to 6 weeks post-delivery.  |
| Incomplete outcome        | Low                   | ITT and dropout rate <10% (12/255 ASB-positive)  |
| data                      |                       |  |
| Selective reporting       | Low                   | Cost-effectiveness was outlined in protocol but not reported in final  |
|                           |                       | study methods or results.  |
| Other bias                | Low                   | No other sources of bias identified.   |
| Overall risk of bias      | Low                   |  |
| Kincaid-Smith, 1965 (RCT) |                       |  |
| Random sequence           | Unclear               | No description of sequence generation process.   |
| generation                |                       |  |
| Allocation                | Low                   | "a code of instructions to the pharmacist ensured that the trial   |
| concealment               |                       | remained double-blind despitealterations in therapeutic regimen".  |
| Blinding of participants  | Low                   | "a code of instructions to the pharmacist ensured that the trial   |
| and personnel             |                       | remained double-blind despitealterations in therapeutic regimen".  |
| Blinding of outcome       | Low                   | "a code of instructions to the pharmacist ensured that the trial   |
| assessment                |                       | remained double-blind despitealterations in therapeutic regimen".  |
| Incomplete outcome        | Unclear               | 240 women initially identified as bacteriuric; no information available  |
| data                      |                       | on 55 (23%) women randomized to treatment but not included in the  |
|                           |                       | analysis because of poor compliance (attended infrequently or failed   |
|                           |                       | to take tablets continuously).   |
| Selective reporting       | Unclear               | Insufficient information to judge.   |

| Domain                                    | Author's<br>judgement | Support for judgement  |
|---|-----------------------|--|
| Other bias                                | Low                   | Insufficient information to judge.   |
| Overall risk of bias                      | Unclear               |  |
| Little, 1966 (RCT)                        |                       |  |
| Random sequence<br>generation             | Unclear               | No information to judge.   |
| Allocation<br>concealment                 | Unclear               | Allocation to treatment or control was drawn for "a pool of sealed<br>envelopes containing a slip of paper", but there was no information<br>provided to ensure appropriate safeguards to prevent investigators<br>being aware of the treatment group. |
| Blinding of participants and personnel    | Unclear               | Participants in the control group "were given placebo"; no further details provided. Objective outcomes.   |
| Blinding of outcome<br>assessment         | Unclear               | No information to judge. Objective outcomes.   |
| Incomplete outcome<br>data                | Low                   | No missing outcome data.   |
| Selective reporting                       | Unclear               | Insufficient information to judge.   |
| Other bias                                | Low                   | Insufficient information to judge.   |
| Overall risk of bias                      | Unclear               |  |
| Mulla, 1960 (RCT)                         |                       |  |
| Random sequence<br>generation             | Unclear               | No description of sequence generation process.   |
| Allocation                                | Unclear               | Women were "randomly divided into two groups"; no other details  |
| concealment                               |                       | provided   |
| Blinding of participants<br>and personnel | Unclear               | Not placebo-controlled. Objective outcomes.  |
| Blinding of outcome<br>assessment         | Unclear               | No information to judge. Objective outcomes.   |
| Incomplete outcome<br>data                | Low                   | No missing outcome data.   |
| Selective reporting                       | High                  | No definition for outcome of cystopyelitis; no pregnancy outcomes (GA, birthweight).   |
| Other bias                                | Low                   | Insufficient information to judge.   |
| Overall risk of bias                      | High                  |  |
| Pathak, 1969 (RCT)                        |                       |  |
| Random sequence<br>generation             | Unclear               | "on a random basis". Insufficient information provided to permit further judgement.  |
| Allocation<br>concealment                 | Unclear               | Method of concealment not described.   |
| Blinding of participants<br>and personnel | Unclear               | No information to judge.   |
| Blinding of outcome assessment            | Unclear               | No information to judge.   |
| Incomplete outcome<br>data                | Low                   | Missing outcome data balanced; reasons similar and unlikely to hav introduced bias.  |
| Selective reporting                       | High                  | No pregnancy outcomes (GA, birthweight).   |
| Other bias                                | Low                   | Insufficient information to judge.   |
| Overall risk of bias                      | High                  |  |

| Domain                                 | Author's<br>judgement | Support for judgement  |
|--|-----------------------|--|
| Random sequence                        | Unclear               | Described as "randomly allocated" but no description of the  |
| generation                             |                       | sequence generation process.   |
| Allocation<br>concealment              | Unclear               | Method of concealment of allocation not described.   |
| Blinding of participants               | Unclear               | Placebo-controlled, described as "double-blinded" but no additional  |
| and personnel                          |                       | data. Objective outcomes.  |
| Blinding of outcome                    | Unclear               | Described as "double-blinded" but no specific information provided   |
| assessment                             |                       | to ensure outcome assessment was blinded. Objective outcomes.  |
| Incomplete outcome<br>data             | Low                   | No missing outcome data.   |
| Selective reporting                    | Unclear               | Insufficient information to judge.   |
| Other bias                             | Low                   | Insufficient information to judge.   |
| Overall risk of bias                   | Unclear               |  |
| Williams, 1969 (RCT)                   |                       |  |
| Random sequence generation             | Unclear               | "allocation at random"; no additional information to judge.  |
| Allocation<br>concealment              | Unclear               | No information to judge.   |
| Blinding of participants and personnel | Unclear               | No blinding, outcome may have been influenced by lack of blinding.<br>No treatment group was given antibiotics to take if symptoms of<br>infection developed. Objective outcomes.  |
| Blinding of outcome assessment         | Unclear               | No blinding; assessment of outcome (pyelonephritis) may have been<br>influenced by knowledge of treatment allocation. Objective<br>outcomes.   |
| Incomplete outcome<br>data             | Unclear               | No explanation for unequal group sizes; no information provided on<br>any missing data. An unknown number of women in the control<br>group were given antibiotic treatment if they developed symptoms<br>UTI.  |
| Selective reporting                    | High                  | No pregnancy outcomes (GA, birthweight).   |
| Other bias                             | Low                   | Insufficient information to judge.   |
| Overall risk of bias                   | High                  |  |
| Wren, 1969 (CCT)                       | 0                     |  |
| Random sequence<br>generation          | High                  | Women "were divided into two groups, alternate patients being treated".  |
| Allocation concealment                 | High                  | Women "were divided into two groups, alternate patients being treated".  |
| Blinding of participants and personnel | Unclear               | No blinding; knowledge of treatment group may have influenced<br>outcome; women in untreated group who developed clinical UTI<br>(33/90) were given antibiotics at the choice of the obstetrician,<br>continued to delivery in 50% of cases. Objective outcomes. |
| Blinding of outcome assessment         | Unclear               | No blinding; however, outcome of birthweight unlikely to be influenced by lack of blinding.  |
| Incomplete outcome<br>data             | Low                   | 10 (6%) women not included in outcomes: 2 sets of twins excluded,<br>moved and 2 could not be traced, 3 delivered before antibiotics cou<br>be started, 1 refused treatment.   |
| Selective reporting                    | Unclear               | Insufficient information to judge; outcome of pyelonephritis not reported.   |
| Other bias                             | Low                   | Insufficient information to judge.   |
| Overall risk of bias                   | High                  |  |

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<sup>a</sup>Assessed using the Cochrane Risk of Bias tool ASB: asymptomatic bacteriuria; g: gram(s); GA: gestational age; UTI: urinary tract infection

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### Supplement 6. GRADE Summary of Findings & Evidence Profiles tables & forest plots

### Evidence Set 1. Table 1.1 GRADE Summary of Findings – Benefits and harms of screening compared to no screening

#### Screening compared to no screening for asymptomatic bacteriuria in pregnant women

Patient or population: asymptomatic bacteriuria in pregnant women

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: screening

**Comparison**: no screening

| Outcomes                | Anticipated a<br>effects <sup>*</sup> (95% |  | Relative<br>effect<br>(95% CI) | № of<br>participants<br>(studies)    | Quality of<br>the<br>evidence  | Comments  |  |  |
|-------------------------|--|--|--------------------------------|--------------------------------------|--------------------------------|---|--|--|
|                         | Risk with no<br>screening                  | Risk with screening  |                                |                                      | (GRADE)                        |   |  |  |
| Maternal<br>mortality   | 0 per 1,000                                | <b>0 per 1,000</b><br>(0 to 0)   | not<br>estimable               | (0 studies)                          | -                              | No study reported on maternal mortality.  |  |  |
| Maternal sepsis         | 0 per 1,000 0 per 1,000 (0 to 0)           |  | not<br>estimable               | (0 studies)                          | -                              | No study reported on maternal sepsis.   |  |  |
| Pyelonephritis          | Median                                     |  | <b>RR 0.28</b> (0.15 to        | 5659<br>(3                           | ⊕○○○<br>VERY LOW <sup>1,</sup> | We are very uncertain ab the effects of screening o                             |  |  |
|                         | 18 per 1,000                               | <b>13 fewer</b><br><b>per 1,000</b><br>(from 8<br>fewer to 16<br>fewer)  | 0.54)                          | observational<br>studies)            | a                              | pyelonephritis.   |  |  |
| Perinatal<br>mortality  | Median                                     |  | <b>RR 1.21</b> (0.01 to        | 724<br>(2                            | ⊕○○○<br>VERY LOW <sup>1,</sup> | We are very uncertain ab the effects of screening o                             |  |  |
|                         | 19 per 1,000                               | <b>4 more per</b><br><b>1,000</b><br>(from 19<br>fewer to<br>1,000 more) | 102.93)                        | observational<br>studies)            | b                              | perinatal mortality.  |  |  |
| Spontaneous<br>abortion | 55 per 1,000                               | <b>2 fewer per</b><br><b>1,000</b><br>(from 32<br>fewer to 70<br>more)   | <b>RR 0.96</b> (0.41 to 2.27)  | 370<br>(1<br>observational<br>study) |                                | We are very uncertain ab<br>the effects of screening o<br>spontaneous abortion. |  |  |

| Screening compared to no screening for asymptomatic bacteriuria in pregnant women |
|---|
|---|

#### Patient or population: asymptomatic bacteriuria in pregnant women

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: screening

Comparison: no screening

| <b>effects</b> <sup>*</sup> (95% | <b>bsolute</b><br>Cl)   | Relative<br>effect<br>(95% CI)  | № of<br>participants<br>(studies)   | Quality of<br>the<br>evidence   | Comments   |  |  |
|----------------------------------|---|---|---|---|--|--|--|
| Risk with no screening           | Risk with screening   | ()  | (,  | (GRADE)   |  |  |  |
| 0 per 1,000                      | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable  | (0 studies)   | -   | No study reported on neonatal sepsis.  |  |  |
| Median                           |   | <b>RR 8.70</b> (0.32 to   | 722   | ⊕○○○<br>VERY LOW <sup>1,</sup>  | We are very uncertain abo<br>the effects of screening on   |  |  |
| 13 per 1,000                     | <b>102 more</b><br><b>per 1,000</b><br>(from 9<br>fewer to<br>1,000 more)   | 240.07)   | observational<br>studies)   | d   | preterm delivery.  |  |  |
| 0 per 1,000                      | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable  | (0 studies)   | -   | No study reported on low birthweight.  |  |  |
| 0 per 1,000                      | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable  | (0 studies)   | 2   | No study reported on maternal serious harms.   |  |  |
| 11 per 1,000                     | <b>5 more per</b><br><b>1,000</b><br>(from 8<br>fewer to 85<br>more)  | <b>RR 1.50</b> (0.25 to 8.87)   | 372<br>(1<br>observational<br>study)  | ⊕⊖⊖⊖<br>VERY LOW <sup>1,</sup><br>e   | We are very uncertain abo<br>the effects of screening on<br>fetal abnormalities.   |  |  |
| ative effect of                  | the intervention  |   | •   | d on the assun  | ned risk in the comparison   |  |  |
| erval; <b>RR:</b> Risk           | ratio   |   |   |   |  |  |  |
| 1                                | screening         0 per 1,000         Median         13 per 1,000         0 per 1,000         0 per 1,000         11 per 1,000         tervention growtive effect of string st | Open 1,000         Open 1,000 (0 to 0)           Median         IO2 more per 1,000 (from 9 fewer to 1,000 more)           13 per 1,000         (from 9 fewer to 1,000 (0 to 0))           0 per 1,000         0 per 1,000 (0 to 0)           0 per 1,000         0 per 1,000 (0 to 0)           11 per 1,000         5 more per 1,000 (0 to 0)           11 per 1,000         (from 8 fewer to 85 more) | screeningscreeningnot<br>estimable0 per 1,000<br>(0 to 0)not<br>estimablenot<br>estimableMedianRR 8.70<br>(0.32 to<br>240.07)RR 8.70<br>(0.32 to<br>240.07)13 per 1,000<br>(from 9<br>fewer to<br>1,000 more)not<br>estimable0 per 1,000<br>(0 to 0)not<br>estimable0 per 1,000<br>(0 to 0)not<br>estimable11 per 1,000<br>(from 8<br>fewer to 85<br>more)not<br>estimable11 per 1,000<br>(from 8<br>fewer to 85<br>more)RR 1.50<br>(0.25 to<br>8.87) | Risk with screeningRisk with screeningImage: screening <th< td=""><td>Risk with no<br/>screeningRisk with<br/>screeningImage: Comparison of the screeningImage: Comparison of the sc</td></th<> | Risk with no<br>screeningRisk with<br>screeningImage: Comparison of the screeningImage: Comparison of the sc |  |  |

Screening compared to no screening for asymptomatic bacteriuria in pregnant women Patient or population: asymptomatic bacteriuria in pregnant women **Setting:** Any primary or clinical care setting providing care to pregnant women Intervention: screening Comparison: no screening Outcomes **Anticipated absolute** Relative Nº of Quality of Comments effects<sup>\*</sup> (95% CI) effect participants the (95% CI) (studies) evidence (GRADE) Risk with no Risk with screening screening **GRADE Working Group grades of evidence High quality:** We are very confident that the true effect lies close to that of the estimate of the effect Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low guality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect <sup>1</sup> The imprecision domain is assessed using GRADE guidance<sup>42</sup> relevant for systematic reviews as follows: when optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25). **Pyelonephritis** [a] → Very Low Quality Evidence: Three non-concurrent cohort studies (Gérard 1983, Gratacós 1994,

Pyeionepnritis [a] → Very Low Quality Evidence: Three non-concurrent cohort studies (Gerard 1983, Gratacos 1994, Uncu 2001) reported this outcome (n=5,659). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics. The optimal information size is met (sample size >5600), therefore downgrading for imprecision is not warranted. There were no serious concerns to warrant downgrading for inconsistency, indirectness, or other considerations.

Perinatal mortality [b] → Very Low Quality Evidence: Two non-concurrent cohort studies (n=724; Gérard 1983, Uncu
 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data.
 Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no
 demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk
 factors or other patient characteristics, and suspected reporting bias as two studies did not report on perinatal
 mortality. Further downgrading is warranted for imprecision due to optimal information size not being met with a small
 sample size. There were no serious concerns to warrant downgrading for inconsistency, indirectness or other
 considerations.

Spontaneous abortion [c] → Very Low Quality Evidence: One non-concurrent cohort study reported this outcome
 (n=370; Gérard 1983). Quality of evidence is downgraded from high to low due to observational level data. Further
 downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no
 demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk

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factors or other patient characteristics, and suspected reporting bias as two studies did not report on spontaneous abortion. Only one study provided data on spontaneous abortion, so this warrants downgrading for **inconsistency**. Further downgrading for **imprecision** is warranted due to low event rates (total of 20) without optimal information size. There were no serious concerns to warrant downgrading for **indirectness** or **other considerations**.

**Preterm delivery [d]** → **Very Low Quality Evidence:** Two non-concurrent cohort studies (n=722; Gérard 1983, Uncu 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on preterm delivery. Further downgrading is warranted for imprecision for inadequate sample size and optimal information size not being met (total of 38 events). There were no serious concerns to warrant downgrading for inconsistency, indirectness or other considerations. 

**Neonatal serious harm: fetal abnormalities (harm)**  $[e] \rightarrow Very Low Quality Evidence: One non-concurrent cohort study$ reported this outcome (n=370; Uncu 2001). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as three studies did not report on fetal abnormalities. Only one study provided data on this outcome so this warrants downgrading for inconsistency. Further downgrading for imprecision is warranted due to the optimal information size not being met for rare events. There were no serious concerns to warrant downgrading for indirectness or other considerations. 

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### Evidence Set 1. Table 1.2 GRADE Evidence Profile – Benefits and harms of screening compared to no screening

Question: Screening compared to no screening for asymptomatic bacteriuria in pregnant women

**Setting**: Any primary or clinical care setting providing care to pregnant women

| y design Risk<br>bias<br>tality | Inconsistance   | y Indirectness                     | Imprecision<br>1                            | Other<br>considerations                             | screening   | no<br>screening   | Relative<br>(95% Cl)   | Absolute<br>(95% CI)  |   |  |
|---------------------------------|-----------------|------------------------------------|---|---|---|---|--|---|---|--|
| tality                          |                 |                                    |   |   |   |   |  |   |   |  |
|                                 |                 |                                    |   |   |   |   |  |   |   |  |
|                                 |                 |                                    | 000   |   |   |   | not<br>estimable   |   | -   | CRITICAL   |
| is                              |                 |                                    |   | 1   |   |   |  |   |   |  |
|                                 |                 |                                    |   | 0   |   |   | not<br>estimable   |   | -   | CRITICAL   |
| ;                               |                 |                                    | Į   | 1   |   |   |  |   |   |  |
|                                 | ous not serious | not serious                        | serious                                     | none  | 10/2008<br>(0.5%)   | 1.8%  | <b>RR 0.28</b> (0.15 to 0.54)  | <b>13 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 8<br>fewer to<br>16<br>fewer)                      | ⊕⊖⊖⊖<br>VERY<br>LOW <sup>1, a</sup>   | CRITICAL   |
|                                 | s               | s rvational serious not serious es | s rvational serious not serious not serious | s rvational serious not serious not serious serious | s<br>rvational serious not serious not serious serious none | s<br>rvational serious not serious not serious serious none 10/2008<br>(0.5%) | s<br>rvational serious not serious not serious serious none 10/2008 1.8%<br>(0.5%) | rvational serious not serious not serious serious none 10/2008 1.8% RR 0.28 (0.15 to 0.54) 10/2008 (0.5%) | s<br>rvational serious not serious not serious serious none 10/2008 1.8% RR 0.28<br>(0.15 to<br>0.54) 13 fewer<br>per<br>1,000<br>(from 8<br>fewer to<br>16<br>fewer) | Image: serious less       not serious less       not serious serious       not serious less       none       10/2008 (0.5%)       1.8%       RR 0.28 (0.15 to less)       13 fewer per loss       VERY LOW 1, a |

| Quality         | assessment               |                 |               |              |             |                         | Nº of patio     | ents             | Effect                                |   | Quality                             | Importance |  |
|-----------------|--------------------------|-----------------|---------------|--------------|-------------|-------------------------|-----------------|------------------|---------------------------------------|---|-------------------------------------|------------|--|
| № of<br>studies | Study design             | Risk of<br>bias | Inconsistency | Indirectness | Imprecision | Other<br>considerations | screening       | no<br>screening  | Relative<br>(95% CI)                  | Absolute<br>(95% Cl)  |                                     |            |  |
| 2               | observational<br>studies | serious         | not serious   | not serious  | serious     | none                    | 6/349<br>(1.7%) | 1.9%             | <b>RR 1.21</b><br>(0.01 to<br>102.93) | <b>4 more</b><br><b>per</b><br><b>1,000</b><br>(from 19<br>fewer to<br>1,000<br>more) | ⊕⊖⊖⊖<br>VERY<br>LOW <sup>1, b</sup> | CRITICAL   |  |
| Spontan         | eous abortion            |                 | ·             |              |             | ·                       |                 |                  |                                       |   |                                     |            |  |
| 1               | observational<br>studies | serious         | serious       | not serious  | serious     | none                    | 9/170<br>(5.3%) | 11/200<br>(5.5%) | <b>RR 0.96</b> (0.41 to 2.27)         | <b>2 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 32<br>fewer to<br>70<br>more)   | ⊕⊖⊖⊖<br>VERY<br>LOW <sup>1, c</sup> | CRITICAL   |  |
| Neonata         | al sepsis                |                 | 1             |              |             | 1                       |                 |                  |                                       |   |                                     |            |  |
| 0               |                          |                 |               |              |             |                         |                 | Y                | not<br>estimable                      |   | -                                   | CRITICAL   |  |
|                 | delivery                 | I               | <u> </u>      | <u> </u>     | <u> </u>    | ļ                       | <u> </u>        | <u> </u>         |                                       | <u> </u>  | <u> </u>                            | I          |  |

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| Quality          | assessment               |                 |               |              |             |                         | Nº of patio      | ents            | Effect                                |  | Quality                             | Importance |
|------------------|--------------------------|-----------------|---------------|--------------|-------------|-------------------------|------------------|-----------------|---------------------------------------|--|-------------------------------------|------------|
| Nº of<br>studies | Study design             | Risk of<br>bias | Inconsistency | Indirectness | Imprecision | Other<br>considerations | screening        | no<br>screening | Relative<br>(95% Cl)                  | Absolute<br>(95% Cl)   |                                     |            |
| 2                | observational<br>studies | serious         | not serious   | not serious  | serious     | none                    | 33/347<br>(9.5%) | 1.3%            | <b>RR 8.70</b><br>(0.32 to<br>240.07) | <b>102</b><br>more<br>per<br><b>1,000</b><br>(from 9<br>fewer to<br>1,000<br>more) | ⊕⊖⊖⊖<br>VERY<br>LOW <sup>1, d</sup> | CRITICAL   |
| Low birt         | hweight                  |                 |               |              |             |                         |                  |                 |                                       |  |                                     |            |
| 0                |                          |                 |               |              |             | 0                       |                  |                 | not<br>estimable                      |  | -                                   | IMPORTAN   |
| Materna          | al serious harm(         | (s)             |               | <u> </u>     | I           |                         | 1                | <u> </u>        | 1                                     | <u> </u>   | <u> </u>                            |            |
| 0                |                          |                 |               |              |             |                         | C                | 51              | not<br>estimable                      |  | -                                   | CRITICAL   |
| Neonata          | al serious harm:         | fetal abn       | ormalities    |              |             |                         | 1                |                 | 1                                     |  |                                     |            |
| 1                | observational<br>studies | serious         | serious       | not serious  | serious     | none                    | 3/186<br>(1.6%)  | 2/186<br>(1.1%) | <b>RR 1.50</b> (0.25 to               | 5 more<br>per  |                                     | CRITICAL   |

CI: Confidence interval; RR: Risk ratio

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<sup>1</sup> The imprecision domain is assessed using GRADE guidance<sup>42</sup> relevant for systematic reviews as follows: when optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25).

 Pyelonephritis [a] → Very Low Quality Evidence: Three non-concurrent cohort studies (Gérard 1983, Gratacós 1994, Uncu 2001) reported this outcome (n=5,659). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics. The optimal information size is met (sample size >5600), therefore downgrading for imprecision is not warranted. There were no serious concerns to warrant downgrading for inconsistency, indirectness, or other considerations.

Perinatal mortality [b] → Very Low Quality Evidence: Two non-concurrent cohort studies (n=724; Gérard 1983, Uncu 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on perinatal mortality. Further downgrading is warranted for imprecision due to optimal information size not being met with a small sample size. There were no serious concerns to warrant downgrading for inconsistency, indirectness or other considerations.

Spontaneous abortion [c] → Very Low Quality Evidence: One non-concurrent cohort study reported this outcome (n=370; Gérard 1983). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on spontaneous abortion. Only one study provided data on spontaneous abortion, so this warrants downgrading for inconsistency. Further downgrading for imprecision is warranted due to low event rates (total of 20) without optimal information size. There were no serious concerns to warrant downgrading for indirectness or other considerations.

Preterm delivery [d] → Very Low Quality Evidence: Two non-concurrent cohort studies (n=722; Gérard 1983, Uncu 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on preterm delivery. Further downgrading is warranted for imprecision for inadequate sample size and optimal information size not being met (total of 38 events). There were no serious concerns to warrant downgrading for inconsistency, indirectness or other considerations.

Neonatal serious harm: fetal abnormalities [e] → Very Low Quality Evidence: One non-concurrent cohort study reported this outcome (n=370; Uncu 2001).
Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk
of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for
risk factors or other patient characteristics, and suspected reporting bias as three studies did not report on fetal abnormalities. Only one study provided data on
this outcome so this warrants downgrading for inconsistency. Further downgrading for imprecision is warranted due to the optimal information size not being
met for rare events. There were no serious concerns to warrant downgrading for indirectness or other considerations.

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# Evidence Set 1. Forest Plots 1.1-1.5 – Benefits and harms of screening compared to no screening

| Outcome   |  |  |  |   |  | o. of  | No. of  |      | Effect size                            |   |
|---|--|--|--|---|--|--|---|------|--|---|
|   |  |  |  |   |  | udies  | participant   |      | (Risk Ratio; M-H, Ra                   | andom, 95%CI)   |
| 1.1 Pyelonep  |  |  |  |   | 3  |  | 5659  |      | 0.28 [0.15, 0.54]                      |   |
| 1.2 Perinatal   |  |  |  |   | 2  |  | 724   |      | 1.21 [0.01, 102.93]                    |   |
| note: Gérard  | >=31 wks   | ; Unc  | u >20 wk   | S   |  |  |   |      |  |   |
| 1.3 Spontane  | eous abort   | tion <   | 20 wks G   | A   | 1  |  | 370   |      | 0.96 [0.41, 2.27]                      |   |
| note: 1 study   | / <=28 wks   | s (all c   | occurred   | 7-21 wl   | <s)< td=""><td></td><td></td><td></td><td></td><td></td></s)<>                       |  |   |      |  |   |
| 1.4 Preterm o   | delivery <   | 37 wk  | s GA   |   | 2  |  | 722   |      | 8.70 [0.32, 240.07]                    |   |
| 1.5 Neonatal  | serious h  | arm: f   | fetal abn  | ormalit   | ies 1  |  | 372   |      | 1.50 [0.25, 8.87]                      |   |
| 1.1 Pyelonephritis  | 5  |  |  |   |  |  |   |      |  |   |
| , .   |  |  |  |   |  |  |   |      |  |   |
|   | Screen   | ina  | No scree   | enina   |  | Ris  | k Ratio   |      | Risk                                   | Ratio   |
| Study or Subgroup   | Events   |  |  |   | Weight   |  | idom, 95% Cl  |      |  | om, 95% Cl  |
| Gratacos 1994   | 9  | 1652   | 60   | 3265  | 86.3%  | 0.3  | 0 [0.15, 0.60]  |      |  |   |
| Gérard 1983   | 0  | 170  | 3  | 200   | 4.8%   |  | 7 [0.01, 3.23]  | •    | •                                      | <u> </u>  |
| Uncu 2001   | 1  | 186  | 4  | 186   | 8.8%   | 0.2  | 5 [0.03, 2.22]  |      | =                                      |   |
| Total (95% CI)  |  | 2008   |  | 3651  | 100.0%   | 0.2  | 8 [0.15, 0.54]  |      | •                                      |   |
| Total events  | 10   |  | 67   |   |  |  |   |      | -                                      |   |
| Heterogeneity: Tau² =   |  |  |  | ° = 0.93)   | ; I² = 0%  |  |   | 0.01 | 0.1                                    | <br>1 10  |
| Test for overall effect   | : Z = 3.80 (I  | P = 0.0  | 0001)  |   |  |  |   | 0.01 |  | Favours no screening  |
|   |  |  |  |   |  |  |   |      |  |   |
|   |  |  |  |   |  |  |   |      |  |   |
|   |  |  |  |   |  |  |   |      |  |   |
| 1.2 Perinatal mort  | tality (>=   | 20 w   | ks GA)   |   |  |  |   |      |  |   |
|   |  |  |  |   |  |  |   |      |  |   |
|   | • •  |  |  |   |  | Diel   |   |      | Diele                                  | Defin   |
|   | Screen   |  | No scree   | -   | Weight   |  | Ratio   |      |  | Ratio   |
| Study or Subgroup   | Screen<br>Events   | Total  | Events   | Total   |  | M-H, Rar   | ndom, 95% Cl  |      |  | Ratio<br>om, 95% Cl   |
|   | Screen   |  |  | -   | Weight<br>47.5%<br>52.5%   | M-H, Rar<br>12.74 (  |   |      |  |   |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001   | Screen<br>Events   | Total<br>163<br>186  | Events<br>0  | Total<br>189<br>186   | 47.5%<br>52.5%   | M-H, Rar<br>12.74 (<br>0.1   | idom, 95% Cl<br>0.71, 228.74]<br>4 [0.02, 1.15]   |      |  |   |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)   | Screen<br>Events<br>5<br>1   | Total<br>163   | Events<br>0<br>7   | Total<br>189<br>186   | 47.5%  | M-H, Rar<br>12.74 (<br>0.1   | ndom, 95% Cl<br>0.71, 228.74]   | _    |  |   |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events   | Screen<br>Events<br>5<br>1   | Total<br>163<br>186<br>349   | <b>Events</b><br>0<br>7<br>7   | Total<br>189<br>186<br>375  | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21  </b>                                  | idom, 95% Cl<br>0.71, 228.74]<br>4 [0.02, 1.15]   |      |  |   |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :  | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>a</sup>  | Total<br>163<br>186<br>349<br><sup>2</sup> = 6.2   | Events<br>0<br>7<br>5, df = 1 (F   | Total<br>189<br>186<br>375  | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21  </b>                                  | idom, 95% Cl<br>0.71, 228.74]<br>4 [0.02, 1.15]   | <br> | M-H, Rando                             | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events   | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>a</sup>  | Total<br>163<br>186<br>349<br><sup>2</sup> = 6.2   | Events<br>0<br>7<br>5, df = 1 (F   | Total<br>189<br>186<br>375  | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21  </b>                                  | idom, 95% Cl<br>0.71, 228.74]<br>4 [0.02, 1.15]   | 0.01 | M-H, Rando<br>0.1<br>Favours screening | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :  | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>a</sup>  | Total<br>163<br>186<br>349<br><sup>2</sup> = 6.2   | Events<br>0<br>7<br>5, df = 1 (F   | Total<br>189<br>186<br>375  | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21  </b>                                  | idom, 95% Cl<br>0.71, 228.74]<br>4 [0.02, 1.15]   | 0.01 | M-H, Rando                             | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :  | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>a</sup>  | Total<br>163<br>186<br>349<br><sup>2</sup> = 6.2   | Events<br>0<br>7<br>5, df = 1 (F   | Total<br>189<br>186<br>375  | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21  </b>                                  | idom, 95% Cl<br>0.71, 228.74]<br>4 [0.02, 1.15]   | 0.01 | M-H, Rando<br>0.1<br>Favours screening | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect   | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (i   | Total<br>163<br>186<br><b>349</b><br><sup>2</sup> = 6.29<br>P = 0.9                                  | Events<br>0<br>7<br>5, df = 1 (F<br>33)  | Total<br>189<br>186<br>375<br>P = 0.01)   | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21  </b>                                  | idom, 95% Cl<br>0.71, 228.74]<br>4 [0.02, 1.15]   | 0.01 | M-H, Rando<br>0.1<br>Favours screening | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :  | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (i   | Total<br>163<br>186<br><b>349</b><br><sup>2</sup> = 6.2:<br>P = 0.9<br>(<20                          | Events<br>0<br>7<br>5, df = 1 (F<br>33)  | Total<br>189<br>186<br>375<br>P = 0.01)   | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21  </b>                                  | idom, 95% Cl<br>0.71, 228.74]<br>4 [0.02, 1.15]   | 0.01 | M-H, Rando<br>0.1<br>Favours screening | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect<br>1.3 Spontaneous a  | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (I<br>abortion<br>Screen   | <u>Total</u><br>163<br>186<br><b>349</b><br><sup>2</sup> = 6.2:<br>P = 0.9<br>P = 0.9<br>(<20<br>ing | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No scree                              | Total<br>189<br>186<br>375<br>P = 0.01)<br>)<br>ening                                     | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%                            | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                           | 1dom, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>k Ratio   |      | M-H, Rando                             | om, 95% Cl<br>1<br>1<br>10<br>Favours no screening<br>Ratio |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :<br>Test for overall effect<br>1.3 Spontaneous a<br>Study or Subgroup   | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>a</sup><br>: Z = 0.08 (I<br>abortion<br>Screen<br>Events   | Total<br>163<br>186<br><b>349</b><br><sup>2</sup> = 6.29<br>P = 0.9<br>(<20<br>ing<br>Total          | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No scree<br>Events                    | Total<br>189<br>186<br>375<br>P = 0.01)<br>P = 0.01)<br>P = 0.01)                         | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br>Weight                  | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b><br>Ris<br><u>M-H, Rar</u> | ndom, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>0.01, 102.93]<br>k Ratio<br>ndom, 95% CI                    |      | M-H, Rando                             | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect<br>1.3 Spontaneous a  | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (I<br>abortion<br>Screen   | <u>Total</u><br>163<br>186<br><b>349</b><br><sup>2</sup> = 6.2:<br>P = 0.9<br>P = 0.9<br>(<20<br>ing | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No scree                              | Total<br>189<br>186<br>375<br>P = 0.01)<br>P = 0.01)<br>P = 0.01)                         | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%                            | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b><br>Ris<br><u>M-H, Rar</u> | 1dom, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>k Ratio   |      | M-H, Rando                             | om, 95% Cl<br>1<br>1<br>10<br>Favours no screening<br>Ratio |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :<br>Test for overall effect<br>1.3 Spontaneous a<br>Study or Subgroup   | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>a</sup><br>: Z = 0.08 (I<br>abortion<br>Screen<br>Events   | Total<br>163<br>186<br><b>349</b><br><sup>2</sup> = 6.29<br>P = 0.9<br>(<20<br>ing<br>Total          | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No scree<br>Events                    | Total<br>189<br>186<br><b>375</b><br>P = 0.01)<br>P = 0.01)<br>P<br>ening<br>Total<br>200 | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br>Weight                  | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                           | ndom, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>0.01, 102.93]<br>k Ratio<br>ndom, 95% CI                    |      | M-H, Rando                             | om, 95% Cl<br>1<br>1<br>10<br>Favours no screening<br>Ratio |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :<br>Test for overall effect<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983  | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>a</sup><br>: Z = 0.08 (I<br>abortion<br>Screen<br>Events   | Total           163           186           349           * = 6.29           P = 0.9           (<20  | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No scree<br>Events                    | Total<br>189<br>186<br><b>375</b><br>P = 0.01)<br>P = 0.01)<br>P<br>ening<br>Total<br>200 | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                           | 100m, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>0.01, 102.93]<br>k Ratio<br>100m, 95% CI<br>16 [0.41, 2.27] |      | M-H, Rando                             | om, 95% Cl<br>1<br>1<br>10<br>Favours no screening<br>Ratio |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :<br>Test for overall effect<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events<br>Heterogeneity: Not aj                                   | Screeni<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (I<br>abortion<br>Screeni<br>Events<br>9<br>9                             | Total<br>163<br>186<br>349<br><sup>2</sup> = 6.2:<br>P = 0.9<br>(<20<br>ing<br>Total<br>170<br>170   | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No screet<br>Events<br>11             | Total<br>189<br>186<br><b>375</b><br>P = 0.01)<br>P = 0.01)<br>P<br>ening<br>Total<br>200 | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                           | 100m, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>0.01, 102.93]<br>k Ratio<br>100m, 95% CI<br>16 [0.41, 2.27] |      | M-H, Rando                             | om, 95% Cl<br>1<br>1<br>10<br>Favours no screening<br>Ratio |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :<br>Test for overall effect<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events  | Screeni<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (I<br>abortion<br>Screeni<br>Events<br>9<br>9                             | Total<br>163<br>186<br>349<br><sup>2</sup> = 6.2:<br>P = 0.9<br>(<20<br>ing<br>Total<br>170<br>170   | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No screet<br>Events<br>11             | Total<br>189<br>186<br><b>375</b><br>P = 0.01)<br>P = 0.01)<br>P<br>ening<br>Total<br>200 | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                           | 100m, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>0.01, 102.93]<br>k Ratio<br>100m, 95% CI<br>16 [0.41, 2.27] |      | M-H, Rando                             | om, 95% CI  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :<br>Test for overall effect<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events<br>Heterogeneity: Not aj                                   | Screeni<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (I<br>abortion<br>Screeni<br>Events<br>9<br>9                             | Total<br>163<br>186<br>349<br><sup>2</sup> = 6.2:<br>P = 0.9<br>(<20<br>ing<br>Total<br>170<br>170   | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No screet<br>Events<br>11             | Total<br>189<br>186<br><b>375</b><br>P = 0.01)<br>P = 0.01)<br>P<br>ening<br>Total<br>200 | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                           | 100m, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>0.01, 102.93]<br>k Ratio<br>100m, 95% CI<br>16 [0.41, 2.27] |      | M-H, Rando                             | om, 95% CI  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :<br>Test for overall effect<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events<br>Heterogeneity: Not aj                                   | Screeni<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (I<br>abortion<br>Screeni<br>Events<br>9<br>9                             | Total<br>163<br>186<br>349<br><sup>2</sup> = 6.2:<br>P = 0.9<br>(<20<br>ing<br>Total<br>170<br>170   | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No screet<br>Events<br>11             | Total<br>189<br>186<br><b>375</b><br>P = 0.01)<br>P = 0.01)<br>P<br>ening<br>Total<br>200 | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                           | 100m, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>0.01, 102.93]<br>k Ratio<br>100m, 95% CI<br>16 [0.41, 2.27] |      | M-H, Rando                             | om, 95% CI  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :<br>Test for overall effect<br><b>1.3 Spontaneous a</b><br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events<br>Heterogeneity: Not aj<br>Test for overall effect | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (I<br>abortion<br>Screen<br>Events<br>9<br>9<br>pplicable<br>: Z = 0.09 (I | Total           163           186           349           * = 6.29           P = 0.9           (<20  | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No scree<br>Events<br>11<br>11<br>33) | Total<br>189<br>186<br><b>375</b><br>P = 0.01)<br>P = 0.01)<br>P<br>ening<br>Total<br>200 | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                           | 100m, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>0.01, 102.93]<br>k Ratio<br>100m, 95% CI<br>16 [0.41, 2.27] |      | M-H, Rando                             | om, 95% CI  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :<br>Test for overall effect<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events<br>Heterogeneity: Not aj                                   | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (I<br>abortion<br>Screen<br>Events<br>9<br>9<br>pplicable<br>: Z = 0.09 (I | Total           163           186           349           * = 6.29           P = 0.9           (<20  | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No scree<br>Events<br>11<br>11<br>33) | Total<br>189<br>186<br><b>375</b><br>P = 0.01)<br>P = 0.01)<br>P<br>ening<br>Total<br>200 | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                           | 100m, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>0.01, 102.93]<br>k Ratio<br>100m, 95% CI<br>16 [0.41, 2.27] |      | M-H, Rando                             | om, 95% CI  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> :<br>Test for overall effect<br><b>1.3 Spontaneous a</b><br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events<br>Heterogeneity: Not aj<br>Test for overall effect | Screen<br>Events<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup><br>: Z = 0.08 (I<br>abortion<br>Screen<br>Events<br>9<br>9<br>pplicable<br>: Z = 0.09 (I | Total           163           186           349           * = 6.29           P = 0.9           (<20  | Events<br>0<br>7<br>5, df = 1 (F<br>33)<br>wks GA<br>No scree<br>Events<br>11<br>11<br>33) | Total<br>189<br>186<br><b>375</b><br>P = 0.01)<br>P = 0.01)<br>P<br>ening<br>Total<br>200 | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                           | 100m, 95% CI<br>0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>0.01, 102.93]<br>k Ratio<br>100m, 95% CI<br>16 [0.41, 2.27] |      | M-H, Rando                             | om, 95% CI  |

## BMJ Open

|        |                                   | Screen   | ing     | No scree | ening   |                        | Risk Ratio           | Risk Ratio                             |
|--------|-----------------------------------|----------|---------|----------|---------|------------------------|----------------------|--|
| 1      | Study or Subgroup                 | Events   | Total   | Events   | Total   | Weight                 | M-H, Random, 95% Cl  | M-H, Random, 95% Cl                    |
| 2      | Gérard 1983                       | 11       | 161     | 5        | 189     | 57.5%                  | 2.58 [0.92, 7.28]    | <b>⊢</b> ∎                             |
| 3      | Uncu 2001                         | 22       | 186     | 0        | 186     | 42.5%                  | 45.00 [2.75, 736.39] | <b>∎</b> →                             |
| 4<br>5 | Total (95% CI)                    |          | 347     |          | 375     | 100.0%                 | 8.70 [0.32, 240.07]  |  |
| 6      | Total events                      | 33       |         | 5        |         |                        |                      |  |
| 7      | Heterogeneity: Tau <sup>2</sup> = | •        |         |          | = 0.02) | ; I <sup>z</sup> = 80% |                      |  |
| 8      | Test for overall effect:          | Z=1.28 ( | P = 0.2 | :0)      |         |                        |                      | Favours screening Favours no screening |
| 9      |                                   |          |         |          |         |                        |                      |  |

#### 1.5 Neonatal serious harm: fetal abnormalities

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| Study or Subaraus                               | Screeni                     |              | No scree    |     | Moight | Risk Ratio                               |      |                   | Ratio                |    |
|---|-----------------------------|--------------|-------------|-----|--------|--|------|-------------------|----------------------|----|
| Study or Subgroup<br>Uncu 2001                  | Events<br>3                 | 10tal<br>186 | Events<br>2 |     | 100.0% | M-H, Random, 95% Cl<br>1.50 [0.25, 8.87] |      | M-H, Kand         | om, 95% Cl           |    |
| 01104 2001                                      | 3                           | 100          | 2           | 100 | 100.0% | 1.50 [0.25, 6.67]                        |      |                   |                      |    |
| Total (95% CI)                                  |                             | 186          |             | 186 | 100.0% | 1.50 [0.25, 8.87]                        |      |                   |                      |    |
| Total events                                    | 3                           |              | 2           |     |        |  |      |                   |                      |    |
| Heterogeneity: Not a<br>Test for overall effect | pplicable<br>t: 7 = 0.45 /5 |              | 201         |     |        |  | 0.01 | 0.1               | 1 10                 | 10 |
| restion overall ellect                          | ι. Ζ = 0.40 (r              | 0.0          | 10)         |     |        |  |      | Favours screening | Favours no screening |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
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|   |                             |              |             |     |        |  |      |                   |                      |    |
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|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
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|   |                             |              |             |     |        |  |      |                   |                      |    |
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|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
|   |                             |              |             |     |        |  |      |                   |                      |    |
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#### Evidence Set 2. Table 2.1 GRADE Summary of Findings - Benefits and harms of frequent screening compared to onetime screening Frequent screening compared to one-time screening for asymptomatic bacteriuria Patient or population: asymptomatic bacteriuria **Setting**: Any primary clinical care setting providing care to pregnant women 10 Intervention: frequent screening 11 12 Comparison: one-time screening 13 14 Anticipated absolute Quality of Outcomes Relative Nº of Comments 15 effects<sup>\*</sup> (95% CI) effect participants the 16 17 (95% CI) (studies) evidence 18 (GRADE) **Risk with** Risk 19 one-time difference 20 screening with 21 22 frequent 23 screening 24 25 **Pyelonephritis** 0 fewer per RR 1.09 1952 $\oplus \bigcirc \bigcirc \bigcirc$ We are very uncertain about 26 27 1,000 (0.27 to (1 VERY LOW <sup>1,</sup> the effects of frequent 28 4 per 1,000 (from 3 4.35) observational <sup>a</sup> screening compared to one-29 fewer to 13 time screening on study) 30 more) pyelonephritis. 31 32 33 28 more per RR 1.57 $\Theta \cap \cap O$ Preterm delivery 1952 We are very uncertain about 34 1,000 VERY LOW <sup>1,</sup> the effects of frequent (1.11 to (1 35 49 per 1,000 (from 5 2.23) observational <sup>b</sup> screening compared to one-36 time screening on preterm more to 60 study) 37 38 more) delivery. 39 40 \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison 41 group and the **relative effect** of the intervention (and its 95% CI). 42 43 44 CI: Confidence interval; RR: Risk ratio 45 46 **GRADE Working Group grades of evidence** 47 48 High quality: We are very confident that the true effect lies close to that of the estimate of the effect 49 Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the 50 estimate of the effect, but there is a possibility that it is substantially different 51 Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the 52 estimate of the effect 53 Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially 54 55 different from the estimate of effect 56 57 58 <sup>1</sup> The imprecision domain is assessed using GRADE guidance<sup>42</sup> relevant for systematic reviews as follows: when 59 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25).

CI: Confidence interval; RR: Risk ratio

**Pyelonephritis [a]**  $\rightarrow$  **Very Low Quality Evidence:** One non-concurrent cohort study (n=1952; Rhode 2007) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious **risk of bias** associated with: 1) no demonstration that pyelonephritis was not present at start of study, 2) no demonstration of comparability between frequent and one-time screening groups, and 3) no adjustment to analyses to account for risk factors or other patient characteristics. Only one study provided data for this outcome so downgrading is warranted for **inconsistency**. Further downgrading is warranted for **indirectness** as the women are predominantly medically underserved, Hispanic and receiving care from a midwifery clinic, with a high rate of gestational diabetes (9%). The optimal information size is not met (8 events) with sample size (n=1952), therefore this warrants downgrading for **imprecision**. There were no serious concerns to warrant downgrading for **other considerations**.

Preterm delivery [b] → Very Low Quality Evidence: One non-concurrent cohort study (n=1952; Rhode 2007) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to very serious risk of bias associated with: 1) no demonstration of comparability between frequent and one-time screening groups, 2) no adjustment to analyses to account for risk factors or other patient characteristics, and 3) suspected reporting bias among outcomes reported by studies (did not report on spontaneous abortion, perinatal mortality or fetal abnormalities). Only one study provided data for this outcome so downgrading is warranted for inconsistency. Further downgrading is warranted for indirectness as the women are predominantly medically underserved, Hispanic and receiving care from a midwifery clinic, with a high rate of gestational diabetes (9%). The event rate is low (122 events) without meeting optimal information size, so this is downgraded for imprecision. There were no serious concerns to warrant downgrading for other considerations.

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### Evidence Set 3. Table 3.1 GRADE Summary of Findings – Benefits and harms of treatment compared to no treatment

### Treatment compared to no treatment for asymptomatic bacteriuria

### Patient or population: asymptomatic bacteriuria

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: treatment

Comparison: no treatment

| Outcomes                | Anticipated a effects <sup>*</sup> (95% |   | Relative<br>effect<br>(95% CI) | № of<br>participants<br>(studies) | Quality of<br>the<br>evidence         | Comments  |  |
|-------------------------|---|---|--------------------------------|-----------------------------------|---------------------------------------|---|--|
|                         | Risk with no<br>treatment               | Risk with<br>treatment  |                                |                                   | (GRADE)                               |   |  |
| Maternal<br>mortality   | 0 per 1,000                             | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable               | (0 studies)                       | -                                     | No study reported on maternal mortality.                |  |
| Maternal sepsis         | 0 per 1,000                             | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable               | (0 studies)                       | -                                     | No study reported on maternal sepsis.                   |  |
| Pyelonephritis          | Median                                  |   | <b>RR 0.24</b> (0.13 to        | 2017<br>(12 RCTs)                 | ⊕⊕○○<br>LOW <sup>1, a</sup>           | There may be a reduction in pyelonephritis from         |  |
|                         | 232 per<br>1,000                        | <b>176 fewer</b><br><b>per 1,000</b><br>(from 137<br>fewer to 202<br>fewer) | 0.41)                          |                                   |                                       | treatment.  |  |
| Perinatal<br>mortality  | Median                                  |   | <b>RR 0.96</b> (0.27 to        | 1104<br>(6 RCTs)                  | <b>O</b> OO<br>VERY LOW <sup>1,</sup> | We are very uncertain about the effects of treatment on |  |
| Perinatal<br>nortality  | 40 per 1,000                            | <b>2 fewer per</b><br><b>1,000</b><br>(from 29<br>fewer to 97<br>more)      | 3.39)                          | (2)                               | b                                     | perinatal mortality.                                    |  |
| Spontaneous<br>abortion | Median                                  |   | <b>RR 0.60</b> (0.11 to        | 379<br>(2 RCTs)                   | ⊕○○○<br>VERY LOW <sup>1,</sup>        | We are very uncertain about the effects of treatment on |  |
|                         | 33 per 1,000                            | 33 per 1,000       (from 30)         fewer to 70       more)                |                                | ,                                 | c                                     | spontaneous abortion.                                   |  |

| Treatment compared to no t | treatment for asymptomati | c bacteriuria |
|----------------------------|---------------------------|---------------|
|----------------------------|---------------------------|---------------|

### Patient or population: asymptomatic bacteriuria

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: treatment

**Comparison**: no treatment

| Outcomes                    |                           |   | Relative<br>effect<br>(95% CI) | № of<br>participants<br>(studies) | Quality of<br>the<br>evidence  | Comments  |  |  |
|-----------------------------|---------------------------|---|--------------------------------|-----------------------------------|--------------------------------|---|--|--|
|                             | Risk with no<br>treatment | Risk with<br>treatment  |                                | (                                 | (GRADE)                        |   |  |  |
| Neonatal sepsis             | Median                    | fects* (95% CI)effectssk with no<br>eatmentRisk with<br>treatmenteffectsedianRisk with<br>treatmentRR (0.00<br>4.54edian17 fewer<br>per 1,000<br>(from 22<br>fewer to 79<br>more)RR (0.00<br>4.54edianS8 fewer<br>per 1,000<br>(from 125<br>fewer to 88<br>more)RR (0.20<br>4.54edian44 fewer<br>per 1,000<br>(from 125<br>fewer to 68<br>more)RR (0.20<br>4.54edian44 fewer<br>per 1,000<br>(from 125<br>fewer to 68<br>more)RR (0.20<br>4.54edian9000<br> | <b>RR 0.22</b> (0.01 to        | 154<br>(2 RCTs)                   | ⊕○○○<br>VERY LOW <sup>1,</sup> | We are very uncertain about the effects of treatment on |  |  |
|                             | 22 per 1,000              | <b>per 1,000</b><br>(from 22<br>fewer to 79   | 4.54)                          |                                   | d                              | neonatal sepsis.  |  |  |
| Preterm delivery            | Median                    |   | <b>RR 0.57</b> (0.21 to        | 533<br>(4 RCTs)                   | ⊕○○○<br>VERY LOW <sup>1,</sup> | We are very uncertain about the effects of treatment or |  |  |
|                             | 158 per<br>1,000          | <b>per 1,000</b><br>(from 125<br>fewer to 88  | 1.56)                          |                                   | e                              | preterm delivery.                                       |  |  |
| Low birth weight            | Median                    |   | <b>RR 0.63</b> (0.45 to        | 1522<br>(7 RCTs)                  | ⊕○○○<br>LOW <sup>1, f</sup>    | There may be a reduction i<br>low birth weight from     |  |  |
|                             | 118 per<br>1,000          | <b>per 1,000</b><br>(from 12<br>fewer to 65   | 0.90)                          | (                                 |                                | treatment.  |  |  |
| Maternal serious<br>harm(s) | 0 per 1,000               | •   | not<br>estimable               | (0 studies)                       | -                              | No study reported on maternal serious harms.            |  |  |
|                             | Median                    |   |                                |                                   |                                |   |  |  |

### Treatment compared to no treatment for asymptomatic bacteriuria

### Patient or population: asymptomatic bacteriuria

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: treatment

Comparison: no treatment

| Outcomes  | Anticipated a<br>effects <sup>*</sup> (95%           |   | Relative<br>effect<br>(95% CI)       | № of<br>participants<br>(studies) | Quality of<br>the<br>evidence       | Comments   |
|---|--|---|--------------------------------------|-----------------------------------|-------------------------------------|--|
|   | Risk with no<br>treatment                            | Risk with<br>treatment  |                                      |                                   | (GRADE)                             |  |
| Neonatal serious<br>harm: fetal<br>abnormalities  | 19 per 1,000   | <b>9 fewer per</b><br><b>1,000</b><br>(from 15<br>fewer to 8<br>more) | <b>RR 0.49</b><br>(0.17 to<br>1.43)  | 821<br>(4 RCTs)                   | ⊕⊖⊖⊖<br>VERY LOW <sup>1,</sup><br>g | We are very uncertain al<br>the effects of treatment<br>harms (fetal abnormaliti |
| Neonatal serious<br>harm: hemolytic<br>anemia   | 0 per 1,000  | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable                     | 265<br>(1 RCT)                    | ⊕⊖⊖⊖<br>VERY LOW <sup>1,</sup><br>h | We are very uncertain al<br>the effects of treatment<br>harms (hemolytic anemi   |
| estimate of the ef  | : We are mode<br>fect, but there                     | erately confide<br>is a possibility                                   | nt in the effect<br>that it is subst | estimate: The<br>antially differe | true effect is li<br>nt             | kely to be close to the  |
| estimate of the ef  | fect<br>We have very                                 | little confidenc  |                                      |                                   | -                                   | antially different from the<br>kely to be substantially                          |
| <sup>1</sup> The imprecision of optimal information of the second s | domain is asse<br>on size (OIS) cr<br>or important l | ssed using GR/<br>iterion is met,<br>narm will be as                  | and the 95% c                        | onfidence inte                    | erval overlaps                      | ews as follows: when<br>no effect, consideration o<br>I.25).                     |
| <b>CI:</b> Confidence inte  |  |   |                                      |                                   |                                     |  |
| <b>Pyelonephritis, ov</b><br>Gold 1966, Kass 19   |  | -   |                                      |                                   |                                     | 71, Foley 1987, Furness 19   |

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associated with use of alternation for sequence generation (Elder 1971, Gold 1966, Kass 1960), inadequate allocation concealment (Elder 1971, Gold 1966, Kass 1960), and incomplete reporting (Brumfitt 1975, Furness 1975). This body of evidence on treatment effectiveness is downgraded from moderate to low for indirectness due to studies that did not explicitly include asymptomatic women (only 3 studies included exclusively asymptomatic women; Kazemier 2015, Mulla 1960, and Williams 1969), and studies that included high-risk women (Elder 1971, Kincaid-Smith 1965, Little 1966, and Pathak 1969). The optimal information size criterion is met (control group event rate=20%; total number of events=253) with an adequate sample size (n=2,017), and the confidence interval (0.13 to 0.41) indicates there may be important benefit; therefore, downgrading is not warranted for imprecision. There were no concerns with inconsistency or other considerations to warrant further downgrading. 10

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11 Perinatal mortality [b] → Very Low Quality Evidence: Six trials (n=1,104; Elder 1971, Kass 1960, Kazemier 2015, Kincaid-12 13 Smith 1965, Little 1966, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate 14 due to serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Kass 1960, Wren 15 1969), and inadequate allocation concealment (Elder 1971, Kass 1960). This body of evidence on treatment 16 effectiveness is downgraded for indirectness due to studies that did not explicitly include asymptomatic women as well 17 as studies that included high-risk women. Further downgrading is warranted for **imprecision** due to the samples size not 18 19 being met for optimal information size criterion (37 events). There were no concerns to warrant downgrading for 20 inconsistency or other considerations. 21

22 Spontaneous abortion [c]→ Very Low Quality Evidence: Two trials (n=379; Furness 1975, Wren 1969) reported this 23 outcome. Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of 24 alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969) and incomplete 25 reporting (Furness 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that 26 did not explicitly include exclusively asymptomatic women. The sample size is inadequate with optimal information size 27 28 not met (10 events) to warrant downgrading twice from low to very low for imprecision. There were no concerns to 29 warrant downgrading for inconsistency or other considerations. 30

31 Neonatal sepsis [d] → Very Low Quality Evidence: Two trials (n=154; Kazemier 2015, Thomsen 1987) reported this 32 outcome. Quality of evidence is downgraded for indirectness due to studies that did not explicitly include exclusively 33 asymptomatic women. The sample size (<2000) is not met with only 2 events to warrant downgrading twice for 34 imprecision. There were no concerns to warrant downgrading for risk of bias, inconsistency or other considerations. 35

36 **Preterm delivery [e]** → Very Low Quality Evidence: Four trials (n=533; Furness 1975, Kazemier 2015, Thomsen 1987, 37 38 Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated 39 with use of alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969), and 40 incomplete reporting (Furness 1975). There is substantial heterogeneity (I<sup>2</sup>=70%) with point estimates on both sides of 41 the line of no effect to warrant downgrading for inconsistency. Downgrading from moderate to low for indirectness is 42 warranted due to studies that did not explicitly include exclusively asymptomatic women. There were no concerns to 43 warrant downgrading for imprecision or other considerations. 44 45

Low birth weight [f] → Low Quality Evidence: Seven trials (n=1,522; Brumfitt 1975, Elder 1971, Kass 1960, Kazemier 46 47 2015, Kincaid-Smith 1965, Little 1966, Wren 1969) reported this outcome. Quality of evidence is downgraded from high 48 to moderate for serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Kass 1960, 49 Wren 1969), inadequate allocation concealment (Elder 1971, Kass 1960, Wren 1969), and incomplete reporting (Brumfitt 50 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly 51 include exclusively asymptomatic women as well as studies that included high-risk women. The optimal information size 52 53 was not quite met (<2000 patients and <200 events), but we did not think the concerns were serious enough to 54 downgrade for this outcome for imprecision. There were no concerns to warrant downgrading for inconsistency or 55 other considerations. 56

57 **Neonatal serious harm: fetal abnormalities [g]**  $\rightarrow$  Very Low Quality Evidence: Four trials (n=821; Elder 1971, Furness 58 1975, Kazemier 2015, Little 1966) reported this outcome. Quality of evidence is downgraded from high to moderate for 59 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 60

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serious risk of bias associated with use of alternation for sequence generation (Elder 1971), inadequate allocation concealment (Elder 1971), and incomplete reporting (Furness 1975). Downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women as well as studies that included high-risk women. Further downgrading from low to very low for imprecision is warranted due to optimal information size (sample size of 821) not being met for rare events. There were no concerns to warrant downgrading for inconsistency or other considerations. 

**Neonatal serious harm: hemolytic anemia [h]**  $\rightarrow$  **Very Low Quality Evidence:** One trial (n=265; Elder 1971) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation and inadequate allocation concealment. Only one study provided data for this outcome so downgrading from moderate to low for inconsistency is warranted. Further downgrading from low to very low is warranted for indirectness due the study not explicitly including exclusively asymptomatic women as well as studies that included high-risk women. Due to optimal information size (sample size of 265) not being met for rare events, downgrading twice is warranted for imprecision. There were no concerns to warrant downgrading for other considerations. 

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### Evidence Set 3. Table 3.1 GRADE Evidence Profile – Benefits and harms of treatment compared to no treatment

Question: Treatment compared to no treatment for asymptomatic bacteriuria

Setting: Any primary or clinical care setting providing care to pregnant women

### Bibliography:

| Quality a | assessment           |                 |               |                  |                  |                         | Nº of patie       | nts             | Effect                              |   | Quality                         | Importance |
|-----------|----------------------|-----------------|---------------|------------------|------------------|-------------------------|-------------------|-----------------|-------------------------------------|---|---------------------------------|------------|
|           | Study<br>design      | Risk of<br>bias | Inconsistency | Indirectness     | Imprecision<br>1 | Other<br>considerations | treatment         | no<br>treatment | Relative<br>(95% CI)                | Absolute<br>(95% CI)  |                                 |            |
| Materna   | al mortality         |                 |               |                  |                  |                         |                   |                 |                                     |   |                                 |            |
| 0         |                      |                 |               | N                | 00               |                         |                   |                 | not<br>estimable                    |   | -                               | CRITICAL   |
| Materna   | al sepsis            |                 |               |                  |                  |                         | I                 | I               |                                     | L   | 1                               | 1          |
| 0         |                      |                 |               |                  |                  | 16                      |                   |                 | not<br>estimable                    |   | -                               | CRITICAL   |
| Pyelone   | phritis              |                 |               |                  |                  | L                       |                   | I               | 1                                   | 1   | 1                               | 1          |
| 12        | randomised<br>trials | serious         | not serious   | serious          | not serious      | none                    | 55/1023<br>(5.4%) | 23.2%           | <b>RR 0.24</b><br>(0.13 to<br>0.41) | <b>176</b><br><b>fewer</b><br><b>per</b><br><b>1,000</b><br>(from<br>137<br>fewer to<br>202<br>fewer) | ⊕⊕⊖<br>⊖<br>LOW <sup>1, a</sup> | CRITICAL   |
| Perinata  | l mortality          |                 | Fc            | or peer review o | nly - http://bm  | jopen.bmj.com/si        | te/about/gui      | delines.xhtml   |                                     |   |                                 |            |

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|                  | assessment           |                 |               |              |                 |                         | Nº of patie      | nts             | Effect                              |  | Quality                                 | Importa  |
|------------------|----------------------|-----------------|---------------|--------------|-----------------|-------------------------|------------------|-----------------|-------------------------------------|--|---|----------|
| Nº of<br>studies | Study<br>design      | Risk of<br>bias | Inconsistency | Indirectness | Imprecision     | Other<br>considerations | treatment        | no<br>treatment | Relative<br>(95% Cl)                | Absolute<br>(95% Cl)   |   |          |
| 6                | randomised<br>trials | serious         | not serious   | serious      | serious         | none                    | 16/529<br>(3.0%) | 4.0%            | <b>RR 0.96</b><br>(0.27 to<br>3.39) | <b>2 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 29<br>fewer to<br>97<br>more)  | ⊕⊖⊖<br>⊖<br>VERY<br>LOW <sup>1, b</sup> | CRITICAL |
| Spontar          | neous abortio        | n               | 1             |              |                 | I                       | I                | I               | I                                   |  | I                                       | 1        |
| 2                | randomised<br>trials | serious         | not serious   | serious      | very<br>serious | none                    | 4/222<br>(1.8%)  | 3.3%            | <b>RR 0.60</b> (0.11 to 3.10)       | <b>13 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 30<br>fewer to<br>70<br>more) | ⊕⊖⊖<br>⊖<br>VERY<br>LOW <sup>1, c</sup> | CRITICAL |
| Neonata          | al sepsis            |                 |               |              |                 |                         |                  |                 |                                     |  |   |          |
| 2                | randomised<br>trials | not<br>serious  | not serious   | serious      | very<br>serious | none                    | 0/77<br>(0.0%)   | 2.2%            | <b>RR 0.22</b> (0.01 to 4.54)       | <b>17 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 22<br>fewer to<br>79          | ⊕⊖⊖<br>⊖<br>VERY<br>LOW <sup>1, d</sup> | CRITICAL |

| trials       (8.3%)       (0.45 to<br>0.90)       per<br>1,000<br>(from 12<br>fewer to<br>65<br>fewer)       0         Maternal serious harm(s)       0  | esign<br>andomised | bias                           | Inconsistency                             | Indirectness   | Imprecision   | Other   |   |   |  |   |  |  |
|--|--------------------|--------------------------------|---|--|---|---|---|---|--|---|--|--|
| trials       Image: serious       serious       (11.4%)       (0.21 to 1.56)       per 1,000 (from 1,000) (from |                    |                                |   |  |   |   | treatment   |   |  |   |  |  |
| 7       randomised trials       serious       not serious       not serious       none       64/769       11.8%       RR 0.63       44 fewer per 1,000       IMPORTA         1000       0.90 </td <td></td> <td>serious</td> <td>serious</td> <td>not serious</td> <td>-</td> <td>none</td> <td>-</td> <td>15.8%</td> <td>(0.21 to</td> <td><b>per</b><br/><b>1,000</b><br/>(from<br/>125<br/>fewer to<br/>88</td> <td>○<br/>VERY</td> <td>CRITICAL</td>  |                    | serious                        | serious                                   | not serious  | -   | none  | -   | 15.8%   | (0.21 to   | <b>per</b><br><b>1,000</b><br>(from<br>125<br>fewer to<br>88  | ○<br>VERY  | CRITICAL   |
| trials       (8.3%)       (0.45 to<br>0.90)       per<br>1,000<br>(from 12<br>fewer to<br>65<br>fewer)       0         Maternal serious harm(s)       0       not       -       CRITICAL   | weight             |                                |   |  |   | L   | I   |   |  |   |  | L  |
| 0 Not estimable - CRITICAL   |                    | serious                        | not serious                               | serious  | not serious   |   |   | 11.8%   | (0.45 to   | <b>per</b><br><b>1,000</b><br>(from 12<br>fewer to<br>65  | $\bigcirc$   | IMPORTAN   |
| estimable  | erious harm        | n(s)                           |   |  |   | <u></u>   |   |   |  |   |  | <u> </u>   |
| Neonatal serious harm: fetal abnormalities   |                    |                                |   |  |   |   |   |   |  |   | -  | CRITICAL   |
|  | erious harm        | n: fetal al                    | onormalities                              |  | <u> </u>  | 1   | 1   |   |  |   |  | 1  |
|  | i                  | ndomised<br>als<br>erious harn | ndomised serious<br>als<br>erious harm(s) | ndomised serious not serious<br>als erious harm(s)<br>erious harm: fetal abnormalities | ndomised serious not serious serious<br>als serious harm(s)<br>erious harm: fetal abnormalities | ndomised serious not serious serious not serious als als als als als als als als als al | ndomised serious not serious serious not serious none<br>als als als als als als also also also a | Indomised als       serious       not serious       not serious       none       64/769<br>(8.3%)         erious harm(s)       Image: Serious harm: fetal abnormalities       Image: Serious harm: fetal abnormalities       Image: Serious harm: fetal abnormalities | Indomised serious not serious serious not serious none 64/769 (8.3%) 11.8% (8.3\%) 11.8% (8.3\%) 11.8\% (8.3\%) 1 | Indomised als       serious       not serious       not serious       not serious       none       64/769 (8.3%)       11.8% (0.45 to 0.90)       RR 0.63 (0.45 to 0.90)         erious harm(s)       Image: serious harm: fetal abnormalities       Image: serious harm: fetal abnormalities       Image: serious harm: fetal abnormalities       Image: serious harm: fetal abnormalities | veight       ndomised als       serious       not serious       not serious       none       64/769       11.8%       RR 0.63       44 fewer per 1,000         als       a | veight       serious       serious       serious       not ser |

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| Quality          | assessment                              |                 |               |              |                 |                         | № of patie      | nts             | Effect                        |   | Quality                                 | Importance |
|------------------|---|-----------------|---------------|--------------|-----------------|-------------------------|-----------------|-----------------|-------------------------------|---|---|------------|
| Nº of<br>studies | Study<br>design                         | Risk of<br>bias | Inconsistency | Indirectness | Imprecision     | Other<br>considerations | treatment       | no<br>treatment | Relative<br>(95% Cl)          | Absolute<br>(95% Cl)  |   |            |
| 4                | randomised<br>trials<br>al serious harn |                 |               | serious      | very<br>serious | none                    | 4/425<br>(0.9%) | 1.9%            | <b>RR 0.49</b> (0.17 to 1.43) | <b>9 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 15<br>fewer to<br>8 more) | ⊕⊖⊖<br>⊖<br>VERY<br>LOW <sup>1, g</sup> | CRITICAL   |
| 1                | randomised<br>trials                    |                 | serious       | serious      | very<br>serious | none                    | 0/122<br>(0.0%) | 0/143<br>(0.0%) | not<br>estimable              |   | ⊕⊖⊖<br>⊖<br>VERY<br>LOW <sup>1, h</sup> | CRITICAL   |

1.25).

CI: Confidence interval; RR: Risk ratio

Pyelonephritis, overall [a] → Low Quality Evidence: Twelve trials (Brumfitt 1975, Elder 1971, Foley 1987, Furness 1975, Gold 1966, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Mulla 1960, Pathak 1969, Williams 1969) reported this outcome (n=2,017). Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Gold 1966, Kass 1960), inadequate allocation concealment (Elder 1971, Gold 1966, Kass 1960), and incomplete reporting (Brumfitt 1975, Furness 1975). This body of evidence on treatment effectiveness is downgraded from moderate to low for indirectness due to studies that did not explicitly include asymptomatic women (only 3 studies included exclusively asymptomatic women; Kazemier 2015, Mulla 1960, and Williams 1969), and studies that included high-risk women (Elder 1971, Kincaid-Smith 1965, Little 1966, and Pathak 1969). The optimal information size criterion is met (control group event rate=20%; total number of events=253) with an adequate sample size (n=2,017), and the confidence interval (0.13 to 0.41) indicates there may be important benefit; therefore, downgrading is not warranted for imprecision. There were no concerns with inconsistency or other considerations to warrant further downgrading.

Perinatal mortality [b] → Very Low Quality Evidence: Six trials (n=1,104; Elder 1971, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Wren 1969)
reported this outcome. Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of alternation for sequence

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generation (Elder 1971, Kass 1960, Wren 1969), and inadequate allocation concealment (Elder 1971, Kass 1960). This body of evidence on treatment effectiveness is downgraded for **indirectness** due to studies that did not explicitly include asymptomatic women as well as studies that included high-risk women. Further downgrading is warranted for **imprecision** due to the samples size not being met for optimal information size criterion (37 events). There were no concerns to warrant downgrading for **inconsistency** or **other considerations**.

Spontaneous abortion [c]→ Very Low Quality Evidence: Two trials (n=379; Furness 1975, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969) and incomplete reporting (Furness 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women. The sample size is inadequate with optimal information size not met (10 events) to warrant downgrading twice from low to very low for imprecision. There were no concerns to warrant downgrading for inconsistency or other considerations.

Neonatal sepsis [d] → Very Low Quality Evidence: Two trials (n=154; Kazemier 2015, Thomsen 1987) reported this outcome. Quality of evidence is downgraded for indirectness due to studies that did not explicitly include exclusively asymptomatic women. The sample size (<2000) is not met with only 2 events to warrant downgrading twice for imprecision. There were no concerns to warrant downgrading for risk of bias, inconsistency or other considerations.

Preterm delivery [e] → Very Low Quality Evidence: Four trials (n=533; Furness 1975, Kazemier 2015, Thomsen 1987, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969), and incomplete reporting (Furness 1975). There is substantial heterogeneity (I<sup>2</sup>=70%) with point estimates on both sides of the line of no effect to warrant downgrading for inconsistency. Downgrading from moderate to low for indirectness is warranted due to studies that did not explicitly include exclusively asymptomatic women. There were no concerns to warrant downgrading for imprecision or other considerations.

Low birth weight [f] → Low Quality Evidence: Seven trials (n=1,522; Brumfitt 1975, Elder 1971, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate for serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Kass 1960, Wren 1969), inadequate allocation concealment (Elder 1971, Kass 1960, Wren 1969), and incomplete reporting (Brumfitt 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women as well as studies that included high-risk women. The optimal information size was not quite met (<2000 patients and <200 events), but we did not think the concerns were serious enough to downgrade for this outcome for imprecision. There were no concerns to warrant downgrading for inconsistency or other considerations.

Neonatal serious harm: fetal abnormalities [g] → Very Low Quality Evidence: Four trials (n=821; Elder 1971, Furness 1975, Kazemier 2015, Little 1966) reported this outcome. Quality of evidence is downgraded from high to moderate for serious risk of bias associated with use of alternation for sequence generation (Elder 1971), inadequate allocation concealment (Elder 1971), and incomplete reporting (Furness 1975). Downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women as well as studies that included high-risk women. Further downgrading from low to very low for imprecision is warranted due to optimal information size (sample size of 821) not being met for rare events. There were no concerns to warrant downgrading for inconsistency or other considerations.

Neonatal serious harm: hemolytic anemia [h] → Very Low Quality Evidence: One trial (n=265; Elder 1971) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation and inadequate allocation concealment. Only one study provided data for this outcome so downgrading from moderate to low for inconsistency is warranted. Further downgrading from low to very low is warranted for indirectness due the study not explicitly including exclusively asymptomatic women as well as studies that included high-risk women. Due to For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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optimal information size (sample size of 265) not being met for rare events, downgrading twice is warranted for **imprecision**. There were no concerns to warrant downgrading for **other considerations**.

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| Outcome   | No. of  | No. of       | Effect size                      |
|---|---------|--------------|----------------------------------|
|   | studies | participants | (Risk Ratio; M-H, Random, 95%CI) |
| 3.1 Pyelonephritis  | 12      | 2017         | 0.24 [0.13, 0.41]                |
| 3.2 Perinatal mortality (≥20 wks, including intrauterine                                      | 6       | 1104         | 0.96 [0.27, 3.39]                |
| demise, stillbirth, early neonatal death)   |         |              |                                  |
| 3.3 Spontaneous abortion (<20 wks)  | 2       | 379          | 0.60 [0.11, 3.10]                |
| 3.4 Neonatal sepsis   | 2       | 154          | 0.22 [0.01, 4.54]                |
| 3.5 Preterm delivery (<38 wks)  | 4       | 533          | 0.57 [0.21, 1.56]                |
| 3.6 Low birth weight (≤2500g; SGA <10 <sup>th</sup> percentile & <5 <sup>th</sup> percentile) | 7       | 1522         | 0.63 [0.45, 0.90]                |
| 3.7 Neonatal serious harm: fetal abnormalities  | 4       | 821          | 0.49 [0.17, 1.43]                |
| 3.8 Neonatal serious harm: hemolytic anemia   | 1       | 265          | Not estimable                    |

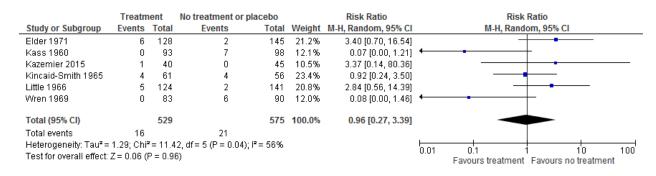
### Evidence Set 3: Forest Plots 3.1-3.8 - KQ4: Benefits and harms of treatment compared to no treatment

CI: confidence interval; g: grams; M-H: Mantel-Haenszel; No.: number; SGA: small for gestational age; wks: weeks

### 3.1 Pyelonephritis

|                                   | Treatm                 | nent                | No treatment or p      | lacebo                               |        | Risk Ratio          | Risk Ratio                                 |                    |
|-----------------------------------|------------------------|---------------------|------------------------|--------------------------------------|--------|---------------------|--|--------------------|
| Study or Subgroup                 | Events                 | Total               | Events                 | Total                                | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl                        |                    |
| Brumfitt 1975                     | 9                      | 87                  | 20                     | 86                                   | 12.8%  | 0.44 [0.21, 0.92]   |  |                    |
| Elder 1971                        | 4                      | 133                 | 27                     | 148                                  | 10.6%  | 0.16 [0.06, 0.46]   |  |                    |
| Foley 1987                        | 3                      | 100                 | 3                      | 120                                  | 7.1%   | 1.20 [0.25, 5.82]   |  |                    |
| Furness 1975                      | 23                     | 139                 | 17                     | 67                                   | 14.1%  | 0.65 [0.37, 1.14]   | _ <b>-</b> +                               |                    |
| Gold 1966                         | 0                      | 35                  | 2                      | 30                                   | 2.9%   | 0.17 [0.01, 3.45]   | •  |                    |
| Kass 1960                         | 1                      | 93                  | 26                     | 98                                   | 5.4%   | 0.04 [0.01, 0.29]   | • • • • · · · · · · · · · · · · · · · ·    |                    |
| Kazemier 2015                     | 0                      | 40                  | 1                      | 45                                   | 2.6%   | 0.37 [0.02, 8.93]   |  | -                  |
| Kincaid-Smith 1965                | 2                      | 61                  | 20                     | 55                                   | 8.0%   | 0.09 [0.02, 0.37]   |  |                    |
| Little 1966                       | 4                      | 124                 | 35                     | 141                                  | 10.7%  | 0.13 [0.05, 0.36]   | <b>-</b>                                   |                    |
| Mulla 1960                        | 1                      | 50                  | 12                     | 50                                   | 5.3%   | 0.08 [0.01, 0.62]   |  |                    |
| Pathak 1969                       | 3                      | 76                  | 17                     | 76                                   | 9.4%   | 0.18 [0.05, 0.58]   |  |                    |
| Williams 1969                     | 5                      | 85                  | 18                     | 78                                   | 11.2%  | 0.25 [0.10, 0.65]   |  |                    |
| Total (95% CI)                    |                        | 1023                |                        | 994                                  | 100.0% | 0.24 [0.13, 0.41]   | ◆  |                    |
| Total events                      | 55                     |                     | 198                    |                                      |        |                     |  |                    |
| Heterogeneity: Tau <sup>2</sup> = | 0.49; Chi <sup>a</sup> | <sup>2</sup> = 27.6 | i9, df = 11 (P = 0.00) | 4); I <sup>2</sup> = 60 <sup>4</sup> | %      |                     |  | +                  |
| Test for overall effect:          | Z = 5.09 (             | P < 0.0             | 0001)                  |                                      |        |                     | 0.01 0.1 1<br>Favours treatment Favours no | 10 11<br>treatment |
|                                   |                        |                     |                        |                                      |        |                     |  |                    |

### 3.2 Perinatal mortality



### 3.3 Spontaneous abortion

#### **BMJ** Open

| Study or Subgroup                 | Treatm<br>Events |          | No treatment or pla<br>Events |       | Weight | Risk Ratio<br>M-H, Random, 95% Cl | Risk Ratio<br>Cl M-H. Random, 95% Cl   |
|-----------------------------------|------------------|----------|-------------------------------|-------|--------|-----------------------------------|--|
|                                   | Lvents           |          | -                             |       |        | , ,                               |  |
| Furness 1975                      | 2                | 139      | 0                             | 67    | 26.3%  | 2.43 [0.12, 49.89]                | 9]                                     |
| Wren 1969                         | 2                | 83       | 6                             | 90    | 73.7%  | 0.36 [0.08, 1.74]                 | 4]                                     |
| Total (95% CI)                    |                  | 222      |                               | 157   | 100.0% | 0.60 [0.11, 3.10]                 | 0]                                     |
| Total events                      | 4                |          | 6                             |       |        |                                   |  |
| Heterogeneity: Tau <sup>2</sup> = |                  |          |                               | = 17% |        |                                   |  |
| Test for overall effect           | 2 = 0.62         | (P = 0.5 | (4)                           |       |        |                                   | Favours treatment Favours no treatment |

### 3.4 Neonatal sepsis

|                          | Treatm       | ent      | No treatment or placebo |           | Risk Ratio          | Risk Ratio                             |
|--------------------------|--------------|----------|-------------------------|-----------|---------------------|--|
| Study or Subgroup        | Events       | Total    | Events Tot              | al Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl                    |
| Kazemier 2015            | 0            | 40       | 2 4                     | 5 100.0%  | 0.22 [0.01, 4.54]   |  |
| Thomsen 1987             | 0            | 37       | 0 3                     | 2         | Not estimable       |  |
| Total (95% CI)           |              | 77       | 7                       | 7 100.0%  | 0.22 [0.01, 4.54]   |  |
| Total events             | 0            |          | 2                       |           |                     |  |
| Heterogeneity: Not ap    | pplicable    |          |                         |           |                     |  |
| Test for overall effect: | : Z = 0.97 ( | (P = 0.3 | (3)                     |           |                     | Favours treatment Favours no treatment |
| 3.5 Preterm de           | livery       |          |                         |           |                     |  |
|                          | Treatm       | ent      | No treatment or placebo |           | Risk Ratio          | Risk Ratio                             |

### 3.5 Preterm delivery

|                                   | Treatm      | ent                | No treatment or p       | lacebo |        | Risk Ratio          |      | Risk Ratio   |     |
|-----------------------------------|-------------|--------------------|-------------------------|--------|--------|---------------------|------|--|-----|
| Study or Subgroup                 | Events      | Total              | Events                  | Total  | Weight | M-H, Random, 95% CI |      | M-H, Random, 95% Cl                                |     |
| Furness 1975                      | 24          | 139                | 10                      | 67     | 32.4%  | 1.16 [0.59, 2.28]   |      | <b>-</b>   |     |
| Kazemier 2015                     | 3           | 40                 | 2                       | 45     | 17.9%  | 1.69 [0.30, 9.59]   |      |  |     |
| Thomsen 1987                      | 2           | 37                 | 12                      | 32     | 21.7%  | 0.14 [0.03, 0.60]   |      | <b>_</b>   |     |
| Wren 1969                         | 5           | 83                 | 15                      | 90     | 28.1%  | 0.36 [0.14, 0.95]   |      |  |     |
| Total (95% CI)                    |             | 299                |                         | 234    | 100.0% | 0.57 [0.21, 1.56]   |      |  |     |
| Total events                      | 34          |                    | 39                      |        |        |                     |      |  |     |
| Heterogeneity: Tau <sup>2</sup> = | = 0.70; Chi | <sup>2</sup> = 9.8 | 5, df = 3 (P = 0.02); l | ²=70%  |        |                     |      |  |     |
| Test for overall effect           |             |                    |                         |        |        |                     | 0.01 | 0.1 1 10<br>Favours treatment Favours no treatment | 100 |

#### 3.6 Low birthweight

|                                   | Treatm     | ent                 | No treatment or pl                  | acebo |        | Risk Ratio          | Risk Ratio   |
|-----------------------------------|------------|---------------------|-------------------------------------|-------|--------|---------------------|--|
| Study or Subgroup                 | Events     | Total               | Events                              | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl  |
| Brumfitt 1975                     | 18         | 235                 | 21                                  | 178   | 23.0%  | 0.65 [0.36, 1.18]   |  |
| Elder 1971                        | 15         | 133                 | 15                                  | 145   | 19.4%  | 1.09 [0.55, 2.14]   | _ <b>_</b>   |
| Kass 1960                         | 7          | 93                  | 21                                  | 98    | 14.8%  | 0.35 [0.16, 0.79]   |  |
| Kazemier 2015                     | 1          | 40                  | 4                                   | 45    | 2.5%   | 0.28 [0.03, 2.41]   |  |
| Kincaid-Smith 1965                | 9          | 61                  | 12                                  | 56    | 15.5%  | 0.69 [0.31, 1.51]   |  |
| Little 1966                       | 10         | 124                 | 13                                  | 141   | 15.4%  | 0.87 [0.40, 1.92]   |  |
| Wren 1969                         | 4          | 83                  | 14                                  | 90    | 9.3%   | 0.31 [0.11, 0.90]   |  |
| Total (95% CI)                    |            | 769                 |                                     | 753   | 100.0% | 0.63 [0.45, 0.90]   | •  |
| Total events                      | 64         |                     | 100                                 |       |        |                     |  |
| Heterogeneity: Tau <sup>2</sup> = | 0.04; Chi  | <sup>2</sup> = 7.52 | . df = 6 (P = 0.28); I <sup>2</sup> | = 20% |        | ۴.<br>L             |  |
| Test for overall effect:          | Z = 2.57 ( | P = 0.0             | 1)                                  |       |        | l                   | 0.01 0.1 1 10 11<br>Favours treatment Favours no treatment |

### 3.7 Neonatal serious harm: fetal abnormalities

|                                   | Treatm     | nent                 | No treatment or p       | lacebo  |        | Risk Ratio          | Risk Ratio  |
|-----------------------------------|------------|----------------------|-------------------------|---------|--------|---------------------|---|
| Study or Subgroup                 | Events     | Total                | Events                  | Total   | Weight | M-H, Random, 95% CI | M-H, Random, 95% Cl   |
| Elder 1971                        | 2          | 122                  | 6                       | 143     | 46.4%  | 0.39 [0.08, 1.90]   |   |
| Furness 1975                      | 0          | 139                  | 1                       | 67      | 11.4%  | 0.16 [0.01, 3.92]   | ← <b>- -</b>  |
| Kazemier 2015                     | 0          | 40                   | 1                       | 45      | 11.5%  | 0.37 [0.02, 8.93]   |   |
| Little 1966                       | 2          | 124                  | 2                       | 141     | 30.7%  | 1.14 [0.16, 7.95]   |   |
| Total (95% CI)                    |            | 425                  |                         | 396     | 100.0% | 0.49 [0.17, 1.43]   |   |
| Total events                      | 4          |                      | 10                      |         |        |                     |   |
| Heterogeneity: Tau <sup>2</sup> = | = 0.00; Ch | i <sup>2</sup> = 1.2 | 9, df = 3 (P = 0.73); l | l² = 0% |        |                     |   |
| Test for overall effect           | Z=1.31     | (P = 0.1             | 9)                      |         |        |                     | 0.01 0.1 1 10 100<br>Favours treatment Favours no treatment |

### 3.8 Neonatal serious harm: hemolytic anemia

| Study or Subgroup                                | Treatm<br>Events |       | No treatment or pla<br>Events |     | Weight | Risk Ratio<br>M-H, Random, 95% Cl | Risk Ratio<br>M-H, Random, 95% Cl      |
|--|------------------|-------|-------------------------------|-----|--------|-----------------------------------|--|
| Elder 1971                                       | 0                | 122   |                               | 143 | weight | Not estimable                     | win, Kandolli, 55% Ci                  |
| T-4-140544 00                                    |                  | 400   |                               |     |        |                                   |  |
| Total (95% CI)                                   |                  | 122   |                               | 143 |        | Not estimable                     |  |
| Total events                                     | O                |       | 0                             |     |        |                                   |  |
| Heterogeneity: Not ap<br>Test for overall effect |                  | oblo  |                               |     |        |                                   | 0.01 0.1 1 10                          |
| Testion overall ellect                           | . Not appin      | Lable |                               |     |        |                                   | Favours treatment Favours no treatment |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |
|  |                  |       |                               |     |        |                                   |  |

# Evidence Set 3. Forest Plots for Subgroup Analyses 3.1.1-3.1.4 – KQ4: Benefits and harms of treatment compared to no treatment

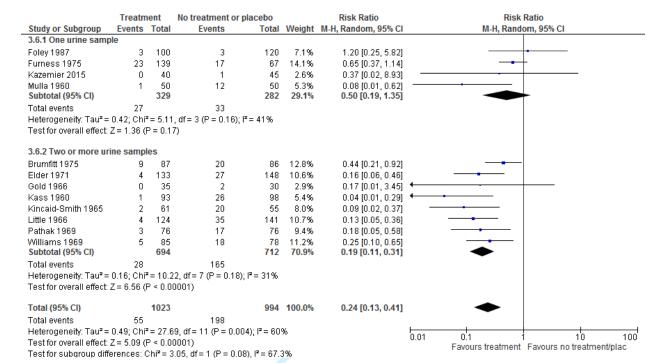
| Outcome   | No. of       | No. of             | Effect size                      |
|---|--------------|--------------------|----------------------------------|
|   | studies      | participants       | (Risk Ratio; M-H, Random, 95%CI) |
| 3.1 Pyelonephritis (overall)  | 12           | 2017               | 0.24 [0.13, 0.41]                |
| 3.1.1 Subgroup analysis: no. of urine samples before con              | firming bact | eriuria and giving | treatment                        |
| One urine sample  | 4            | 611                | 0.50 [0.19, 1.35]                |
| Two or more urine samples   | 8            | 1406               | 0.19 [0.11, 0.31]                |
| 3.1.2 Subgroup analysis: testing for persistent bacteriuria           | 3            | ·                  | •                                |
| Tested for persistent bacteriuria during pregnancy                    | 8            | 1352               | 0.26 [0.15, 0.45]                |
| Testing for persistent bacteriuria post-delivery only                 | 1            | 206                | 0.65 [0.37, 1.14]                |
| Testing for persistent bacteriuria during pregnancy and post-delivery | 3            | 459                | 0.11 [0.05, 0.25]                |
| 3.1.3 Subgroup analysis: follow-up                                    | •            |                    | •                                |
| Follow-up until delivery or puerperium (≤6 wks post-<br>delivery)     | 9            | 1558               | 0.31 [0.18, 0.54]                |
| Follow-up until >6 wks post-delivery                                  | 3            | 459                | 0.11 [0.05, 0.25]                |

CI: confidence interval; M-H: Mantel-Haenszel; No.: number; wks: weeks

### 3.1 Pyelonephritis (overall)

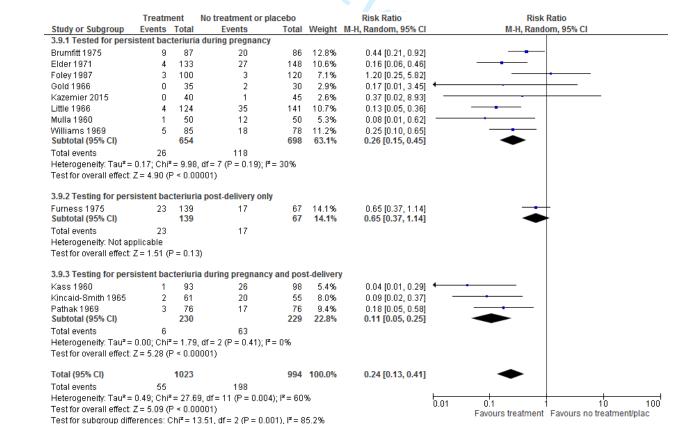
|                                   | Treatm     |                     | No treatment or       |                          |        | Risk Ratio          | Risk Ratio  |
|-----------------------------------|------------|---------------------|-----------------------|--------------------------|--------|---------------------|---|
| Study or Subgroup                 | Events     | Total               | Events                | Total                    | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl                                     |
| Brumfitt 1975                     | 9          | 87                  | 20                    | 86                       | 12.8%  | 0.44 [0.21, 0.92]   |   |
| Elder 1971                        | 4          | 133                 | 27                    | 148                      | 10.6%  | 0.16 [0.06, 0.46]   |   |
| Foley 1987                        | 3          | 100                 | 3                     | 120                      | 7.1%   | 1.20 [0.25, 5.82]   |   |
| Furness 1975                      | 23         | 139                 | 17                    | 67                       | 14.1%  | 0.65 [0.37, 1.14]   |   |
| Gold 1966                         | 0          | 35                  | 2                     | 30                       | 2.9%   | 0.17 [0.01, 3.45]   | •                 |
| Kass 1960                         | 1          | 93                  | 26                    | 98                       | 5.4%   | 0.04 [0.01, 0.29]   | <b>← →</b>  |
| Kazemier 2015                     | 0          | 40                  | 1                     | 45                       | 2.6%   | 0.37 [0.02, 8.93]   |   |
| Kincaid-Smith 1965                | 2          | 61                  | 20                    | 55                       | 8.0%   | 0.09 [0.02, 0.37]   |   |
| Little 1966                       | 4          | 124                 | 35                    | 141                      | 10.7%  | 0.13 [0.05, 0.36]   |   |
| Mulla 1960                        | 1          | 50                  | 12                    | 50                       | 5.3%   | 0.08 [0.01, 0.62]   |   |
| Pathak 1969                       | 3          | 76                  | 17                    | 76                       | 9.4%   | 0.18 [0.05, 0.58]   |   |
| Williams 1969                     | 5          | 85                  | 18                    | 78                       | 11.2%  | 0.25 [0.10, 0.65]   |   |
| Total (95% CI)                    |            | 1023                |                       | 994                      | 100.0% | 0.24 [0.13, 0.41]   | ◆   |
| Total events                      | 55         |                     | 198                   |                          |        |                     |   |
| Heterogeneity: Tau <sup>2</sup> = | 0.49; Chi  | <sup>2</sup> = 27.8 | i9, df = 11 (P = 0.00 | )4); I <sup>2</sup> = 60 | %      |                     |   |
| Test for overall effect:          | 7 = 5.09.0 | P < ∩ ∩             | 0001)                 |                          |        |                     | 0.01 0.1 1 10<br>Favours treatment Favours no treatment |

### 3.1.1 Pyelonephritis subgroup: number of urine samples at each screening visit\*



\*The additional culture(s) was used to confirm levels of bacteriuria.

### 3.1.2 Pyelonephritis subgroup: timing of testing for persistent bacteriuria



4 5

### 3.1.3 Pyelonephritis subgroup: duration of follow-up

| 6        |   |                                    |                             |                           |               |  |  |
|----------|---|------------------------------------|-----------------------------|---------------------------|---------------|--|--|
| 7        |   | Treatment                          | No treatment or             |                           |               | Risk Ratio                             | Risk Ratio   |
| 8        | Study or Subgroup<br>3.5.1 Follow-up to del                   | Events Total                       |                             |                           |               | M-H, Random, 95% Cl                    | M-H, Random, 95% Cl  |
| 9        | Brumfitt 1975   | 9 87                               |                             |                           | 12.8%         | 0.44 [0.21, 0.92]                      | <b>_</b>   |
| 10       | Elder 1971  | 4 133                              |                             | 148                       | 10.6%         | 0.16 [0.06, 0.46]                      |  |
| 11       | Foley 1987<br>Furness 1975                                    | 3 100<br>23 139                    |                             | 120<br>67                 | 7.1%<br>14.1% | 1.20 [0.25, 5.82]<br>0.65 [0.37, 1.14] |  |
| 12       | Gold 1966   | 0 35                               | 2                           | 30                        | 2.9%          | 0.17 [0.01, 3.45]                      | •  |
| 13       | Kazemier 2015<br>Little 1966                                  | 0 40<br>4 124                      |                             | 45<br>141                 | 2.6%<br>10.7% | 0.37 [0.02, 8.93]<br>0.13 [0.05, 0.36] |  |
| 14       | Mulla 1960  | 1 50                               |                             | 50                        | 5.3%          | 0.08 [0.01, 0.62]                      |  |
| 15       | Williams 1969<br>Subtotal (05% CD                             | 5 85<br>793                        |                             | 78<br>765                 | 11.2%         | 0.25 [0.10, 0.65]                      |  |
| 16       | Subtotal (95% CI)<br>Total events                             | 49<br>49                           | 135                         | 765                       | 77.2%         | 0.31 [0.18, 0.54]                      | -  |
| 17       | Heterogeneity: Tau <sup>2</sup> =                             |                                    |                             | ); l² = 53%               |               |  |  |
| 18       | Test for overall effect:                                      | Z = 4.07 (P < 0.0                  | )001)                       |                           |               |  |  |
| 19       | 3.5.3 Follow-up until >                                       | • 6 weeks post-                    | delivery                    |                           |               |  |  |
|          | Kass 1960   | 1 93                               |                             | 98                        | 5.4%          | 0.04 [0.01, 0.29]                      | <b>←</b>   |
| 20       | Kincaid-Smith 1965<br>Pathak 1969                             | 2 61<br>3 76                       |                             | 55<br>76                  | 8.0%<br>9.4%  | 0.09 [0.02, 0.37]<br>0.18 [0.05, 0.58] |  |
| 21       | Subtotal (95% CI)   | 230                                |                             | 229                       | 22.8%         | 0.11 [0.05, 0.25]                      |  |
| 22       | Total events  | 6                                  | 63                          |                           |               |  |  |
| 23       | Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect: |                                    |                             | I <sup>2</sup> = 0%       |               |  |  |
| 24       |   |                                    |                             |                           |               |  |  |
| 25       | Total (95% Cl)  | 1023                               |                             | 994                       | 100.0%        | 0.24 [0.13, 0.41]                      | •  |
| 26       | Total events<br>Heterogeneity: Tau <sup>2</sup> =             | 55<br>0.49: Chi <sup>2</sup> = 27. | 198<br>69. df = 11 (P = 0.0 | 04): I <sup>2</sup> = 60% | %             |  |  |
| 27       | Test for overall effect:                                      | Z = 5.09 (P < 0.0                  | 00001)                      |                           |               |  | 0.01 0.1 1 10 100<br>Favours treatment Favours no treatment/plac |
| 28       | Test for subgroup diff  | erences: Chi <sup>z</sup> =        | 4.23, df = 1 (P = 0.0       | I4), I² = 76.4            | 1%            |  |  |
| 29       |   |                                    |                             |                           |               |  |  |
| 30       |   |                                    |                             |                           |               |  |  |
| 31       |   |                                    |                             |                           |               |  |  |
| 32       |   |                                    |                             |                           |               |  |  |
| 33       |   |                                    |                             |                           |               |  |  |
| 34       |   |                                    |                             |                           |               |  |  |
| 35       |   |                                    |                             |                           |               |  |  |
| 36       |   |                                    |                             |                           |               |  |  |
| 37       |   |                                    |                             |                           |               |  |  |
| 38       |   |                                    |                             |                           |               |  |  |
| 39       |   |                                    |                             |                           |               |  |  |
| 40       |   |                                    |                             |                           |               |  |  |
| 41       |   |                                    |                             |                           |               |  |  |
| 42       |   |                                    |                             |                           |               |  |  |
| 42       |   |                                    |                             |                           |               |  |  |
| 43       |   |                                    |                             |                           |               |  |  |
| 44 45    |   |                                    |                             |                           |               |  |  |
| 45<br>46 |   |                                    |                             |                           |               |  |  |
|          |   |                                    |                             |                           |               |  |  |
| 47       |   |                                    |                             |                           |               |  |  |
| 48       |   |                                    |                             |                           |               |  |  |
| 49       |   |                                    |                             |                           |               |  |  |
| 50       |   |                                    |                             |                           |               |  |  |
| 51       |   |                                    |                             |                           |               |  |  |
| 52       |   |                                    |                             |                           |               |  |  |
| 53       |   |                                    |                             |                           |               |  |  |
| 54       |   |                                    |                             |                           |               |  |  |
| 55       |   |                                    |                             |                           |               |  |  |
| 56       |   |                                    |                             |                           |               |  |  |
| 57       |   |                                    |                             |                           |               |  |  |
| 58       |   |                                    |                             |                           |               |  |  |
| 59       |   | F .                                |                             | L.u. 73                   | •             |  |  |
| 60       |   | For peer                           | review only                 | nttp://                   | omjop         | en.pmj.com/site                        | e/about/guidelines.xhtml   |
|          |   |                                    |                             |                           |               |  |  |

RR 100

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# Supplement 7. Funnel Plot Asymmetry Test for outcome of pyelonephritis for treatment

# PRISMA 2009 Checklist

| Section/topic                      | #  | Checklist item   | Reported<br>on page #                 |
|------------------------------------|----|--|---------------------------------------|
| TITLE                              |    |  |                                       |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.  | Title page                            |
|                                    |    |  |                                       |
| Structured summary                 | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | p. 2                                  |
|                                    |    |  |                                       |
| Rationale                          | 3  | Describe the rationale for the review in the context of what is already known.   | р. З                                  |
| objectives                         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).   | p. 3 & 4                              |
| METHODS                            |    |  |                                       |
| Protocol and registration          | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | Abstract;<br>p. 3;<br>Supplement<br>1 |
| Eligibility criteria               | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.   | p. 4;<br>Supplement<br>3              |
| Information sources                | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.   | р. 3-4                                |
| Search                             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | Supplement<br>2                       |
| Study selection                    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | p. 4                                  |
| Data collection process            | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.   | р. 4-5                                |
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | р. 4-5                                |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.   | р. 4-5                                |
| Summary measures                   | 13 | State the principal suminyary measteres reign as white the second state of the second se | р. 5                                  |



# PRISMA 2009 Checklist

| Synthesis of results          | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.  | р. 5                                       |
|-------------------------------|----|--|--|
|                               |    | Page 1 of 2  |  |
| Section/topic                 | #  | Checklist item   | Reported<br>on page #                      |
| Risk of bias across studies   | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).   | p. 4-5                                     |
| Additional analyses           | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.   | p. 5                                       |
| RESULTS                       | •  |  |  |
| Study selection               | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | p. 5-7;<br>Figure 1                        |
| Study characteristics         | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.   | p. 5-7;<br>Table 1;<br>Supplemen<br>4      |
| Risk of bias within studies   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | p. 8-10;<br>Supplemen<br>5                 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | p. 8-10;<br>Table 2;<br>Supplemen<br>4 & 6 |
| Synthesis of results          | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | p. 9-13;<br>Table 2;<br>Supplemen<br>6     |
| Risk of bias across studies   | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | p.10-13;<br>Supplemen<br>5                 |
| Additional analysis           | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | p. 10-12<br>Supplemen<br>6                 |
| DISCUSSION                    |    | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml  |  |

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### **PRISMA 2009 Checklist**

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| 4<br>5         | Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | p. 12    |
| 6<br>7         | Limitations         | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of  | p. 12;   |
| 8              |                     |    | identified research, reporting bias).  | Box      |
| 9<br>10        | Conclusions         | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | p. 12-13 |
| 11             | FUNDING             |    |  |          |
| 12<br>13<br>14 | Funding             | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.   | p.14     |

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16 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. 17 doi:10.1371/journal.pmed1000097

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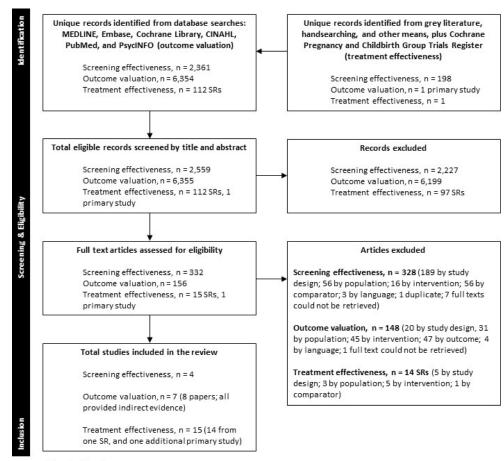
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# **BMJ Open**

### Asymptomatic Bacteriuria in Pregnancy: Systematic Reviews of Screening and Treatment Effectiveness and Patient Preferences

| Journal:                             | BMJ Open   |
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| Manuscript ID                        | bmjopen-2017-021347.R1   |
| Article Type:                        | Research   |
| Date Submitted by the<br>Author:     | 16-Aug-2018  |
| Complete List of Authors:            | Wingert, Aireen; University of Alberta, Alberta Research Centre for<br>Health Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87<br>Ave.,, Pediatrics<br>Pillay, Jennifer; University of Alberta, Alberta Research Centre for Health<br>Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87 Ave.,<br>Pediatrics<br>Sebastianski, Meghan; University of Alberta, Alberta Research Centre for<br>Health Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87<br>Ave., Pediatrics<br>Gates, Michelle; University of Alberta, Alberta Research Centre for Health<br>Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87<br>Ave., Pediatrics<br>Gates, Michelle; University of Alberta, Alberta Research Centre for Health<br>Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87 Ave.,<br>Pediatrics<br>Featherstone, Robin; University of Alberta, Alberta Research Centre for<br>Health Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87<br>Ave., Pediatrics<br>Shave, Kassi; University of Alberta, Alberta Research Centre for Health<br>Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87<br>Ave., Pediatrics<br>Shave, Kassi; University of Alberta, Alberta Research Centre for Health<br>Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87<br>Ave., Pediatrics<br>Vandermeer, Ben; University of Alberta, Alberta Research Centre for<br>Health Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87<br>Ave., Pediatrics<br>Hartling, Lisa; University of Alberta, Alberta Research Centre for<br>Health Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87<br>Ave., Pediatrics<br>Hartling, Lisa; University of Alberta, Alberta Research Centre for Health<br>Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87<br>Ave., Pediatrics<br>Hartling, Lisa; University of Alberta, Alberta Research Centre for Health<br>Evidence (ARCHE), Edmonton Clinic Health Academy, 11405-87 Ave.,<br>Pediatrics |
| <b>Primary Subject<br/>Heading</b> : | Obstetrics and gynaecology   |
| Secondary Subject Heading:           | Evidence based practice  |
| Keywords:                            | asymptomatic infections, bacteriuria, pregnancy, mass screening, anti-<br>bacterial agents, systematic review  |
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|   | Brumfit 1975<br>Elder 1971<br>Foley 1987<br>Furness 1975<br>Gold 1966<br>Kass 1960<br>Kazemier 2015<br>Kincaid-Smith 1965<br>Little 1966<br>Mulia 1960<br>Pathak 1969<br>Williams 1969 | 9         87           4         133           3         100           23         139           0         35           1         93           0         40           2         61           4         124           1         50           3         76           5         85 | 20<br>27<br>3<br>17<br>2<br>26<br>1<br>20<br>35<br>12<br>17<br>18 | 86         12.8%           148         10.6%           120         7.1%           67         14.1%           30         2.9%           98         5.4%           45         2.6%           55         8.0%           141         10.7%           50         5.3%           76         9.4%           78         11.2% | 0.44 [0.21, 0.92]<br>0.16 [0.06, 0.46]<br>1.20 [0.25, 5.82]<br>0.65 [0.37, 1.14]<br>0.17 [0.01, 3.45] ←<br>0.37 [0.02, 8.93] −<br>0.39 [0.02, 0.37]<br>0.13 [0.05, 0.36]<br>0.08 [0.01, 0.62] −<br>0.18 [0.05, 0.58]<br>0.25 [0.10, 0.65] |                                      | _                        |
|   | Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> = 0.<br>Test for overall effect: Z =   | 1023<br>55<br>49; Chi² = 27.69, df =<br>= 5.09 (P < 0.00001)   | 198<br>11 (P = 0.004); I  | 994 100.0%<br><sup>2</sup> =60%   | 0.24 [0.13, 0.41]   | 1 0.1 1<br>Favours treatment Favours | 10 100<br>s no treatment |
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|                                   | Treatment |         | No treatment or placebo |       |        | <b>Risk Ratio</b>   | Risk Ratio   |
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| Study or Subgroup                 | Events    | Total   | Events                  | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% Cl  |
| Brumfitt 1975                     | 18        | 235     | 21                      | 178   | 23.0%  | 0.65 [0.36, 1.18]   |  |
| Elder 1971                        | 15        | 133     | 15                      | 145   | 19.4%  | 1.09 [0.55, 2.14]   |  |
| Kass 1960                         | 7         | 93      | 21                      | 98    | 14.8%  | 0.35 [0.16, 0.79]   |  |
| Kazemier 2015                     | 1         | 40      | 4                       | 45    | 2.5%   | 0.28 [0.03, 2.41]   |  |
| Kincaid-Smith 1965                | 9         | 61      | 12                      | 56    | 15.5%  | 0.69 [0.31, 1.51]   |  |
| Little 1966                       | 10        | 124     | 13                      | 141   | 15.4%  | 0.87 [0.40, 1.92]   |  |
| Wren 1969                         | 4         | 83      | 14                      | 90    | 9.3%   | 0.31 [0.11, 0.90]   |  |
| Total (95% CI)                    |           | 769     |                         | 753   | 100.0% | 0.63 [0.45, 0.90]   | •  |
| Total events                      | 64        |         | 100                     |       |        |                     |  |
| Heterogeneity: Tau <sup>2</sup> = | 0.04; Chi | = 7.52  | , df = 6 (P = 0.28); P  | = 20% |        | 1                   |  |
| Test for overall effect:          | Z= 2.57 ( | P = 0.0 | 1)                      |       |        |                     | 0.01 0.1 1 10 10<br>Favours treatment Favours no treatment |

Figure 3. Forest plot of the effect of antibiotic treatment on incidence of babies born at low birth weight

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### Supplement 1. Protocol: Screening for asymptomatic bacteriuria in pregnancy

December 1, 2016

ERSC Project Lead Investigator: Lisa Hartling ERSC Project Staff: Aireen Wingert, Jennifer Pillay, Robin Featherstone (MLIS), and Ben Vandermeer (Statistician)

Suggested citation: Wingert A, Pillay J, Featherstone R, Vandermeer B, and Hartling L. Screening for asymptomatic bacteriuria in pregnancy: protocol for evidence review. Edmonton, AB; Evidence Review Synthesis Centre. Available at: <u>http://canadiantaskforce.ca/ctfphc-guidelines/overview/</u>

### **Author Contributions**

AW and JP drafted the protocol and RF developed the search strategy and provided text for the protocol. AW, JP, and LH contributed to discussions with the CTFPHC and PHAC on the scope for this work. LH and BV critically reviewed the protocol. All of the authors approved the final version of this protocol.

### Acknowledgements

We would like to acknowledge the contribution of the following individuals for their clinical and methodological input and/or their review of the protocol:

<u>CTFPHC Asymptomatic Bacteriuria Working Group</u>: Ainsley Moore (Chair), Roland Grad, Stéphane Groulx, Kevin Pottie, Brett Thombs, and Marcello Tonelli

<u>PHAC Global Health & Guidance Division Staff:</u> Marion Doull, Alejandra Jaramillo Garcia, Susan Courage, Nicki Sims-Jones

### **Declaration of funding**

Funding for this protocol and evidence review is provided by the Public Health Agency of Canada. This funding will support the collection of the data, data management, analyses, and writing of the protocol and the technical report.

## Section I. Background and Purpose

### Asymptomatic Bacteriuria in Pregnancy

Asymptomatic bacteriuria (ASB) - synonymous with asymptomatic urinary tract infection (UTI) - signifies a significant quantitative count of bacteria in the urine without symptoms of a lower (acute cystitis) or upper urinary tract (acute pyelonephritis) infection (1, 2). There is a 2-10% prevalence of ASB in premenopausal, ambulatory women (1), but due to anatomical and physiological changes (e.g., urinary stasis - difficulty emptying the bladder due to extended accumulation of urine) to the urinary tract in pregnancy there are theoretical reasons to suspect a greater chance of progression to symptomatic UTI and other pregnancy complications (e.g., maternal kidney infection, preterm delivery) (1, 3). Numerous risk factors for ASB in pregnancy have been identified, with low socioeconomic status, parity, a history of recurrent UTI, diabetes, and anatomical abnormalities of the urinary tract most cited (1, 2, 4).

# Consequences of Untreated Bacteriuria in Pregnancy and Rationale for Review of Screening

There is a potentially greater risk in pregnant women compared to other populations for ASB developing into pyelonephritis (upper urinary tract infection) (3) with its associated inflammation of the renal parenchyma, calices and pelvis (5), although controversy exists. There is significant heterogeneity in reports of the incidence of pyelonephritis in untreated ASB during pregnancy. Some reports suggest low incidences of 1% or less after the introduction of screening and treatment for ASB and 4% or higher before the era of screening and treatment of ASB in pregnancy. Historical reports prior to 1966 indicated up to 40% of pregnant women with ASB developed pyelonephritis. These higher rates were before modern obstetrical care; however, these numbers continue to be cited in current systematic reviews (4) and guidelines (6) of ASB in pregnancy (1, 7). Furthermore, whether there is evidence to support a causal link between ASB and pyelonephritis in contemporary practice is uncertain.

There is an association between clinical signs of pyelonephritis and maternal respiratory insufficiency, septicemia, renal dysfunction and anemia, as well as evidence of a 20 to 50% higher incidence of preterm birth and low birth weight (4, 8). However, controversy exists over the direct link between ASB, pyelonephritis, and adverse perinatal outcomes (e.g., whether ASB affects pregnancy and neonatal outcomes solely through pyelonephritis or also other mechanisms) (2, 4), and also about whether treatment of ASB will reduce the risk of such adverse outcomes. A 2015 Cochrane review (4) found that antibiotic treatment for ASB in pregnancy may greatly reduce the incidence of pyelonephritis, preterm birth, and low birth weight babies. However, the authors' confidence in the findings were low due to poor quality evidence. A preliminary search identified a recent cohort study (9) with an embedded RCT, which found no statistically significant difference between ASB-positive women who were untreated or placebo-treated compared to ASB-negative women in terms of both pyelonephritis and preterm birth (6/208 [2.9%] vs 77/4035 [1.9%]; adjusted odds ratio [OR] 1.5, 95% CI 0.6–3.5).

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Although the direct link between pyelonephritis and adverse perinatal outcomes may not be easily resolved (4), some main issues to examine include: 1) which, if any, screening tests and methods (e.g., collection methods, timing) are most accurate, and; 2) whether screening of all pregnant women and treatment for positive cases is effective (9). The effectiveness of screening for reducing risk of pyelonephritis and neonatal and maternal complications need to be examined in an era of modern obstetrical care.

### Issues to Consider for Screening Tests

Significant bacteriuria is usually defined by the presence of at least 10<sup>5</sup> colony-forming units (CFU) per mL of urine of a single uropathogen, in two consecutive clean-catch specimens (4, 7). Acceptable thresholds and repetitions considered positive for bacteriuria in pregnancy may vary in practice. The quantitative urine culture is considered to be the gold standard for accurate detection of ASB. However, it is costlier, more labor intensive and more time-consuming compared with other rapid urine screening tests (urinalysis, dipstick nitrite tests) which reportedly have lower sensitivity (1, 2). A preliminary search for recent literature identified a systematic review of onsite tests (point-of-care tests that are widely available in resource-limited settings) compared with urine culture that concluded specificity<sup>2</sup> was high overall but sensitivity was low and therefore onsite tests were not reliable in detecting pregnant women with ASB (10). There is no consistent recommendation for urine specimen collection in pregnancy (clean-catch with or without perineal cleansing) or optimal timing and frequency of screening tests or followup cultures (2). It is unclear whether universal screening (with subsequent treatment) for ASB confers benefits, and whether available screening tests for ASB are comparable to the current gold standard (urine culture) for identifying bacteriuric patients. The standard urine culture protocol is evolving with the testing of emerging techniques that may improve the detection of uropathogens (11, 12). However, at this time, urine culture is considered the reference standard. Resource needs for screening may be an important factor to consider. For example, an economic analysis indicated that screening with a dipstick and providing screen positive women treatment with antibiotics remained cost-beneficial for reducing pyelonephritis when prevalence of ASB is <2% or when the proportion of patients with ASB who develop pyelonephritis dropped to 10%, but the cost-benefit was not seen for culture diagnostics where the absolute clinical benefit was shown to be reduced (13).

<sup>1</sup>Sensitivity is a diagnostic test accuracy outcome that refers to how well a test correctly identifies individuals with a disease/condition; <sup>2</sup>Specificity is a diagnostic test accuracy outcome that refers to how well a test correctly identifies individuals without a disease/condition.

### **Issues to Consider for Harms of Screening**

Patients may have preferences for avoiding harms due to screening and treatment in asymptomatic conditions (e.g., test anxiety/distress). Although the harms from screening tests may be considered minimal, harms from antibiotic treatment need to be considered when making decisions about screening practices for ASB in pregnancy. Some sources have outlined concerns with incidence and reporting on adverse effects of antibiotic treatment for ASB, UTIs, or antibiotic use in general during pregnancy (2, 4, 14). Some trials evaluating treatment versus no treatment/placebo of ASB in pregnancy have been critiqued for poorly reporting harms (4), such that making judgments on the net balance of benefits and harms may be difficult. The significance of the expected side effects from a short course of antibiotics may be small although increasingly there are concerns about the effect of antibiotics on the human microbiome and the

ASB Protocol - Page 3

immune system. Antimicrobial resistance has certainly made the selection of an antibiotic for an individual woman more difficult (4). Additionally, patients may have preferences for avoiding treatment harms in asymptomatic conditions that need to be considered.

The goal of this review is to determine the effectiveness of screening for ASB among pregnant women. This evidence synthesis will inform recommendations on screening for ASB made by the Canadian Task Force for Preventive Healthcare (CTFPHC). As part of the guideline development process, the CTFPHC will also engage organizational stakeholders and peer-reviewers to gather information on key implementation considerations, such as strategies to help address potential health inequities and any concerns about the acceptability and feasibility of the guideline.

## Section II. Recommendations in Other Guidelines and Current Practice

### **Canadian Organizations**

The Society of Obstetricians and Gynecologists of Canada (SOGC), concerned over maternal and perinatal risks associated with ASB, recommends to treat single-strain colony counts of 10<sup>5</sup> CFU/mL (or 10<sup>8</sup> CFU/L) or greater with appropriate antibiotics during pregnancy to prevent adverse outcomes such as pyelonephritis and pretern birth (15). They support a single quantitative culture in any trimester as sufficient and recommend re-treatment with sensitivities for women with recurrent bacteriuria although they do not make recommendations for timing or frequency of re-testing. Similar recommendations apply when group B streptococcal (GBS) bacteria is detected in the urine during screening in pregnancy; separate recommendations (not relevant for this review) are made for screening and treating GBS (at any colony counts) at time of labour or rupture of membranes for prevention of early-onset neonatal GBS disease.

### **Guidelines from International Organizations**

The U.S. Preventive Services Task Force 2008 guideline (16) on screening of ASB in adults recommends all pregnant women be screened at 12 to 16 weeks' gestation (or first prenatal visit) for ASB using a urine culture, and that treatment with antibiotics significantly reduces the incidence of symptomatic maternal urinary tract infections. The evidence informing this reaffirmation of the original recommendation from 2004 is mainly drawn from a Cochrane review of treatment effectiveness (17). The American Academy of Family Physicians (AAFP) (18) endorses the recommendations of the USPSTF. The Infectious Diseases Society of America (6) recommends screening for bacteriuria by urine culture for pregnant women in early pregnancy, and treatment if results are positive, with periodic re-testing for recurrent bacteriuria after therapy. The American Academy of Pediatrics (AAP), jointly with the American College of Obstetricians and Gynecologists (ACOG) recommend to treat ASB and then to test for cure (19).

The UK's National Institute for Health and Care Excellence (NICE) states that women should be offered routine screening for ASB by midstream urine culture early in pregnancy to reduce the risk of developing pyelonephritis (20).

The Scottish Intercollegiate Guidelines Network (SIGN) recommends that pregnant women be tested for ASB by urine culture at the first antenatal visit and culture-positive patients be treated with an antibiotic (21).

### **Current Practice**

Several major healthcare organizations in North America (USPSTF, IDSA, ACOG, AAP, AAFP) advocate screening of pregnant women, and nearly all recommend treating patients who have been confirmed with ASB using antibiotics. In Canada, the current usual practice is to obtain a urine sample at each prenatal visit, where testing may typically be done by culture early in pregnancy and then followed with subsequent testing if indicated. It is clear there is diversity in which of these samples are collected for the presence of significant bacteriuria, how the sample is collected, how presence of bacteriuria is determined, and when sample(s) for ASB is/are collected in pregnancy. It is unclear whether and to what degree practices use screening methods incorporating tests other than urine culture.

### Section III. Review Approach and Scope

This review will be completed by the Evidence Review and Synthesis Centre (ERSC) at the University of Alberta. The review will be developed, conducted, and prepared according to the CTFPHC methods (http://canadiantaskforce.ca/methods/methods-manual/). A working group of CTFPHC members was formed for development of the topic, refinement of the key questions and scope, and rating of patient-important outcomes considered most important for creating a recommendation. The CTFPHC will not be involved in the conduct of the review including selection of studies and data analysis, but will comment on the draft report and provide input on the interpretations of findings. The Global Health and Guidelines Division science team at the Public Health Agency of Canada provided assistance and input on CTFPHC methodological considerations during the topic refinement and development of the protocol. Perspectives of patients, and members of the public have been be incorporated regarding prioritization of outcomes (benefits and harms), as well as other aspects of guideline development. A draft version of this protocol was reviewed by nine external topic experts and stakeholders and all comments were considered when finalizing this protocol. This final version of the protocol has been approved by the entire CTFPHC and will be posted on the CTFPHC website and registered with the International Prospective Registry of Systematic Reviews (PROSPERO) database.

### **Analytical Framework and Staged Approach**

Figure 1 is an analytical framework that depicts the structure used to address the Key Questions (KQs) for evaluating the benefits and harms of screening asymptomatic women during pregnancy for bacteriuria.

A staged approach will be followed based on the availability and quality of the body of evidence. Quality of evidence (classified as high, moderate, low, very low) will be assessed using methods developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (<u>http://www.gradeworkinggroup.org/</u>), whereby high quality evidence relies on precise and consistent effect estimates from studies having few limitations on internal validity (i.e., low bias) and examining directly relevant populations, interventions, comparators, and outcomes (i.e., PICOs) (see Section IV for more details). The staging approach of the

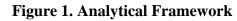
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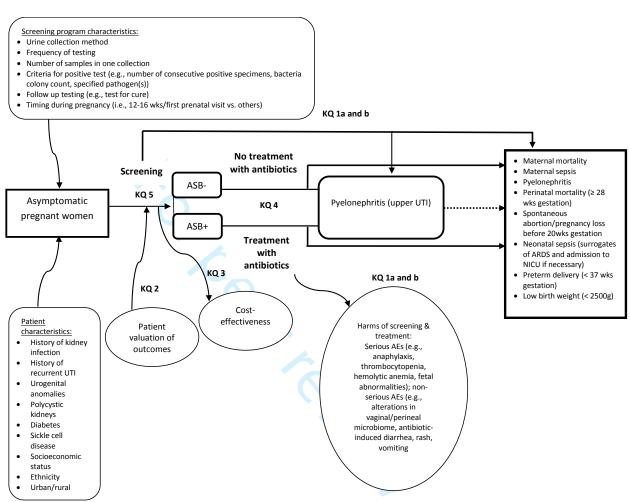
CTFPHC relies on choices made when considering, primarily, the GRADE domains of study limitations and indirectness. Moreover, decisions made during the evidence review are based on the information needs of the CTFPHC for making a screening recommendation based on the balance of critical patient-important benefits and harms.

The most direct and least biased evidence for the effectiveness of screening for ASB will be prioritized. This review will start by examining evidence from randomized-controlled trials (RCTs) on the clinical effectiveness of screening on patient-important outcomes. Staging beyond this point will require careful deliberation with documentation of rationale. If data from the initial stage is scarce for critical benefits or harms the CTFPHC will consider searching for data from (potentially) more biased study designs or indirect evidence (e.g., evidence from observational studies treatment RCTs, test accuracy studies. In cases where evidence on test accuracy and treatment effects will be used to provide indirect evidence on screening effectiveness, the limitations of such an indirect approach will be described. Examining both accuracy and treatment data may not be useful in all cases; for example, if the CTFPHC becomes confident that treatment is ineffective there would be no need to further examine test accuracy. In general, subsequent stages will only be conducted when the evidence from the previous stage(s) is non-existent or of too poor quality (e.g., very low quality based on GRADE tables) for the Task Force to make a screening recommendation based on the balance of patient-important benefits and harms.

For this review, the first stage will focus on identifying and using data from studies directly linking screening for ASB to patient-important benefits and harms (KQ1). Study designs providing the highest internal validity (e.g., RCTs) for this KQ will be preferred with a hierarchy of evidence used after this point if necessary. After RCTs we will consider controlled clinical trials (CCTs; defined for this review as *experimental trials without random allocation but where intervention(s) are introduced, standardized, and allocated objectively [e.g., by date of birth, but not using subjective means such as patient or clinician preferences] by investigators and blinding of participants is typically possible)* and then prospective and retrospective controlled observational studies. This stage will also include examination of KQ2 on women's valuation of benefit and harm outcomes of screening for ASB (and more broadly/indirectly treatment with antibiotics) in pregnancy. The cost-effectiveness of screening for ASB (KQ3) will also be considered only if there is evidence from KQ1 indicating a favorable benefit-harm ratio such that screening may be recommended.

If this first stage does not provide high enough quality of evidence for making a recommendation, the CTFPHC will carefully consider pursuing stage two with documentation of rationale before proceeding. Stage two will commence with examination of effectiveness of treatment of ASB in pregnancy (KQ4). If there is sufficient quality evidence indicating favorable treatment effectiveness from KQ4, an examination of KQ5 on diagnostic test accuracy will be considered in stage 3. Due to the indirectness of evidence provided by KQs 4 and 5 for making recommendations for the clinical effectiveness of screening, we will only seek data from study designs offering the greatest potential for high internal validity. That is, for KQ4 (treatment) we will focus on RCTs, and for KQ5 (test accuracy) we will exclude case-control designs. Where high quality systematic reviews exist examining these indirect evidence links, we will utilize these when possible.





AEs: adverse events; ARDS: acute respiratory distress syndrome; ASB: asymptomatic bacteriuria; d: day; g: grams; KQ: key question; NICU: neonatal intensive care unit; UTI: urinary tract infection; wks: weeks

### Key Questions (KQs)\*

### Stage 1:

### Benefits and harms of screening

**KQ1a:** What are the benefits and harms of screening compared with no screening for asymptomatic bacteriuria in pregnancy? Are there subgroup differences with SES or other patient characteristics?

**KQ1b:** What are the comparative benefits and harms of screening with different screening tests/algorithms for asymptomatic bacteriuria in pregnancy?

### **Outcome valuation**

**KQ2a:** How do women weigh the benefits and harms of screening and treatment of asymptomatic bacteriuria in pregnancy?

**KQ2b:** How do women's valuation of benefits and harms of screening and treatment inform their decisions to undergo screening?

### **Resource use\*\***

**KQ3:** What is the cost-effectiveness of screening for asymptomatic bacteriuria in pregnancy?

### Stage 2:

### Treatment

**KQ4:** What are the benefits and harms of antibiotic treatment compared with no treatment for asymptomatic bacteriuria in pregnancy?

### Stage 3:

### **Diagnostic accuracy of screening tests**

**KQ5:** What is the diagnostic accuracy of screening tests for asymptomatic bacteriuria in pregnancy?

\*Decision process for staging outlined in section on Analytical Framework and Staged Approach \*\*Conducted if benefit-harm ratio deemed beneficial based on KQ1

### **Section IV. Review Methods**

### **Literature Search**

The literature search strategy will be developed and implemented by a research librarian. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords, and will be peer-reviewed. Methodological filters will not be applied to limit retrieval by study design; study designs included for each KQ are identified in the section on inclusion and exclusion criteria. Searches will be restricted by language to include full texts published in English and French, without a publication date restriction.

We will conduct comprehensive searches in bibliographic databases most relevant for each KQ. For evidence informing stage 1 of our review we will perform comprehensive searches for studies meeting our inclusion criteria as described below. For KQ1, we will search MEDLINE (1946-) via Ovid; Embase (1974-) via Ovid; Cochrane Library; CINAHL (1937-present) via EBSCOhost; and PubMed via NCBI Entrez. The detailed search strategy for MEDLINE is reported in Appendix 1 and will be adapted to accommodate the controlled vocabularies of each database. For KQs 2 (women's outcome valuation) and 3 (cost-effectiveness of screening), we will modify the search to include relevant terms and will add suitable databases (e.g. PsycINFO for patient preferences, NHS Economic Evaluation Database [EED] for cost effectiveness). Full search strategies for all databases will be included in the final report.

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For evidence used in stages 2 and 3, we are aware of at least one high-quality systematic review for KQs 4 (4) and 5 (10) which we may rely on. For KQ4 on effectiveness of antibiotic treatment compared with no treatment, we anticipate updating a recent Cochrane review of treatment for asymptomatic bacteriuria in pregnancy (4); if an update is not possible, we will follow methods adopted by the CTFPHC for integrating systematic reviews (see Appendix 2). If we update this review, the original search will be updated. For KQ5 (test accuracy), we anticipate using a recent review of screening tests for asymptomatic bacteriuria in pregnancy (10) and any additional reviews that may be identified as similar in scope. While multiple reviews may be considered for KO5 (test accuracy) if found, we will not attempt to update the search(es) to identify more recent studies. If the scope of any review is narrower (e.g., does not include all interventions applicable to our topic), we may screen the excluded studies list(s) to identify potentially relevant studies for inclusion. To ensure we have identified all potentially relevant systematic reviews relevant to KQs 4 and 5, we will conduct a database search for systematic reviews. We will search PubMed (1946-) via NCBI Entrez, the Cochrane Database of Systematic Reviews (inception-) and the Database of Abstracts of Reviews of Effects (DARE) (inception-2013) via Wiley Cochrane Library to identify systematic reviews, meta-analyses and health technology assessments. Our PubMed search will utilize a search filter from CADTH (https://www.cadth.ca/resources/findingevidence).

Grey literature will be searched and documented according to CTFPHC methods and will include internet-based searches (via adapted Canadian Agency for Drugs and Therapeutics in Health [CADTH] checklists; https://www.cadth.ca/resources/finding-evidence/grey-matters), electronic libraries (e.g., Health Canada Library, Canadian Electronic Library), and trial registries (ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform). Based on consultation with clinical experts, the following highly relevant conference proceedings will be hand-searched for recent studies not yet published (2014-present): Society of Obstetricians and Gynaecologists of Canada, Association of Medical Microbiology and Infectious Disease Canada, ID Week, and American Society for Microbiology meeting (ICAAC). Clinical and content experts identified by the CTFPHC will be contacted and invited to identify relevant research reports for consideration; websites of relevant Canadian stakeholder organizations will be searched.

# **Eligibility Criteria**

Table 1 outlines the inclusion and exclusion criteria for all KQs, and details are provided below.

# Population

Studies will be considered for inclusion in all KQs if they examine pregnant women at any stage of pregnancy where the population represents a "routine screening" scenario (e.g., the majority of patients do not have a degree of signs or symptoms prompting diagnostic testing and/or treatment for upper or lower UTI). It is recognized that many women experience nocturnal and increased frequency of urination, or other symptoms, which do not necessarily indicate bacteriuria or infections. We will include studies where a proportion of, but not all, women have risk factors for UTIs or other outcomes of the review. KQ2 on women's outcome valuation, we will include studies of women of child-bearing age if no evidence is found from studies with pregnant women; studies will still be required to examine screening or antibiotic treatment during pregnancy.

We will exclude studies *exclusively* including women with conditions that place them at substantially higher than average risk for bacteriuria (i.e., kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infections [UTI], diabetes, sickle-cell disease), or with symptoms of UTI.

**Population subgroups of interest:** history of kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection (UTI), diabetes, sickle cell disease, socioeconomic status (i.e., education, income), ethnicity (i.e., percent South Asian versus others), and urban/rural setting.

#### **Interventions & Comparators**

For clinical effectiveness of screening (KQ1), any screening test/algorithm for ASB will be eligible for inclusion and the comparator is absence of screening (1a) or a different urine test or screening algorithm (1b). Studies that compare urine cultures of differing criteria (e.g., threshold 10<sup>3</sup> CFU/mL versus 10<sup>5</sup> CFU/mL) will also be eligible for inclusion. For women's outcome valuation (KQ2), any screening test for ASB during pregnancy will be eligible for inclusion; indirect evidence about antibiotic treatment during pregnancy broadly will be used if needed. For cost-effectiveness (KQ3), any screening test compared with no screening or another screening test (i.e., urine culture) will be eligible for inclusion; costs must be compared with outcomes/effects such that studies examining costs only will be excluded. For treatment effectiveness (KQ4), any antibiotic treatment for ASB compared to no treatment or placebo will be eligible for inclusion. For diagnostic accuracy (KQ5), any index test compared with a urine culture for detecting ASB will be eligible for inclusion. For all KQs, studies that include screening or treatment for group B streptococcus (GBS) at any time of pregnancy for any of the outcomes of interest will be included.

We will exclude studies exclusively examining urine tests used for screening for other conditions (e.g., proteinuria, glycosuria), and non-urine screening tests (e.g., vaginal/rectal swab culture for GBS testing).

*Screening subgroups of interest*: urine collection methods (e.g., clean-catch and/or midstream; excluding catheter methods/samples), frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified pathogen(s)), follow-up testing during pregnancy, and timing during pregnancy.

# Outcomes

As with the KQs, the outcomes for inclusion for KQ1 (screening effectiveness) and KQ4 (treatment) will be staged to some extent, if necessary. Each outcome has been rated independently by members of the CTFPHC and by women, as per the patient engagement activities of an independent group with expertise in knowledge translation from St. Michael's Hospital in Toronto, Ontario. All patient-important outcomes rated as critical (7 to 9 out of 9) or important (4 to 6 out of 9) for decision making were considered for inclusion. From these ratings, the eight outcomes were rated as critical will be included in stage 1; of three outcomes rated as important, low birth weight (but not hypertension or acute kidney injury) will be included

| 1<br>2<br>3<br>4<br>5                  |  |
|--|--|
| 6<br>7<br>8<br>9<br>10<br>11<br>12     |  |
| 13<br>14<br>15<br>16<br>17<br>18<br>19 |  |
| 20<br>21<br>22<br>23<br>24<br>25       |  |
| 26<br>27<br>28<br>29<br>30<br>31       |  |
| 32<br>33<br>34<br>35<br>36<br>37<br>38 |  |
| 39<br>40<br>41<br>42<br>43<br>44       |  |
| 45<br>46<br>47<br>48<br>49<br>50       |  |
| 51<br>52<br>53<br>54<br>55<br>56       |  |
| 57<br>58<br>59<br>60                   |  |

because in the past (i.e. older studies) this was conceptually considered the same as "pre-term birth", which both the CTFPHC members and patients rated as critical. Considering harms separately, if no evidence is found for any of the outcomes (serious adverse events [AEs]) in stage 1, there will be inclusion of the outcomes (non-serious AEs) from stage 2. This grouped and staged approach to harms will address infrequent reporting, reporting of different harms across studies, and also uncertainty regarding all the potential harms that may be reported. Non-serious AEs, particularly if frequent or severe, are considered important but not critical for decision making by the CTFPHC. This approach acknowledges guidance to limit the number of total outcomes (maximum 7) to those which can be successfully managed cognitively by guideline panels when balancing multiple benefits and harms.

Outcomes for KQs 1 and 4 with ratings:

# Benefits (reduced incidence for all):

- 1. maternal mortality (9)
- 2. maternal sepsis (8)
- 3. pyelonephritis (7)
- 4. perinatal mortality ( $\geq$  28 weeks of gestation (e.g., intrauterine demise, stillbirth, early neonatal death)) (9)
- 5. spontaneous abortion/pregnancy loss before 20 weeks of gestation (8)
- 6. neonatal sepsis (if not reported will include surrogate outcomes of acute respiratory distress syndrome [ARDS] or admission to neonatal intensive care unit [NICU]) (8)
- 7. preterm delivery (live fetus passed < 37 weeks of gestation) (7)
- 8. low birth weight (< 2500g) (6)

#### Harms:

1. serious adverse event(s)<sup>a</sup> associated with antibiotic treatment, *including but not limited to*: (7)

- a. anaphylaxis,
- b. thrombocytopenia,
- c. hemolytic anemia,
- d. fetal abnormalities; and,
- 2. non-serious adverse event(s) associated with treatment, *including but not limited to*: (4)
  - a. alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis),
  - b. antibiotic-induced diarrhea,
  - c. rash,
  - d. vomiting

<sup>a</sup>Serious adverse event (experience) or reaction is any untoward medical occurrence that: a) results in death, b) is lifethreatening, c) requires in-patient hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect (Health Canada, 2011);

We will exclude studies that screen pregnant women for group B streptococcus near delivery or at time of rupture of membranes for the prevention or treatment of chorioamnionitis or neonatal GBS (without other outcomes of interest listed above).

Women's outcome valuation (KQ2) include several possible outcomes related to the weighing of benefits and harms of screening and treatment (KQs 1 and 4) and how this may affect their decisions to undergo screening (e.g., relative weight/utilities of benefit and harms; willingness to be screened based on relative value placed on benefits and harms of screening programs or treatment); these outcomes will be based on considerations of the possibility or perceived/expected magnitude of effects for the outcomes identified for KQs 1 and 4.

During focus groups, women identified an additional outcome - psychological distress/anxiety - and rated this as critical (7 out of 9), although it was interpreted differently by some women as either a benefit (e.g., reduction in psychological distress/anxiety by knowing the health status of themselves and their baby) or a harm (e.g., another of many tests and potential worries during pregnancy). Anxiety as a critical outcome will be sought and synthesized within findings from KQ2 on women's valuation of benefits and harms of screening and treatment, as well as within interpretation of test accuracy outcomes from KQ5 (TP, TN, FP, FN) which will be *interpreted based on the CTFPHC judgments* on the magnitude of potential consequences of each (e.g., unnecessary anxiety from high FP, loss of potential benefit in FN) as identified in the section below "Assessment of the Overall Quality of the Evidence using GRADE".

Cost-effectiveness (KQ3) outcomes include cost per quality-adjusted life year (QALYs), incremental cost-effectiveness ratios (ICERs), and net benefit (in dollars from cost-benefit studies.

Diagnostic test accuracy (KQ5) outcomes include: sensitivity, specificity, false positives, false negatives, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio.

# Setting, Study Design & Timing

Studies conducted in primary care, or relevant clinical settings (e.g., prisons, remote stations, community health centers, midwifery practice) will be included. For KQ3 on cost-effectiveness we will limit studies to those conducted using data relevant to Canada, thus within countries having a very high Human Development Index (22).

For KQ1 (screening effectiveness), we will include RCTs initially and then, if needed based on the GRADE assessment of overall quality of the evidence, we will search for CCTs (defined in Section III) and then controlled observational studies (i.e., prospective and retrospective cohort, case-control, controlled before-after). For KQ2 (outcome valuation), we will include any study where women are asked to balance the benefits and harms of screening and treatment for ASB and state/choose their willingness to be screened and treated; surveys, experimental designs (e.g., contingent valuation), and qualitative research are examples. Cost-effectiveness (KQ3) will look at any study comparing effects and costs (e.g., cost-effectiveness, cost-utility, cost-benefit) and may include modelling of effects and/or costs. For KQ4 (treatment), we will rely on RCTs. For KQ5 (test accuracy), we will rely on prospective and retrospective studies where a consecutive or random sample of participants receive both the index test(s) and reference standard, or where participants are randomized to different index tests but all receive the reference standard, and

assessment in a cross-sectional manner. We will exclude case-control studies and studies with longitudinal assessment of the reference standard.

For all KQs, case reports and case series (i.e., group of patients selected based on particular outcome) will be excluded as will papers not reporting primary research (e.g. editorials, commentaries, opinion pieces). Conference abstracts will not be eligible for inclusion, but will be captured and serve to help identify full study reports and assess the quality of evidence in relation to potential publication and reporting biases. No limits will be applied to publication year.

# Additional considerations

We do not have a minimum sample size for inclusion, nor do we have a minimum threshold for extent of incomplete follow-up or participant attrition; these factors will be considered during assessment of the quality of evidence (e.g., precision domain accounts for sample size across studies), and during sensitivity analyses in cases of substantial heterogeneity in findings at the data synthesis stage (see relevant sections).

# Tables 1 to 5. Inclusion and Exclusion Criteria for Key Questions

| Population    | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria.   |
|---------------|---|
|               | <u>Patient subgroups</u> : women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI]), diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural   |
|               | Exclude: studies <i>exclusively</i> including women with conditions that place them at substantially higher than average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI], diabetes, and sickle cell disease), or with symptoms of UTI  |
| Interventions | Any screening program or test   |
|               | <u>Screening subgroups/algorithms, including</u> : urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy  |
|               | Exclude: urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for group B streptococcus (GBS) testing)  |
| Comparator    | <ul> <li>KQ1a: No screening (but may include indicated/targeted testing and/or treatment upon development of symptoms or for high-risk groups)</li> <li>KQ1b: A different screening test or algorithm (see intervention subgroups)</li> </ul>   |
| Outcomes      | Benefits (reduced incidence for all):         1. maternal mortality (9)         2. maternal sepsis (8)\         3. pyelonephritis (7)         4. perinatal mortality (≥ 28 week's gestation (e.g., intrauterine demise, stillbirth, early neonatal death)) (9)         5. spontaneous abortion/pregnancy loss before 20 week's gestation (8)         6. neonatal sepsis (if not reported will include surrogate outcomes of acute respiratory distress syndrome [ARDS] or admission to neonatal intensive care unit [NICU]) (8)         7. preterm delivery (live fetus passed < 37 week's gestation) (7) |
|               | <ol> <li>serious adverse event(s)<sup>a</sup> associated with antibiotic treatment, <i>including but not limited to</i>: (7)         <ol> <li>anaphylaxis,</li> </ol> </li> </ol>   |

# Table 1. KQ1a, b: Benefits and harms of screening

|                 | b. thrombocytopenia.  |
|-----------------|---|
|                 |   |
|                 | 5   |
|                 | d. fetal abnormalities; and,  |
|                 | 2. non-serious adverse event(s) associated with treatment, <i>including but not limited to</i> : (4)        |
|                 | a. alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis),                               |
|                 | b. antibiotic-induced diarrhea,   |
|                 | c. rash,  |
|                 | d. vomiting   |
|                 |   |
|                 | Exclude: screening for GBS near delivery or at time of rupture of membranes for the prevention or treatment |
|                 | of chorioamnionitis or neonatal GBS (without other outcomes of interest in list above)                      |
| Study Designs   | Staged: RCTs, CCTs, controlled observational (i.e., prospective and retrospective cohorts, case-control,    |
|                 | controlled before-after)  |
| Language        | English and French  |
| Setting         | Primary care and clinical settings (e.g., prisons, remote stations, community centers, midwifery practices) |
| Timeframe       | No publication date limits  |
| COT (11 1 1 1 1 |   |

CCT: controlled clinical trial; KQ: key question; RCT: randomized controlled trial

<sup>a</sup>Serious adverse event (experience) or reaction is any untoward medical occurrence that: a) results in death, b) is life-threatening, c) requires in-patient hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect (Health Canada, 2011)

#### Table 2. KQ2: Outcome valuation

| Population            | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria; will also accept asymptomatic women who are not pregnant if necessary  |
|-----------------------|--|
|                       | <u>Patient subgroups</u> : women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI]), diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural  |
|                       | <u>Exclude</u> : studies <i>exclusively</i> including women with conditions that place them at substantially higher than average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI], diabetes, and sickle cell disease), or with symptoms of UTI   |
| Interventions/Index   | Any screening program or test, and any antibiotic; will accept studies on treatment for any bacterial  |
| Test                  | condition in pregnancy   |
|                       | <u>Screening subgroups/algorithms, including</u> : urine collection method, frequency of testing, criteria for a positive test (including number of consecutive positive specimens, bacteria colony count, and specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy<br><u>Exclude</u> : urine <i>screening</i> is done for other conditions (e.g., proteinuria, glycosuria), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing) |
| Comparator/Reference  | Not applicable   |
| Standard              |  |
| Outcomes <sup>§</sup> | Several possible outcomes (e.g., relative weight/utilities of benefit and harms; willingness to be screened based on relative value placed on benefits and harms of screening programs or treatment)   |
| Study Designs         | Qualitative, mixed methods, surveys/cross-sectional  |
| Language              | English and French   |
| Setting               | Primary care and clinical settings (e.g., prisons, remote stations, community centers, midwifery practices)  |
| Time frame            | No publication date limits   |

KQ: key question

<sup>§</sup>If there is a very limited quality of evidence base for KQ2 (i.e., in terms of quantity/sample size, methodological quality, inconsistency between studies, or applicability to our population or setting) we will consider including studies examining women's valuation of harms *or* benefits rather than the trade-off between the two. For example, studies examining women's acceptance of screening and/or treatment for ASB when only considering their perspectives on the potential

risks of antibiotic treatment to their baby, or the importance placed on reassurance about the potential to prevent preterm delivery et cetera, could offer some indirect evidence to help the CTFPHC in their deliberations. Likewise, the relative value placed on different benefit or harm outcomes (e.g., serious versus non-serious AEs) could be informative.

Table 3. KQ3: Cost-effectiveness of screening

| Population                             | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria.  |
|--|--|
|  | Patient subgroups: women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI], diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural   |
|  | Exclude: studies <i>exclusively</i> including women with conditions that place them at substantially higher than average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI], diabetes, and sickle cell disease), or with symptoms of UTI                       |
| Interventions/Index<br>Test            | Any screening program or test  |
|  | <u>Screening subgroups/algorithms, including</u> : urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy |
|  | <u>Exclude</u> : urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing)   |
| Comparator/Reference<br>Standard       | No screening (but may include indicated/targeted testing and/or treatment upon development of symptoms or for high-risk groups), or a different screening test or algorithm (see intervention subgroups)   |
| Outcomes                               | Cost per quality-adjusted life-years (cost per QALY), incremental cost-effectiveness ratio (ICER), net benefit/cost  |
| Study Designs                          | Economic evaluations   |
| Language                               | English and French   |
| Setting                                | Primary care and clinical settings (e.g., prisons, remote stations, community centers, midwifery practices); limited to countries rated as having very high Human Development Index (22)   |
| Time frame                             | No publication date limits   |
| XQ: key question<br>Fable 4. KQ4: Trea | tmont  |

# **Table 4. KQ4: Treatment**

| -                    |   |
|----------------------|---|
| Population           | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria.   |
|                      | <u>Patient subgroups</u> : women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI]), diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural   |
|                      | Exclude: studies exclusively including women with conditions that place them at substantially higher than   |
|                      | average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary  |
|                      | tract infection [UTI], diabetes, and sickle cell disease), or with symptoms of UTI  |
| Interventions/Index  | Any antibiotic  |
| Test                 | Screening subgroups/algorithms, including: urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy<br><u>Exclude</u> : urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia,), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing) |
| Comparator/Reference | No treatment or placebo   |
| Standard             |   |
| Outcomes*            | Benefits (reduced incidence for all):   |
|                      | 1. maternal mortality (9)   |

| Time frame    | No publication date limits       T: randomized controlled trial   |
|---------------|---|
| Setting       | Primary care and clinical settings (e.g., prisons, remote stations, community centers, midwifery practices)                       |
| Language      | English and French  |
| Study Designs | RCTs  |
|               | prevention or treatment of chorioamnionitis or neonatal GBS (without other outcomes of interest listed above)                     |
|               | Exclude: screening for group B streptococcus near delivery or at time of rupture of membranes for the                             |
|               | d. vomiting   |
|               | c. rash,  |
|               | b. antibiotic-induced diarrhea,   |
|               | a. alterations in vaginal/perineal microbiome (e.g., candidiasis, vaginitis),   |
|               | 2. non-serious adverse event(s) associated with treatment, <i>including but not limited to</i> : (4)                              |
|               | d. fetal abnormalities; and,  |
|               | b. thrombocytopenia,<br>c. hemolytic anemia,  |
|               | a. anaphylaxis,   |
|               | 1. serious adverse event(s) <sup>a</sup> associated with antibiotic treatment, <i>including but not limited to</i> : (7)          |
|               | Harms:  |
|               | 8. low birth weight ( $< 2500$ g) (6)   |
|               | 7. preterm delivery (live fetus passed < 37 week's gestation) (7)   |
|               | syndrome [ARDS] or admission to neonatal intensive care unit [NICU]) (8)  |
|               | <ul> <li>6. neonatal sepsis (if not reported will include surrogate outcomes of acute respiratory distress</li> </ul>             |
|               | 5. spontaneous abortion/pregnancy loss before 20 week's gestation (8)   |
|               | <ol> <li>perinatal mortality (≥ 28 week's gestation (e.g., intrauterine demise, stillbirth, early neonatal death)) (9)</li> </ol> |
|               | 3. pyelonephritis (7)   |
|               | 2. maternal sepsis (8)  |

<sup>a</sup>Serious adverse event (experience) or reaction is any untoward medical occurrence that: a) results in death, b) is life-threatening, c) requires in-patient hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect (Health Canada, 2011)

# Table 5. KQ5: Diagnostic accuracy of screening tests

| Population           | Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria.   |
|----------------------|---|
|                      | <u>Patient subgroups</u> : women with kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary tract infection [UTI]), diabetes, sickle cell disease, socioeconomic status, ethnicity, urban/rural   |
|                      | Exclude: studies exclusively including women with conditions that place them at substantially higher than   |
|                      | average risk of bacteriuria (kidney infection, urogenital anomalies, polycystic kidneys, recurrent urinary  |
|                      | tract infection [UTI], diabetes, and sickle cell disease), or with symptoms of UTI  |
| Interventions/Index  | Any index test  |
| Test                 | Screening subgroups/algorithm, including: urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy |
|                      | Exclude: urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing)  |
| Comparator/Reference | A urine culture   |
| Standard             | Screening subgroups/algorithm, including: urine collection method, frequency of testing, number of samples in one collection, criteria for a positive test (including number of consecutive positive specimens, bacterial colony count, and specified pathogen(s)), follow-up testing during pregnancy, timing during pregnancy |

|               | Exclude: urine screening is done for other conditions (e.g., proteinuria, glycosuria, Chlamydia), non-urine screening test (e.g., vaginal/rectal swab culture for GBS testing)   |
|---------------|--|
| Outcomes      | Sensitivity, specificity, false positives, true positive, false negatives, true negatives, positive and negative   |
|               | likelihood ratios, prevalence/pre-test probability (true positive + false positive)/total number of people)  |
| Study Designs | Prospective and retrospective studies where a consecutive or random sample of participants receive both<br>the index test(s) and the reference standard, or where participants are randomized to different index tests<br>but all receive the reference standard, and assessment in a cross-sectional manner<br>Exclude: case-control studies and studies with longitudinal assessment of the reference standard |
| Language      | English and French   |

### Screening and Selecting Studies for Inclusion

For the database searches, two reviewers will independently screen the titles and abstracts (when available) using broad inclusion/exclusion criteria. Citations will be classified as "include/unsure," "exclude," or "reference" (i.e., conference abstracts, protocols, and systematic reviews). One reviewer will review the "reference" group and will conduct all other searching as outlined in the above section. The full text of all studies classified as "include/unsure" or identified after reviewing the reference citations will be retrieved for full review; two reviewers will independently assess eligibility using a standard form that outlines the inclusion and exclusion criteria. Disagreements on final inclusion of all studies will be resolved through consensus or third party adjudication. For KOs 4 and 5, any existing systematic review(s) identified as relevant will be assessed for eligibility based on whether the authors: i) searched more than one database, ii) report their selection criteria, and iii) use PICOTS criteria that are a close match to that for the relevant KQ. In cases where there is more than one possible review providing results for the same intervention-outcome pair, we will choose one based on: AMSTAR (23) rating (score 8 or higher preferred), comprehensiveness of search (i.e., reports on most or more papers included by other existing reviews), closest match to our PICOTS, most recent date of study inclusion/search, and the quality and extent of reporting on individual study characteristics, data, and quality assessments. All decisions to exclude a study at full text review will be provided. The title/abstract screening and full-text selection processes will be conducted and documented in DistillerSR. The flow of literature and reasons for full text exclusions will be recorded in a PRISMA Flow Chart.

# **Data Extraction & Reporting**

One reviewer will independently extract data from each included study or systematic review into DistillerSR; a second reviewer will verify all data. Disagreements will be resolved through discussion or third-party consultation until consensus is reached.

When using individual studies for a KQ, a narrative summary (with accompanying tables) will be provided to report on all studies by design, country of origin, sample sizes, population(s) (including subgroups), intervention(s)/index tests (including data on thresholds and for subgroup questions), comparator(s)/reference test, setting, and outcome measures, as reported by studies. When there are multiple publications associated with a study we will consider the earliest report of the main (primary) outcome data to be the primary data source. We will extract data from the primary source first and then add outcome data reported in the secondary/associated publications and data sources. We will reference the primary source throughout the evidence report; all associated literature will be tabulated for reference.

When relying on systematic reviews for KQs 4 (treatment) and 5 (test accuracy), we will extract data on the characteristics of the systematic review (PICOTS), the included studies with specifics related to the population (size and characteristics), outcomes evaluated (including definitions and timing of assessment), quality/risk of bias (by domain/construct if available), the methods of analysis (meta-analytical approach and its findings in relation to heterogeneity, if applicable), findings from their syntheses including subgroup analysis and GRADE or other quality assessments if performed across studies, and any limitations noted by the systematic review authors. For KQs 4 and 5, data verification will be completed on 5 to 10% of included studies in any existing systematic review(s), and if satisfied with concordance, we will consider incorporating the reported data on study and participant characteristics without returning to the primary studies. If additional studies are included (e.g., new studies from updated search [KQ4] or excluded studies in the identified systematic review that is subsequently included for current review to ensure coverage of scope [KQ5]), these will be clearly identified and presented.

When using individual studies, we will record intention-to-treat results, if possible. For continuous outcomes measures, we will extract (by arm) the mean baseline and endpoint or change scores, standard deviations (SD) or other measure of variability, and number analyzed. We will not include outcome data from studies that did not provide a follow up change or endpoint mean or data that could be used to calculate follow up scores. If necessary, we will approximate means by medians. If standard deviations are not given, they will be computed from p-values, 95% confidence intervals (95% CIs), standard errors, z-statistics, or t-statistics. If computation is not possible they will be estimated from upper bound p-values, ranges, interquartile ranges, or (as a last resort) by imputation using the largest reported SD from the other studies in the same meta-analysis. When computing SDs for change from baseline values, we will assume a correlation of 0.5, unless other information is present in the study that allows us to compute it more precisely. For dichotomous outcomes, we will report counts or proportions, and sample size, by study arm.

For dichotomous data on harms, each adverse event (AE) will be counted as if it represents a unique individual; because a single individual might experience more than one AE, this assumption may overestimate the number of people having an AE. Only numerical data for AEs will be extracted; that is, we will make no assumptions on lack or presence of an AE if this is not reported; authors that report only p-values or that one arm had fewer events than another (but where it is explicit that the outcome was captured in the study) will be contacted (3 times via email) to provide the data.

Data on within-study subgroup analysis will be collected, including: subgroups (independent variables), the type of analysis (e.g., subgroup/stratified or regression analysis), the outcomes assessed (dependent variables), and the authors' conclusions. We will collect data suitable for all patient and intervention subgroups (see Table 1) for performing our own subgroup analyses (e.g., stratified analysis, meta-regression) based on study-level data.

#### **Risk of Bias/Methodological Quality Assessment**

Two reviewers will independently assess the risk of bias (ROB) of each included study (KQs 1-3), with disagreements resolved through discussion or third-party consultation to reach consensus. The results for each study and across studies will be reported by each domain and for

the overall ROB score. The ROB for each study will be assessed on an outcome basis where needed, particularly when different outcomes are assumed to have different susceptibilities to bias; for example, subjective outcomes and expected harms are more prone to bias from non-blinding than objective outcomes and unexpected/rare harms.

RCTs and CCTs (theoretically only differing from RCTs by lack of random sequence generation and not by other ROB domains) will be appraised using the Cochrane Risk of Bias tool (24). This tool consists of six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other" sources of bias) and a categorization of the overall risk of bias. Blinding will be assessed separately for patients/providers and outcome assessors taking into account the type of outcome that may be affected (e.g. subjective vs. objective). To assist with outcome reporting bias assessments, we will seek study protocols and studies/data from registries. The overall assessment is based on the responses to individual domains. If one or more individual domains are assessed as having a high risk of bias, the overall score will be rated as high risk of bias. If at least one domain is assessed as unclear, and no domains are assessed as high, the overall score will be rated as unclear risk of bias. The overall risk of bias will be considered low only if all components are rated as having a low risk of bias.

Controlled observational studies will be appraised using the Newcastle-Ottawa Quality Assessment Scale (25); three domains (sample selection, comparability of cohorts, and assessment of outcomes) are evaluated. Each item that is adequately addressed is awarded one star, except for the "comparability of cohorts" item, for which a maximum of two stars can be given. The overall score is calculated by tallying the stars. We will consider a total score of 6 to 8 stars to indicate low ROB, 4 or 5 stars to indicate moderate ROB, and 3 or fewer stars to indicate high ROB.

For diagnostic accuracy studies (KQ5), we will rely on the Quality of Diagnostic Accuracy Studies (QUADAS-2) (26) used to assess ROB. This tool assesses concerns of risk of bias among four domains (patient selection, index test, reference standard, and flow and timing) and concerns of applicability across the first three domains.

If one or more systematic review(s) is used to provide evidence for KQ4 (treatment) or KQ5 (accuracy), we will assess if the review used an explicit tool (e.g., Cochrane ROB [KQ4], QUADAS [KQ5]) for assessing the main sources of potential bias. If so, we will complete assessments on 5 to 10% of included studies to establish concordance before considering the use of assessments reported by each review.

Studies answering KQ2 (outcome valuation) will be evaluated by tools appropriate to their study design: for surveys and qualitative studies we will use tools developed by the Center for Evidence-based Management (<u>http://www.cebma.org/resources-and-tools/what-is-critical-appraisal/</u>). The quality of economic evaluation studies (KQ3) will be assessed using Drummond's checklist for economic evaluation studies (27).

# Data Analysis & Synthesis

We will provide summaries of intervention effects for each study by calculating the appropriate statistics based on types of outcomes.

#### Key Question 1

For pair-wise meta-analysis in KQ1 (screening effectiveness), we will employ a random effects model. For continuous outcomes, we will report a pooled mean difference (MD) when one measurement tool is used, or other options that exist for communicating results when combining two or more outcome scales measuring similar constructs (28, 29). For dichotomous outcomes, we will report relative risks (RR) and risk differences (RD) between groups with corresponding 95% CIs. For those outcomes (e.g. serious adverse events) where at least one intervention group contains zero events, only the risk difference will be used. For calculating the RD, we will use the median baseline risk for the control group in the included studies, although may perform sensitivity analysis using differing baseline risks if thought suitable (30, 31). The decision to pool studies will not be based on the statistical heterogeneity (I<sup>2</sup> statistic will be reported), but rather on interpretation of the clinical and methodological differences between studies. When substantial heterogeneity is suspected, we will conduct sensitivity analyses if appropriate (e.g., in the presence of studies with outlying effect sizes, for studies rated as high risk of bias in some domains such as incomplete outcome data [<80 percent] or lack of allocation concealment, parallel versus cross-over designs). Heterogeneity will also be examined during our planned subgroup analyses for important patient and intervention variables (see Table 1). Where there are at least eight studies in a meta-analysis, we will analyze publication bias both visually using the funnel plot and quantitatively using Egger's test (32). We will not combine results from RCTs with CCTs or controlled observational studies (if used via staging approach for KQ on screening); rather, the latter two will be used to support or provide context for the evidence from RCTs.

#### Key Questions 2 & 3

For KQs 2 (outcome valuation) and 3 (cost-effectiveness), results will be narratively described in most cases. If more than one study is identified providing numerical values for ranking benefits and/or harms (KQ2) or similar outcomes (KQ3) these will be summarized descriptively and results across studies compared. Thematic analysis may be undertaken for KQ2, including coding data (meaning and context) into descriptive themes that accurately reflect the data and then summarizing this in a narrative format.

#### Key Questions 4 and 5

When using systematic reviews for stages 2 and 3, any meta-analysis will be reconstructed if possible to provide graphical representation of the findings to support our interpretations. Meta-analysis may be recalculated, if possible, when new studies are found in search updates (KQ4), analysis methods are not thought appropriate (e.g., use of random rather than fixed effects models, ability but no use of HSROC models [see below]) or if further analysis (e.g. between-study stratification) may be possible for subgroups of interest. When substantial methodological heterogeneity was found, we may conduct sensitivity analyses if appropriate and able (e.g., for studies rated as high risk of bias, different study designs) or decide to not use the pooled/combined estimate. If not conducted by the authors and when there are at least eight studies in a meta-analysis, we will if possible analyze publication bias both visually using the

funnel plot and quantitatively using Egger's test (32). If meta-analysis was not performed, we will summarize the findings of the systematic review authors.

For KQ5 (diagnostic accuracy), if individual studies are incorporated we will construct 2 x 2 tables and calculate sensitivity, specificity, and positive and negative likelihood ratios (LR+, LR-). Sensitivity and specificity are measures of test accuracy. Likelihood ratios are used to estimate the increased or decreased probability of disease (i.e., ASB) for a patient and can be used to refine clinical judgement based on varying pre-test probabilities. The larger the LR+, the more accurate the test is and the greater the likelihood of disease following a positive test; the smaller the LR-, the more accurate the test is, the lesser the likelihood of disease following a negative test (33). A LR+ that is >10 indicates a large and often conclusive probability that the condition is present; a LR- that is <0.10 suggests a large and often conclusive probability that the condition is not present. A likelihood ratio of one means that a positive or negative result is equally probable in a patient with and without the disease/condition.

If there are more than three studies and they are clinically homogenous (i.e., timing in pregnancy, thresholds, diagnostic criteria), we will pool data using a hierarchical summary receiver-operator curve (HSROC) and bivariate analysis of sensitivity and specificity (34). The HSROC simultaneously compares the sensitivity and specificity (taking their correlation into account) for all studies comparing a particular screening test with ASB diagnostic criteria. We will use Review Manager Version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark) to perform meta-analyses, and Stata 11.0 (metandi program; StataCorp LP, College Station, TX, USA) to fit the bivariate and HSROC models and produce the pooled estimates of sensitivity, specificity, and likelihood ratios.

The results will be organized by type of screening test. If possible, we will examine the impact of screening before and after 12-16 weeks' gestation and in relation to other intervention subgroups described in Table 5. Sensitivities, specificities, and likelihood ratios and their 95% confidence intervals (CI) will be presented in summary tables that include all screening tests and diagnostic criteria. Based on the findings for sensitivity and specificity and estimates of one or more relevant baseline prevalence, an evidence profile will be generated for the outcomes FN, FP, TN, and TP (30).

# **Subgroup Analyses**

Our primary approach for evaluating differential effect for subgroups will be to record any within-study subgroup analyses performed by study investigators using individual patient data; these results preserve the within-study randomization. Because these results are often based on diverse methodology and may be difficult to interpret across the body of evidence, we will also perform our own subgroup analyses using study-level data, as possible, using formal statistical approaches (e.g., meta-regressions) or by stratifying the results of the pairwise meta-analyses by subgroup variables. When determining whether entire studies fall into a particular subgroup category (e.g., recurrent UTI), we will consider  $\geq$ 80 percent of the study population meeting the criteria as sufficient. We will employ regression analyses when: for continuous variables (e.g., timing during pregnancy) there are at least six to ten studies reporting on the outcome within a specific subgroup, and for categorical variables (e.g., history of recurrent UTI) there are at least three studies for each category level. The number of sufficient studies serves as a rule of thumb

for the lower bound that investigators can consider for a meta-regression, but power will vary according to the size and variability of the effect. These analyses would rely on study-level data, such that the results would be considered observational in nature.

# Assessment of the Overall Quality of the Evidence using GRADE

Two reviewers will independently assess the quality of the body of evidence or confidence in the effect for each outcome of interest (see Table 1) using the GRADE methodology. Discrepancies will be resolved through discussion or third-party consultation to reach consensus. Assessments will be entered into the GRADEPro software and summarized in GRADE evidence profiles, Summary of Findings tables and Evidence to Decision Tables. Footnotes to the tables will explain all decisions. The CTFPHC will then use this evidence on each outcome, to assess the net benefits and harms of each service, consider patient preferences and values, and other elements of the GRADE methodology to develop the recommendations on screening for bacteriuria (feasibility, acceptability and equity).

The general approach is outlined here although methods will align with GRADE guidance (30, 35). When using systematic reviews, GRADE assessments will be based on the individual studies and reporting by review authors (e.g., on ROB assessments and PICOTS characteristics) and upon validation of a sample by the review team. For evidence on the benefits and harms of screening (KQ1), as a starting point the quality is assigned as high for evidence from RCTs and low for evidence from observational studies, when used. For accuracy studies, cross-sectional or cohort studies in patients with diagnostic uncertainty and direct comparison of test results with an appropriate reference standard will be considered high quality. Thereafter, we will examine and potentially downgrade the quality based on five core domains: study limitations/ROB, inconsistency, indirectness, imprecision, and publication/reporting bias. For outcomes where there is evidence from observational studies and no other reason to downgrade the evidence, we will also consider the additional domains of dose-response association, plausible confounding, and strength of association (i.e., large magnitude of effect [i.e., large  $\leq 0.5$  or  $\geq 2.0$  or very large RR  $\leq 0.2$  or  $\geq 5.0$ ]), to potentially upgrade the quality (36).

For the *study limitations (risk of bias)* domain RCTs and CCTs may be downgraded one or two levels depending on the proportion of trials (e.g., one very large trial may outweigh two very small trials) assessed as having high ROB for the particular outcome under consideration (37). Evidence from observational studies will be downgraded when most studies have moderate or high ROB. For *inconsistency* (consistent, inconsistent) we will assess the magnitude of the effects of the included studies (e.g., inconsistent when lack of overlap in 95% CIs for some studies) (38). *Indirectness* of the evidence (direct or indirect) is based on evaluating the relevance of the study's PICOs compared to ours for our primary KQ1 (effectiveness of screening); when relying on test accuracy and treatment studies there will be downgrading by at least one level for this domain (36). We will assess *imprecision* (precise or imprecise) on the basis of clinical thresholds and Optimal Information Size (39). For outcomes where clinical thresholds are used/determined, we will typically downgrade this domain once if the entire pooled 95% CI crosses the threshold (i.e. only one limit of the CI crosses), and downgrade twice if the 95% CI crosses the threshold and no difference (0 MD or 1.0 RR) or does not cross

the threshold at all. Thresholds may be determined a priori (prior to viewing results from studies) but may also be revised post hoc based on careful benefit-harm considerations when considering all outcomes together (e.g., lower benefit threshold in cases of few and minor harms). A precise estimate is one that allows for a clinically useful conclusion. *Reporting bias* (suspected or undetected) will be evaluated with respect to publication bias.

Interpreting these domains when relying on evidence from diagnostic test (KQ5) data has certain considerations, including how certain the CTFPHC is about the consequences of each outcome (FP, FN, TP, TN) in relation to the main outcomes of interest for KQs 1, 2 & 4 (30).

# **External Review**

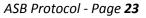
The evidence review will be peer-reviewed by external content experts (minimum 3) and invited stakeholder organizations (minimum 10), with response to all comments shared with all reviewers approximately two months after posting of the final review.

# **Planned Schedule and Timeline**

Draft protocol approved by CTFPHC members: July 29, 2016 External peer review: August 1-10, 2016 Final protocol: November 30, 2016 Draft evidence review: January 31, 2017 Final evidence review: March 31, 2017

# **Conflict of Interest Statement**

None of the study team members have any known actual or perceived conflicts of interest related to this review.



# References

1. Glaser AP, Schaeffer AJ. Urinary Tract Infection and Bacteriuria in Pregnancy. The Urologic clinics of North America. 2015;42(4):547-60.

2. Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. European journal of clinical investigation. 2008;38 Suppl 2:50-7.

3. Ipe DS, Sundac L, Benjamin WH, Jr., Moore KH, Ulett GC. Asymptomatic bacteriuria: prevalence rates of causal microorganisms, etiology of infection in different patient populations, and recent advances in molecular detection. FEMS microbiology letters. 2013;346(1):1-10.

4. Smaill FM, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. The Cochrane database of systematic reviews. 2015;8:CD000490.

5. Connolly A, Thorp JM, Jr. Urinary tract infections in pregnancy. The Urologic clinics of North America. 1999;26(4):779-87.

6. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2005;40(5):643-54.

7. Kass EH. Bacteriuria and the pathogenesis of pyelonephritis. Laboratory investigation; a journal of technical methods and pathology. 1960;9:110-6.

8. Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. American journal of obstetrics and gynecology. 2014;210(3):219 e1-6.

9. Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, de Miranda E, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. The Lancet Infectious diseases. 2015;15(11):1324-33.

10. Rogozinska E, Formina S, Zamora J, Mignini L, Khan KS. Accuracy of Onsite Tests to Detect Asymptomatic Bacteriuria in Pregnancy: A Systematic Review and Meta-analysis. Obstet Gynecol. 2016;128(3):495-503. Epub 2016/08/09.

11. Hilt EE, McKinley K, Pearce MM, Rosenfeld AB, Zilliox MJ, Mueller ER, et al. Urine Is Not Sterile: Use of Enhanced Urine Culture Techniques To Detect Resident Bacterial Flora in the Adult Female Bladder. Journal of Clinical Microbiology. 2014;52(3):871-6.

12. Price TK, Dune T, Hilt EE, Thomas-White KJ, Kliethermes S, Brincat C, et al. The Clinical Urine Culture: Enhanced Techniques Improve Detection of Clinically Relevant Microorganisms. Journal of Clinical Microbiology. 2016;54(5):1216-22.

13. Rouse DJ, Andrews WW, Goldenber RL, Owen J. Screening and Treatment of Asymptomatic Bacteriuria of Pregnancy to Prevent Pyelonephritis - a Cost-Effectiveness and Cost-Benefit-Analysis. Obstet Gynecol. 1995;86(1):119-23.

14. Guinto VT, De Guia B, Festin MR, Dowswell T. Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. The Cochrane database of systematic reviews. 2010(9):CD007855.

15. Allen VM, Yudin MH, Bouchard C, Boucher M, Caddy S, Castillo E, et al. Management of group B streptococcal bacteriuria in pregnancy. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC. 2012;34(5):482-6.

16. United States Preventive Services Task Force. Screening for asymptomatic bacteriuria in adults: U.S. Preventive Services Task Force reaffirmation recommendation statement. Annals of internal medicine. 2008;149(1):43-7.

17. Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. The Cochrane database of systematic reviews. 2007(2):CD000490.

18. American Academy of Family Physicians. Summary of Recommendations for Clinical Preventive Services. Leawood, KS: 2015.

19. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Guidelines for perinatal care. 7 ed: Amer Academy of Pediatrics; 2012.

20. NICE (National Institute for Health and Care Excellence). Antenatal care for uncomplicated pregnancies. Clincial guideline 62. United Kingdom: NICE; 2016. Available from: https://www.nice.org.uk/guidance/cg62.

21. SIGN (Scottish Intercollegiate Guidelines Network). SIGN 88. Management of suspected bacterial urinary tract infections in adults. Edinburgh, Scotland: SIGN; 2012. Available from: <u>http://www.sign.ac.uk/guidelines/fulltext/88/index.html</u>.

22. Malik K, Human Development Report 2013 Team. Human Development Report 2013. The Rise of the South: Human Progress in a Diverse World. N.Y., New York. : United Nations Development Programme, 2013.

23. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 2007;7(1):10.

24. Higgins JP, Green S. Section 8. Assessing risk of bias in included studies.: The Cochrane Collaboration; 2011. Available from: <u>http://handbook.cochrane.org</u>

25. Wells GA, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.

26. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-36.

27. Drummond MF SM, Torrance G, O'Brien B, Stoddart G. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. Oxford, UK: Oxford University Press; 2005.

28. Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. Journal of clinical epidemiology. 2013;66(2):173-83.

29. Johnston BC, Patrick DL, Thorlund K, Busse JW, da Costa BR, Schunemann HJ, et al. Patient-reported outcomes in meta-analyses-part 2: methods for improving interpretability for decision-makers. Health and quality of life outcomes. 2013;11:211.

30. Hsu J, Brozek JL, Terracciano L, Kreis J, Compalati E, Stein AT, et al. Application of GRADE: making evidence-based recommendations about diagnostic tests in clinical practice guidelines. Implementation science : IS. 2011;6:62.

31. Spencer FA, Iorio A, You J, Murad MH, Schunemann HJ, Vandvik PO, et al. Uncertainties in baseline risk estimates and confidence in treatment effects. BMJ. 2012;345:e7401.

32. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed). 1997;315(7109):629-34.

33. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. Jama. 1994;271(9):703-7.

34. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. Journal of clinical epidemiology. 2005;58(10):982-90.

35. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology. 2011;64(4):380-2.

36. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. Journal of clinical epidemiology. 2011;64(12):1311-6.

37. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). Journal of clinical epidemiology. 2011;64(4):407-15.

38. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. Journal of clinical epidemiology. 2011;64(12):1294-302.

39. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. Journal of clinical epidemiology. 2011;64(12):1283-93.

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# Appendix 1. MEDLINE Search Strategy (KQ1 [screening effectiveness])

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R)

Daily and Ovid MEDLINE(R) 1946 to Present

- Search Title: PHTF Bacteriuria Screening in Pregnancy
- Strategy:

1. Asymptomatic Infections/ and (bacteriuria\* or bladder\* or cystitis\* or kidney\* or pyelocystiti\* or pyelocystiti\* or pyelo-nephriti\* or pyelonephriti\* or urin\* or UTI\*).mp.

- 2. Bacteriuria/
- 3. exp Cystitis/
- 4. Dysuria/
- 5. Pyelonephritis/
- 6. Urinary Tract Infections/
- 7. bacilluria\*.tw,kf.
- 8. bacteriuria\*.tw,kf.
- 9. cystiti\*.tw,kf.
- 10. (cysto-pyeliti\* or cystopyeliti\*).tw,kf.
- 11. dysuria\*.tw,kf.
- 12. (infection\* adj2 (bladder\* or genitourin\* or kidney\* or urin\* or urogenita\*)).tw,kf.
- 13. (pyelo-cystiti\* or pyelocystiti\*).tw,kf.
- 14. (pyelo-nephriti\* or pyelonephriti\*).tw,kf.
- 15. (UTI or UTIs).tw,kf.
- 16. or/1-15 [Combined MeSH & text words for bacteriuria]
- 17. Antibody-Coated Bacteria Test, Urinary/
- 18. \*Bacteriuria/di, pc, mi, ur
- 19. exp \*Cystitis/di, pc, mi, ur
- 20. Mass Screening/
- 21. Microbial Sensitivity Tests/
- 22. Microscopy/
- 23. Predictive Value of Tests/
- 24. \*Pyelonephritis/di, pc, mi, ur
- 25. Reagent Kits, Diagnostic/
- 26. Reagent Strips/
- 27. "Sensitivity and Specificity"/
  - 28. Urinalysis/
  - 29. \*Urinary Tract Infections/di, pc, mi, ur
  - 30. ((accurac\* or diagnostic) adj5 (algorithm\* or test\*)).tw,kf.
  - 31. diagnostic accurac\*.tw,kf.
  - 32. culture\*.tw,kf.
  - 33. (detect\* or predict\* or screen\*).tw,kf.
- 34. (dip slide\* or dipslide\* or dip stick\* or dipstick\*).tw,kf.
- 35. (micro-scopy or microscopy).tw,kf.
- 36. (microb\* adj2 test\*).tw,kf.
- 37. ((re-agent\* or reagent) adj3 (strip\* or test\*)).tw,kf.
- 56 57

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| 1        |   |
|----------|---|
| 2<br>3   |   |
| 4        | 38. strip* test*.tw,kf.   |
| 5        | 39. urine test*.tw,kf.  |
| 6        | 40. (urinalys* or urine analys*).tw,kf.   |
| 7        | 41. uriscreen.tw,kf.  |
| 8        | 42. or/17-41 [Combined MeSH & text words for screening]   |
| 9        | 43. exp Pregnancy/  |
| 10       | 44. Pregnancy Complications, Infectious/  |
| 11       | 45. Pregnant Women/   |
| 12       | 46. Prenatal Care/  |
| 13<br>14 | 47. Prenatal Diagnosis/   |
| 14       | 48. (antenatal* or pre-natal* or prenatal*).mp.   |
| 16       | 49. (expect* adj (female? or mother? or wom#n)).tw,kf.  |
| 17       | 50. pregnan*.mp.  |
| 18       | 51. or/43-50 [Combined MeSH & text words for pregnancy]   |
| 19       | 52. and/16,42,51 [Combined searches for bacteriuria, screening & pregnancy]   |
| 20       | 53. Male/ not (Female/ and Male/)   |
| 21       |   |
| 22       | 54. 52 not 53 [Male only records excluded]  |
| 23       | 55. exp Animals/ not (exp Animals/ and Humans/)   |
| 24       | 56. 54 not 55 [Animal only records excluded]  |
| 25       | 57. (comment or editorial or news or newspaper article).pt.   |
| 26<br>27 | 58. (letter not (letter and randomized controlled trial)).pt.   |
| 28       | 59. 56 not (57 or 58) [Opinion pieces excluded]   |
| 29       | 60. case reports.pt.  |
| 30       | 61. 59 not 60 [Case reports excluded]   |
| 31       | 62. limit 61 to (english or french)   |
| 32       | 63. remove duplicates from 62   |
| 33       |   |
| 34       |   |
| 35       |   |
| 36       | <ul> <li>60. case reports.pt.</li> <li>61. 59 not 60 [Case reports excluded]</li> <li>62. limit 61 to (english or french)</li> <li>63. remove duplicates from 62</li> </ul> |
| 37<br>38 |   |
| 38<br>39 |   |
| 40       |   |
| 41       |   |
| 42       |   |
| 43       |   |
| 44       |   |
| 45       |   |
| 46       |   |
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| 48<br>49 |   |
| 49<br>50 |   |
| 50       |   |
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| 55       |   |
| 56       |   |
| 57       |   |
| 58       | ASB Propos  |

#### Appendix 2. Methods for Integrating Existing Systematic Reviews into New Reviews

One or more systematic reviews may exist that align with one or more key questions (KQs) of the reviews undertaken to inform CTFPHC guidelines. The CTFPHC and ERSCs have considered the manner in which new reviews conducted for CTFPHC guidelines can benefit from efficiencies by incorporating existing systematic reviews, while maintaining methodological rigor in their own systematic review conduct, closely aligning existing reviews within their review scope (i.e., inclusion/exclusion criteria), and maintaining consistency with other CTFPHC Methods. They have based their approach on work conducted by a methods working group composed of investigators from the Evidence-based Practice Center Program funded by the U.S. Agency for Healthcare Research and Quality.<sup>1,2</sup> A summary of the way the ERSCs will operationalize the 12 AHRQ recommendations (Box 1) to meet their needs is outlined below. This approach differs from situations when "updating" a single existing systematic review is deemed suitable, that is, in some cases a high-quality review will be used to answer one or more of the CTFPHC KQs in entirety, usually without revisions to the review's scope, search for evidence (apart from updating to present), methodological quality/risk of bias assessments, data extraction, or data analysis.

### Summary of CTFPHC Approach

The recommendations developed by AHRQ (Box 1) will serve as an overall framework for ERSC reviews, although in most cases existing systematic reviews will be used to build efficiencies in discrete steps within the review process—mainly search and selection of literature, and data extraction—which will not generally include refinement of the scope or data analysis and interpretation. Moreover, we will not in most circumstances include a systematic review itself as a study design for inclusion (unless the intention is to specifically conduct an overview of reviews). The ability to use any given systematic review will largely depend on how it aligns with the CTFPHC review's scope (PICOTS). A further primary consideration will be the comprehensiveness of its search strategy and reporting of literature flow. It is important to note that some CTFPHC reviews need to be complex with multiple stages (e.g., a review of screening effectiveness for patient-important benefits and harms may require including evidence on indirect evidence of test accuracy and treatment) such that existing systematic reviews may exist for one or more discrete stages but not for others. Some key points on the operationalization, and minor revision, by the ERSCs of these recommendations are provided below.

1. **Choosing systematic reviews**: Following the identification of relevant reviews (a search for systematic reviews may be undertaken for some topics), the evidence for each will be mapped to the PICOTS elements and the quality of the review will be assessed (e.g., using the AMSTAR tool which has been evaluated and found effective to discriminate reviews with high and low quality of methods and reporting).<sup>3</sup> Some of the CTFPHC KQs may only have a single existing systematic review for possible incorporation, while others may have more than one; if suitable, a decision between systematic reviews will be based on methodological quality, comprehensiveness and quality of its literature search and reporting (e.g., assessed using PRESS checklist), comprehensiveness of reporting on included studies, and the best fit within the CTFPHC scope and methods. In some cases two or more reviews may be integrated because, together, they capture the full scope of the CTFPHC KQ(s). Rationale will be provided for choices made.

**Note:** If no review is deemed a good fit for purpose for integration (i.e., de novo process all together appears to be best option) we will at minimum examine available reviews for their search strategies (to ensure that our search strategies are comprehensive) and review their reference lists for identification of studies.

- 2. Searching: Various strategies will be considered. If one or more reviews are fit for purpose (but do not meet criteria for classification as a systematic review update) and cover a scope that is very similar or broader than the CTFPHC topic, we may update the search(es) if the last search date was prior to 6 months before commencing our review. When there are multiple reviews being considered, updating the literature to present may involve a new comprehensive search strategy to identify studies published after the date of the earliest existing review; this may reduce complexities when trying to implement, document, and remove duplicates from multiple searches. Alternatively, if the scope of the existing review(s) is *narrower* (e.g., missing an element in PICOTS) or the search deemed sub-optimal in some manner (e.g., missing key terms, additional database viewed as highly relevant) we may re-run the existing review's search concurrent with an original (e.g., broader) search and remove the citations previously screened for the other review. If more appropriate, we may update the other review's search and use a new search for the missing PICO element(s) (e.g., one additional intervention) for a longer time period to meet our timeframe. In cases where we feel screening excluded studies lists is appropriate we will also undertake this. Careful consideration will be used to ensure a comprehensive search is conducted regardless of approach taken; moreover, the ERSC librarians will help determine on a case-by-case basis what approach would be feasible for implementation to ensure aims of building efficiencies are possible.
- 3. Screening and selection: We will assess articles included in all relevant reviews (based on full text if necessary) to determine if they meet our inclusion criteria.
- 4. **Data extraction and methodological quality assessments**: We will consider incorporating the data on study and participant characteristics rather than extracting these data anew; we may also use the review author's risk of bias assessments if the tools/methods are consistent with CTFPHC methods. These steps will create efficiencies but because they are dependent on the quality of the systematic review and extent of reporting, the ERSC staff will verify the data on at least 5 to 10% of studies.<sup>1</sup>
- 5. **Data analysis**: We will consider using quantitative outcome data from reviews (with verification), but will not typically use meta-analyses or quality (GRADE) assessments of existing reviews.
- 6. **Reporting**: Transparent reporting of all integration steps used will be included in the evidence review report.

# Box 1. Recommendations developed by AHRQ EPCs\*1,2

\*Strength of evidence refers to AHRQ's slightly modified approach to the GRADE quality of evidence approach

| 1.  | Existing reviews should be confirmed as systematic reviews through the application of a minimum set of eligibility criteria. We propose that the minimum eligibility criteria for systematic reviews include an explicit and adequate search, application of predefined eligibility criteria to select studies, risk of bias assessment for included studies, and synthesis of results.  |
|-----|--|
| 2.  | Criteria to assess the relevance, in terms of question elements and currency, and quality of existing systematic reviews under consideration for inclusion in reviews should be predefined.  |
| 3.  | The quality of relevant existing systematic reviews should be assessed in an explicit manner with a minimum set of quality criteria that include search of multiple sources, use of a generally accepted tool for risk of bias assessment, and sufficient information to assess the strength of the body of evidence that includes the major domains of risk of bias, directness, consistency, precision, and reporting bias.                          |
| 4.  | The risk of bias assessments from the existing systematic review may be used when the review described an explicit process, including the use of a tool or method that is compatible with the approach of the current review and that assessed the key sources of potential bias.  |
| 5.  | We suggest that risk of bias assessment be repeated in a sample of studies from an existing review under consideration for inclusion in a new review to confirm concordance with current review team approach.   |
| 6.  | We recommend that at a minimum, reviews should narratively describe findings of the prior review(s), including the number and types of studies included, and the overall findings.   |
| 7.  | We recommend that newly identified studies be clearly distinguished from studies in the existing review(s) when presented in the narrative and any tables (eg, separate tables).   |
| 8.  | Summary tables should include sufficient information to support ratings for overall strength of evidence, including ratings for individual strength of evidence domains (study limitations, consistency, precision, directness, reporting bias). The strength of evidence ratings should be based on the underlying primary evidence, not the number or quality of existing systematic reviews.  |
| 9.  | Using strength of evidence domains as a framework (study limitations, consistency, precision, directness, and reporting bias), review authors should consider how new evidence would change estimates of effect or ratings for strength of evidence. A new quantitative synthesis (ie, pooled estimate) is needed if new studies would change conclusions or strength of evidence judgements, or to obtain a more precise or more up-to-date estimate. |
| 10. | In cases where the existing systematic review(s) did not complete strength of evidence grading for a comparison<br>and outcome of interest, the strength of evidence should be assessed for the body of evidence, considering primary<br>studies from prior review(s) and any new studies identified.  |
| 11. | In cases where no new studies are added to the body of evidence, the strength of evidence assessment from the existing systematic review may be used if conducted using an acceptable grading approach consistent with current review context. In these cases, we suggest that the overall strength of evidence assessment be reviewed, considering the strength of evidence domains, to confirm consistency with current review team assessments.     |

12. In cases where new studies are added to the body of evidence, the strength of evidence may need to be reassessed on the basis of all studies/evidence.

# **Appendix 2 References**

- 1. Robinson KA, Chou R, Berkman ND, et al. Integrating bodies of evidence: existing systematic reviews and primary studies. Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2015 Feb.
- 2. Robinson KA, Chou R, Berkman ND, et al. Twelve recommendations for integrating existing systematic reviews into new reviews: EPC guidance. J Clin Epidemiol. 2016 Feb;70:38-44. PMID: 26261004.
- 3. Foisy M, Hartling L. Challenges and considerations involved in using AMSTAR in overviews of reviews. 22<sup>nd</sup> Cochrane Colloquium. Hyderabad (India); 2014 Sept 21-26.

Topper tories only

| KQ1: Screening Effectiveness   |
|--|
| Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citatio        |
| MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present   |
| Date Searched: 13 June 2016  |
| Date Updated: 6 September 2017   |
| Records Retrieved: 1437  |
| 1. Asymptomatic Infections/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-c |
| pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.                     |
| 2. Bacteriuria/  |
| 3. exp Cystitis/   |
| 4. Dysuria/  |
| 5. Pyelonephritis/   |
| 6. Urinary Tract Infections/   |
| 7. bacilluria*.tw,kf.  |
| 8. bacteriuria*.tw,kf.   |
| 9. cystiti*.tw,kf.   |
| 10. (cysto-pyeliti* or cystopyeliti*).tw,kf.   |
| 11. dysuria*.tw,kf.  |
| 12. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw,kf.     |
| 13. (pyelo-cystiti* or pyelocystiti*).tw,kf.   |
| 14. (pyelo-nephriti* or pyelonephriti*).tw,kf.   |
| 15. (UTI or UTIs).tw,kf.   |
| 16. or/1-15 [Combined MeSH & text words for bacteriuria]                                     |
| 17. Antibody-Coated Bacteria Test, Urinary/  |
| 18. *Bacteriuria/di, pc, mi, ur  |
| 19. exp *Cystitis/di, pc, mi, ur   |
| 20. Mass Screening/  |
| 21. Microbial Sensitivity Tests/   |
| 22. Microscopy/  |
| 23. Predictive Value of Tests/   |
| 24. *Pyelonephritis/di, pc, mi, ur   |
| 25. Reagent Kits, Diagnostic/  |
| 26. Reagent Strips/  |
| 27. "Sensitivity and Specificity"/   |
| 28. Urinalysis/  |
| 29. *Urinary Tract Infections/di, pc, mi, ur   |
| 30. ((accurac* or diagnostic) adj5 (algorithm* or test*)).tw,kf.                             |
| 31. diagnostic accurac*.tw,kf.   |
| 32. culture*.tw,kf.  |
| 33. (detect* or predict* or screen*).tw,kf.  |
|  |
| 34. (dip slide* or dipslide* or dip stick* or dipstick*).tw,kf.                              |
| 35. (micro-scopy or microscopy).tw,kf.   |
| 36. (microb* adj2 test*).tw,kf.  |
| 37. ((re-agent* or reagent) adj3 (strip* or test*)).tw,kf.<br>38. strip* test*.tw,kf.        |

| 2        |   |
|----------|---|
| 3        | 39. urine test*.tw,kf.  |
| 4        | 40. (urinalys* or urine analys*).tw,kf.   |
| 5        | 41. uriscreen.tw,kf.  |
| 6        | 42. or/17-41 [Combined MeSH & text words for screening]   |
| 7        | 43. exp Pregnancy/  |
| 8<br>9   | 44. Pregnancy Complications, Infectious/  |
| 9<br>10  | 45. Pregnant Women/   |
| 11       | 46. Prenatal Care/  |
| 12       |   |
| 13       | 47. Prenatal Diagnosis/   |
| 14       | 48. (antenatal* or pre-natal* or prenatal*).mp.   |
| 15       | 49. (expect* adj (female? or mother? or wom#n)).tw,kf.  |
| 16       | 50. pregnan*.mp.  |
| 17       | 51. or/43-50 [Combined MeSH & text words for pregnancy]   |
| 18       | 52. and/16,42,51 [Combined searches for bacteriuria, screening & pregnancy]                           |
| 19       | 53. Male/ not (Female/ and Male/)   |
| 20       | 54. 52 not 53 [Male only records excluded]  |
| 21       | 55. exp Animals/ not (exp Animals/ and Humans/)   |
| 22       | 56. 54 not 55 [Animal only records excluded]  |
| 23       | 57. (comment or editorial or news or newspaper article).pt.   |
| 24<br>25 | 58. (letter not (letter and randomized controlled trial)).pt.   |
| 26       | 59. 56 not (57 or 58) [Opinion pieces excluded]   |
| 27       | 60. case reports.pt.  |
| 28       | 61. 59 not 60 [Case reports excluded]   |
| 29       | 62. limit 61 to (english or french)   |
| 30       | 63. remove duplicates from 62   |
| 31       |   |
| 32       |   |
| 33       | KQ1: Screening Effectiveness  |
| 34       | Database: Ovid Embase 1974 to 2016 Week 24  |
| 35       | Database. Ovid Embase 1974 to 2016 Week 24  |
| 36       |   |
| 37       | Date Updated: 6 September 2017  |
| 38<br>39 | Records Retrieved: 1613   |
| 40       |   |
| 40       | 1. acute pyelonephritis/  |
| 42       | 2. asymptomatic bacteriuria/  |
| 43       | 3. asymptomatic infection/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or |
| 44       | pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.                              |
| 45       | 4. bacteriuria/   |
| 46       | 5. exp cystitis/  |
| 47       | 6. dysuria/   |
| 48       | 7. kidney infection/  |
| 49       | 8. pyelonephritis/  |
| 50       | 9. urinary tract infections/  |
| 51       | 10. bacilluria*.tw.   |
| 52       | 11. bacteriuria*.tw.  |
| 53<br>54 | 12. cystiti*.tw.  |
| 54<br>55 | 13. (cysto-pyeliti* or cystopyeliti*).tw.   |
| 55<br>56 | 14. dysuria*.tw.  |
| 57       | IT. UYJUHA .LW.   |
| 58       |   |
| 59       |   |
| J2       |   |

15. (infection\* adj2 (bladder\* or genitourin\* or kidney\* or urin\* or urogenita\*)).tw. 16. (pyelo-cystiti\* or pyelocystiti\*).tw. 17. (pyelo-nephriti\* or pyelonephriti\*).tw. 18. (UTI or UTIs).tw. 19. or/1-18 [Combined Emtree & text words for bacteriuria] 20. \*asymptomatic bacteriuria/di, pc 21. \*acute pyelonephritis/di, pc 22. \*bacteriuria/di, pc 23. exp \*cystitis/di, pc 24. diagnostic kit/ 25. fluorescent antibody technique/ 26. \*kidney infection/di, pc 27. mass screening/ 28. microbial sensitivity test/ 29. microscopy/ 30. predictive value/ 31. \*pyelonephritis/di, pc 32. "sensitivity and specificity"/ 33. screening/ 34. test strip/ 35. exp urinalysis/ 36. \*urinary tract infection/di, pc 37. ((accurac\* or diagnostic) adj5 (algorithm\* or test\*)).tw. 38. diagnostic accurac\*.tw. 39. culture\*.tw. 40. (detect\* or predict\* or screen\*).tw. 41. (dip slide\* or dipslide\* or dip stick\* or dipstick\*).tw. 42. (micro-scopy or microscopy).tw. 43. (microb\* adj2 test\*).tw. 44. ((re-agent\* or reagent) adj3 (strip\* or test\*)).tw. 45. strip\* test\*.tw. 46. urine test\*.tw. 47. (urinalys\* or urine analys\*).tw. 48. uriscreen.tw. 49. or/20-48 [Combined Emtree & text words for screening] 50. exp pregnancy/ 51. pregnancy complication/ 52. pregnant woman/ 53. prenatal care/ 54. prenatal diagnosis/ 55. prenatal screening/ 56. (antenatal\* or pre-natal\* or prenatal\*).mp. 57. (expect\* adj (female? or mother? or wom#n)).tw. 58. pregnan\*.mp. 59. or/50-58 [Combined Emtree & text words for pregnancy] 60. and/19,49,59 [Combined Emtree & text words for pregnancy] 61. Male/ not (Female/ and Male/) 62. 60 not 61 [Male only records excluded]

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| 2        |           |   |
| 3<br>4   |           | nimals/ not (animals/ and humans/)  |
| 5        |           | 2 not 63 [Animal only records excluded]   |
| 6        | -         | onference* or editorial or letter).pt.  |
| 7        |           | I not 65 [Excluded publication types – RF note: will search conference proceedings separately |
| 8        |           | lifferent strategy]   |
| 9        | 67. ca    | se report/ or case report*.ti.  |
| 10       |           | 5 not 67 [Case reports excluded]  |
| 11       | 69. lin   | nit 68 to (english or french)   |
| 12       | 70. re    | move duplicates from 69   |
| 13       |           |   |
| 14<br>15 |           |   |
| 15       | KQ1: 5    | Screening Effectiveness   |
| 17       | Datab     | base: Wiley Cochrane Library  |
| 18       | Date S    | Searched: 13 June 2016  |
| 19       | Date I    | Update: 6 September 2017  |
| 20       |           | ds Retrieved: 11 in Cochrane Database of Systematic Reviews                                   |
| 21       |           | ds Retrieved: 1 in Database of Abstracts of Reviews of Effects (DARE)                         |
| 22       |           | ds Retrieved: 112 in Cochrane Central Register of Controlled Trials (CENTRAL)                 |
| 23       |           | ds Retrieved: 1 in Health Technology Assessment Database                                      |
| 24       | necoi     | us hetheved. I in health reenhology Assessment Database                                       |
| 25<br>26 | #1        | [mh ^"Asymptomatic Infections"] and (bacteriuria* or bladder* or cystitis* or kidney* or      |
| 20       |           | -cystiti* or pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*):ti,ab,kw    |
| 28       | #2        | [mh ^Bacteriuria]   |
| 29       |           |   |
| 30       | #3<br>#4  | [mh Cystitis]   |
| 31       |           | [mh ^Dysuria]   |
| 32       | #5        | [mh ^Pyelonephritis]  |
| 33       | #6        | [mh ^"Urinary Tract Infections"]  |
| 34       | #7<br>#0  | bacilluria*:ti,ab,kw  |
| 35<br>36 | #8<br>#0  | bacteriuria*:ti,ab,kw<br>cystiti*:ti,ab,kw  |
| 30       | #9<br>#10 |   |
| 38       | #10       | (cysto-pyeliti* or cystopyeliti*):ti,ab,kw  |
| 39       | #11       | dysuria*:ti,ab,kw   |
| 40       | #12       | (infection* near/2 (bladder* or genitourin* or kidney* or urin* or urogenita*)):ti,ab,kw      |
| 41       | #13       | (pyelo-cystiti* or pyelocystiti*):ti,ab,kw  |
| 42       | #14       | (pyelo-nephriti* or pyelonephriti*):ti,ab,kw  |
| 43       | #15       | (UTI or UTIs):ti,ab,kw  |
| 44       | #16       | {or #1-#15}   |
| 45<br>46 | #17       | [mh ^"Antibody-Coated Bacteria Test, Urinary"]  |
| 40<br>47 | #18       | [mh ^Bacteriuria [mj]/DI,PC,MI,UR]  |
| 48       | #19       | [mh Cystitis [mj]/DI,PC,MI,UR]  |
| 49       | #20       | [mh ^"Mass Screening"]  |
| 50       | #21       | [mh ^"Microbial Sensitivity Tests"]   |
| 51       | #22       | [mh ^Microscopy]  |
| 52       | #23       | [mh ^"Predictive Value of Tests"]   |
| 53       | #24       | [mh ^Pyelonephritis [mj]/DI,PC,MI,UR]   |
| 54       | #25       | [mh "Reagent Kits, Diagnostic"]   |
| 55<br>56 | #26       | [mh "Reagent Strips"]   |
| 56<br>57 |           |   |
| 57       |           |   |
| 59       |           |   |
| 60       |           | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                     |

[mh ^"Sensitivity and Specificity"]

"diagnostic accurac\*":ti,ab,kw

(microb\* near/2 test\*):ti,ab,kw

"strip\* test\*":ti,ab,kw

"urine test\*":ti,ab,kw

[mh ^"Pregnant Women"]

[mh ^"Prenatal Diagnosis"]

[mh ^"Prenatal Care"]

pregnan\*:ti,ab,kw

{and #16, #42, #51}

{or #43-#50}

**KQ1: Screening Effectiveness** 

Date Searched: 13 June 2016 Date Updated: 6 September 2017

**Records Retrieved: 249** 

uriscreen:ti,ab,kw

[mh Pregnancy]

{or #17-#41}

(detect\* or predict\* or screen\*):ti,ab,kw

(micro-scopy or microscopy):ti,ab,kw

(urinalys\* or "urine analys\*"):ti,ab,kw

[mh ^"Pregnancy Complications, Infectious"]

(antenatal\* or pre-natal\* or prenatal\*):ti,ab,kw

(expect\* near/1 (female\* or mother\* or wom?n)):ti,ab,kw

Database: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost

[mh ^"Urinary Tract Infections" [mj]/DI,PC,MI,UR]

((accurac\* or diagnostic) near/5 (algorithm\* or test\*)):ti,ab,kw

("dip slide\*" or dipslide\* or "dip stick\*" or dipstick\*):ti,ab,kw

((re-agent\* or reagent) near/3 (strip\* or test\*)):ti,ab,kw

[mh ^Urinalysis]

culture\*:ti,ab,kw

#27 #28

#29

#30

#31 #32

#33

#34

#35

#36

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| Records Retrieved. 249   |
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| S1. (MH "Bacteriuria")   |
| S2. (MH "Cystitis+")   |
| S3. (MH "Dysuria")   |
| S4. (MH "Pyelonephritis")  |
| S5. (MH "Urinary Tract Infections")  |
| S6. bacilluria*  |
| S7. bacteriuria*   |
| S8. cystiti*   |
| S9. "cysto-pyeliti*" or cystopyeliti*  |
| S10. dysuria*  |
| S11. (infection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*)) |
| S12. "pyelo-cystiti*" or pyelocystiti*   |
| S13. "pyelo-nephriti*" or pyelonephriti*   |
| S14. UTI or UTIs   |
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| For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml        |
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| 3        | S15. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14   |
| 4        | S16. (MM "Bacteriuria/DI/PC/MI/UR")  |
| 5        | S17. (MM "Cystitis+/DI/MI/PC/UR")  |
| 6        | S18. (MH "Fluorescent Antibody Technique")   |
| 7        |  |
| 8        | S19. (MH "Health Screening")   |
| 9        | S20. (MH "Microbial Culture and Sensitivity Tests")  |
| 10       | S21. (MH "Microscopy")   |
| 11       | S22. (MH "Predictive Value of Tests")  |
| 12       | S23. (MM "Pyelonephritis/DI/PC/MI/UR")   |
| 13       | S24. (MH "Reagent Kits, Diagnostic+")  |
| 14<br>15 | S25. (MH "Sensitivity and Specificity")  |
| 16       | S26. (MH "Urinalysis")   |
| 17       | S27. (MM "Urinary Tract Infections/DI/PC/MI/UR")   |
| 18       | S28. (accurac* or diagnostic) N5 (algorithm* or test*)                                       |
| 19       | S29. "diagnostic accurac*"   |
| 20       | S30. culture*  |
| 21       | S31. detect* or predict* or screen*  |
| 22       | S32. "dip slide*" or dipslide* or "dip stick*" or dipstick*                                  |
| 23       | S32. up side of up side of up side of up side of up side                                     |
| 24       |  |
| 25       | S34. microb* N2 test*  |
| 26       | S35. ("re-agent*" or reagent) N3 (strip* or test*)   |
| 27       | S36. "strip* test*"  |
| 28       | S37. "urine test*"   |
| 29       | S38. urinalys* or "urine analys*"  |
| 30       | S39. uriscreen   |
| 31       | S40. S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 |
| 32       | OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39                 |
| 33       | S41. (MH "Expectant Mothers")  |
| 34<br>35 | S42. (MH "Pregnancy+")   |
| 36       | S43. (MH "Pregnancy Complications, Infectious")  |
| 37       | S44. (MH "Prenatal Care")  |
| 38       | S45. (MH "Prenatal Diagnosis")   |
| 39       | S46. antenatal* or "pre-natal*" or prenatal*   |
| 40       | S40. antenatal of pre-natal of pre-natal S47. expect* N1 (female? or mother? or wom?n)       |
| 41       | S47. expect N1 (remain of mother) of womeny<br>S48. pregnan*                                 |
| 42       |  |
| 43       | S49. S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48                                    |
| 44       | S50. S15 AND S40 AND S49   |
| 45       | S51. MH "Male" NOT ((MH "Female") AND (MH "Male"))   |
| 46       | S52. S50 NOT S51   |
| 47       | S53. ((MH "Vertebrates+") NOT MH Human)  |
| 48       | S54. S52 NOT S53   |
| 49       | S55. Limiters - Publication Type: Anecdote, Case Study, Commentary, Editorial, Letter        |
| 50       | S56. S54 NOT S55   |
| 51       | S57. S56 Narrow by Language: - english [RF: No French records in results to include]         |
| 52       |  |
| 53       |  |
| 54<br>55 | KQ1: Screening Effectiveness   |
| 55<br>56 | Database: PubMed via NCBI Entrez (1946 to Present)   |
| 57       |  |
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| 60       | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                    |
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Date Searched: 14 June 2016 Records Retrieved: 1246

((((("asymptomatic infections"[mh] AND (("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields]) OR ("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields] OR "bacteriurias"[All Fields]) OR ("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields]) OR ("cystitis"[MeSH Terms] OR "cystitis"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields]) OR ("pyelocystitis"[MeSH Terms] OR "pyelocystitis"[All Fields]) OR ("pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]) OR ("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR ("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) OR UTI[all] OR ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections" [All Fields] OR "utis" [All Fields]))) OR "bacteriuria" [MeSH Terms: noexp] OR "cystitis" [MeSH Terms] OR "dysuria" [MeSH Terms: noexp] OR "pyelonephritis" [MeSH Terms:noexp] OR "Urinary Tract Infections"[mh:noexp] OR bacilluria[tiab] OR bacteriuria[tiab] OR bacteriurias[tiab] OR "bladder infection"[tiab] OR "bladder infections"[tiab] OR cystitis[tiab] OR cystopyelitis[tiab] OR dysuria[tiab] OR "genito-urinary infection"[tiab] OR "genitourinary infection"[tiab] OR "genito-urinary infections"[tiab] OR "genitourinary infections"[tiab] OR "kidney infection"[tiab] OR "kidney infections"[tiab] OR "pyelo-nephritis"[tiab] OR pyelocystitis[tiab] OR pyelonephritis[tiab] OR "urinary infection"[tiab] OR "urinary infections"[tiab] OR "urogenital infection"[tiab] OR "urogenital infections"[tiab] OR UTI[tiab] OR UTIs[tiab]) AND ("Antibody-Coated Bacteria Test, Urinary"[mh] OR "Bacteriuria/diagnosis"[Majr] OR "Bacteriuria/prevention and control" [Majr] OR ("bacteriuria/microbiology" [Mesh Terms] AND Majr[All Fields]) OR "Bacteriuria/urine"[Majr] OR "Cystitis/diagnosis"[Majr] OR "Cystitis/prevention and control"[Majr] OR "Cystitis/microbiology"[Majr] OR "Cystitis/urine"[Majr] OR "Mass Screening"[mh:noexp] OR "Microbial Sensitivity Tests"[mh:noexp] OR "Microscopy"[mh:noexp] OR "Predictive Value of Tests"[mh:noexp] OR "Pyelonephritis/diagnosis"[Majr] OR "Pyelonephritis/prevention and control" [Majr] OR "Pyelonephritis/microbiology" [Majr] OR "Pyelonephritis/urine" [Majr] OR "Reagent Kits, Diagnostic"[mh:noexp] OR "Reagent Strips"[mh:noexp] OR "Sensitivity and Specificity"[mh:noexp] OR "Urinalysis"[mh:noexp] OR "Urinary Tract Infections/diagnosis"[Majr] OR "Urinary Tract Infections/prevention and control"[Majr] OR "Urinary Tract Infections/microbiology" [Majr] OR "Urinary Tract Infections/urine" [Majr] OR detect[tiab] OR detected[tiab] OR detection[tiab] OR detecting[tiab] OR detects[tiab] OR "diagnostic accuracy"[tiab] OR "diagnostic algorithm"[tiab] OR "dip slide"[tiab] OR "dip slides"[tiab] OR "dip stick"[tiab] OR "dip sticks"[tiab] OR dipslide[tiab] OR dipslides[tiab] OR dipstick[tiab] OR dipsticks[tiab] OR culture[tiab] OR cultures[tiab] OR "diagnostic test"[tiab] OR "diagnostic tests"[tiab] OR "microbial test"[tiab] OR "microbial tests"[tiab] OR microscopy[tiab] OR predict[tiab] OR predicted[tiab] OR prediction[tiab] OR predicting[tiab] OR predicts[tiab] OR "reagent strip"[tiab] OR "reagent strips"[tiab] OR "reagent test"[tiab] OR "reagent testing"[tiab] OR "reagent tests"[tiab] OR screen[tiab] OR screened[tiab] OR screening[tiab] OR screens[tiab] OR "strip test"[tiab] OR "strip tests"[tiab] OR "strip testing"[tiab] OR "test accuracy"[tiab] OR urinalyses[tiab] OR urinalysis[tiab] OR "urine analyses"[tiab] OR "urine analysis"[tiab] OR "urine test"[tiab] OR "urine tested"[tiab] OR "urine testing"[tiab] OR "urine tests"[tiab] OR uriscreen[tiab]) AND ("Pregnancy"[mh] OR "Pregnancy Complications, Infectious"[mh:noexp] OR "Pregnant Women"[mh:noexp] OR "Prenatal Care"[mh:noexp] OR "Prenatal Diagnosis"[mh:noexp] OR antenatal[tiab] OR "pre-natal"[tiab] OR prenatal[tiab] OR "expectant mother"[tiab] OR "expectant mothers"[tiab] OR "expecting mothers"[tiab] OR "expecting mothers"[tiab] OR "expectant woman"[tiab] OR "expectant women"[tiab] OR "expecting

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| 2        |  |
| 3        | women"[tiph] OP programsics[tiph] OP programs(tiph] OP programt[tiph])) NOT ("Male"[mh] NOT            |
| 4        | women"[tiab] OR pregnancies[tiab] OR pregnancy[tiab] OR pregnant[tiab])) NOT ("Male"[mh] NOT           |
| 5        | ("Female"[mh] AND "Male"[mh]))) NOT (((Animals[MESH] OR Animal Experimentation[MESH] OR                |
| 6        | "Models, Animal"[MESH] OR Vertebrates[MESH]) NOT (Humans[MESH] OR Human                                |
| 7        | experimentation[MESH])) OR (((animals[tiab] OR animal model[tiab] OR rat[tiab] OR rats[tiab] OR        |
| 8        | mouse[tiab] OR mice[tiab] OR rabbit[tiab] OR rabbits[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] |
| 9        | OR swine[tiab] OR dog[tiab] OR dogs[tiab] OR hamster[tiab] OR hamsters[tiab] OR chicken[tiab] OR       |
| 10       | chickens[tiab] OR sheep[tiab]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])) NOT       |
| 11       | (human[ti] OR humans[ti] OR people[ti] OR children[ti] OR adults[ti] OR seniors[ti] OR patient[ti] OR  |
| 12       |  |
| 13       | patients[ti])))) NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR newspaper      |
| 14       | article[pt])   |
| 15       | > limit to English or French   |
| 16       |  |
| 10       |  |
| 18       | KQ2: Women's Outcome Valuation   |
| 19       | Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid          |
| 20       | MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present   |
| 21       |  |
| 22       | Date Searched: 4 July 2016   |
| 23       | Date Updated: 5 September 2017   |
| 24       | Records Retrieved: 2965  |
| 25       |  |
| 26       | 1. Asymptomatic Infections/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or |
| 27       | pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.                               |
| 28       | 2. Bacteriuria/  |
| 29       | 3. exp Cystitis/   |
| 30       | 4. Dysuria/  |
| 31       | 5. Pyelonephritis/   |
| 32       | 6. Urinary Tract Infections/   |
| 33       | 7. bacilluria*.tw,kf.  |
| 34       | 8. bacteriuria*.tw,kf.   |
| 35       |  |
| 36       | 9. cystiti*.tw,kf.   |
| 37       | 10. (cysto-pyeliti* or cystopyeliti*).tw,kf.   |
| 38       | 11. dysuria*.tw,kf.  |
| 39<br>40 | 12. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw,kf.               |
| 40<br>41 | 13. (pyelo-cystiti* or pyelocystiti*).tw,kf.   |
| 41<br>42 | 14. (pyelo-nephriti* or pyelonephriti*).tw,kf.   |
| 43       | 15. (UTI or UTIs).tw,kf.   |
| 44       | 16. or/1-15 [Combined MeSH & text words for bacteriuria]   |
| 45       | 17. Antibody-Coated Bacteria Test, Urinary/  |
| 46       | 18. *Bacteriuria/di, pc, mi, ur  |
| 47       | 19. exp *Cystitis/di, pc, mi, ur   |
| 48       | 20. Mass Screening/  |
| 49       | 21. Microbial Sensitivity Tests/   |
| 50       | •  |
| 51       | 22. Microscopy/  |
| 52       | 23. Predictive Value of Tests/   |
| 53       | 24. *Pyelonephritis/di, pc, mi, ur   |
| 54       | 25. Reagent Kits, Diagnostic/  |
| 55       | 26. Reagent Strips/  |
| 56       | 27. "Sensitivity and Specificity"/   |
| 57       |  |
| 58       |  |
| 59<br>60 | For peer review only - http://bmiopen.bmi.com/site/about/guidelines.xhtml                              |
| 60       |  |

| 28. Urinalysis/                                |                                    |  |
|--|------------------------------------|--|
| 29. *Urinary Tract Infections                  | s/di, pc, mi, ur                   |  |
| 30. ((accurac* or diagnostic)                  | adj5 (algorithm* or test*)).tw,kf. |  |
| 31. diagnostic accurac*.tw,k                   | f.                                 |  |
| 32. culture*.tw,kf.                            |                                    |  |
| 33. (detect* or predict* or se                 | creen*).tw,kf.                     |  |
| 34. (dip slide* or dipslide* o                 | r dip stick* or dipstick*).tw,kf.  |  |
| 35. (micro-scopy or microsco                   |                                    |  |
| 36. (microb* adj2 test*).tw,l                  |                                    |  |
| 37. ((re-agent* or reagent) a                  | ıdj3 (strip* or test*)).tw,kf.     |  |
| 38. strip* test*.tw,kf.                        |                                    |  |
| 39. urine test*.tw,kf.                         |                                    |  |
| 40. (urinalys* or urine analys                 | s*).tw,kf.                         |  |
| 41. uriscreen.tw,kf.                           |                                    |  |
|  | SH & text words for screening]     |  |
| · · · · -                                      | arches for ASB and screening]      |  |
| 44. Anti-Bacterial Agents/                     |                                    |  |
| 45. Antibiotic Prophylaxis/                    |                                    |  |
| 46. Anti-Infective Agents, Ur                  |                                    |  |
| 47. Asymptomatic Infections                    | s/dt, th                           |  |
| 48. *Bacteriuria/dt, th                        | ion /                              |  |
| 49. Drug Therapy, Combinat<br>50. Norfloxacin/ | ion/                               |  |
| 51. exp Penicillins/                           |                                    |  |
| 52. exp Sulfonamides/                          |                                    |  |
| 53. *Urinary Tract Infections                  | /dt th                             |  |
| 54. amoxicillin*.mp.                           | yut, th                            |  |
| 55. ampicillin*.mp.                            |                                    |  |
| 56. (anti-bacteria* or antiba                  | cteria*).tw.kf.                    |  |
| 57. (anti-biotic* or antibiotic                |                                    |  |
| 58. aztreonam*.mp.                             |                                    |  |
| 59. cefadroxil*.mp.                            |                                    |  |
| 60. cefepime*.mp.                              |                                    |  |
| 61. ceftibuten*.mp.                            |                                    |  |
| 62. ceftri?xone*.mp.                           |                                    |  |
| 63. cefuroxime*.mp.                            |                                    |  |
| 64. cephalexin*.mp.                            |                                    |  |
| 65. cephalosporin*.mp.                         |                                    |  |
| 66. cephradine*.mp.                            |                                    |  |
| 67. clindamycin*.mp.                           |                                    |  |
| 68. (co-trimoxazole* or cotri                  | imoxazole*).mp.                    |  |
| 69. cycloserine*.mp.                           |                                    |  |
| 70. fosfomycin*.mp.                            |                                    |  |
| 71. gentam#cin*.mp.                            |                                    |  |
| 72. nalidixic acid*.mp.                        |                                    |  |
| 73. nitrofurantoin*.mp.                        |                                    |  |
| 74. penicillin*.mp.                            |                                    |  |
| 75. piperacillin*.mp.                          |                                    |  |

1 2 3 76. pivampicillin\*.mp. 4 77. pivmecillinam\*.mp. 5 78. sulfadimethoxine\*.mp. 6 79. sulfadiazine\*.mp. 7 80. sulfamethizole\*.mp. 8 81. sulfamethoxazole\*.mp. 9 10 82. sulfamethoxypyridazine\*.mp. 11 83. sulfonamide\*.mp. 12 84. sulphadimidine\*.mp. 13 85. sulphonamide\*.mp. 14 86. tetracycline\*.mp. 15 87. vancomycin\*.mp. 16 88. or/44-87 [Combined MeSH & text words for antibiotic treatment] 17 89. exp Pregnancy/ 18 19 90. Pregnancy Complications, Infectious/ 20 91. Pregnant Women/ 21 92. Prenatal Care/ 22 93. Prenatal Diagnosis/ 23 94. (antenatal\* or pre-natal\* or prenatal\*).mp. 24 95. (expect\* adj (female? or mother? or wom#n)).tw,kf. 25 96. pregnan\*.mp. 26 97. or/89-96 [Combined MeSH & text words for pregnancy] 27 98. and/88,97 [Combined searches for antibiotic treatment and pregnancy] 28 29 99. Choice Behavior/ 30 100. \*Consumer Behavior/ 31 101. exp Consumer Participation/ 32 102. Cooperative Behavior/ 33 103. exp Decision Making/ 34 104. Focus Groups/ 35 105. Health Care Surveys/ 36 106. exp Informed Consent/ 37 38 107. Interviews as Topic/ 39 108. Patient Acceptance of Health Care/ 40 109. exp Patient Education as Topic/ 41 110. Patient Participation/ 42 111. Patient Preference/ 43 112. Social Values/ 44 113. "Surveys and Questionnaires"/ 45 114. Treatment Refusal/ 46 115. (15D\* and (HRQoL or QoL or "quality of life")).mp. 47 48 116. ((accept\* or consider\* or choice? or choos\* or chose? or decid\* or decis\* or input\* or involv\* or 49 opinion\* or participat\* or perceiv\* or percepti\* or perspective? or prefer\* or refus\* or respons\* or 50 valuation or value? or valuing or view\*) adj3 (citizen? or client? or consumer? or female? or male? or 51 men or patient? or public or stake?holder\* or user? or wom#n)).tw,kf. 52 117. ((analys#s or valuation? or value? or valuing) adj3 (conjoint or contingent)).tw,kf. 53 118. (choice? adj2 (behavio?r\* or discrete or experiment\*)).tw,kf. 54 119. ((choice? or choos\* or consent\* or decision\*) adj1 informed).tw,kf. 55 56 57 58 59

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| 1        |  |
| 2        |  |
| 3        | 120. ((choice? or choos* or decision*) adj2 (made or make or makes or making or shar* or   |
| 4<br>5   | support*)).tw,kf.  |
| 6        | 121. (EQ 5D or EQ5D or EuroQoL 5D or EuroQoL5D).mp.  |
| 7        | 122. (focus group? or interview* or questionnaire? or survey*).tw,kf.  |
| 8        | 123. gambl*.tw,kf.   |
| 9        | 124. health utilit*.tw,kf.   |
| 10       | 125. HUI.tw,kf.  |
| 11       | 126. (multi?attribute or multi?criteria).tw,kf.  |
| 12<br>13 | 127. (preference? adj1 (elicit* or scor* or state*)).tw,kf.  |
| 14       | 128. prospect theor*.tw,kf.  |
| 15       | 129. (SF 12 or SF 36 or SF 6D or SF12 or SF36 or SF6D).mp.   |
| 16       | 130. (trade off? or tradeoff?).tw,kf.  |
| 17       | 131. (willing* adj2 pay*).tw,kf.   |
| 18       | 132. or/99-131 [Combined MeSH & text words for patient preferences & values]   |
| 19       | 133. and/43,132 [Combined searches for patient preferences & ASB screening]  |
| 20       | 134. and/98,132 [Combined searches for patient preferences & antibiotic treatment and pregnancy]   |
| 21<br>22 | 135. or/133-134 [Combined sets of patient preferences for ASB screening & patient preferences for  |
| 23       | antibiotic treatment in pregnancy]   |
| 24       | 136. Male/ not Female/   |
| 25       | 137. 135 not 136 [Male only records excluded]  |
| 26       | 138. exp Animals/ not (exp Animals/ and Humans/)   |
| 27       | 139. 137 not 138 [Animal only records excluded]  |
| 28       | 140. (comment or editorial or news or newspaper article).pt.   |
| 29<br>30 | 141. (letter not (letter and randomized controlled trial)).pt.   |
| 31       | 142. 139 not (140 or 141) [Opinion pieces excluded]  |
| 32       | 143. case reports.pt.  |
| 33       | 144. 142 not 143 [Case reports excluded]   |
| 34       | 145. limit 144 to (english or french)  |
| 35       | 146. remove duplicates from 145  |
| 36       |  |
| 37       | KQ2: Women's Outcome Valuation   |
| 38<br>39 | KQ2: Women's Outcome ValuationDatabase: Ovid Embase 1974 to 2016 Week 27Date Searched: 4 July 2016Date Updated: 5 September 2017Date Searched: 4 July 2022 |
| 40       | Database: Ovid Embase 1974 to 2016 week 27   |
| 41       | Date Searched: 4 July 2016   |
| 42       | Date Updated: 5 September 2017   |
| 43       | Records Retrieved: 3922  |
| 44       | 1 - secto musica sector itis (   |
| 45       | 1. acute pyelonephritis/   |
| 46       | 2. asymptomatic bacteriuria/   |
| 47<br>48 | 3. asymptomatic infection/ and (bacteriuria* or bladder* or cystitis* or kidney* or pyelo-cystiti* or  |
| 49       | pyelocystiti* or pyelo-nephriti* or pyelonephriti* or urin* or UTI*).mp.   |
| 50       | 4. bacteriuria/  |
| 51       | 5. exp cystitis/   |
| 52       | 6. dysuria/  |
| 53       | 7. kidney infection/<br>8. pyelonephritis/   |
| 54       | 9. urinary tract infections/   |
| 55<br>56 | 10. bacilluria*.tw.  |
| 57       |  |
| 58       |  |
| 59       |  |
| 60       | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml  |
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| 2<br>3   |   |
| 3<br>4   | 11. bacteriuria*.tw.  |
| 4<br>5   | 12. cystiti*.tw.  |
| 6        | <ol><li>13. (cysto-pyeliti* or cystopyeliti*).tw.</li></ol>                           |
| 7        | 14. dysuria*.tw.  |
| 8        | 15. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).tw. |
| 9        | 16. (pyelo-cystiti* or pyelocystiti*).tw.   |
| 10       | 17. (pyelo-nephriti* or pyelonephriti*).tw.   |
| 11       | 18. (UTI or UTIs).tw.   |
| 12       | 19. or/1-18 [Combined Emtree & text words for bacteriuria]                            |
| 13       | 20. *asymptomatic bacteriuria/di, pc  |
| 14       | 21. *acute pyelonephritis/di, pc  |
| 15       | 22. *bacteriuria/di, pc   |
| 16<br>17 | 23. exp *cystitis/di, pc  |
| 17       | 24. diagnostic kit/   |
| 19       | 25. fluorescent antibody technique/   |
| 20       | 26. *kidney infection/di, pc  |
| 21       | 27. mass screening/   |
| 22       | 28. microbial sensitivity test/   |
| 23       | 29. microscopy/   |
| 24       | 30. predictive value/   |
| 25       | 31. *pyelonephritis/di, pc  |
| 26       | 32. "sensitivity and specificity"/  |
| 27       | 33. screening/  |
| 28<br>29 | 34. test strip/   |
| 30       |   |
| 31       | 35. exp urinalysis/   |
| 32       | 36. *urinary tract infection/di, pc   |
| 33       | 37. ((accurac* or diagnostic) adj5 (algorithm* or test*)).tw.                         |
| 34       | 38. culture*.tw.  |
| 35       | 39. (detect* or predict* or screen*).tw.  |
| 36       | 40. diagnostic accurac*.tw.   |
| 37       | 41. (dip slide* or dipslide* or dip stick* or dipstick*).tw.                          |
| 38       | 42. (micro-scopy or microscopy).tw.   |
| 39<br>40 | 43. (microb* adj2 test*).tw.  |
| 40       | 44. ((re-agent* or reagent) adj3 (strip* or test*)).tw.                               |
| 42       | 45. strip* test*.tw.  |
| 43       | 46. urine test*.tw.   |
| 44       | 47. (urinalys* or urine analys*).tw.  |
| 45       | 48. uriscreen.tw.   |
| 46       | 49. or/20-48 [Combined Emtree & text words for screening]                             |
| 47       | 50. and/19,49 [Combined searches for ASB and screening]                               |
| 48       | 51. antibiotic agent/   |
| 49<br>50 | 52. antibiotic prophylaxis/   |
| 50<br>51 | 53. antiinfective agent/  |
| 52       | 54. *asymptomatic bacteriuria/dt, th  |
| 53       | 55. *asymptomatic infection/dt, th  |
| 54       | 56. *bacteriuria/dt, th   |
| 55       | 57. exp *cystitis/dt, th  |
| 56       | 58. drug combination/   |
| 57       |   |
| 58       |   |
| 59       | For poor roview only http://hmienen.hmi.com/rite/about/ruidelines.ubt                 |
| 60       | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xht               |

59. \*kidney infection/dt, th 60. norfloxacin/ 61. penicillin derivative/ 62. \*pyelonephritis/dt, th 63. sulfonamide/ 64. urinary tract antiinfective agent/ 65. \*urinary tract infection/dt, th 66. amoxicillin\*.mp. 67. ampicillin\*.mp. 68. (anti-bacteria\* or antibacteria\*).tw. 69. (anti-biotic\* or antibiotic\*).tw. 70. aztreonam\*.mp. 71. cefadroxil\*.mp. 72. cefepime\*.mp. 73. ceftibuten\*.mp. 74. ceftri?xone\*.mp. 75. cefuroxime\*.mp. 76. cephalexin\*.mp. 77. cephalosporin\*.mp. 78. cephradine\*.mp. 79. clindamycin\*.mp. 80. (co-trimoxazole\* or cotrimoxazole\*).mp. 81. cycloserine\*.mp. 82. fosfomycin\*.mp. 83. gentam#cin\*.mp. 84. nalidixic acid\*.mp. 85. nitrofurantoin\*.mp. 86. penicillin\*.mp. 87. piperacillin\*.mp. 88. pivampicillin\*.mp. 89. pivmecillinam\*.mp. 90. sulfadimethoxine\*.mp. 91. sulfadiazine\*.mp. 92. sulfamethizole\*.mp. 93. sulfamethoxazole\*.mp. 94. sulfamethoxypyridazine\*.mp. 95. sulfonamide\*.mp. 96. sulphadimidine\*.mp. 97. sulphonamide\*.mp. 98. tetracycline\*.mp. 99. vancomycin\*.mp. 100. or/51-99 [Combined Emtree & text words for antibiotic treatment] 101. exp pregnancy/ 102. pregnancy complication/ 103. pregnant woman/ 104. prenatal care/ 105. prenatal diagnosis/ 106. prenatal screening/

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| 3<br>4   | 107. (antenatal* or pre-natal* or prenatal*).mp.   |
| 5        | 108. (expect* adj (female? or mother? or wom#n)).tw.   |
| 6        | 109. pregnan*.mp.  |
| 7        | 110. or/101-109 [Combined Emtree & text words for pregnancy]   |
| 8        | 111. and/100,110 [Combined searches for antibiotic treatment and pregnancy]                            |
| 9        | 112. cooperation/  |
| 10       | 113. *consumer attitude/   |
| 11       | 114. exp decision making/  |
| 12       | 115. health care survey/   |
| 13       | 116. informed consent/   |
| 14<br>15 | 117. exp interview/  |
| 16       | 118. exp patient attitude/   |
| 17       | 119. patient education/  |
| 18       | 120. exp questionnaire/  |
| 19       | 121. social psychology/  |
| 20       | 122. treatment refusal/  |
| 21       | 123. (15D* and (HRQoL or QoL or "quality of life")).mp.  |
| 22       | 124. ((accept* or consider* or choice? or choos* or chose? or decid* or decis* or input* or involv* or |
| 23       | opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or refus* or respons* or   |
| 24<br>25 | valuation or value? or valuing or view*) adj3 (citizen? or client? or consumer? or female? or male? or |
| 26       | men or patient? or public or stake?holder* or user? or wom#n)).tw,kw.                                  |
| 27       | 125. (choice? adj2 (behavio?r* or discrete or experiment*)).tw,kw.                                     |
| 28       | 126. ((choice? or choos* or consent* or decision*) adj1 informed).tw,kw.                               |
| 29       | 127. ((choice? or choos* or decision*) adj2 (made or make or makes or making or shar* or               |
| 30       | support*)).tw,kw.  |
| 31       | 128. (EQ 5D or EQ5D or EuroQoL 5D or EuroQoL5D).mp.  |
| 32       | 129. (focus group? or interview* or questionnaire? or survey*).tw,kw.                                  |
| 33<br>34 | 130. gambl*.tw,kw.   |
| 35       | 131. health utilit*.tw,kw.   |
| 36       | 132. HUI.tw,kw.  |
| 37       | 133. (multi?attribute or multi?criteria).tw,kw.  |
| 38       | 134. (preference? adj1 (elicit* or scor* or state*)).tw,kw.  |
| 39       | 135. prospect theor*.tw,kw.  |
| 40       | 136. (SF 12 or SF 36 or SF 6D or SF12 or SF36 or SF6D).mp.   |
| 41       | 137. (trade off? or tradeoff?).tw,kw.  |
| 42<br>43 | 138. (willing* adj2 pay*).tw,kw.   |
| 44       | 139. or/112-138 [Combined Emtree & text words for patient preferences & values]                        |
| 45       | 140. and/50,139 [Combined searches for patient preferences & ASB screening]                            |
| 46       | 141. and/111,139 [Combined searches for patient preferences & antibiotic treatment and pregnancy]      |
| 47       | 142. or/140-141 [Combined sets of patient preferences for ASB screening & patient preferences for      |
| 48       | antibiotic treatment in pregnancy]   |
| 49       | 143. Male/ not (Female/ and Male/)   |
| 50       | 144. 142 not 143 [Male only records excluded]  |
| 51       | 145. animals/ not (animals/ and humans/)   |
| 52<br>53 | 146. 144 not 145 [Animal only records excluded]  |
| 55       | 147. (conference* or editorial or letter).pt.  |
| 55       | 148. 146 not 147 [Excluded publication types – RF note: will search conference proceedings             |
| 56       | separately with different strategy]  |
| 57       |  |
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| 60       | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                              |

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| 3        | 149. case report/ or case report*.ti.                            |  |  |
| 4        | 150. 148 not 149 [Case reports excluded]                         |  |  |
| 5        | 151. limit 150 to (english or french)                            |  |  |
| 6        | 152. remove duplicates from 151                                  |  |  |
| 7        | 152. Temove duplicates from 151                                  |  |  |
| 8        |  |  |  |
| 9<br>10  | KQ2: Women's Outcome Valuation                                   |  |  |
| 11       | Database: Wiley Cochrane Library                                 |  |  |
| 12       | Date Searched: 5 July 2016                                       |  |  |
| 13       | •  |  |  |
| 14       | Date Updated: 5 September 2017                                   |  |  |
| 15       | Records Retrieved: 45 in Cochrane Database of                    |  |  |
| 16       | Records Retrieved: 1 in Database of Abstracts                    |  |  |
| 17       | Records Retrieved: 321 in Cochrane Central Re                    | gister of Controlled Trials (CENTRAL)                |  |
| 18       | Records Retrieved: 4 in Cochrane Methodology                     | / Register   |  |
| 19       | Records Retrieved: 14 in Economic Evaluations                    | Database   |  |
| 20       |  |  |  |
| 21       | #1 [mh ^"Asymptomatic Infections"] and                           | (bacteriuria* or bladder* or cystitis* or kidney* or |  |
| 22       | pyelo-cystiti* or pyelocystiti* or pyelo-nephriti                |  |  |
| 23       | #2 [mh ^Bacteriuria]   |  |  |
| 24<br>25 | #3 [mh Cystitis]   |  |  |
| 26       | #4 [mh ^Dysuria]   |  |  |
| 27       | #5 [mh ^Pyelonephritis]  |  |  |
| 28       | #6 [mh ^"Urinary Tract Infections"]                              |  |  |
| 29       |  |  |  |
| 30       | #7 bacilluria*:ti,ab,kw  |  |  |
| 31       | #8 bacteriuria*:ti,ab,kw   |  |  |
| 32       | #9 cystiti*:ti,ab,kw   |  |  |
| 33       | #10 (cysto-pyeliti* or cystopyeliti*):ti,ab,kv                   | V  |  |
| 34       | #11 dysuria*:ti,ab,kw  |  |  |
| 35       |  | urin* or kidney* or urin* or urogenita*)):ti,ab,kw   |  |
| 36       | #13 (pyelo-cystiti* or pyelocystiti*):ti,ab,kv                   |  |  |
| 37       | #14 (pyelo-nephriti* or pyelonephriti*):ti,a                     | b,kw   |  |
| 38       | #15 (UTI or UTIs):ti,ab,kw                                       |  |  |
| 39<br>40 | #16 {or #1-#15}  |  |  |
| 40       | #17 [mh ^"Antibody-Coated Bacteria Test,                         | Urinary"]  |  |
| 42       | #18 [mh ^Bacteriuria [mj]/DI,PC,MI,UR]                           |  |  |
| 43       | #19 [mh Cystitis [mj]/DI,PC,MI,UR]                               |  |  |
| 44       | #20 [mh ^"Mass Screening"]                                       |  |  |
| 45       | #21 [mh ^"Microbial Sensitivity Tests"]                          |  |  |
| 46       | #22 [mh ^Microscopy]   |  |  |
| 47       | #23 [mh ^"Predictive Value of Tests"]                            |  |  |
| 48       | #24 [mh ^Pyelonephritis [mj]/DI,PC,MI,UR]                        |  |  |
| 49       | #25 [mh "Reagent Kits, Diagnostic"]                              |  |  |
| 50       | #26 [mh "Reagent Strips"]  |  |  |
| 51       | #20 [mh /"Sensitivity and Specificity"]                          |  |  |
| 52       | #27 [min * Sensitivity and Specificity ]<br>#28 [mh ^Urinalysis] |  |  |
| 53<br>54 | #28 [mh ^"Urinary Tract Infections" [mj]/D                       |  |  |
| 54<br>55 |  |  |  |
| 56       | #30 ((accurac* or diagnostic) near/5 (algor                      | unin of lest jj.li,ab,kw                             |  |
| 57       |  |  |  |
| 58       |  |  |  |
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| 60       | For peer review only - http://bmj                                | open.bmj.com/site/about/guidelines.xhtml             |  |
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| 2        |            |   |
| 3        | #21        | "diagnostic accurac*", ti ab ku                                   |
| 4        | #31        | "diagnostic accurac*":ti,ab,kw                                    |
| 5        | #32        | culture*:ti,ab,kw   |
| 6        | #33        | (detect* or predict* or screen*):ti,ab,kw                         |
| 7        | #34        | ("dip slide*" or dipslide* or "dip stick*" or dipstick*):ti,ab,kw |
| 8        | #35        | (micro-scopy or microscopy):ti,ab,kw                              |
| 9        | #36        | (microb* near/2 test*):ti,ab,kw                                   |
| 10       | #37        | ((re-agent* or reagent) near/3 (strip* or test*)):ti,ab,kw        |
| 11       | #38        | "strip* test*":ti,ab,kw   |
| 12       | #39        | "urine test*":ti,ab,kw  |
| 13       | #40        | (urinalys* or "urine analys*"):ti,ab,kw                           |
| 14       | #41        | uriscreen:ti,ab,kw  |
| 15       | #42        | {or #17-#41}  |
| 16<br>17 | #43        | #16 and #42   |
| 17<br>18 | #44        | [mh ^"Anti-Bacterial Agents"]                                     |
| 18       | #45        | [mh ^"Antibiotic Prophylaxis"]                                    |
| 20       | #43<br>#46 | [mh ^"Anti-Infective Agents, Urinary"]                            |
| 20       |            |   |
| 22       | #47        | [mh ^"Asymptomatic Infections"/DT,TH]                             |
| 23       | #48        | [mh ^Bacteriuria [mj]/DT,TH]                                      |
| 24       | #49        | [mh ^"Drug Therapy, Combination"]                                 |
| 25       | #50        | [mh ^Norfloxacin]   |
| 26       | #51        | [mh Penicillins]  |
| 27       | #52        | [mh Sulfonamides]   |
| 28       | #53        | [mh ^"Urinary Tract Infections" [mj]/DT,TH]                       |
| 29       | #54        | amoxicillin*:ti,ab,kw   |
| 30       | #55        | ampicillin*:ti,ab,kw  |
| 31       | #56        | ("anti-bacteria*" or antibacteria*):ti,ab,kw                      |
| 32       | #57        | ("anti-biotic*" or antibiotic*):ti,ab,kw                          |
| 33       | #58        | aztreonam*:ti,ab,kw   |
| 34       | #59        | cefadroxil*:ti,ab,kw  |
| 35       | #60        | cefepime*:ti,ab,kw  |
| 36<br>37 | #61        | ceftibuten*:ti,ab,kw  |
|          |            | ceftri?xone*:ti,ab,kw   |
| 38<br>39 | #62<br>#62 |   |
| 40       | #63        | cefuroxime*:ti,ab,kw  |
| 41       | #64        | cephalexin*:ti,ab,kw  |
| 42       | #65        | cephalosporin*:ti,ab,kw   |
| 43       | #66        | cephradine*:ti,ab,kw  |
| 44       | #67        | clindamycin*:ti,ab,kw   |
| 45       | #68        | ("co-trimoxazole*" or cotrimoxazole*):ti,ab,kw                    |
| 46       | #69        | cycloserine*:ti,ab,kw   |
| 47       | #70        | fosfomycin*:ti,ab,kw  |
| 48       | #71        | gentam?cin*:ti,ab,kw  |
| 49       | #72        | "nalidixic acid*":ti,ab,kw  |
| 50       | #73        | nitrofurantoin*:ti,ab,kw  |
| 51       | #74        | penicillin*:ti,ab,kw  |
| 52       | #75        | piperacillin*:ti,ab,kw  |
| 53       | #76        | pivampicillin*:ti,ab,kw   |
| 54<br>55 | #77        | pivmecillinam*:ti,ab,kw   |
| 55<br>56 | #78        | sulfadimethoxine*:ti,ab,kw  |
| 50<br>57 | #/0        |   |
| 58       |            |   |
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| 1<br>2   |       |   |
| 2        |       |   |
| 4        | #79   | sulfadiazine*:ti,ab,kw  |
| 5        | #80   | sulfamethizole*:ti,ab,kw  |
| 6        | #81   | sulfamethoxazole*:ti,ab,kw  |
| 7        | #82   | sulfamethoxypyridazine*:ti,ab,kw  |
| 8        | #83   | sulfonamide*:ti,ab,kw   |
| 9        | #84   | sulphadimidine*:ti,ab,kw  |
| 10       | #85   | sulphonamide*:ti,ab,kw  |
| 11<br>12 | #86   | tetracycline*:ti,ab,kw  |
| 12       | #87   | vancomycin*:ti,ab,kw  |
| 14       | #88   | {or #44-#87}  |
| 15       | #89   | [mh Pregnancy]  |
| 16       | #90   | [mh ^"Pregnancy Complications, Infectious"]   |
| 17       | #91   | [mh ^"Pregnant Women"]  |
| 18       | #92   | [mh ^"Prenatal Care"]   |
| 19       | #93   | [mh ^"Prenatal Diagnosis"]  |
| 20       | #94   | (antenatal* or "pre-natal*" or prenatal*):ti,ab,kw  |
| 21       | #95   | (expect* near/1 (female* or mother* or wom?n)):ti,ab,kw   |
| 22       | #96   | pregnan*:ti,ab,kw   |
| 23<br>24 | #97   | {or #89-#96}  |
| 24       | #98   | #88 and #97   |
| 26       | #99   | [mh ^"Choice Behavior"]   |
| 27       | #100  | [mh ^"Consumer Behavior" [mj]]  |
| 28       | #101  | [mh "Consumer Participation"]   |
| 29       | #102  | [mh ^"Cooperative Behavior"]  |
| 30       | #103  | [mh "Decision Making"]  |
| 31       | #104  | [mh ^"Focus Groups"]  |
| 32       | #105  | [mh ^"Health Care Surveys"]   |
| 33       | #106  | [mh "Informed Consent"]   |
| 34<br>35 | #107  | [mh ^"Interviews as Topic"]   |
| 36       | #108  | [mh ^"Patient Acceptance of Health Care"]   |
| 37       | #109  | [mh "Patient Education as Topic"]   |
| 38       | #110  | [mh ^"Patient Participation"]   |
| 39       | #111  | [mh ^"Patient Preference"]  |
| 40       | #112  | [mh ^"Social Values"]   |
| 41       | #113  | [mh ^"Surveys and Questionnaires"]  |
| 42       | #114  | [mh ^"Treatment Refusal"]   |
| 43       | #115  | (15D* and (HRQoL or QoL or "quality of life")):ti,ab,kw   |
| 44<br>45 | #116  | (accept* or consider* or choice? or choos* or chose? or decid* or decis* or input* or involv*     |
| 45<br>46 |       | nion* or participat* or perceiv* or percepti* or perspective? or prefer* or refus* or respons* or |
| 40       | -     | ion or value? or valuing or view*) near/3 (citizen? or client? or consumer? or female? or male?   |
| 48       |       | n or patient? or public or stake?holder* or user? or wom?n)):ti,ab,kw                             |
| 49       | #117  | ((analys?s or valuation? or value? or valuing) near/3 (conjoint or contingent)):ti,ab,kw          |
| 50       | #118  | (choice? near/2 (behavio?r* or discrete or experiment*)):ti,ab,kw                                 |
| 51       | #119  | ((choice? or choos* or consent* or decision*) near/1 informed):ti,ab,kw                           |
| 52       | #115  | ((choice? or choos* or decision*) near/2 (made or make or makes or making or shar* or             |
| 53       |       | rt*)):ti,ab,kw  |
| 54       | #121  | ("EQ 5D" or EQ5D or "EuroQoL 5D" or EuroQoL5D):ti,ab,kw   |
| 55<br>56 | #121  | ("focus group?" or interview* or questionnaire? or survey*):ti,ab,kw                              |
| 57       | 11775 | ( isous Broup: of interview of questionnume; of survey Juliab, ww                                 |
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| 60       |       | For peer review only - http://bmiopen.hmi.com/site/about/guidelines.xhtml                         |

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| 2        |  |
| 3        | #123 gambl*:ti,ab,kw   |
| 4        | #124 "health utilit*":ti,ab,kw   |
| 5        | #125 HUI:ti,ab,kw  |
| 6        | #126 ("multi-attribute" or "multi-criteria" or multiattribute or multicriteria):ti,ab,kw     |
| 7        | #120 (preference? near/1 (elicit* or scor* or state*)):ti,ab,kw                              |
| 8        |  |
| 9        |  |
| 10<br>11 | #129 ("SF 12" or "SF 36" or "SF 6D" or SF12 or SF36 or SF6D):ti,ab,kw                        |
| 12       | #130 ("trade off?" or tradeoff?):ti,ab,kw  |
| 13       | #131 (willing* near/2 pay*):ti,ab,kw   |
| 14       | #132 {or #99-#131}   |
| 15       | #133 #43 and #132  |
| 16       | #134 #98 and #132  |
| 17       | #135 #133 or #134  |
| 18       |  |
| 19       |  |
| 20       | KQ2: Women's Outcome Valuation   |
| 21       | Database: Ovid PsycINFO 1806 to June Week 5 2016   |
| 22       | Date Searched: 5 July 2016   |
| 23       | Date Updated: 5 September 2017 🚫   |
| 24       | Records Retrieved: 113   |
| 25       |  |
| 26<br>27 | 1. Bacterial Disorders/ and (bladder* or genitourin* or kidney* or urin* or urogenita*).mp.  |
| 27       |  |
| 28       | 2. Infectious Disorders/ and (bladder* or genitourin* or kidney* or urin* or urogenita*).mp. |
| 30       | 3. Urinary Function Disorders/ and infection*.mp.  |
| 31       | 4. Urogenital Disorders/ and infection*.mp.  |
| 32       | 5. bacilluria*.mp.   |
| 33       | 6. bacteriuria*.mp.  |
| 34       | 7. cystiti*.mp.  |
| 35       | 8. (cysto-pyeliti* or cystopyeliti*).mp.   |
| 36       | 9. dysuria*.mp.  |
| 37       | 10. (infection* adj2 (bladder* or genitourin* or kidney* or urin* or urogenita*)).mp.        |
| 38       | 11. (pyelo-cystiti* or pyelocystiti*).mp.  |
| 39       | 12. (pyelo-nephriti* or pyelonephriti*).mp.  |
| 40       | 13. (UTI or UTIs).mp.  |
| 41       | 14. or/1-13 [Combined subject headings & text words for bacteriuria]                         |
| 42<br>43 | 15. Health Screening/  |
| 45<br>44 | 16. Screening/   |
| 44       | 17. Screening Tests/   |
| 46       | 18. Test Reliability/  |
| 47       | 19. exp Test Validity/   |
| 48       | 20. Urinalysis/  |
| 49       | 21. ((accurac* or diagnostic) adj5 (algorithm* or test*)).ti,ab.                             |
| 50       |  |
| 51       | 22. diagnostic accurac*.ti,ab.   |
| 52       | 23. culture*.ti,ab.  |
| 53       | 24. (detect* or predict* or screen*).ti,ab.  |
| 54       | 25. (dip slide* or dipslide* or dip stick* or dipstick*).ti,ab.                              |
| 55       | 26. (micro-scopy or microscopy).ti,ab.   |
| 56       | 27. (microb* adj2 test*).ti,ab.  |
| 57       |  |
| 58       |  |
| 59       |  |

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| 3        | 28. ((re-agent* or reagent) adj3 (strip* or test*)).ti,ab.                     |
| 4        |  |
| 5        | 29. strip* test*.ti,ab.  |
| 6        | 30. urine test*.ti,ab.   |
| 7        | 31. (urinalys* or urine analys*).ti,ab.  |
| 8        | 32. uriscreen.ti,ab.   |
| 9        | 33. or/15-32 [Combined subject headings & text words for screening]            |
| 10       | 34. and/14,33 [Combined searches for ASB and screening]                        |
| 11<br>12 | 35. antibiotics/   |
| 12       | 36. penicillins/   |
| 14       | 37. amoxicillin*.mp.   |
| 15       | 38. ampicillin*.mp.  |
| 16       | 39. (anti-bacteria* or antibacteria*).mp.                                      |
| 17       | 40. (anti-biotic* or antibiotic*).mp.  |
| 18       | 41. aztreonam*.mp.   |
| 19       | 42. cefadroxil*.mp.  |
| 20       | 43. cefepime*.mp.  |
| 21       | 44. ceftibuten*.mp.  |
| 22       | 45. ceftri?xone*.mp.   |
| 23<br>24 | 46. cefuroxime*.mp.  |
| 24       | 47. cephalexin*.mp.  |
| 26       | 48. cephalosporin*.mp.   |
| 27       | 49. cephradine*.mp.  |
| 28       | 50. clindamycin*.mp.   |
| 29       | 51. (co-trimoxazole* or cotrimoxazole*).mp.                                    |
| 30       | 52. cycloserine*.mp.   |
| 31       | 53. fosfomycin*.mp.  |
| 32       | 54. gentam#cin*.mp.  |
| 33       | 55. nalidixic acid*.mp.  |
| 34<br>35 | 56. nitrofurantoin*.mp.  |
| 36       | 57. penicillin*.mp.  |
| 37       | 58. piperacillin*.mp.  |
| 38       | 59. pivampicillin*.mp.   |
| 39       | 60. pivmecillinam*.mp.   |
| 40       | 61. sulfadimethoxine <sup>*</sup> .mp.   |
| 41       | 62. sulfadiazine*.mp.  |
| 42       | 63. sulfamethizole*.mp.  |
| 43       | 64. sulfamethoxazole*.mp.  |
| 44       | 65. sulfamethoxypyridazine*.mp.  |
| 45<br>46 | 66. sulfonamide*.mp.   |
| 47       | 67. sulphadimidine*.mp.  |
| 48       | 68. sulphonamide*.mp.  |
| 49       | 69. tetracycline*.mp.  |
| 50       | 70. vancomycin*.mp.  |
| 51       | 71. or/35-70 [Combined subject headings & text words for antibiotic treatment] |
| 52       | 72. adolescent pregnancy/  |
| 53       | 73. pregnancy/   |
| 54<br>55 | 74. prenatal care/   |
| 55<br>56 | 75. (antenatal* or pre-natal* or prenatal*).ti,ab.                             |
| 56<br>57 | יס. נמונכוומנמו טו פרביומנמו טו פרפוומנמו ז.נו,מט.                             |
| 58       |  |
| 59       |  |
| 60       | For peer review only - http://bmjopen.bmj.com/site/about/guidelines            |
|          |  |

| 1        |   |
|----------|---|
| 2<br>3   |   |
| 4        | 76. (expect* adj (female? or mother? or wom#n)).ti,ab.  |
| 5        | 77. pregnan*.mp.  |
| 6        | 78. or/72-77 [Combined subject headings & text words for pregnancy]                                     |
| 7        | 79. and/71,78 [Combined searches for antibiotic treatment and pregnancy]                                |
| 8        | 80. Choice Behavior/  |
| 9        | 81. Client Attitudes/   |
| 10       | 82. Client Participation/   |
| 11       | 83. Client Rights/  |
| 12<br>13 | 84. Cooperation/  |
| 13       | 85. Decision Making/  |
| 15       | 86. *Consumer Behavior/   |
| 16       | 87. Informed Consent/   |
| 17       | 88. Interviews/   |
| 18       | 89. Preferences/  |
| 19       | 90. Questionnaires/   |
| 20       | 91. Social Values/  |
| 21       | 92. Surveys/  |
| 22       | 93. Treatment Barriers/   |
| 23<br>24 | 94. Treatment Refusal/  |
| 25       | 95. (15D* and (HRQoL or QoL or "quality of life")).mp.  |
| 26       | 96. ((accept* or consider* or choice? or choos* or chose? or decid* or decis* or input* or involv* or   |
| 27       | opinion* or participat* or perceiv* or percepti* or perspective? or prefer* or respons* or valuation or |
| 28       | value? or valuing or view*) adj3 (citizen? or client? or consumer? or female? or male? or men or        |
| 29       | patient? or public or stake?holder* or user? or wom#n)).ti,ab.  |
| 30       | 97. ((analys#s or valuation? or value? or valuing) adj3 (conjoint or contingent)).ti,ab.                |
| 31       | 98. (choice? adj2 (behavio?r* or discrete or experiment*)).mp.  |
| 32<br>33 | 99. ((choice? or choos* or consent* or decision*) adj1 informed).ti,ab.                                 |
| 33<br>34 | 100. ((choice? or choos* or decision*) adj2 (made or make or makes or making or shar* or                |
| 35       | support*)).ti,ab.   |
| 36       | 101. (EQ 5D or EQ5D or EuroQoL 5D or EuroQoL5D).mp.   |
| 37       | 102. (focus group? or interview* or questionnaire? or survey*).ti,ab.                                   |
| 38       | 103. gambl*.ti,ab.  |
| 39       | 104. health utilit*.ti,ab.  |
| 40       | 105. HUI.mp.  |
| 41<br>42 | 106. (multi?attribute or multi?criteria).mp.  |
| 42<br>43 | 107. (preference? adj1 (elicit* or scor* or state*)).mp.  |
| 44       | 108. prospect theor*.ti,ab.   |
| 45       | 109. (SF 12 or SF 36 or SF 6D or SF12 or SF36 or SF6D).mp.  |
| 46       | 110. (trade off? or tradeoff?).ti,ab.   |
| 47       | 111. (willing* adj2 pay*).ti,ab.  |
| 48       | 112. or/80-111 [Combined subject & text words for patient preferences & values]                         |
| 49       | 113. and/34,112 [Combined searches for patient preferences & ASB screening]                             |
| 50       | 114. and/79,112 [Combined searches for patient preferences & antibiotic treatment and pregnancy]        |
| 51<br>52 | 115. or/113-114 [Combined sets of patient preferences for ASB screening & patient preferences for       |
| 52       | antibiotic treatment in pregnancy]  |
| 54       | 116. (boy* or male* or men).ti.   |
| 55       | 117. 115 not 116 [Male records excluded]  |
| 56       | 118. (case report* or comment* or editorial or letter).ti.  |
| 57       |   |
| 58       |   |
| 59<br>60 | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                               |
| 60       | For peer review only inter, / only open.only.com/site/about/guidelines.knith                            |

| 1        |   |
|----------|---|
| 2        |   |
| 3        | 119. 117 not 118 [Opinion pieces & case reports excluded]   |
| 4        | 120. limit 119 to (english or french)   |
| 5        | 121. remove duplicates from 120   |
| 6        | 121. Temove dupicates from 120  |
| 7        |   |
| 8        |   |
| 9        | KQ2: Women's Outcome Valuation  |
| 10       | Database: CINAHL Plus with Full Text (1937 to the present) via EBSCOhost  |
| 11       | Date Searched: 5 July 2016  |
| 12       | Date Updated: 5 September 2017  |
| 13       | Records Retrieved: 872  |
| 14       |   |
| 15       | S1. (MH "Bacteriuria")  |
| 16       |   |
| 17       | S2. (MH "Cystitis+")  |
| 18       | S3. (MH "Dysuria")  |
| 19       | S4. (MH "Pyelonephritis")   |
| 20       | S5. (MH "Urinary Tract Infections")   |
| 21       | S6. bacilluria*   |
| 22       | S7. bacteriuria*  |
| 23<br>24 | S8. cystiti*  |
| 25       | S9. "cysto-pyeliti*" or cystopyeliti*   |
| 26       | S10. dysuria*   |
| 27       | S11. (infection* N2 (bladder* or genitourin* or kidney* or urin* or urogenita*))                                |
| 28       | S12. "pyelo-cystiti*" or pyelocystiti*  |
| 29       | S13. "pyelo-nephriti*" or pyelonephriti*  |
| 30       | S14. UTI or UTIs  |
| 31       | S14. OT OF OT S13<br>S15. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 |
| 32       |   |
| 33       | S16. (MM "Bacteriuria/DI/PC/MI/UR")   |
| 34       | S17. (MM "Cystitis+/DI/MI/PC/UR")   |
| 35       | S18. (MH "Fluorescent Antibody Technique")  |
| 36       | S19. (MH "Health Screening")  |
| 37       | S20. (MH "Microbial Culture and Sensitivity Tests")   |
| 38       | S21. (MH "Microscopy")  |
| 39       | S22. (MH "Predictive Value of Tests")   |
| 40       | S23. (MM "Pyelonephritis/DI/PC/MI/UR")  |
| 41       | S24. (MH "Reagent Kits, Diagnostic+")   |
| 42       | S25. (MH "Sensitivity and Specificity")   |
| 43       | S26. (MH "Urinalysis")  |
| 44<br>45 | S27. (MM "Urinary Tract Infections/DI/PC/MI/UR")  |
| 43<br>46 | S28. (accurac* or diagnostic) N5 (algorithm* or test*)  |
| 40       | S29. "diagnostic accurac*"  |
| 48       | S29. diagnostic accuración<br>S30. culture*   |
| 49       |   |
| 50       | S31. detect* or predict* or screen*   |
| 51       | S32. "dip slide*" or dipslide* or "dip stick*" or dipstick*   |
| 52       | S33. "micro-scopy" or microscopy  |
| 53       | S34. microb* N2 test*   |
| 54       | S35. ("re-agent*" or reagent) N3 (strip* or test*)  |
| 55       | S36. "strip* test*"   |
| 56       | S37. "urine test*"  |
| 57       |   |
| 58       |   |
| 59       | For poor review only, http://bmiepon.hmi.com/site/about/guidelines.yhtml  |
| ~~~      | For beer review only - http://pmionon.hmi.com/site/about/suidelines.yhtml                                       |

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| 1        |  |
|----------|--|
| 2        |  |
| 3        | S38. urinalys* or "urine analys*"  |
| 4        | S39. uriscreen   |
| 5        | S40. S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 |
| 6        | OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39                 |
| 7        | S41. S15 AND S40 [Combined searches for ASB and screening]                                   |
| 8        | S42. (MH "Antibiotic Prophylaxis")   |
| 9        |  |
| 10<br>11 | S43. (MH "Antibiotics")  |
| 12       | S44. (MH "Antibiotics, Combined")  |
| 13       | S45. (MH "Antiinfective Agents, Urinary+")   |
| 14       | S46. (MM "Bacteriuria/DT/TH")  |
| 15       | S47. (MH "Penicillins")  |
| 16       | S48. (MH "Sulfonamides")   |
| 17       | S49. (MM "Urinary Tract Infections/DT/TH")   |
| 18       | S50. amoxicillin*  |
| 19       | S51. ampicillin*   |
| 20       | S52. ("anti-bacteria*" or antibacteria*)   |
| 21       | S53. ("anti-biotic*" or antibiotic*)   |
| 22       | S54. aztreonam*  |
| 23       | S55. cefadroxil*   |
| 24       | S56. cefepime*   |
| 25       | S57. ceftibuten*   |
| 26       | S58. ceftri?xone*  |
| 27       | S59. cefuroxime*   |
| 28<br>29 |  |
| 30       | S60. cephalexin*   |
| 31       | S61. cephalosporin*  |
| 32       | S62. cephradine*   |
| 33       | S63. clindamycin*  |
| 34       | S64. ("co-trimoxazole*" or cotrimoxazole*)   |
| 35       | S65. cycloserine*  |
| 36       | S66. fosfomycin*   |
| 37       | S67. gentam?cin*   |
| 38       | S68. "nalidixic acid*"   |
| 39       | S69. nitrofurantoin*<br>S70. penicillin*<br>S71. piperacillin*                               |
| 40       | S70. penicillin*   |
| 41       | S71. piperacillin*   |
| 42<br>43 | S72. pivampicillin*  |
| 43<br>44 | S73. pivmecillinam*  |
| 44       | S74. sulfadimethoxine*   |
| 46       | S75. sulfadiazine*   |
| 47       | S76. sulfamethizole*   |
| 48       | S77. sulfamethoxazole*   |
| 49       | S78. sulfamethoxypyridazine*   |
| 50       | S79. sulfonamide*  |
| 51       | S80. sulphadimidine*   |
| 52       | S80. sulphaamide*  |
| 53       |  |
| 54       | S82. tetracycline*   |
| 55       | S83. vancomycin*   |
| 56       |  |
| 57<br>58 |  |

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\$84, \$42 OR \$43 OR \$44 OR \$45 OR \$46 OR \$47 OR \$48 OR \$49 OR \$50 OR \$51 OR \$52 OR \$53 OR \$54 OR \$55 OR \$56 OR \$57 OR \$58 OR \$59 OR \$60 OR \$61 OR \$62 OR \$63 OR \$64 OR \$65 OR \$66 OR \$67 5 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 6 OR S81 OR S82 OR S83 S85. (MH "Expectant Mothers") 8 S86. (MH "Pregnancy+") 9 10 S87. (MH "Pregnancy Complications, Infectious") 11 S88. (MH "Prenatal Care") 12 S89. (MH "Prenatal Diagnosis") 13 S90. antenatal\* or "pre-natal\*" or prenatal\* 14 S91. expect\* N1 (female? or mother? or wom?n) 15 S92. pregnan\* 16 S93. S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 17 S94. S84 AND S93 18 19 S95. (MH "Consumer Participation") 20 S96. (MH "Consensus") 21 S97. (MH "Consent+") 22 S98. (MH "Cooperative Behavior") 23 S99. (MH "Decision Making") 24 S100. (MH "Decision Making, Patient") 25 S101. (MH "Dissent and Disputes+") 26 ielieu S102. (MH "Focus Groups") 27 S103. (MH "Interviews+") 28 29 S104. (MH "Patient Education") 30 S105. (MH "Quality of Health Care") 31 S106. (MH "Questionnaires+") 32 S107. (MH "Self Report") 33 S108. (MH "Social Values+") 34 S109. (MH "Surveys") 35 S110. (MH "Treatment Refusal") 36 S111. (15D\* and (HRQoL or QoL or "quality of life")) 37 S112. ((accept\* or consider\* or choice\* or choos\* or chose\* or decid\* or decis\* or input\* or involv\* 38 39 or opinion\* or participat\* or perceiv\* or percepti\* or perspective\* or prefer\* or refus\* or respons\* or 40 valuation or value\* or valuing or view\*) N3 (citizen\* or client\* or consumer\* or female\* or male\* or 41 men or patient\* or public or "stake-holder\*" or stakeholder\* or user\* or wom?n)) 42 S113. ((analys?s or valuation\* or value\* or valuing) N3 (conjoint or contingent)) 43 S114. (choice\* N2 (behavio\* or discrete or experiment\*)) 44 S115. ((choice\* or choos\* or consent\* or decision\*) N1 informed) 45 S116. ((choice\* or choos\* or decision\*) N2 (made or make or makes or making or shar\* or support\*)) 46 S117. ("EQ 5D" or EQ5D or "EuroQoL 5D" or EuroQoL5D) 47 48 S118. ("focus group\*" or interview\* or questionnaire\* or survey\*) 49 S119. gambl\* 50 S120. "health utilit\*" 51 S121. HUI 52 S122. ("multi-attribute" or "multi-criteria" or multiattribute or multicriteria) 53 S123. (preference\* N1 (elicit\* or scor\* or state\*)) 54 S124. "prospect theor\*" 55 S125. ("SF 12" or "SF 36" or "SF 6D" or SF12 or SF36 or SF6D) 56 57 58 59

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| 2        |   |
|----------|---|
| 3<br>4   | S126. ("trade off*" or tradeoff*)   |
| 5        | S127. (willing* N2 pay*)  |
| 6        | S128. S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR                    |
| 7        | S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR                     |
| 8        | S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127                        |
| 9        | S129. S41 AND S128  |
| 10       | \$130. \$94 AND \$128   |
| 11       | \$131. \$129 OR \$130   |
| 12       | S132. MH "Male" NOT ((MH "Female") AND (MH "Male"))   |
| 13       | \$133. \$131 NOT \$132  |
| 14       | S133. ((MH "Vertebrates+") NOT MH Human)  |
| 15       | S135. S133 NOT S134   |
| 16       |   |
| 17       | S136. Limiters - Publication Type: Anecdote, Case Study, Commentary, Editorial, Letter                      |
| 18       | S137. S135 NOT S136   |
| 19       | S138. S135 NOT S136 Narrow by Language: - english [RF: No French records in results to include]             |
| 20       |   |
| 21<br>22 |   |
| 22       | KQ2: Women's Outcome Valuation  |
| 24       | Database: PubMed via NCBI Entrez (1946 to Present)  |
| 25       | Date Searched: 5 July 2016  |
| 26       | Records Retrieved: 65   |
| 27       |   |
| 28       | ((((((("asymptomatic infections"[mh] AND (("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields])          |
| 29       | OR ("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields] OR "bacteriurias"[All Fields]) OR ("urinary      |
| 30       | bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All          |
| 31       | Fields] OR "bladder"[All Fields]) OR ("cystitis"[MeSH Terms] OR "cystitis"[All Fields]) OR                  |
| 32       | ("kidney"[MeSH Terms] OR "kidney"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR          |
| 33       | "kidneys"[All Fields]) OR ("pyelocystitis"[MeSH Terms] OR "pyelocystitis"[All Fields]) OR                   |
| 34<br>35 | ("pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]) OR ("urinary tract"[MeSH Terms] OR           |
| 36       | ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR |
| 37       | ("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) OR UTI[all] OR ("urinary tract          |
| 38       | infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields])     |
| 39       | OR "urinary tract infections"[All Fields] OR "utis"[All Fields]))) OR "bacteriuria"[MeSH Terms:noexp]       |
| 40       | OR "cystitis"[MeSH Terms] OR "dysuria"[MeSH Terms:noexp] OR "pyelonephritis"[MeSH                           |
| 41       | Terms:noexp] OR "Urinary Tract Infections"[mh:noexp] OR bacilluria[tiab] OR bacteriuria[tiab] OR            |
| 42       | bacteriurias[tiab] OR "bladder infection"[tiab] OR "bladder infections"[tiab] OR cystitis[tiab] OR          |
| 43       |   |
| 44       | cystopyelitis[tiab] OR dysuria[tiab] OR "genito-urinary infection"[tiab] OR "genitourinary                  |
| 45       | infection"[tiab] OR "genito-urinary infections"[tiab] OR "genitourinary infections"[tiab] OR "kidney        |
| 46       | infection"[tiab] OR "kidney infections"[tiab] OR "pyelo-nephritis"[tiab] OR pyelocystitis[tiab] OR          |
| 47<br>48 | pyelonephritis[tiab] OR "urinary infection"[tiab] OR "urinary infections"[tiab] OR "urogenital              |
| 48<br>49 | infection"[tiab] OR "urogenital infections"[tiab] OR UTI[tiab] OR UTIs[tiab]) AND ("Antibody-Coated         |
| 50       | Bacteria Test, Urinary"[mh] OR "Bacteriuria/diagnosis"[Majr] OR "Bacteriuria/prevention and                 |
| 51       | control"[Majr] OR ("bacteriuria/microbiology"[Mesh Terms] AND Majr[All Fields]) OR                          |
| 52       | "Bacteriuria/urine"[Majr] OR "Cystitis/diagnosis"[Majr] OR "Cystitis/prevention and control"[Majr] OR       |
| 53       | "Cystitis/microbiology"[Majr] OR "Cystitis/urine"[Majr] OR "Mass Screening"[mh:noexp] OR                    |
| 54       | "Microbial Sensitivity Tests"[mh:noexp] OR "Microscopy"[mh:noexp] OR "Predictive Value of                   |
| 55       | Tests"[mh:noexp] OR "Pyelonephritis/diagnosis"[Majr] OR "Pyelonephritis/prevention and                      |
| 56       | control"[Majr] OR "Pyelonephritis/microbiology"[Majr] OR "Pyelonephritis/urine"[Majr] OR "Reagent           |
| 57       |   |
| 58       |   |
| 50       |   |

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Kits, Diagnostic"[mh:noexp] OR "Reagent Strips"[mh:noexp] OR "Sensitivity and Specificity"[mh:noexp] OR "Urinalysis"[mh:noexp] OR "Urinary Tract Infections/diagnosis"[Majr] OR "Urinary Tract Infections/prevention and control"[Majr] OR "Urinary Tract Infections/microbiology"[Majr] OR "Urinary Tract Infections/urine"[Majr] OR detect[tiab] OR detected[tiab] OR detection[tiab] OR detecting[tiab] OR detects[tiab] OR "diagnostic accuracy"[tiab] OR "diagnostic algorithm" [tiab] OR "dip slide" [tiab] OR "dip slides" [tiab] OR "dip stick" [tiab] OR "dip sticks"[tiab] OR dipslide[tiab] OR dipslides[tiab] OR dipstick[tiab] OR dipsticks[tiab] OR culture[tiab] OR cultures[tiab] OR "diagnostic test"[tiab] OR "diagnostic tests"[tiab] OR "microbial test"[tiab] OR "microbial tests"[tiab] OR microscopy[tiab] OR predict[tiab] OR predicted[tiab] OR prediction[tiab] OR predicting[tiab] OR predicts[tiab] OR "reagent strip"[tiab] OR "reagent strips"[tiab] OR "reagent test"[tiab] OR "reagent testing"[tiab] OR "reagent tests"[tiab] OR screen[tiab] OR screened[tiab] OR screening[tiab] OR screens[tiab] OR "strip test"[tiab] OR "strip tests"[tiab] OR "strip testing"[tiab] OR "test accuracy"[tiab] OR urinalyses[tiab] OR urinalysis[tiab] OR "urine analyses"[tiab] OR "urine analysis"[tiab] OR "urine test"[tiab] OR "urine tested"[tiab] OR "urine testing"[tiab] OR "urine tests"[tiab] OR uriscreen[tiab])) AND ("Choice Behavior"[mh:noexp] OR "Consumer Behavior"[majr:noexp] OR "Consumer Participation"[mh] OR "Cooperative Behavior"[mh:noexp] OR "Decision Making"[mh] OR "Focus Groups"[mh:noexp] OR "Health Care Surveys"[mh:noexp] OR "Informed Consent"[mh] OR "Interviews as Topic"[mh:noexp] OR "Patient Acceptance of Health Care"[mh:noexp] OR "Patient Education as Topic"[mh] OR "Patient Participation"[mh] OR "Patient Preference"[mh:noexp] OR "Social Values"[mh:noexp] OR "Surveys and Questionnaires"[mh:noexp] OR "Treatment Refusal" [mh:noexp] OR (15D[tiab] AND (HRQoL[tiab] OR QoL[tiab] OR "guality of life"[tiab])) OR ((accept[tiab] OR accepted[tiab] OR accepting[tiab] OR accepts[tiab] OR consider[tiab] OR consideration[tiab] OR considerations[tiab] OR considered[tiab] OR considering[tiab] OR considers[tiab] OR choice[tiab] OR choices[tiab] OR choose[tiab] OR choosing[tiab] OR chose[tiab] OR chosen[tiab] OR decide[tiab] OR decided[tiab] OR deciding[tiab] OR decides[tiab] OR decision[tiab] OR decisionmaker[tiab] OR decisionmaking[tiab] OR decisions[tiab] OR decisive[tiab] OR input[tiab] OR involve[tiab] OR involved[tiab] OR involving[tiab] OR involvement[tiab] OR involves[tiab] OR opinion[tiab] OR opinionated[tiab] OR opinions[tiab] OR participate[tiab] OR participated[tiab] OR participating[tiab] OR participation[tiab] OR participates[tiab] OR perceive[tiab] OR perceived[tiab] OR perceiving[tiab] OR perceives[tiab] OR perception[tiab] OR perceptions[tiab] OR perceptive[tiab] OR perspective[tiab] OR perspectives[tiab] OR prefer[tiab] OR preference[tiab] OR preferences[tiab] OR preferred[tiab] OR preferring[tiab] OR refusal[tiab] OR refuse[tiab] OR refused[tiab] OR refusing[tiab] OR refuses[tiab] OR response[tiab] OR responses[tiab] OR valuation[tiab] OR value[tiab] OR valued[tiab] OR values[tiab] OR valuing[tiab] OR view[tiab] OR viewed[tiab] OR viewing[tiab] OR viewpoint[tiab] OR viewpoints[tiab] OR views[tiab]) AND (citizen[tiab] OR citizens[tiab] OR client[tiab] OR clients[tiab] OR consumer[tiab] OR consumers[tiab] OR female[tiab] OR females[tiab] OR male[tiab] OR males[tiab] OR men[tiab] OR patient[tiab] OR patients[tiab] OR public[tiab] OR "stake-holder"[tiab] OR "stake-holders"[tiab] OR stakeholder[tiab] OR stakeholders[tiab] OR user[tiab] OR users[tiab] OR woman[tiab] OR women[tiab])) OR ((analyses[tiab] OR analysis[tiab] OR valuation[tiab] OR valuations[tiab] OR value[tiab] OR values[tiab] OR valuing[tiab]) AND (conjoint[tiab] OR contingent[tiab])) OR "choice behavior"[tiab] OR "choice behaviour"[tiab] OR "choice experiment"[tiab] OR "choice experiments"[tiab] OR "discrete choice"[tiab] OR "EQ 5D"[tiab] OR EQ5D[tiab] OR "EuroQoL 5D"[tiab] OR EuroQoL5D[tiab] OR "focus group"[tiab] OR "focus groups"[tiab] OR gamble[tiab] OR gambled[tiab] OR gambling[tiab] OR gambles[tiab] OR "health utilities"[tiab] OR "health utility"[tiab] OR HUI[tiab] OR "informed choice"[tiab] OR "informed choices"[tiab] OR "informed consent"[tiab] OR "informed decision"[tiab] OR interview[tiab] OR interviewed[tiab] OR interviewing[tiab] OR interviews[tiab] OR "multi-attribute"[tiab] OR "multi-criteria"[tiab] OR multiattribute[tiab] OR

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## BMJ Open

3 multicriteria[tiab] OR "preference score"[tiab] OR "preference scores"[tiab] OR "preference 4 scoring"[tiab] OR "prospect theory"[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR "SF 5 12"[tiab] OR "SF 36"[tiab] OR "SF 6D"[tiab] OR SF12[tiab] OR SF36[tiab] OR SF6D[tiab] OR "stated 6 preference"[tiab] OR survey[tiab] OR surveyed[tiab] OR surveys[tiab] OR "trade off"[tiab] OR "trade 7 offs"[tiab] OR tradeoff[tiab] OR tradeoffs[tiab] OR "willing to pay"[tiab] OR "willingness to pay"[tiab])) 8 OR ((("Anti-Bacterial Agents"[mh:noexp] OR "Antibiotic Prophylaxis"[mh:noexp] OR "Anti-Infective 9 10 Agents, Urinary"[mh] OR "Asymptomatic Infections/therapy"[mh] OR "Bacteriuria/drug 11 therapy"[Majr] OR "Bacteriuria/therapy"[Majr] OR "Drug Therapy, Combination"[mh:noexp] OR 12 "Norfloxacin"[mh:noexp] OR "Penicillins"[mh] OR "Sulfonamides"[mh] OR "Urinary Tract 13 Infections/drug therapy"[Majr] OR "Urinary Tract Infections/therapy"[Majr] OR amoxicillin[tiab] OR 14 amoxicillins[tiab] OR ampicillin[tiab] OR ampicillins[tiab] OR "anti-bacteria"[tiab] OR "anti-15 bacterial"[tiab] OR "anti-bacterials"[tiab] AND "anti-biotic"[tiab] OR "anti-biotics"[tiab] OR 16 antibacteria[tiab] OR antibacterial[tiab] OR antibacterials[tiab] OR antibiotic[tiab] OR antibiotics[tiab] 17 OR aztreonam[tiab] OR cefadroxil[tiab] OR cefepime[tiab] OR ceftibuten[tiab] OR ceftriaxone[tiab] OR 18 cefuroxime[tiab] OR cephalexin[tiab] OR cephalosporin[tiab] OR cephalosporins[tiab] OR 19 20 cephradine[tiab] OR clindamycin[tiab] OR "co-trimoxazole"[tiab] OR cotrimoxazole[tiab] OR 21 cycloserine[tiab] OR cycloserines[tiab] OR fosfomycin[tiab] OR gentamicin[tiab] OR gentamycin[tiab] 22 OR "nalidixic acid" [tiab] OR nitrofurantoin [tiab] OR penicillin [tiab] OR penicillins [tiab] OR 23 piperacillin[tiab] OR pivampicillin[tiab] OR pivmecillinam[tiab] OR sulfadimethoxine[tiab] OR 24 sulfadiazine[tiab] OR sulfamethizole[tiab] OR sulfamethoxazole[tiab] OR sulfamethoxypyridazine[tiab] 25 OR sulfonamide[tiab] OR sulfonamides[tiab] OR sulphadimidine[tiab] OR sulphonamide[tiab] OR 26 tetracycline[tiab] OR tetracyclines[tiab] OR vancomycin[tiab]) AND ("Pregnancy"[mh] OR "Pregnancy 27 Complications, Infectious"[mh:noexp] OR "Pregnant Women"[mh:noexp] OR "Prenatal 28 29 Care"[mh:noexp] OR "Prenatal Diagnosis"[mh:noexp] OR antenatal[tiab] OR "pre-natal"[tiab] OR 30 prenatal[tiab] OR "expectant mother"[tiab] OR "expectant mothers"[tiab] OR "expecting 31 mothers"[tiab] OR "expecting mothers"[tiab] OR "expectant woman"[tiab] OR "expectant 32 women"[tiab] OR "expecting women"[tiab] OR pregnancies[tiab] OR pregnancy[tiab] OR 33 pregnant[tiab])) AND ("Choice Behavior"[mh:noexp] OR "Consumer Behavior"[majr:noexp] OR 34 "Consumer Participation"[mh] OR "Cooperative Behavior"[mh:noexp] OR "Decision Making"[mh] OR 35 "Focus Groups"[mh:noexp] OR "Health Care Surveys"[mh:noexp] OR "Informed Consent"[mh] OR 36 "Interviews as Topic"[mh:noexp] OR "Patient Acceptance of Health Care"[mh:noexp] OR "Patient 37 Education as Topic"[mh] OR "Patient Participation"[mh] OR "Patient Preference"[mh:noexp] OR 38 39 "Social Values"[mh:noexp] OR "Surveys and Questionnaires"[mh:noexp] OR "Treatment 40 Refusal"[mh:noexp] OR (15D[tiab] AND (HRQoL[tiab] OR QoL[tiab] OR "quality of life"[tiab])) OR 41 ((accept[tiab] OR accepted[tiab] OR accepting[tiab] OR accepts[tiab] OR consider[tiab] OR 42 consideration[tiab] OR considerations[tiab] OR considered[tiab] OR considering[tiab] OR 43 considers[tiab] OR choice[tiab] OR choices[tiab] OR choose[tiab] OR choosing[tiab] 44 OR chose[tiab] OR chosen[tiab] OR decide[tiab] OR decided[tiab] OR deciding[tiab] OR decides[tiab] 45 OR decision[tiab] OR decisionmaker[tiab] OR decisionmaking[tiab] OR decisions[tiab] OR 46 47 decisive[tiab] OR input[tiab] OR involve[tiab] OR involved[tiab] OR involving[tiab] OR 48 involvement[tiab] OR involves[tiab] OR opinion[tiab] OR opinionated[tiab] OR opinions[tiab] OR 49 participate[tiab] OR participated[tiab] OR participating[tiab] OR participation[tiab] OR 50 participates[tiab] OR perceive[tiab] OR perceived[tiab] OR perceiving[tiab] OR perceives[tiab] OR 51 perception[tiab] OR perceptions[tiab] OR perceptive[tiab] OR perspective[tiab] OR perspectives[tiab] 52 OR prefer[tiab] OR preference[tiab] OR preferences[tiab] OR preferred[tiab] OR preferring[tiab] OR 53 refusal[tiab] OR refuse[tiab] OR refused[tiab] OR refusing[tiab] OR refuses[tiab] OR response[tiab] OR 54 responses[tiab] OR valuation[tiab] OR value[tiab] OR valued[tiab] OR values[tiab] OR valuing[tiab] OR 55 view[tiab] OR viewed[tiab] OR viewing[tiab] OR viewpoint[tiab] OR viewpoints[tiab] OR views[tiab]) 56 57 58

AND (citizen[tiab] OR citizens[tiab] OR client[tiab] OR clients[tiab] OR consumer[tiab] OR consumers[tiab] OR female[tiab] OR females[tiab] OR male[tiab] OR males[tiab] OR men[tiab] OR patient[tiab] OR patients[tiab] OR public[tiab] OR "stake-holder"[tiab] OR "stake-holders"[tiab] OR stakeholder[tiab] OR stakeholders[tiab] OR user[tiab] OR users[tiab] OR woman[tiab] OR women[tiab])) OR ((analyses[tiab] OR analysis[tiab] OR valuation[tiab] OR valuations[tiab] OR value[tiab] OR values[tiab] OR valuing[tiab]) AND (conjoint[tiab] OR contingent[tiab])) OR "choice 10 behavior"[tiab] OR "choice behaviour"[tiab] OR "choice experiment"[tiab] OR "choice 11 experiments"[tiab] OR "discrete choice"[tiab] OR "EQ 5D"[tiab] OR EQ5D[tiab] OR "EuroQoL 5D"[tiab] 12 OR EuroQoL5D[tiab] OR "focus group"[tiab] OR "focus groups"[tiab] OR gamble[tiab] OR 13 gambled[tiab] OR gambling[tiab] OR gambles[tiab] OR "health utilities"[tiab] OR "health utility"[tiab] 14 OR HUI[tiab] OR "informed choice"[tiab] OR "informed choices"[tiab] OR "informed consent"[tiab] OR 15 "informed decision"[tiab] OR interview[tiab] OR interviewed[tiab] OR interviewing[tiab] OR 16 interviews[tiab] OR "multi-attribute"[tiab] OR "multi-criteria"[tiab] OR multiattribute[tiab] OR 17 multicriteria[tiab] OR "preference score"[tiab] OR "preference scores"[tiab] OR "preference 18 scoring"[tiab] OR "prospect theory"[tiab] OR questionnaire[tiab] OR questionnaires[tiab] OR "SF 19 20 12"[tiab] OR "SF 36"[tiab] OR "SF 6D"[tiab] OR SF12[tiab] OR SF36[tiab] OR SF6D[tiab] OR "stated 21 preference"[tiab] OR survey[tiab] OR surveyed[tiab] OR surveys[tiab] OR "trade off"[tiab] OR "trade 22 offs"[tiab] OR tradeoff[tiab] OR tradeoffs[tiab] OR "willing to pay"[tiab] OR "willingness to 23 pay"[tiab]))) NOT ("Male"[mh] NOT ("Female"[mh] AND "Male"[mh]))) NOT (((Animals[MESH] OR 24 Animal Experimentation[MESH] OR "Models, Animal"[MESH] OR Vertebrates[MESH]) NOT 25 (Humans[MESH] OR Human experimentation[MESH])) OR (((animals[tiab] OR animal model[tiab] OR 26 rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR rabbit[tiab] OR rabbits[tiab] OR pig[tiab] OR 27 pigs[tiab] OR porcine[tiab] OR swine[tiab] OR dog[tiab] OR dogs[tiab] OR hamster[tiab] OR 28 29 hamsters[tiab] OR chicken[tiab] OR chickens[tiab] OR sheep[tiab]) AND (publisher[sb] OR 30 inprocess[sb] OR pubmednotmedline[sb])) NOT (human[ti] OR humans[ti] OR people[ti] OR 31 children[ti] OR adults[ti] OR seniors[ti] OR patient[ti] OR patients[ti]))) NOT (case reports[pt] OR 32 comment[pt] OR editorial[pt] OR letter[pt] OR newspaper article[pt])) AND ((publisher[sb] NOT 33 pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint)) 34 > limit to English or French 35 36 37 38

## KQs4,5: Systematic Review & HTA Search Database: PubMed via NCBI Entrez (1946 to Present) Date Searched: 14 October 2016 **Records Retrieved: 104**

(((((("asymptomatic infections"[mh] AND (("bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields]) OR ("bacteriuria" [MeSH Terms] OR "bacteriuria" [All Fields] OR "bacteriurias" [All Fields]) OR ("urinary bladder"[MeSH Terms] OR ("urinary"[All Fields] AND "bladder"[All Fields]) OR "urinary bladder"[All Fields] OR "bladder"[All Fields]) OR ("cystitis"[MeSH Terms] OR "cystitis"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields]) OR ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields]) OR ("pyelocystitis"[MeSH Terms] OR "pyelocystitis"[All Fields]) OR ("pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]) OR ("urinary tract"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields]) OR "urinary tract"[All Fields] OR "urinary"[All Fields]) OR ("urine"[Subheading] OR "urine"[All Fields] OR "urine"[MeSH Terms]) OR UTI[all] OR ("urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields] OR "utis"[All Fields]))) OR "bacteriuria"[MeSH Terms:noexp] OR "cystitis" [MeSH Terms] OR "dysuria" [MeSH Terms: noexp] OR "pyelonephritis" [MeSH

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#### **BMJ** Open

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Terms:noexp] OR "Urinary Tract Infections" [mh:noexp] OR bacilluria[tiab] OR bacteriuria[tiab] OR bacteriurias[tiab] OR "bladder infection"[tiab] OR "bladder infections"[tiab] OR cystitis[tiab] OR cystopyelitis[tiab] OR dysuria[tiab] OR "genito-urinary infection"[tiab] OR "genitourinary infection"[tiab] OR "genito-urinary infections"[tiab] OR "genitourinary infections"[tiab] OR "kidney infection"[tiab] OR "kidney infections"[tiab] OR "pyelo-nephritis"[tiab] OR pyelocystitis[tiab] OR pyelonephritis[tiab] OR "urinary infection"[tiab] OR "urinary infections"[tiab] OR "urogenital infection"[tiab] OR "urogenital infections"[tiab] OR UTI[tiab] OR UTIs[tiab]) AND (("Antibody-Coated Bacteria Test, Urinary"[mh] OR "Bacteriuria/diagnosis"[Majr] OR "Bacteriuria/prevention and control"[Majr] OR ("bacteriuria/microbiology"[Mesh Terms] AND Majr[All Fields]) OR "Bacteriuria/urine"[Mair] OR "Cystitis/diagnosis"[Mair] OR "Cystitis/prevention and control"[Mair] OR "Cystitis/microbiology"[Majr] OR "Cystitis/urine"[Majr] OR "Mass Screening"[mh:noexp] OR "Microbial Sensitivity Tests"[mh:noexp] OR "Microscopy"[mh:noexp] OR "Predictive Value of Tests"[mh:noexp] OR "Pyelonephritis/diagnosis"[Majr] OR "Pyelonephritis/prevention and control" [Majr] OR "Pyelonephritis/microbiology" [Majr] OR "Pyelonephritis/urine" [Majr] OR "Reagent Kits, Diagnostic"[mh:noexp] OR "Reagent Strips"[mh:noexp] OR "Sensitivity and Specificity"[mh:noexp] OR "Urinalysis"[mh:noexp] OR "Urinary Tract Infections/diagnosis"[Majr] OR "Urinary Tract Infections/prevention and control" [Majr] OR "Urinary Tract Infections/microbiology"[Majr] OR "Urinary Tract Infections/urine"[Majr] OR detect[tiab] OR detected[tiab] OR detection[tiab] OR detecting[tiab] OR detects[tiab] OR "diagnostic accuracy"[tiab] OR "diagnostic algorithm"[tiab] OR "dip slide"[tiab] OR "dip slides"[tiab] OR "dip stick"[tiab] OR "dip sticks"[tiab] OR dipslide[tiab] OR dipslides[tiab] OR dipstick[tiab] OR dipsticks[tiab] OR culture[tiab] OR cultures[tiab] OR "diagnostic test"[tiab] OR "diagnostic tests"[tiab] OR "microbial test"[tiab] OR "microbial tests"[tiab] OR microscopy[tiab] OR predict[tiab] OR predicted[tiab] OR prediction[tiab] OR predicting[tiab] OR predicts[tiab] OR "reagent strip"[tiab] OR "reagent strips"[tiab] OR "reagent test"[tiab] OR "reagent testing"[tiab] OR "reagent tests"[tiab] OR screen[tiab] OR screened[tiab] OR screening[tiab] OR screens[tiab] OR "strip test"[tiab] OR "strip tests"[tiab] OR "strip testing"[tiab] OR "test accuracy"[tiab] OR urinalyses[tiab] OR urinalysis[tiab] OR "urine analyses"[tiab] OR "urine analysis"[tiab] OR "urine test"[tiab] OR "urine tested"[tiab] OR "urine testing"[tiab] OR "urine tests"[tiab] OR uriscreen[tiab]) OR ("Anti-Bacterial Agents"[mh:noexp] OR "Antibiotic Prophylaxis"[mh:noexp] OR "Anti-Infective Agents, Urinary"[mh] OR "Asymptomatic Infections/therapy"[mh] OR "Bacteriuria/drug therapy"[Majr] OR "Bacteriuria/therapy"[Majr] OR "Drug Therapy, Combination"[mh:noexp] OR "Norfloxacin"[mh:noexp] OR "Penicillins"[mh] OR "Sulfonamides"[mh] OR "Urinary Tract Infections/drug therapy"[Mair] OR "Urinary Tract Infections/therapy"[Mair] OR amoxicillin[tiab] OR amoxicillins[tiab] OR ampicillin[tiab] OR ampicillins[tiab] OR "anti-bacteria"[tiab] OR "anti-bacterial"[tiab] OR "anti-bacterials"[tiab] AND "antibiotic"[tiab] OR "anti-biotics"[tiab] OR antibacteria[tiab] OR antibacterial[tiab] OR antibacterials[tiab] OR antibiotic[tiab] OR antibiotics[tiab] OR aztreonam[tiab] OR cefadroxil[tiab] OR cefepime[tiab] OR ceftibuten[tiab] OR ceftriaxone[tiab] OR cefuroxime[tiab] OR cephalexin[tiab] OR cephalosporin[tiab] OR cephalosporins[tiab] OR cephradine[tiab] OR clindamycin[tiab] OR "co-trimoxazole"[tiab] OR cotrimoxazole[tiab] OR cycloserine[tiab] OR cycloserines[tiab] OR fosfomycin[tiab] OR gentamicin[tiab] OR gentamycin[tiab] OR "nalidixic acid"[tiab] OR nitrofurantoin[tiab] OR penicillin[tiab] OR penicillins[tiab] OR piperacillin[tiab] OR pivampicillin[tiab] OR pivmecillinam[tiab] OR sulfadimethoxine[tiab] OR sulfadiazine[tiab] OR sulfamethizole[tiab] OR sulfamethoxazole[tiab] OR sulfamethoxypyridazine[tiab] OR sulfonamide[tiab] OR sulfonamides[tiab] OR sulphadimidine[tiab] OR sulphonamide[tiab] OR tetracycline[tiab] OR tetracyclines[tiab] OR vancomycin[tiab]))) AND ("Pregnancy"[mh] OR "Pregnancy Complications, Infectious"[mh:noexp] OR "Pregnant Women"[mh:noexp] OR "Prenatal Care"[mh:noexp] OR "Prenatal Diagnosis"[mh:noexp] OR antenatal[tiab] OR "pre-natal"[tiab] OR prenatal[tiab] OR "expectant mother"[tiab] OR "expectant

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mothers" [tiab] OR "expecting mothers" [tiab] OR "expecting mothers" [tiab] OR "expectant woman"[tiab] OR "expectant women"[tiab] OR "expecting women"[tiab] OR pregnancies[tiab] OR pregnancy[tiab] OR pregnant[tiab])) AND (systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy\*[tw] OR metanaly\*[tw] OR metaanaly\*[tw] OR met analy\*[tw] OR integrative research[tiab] OR integrative review\*[tiab] OR integrative overview\*[tiab] OR research integration\*[tiab] OR research overview\*[tiab] OR collaborative review\*[tiab] OR collaborative overview\*[tiab] OR systematic review\*[tiab] OR technology assessment\*[tiab] OR technology overview\*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison\*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab]) AND comparison\*[tiab]) OR Embase\*[tiab] OR Cinahl\*[tiab] OR systematic overview\*[tiab] OR methodological overview\*[tiab] OR methodologic overview\*[tiab] OR methodological review\*[tiab] OR methodologic review\*[tiab] OR quantitative review\*[tiab] OR quantitative overview\*[tiab] OR quantitative synthes\*[tiab] OR pooled analy\*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch\*[tiab] OR hand search\*[tiab] OR metaregression\*[tiab] OR metaregression\*[tiab] OR data synthes\*[tiab] OR data extraction[tiab] OR data abstraction\*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect\*[tiab] OR "Cochrane Database Syst Rev"[Journal] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal])) NOT ("Male"[mh] NOT ("Female"[mh] AND "Male"[mh]))) NOT (((Animals[MESH] OR Animal Experimentation[MESH] OR "Models, Animal"[MESH] OR Vertebrates[MESH]) NOT (Humans[MESH] OR Human experimentation[MESH])) OR (((animals[tiab] OR animal model[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR rabbit[tiab] OR rabbits[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR swine[tiab] OR dog[tiab] OR dogs[tiab] OR hamster[tiab] OR hamsters[tiab] OR chicken[tiab] OR chickens[tiab] OR sheep[tiab]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])) NOT (human[ti] OR humans[ti] OR people[ti] OR children[ti] OR adults[ti] OR seniors[ti] OR patient[ti] OR patients[ti]))) NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR newspaper article[pt])

## KQs4,5: Systematic Review & HTA Search

## **Database: Wiley Cochrane Library**

Date Searched: 14 October 2016

D'S Records Retrieved: 19 in Cochrane Database of Systematic Reviews Records Retrieved: 4 in Database of Abstracts of Reviews of Effects (DARE) Records Retrieved: 1 in Health Technology Assessment Database Records Retrieved: 3 in Economic Evaluations Database

[mh ^"Asymptomatic Infections"] and (bacteriuria\* or bladder\* or cystitis\* or kidney\* or #1 pyelo-cystiti\* or pyelocystiti\* or pyelo-nephriti\* or pyelonephriti\* or urin\* or UTI\*):ti,ab,kw

- #2 [mh ^Bacteriuria]
- #3 [mh Cystitis]
- #4 [mh ^Dysuria]
- #5 [mh ^Pyelonephritis]
- [mh ^"Urinary Tract Infections"] #6

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| 2        |            |  |
|----------|------------|--|
| 3        | #7         | bacilluria*:ti,ab,kw   |
| 4        | #8         | bacteriuria*:ti,ab,kw  |
| 5        | #8<br>#9   | cystiti*:ti,ab,kw  |
| 6        | #9<br>#10  | (cysto-pyeliti* or cystopyeliti*):ti,ab,kw   |
| 7        | #10<br>#11 | dysuria*:ti,ab,kw  |
| 8        | #11<br>#12 | (infection* near/2 (bladder* or genitourin* or kidney* or urin* or urogenita*)):ti,ab,kw |
| 9<br>10  |            |  |
| 10       | #13<br>#14 | (pyelo-cystiti* or pyelocystiti*):ti,ab,kw   |
| 12       | #14<br>#15 | (pyelo-nephriti* or pyelonephriti*):ti,ab,kw   |
| 13       | #15        | (UTI or UTIs):ti,ab,kw   |
| 14       | #16        | {or #1-#15}  |
| 15       | #17        | [mh ^"Antibody-Coated Bacteria Test, Urinary"]   |
| 16       | #18        | [mh ^Bacteriuria [mj]/DI,PC,MI,UR]   |
| 17       | #19        | [mh Cystitis [mj]/DI,PC,MI,UR]   |
| 18       | #20        | [mh ^"Mass Screening"]   |
| 19       | #21        | [mh ^"Microbial Sensitivity Tests"]  |
| 20       | #22        | [mh ^Microscopy]   |
| 21<br>22 | #23        | [mh ^"Predictive Value of Tests"]  |
| 22       | #24        | [mh ^Pyelonephritis [mj]/DI,PC,MI,UR]  |
| 24       | #25        | [mh "Reagent Kits, Diagnostic"]  |
| 25       | #26        | [mh "Reagent Strips"]  |
| 26       | #27        | [mh ^"Sensitivity and Specificity"]  |
| 27       | #28        | [mh ^Urinalysis]   |
| 28       | #29        | [mh ^"Urinary Tract Infections" [mj]/DI,PC,MI,UR]  |
| 29       | #30        | ((accurac* or diagnostic) near/5 (algorithm* or test*)):ti,ab,kw                         |
| 30       | #31        | "diagnostic accurac*":ti,ab,kw   |
| 31<br>22 | #32        | culture*:ti,ab,kw  |
| 32<br>33 | #33        | (detect* or predict* or screen*):ti,ab,kw  |
| 34       | #34        | ("dip slide*" or dipslide* or "dip stick*" or dipstick*):ti,ab,kw                        |
| 35       | #35        | (micro-scopy or microscopy):ti,ab,kw   |
| 36       | #36        | (microb* near/2 test*):ti,ab,kw  |
| 37       | #37        | ((re-agent* or reagent) near/3 (strip* or test*)):ti,ab,kw 💦 🦳                           |
| 38       | #38        | "strip* test*":ti,ab,kw  |
| 39       | #39        | "urine test*":ti,ab,kw   |
| 40       | #40        | (urinalys* or "urine analys*"):ti,ab,kw  |
| 41       | #41        | uriscreen:ti,ab,kw   |
| 42<br>43 | #42        | {or #17-#41}   |
| 44       | #43        | [mh ^"Anti-Bacterial Agents"]  |
| 45       | #44        | [mh ^"Antibiotic Prophylaxis"]   |
| 46       | #45        | [mh ^"Anti-Infective Agents, Urinary"]   |
| 47       | #46        | [mh ^"Asymptomatic Infections"/DT,TH]  |
| 48       | #47        | [mh ^Bacteriuria [mj]/DT,TH]   |
| 49       | #48        | [mh ^"Drug Therapy, Combination"]  |
| 50       | #49        | [mh ^Norfloxacin]  |
| 51<br>52 | #50        | [mh Penicillins]   |
| 52<br>53 | #51        | [mh Sulfonamides]  |
| 53<br>54 | #52        | [mh ^"Urinary Tract Infections" [mj]/DT,TH]  |
| 55       | #53        | amoxicillin*:ti,ab,kw  |
| 56       | #54        | ampicillin*:ti,ab,kw   |
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| 50       |            |  |

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| 2        |            |   |
| 3        | #55        | ("anti-bacteria*" or antibacteria*):ti,ab,kw            |
| 4<br>5   | #56        | ("anti-biotic*" or antibiotic*):ti,ab,kw                |
| 6        | #57        | aztreonam*:ti,ab,kw                                     |
| 7        | #58        | cefadroxil*:ti,ab,kw                                    |
| 8        | #59        | cefepime*:ti,ab,kw                                      |
| 9        | #60        | ceftibuten*:ti,ab,kw                                    |
| 10       | #61        | ceftri?xone*:ti,ab,kw                                   |
| 11       | #62        | cefuroxime*:ti,ab,kw                                    |
| 12       | #63        | cephalexin*:ti,ab,kw                                    |
| 13       | #64        | cephalosporin*:ti,ab,kw                                 |
| 14       | #65        | cephradine*:ti,ab,kw                                    |
| 15       | #65        | clindamycin*:ti,ab,kw                                   |
| 16       | #00<br>#67 | ("co-trimoxazole*" or cotrimoxazole*):ti,ab,kw          |
| 17       |            |   |
| 18       | #68        | cycloserine*:ti,ab,kw                                   |
| 19<br>20 | #69        | fosfomycin*:ti,ab,kw                                    |
| 20<br>21 | #70        | gentam?cin*:ti,ab,kw                                    |
| 21       | #71        | "nalidixic acid*":ti,ab,kw                              |
| 23       | #72        | nitrofurantoin*:ti,ab,kw                                |
| 24       | #73        | penicillin*:ti,ab,kw                                    |
| 25       | #74        | piperacillin*:ti,ab,kw                                  |
| 26       | #75        | pivampicillin*:ti,ab,kw                                 |
| 27       | #76        | pivmecillinam*:ti,ab,kw                                 |
| 28       | #77        | sulfadimethoxine*:ti,ab,kw                              |
| 29       | #78        | sulfadiazine*:ti,ab,kw                                  |
| 30       | #79        | sulfamethizole*:ti,ab,kw                                |
| 31       | #80        | sulfamethoxazole*:ti,ab,kw                              |
| 32       | #81        | sulfamethoxypyridazine*:ti,ab,kw                        |
| 33       | #82        | sulfonamide*:ti,ab,kw                                   |
| 34<br>35 | #83        | sulphadimidine*:ti,ab,kw                                |
| 36       | #84        | sulphonamide*:ti,ab,kw                                  |
| 37       | #85        | tetracycline*:ti,ab,kw                                  |
| 38       | #86        | vancomycin*:ti,ab,kw                                    |
| 39       | #87        | {or #43-#86}  |
| 40       | #88        | #16 and (#42 or #87)                                    |
| 41       | #89        | [mh Pregnancy]  |
| 42       | #90        | [mh ^"Pregnancy Complications, Infectious"]             |
| 43       | #91        | [mh ^"Pregnant Women"]                                  |
| 44       | #92        | [mh ^"Prenatal Care"]                                   |
| 45       | #93        | [mh ^"Prenatal Diagnosis"]                              |
| 46<br>47 | #93<br>#94 | (antenatal* or "pre-natal*" or prenatal*):ti,ab,kw      |
| 47<br>48 |            |   |
| 48<br>49 | #95<br>#06 | (expect* near/1 (female* or mother* or wom?n)):ti,ab,kw |
| 50       | #96<br>#07 | pregnan*:ti,ab,kw                                       |
| 51       | #97<br>#99 | {or #89-#96}  |
| 52       | #98        | #88 and #97   |
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## **BMJ** Open

Additional Search Sources Database: ProQuest Dissertations & Theses Global (1861 to current) Date Searched: 10 August 2016 Records Retrieved: 135

(((TI,AB(bacilluria\* OR bacteriuria\* OR cystiti\* OR cystopyeliti\* OR dysuria\* OR (infection\* NEAR/2 (bladder\* OR genitourin\* OR kidney\* OR urin\* OR urogenita\*)) OR pyelocystiti\* OR pyelonephriti\* OR UTI OR UTIs) AND (su.Exact("prenatal care" OR "pregnancy") OR TI,AB(prenatal\* OR (expect\* NEAR/1 (female\* OR mother\* OR wom?n)) OR pregnan\*)) AND ((su.Exact("urinalysis" OR "medical screening" OR "sensitivity analysis" OR "microscopy") OR TI,AB(((accurac\* OR diagnostic) NEAR/5 (algorithm\* OR test\*)) OR "diagnostic accurac\*" OR culture\* OR detect\* OR "dip slide\*" OR dipslide\* OR "dip stick\*" OR dipstick\* OR microscopy OR (microb\* NEAR/2 test\*) OR predict\* OR ((re-agent\* OR reagent\*) NEAR/3 (strip\* OR test\*)) OR screen\* OR "strip\* test\*" OR "urine test\*" OR urinalys\* OR "urine analys\*" OR uriscreen)) OR (su.Exact("antibiotics") OR TI,AB(amoxicillin\* OR ampicillin\* OR antibacteria\* OR antibacteria\* OR anti-biotic\* OR antibiotic\* OR aztreonam\* OR cefadroxil\* OR cefepime\* OR ceftibuten\* OR ceftri\*xone\* OR cefuroxime\* OR cephalexin\* OR cephalosporin\* OR cephradine\* OR clindamycin\* OR co-trimoxazole\* OR cotrimoxazole\* OR cycloserine\* OR fosfomycin\* OR gentam?cin\* OR "nalidixic acid\*" OR nitrofurantoin\* OR penicillin\* OR piperacillin\* OR pivampicillin\* OR pivmecillinam\* OR sulfadimethoxine\* OR sulfadiazine\* OR sulfamethizole\* OR sulfamethoxazole\* OR sulfamethoxypyridazine\* OR sulfonamide\* sulphadimidine\* OR sulphonamide\* OR tetracycline\* OR vancomycin\*)))) OR ((su.Exact("prenatal care" OR "pregnancy") OR TI,AB(prenatal\* OR (expect\* NEAR/1 (female\* OR mother\* OR wom?n)) OR pregnan\*)) AND (su.Exact("antibiotics") OR TI,AB(amoxicillin\* OR ampicillin\* OR anti-bacteria\* OR antibacteria\* OR anti-biotic\* OR antibiotic\* OR aztreonam\* OR cefadroxil\* OR cefepime\* OR ceftibuten\* OR ceftri\*xone\* OR cefuroxime\* OR cephalexin\* OR cephalosporin\* OR cephradine\* OR clindamycin\* OR co-trimoxazole\* OR cotrimoxazole\* OR cycloserine\* OR fosfomycin\* OR gentam?cin\* OR "nalidixic acid\*" OR nitrofurantoin\* OR penicillin\* OR piperacillin\* OR pivampicillin\* OR pivmecillinam\* OR sulfadimethoxine\* OR sulfadiazine\* OR sulfamethizole\* OR sulfamethoxazole\* OR sulfamethoxypyridazine\* OR sulfonamide\* sulphadimidine\* OR sulphonamide\* OR tetracycline\* OR vancomycin\*)))) NOT (su.Exact("laboratory animals") OR TI(animal OR animal-model\* OR animals OR canine\* OR cat OR cats OR dog OR dogs OR feline OR felines OR hamster OR hamsters OR mice OR monkey OR monkeys OR mouse OR pig OR piglet OR piglets OR pigs OR porcine OR primate\* OR rabbit OR rabbits OR rat OR rats OR rodent OR rodents OR sheep OR swine OR swines))) AND Ia("ENG" OR "FRE")

#### Additional Search Sources

#### Registry: ClinicalTrials.gov

URL: <u>https://clinicaltrials.gov/</u> Date Searched: 10 August 2016 Records Retrieved: 48

S1. Advanced search:
Search Terms: pregnancy OR pregnant OR prenatal
AND
Conditions: "Bacteriuria" OR "Cystitis" OR "Dysuria" OR "Urinary Tract Infections"
Limit to studies with female participants
Retrieved: 15



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| 4  | S2. Advanced search:   |
| 5  |  |
| 6  | Search Terms: pregnancy OR pregnant OR prenatal  |
| 7  | AND  |
| 8  | Interventions: amoxicillin OR ampicillin OR antibiotic OR antibiotics OR "antibacterial agent" OR        |
| 9  | "antibacterial agents" OR antibacterials OR cephalosporin OR clindamycin OR cotrimoxazole OR             |
| 10 |  |
|    | fosfomycin OR nitrofurantoin OR penicillin OR sulphonamide OR tetracycline OR vancomycin                 |
| 11 | Retrieved: 162   |
| 12 |  |
| 13 | S3. Advanced search:   |
| 14 | Search Terms: pregnancy OR pregnant OR prenatal  |
| 15 | AND  |
| 16 |  |
| 17 | Condition: "Infections"  |
| 18 | Interventions: "urine culture" OR "urine test" OR "urine tests" OR "urinary screening" OR urinalysis     |
| 19 | Limit to studies with female participants  |
| 20 | Retrieved: 4 [RF Note: Removed 4 duplicates in EndNote, and 133 pre-2014 records]                        |
| 21 |  |
| 22 |  |
| 23 |  |
| 24 | Additional Search Sources  |
| 25 | Registry: World Health Organization's International Clinical Trial Registry Platform (ICTRP)             |
| 26 | URL: http://apps.who.int/trialsearch/  |
|    | Records Retrieved: 11  |
| 27 | Records Retrieved: 11  |
| 28 |  |
| 29 | S1. Advanced search:   |
| 30 | Title Search Terms: antenatal OR pregnancy OR pregnant OR prenatal                                       |
| 31 | AND  |
| 32 | Conditions: bacteriuria OR cystitis OR dysuria OR urinary tract infection OR urinary tract infections OR |
| 33 | UTI OR UTIs  |
| 34 |  |
| 35 | Recruitment status is: All   |
| 36 | Date of registration is between: 01/01/2014 and 10/08/2016 🥢   |
| 37 | Retrieved: 5   |
| 38 |  |
| 39 | S2. Advanced search:   |
| 40 |  |
| 41 | Title Search Terms: antenatal OR pregnancy OR pregnant OR prenatal                                       |
|    | AND  |
| 42 | Interventions: antibiotic OR antibiotics OR antibacterial agent OR antibacterial agents                  |
| 43 | Recruitment status is: All   |
| 44 | Date of registration is between: 01/01/2014 and 10/08/2016   |
| 45 | -  |
| 46 | Retrieved: 6   |
| 47 |  |
| 48 | S3. Advanced search:   |
| 49 | Title Search Terms: antenatal OR pregnancy OR pregnant OR prenatal                                       |
| 50 | AND  |
| 51 |  |
| 52 | Interventions: urine culture OR urine test OR urine tests OR urine screening OR urinary screening OR     |
| 53 | urinalysis   |
| 54 | Recruitment status is: All   |
| 55 | Date of registration is between: 01/01/2014 and 10/08/2016   |
| 56 | Retrieved: 0   |
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| 59 | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                                |
| 60 | i or peer review only interpriving openioning convolter about guidelines. And in                         |

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| 3  |  |
| 4  | Additional Search Sources  |
| 5  | Database: University of York, Centre for Reviews and Dissemination – Health Technology           |
| 6  | Assessment (HTA) Database  |
| 7  |  |
| 8  | Date Searched: 10 August 2016  |
| 9  | Records Retrieved: 1   |
| 10 |  |
| 11 | S1. Search HTA Database  |
| 12 | Any field: bacteriuria   |
| 13 | AND  |
| 14 | Any field: antenatal OR pregnan <sup>*</sup> OR prenatal   |
| 15 | Retrieved: 1   |
| 16 | Retrieved: 1   |
| 17 |  |
| 18 | S2. Search HTA Database  |
| 19 | Any field: urin*   |
| 20 | AND  |
| 21 | Any field: antenatal OR pregnan* OR prenatal   |
| 22 | Retrieved: 14 (retained 0 ; 1 duplicate)   |
| 23 |  |
| 24 | S3. Search HTA Database  |
| 25 |  |
| 26 | Any field: antibiotic* OR antibacterial  |
| 27 | AND  |
| 28 | Any field: antenatal OR pregnan* OR prenatal   |
| 29 | Retrieved: 10 (retained 0)   |
| 30 |  |
| 31 |  |
| 32 | Additional Search Sources  |
| 33 |  |
| 34 | Database: TRIP Database  |
| 35 | URL: <u>https://www.tripdatabase.com/</u>  |
| 36 | Date Searched: 11 August 2016  |
| 37 | Records Retrieved: 9   |
| 38 |  |
| 39 | S1. TRIP Search  |
| 40 | Simple search field: bacteriuria* AND (antenatal OR pregnan* OR prenatal)                        |
| 41 | Retrieved: 84 results in All Secondary Evidence (retained 8)                                     |
| 42 | Retrieved: 84 results in Air Secondary Evidence (retained 8)                                     |
| 43 |  |
| 44 | S2. TRIP Search  |
| 45 | Simple search field: ("urine test" OR "urine testing" OR "urine tests" OR "urine screening") AND |
| 46 | (antenatal OR pregnan* OR prenatal) AND infect*  |
| 47 | Retrieved: 131 results in All Secondary Evidence (retained 0 – 8 duplicates from search 1)       |
| 48 |  |
| 49 | S3. TRIP Search  |
| 50 | Simple search field: (antibiotic* OR antibacterial) AND (antenatal OR pregnan* OR prenatal) AND  |
| 51 |  |
| 52 | prefer*  |
| 53 | Retrieved: 372 results in All Secondary Evidence (retained 1)                                    |
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| Additional Search Sources<br>Website: Health Quality Ontario Publications and OHTAC Recommendations   |
|---|
| URL: http://www.hqontario.ca/Evidence-to-Improve-Care/Recommendations-and-Reports   |
| Date Searched: 11 August 2016   |
| Records Retrieved: 0  |
| C4. Consult has a second character in the   |
| S1. Search box search: bacteriuria  |
| Retrieved: 4 results (retained 0)   |
| S2. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (urinalysis OR urine) Retrieved: 20 results (retained 0)  |
| S3. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (antibiotic OR<br>antibiotics OR antibacterial)<br>Retrieved: 23 results (retained 0)   |
| S4. Browsed recommendations documents from 2011- 2016 (retained 0)  |
| S5. Browsed clinical handbooks for quality based procedures (retained 0)  |
| S6. Browsed Choosing Wisely Canada (retained 0)   |
| S7. Browsed Special Reports from 2005 – 2016 (retained 0)   |
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| Additional Search Sources   |
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| Additional Search Sources<br>Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)<br>URL: http://www.inesss.gc.ca   |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)<br>URL: <u>http://www.inesss.qc.ca</u>   |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)  |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)<br>URL: <u>http://www.inesss.qc.ca</u><br>Date Searched: 11 August 2016  |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)<br>URL: <u>http://www.inesss.qc.ca</u><br>Date Searched: 11 August 2016  |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)<br>URL: <u>http://www.inesss.qc.ca</u><br>Date Searched: 11 August 2016<br>Records Retrieved: 0  |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)         URL: <a href="http://www.inesss.qc.ca">http://www.inesss.qc.ca</a> Date Searched: 11 August 2016         Records Retrieved: 0         S1. Search box search: bacteriuria         Retrieved: 0 results (retained 0)   |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)         URL: <a href="http://www.inesss.qc.ca">http://www.inesss.qc.ca</a> Date Searched: 11 August 2016         Records Retrieved: 0         S1. Search box search: bacteriuria         Retrieved: 0 results (retained 0)         S2. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (urinalysis OR urine)   |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)         URL: <a href="http://www.inesss.qc.ca">http://www.inesss.qc.ca</a> Date Searched: 11 August 2016         Records Retrieved: 0         S1. Search box search: bacteriuria         Retrieved: 0 results (retained 0)   |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS) URL: <a href="http://www.inesss.qc.ca">http://www.inesss.qc.ca</a> Date Searched: 11 August 2016 Records Retrieved: 0 S1. Search box search: bacteriuria Retrieved: 0 results (retained 0) S2. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (urinalysis OR urine) Retrieved: 2 results (retained 0)   |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)         URL: <a href="http://www.inesss.qc.ca">http://www.inesss.qc.ca</a> Date Searched: 11 August 2016         Records Retrieved: 0         S1. Search box search: bacteriuria         Retrieved: 0 results (retained 0)         S2. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (urinalysis OR urine)         Retrieved: 2 results (retained 0)         S3. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (antibiotic OR  |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)         URL: <a href="http://www.inesss.qc.ca">http://www.inesss.qc.ca</a> Date Searched: 11 August 2016         Records Retrieved: 0         S1. Search box search: bacteriuria         Retrieved: 0 results (retained 0)         S2. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (urinalysis OR urine)         Retrieved: 2 results (retained 0)         S3. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (antibiotic OR antibiotics OR antibacterial)  |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)         URL: <a href="http://www.inesss.qc.ca">http://www.inesss.qc.ca</a> Date Searched: 11 August 2016         Records Retrieved: 0         S1. Search box search: bacteriuria         Retrieved: 0 results (retained 0)         S2. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (urinalysis OR urine)         Retrieved: 2 results (retained 0)         S3. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (antibiotic OR  |
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| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)URL: <a href="http://www.inesss.qc.ca">http://www.inesss.qc.ca</a> Date Searched: 11 August 2016Records Retrieved: 0S1. Search box search: bacteriuriaRetrieved: 0 results (retained 0)S2. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (urinalysis OR urine)Retrieved: 2 results (retained 0)S3. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (antibiotic OR antibiotics OR antibacterial)Retrieved: 6 results (retained 0)S4. Browsed all publications  |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)         URL: <a href="http://www.inesss.qc.ca">http://www.inesss.qc.ca</a> Date Searched: 11 August 2016         Records Retrieved: 0         S1. Search box search: bacteriuria         Retrieved: 0 results (retained 0)         S2. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (urinalysis OR urine)         Retrieved: 2 results (retained 0)         S3. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (antibiotic OR antibiotics OR antibacterial)         Retrieved: 6 results (retained 0)        |
| Website: L'Institut national d'excellence en santé et en services sociaux (INESSS)URL: <a href="http://www.inesss.qc.ca">http://www.inesss.qc.ca</a> Date Searched: 11 August 2016Records Retrieved: 0S1. Search box search: bacteriuriaRetrieved: 0 results (retained 0)S2. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (urinalysis OR urine)Retrieved: 2 results (retained 0)S3. Search box search: (antenatal OR pregnancy OR pregnant OR prenatal) AND (antibiotic OR antibiotics OR antibacterial)Retrieved: 6 results (retained 0)S4. Browsed all publications  |
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| 3        | Date Searched: 11 August 2016   |
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| 7        | S1. Search box search: bacteriuria                                    |
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| 8        | Retrieved: 17 results (retained 0)                                    |
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| 10       | S2. Search box search: antenatal OR pregnancy OR pregnant OR prenatal |
| 11       | Retrieved: 13 results (retained 0)                                    |
| 12       | Refleved. 15 lesuits (letailled 0)                                    |
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| 13       | S3. Search box search: antibiotic OR antibiotics OR antibacterial     |
| 14       | Retrieved: 25 results (retained 0)                                    |
| 15       |   |
| 16       | S4. Search box search: urine test pregnancy                           |
| 17       | Retrieved 67 results (retained 0)                                     |
| 18       |   |
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| 19       | S5. Browsed laboratory test publications                              |
| 20       | Retrieved: 46 (retained 0)  |
| 21       |   |
| 22       |   |
| 23       | S6. Browsed Kidney/Urologic publications                              |
|          | Retrieved: 90 (retained 0)  |
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| 30       | Retrieved: 90 (retained 0)  |
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| <u> </u> | For peer review only - http://bmionen.hmi.com/site/about/quidel       |

# Supplement 3. Eligibility criteria for screening effectiveness, women's outcome valuation, and treatment effectiveness

|                                 | PICOTS  | Study designs;<br>Language  |
|---------------------------------|---|---|
| Benefits and harms of screening | P: Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria   | RCTs, CCTs, controlled<br>observational designs (i.e.,                        |
|                                 | I: Any screening program, whereby there is an intent (i.e., clinical algorithm) for all pregnant women to receive a screening test with follow-up of screen-positive cases  | prospective and<br>retrospective cohort, case-<br>control, controlled before- |
|                                 | C: No screening program (but may include indicated testing and/or treatment upon development of symptoms), or a different screening test or algorithm   | after)  |
|                                 | O*: Maternal mortality (9), maternal sepsis (8), pyelonephritis (7), perinatal mortality ≥20 weeks' gestation (9), spontaneous abortion/pregnancy loss before 20 weeks' gestation (8), neonatal sepsis (8), preterm delivery <37 weeks' gestation (7), low birth weight <2500g (6), serious maternal and neonatal harms (7) | English and French  |
|                                 | T: Any timing   |   |
|                                 | S: Any primary care or clinical setting providing antenatal care to pregnant women  |   |
| Outcome valuation               | P: Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria; will also accept asymptomatic women who are not pregnant if necessary  | Qualitative, mixed methods<br>surveys/cross-sectional<br>designs              |
|                                 | I: Any screening program or test, and any antibiotic; will accept studies on treatment for any bacterial condition in pregnancy   | English and French  |
|                                 | C: Not applicable   |   |
|                                 | <b>O:</b> Several possible outcomes (e.g., relative weight/utilities of benefits and harms; willingness to be screened based on relative value placed on benefits and harms of screening programs or treatment)   |   |
|                                 | T: Any timing   |   |
|                                 | S: Any primary care or clinical setting providing antenatal care to pregnant women  |   |
| Benefits and harms of treatment | P: Asymptomatic pregnant women at any stage of pregnancy who are not at high risk for bacteriuria   | RCTs (or systematic review(s))  |
|                                 | I: Any antibiotic   | English and French  |
|                                 | C: No treatment or placebo  |   |
|                                 | O*: Maternal mortality (9), maternal sepsis (8), pyelonephritis (7), perinatal mortality ≥20 weeks' gestation (9), spontaneous abortion/pregnancy loss before 20 weeks' gestation (8), neonatal sepsis (8), preterm delivery <37 weeks' gestation (7), low birth weight <2500g (6), serious maternal and neonatal harms (7) |   |

|             | T: Any timing   |
|-------------|---|
|             | S: Any primary care or clinical setting providing antenatal care to pregnant women  |
| CCT: contro | blled clinical trial; g: grams: PICOTS: populations, interventions, comparators, outcomes, timing, and setting; RCT: randomized clinical trial  |
| * Outcome   | is ratings included in brackets; these were rated as critical/important for decision-making by CTFPHC members and by women recruited for patient engagement   |
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|             | S: Any primary care or clinical setting providing antenatal care to pregnant women lled clinical trial; g: grams: PICOTS: populations, interventions, comparators, outcomes, timing, and setting; RCT: randomized clinical trial s ratings included in brackets; these were rated as critical/important for decision-making by CTFPHC members and by women recruited for patient engagement |
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|             | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml   |
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# Supplement 4. Characteristics of included studies on screening effectiveness, outcome valuation, and treatment effectiveness

## Characteristics of included studies on screening effectiveness

| Objective     | To determine if a routine screening program for ASB can reduce the incidence of   |
|---------------|---|
|               | pyelonephritis and other adverse pregnancy outcomes, and if such a program would be   |
|               | economically feasible   |
| Methods       | Design: Non-concurrent cohort   |
|               | Inclusion criteria: All pregnant women followed at the Centre Hospitalier de Corbeil-   |
|               | Essonnes (prospective). Controls were all women who were not involved in the screening  |
|               | program (retrospective).  |
|               | Exclusion criteria: NR  |
| Participants  | Setting: Centre Hospitalier de Corbeil-Essonnes (a Hospital)  |
|               | Study period: January-October 1979 (and 10 previous months for the control group)   |
|               | Sample: n=370 pregnant women; n=170 in study group; n=200 in control group  |
|               | Mean age, y (SD): NR  |
|               | Risk factors: NR  |
|               | Length of follow-up: until delivery, and for 3-6 months after in those with $\geq 2$ instances of ASB; loss to follow-up: n=0.      |
| Interventions | Implementation of a routine screening and treatment program for ASB:  |
|               | 1) Screening of all women at 3, 5, 7 and 9 months of pregnancy, and treatment of thos diagnosed with ASB                            |
|               | 2) Controls only screened after presenting with clinical signs  |
|               | Urine testing characteristics:  |
|               | Urine collection: Midstream urine sample with cleansing of the vulva before micturition   |
|               | Urine testing: Microscopy, urine culture and Gram staining  |
|               | Criteria for positive test: $\geq 10^5$ CFU/mL  |
|               | Costational age (weeks) at first proposed wisity 22 menths for the treatment group, ND for  |
|               | Gestational age (weeks) at first prenatal visit: ~3 months for the treatment group; NR for the control group                        |
|               | Number of prenatal visits: at least 4 (every 2 months) for the treatment group; NR for  |
|               | control group   |
|               | Treatment: Treatment based on antibiotic sensitivity and at the discretion of the prescribin  |
|               | physician   |
| Outcomes      | Acute pyelonephritis: Clinical signs (fever, lumbar pain, dysuria, pollakiuria (urinary   |
|               | frequency)) and positive urine culture of 10 <sup>5</sup> CFU/mL  |
|               | Spontaneous abortion: ≤28 wks GA  |
|               | Preterm delivery: Delivery at <37 wks GA<br>Birth weight: Reported means for ASR vs. pop-ASR in study group: symptomatic + positive |
|               | Birth weight: Reported means for ASB vs. non-ASB in study group; symptomatic + positive culture vs. asymptomatic in controls        |
|               | Perinatal mortality: "stillbirth" as either death in utero or during delivery, all $\geq$ 31 wks GA                                 |

| Notos            | Adverse event(s): NR   |
|------------------|--|
| Notes            | Study is descriptive, no between-group associations tested<br>tic bacteriuria; CFU/mL: colony-forming units per millilitre; GA: gestational age; n: number; NI |
|                  | : standard deviation; wks: weeks; y: year  |
| Gratacós et al., | 1994   |
| Objective        | To determine the incidence of pyelonephritis in pregnant women before and after the introduction of a screening program for ASB                                |
| Methods          | Design: Non-concurrent cohort  |
|                  |  |
|                  | Inclusion criteria: Study group were women who were seen at the clinic at <25 wks GA wh  |
|                  | subsequently delivered January 1991-December 1992. Controls were women who were  |
|                  | seen at the clinic at <25 wks GA and delivered January 1987-December 1990.   |
|                  |  |
|                  | Exclusion criteria: NR   |
| Participants     | Setting: An obstetrics clinic in Barcelona, Spain  |
|                  | $\sim$   |
|                  | Study period: January 1987-December 1992 (study group: January 1991-December 1992;   |
|                  | controls: January 1987-December 1990)  |
|                  |  |
|                  | Sample: n=4,917 pregnant women; n=1,652 in study group, n=3,265 in control group   |
|                  |  |
|                  | Mean age, y (SD): NR   |
|                  |  |
|                  | Risk factors: NR   |
|                  | Length of follow-up: until delivery; loss to follow-up: n=10   |
| Interventions    | Implementation of a routine screening and treatment program for ASB:   |
| merventions      | 1) Screening of all women <25 wks pregnant and treatment of those diagnosed with   |
|                  | ASB  |
|                  | 2) Controls: no routine screening  |
|                  | 2) controis. no routine screening  |
|                  | Urine testing characteristics:   |
|                  | Urine collection: Midstream morning urine sample. Women with positive culture returned   |
|                  | within 1-2 wks for a second midstream urine culture, after stressing the importance of   |
|                  | cleansing the vulva before micturition.  |
|                  | Urine testing: Urine culture following the guidelines of the National Committee for Clinica  |
|                  | Laboratory Standards   |
|                  | Criteria for positive test: Two consecutive positive urine cultures (number of organisms NF  |
|                  | with growth of the same species  |
|                  | Gestational age (wks), at first prenatal visit: <25  |
|                  | Number of prenatal visits: study group: NR; controls: NR   |
|                  | Treatment: 7-day course of antibiotics based on antibiotic consitivity testing, started 1.2  |
|                  | Treatment: 7-day course of antibiotics based on antibiotic sensitivity testing, started 1-2  |
|                  | wks after the second culture. At 1-4 wks after treatment and at least once more before   |
|                  | delivery, additional midstream urine samples were obtained. If repeat cultures were  |
| Outograd         | positive, antibacterial therapy was repeated until cultures were negative for ASB.   |
| Outcomes         | Pyelonephritis: fever, flank pain, tenderness in costovertebral angle, ≥1 positive culture   |

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|       | Adverse event(s): NR   |
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| Notes | Also investigated prevalence of ASB and response to treatment in the study group, but this |
|       | was not compared to the controls who did not receive routine screening                     |

ASB: asymptomatic bacteriuria; n: number; ND: not defined; NR: not reported; SD: standard deviation; wks: weeks; y: year(s)

| Rhode, 2007   |   |
|---------------|---|
| Objective     | To determine if urinary tract infection, high blood pressure, and gestational diabetes mellitus are underdiagnosed when prenatal urine testing is done on a clinically indicated basis versus a routine basis   |
| Methods       | <ul> <li>Design: Non-concurrent cohort</li> <li>Inclusion criteria: Routine screening group were all pregnant women who enrolled for care and delivered before August 15, 2002. Indicated screening group were all women who enrolled for care and delivered after August 15, 2002.</li> <li>Exclusion criteria: Women who were in the transitional urine screening group (enrollment prior to and delivery after August 15, 2002), who received both screening techniques (n=570)</li> </ul>   |
| Participants  | Setting: Hospital-based nurse-midwifery practice, Aurora, Colorado; provides care to<br>predominantly medically underserved and Hispanic women<br>Study period: Charts of patients enrolled for care and delivered November 2000-March<br>2004<br>Sample: n= 1,952 pregnant women; n=933 in routine screening group; n=1019 in indicated<br>screening group   |
|               | Mean age, y (SD): Routine screening= 24.4 (5.6); Indicated screening= 24.9 (5.1)<br>Risk factors:<br>Gestational diabetes: routine screening=81 (9.3%), indicated screening=42 (4.2%)<br>Race (ethnicity): Hispanic; routine screening=669 (72.1%), indicated screening=783 (76.9%)<br>Length of follow-up: until delivery or patient left the practice; loss to follow-up (n=112;<br>4.6%); total ineligible=459 (19%), due to: spontaneous abortion (n=58), transfer of care<br>(n=218), transfer to high risk care (n=71)  |
| Interventions | Routine urine screening (enrollment and delivery before August 15, 2002): first visit with<br>chemical reagent strips, lab urinalysis and culture; subsequent visits with chemical reagent<br>strips, culture or urinalysis as indicated1<br>Indicated urine screening (enrollment on and delivery after August 15, 2002): first visit with<br>chemical reagent strips, lab urinalysis and culture; subsequent visits with chemical reagent<br>strip only if one of the criteria was present (risk factors for UTI, GDM). Follow-up of culture<br>or lab urinalysis as indicated1Urine testing characteristics:<br>Urine collection: midstream morning urine sample, first visit<br>Urine testing: chemical reagent strip test, lab urinalysis and culture; |

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|          | Mean number of strip tests performed (SD): Routine screening= 7.8 (3.4), range 0-19;                        |
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|          | Indicated screening= 1.4 (1.3), range 0-16  |
|          | Criteria for positive test: NR  |
|          | Contrational and (who) at start of any (CD). Doubles approximately 20 5 (0.4) is directed                   |
|          | Gestational age (wks) at start of care (SD): Routine screening= 20.5 (9.4); Indicated screening= 20.3 (8.9) |
|          |   |
|          | Number of prenatal visits: NR   |
|          |   |
|          | Treatment: NR   |
| Outcomes | Pyelonephritis: ND; however, clearly differentiated from ASB, cystitis and undetermined UTI                 |
|          | Preterm delivery: <37 wks GA <sup>2</sup>   |
|          |   |
|          | Adverse event(s): NR  |
| Notes    | Authors compared eligible participants to those who became ineligible during the study                      |
|          | period. In the routine screening group, eligible and ineligible women differed in terms of                  |
|          | marital status, race, payment source, # preterm deliveries, and # weeks gestation at start of               |
|          | care. In the indicated screening group, eligible and ineligible women differed in terms of                  |
|          | race, # of abortions, and # weeks of gestation at start of care.  |
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ASB: asymptomatic bacteriuria; n: number; ND: not defined; NR: not reported; SD: standard deviation; UTI: urinary tract infection; GDM: gestational diabetes mellitus; wks: weeks; y: year(s)

<sup>1</sup> lab urinalysis may be used instead of culture due to presence of blood in urine; culture typically done to confirm reagent strip, unless reagent strip was used to test for elevated blood pressure (information provided by study author)

<sup>2</sup> Criteria for outcomes were confirmed by study author(s)

| Uncu, 2001   |   |
|--------------|---|
| Objective    | To determine the incidence of asymptomatic bacteriuria during pregnancy and its relation  |
|              | to pregnancy complications  |
| Methods      | Design: Non-concurrent cohort   |
|              | Inclusion criteria: Screened group were pregnant women ≤32 wks GA seen at the antenatal outpatient clinic. Controls were women who delivered in clinic before study and were not screened for ASB; formed in retrospective manner from first day of study |
|              | Exclusion criteria: Patients who were followed-up at clinic due to prior renal disease,   |
|              | positive for ASB or were taking antibiotics   |
| Participants | Setting: Antenatal outpatient clinic, Uludag University Faculty of Medicine, Department of Obstetrics and Gynecology, Turkey  |
|              | Study period: June 1998-January 1999  |
|              | Sample: Screened= 186; Controls= 186  |
|              | Mean age, y (SD): Screened= 27.7 (5.1); Controls= 27.7 (4.6)  |
|              | Risk factors:   |
|              | Gestational diabetes mellitus: Screened=7 (3.8%); Controls= 5 (2.7%)  |
|              | Socioeconomic status: lower SES correlated with high prevalence of ASB*   |
|              | Length of follow-up: NR; loss to follow-up: NR  |

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| pregnancy complications:         1)       Screening group: All pregnant women routinely screened at first visit with w<br>blood count, total urine analysis and urine culture.         2)       Controls: Formed in a retrospective manner from the first day of the study w<br>pregnant women who delivered in the clinic and who were not routinely scr         Urine testing characteristics:       Urine testing: whole blood count, total urine analysis, and urine culture<br>Criteria for positive test: >10 <sup>5</sup> CFU/mL of the same organism         Gestational age (wks), at time of urine culture: beginning of pregnancy         Number of prenatal visits: NR         Treatment: n=23 [7-10 days of antibiotics based on sensitivity testing, Follow-up 7-datantibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)         Outcomes       Pyelonephritis: ND         Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation<br>Prematurity <sup>2</sup> : <37 wks of gestation         Adverse event(s): NR         Fetal abnormalities: ND         Notes       Total screened for ASB=270→ with urine cultures=247→ sufficient delivery records=<br>excluded)         *statistically significant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: grige; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrason<br>wks: weeks; y: year(s)         'Criteria for outcomes were confirmed by study author(s) |            |
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| blood count, total urine analysis and urine culture.         2)       Controls: Formed in a retrospective manner from the first day of the study were pregnant women who delivered in the clinic and who were not routinely scription of the study were collection: midstream morning urine sample, first visit         Urine testing characteristics:       Urine collection: midstream morning urine sample, first visit         Urine testing: whole blood count, total urine analysis, and urine culture       Criteria for positive test: >10° CFU/mL of the same organism         Gestational age (wks), at time of urine culture: beginning of pregnancy       Number of prenatal visits: NR         Treatment: n=23 [7-10 days of antibiotics based on sensitivity testing, Follow-up 7-data antibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)         Outcomes       Pyelonephritis: ND         Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation         Prematurity <sup>2</sup> : <37 wks of gestation   | whole      |
| pregnant women who delivered in the clinic and who were not routinely scr         Urine testing characteristics:         Urine collection: midstream morning urine sample, first visit         Urine testing: whole blood count, total urine analysis, and urine culture         Criteria for positive test: >10 <sup>5</sup> CFU/mL of the same organism         Gestational age (wks), at time of urine culture: beginning of pregnancy         Number of prenatal visits: NR         Treatment: n=23 [7-10 days of antibiotics based on sensitivity testing, Follow-up 7-da antibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)         Outcomes       Pyelonephritis: ND         Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation         Adverse event(s): NR         Fetal abnormalities: ND         Notes       Total screened for ASB=270 → with urine cultures=247 → sufficient delivery records= excluded)         statistically significant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: gr         ge; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrason rks: weeks; y: year(s)         Criteria for outcomes were confirmed by study author(s)   |            |
| Urine collection: midstream morning urine sample, first visit         Urine testing: whole blood count, total urine analysis, and urine culture         Criteria for positive test: >10 <sup>5</sup> CFU/mL of the same organism         Gestational age (wks), at time of urine culture: beginning of pregnancy         Number of prenatal visits: NR         Treatment: n=23 [7-10 days of antibiotics based on sensitivity testing, Follow-up 7-da antibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)         Outcomes       Pyelonephritis: ND         Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation         Prematurity <sup>2</sup> : <37 wks of gestation  |            |
| Urine testing: whole blood count, total urine analysis, and urine culture<br>Criteria for positive test: >10 <sup>5</sup> CFU/mL of the same organism         Gestational age (wks), at time of urine culture: beginning of pregnancy         Number of prenatal visits: NR         Treatment: n=23 [7-10 days of antibiotics based on sensitivity testing, Follow-up 7-da<br>antibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)         Outcomes       Pyelonephritis: ND<br>Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation<br>Prematurity <sup>2</sup> : <37 wks of gestation  |            |
| Criteria for positive test: >10 <sup>5</sup> CFU/mL of the same organism         Gestational age (wks), at time of urine culture: beginning of pregnancy         Number of prenatal visits: NR         Treatment: n=23 [7-10 days of antibiotics based on sensitivity testing, Follow-up 7-datantibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)         Outcomes       Pyelonephritis: ND         Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation         Prematurity <sup>2</sup> : <37 wks of gestation  |            |
| Gestational age (wks), at time of urine culture: beginning of pregnancy         Number of prenatal visits: NR         Treatment: n=23 [7-10 days of antibiotics based on sensitivity testing, Follow-up 7-datantibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)         Outcomes       Pyelonephritis: ND         Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation         Prematurity <sup>2</sup> : <37 wks of gestation   |            |
| Number of prenatal visits: NR         Treatment: n=23 [7-10 days of antibiotics based on sensitivity testing, Follow-up 7-data antibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)         Outcomes       Pyelonephritis: ND<br>Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation<br>Prematurity <sup>2</sup> : <37 wks of gestation   |            |
| Treatment: n=23 [7-10 days of antibiotics based on sensitivity testing, Follow-up 7-data antibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)         Outcomes       Pyelonephritis: ND         Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation Prematurity <sup>2</sup> : <37 wks of gestation   |            |
| antibiotics for recurrent ASB (n=5)]; ASB recurrence 5/23 (21.7%)         Outcomes       Pyelonephritis: ND<br>Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation<br>Prematurity <sup>2</sup> : <37 wks of gestation  |            |
| Outcomes       Pyelonephritis: ND         Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation         Prematurity <sup>2</sup> : <37 wks of gestation  | lays of    |
| Intrauterine death <sup>2</sup> : no fetal cardiac activity by USG, after 20 weeks' gestation         Prematurity <sup>2</sup> : <37 wks of gestation         Adverse event(s): NR         Fetal abnormalities: ND         Notes       Total screened for ASB=270→ with urine cultures=247→ sufficient delivery records=         excluded)         statistically significant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: ge; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrason vks: weeks; y: year(s)         Criteria for outcomes were confirmed by study author(s)   |            |
| Prematurity²: <37 wks of gestation         Adverse event(s): NR         Fetal abnormalities: ND         Notes       Total screened for ASB=270→ with urine cultures=247→ sufficient delivery records=<br>excluded)         statistically significant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: ge<br>ge; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrason<br>vks: weeks; y: year(s)         Criteria for outcomes were confirmed by study author(s)  |            |
| Adverse event(s): NR         Fetal abnormalities: ND         Notes       Total screened for ASB=270→ with urine cultures=247→ sufficient delivery records=<br>excluded)         statistically significant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: ge<br>ge; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrason<br>vks: weeks; y: year(s)         Criteria for outcomes were confirmed by study author(s)   |            |
| Fetal abnormalities: ND         Notes       Total screened for ASB=270→ with urine cultures=247→ sufficient delivery records=<br>excluded)         statistically significant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: ge         ge; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrason         vks: weeks; y: year(s)         Criteria for outcomes were confirmed by study author(s)  |            |
| Fetal abnormalities: ND         Notes       Total screened for ASB=270→ with urine cultures=247→ sufficient delivery records=<br>excluded)         statistically significant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: ge         ge; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrason         vks: weeks; y: year(s)         Criteria for outcomes were confirmed by study author(s)  |            |
| Notes       Total screened for ASB=270→ with urine cultures=247→ sufficient delivery records=<br>excluded)         statistically significant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: ge; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrason vks: weeks; y: year(s)         Criteria for outcomes were confirmed by study author(s)   |            |
| excluded)<br>statistically significant; ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millitre; GA: ge<br>ge; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrason<br><i>v</i> ks: weeks; y: year(s)<br>Criteria for outcomes were confirmed by study author(s)   | =186 (61   |
| ge; ND: not defined; NR: not reported; SD: standard deviation; SES: socioeconomic status; USG: ultrason<br>ks: weeks; y: year(s)<br>Criteria for outcomes were confirmed by study author(s)  |            |
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| Butters, 1990  |  |
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| Objective      | To determine the level of knowledge of the effects of commonly used drugs on a fetus   |
| Methods        | Design: Cross-sectional (self-completed questionnaire)   |
|                | Recruitment: Participants were recruited from postnatal wards of the hospitals on a weekly basis   |
| Participants   | Setting: Two maternity hospitals: one serves a white urban and semirural population, the other serves a population mix from rural to urban and includes ethnic minorities. Both are located in Glasgow, Scotland |
|                | Inclusion criteria: Postnatal women who were still in hospital after delivering. They had to be given the  |
|                | questionnaire in person (i.e. they were either in their bed or in the sitting room when the questionnaire distributed).  |
|                | Exclusion criteria: Women who had vaginal delivery on the day of the study, women one or two days pos<br>delivery by caesarean section, and women who were unable to read English.                               |
|                | Study period: October 1, 1987 and March 31, 1988.  |
|                | Sample: n=514  |
|                | Age range: 15 to 40 years; 66 (13%) between 15 and 20 years, 141 (27%) between 21 and 25 years, 176 (<br>between 26 and 30 years, and 127 (25%) aged over 30 years.  |
|                | Gestational age: NA  |
|                | Parity: First pregnancy (53%)  |
|                | Race/ethnicity: Multiple ethnicities, mainly Scottish.   |
|                | Education level: NR  |
| Interventions  | Anonymous short questionnaire with mostly tick boxes.  |
| Outcomes       | -254 (49%) said they would take an antibiotic prescribed by their doctor, 246 (48%) said they would not,   |
|                | 14 (3%) did not respond.   |
|                | -The responses were similar for all ages and social class groups.<br>-There was a strong relationship between the women that would avoid taking an analgesic (n=80, 74%))  |
|                | those that would avoid taking an antibiotic (187, 45%), p<0.0001.  |
| NA: not        | applicable; NR: not reported   |
|                |  |
| Kazemier, 2015 |  |
| Objective      | To investigate the consequences of treated and untreated ASB in pregnancy  |
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Methods

1 2

| Methods          | Design: Prospective cohort (screening vs. no screening) with embedded RCT (decision on entry into the study   |
|------------------|---|
|                  | considered cross-sectional)   |
|                  | Recruitment: Pregnant women attending antenatal clinics offering screening (not routinely available)  |
| Participants     | Setting: 8 hospitals and 5 ultrasound centres, the Netherlands  |
|                  | Inclusion criteria: Pregnant women aged ≥18 years with a singleton pregnancy who were between 16 and 22 wks GA, tested positive for ASB, and did not have symptoms of UTI.  |
|                  | Exclusion criteria: History of preterm delivery <34 wks GA, warning signs of imminent preterm delivery, fetal congenital malformations, antibiotic use within 2 weeks of screening, known glucose-6-phosphate dehydrogenase deficiency, hypersensitivity to nitrofurantoin, risk factors for complicated UTI (e.g., pregestational DM, use of immunosuppressive medication or functional or structural abnormalities of the urinary tract). |
|                  | Study period: October 11, 2011-August 22, 2014  |
|                  | Sample: n=248   |
|                  | Mean age (SE), years: treated=29 (0.74), placebo or untreated=31 (0.33)   |
|                  | Median gestational age (wks + days at screening (IQR)): treated=20+2 (19+6 to 20+5), placebo or untreated=20+0 (19+3 to 20+3)   |
|                  | Parity (% nulliparous): treated=50%, placebo or untreated=42%   |
|                  | Ethnicity (non-white): treated n=3 (8%), placebo or untreated n=36 (17%)  |
|                  | Low education (≤pre-vocational level): treated n=6 (15%), placebo or untreated n=21 (10%)   |
| Interventions    | Women who were positive for ASB were invited to participate in a treatment RCT. Reasons for declining participation were recorded.  |
| Outcomes         | Most women (155/163 positive for ASB, 94%) who did not want to participate made this choice because they did not want to receive antibiotics during pregnancy for an asymptomatic condition.  |
|                  | mptomatic bacteriuria; DM: diabetes mellitus; GA: gestational age; NA: not applicable; NR: not reported;<br>domized controlled trial; SE: standard error; UTI: urinary tract infection; wks: weeks  |
| Lupattelli, 2014 |   |
| Objective        | To investigate the association between health literacy and perception of medication risk, beliefs about medications, use and non-adherence to prescribed pharmacotherapy during pregnancy.  |
|                  |   |

| Recruitment: Banners announcing the study were placed on one to four websites per country and/or social |
|---|
| networks commonly visited by pregnant women that had a high number of daily users.                      |

Design: Cross-sectional internet-based questionnaire

| Participants                                      | Setting: Anonymous internet questionnaire with participants from 18 countries: Australia, Austria, Canada  |
|---|--|
| • • •   | Croatia, Finland, France, Iceland, Italy, The Netherlands, Norway, Poland, Russia, Serbia, Slovenia, Sweder  |
|   | Switzerland, United Kingdom and United Sates as well as some South American countries.   |
|   | Inclusion criteria: Pregnant women at any stage of gestation.  |
|   | Exclusion criteria: Women who were not currently pregnant.   |
|   | Study period: October 1 2011 to February 29, 2012  |
|   | Sample: n=4999   |
|   |  |
|   | Mean age (SD): NR overall  |
|   | Costational again wasks maan (SD): 22.4 (10.2)   |
|   | Gestational age in weeks, mean (SD): 22.4 (10.3)   |
|   | Race/ethnicity: Multinational  |
| Interventions                                     | Health literacy was measured using a self-assessment scale of 0 to 4 for three questions.  |
|   | Perceived risk of medications was measured using 13 agents on a scale of 0 to 10.  |
|   | Beliefs about medications were measured using a 5-point agreement scale for three questions.   |
|   |  |
|   | Participants were asked standardized questions about medication use for specific illnesses, non-adherence  |
|   | Participants were asked standardized questions about medication use for specific illnesses, non-adherence over-the-counter medication use with free text entry.  |
|   | -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.<br>reported; SD: standard deviation   |
|   | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation  |
| NR: not<br>Mashayekhi, 20                         | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation  |
| NR: not   | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation  |
| NR: not<br>Mashayekhi, 20<br>Objective            | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire   |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         009         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.   |
| NR: not<br>Mashayekhi, 20<br>Objective            | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire   |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         009         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.   |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.         Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.  |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.         Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.         Inclusion criteria: Antenatal and postnatal women.   |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.         Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.         Inclusion criteria: Antenatal and postnatal women.         Exclusion criteria: Women who had a complicated labor.  |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation         09         To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.         Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.         Inclusion criteria: Antenatal and postnatal women.         Exclusion criteria: Women who had a complicated labor.         Study period: August 2006 and May 2007               |
| NR: not<br>Mashayekhi, 20<br>Objective<br>Methods | over-the-counter medication use with free text entry.         -96.2% of participants felt penicillin antibiotics posed a teratogenic risk.         reported; SD: standard deviation <b>109</b> To examine the awareness of pregnant women about the effects of drugs in pregnancy         Design: Cross sectional, questionnaire         Recruitment: Women in the postnatal and prenatal wards were invited.         Setting: Pre and Post-natal wards of two maternity hospitals in Iran, one private and one public.         Inclusion criteria: Antenatal and postnatal women.         Exclusion criteria: Women who had a complicated labor.         Study period: August 2006 and May 2007         Sample: n=400 |

|                                       | Parity: None – 200 (50.0%), one – 127 (31.8%), two (54, 13.5%), more than two – 19 (4.8%)  |
|---------------------------------------|--|
|                                       | Race/ethnicity: Iranian  |
|                                       | Education level: High school or lower – 184 (46.0%), diploma – 147 (36.8%), University education – 69 (17.3%)  |
| Interventions                         | Face-to-face questionnaire divided into three sections: demographic information, drug use before and during pregnancy including drug safety, source of information regarding drugs safety during pregnancy. Majority of response options were tick boxes.  |
| Outcomes                              | <ul> <li>-Specific antibiotics the women felt were safe: penicillin – 51 (12.8%), ampicillin – 36 (9.0%), amoxicillin – 66 (16.5%), metronidazole - 20 (5.0%), cephalosporin - 10 (2.5%), other antibiotics - 6 (1.5%).</li> <li>-For penicillin use none felt it was unsafe for the mother, 143 (35.8%) felt it was unsafe for the fetus, 40 (10.0%) felt it was unsafe for both.</li> <li>-For ampicillin use 4 (1.0%) felt it was unsafe for the mother, 145 (36.3%) felt it was unsafe for the fetus, 28 (7.0%) felt it was unsafe for both.</li> <li>-For amoxicillin use 5 (1.3%) felt it was unsafe for the mother, 147 (36.8%) felt it was unsafe for the fetus, 18 (4.5%) felt it was unsafe for both.</li> <li>-For metronidazole use none felt it was unsafe for the mother, 129 (32.3%) felt it was unsafe for the fetus, 21 (5.3%) felt it was unsafe for both.</li> <li>-For cephalosporin use none felt it was unsafe for the mother, 127 (31.8%) felt it was unsafe for the fetus, 18 (4.5%) felt it was unsafe for both.</li> <li>-For other antibiotic use none felt it was unsafe for the mother, 125 (31.3%) felt it was unsafe for the fetus, 28 (7.0%) felt it was unsafe for both.</li> </ul> |
| NA: not a Nordeng, 2010               | applicable; SE: standard error; SD: standard deviation   |
|                                       | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most   |
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| Nordeng, 2010<br>Objective            | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used   |
| Nordeng, 2010<br>Objective            | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by  |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.  |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.         Setting: Internet  |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.         Setting: Internet         Inclusion criteria: Pregnant woman or a mother of a child less than 5 years old.   |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.         Setting: Internet         Inclusion criteria: Pregnant woman or a mother of a child less than 5 years old.         Exclusion criteria: NR  |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.         Setting: Internet         Inclusion criteria: Pregnant woman or a mother of a child less than 5 years old.         Exclusion criteria: NR         Study period: September 16, 2008 to October 25, 2008   |
| Nordeng, 2010<br>Objective<br>Methods | To evaluate the perception of risk of drugs during pregnancy and sources of drug exposure information most commonly used         Design: Retrospective web-based questionnaire         Recruitment: Invitation to participate in the questionnaire was posted to four webpages commonly used by pregnant women and mothers.         Setting: Internet         Inclusion criteria: Pregnant woman or a mother of a child less than 5 years old.         Exclusion criteria: NR         Study period: September 16, 2008 to October 25, 2008         Sample: n=1793; 866 (48.3%) pregnant, 927 (51.7%) mothers   |

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|               | Race/ethnicity: Norwegian   |
|---------------|---|
|               | Education level: Basic school level – 88 (4.9%), upper secondary education – 390 (21.8%), tertiary education (<4 years) – 810 (45.2%), tertiary education (>4 years) – 421 (23.5%), other education – 84 (4.7%) |
| Interventions | Questionnaire consisted of open-ended questions and numeric rating scales from 0 to 10 relating to  |
|               | teratogenic risk of 17 drugs, foods, chemicals and radiation.   |
| Outcomes      | -There was a significant difference in mean risk perception scores between non-users of the indicated drugs   |
|               | and users of 4.3 vs. 3.0 (p<0.001) with a ratio between non-users/users of 1.4.   |

NR: not reported

| Objective     | To assess the perception of the teratogenic risk of common medication by professionals and the public             |
|---------------|---|
| Methods       | Design: Cross-sectional   |
|               | Recruitment: Pregnant women attending a regular obstetric follow up in an out-patient clinic at a University      |
|               | hospital; non-pregnant women from an obstetric and gynecological out-patient clinic in the hospital and in a      |
|               | randomized manner from four different neighborhoods. Medical staff (general physicians, gynecologists and         |
|               | medical students were also recruited and interviewed, their data are not included here).                          |
| Participants  | Setting: Outpatient clinic at a University hospital, home setting   |
| -             |   |
|               | Inclusion criteria:   |
|               | Currently pregnant for the pregnant women group, not pregnant for the comparison group                            |
|               |   |
|               | Exclusion criteria: NR  |
|               | Study period: NR  |
|               |   |
|               | Sample: n=81 pregnant women, n=63 non-pregnant women  |
|               |   |
|               | Median age: NR  |
|               |   |
|               | Gestational age: NR   |
|               | Gravidity: NR   |
|               | Graviarty. INA  |
|               | Parity: NR  |
|               |   |
|               | Race/ethnicity: Spanish   |
|               | Education level: NR   |
| Interventions | A visual analogue scale with a 10 cm horizontal line with a short vertical line at each end, with a scale of 0 to |
|               | 100%. Participants were asked to mark on the scale what they thought was the potential risk for fetal             |
|               | malformations and malformations in non-pregnant women given exposure to a particular drug.                        |

| Gestational age: First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.94         Gravidity: 243 primigravida; 152 multigravida         Race/ethnicity: Indian         Education level: Undergraduates – 220 (54.32%), graduates - 185 (45.68%)         Interventions         98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed a written questionnaire after interviewing each participant. The participants' statements were confirmed by their records if available.         Outcomes       -190 (46.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should be used in pregnancy while 25 (6   | Outcomes      | -The mean value of the perceived teratogenic risk by non-pregnant women was higher than that perceived       |
|--|---------------|--|
| by pregnant women for erythromycin (S0.0 vs. 30.0) and amoxicillin (S0.5 vs. 34.0).         -The Mann-Whitney U test showed a significant difference between groups for erythromycin and amoxicil respectively (pc.00.5 vs. 20.001, non-pregnant vs. pregnant women).         -In comparison to the "true" limits, risk from antibiotics was rated higher by pregnant women (erythromy chi-square: 3.99, p=0.045; amoxicillin chi-square: 17.21, p=0.0001).         cm: centimeter(s); NR: not reported         Sharma, 2006         Objective       To evaluate the drug utilization pattern in pregnant women and the effect of education and economic stat         Methods       Design: Retrospective cross-sectional study         Recruitment: Medical students interviewed pregnant women visiting the antenatal clinic.         Participants       Setting: Antenatal clinic of a medical college in North India         Inclusion criteria: Pregnant women       Exclusion criteria: NR         Study period: June 2005 to December 2005       Sample: n=405         Age range: Less than 20 years – 25 (6.17%), 20 to 35 years – 240 (59.26%), more than 35 years – 90 (22.22         Gestational age: First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.9)         Gravidity: 243 primigravida; 152 multigravida         Race/ethnicity: Indian         Education level: Undergraduates – 220 (54.32%), graduates - 185 (45.68%)         Interventions       98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy co  |               |  |
| -The Mann-Whitney U test showed a significant difference between groups for erythromycin and amoxicil respectively (p6.0.05 vs. pc0.001, non-pregnant vs. pregnant women).         -In comparison to the "true" limits, risk from antibilotics was rated higher by pregnant women (erythromy chi-square: 3.99, p=0.045; amoxicillin chi-square: 17.21, p=0.0001).         cm: centimeter(s); NR: not reported         Sharma, 2006         Objective       To evaluate the drug utilization pattern in pregnant women and the effect of education and economic state (the drug utilization pattern) in pregnant women visiting the antenatal clinic.         Methods       Design: Retrospective cross-sectional study         Recruitment: Medical students interviewed pregnant women visiting the antenatal clinic.         Participants       Setting: Antenatal clinic of a medical college in North India         Inclusion criteria: Pregnant women       Exclusion criteria: NR         Study period: June 2005 to December 2005       Sample: n=405         Age range: Less than 20 years – 25 (6.17%), 20 to 35 years – 240 (59.26%), more than 35 years – 90 (22.22         Gestational age: First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.9         Gravidity: 243 primigravida; 152 multigravida         Race/ethnicity: Indian         Education level: Undergraduates – 220 (54.32%), graduates -185 (45.68%)         Interventions       % medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed a written questionnaire after   |               |  |
| respectively (p<0.05 vs. p<0.001, non-pregnant vs. pregnant women).         -in comparison to the "true" limits, risk from antibiotics was rated higher by pregnant women (erythromy chi-square: 399, p=0.045; amoxicillin chi-square: 17.21, p=0.0001).         cm: centimeter(s); NR: not reported         Sharma, 2006         Objective       To evaluate the drug utilization pattern in pregnant women and the effect of education and economic state the drug utilization pattern in pregnant women visiting the antenatal clinic.         Methods       Design: Retrospective cross-sectional study         Recruitment: Medical students interviewed pregnant women visiting the antenatal clinic.         Participants       Setting: Antenatal clinic of a medical college in North India         Inclusion criteria: Pregnant women       Exclusion criteria: Pregnant women         Exclusion criteria: NR       Study period: June 2005 to December 2005         Sample: n=405       Age range: Less than 20 years – 25 (6.17%), 20 to 35 years – 240 (59.26%), more than 35 years – 90 (22.22         Gestational age: First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.9)         Gravidity: 243 primigravida; 152 multigravida         Race/ethnicity: Indian         Education level: Undergraduates – 220 (54.32%), graduates - 185 (45.68%)         Interventions       98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed is written questionnaire after interviewing each participant. The participants' stat   |               |  |
| -In comparison to the "true" limits, risk from antibiotics was rated higher by pregnant women (erythromy chi-square: 3.99, p=0.045; amoxicillin chi-square: 17.21, p=0.0001).         cm: centimeter(s); NR: not reported         Sharma, 2006         Objective       To evaluate the drug utilization pattern in pregnant women and the effect of education and economic states and the effect of education effect of education economic and economic states and the effect of education economic e   |               |  |
| chi-square: 3.99, p=0.045; amoxicillin chi-square: 17.21, p=0.0001).         cm: centimeter(s); NR: not reported         Sharma, 2006         Objective       To evaluate the drug utilization pattern in pregnant women and the effect of education and economic states and the effect of education economic and economic and economic and the effect of education economic and economic an   |               |  |
| cm: centimeter(s); NR: not reported         Sharma, 2006         Objective       To evaluate the drug utilization pattern in pregnant women and the effect of education and economic sta         Methods       Design: Retrospective cross-sectional study         Recruitment: Medical students interviewed pregnant women visiting the antenatal clinic.         Participants       Setting: Antenatal clinic of a medical college in North India         Inclusion criteria: NR       Study period: June 2005 to December 2005         Sample: n=405       Age range: Less than 20 years – 25 (6.17%), 20 to 35 years – 240 (59.26%), more than 35 years – 90 (22.22         Gestational age: First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.9)         Gravidity: 243 primigravida; 152 multigravida         Race/ethnicity: Indian         Education level: Undergraduates – 220 (54.32%), graduates - 185 (45.68%)         Interventions       98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed a written questionnaire after interviewing each participant. The participants' statements were confirmed by their records if available.         Outcomes       -190 (26.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should be u         NR: not reported       Twigg, 2016   |               |  |
| Sharma, 2006         Objective       To evaluate the drug utilization pattern in pregnant women and the effect of education and economic statements         Methods       Design: Retrospective cross-sectional study         Recruitment: Medical students interviewed pregnant women visiting the antenatal clinic.         Participants       Setting: Antenatal clinic of a medical college in North India         Inclusion criteria: Pregnant women       Exclusion criteria: Pregnant women         Exclusion criteria: NR       Study period: June 2005 to December 2005         Sample: n=405       Age range: Less than 20 years – 25 (6.17%), 20 to 35 years – 240 (59.26%), more than 35 years – 90 (22.22         Gestational age: First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.9)         Gravidity: 243 primigravida; 152 multigravida         Race/ethnicity: Indian         Education level: Undergraduates – 220 (54.32%), graduates - 185 (45.68%)         Interventions       98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed a written questionnaire after interviewing each participant. The participants' statements were confirmed by their records if available.         Outcomes       -190 (46.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should be ux         NR: not reported       Twigg, 2016   | cm: cent      |  |
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| Recruitment: Medical students interviewed pregnant women visiting the antenatal clinic.         Participants       Setting: Antenatal clinic of a medical college in North India         Inclusion criteria: Pregnant women       Exclusion criteria: NR         Study period: June 2005 to December 2005       Sample: n=405         Age range: Less than 20 years – 25 (6.17%), 20 to 35 years – 240 (59.26%), more than 35 years – 90 (22.22         Gestational age: First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.9)         Gravidity: 243 primigravida; 152 multigravida         Race/ethnicity: Indian         Education level: Undergraduates – 220 (54.32%), graduates - 185 (45.68%)         Interventions       98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed a written questionnaire after interviewing each participant. The participants' statements were confirmed by their records if available.         Outcomes       -130 (46.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should be ux NR: not reported         Twigg, 2016       Twigg, 2016  | Objective     | To evaluate the drug utilization pattern in pregnant women and the effect of education and economic stat     |
| Participants       Setting: Antenatal clinic of a medical college in North India         Inclusion criteria: Pregnant women       Exclusion criteria: NR         Study period: June 2005 to December 2005         Sample: n=405         Age range: Less than 20 years – 25 (6.17%), 20 to 35 years – 240 (59.26%), more than 35 years – 90 (22.22         Gestational age: First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.9)         Gravidity: 243 primigravida; 152 multigravida         Race/ethnicity: Indian         Education level: Undergraduates – 220 (54.32%), graduates - 185 (45.68%)         Interventions       98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed a written questionnaire after interviewing each participant. The participants' statements were confirmed by their records if available.         Outcomes       -190 (46.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should be us NR: not reported         Twigg, 2016       Twigg, 2016  | Methods       | Design: Retrospective cross-sectional study  |
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| Race/ethnicity: Indian         Education level: Undergraduates – 220 (54.32%), graduates - 185 (45.68%)         Interventions       98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed a written questionnaire after interviewing each participant. The participants' statements were confirmed by their records if available.         Outcomes       -190 (46.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should  |               | Gestational age: First trimester – 30 (7.40%), second trimester – 100 (24.69%), third trimester – 275 (67.90 |
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| written questionnaire after interviewing each participant. The participants' statements were confirmed by their records if available.         Outcomes       -190 (46.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should be used.         NR: not reported  |               | Education level: Undergraduates – 220 (54.32%), graduates - 185 (45.68%)                                     |
| their records if available.       Outcomes       -190 (46.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should be used in pregnancy                      | Interventions | 98 medical students trained in pharmacokinetic and pharmacodynamic changes in pregnancy completed a          |
| Outcomes       -190 (46.91%) believed antibiotics should not be used in pregnancy while 25 (6.17%) felt they should be used in pregnancy |               |  |
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|  |               |  |
| Objective         To describe beliefs and risk perception associated with medicines for treatment of common acute condition  | Twigg, 2016   |  |
|  | Objective     | To describe beliefs and risk perception associated with medicines for treatment of common acute condition    |
|  |               |  |
|  |               | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml                                    |
| For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml  |               |  |

|               | Design: Cross-sectional internet-based questionnaire   |
|---------------|--|
|               | Recruitment: Advertisements announcing the study were placed on two commonly visited by pregnant wome  |
|               | or new mothers   |
| Participants  | Setting: Anonymous internet questionnaire with participants from across the United Kingdom (England,   |
|               | Scotland, Wales and Northern Ireland).   |
|               | Inclusion criteria: Women who were pregnant or within one year of giving birth.  |
|               | Exclusion criteria: NR   |
|               | Study period: November 15, 2011 to January 15, 2012  |
|               | Sample: n=1120   |
|               | Mean age (SD): 30.5 (5.2) years  |
|               | Gestational age: 442 (39.5%) were currently pregnant   |
|               | Parity (95% Cl): No previous children – 48.0% (45.1-50.9%)   |
|               | Race/ethnicity: NR   |
|               | Education level (95% CI): Less than high school – 0.6% (0.14-1.05), high school – 27.9% (25.3-30.5), more than high school – 52.1% (49.2 – 55.0), other – 19.3% (17.0-21.6). |
| Interventions | Health literacy was measured using a self-assessment scale of 0 to 4 for three questions.  |
|               | General beliefs about medicine were obtained using the validated Beliefs about Medicines Questionnaire   |
|               | (BMQ-General) with an additional four questions regarding the benefit of medications on a scale of 1 to 5.   |
| Outcomes      | -Women with a UTI using medication for treatment had lower mean risk perception scores relating to the   |
|               | overuse and harm of medication and a higher mean risk score relating to the benefits of medication compare   |
|               | to women with a UTI who did not undergo treatment with medication.   |
|               | Overuse [mean(SD)]: 11.5 (2.8) vs. 12.6 (2.7), p=0.006   |
|               | Harm [mean(SD)]: 9.3 (2.7) vs. 10.4 (2.9), p=0.014   |
|               | Benefit [mean(SD)]: 16.3 (2.2) vs. 14.9 (2.3), p<0.001   |
| Notes         | Sub-study of the Multinational Medication Use in Pregnancy Study which was reported by Lupattelli et al. and   |
|               | another paper from that study is included in this review.  |

## Characteristics of included studies on treatment effectiveness

| Brumfitt, 1975 |   |
|----------------|---|
| Objective      | To assess the impact of screening and treatment for ASB on maternal and fetal health  |
| Methods        | Design: RCT (randomization ND); placebo controlled  |
|                | Recruitment: Pregnant women attending one of three antenatal clinics for the first time   |
|                | Inclusion criteria: Pregnant women who were screened and found to be positive for<br>'significant bacteriuria' at their first antenatal visit and 7-10 days later                       |
|                | Exclusion criteria: Home delivery, abortions, treatment before confirmation of bacteriuria and other complicating factors   |
| Participants   | Setting: Birmingham (1 clinic) and London (2 clinics), UK; urban  |
|                | Study period: NR; ~1967-1968  |
|                | Sample: n=426; treated (n=235), placebo (n=179)   |
|                | Mean age (SD), years: Treated=26.5 (6.8); Placebo=26.2 (6.9)  |
|                | Risk factors:   |
|                | Ethnicity (Asian and West Indian): Treated n=49 (20.8%); Placebo n=35 (14.1%)   |
|                | Length of follow-up: until delivery and the postpartum period for perinatal mortality   |
|                | Loss to follow-up: NR; outcome of pyelonephritis reported only for a subset (n=173); n=413 for outcome of low birth weight.   |
| Interventions  | Screening characteristics:  |
|                | Timing: First antenatal visit<br>Urine collection: Clean-catch urine sample   |
|                | Urine testing method: Urine culture   |
|                | Criteria for positive test: Two positive tests; women with one positive test were recalled for a second test 7-10 days later and 'detailed documentation'. Microbiological criteria NR. |
|                | Treatment characteristics (Williams, 1968):   |
|                | Type of antibiotic and length of treatment: 2g sulphonamide in a single dose; additional  |
|                | courses of treatment for persistent bacteriuria<br>Control group: Received placebo under 'double-blind conditions'  |
|                | Follow-up testing: Subset of treated women (n=87) retested after 1 and 2 courses of   |
|                | treatment (as applicable)   |
| Outcomes       | Benefits:   |
|                | Pyelonephritis: Presence of loin pain and tenderness together with a temperature of $\geq 100 \circ F$<br>and $>10^5 CFU/mL$ (Condie, 1968)   |
|                | Low birth weight (reported as prematurity): ≤2500g  |
|                | Harms: NR   |
| Notes          | Study also included a non-bacteriuric control group. There are two preliminary reports  |
|                | associated with this study (Condie, 1968; Williams, 1968). Brumfitt, 1975 reported outcome  |
|                | of pyelonephritis for the placebo group only (55/179), comparison between groups only   |

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|   | available for a subset of treatment group (Condie, 1968). No explanation for variation in |  |
|---|---|--|
|   | number of participants across reports for this study, nor for the various outcomes.       |  |
| ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millilitre; F: Fahrenheit; g: gram(s); n: number; |   |  |
| ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; UK: United Kingdom   |   |  |

| Objective     | To evaluate the effectiveness of sulfasymazine for the treatment of ASB in pregnant women  |
|---------------|--|
| Methods       | Design: RCT; placebo-controlled  |
|               | Recruitment: Pregnant women registering for prenatal care  |
|               | Inclusion criteria: Pregnant women ≤32 wks GA with bacteriuria at registration confirmed in two additional samples   |
|               | Exclusion criteria: >32 wks GA, included in other bacteriuria studies, given treatment in error, moved away  |
| Participants  | Setting: Boston City Hospital, Boston, US; urban   |
|               | Study period: June 9, 1965-March 9, 1966   |
|               | Sample: n=106; treated (n=54); placebo (n=52)  |
|               | Mean age (SD): NR  |
|               | Risk factors: NR   |
|               | Length of follow-up: Until delivery  |
|               | Loss to follow-up: 5 (5%) lost; 2(4%) treated patients left the community, 3 (6%) placebo-<br>treated patients dropped out of the study  |
| Interventions | Screening characteristics:<br>Timing: At registration for prenatal care<br>Urine collection: Clean-voided urine sample<br>Urine testing method: Urine culture  |
|               | Criteria for a positive test: Three uncontaminated urine specimens containing the same species of bacteria with $\geq 10^4$ CFU/mL in one and $\geq 10^5$ CFU/mL in the other two.   |
|               | Treatment characteristics<br>Type of antibiotic and length of treatment: 0.5g sulfasymazine once daily until delivery; if<br>there was evidence of persistent bacteriuria, another treatment was given according to<br>clinical judgment (usually nitrofurantoin)<br>Control group: Received placebo |
|               | Follow-up testing: Retested after one week of treatment, and at each clinic visit (at least weekly for the first 3 wks, then at least biweekly until 36 wks GA, then weekly until delivery   |
| Outcomes      | Benefits: NR   |
|               | Harms: NR  |

| Notes | There are no relevant results reported in this study. Study also included non-bacteriuric control patients. 7/52 (13%) of women in the placebo group developed 'asymptomatic |
|-------|--|
|       | pyelonephritis', but not information provided for the treated group.   |

ASB: asymptomatic bacteriuria; CFU/mL: colony-forming units per millilitre; g: gram(s); GA: gestational age; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; US: United States; wks: weeks

| Objective     | To assess the effect of treatment of ASB on pregnancy outcomes   |
|---------------|--|
| Methods       | Design: Quasi-RCT; placebo-controlled  |
|               |  |
|               | Recruitment: Patients registering for prenatal care  |
|               |  |
|               | Inclusion criteria: Pregnant women ≤32 wks GA, with confirmed bacteriuria at the first   |
|               | prenatal visit   |
|               | Exclusion criteria: Treated for UTI during the current pregnancy and before the first  |
|               | obstetric appointment, >32 wks GA, delivered or had aborted before the first obstetric visi  |
|               | went elsewhere for prenatal care, delivered twins  |
| Participants  | Setting: Boston City Hospital, Boston, US; urban   |
|               |  |
|               | Study period: January 28, 1963-July 2, 1965  |
|               |  |
|               | Sample: n=281; treated (n=133), placebo (n=148)  |
|               |  |
|               | Mean age (SE), years: Treated=24.8 (0.60); Placebo=25.3 (0.46)   |
|               | Risk factors:  |
|               | Ethnicity (non-white): Treated=66.2%; Placebo=54.7%  |
|               | Previous UTI: Treated=35.9%; Placebo=40.1%   |
|               |  |
|               | Length of follow-up: Until delivery, and postpartum (time frame ND) for complications  |
|               | Loss to follow-up: Of original n=289, 8 (3%) were excluded because they moved away. No   |
|               | loss to follow-up for pyelonephritis; 3 (1%) patients in the placebo group lost for low  |
|               | birthweight because they were treated for reasons other than UTI; 8 (3%) lost for perinata   |
|               | mortality, 11 (4%) for neonatal sepsis, and 16 (6%) fetal abnormalities and hemolytic  |
|               | anemia, reasons NR.  |
| Interventions | Screening characteristics:   |
|               | Timing: Upon registration at the clinic  |
|               | Urine collection: Clean-voided urine sample  |
|               | Urine testing method: Urine culture  |
|               | Criteria for a positive test: Three samples (two at registration and one at the first obstetric visit); colony count from 2 of 3 specimens $\geq 10^5$ CFU/mL and no specimens with $< 10^4$ |
|               | CFU/mL, with the same species predominating in all 3 specimens   |
|               | Treatment characteristics:   |
|               | Type of antibiotic and length of treatment: 250mg tetracycline, 4 times daily for 6 wks; if  |
|               | infection did not clear in 2 wks, another antibiotic (usually nitrofurantoin) was given until in   |
|               | cleared  |
|               | Control group: Given identically appearing placebo to be taken similarly   |

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|          | Follow-up testing: Retested at each clinic visit until delivery (includes recurrence and excludes those who became symptomatic); colony count <10 <sup>3</sup> CFU/mL on two successive cultures considered cleared  |
|----------|--|
| Outcomes | Benefits:<br>Pyelonephritis: Temperature of ≥100°F with signs and symptoms localized to the urinary<br>tract and not otherwise explained<br>Perinatal mortality: Stillbirth or neonatal death prior to hospital discharge<br>Respiratory distress: Respiratory distress syndrome and other causes of 'respiratory<br>embarrassment'<br>Low birth weight (defined as prematurity): ≤2500g   |
|          | Harms:<br>Serious adverse events: Congenital malformations of bone, genitourinary system, other;<br>hemolytic anemia (erythroblastosis fetalis)  |
| Notes    | Study also included a non-bacteriuric control group. Some patients may have participated<br>more than once if they had more than one pregnancy during the study period (treatment<br>assigned by alternation regardless of assignment for previous pregnancy). Outcomes of low<br>birth weight, fetal abnormalities and hemolytic anemia reported for live births only. 4<br>bacteriuric women delivered twins and are not included. |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; °F: degrees Fahrenheit; g: gram(s); GA: gestational age; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SE: standard error; US: United States; UTI: urinary tract infection; wks: weeks

| Foley, 1987   |   |
|---------------|---|
| Objective     | Test of treatment vs. non-treatment of ASB for the prevention of symptomatic UTI in pregnancy |
| Methods       | Design: RCT   |
|               | Recruitment: Pregnant women attending an antenatal clinic for the first time                  |
|               | Inclusion criteria: Pregnant women with bacteriuria at the first prenatal visit               |
|               | Exclusion criteria: NR  |
| Participants  | Setting: National Maternity Hospital, Dublin, Ireland; urban                                  |
|               | Study period: 1985  |
|               | Sample: n=220; treated (n=100); not treated (n=120)   |
|               | Mean age (SD), years: NR  |
|               | Risk factors:   |
|               | Previous history of UTI: 42% of bacteriuric patients (distribution among groups NR)           |
|               |   |
|               | Length of follow-up: Until delivery (patients interviewed post-delivery)                      |
|               | Loss to follow-up: Reported follow-up rate of 81%, unclear if these were from treatment or    |
|               | control groups (total n used in analysis).  |
| Interventions | Screening characteristics:  |
|               | Timing: First antenatal visit   |

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|          | Urine collection: Midstream urine sample  |
|----------|---|
|          | Urine testing method: NR  |
|          | Criteria for a positive test: One urine sample with $>10^5$ CFU/mL                              |
|          | Treatment characteristics:  |
|          | Type of antibiotic and length of treatment: 300mg sulphamethizole or 150mg nitrofurantoin       |
|          | daily for 3 days, on the basis of sensitivity testing; further treatment, including maintenance |
|          | treatment, provided if needed to render urine sterile   |
|          | Control group: Received no treatment  |
|          | Follow-up testing: Retested 'at follow-up'; not further defined                                 |
| Outcomes | Benefits:   |
|          | Pyelonephritis: ND; 'admitted with pyelonephritis'  |
|          |   |
|          | Harms: NR   |
| Notes    | Reported as a letter to the editor, not a full publication.                                     |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; mg: milligram(s); ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; UTI: urinary tract infection

| Furness, 1975 |  |
|---------------|--|
|               |  |
| Objective     | To examine the effectiveness of urinary antiseptics in preventing pyelonephritis and adverse     |
|               | among pregnant women with ASB  |
| Methods       | Design: RCT  |
|               | Recruitment: Pregnant women attending their initial prenatal visit                               |
|               | Inclusion criteria: Pregnant women with 'significant' bacteriuria at the second prenatal visit   |
|               | Exclusion criteria: NR   |
| Participants  | Setting: Queen Victoria Hospital, Adelaide, Australia; urban                                     |
|               | Study period: NR   |
|               | Sample: n=206; treated (n=139); not treated (n=67)   |
|               | Mean age (SD), years: NR   |
|               | Risk factors: NR   |
|               | Length of follow-up: Until 6 wks postpartum  |
|               | Loss to follow-up: None reported   |
| Interventions | Screening characteristics:   |
|               | Timing: At the second antenatal visit  |
|               | Urine collection: Midstream urine sample   |
|               | Urine testing method: Dipslide   |
|               | Criteria for a positive test: One specimen with $>10^5$ CFU/mL or two specimens each with $10^4$ |
|               | to 10 <sup>5</sup> CFU/mL  |
|               | Treatment characteristics  |

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|              | Type of antibiotic and length of treatment: 1g methenamine mandelate 4 times daily or 1g methenamine hippurate twice daily until delivery; if pyelonephritis developed the patient was treated with the appropriate antibiotic and no further antiseptics were given Control group: Received no treatment Follow-up testing: A postnatal urine specimen was obtained at the 6-week postnatal visit |
|--------------|--|
|              | from women who did not develop clinical pyelonephritis during pregnancy or the   |
|              | puerperium   |
| Outcomes     | Benefits:  |
|              | Pyelonephritis: Frequency and burning on micturition accompanied by pyrexia or loin  |
|              | tenderness, with presence of a significant number of bacteria in urine   |
|              | Spontaneous abortion: ND; 'abortions'  |
|              | Preterm delivery: <38 wks GA   |
|              |  |
|              | Harms:   |
|              | Serious adverse events: Major fetal abnormality (anencephaly)  |
| Notes        | The treatment group received one of two antiseptics, the two groups were combined for  |
|              | reporting of outcomes. Outcome of pyelonephritis includes both during pregnancy and the  |
|              | puerperium. Three intrauterine deaths reported but it is unclear which group the patients  |
|              | belonged to. GA at delivery reported for 118 treated and 52 placebo untreated patients   |
|              | with no explanation given, total n used as denominator in analysis.  |
| SP: acumptom | atic bacteriuria: CEU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; p:   |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; wks: weeks

| Gold, 1966   |   |
|--------------|---|
| Objective    | To determine whether chemotherapy for ASB, continued throughout the rest of the prenatal period, reduces the incidence of prematurity |
| Methods      | Design: Quasi-RCT; placebo-controlled   |
|              | Recruitment: Pregnant women registering at a prenatal clinic  |
|              | Inclusion criteria: Pregnant women with two consecutive positive tests for bacteriuria at any prenatal visit                          |
|              | Exclusion criteria: Failed to return to the clinic, aborted, delivered at other hospitals, found                                      |
|              | to not be pregnant, ectopic pregnancy, transferred to other care, delivered by a private physician                                    |
| Participants | Setting: Prenatal clinic at a hospital in New York, NY, US; urban   |
|              | Study period: February 2, 1962-December 21, 1964  |
|              | Sample: n=65; treated (n=35); placebo (n=30)  |
|              | Mean age (SD), years: NR  |
|              | Risk factors:<br>Ethnicity: 85% non-white, 6% Puerto-Rican, 9% other white (distribution among groups NR)                             |
|              | Length of follow-up: Until the 'postpartum period' (exact time NR)  |
|              | Loss to follow-up: None reported  |

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| Interventions | Screening characteristics:   |
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|               | Timing: First prenatal visit and each visit thereafter   |
|               | Urine collection: Clean-voided midstream urine sample  |
|               | Urine testing method: Urine culture  |
|               | Criteria for a positive test: Two consecutive laboratory reports with >10 <sup>5</sup> CFU/mL of the same species  |
|               | Treatment characteristics:   |
|               | Type of antibiotic and length of treatment: 0.5g sulfadimethoxine once per day until 36 wks GA, 1g sulfadiazine 3 times daily thereafter until delivery  |
|               | Control group: Received placebo tablets taken in the same manner   |
|               | Follow-up testing: Each patient had repeat tests at each antenatal visit until delivery (either for diagnosis or persistent bacteriuria); data presented for persistent bacteriuria at delivery. |
| Outcomes      | Benefits:  |
|               | Pyelonephritis: ND<br>Harms: NR  |
| Notes         | Also reported delivery data for non-bacteriuric patients. Only antepartum pyelonephritis   |
|               | included in the analysis (postpartum excluded). 'Preterm delivery' reported for 2/35 treated   |
|               | and 0/30 placebo patients, but this is not further defined.  |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; n: number; ND: not defined; NR: not reported; NY: New York; RCT: randomized controlled trial; SD: standard deviation; US: United States; wks: weeks

| Kass, 1960   |   |
|--------------|---|
| Objective    | To assess the effect of early detection and eradication of bacteriuria on excessive morbidity   |
|              | in pregnant women   |
| Methods      | Design: Quasi-RCT; placebo controlled   |
|              | Recruitment: Pregnant women ≤32 wks GA registering for a prenatal clinic  |
|              | Inclusion criteria: Pregnant women with bacteriuria at the first prenatal visit and confirmed on two repeat cultures  |
|              | Exclusion criteria: >32 wks GA, chronic renal insufficiency, given treatment in error, did not have further prenatal care, records were inadequate or unobtainable, urine samples were contaminated, unable to void, found to not be pregnant |
| Participants | Setting: Boston City Hospital, Boston, US; urban  |
|              | Study period: October 1956-April 1960   |
|              | Sample: n=214 (n=11 recruited via renal clinic); treatment (n=93); placebo (n=98)   |
|              | Mean age (SD), years: NR; similar distribution between treated and placebo groups   |
|              | Risk factors:<br>Ethnicity (black): Treated (~50%); placebo (slightly <50%)   |
|              | History of UTI: ~15% (distribution by group NR)<br>Diabetes: n=2 (distribution by group NR)   |

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|               | Uterine abnormalities: reported for n=2 bacteriuric women with cesarean section; prevalence in rest of population NR  |
|---------------|---|
|               | Length of follow-up: Until the post-delivery period and up to 12 months postpartum; records reviewed 3-4 years later  |
|               | Loss to follow-up: n=23 (11%) lost; 13 (12%) in the treatment group (7 not seen in last 4 wk before delivery, 5 delivered out of state, 1 incorrectly assigned), 10 (9%) in the placebo group (8 cleared spontaneously or false positive, 2 lost)   |
| Interventions | Screening characteristics:  |
|               | Timing: At the time of registration for the clinic<br>Urine collection: Clean-voided urine sample   |
|               | Urine testing method: Urine culture<br>Criteria for a positive test: $10^3$ - $10^5$ CFU/mL at registration, then two additional cultures with<br>> $10^5$ CFU/mL of the same species   |
|               | Treatment characteristics:<br>Type of antibiotic and length of treatment: 0.5g sulfamethoxypyridazine daily until delivery<br>if infection did not clear in one week, the patient was given 100mg nitrofurantoin 3 times<br>daily until delivery  |
|               | Control group: Received a placebo tablet supplied by the same manufacturer<br>Follow-up testing: Treated patients were retested within the 4 wks preceding delivery. Data<br>for 3-12 months postpartum bacteriuria presented for a subset of women (n=91) (Kass,<br>1960).   |
| Outcomes      | Benefits:<br>Pyelonephritis: dysuria, frequency, and flank pain or other localizing evidence of<br>inflammation, with either documented temperature of 100°F or above or a history of chills<br>and fever. When patients were seen outside the clinic (e.g., accident floor or emergency<br>department), it was not always clear that patients were indeed febrile.<br>Perinatal mortality: ND; 'perinatal death' and fetal loss >20 wks GA<br>Low birth weight (defined as prematurity): <2500g  |
|               | Harms: NR   |
| Notes         | Kass, 1960 is a preliminary report, updated and more complete data retrieved from Savage,<br>1967 are presented. The study also includes a group of non-bacteriuric women. Some<br>patients participated for >1 pregnancy, and were reassigned to the same treatment they<br>received in the first pregnancy. Outcome of pyelonephritis reported only for the antenatal<br>period, postpartum excluded. Outcome of low birth weight given for the total number of<br>deliveries (3 twin deliveries in the placebo group and none in the treated group). |
|               | ic bacteriuria; CFU/mL: colony forming units per millilitre; F: Fahrenheit; g: gram(s); GA:<br>ng: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled tri   |

| Kazemier, 2015 |  |
|----------------|--|
| Objective      | To investigate the consequences of treated and untreated ASB in pregnancy  |
| Methods        | Design: Prospective cohort (screening vs. no screening) with embedded RCT<br>Recruitment: Pregnant women attending antenatal clinics offering screening (not routinely<br>available) |

|               | Inclusion criteria: Pregnant women aged ≥18 years with a singleton pregnancy who were between 16 and 22 wks GA, tested positive for ASB, and did not have symptoms of UTI                                  |
|---------------|--|
|               | Exclusion criteria: History of preterm delivery <34 wks, warning signs of imminent preter<br>delivery, fetal congenital malformations, antibiotic use within 2 wks of screening, known                     |
|               | glucose-6-phosphate dehydrogenase deficiency, hypersensitivity to nitrofurantoin, risk<br>factors for complicated UTI (e.g., pre-gestational DM, use of immunosuppressive                                  |
|               | medication or functional or structural abnormalities of the urinary tract)   |
| Participants  | Setting: 8 hospitals and 5 ultrasound centres, the Netherlands   |
|               | Study period: October 11, 2011-August 22, 2014   |
|               | Sample: n=248; treated (n=40); placebo (n=45), untreated (n=163)   |
|               | Mean age (SE), years: treated=29 (0.74), placebo or untreated=31 (0.33)  |
|               | Risk factors:  |
|               | Ethnicity (non-white): treated n=3 (8%), placebo or untreated n=36 (17%)<br>Low education (≤pre-vocational level): treated n=6 (15%), placebo or untreated n=21 (10  |
|               | Length of follow-up: Until 6 wks postpartum  |
|               | Loss to follow-up: n=12 (5%) lost, all from the untreated or placebo group; 5 women coul   |
|               | not be contacted for outcomes because of errors in their contact information. Missing da were imputed (see notes).   |
| Interventions | Screening characteristics:   |
|               | Timing, median (IQR) wks + days GA: treated=20+2 (19+6 to 20+5), placebo or untreated=20+0 (19+3 to 20+3)  |
|               | Urine collection: Midstream urine sample   |
|               | Urine testing method: Dipslide   |
|               | Criteria for a positive test: $\geq 10^5$ CFU/mL of a single microorganism or when two different colony types were present but one had a concentration of $\geq 10^5$ CFU/mL                               |
|               | Treatment characteristics:   |
|               | Type of antibiotic and length of treatment: 100mg nitrofurantoin twice daily for 5 days, based on sensitivity testing; if bacteriuria did not clear the treatment was repeated for a maximum of two rounds |
|               | Control group: Received identical placebo capsules on the same dose and schedule as treated patients, or no treatment  |
|               | Follow-up testing: All participants provided a follow-up dipslide 1 week after the end of  |
|               | treatment; those who remained positive were retested after each new round of treatment for a maximum of two rounds   |
| Outcomes      | Benefits:  |
|               | Pyelonephritis: Hospital admission with $\geq 2$ of the following: fever (body temperature   |
|               | $\geq$ 38°C), symptoms of pyelonephritis (nausea, vomiting, chills, and costovertebral   |
|               | tenderness), and a positive urine culture indicating the presence of bacteria in the urine.  |
|               | Perinatal mortality: neonatal death before discharge from the neonatal ward<br>Preterm delivery: spontaneous birth between 32 and 37 wks GA  |
|               | Low birth weight: <10 <sup>th</sup> or 5 <sup>th</sup> percentile  |
|               | Neonatal sepsis: Confirmed with culture, includes group B streptococcal sepsis   |
|               |  |
|               | Harms:   |

|       | Serious adverse events: Congenital abnormalities (ND)  |
|-------|--|
| Notes | Cohort study addressed screening, results reported here for treatment RCT only. Study        |
|       | included both placebo and untreated groups who were combined in the analysis. When           |
|       | data were missing, these were imputed taking into account patient characteristics and        |
|       | outcomes. Differences in outcomes between groups were controlled for potential               |
|       | confounders (smoking, low education, conception through in-vitro fertilization or            |
|       | intracytoplasmic sperm injection, pre-existing hypertension). 5 women originally assigned to |
|       | treatment group were later found to not have ASB, but remained in their assigned group       |
|       | (intention-to-treat analysis).   |

ASB: asymptomatic bacteriuria; C: Celsius; CFU/mL: colony forming units per millilitre; DM: diabetes mellitus; g: gram(s); GA: gestational age; IQR: interquartile range; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SE: standard error; UTI: urinary tract infection; wks: weeks

| Objective     | To assess the effectiveness of antibacterial drugs for pregnant women with bacteriuria in  |
|---------------|--|
|               | preventing pyelonephritis, perinatal mortality, and low birth weight   |
| Methods       | Design: RCT; placebo-controlled  |
|               |  |
|               | Recruitment: Pregnant women attending their first antenatal visit before 26 wks GA   |
|               | Inclusion criteria: Pregnant women <26 wks GA with ASB at the first antenatal visit and  |
|               | confirmed by a subsequent positive test  |
|               | Exclusion criteria: NR   |
| Participants  | Setting: Queen Victoria Hospital, Melbourne, Australia; urban  |
|               | Study period: 1964-1965  |
|               | Sample: n=145; treated (n=61), placebo (n=56) (see notes)  |
|               | Mean age (SD), years: NR   |
|               | Risk factors: (see notes)  |
|               | Socioeconomic status: All from lowest income category in community, but the community  |
|               | has a high standard of living  |
|               | Urogenital anomalies: At post-delivery testing, 51.4% of patients had an abnormal  |
|               | intravenous pyelogram and 5 patients had poorly functioning or non-functioning kidneys on one side due to ureteric obstruction.  |
|               | Length of follow-up: Until 6 months postpartum   |
|               | Loss to follow-up: Of initial 240 women with completed pregnancies, no outcomes reported   |
|               | for 95 women for various reasons (6 aborted before treatment, 20 developed symptoms before treatment, 22 attended infrequently, 33 failed to take tablets continuously, 14 had |
|               | coagulase-negative staphylococcal bacteriuria); further information on non-compliant   |
|               | patients NR  |
| Interventions | Screening characteristics:   |
|               | Timing: First antenatal visit  |
|               | Urine collection: Midstream urine sample; the second test was clean-voided (first was not)   |
|               | Urine testing method: Urine culture  |

|          | Criteria for a positive test: >10 <sup>5</sup> CFU/mL on two occasions                                |
|----------|---|
|          | Treatment characteristics:  |
|          | Type of antibiotic and length of treatment: 0.5g sulphamexydiazine daily, changing to 1g              |
|          | sulphadimidine 3 times daily in the 13 <sup>th</sup> week of gestation, continuing until delivery; if |
|          | resistance to sulphonamides was indicated by sensitivity tests, 500mg ampicillin 3 times              |
|          | daily or 50mg nitrofurantoin 4 times daily was prescribed instead.                                    |
|          | Control group: Received identical placebo capsules and tablets  |
|          | Follow-up testing: Patients re-examined at monthly intervals, on any hospital admission,              |
|          | and at delivery. Retesting at 6 wks-3 months and 6 months postpartum ongoing at the time              |
|          | of publication. These subsequent samples involved cleansing of the periurethral area and              |
| Outcomes | insertion of a vaginal tampon to avoid contamination. Benefits:                                       |
| Outcomes | Pyelonephritis: Loin pain and tenderness, with or without pyrexia, and rigors, with or                |
|          | without symptoms of dysuria and frequency   |
|          | Perinatal mortality: >28 wks GA   |
|          | Low birth weight (reported as preterm delivery): <2500g   |
|          |   |
|          | Harms: NR   |
| Notes    | Study also included a non-bacteriuric group. 29/145 (20%) patients were given treatment or            |
|          | placebo prior to confirmation of ASB (before the second culture was analyzed); outcomes               |
|          | for these patients were reported separately, leaving 116 in the current analysis. 11 fetal            |
|          | losses reported but group assignment NR.  |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; mg: milligram(s); NR: not reported; RCT: randomized controlled trial; SD: standard deviation; wks: weeks

| Little, 1966 |  |
|--------------|--|
| Objective    | To assess the effect of antibiotic treatment for pregnant women with ASB on incidence of pyelonephritis and adverse pregnancy outcomes |
| Methods      | Design: RCT; placebo-controlled  |
|              | Recruitment: Pregnant women attending their first antenatal visit  |
|              | Inclusion criteria: Pregnant women with bacteriuria at the first antenatal visit and confirmed   |
|              | with a subsequent culture  |
|              | Exclusion criteria: NR   |
| Participants | Setting: Charing Cross Hospital and Fulham Maternity Hospital, London, England; urban  |
|              | Study period: 1962-1965  |
|              | Sample: n=265; treated (n=124), placebo (n=141)  |
|              | Mean age (SD), years: NR; 6.89% 10-20, 4.99% 21-30, 4.62% 31-40, 4.25% ≥40   |
|              | Risk factors:  |
|              | Past history of urinary tract disease: 62 (23.4%) recalled a past episode (both groups combined)                                       |
|              | Length of follow-up: Until 6 wks postpartum  |

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|               | Loss to follow-up: None reported.   |
|---------------|---|
| Interventions | Screening characteristics:  |
|               | Timing: First antenatal visit, usually ~12 <sup>th</sup> week of gestation  |
|               | Urine collection: Clean-voided midstream urine sample   |
|               | Urine testing method: Urine culture   |
|               | Criteria for a positive test: Two consecutive urine cultures with >10 <sup>5</sup> CFU/mL   |
|               | Treatment characteristics:  |
|               | Type of antibiotic and length of treatment: At start of trial, patients were given 0.5g sulphamethoxypyridazine daily for 30 days; if bacteriuria did not clear, 1.5g ampicillin daily was given for 1 week, then a maintenance dose of 1g daily until delivery. Because treatment with ampicillin was generally not successful, later in the trial, a single dose of 100mg |
|               | nitrofurantoin became the first form of treatment.  |
|               | Control group: Received placebo tablets   |
|               | Follow-up testing: Retested monthly throughout pregnancy  |
| Outcomes      | Benefits:   |
|               | Pyelonephritis: Loin pain and tenderness, a fever >100°F, >10 <sup>5</sup> CFU/mL. Usually there was  |
|               | also frequency and dysuria, and sometimes rigors and hematuria  |
|               | Perinatal mortality: ND   |
|               | Low birth weight (reported as prematurity): <2500g  |
|               |   |
|               | Harms:  |
|               | Serious adverse events: fetal abnormalities, ND   |
| Notes         | No additional notes   |
|               |   |
|               |   |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; F: Fahrenheit; g: gram(s); mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation

| Mulla, 1960  |   |
|--------------|---|
| Objective    | To evaluate the clinical results of treatment of bacteriuria in pregnant women with long-<br>acting sulfonamide |
| Methods      | Design: RCT<br>Recruitment: Pregnant women attending the obstetrical clinic                                     |
|              | Inclusion criteria: Pregnant women with ASB at their 30-32 wks GA obstetric visit                               |
|              | Exclusion criteria: NR  |
| Participants | Setting: St. Elizabeth Hospital, Ohio, US; urban  |
|              | Study period: NR  |
|              | Sample: n=100; treated (n=50), not treated (n=50)   |
|              | Mean age (SD), years: NR  |
|              | Risk factors: NR  |
|              | 1   |

|               | Length of follow-up: Until delivery and immediately after                                     |
|---------------|---|
|               | Loss to follow-up: None reported.   |
| Interventions | Screening characteristics:  |
|               | Timing: Obstetric visit at 30-32 wks GA   |
|               | Urine collection: Catheter urinalysis (antimicrobial jelly used on the catheter)              |
|               | Urine testing method: Urine culture   |
|               | Criteria for a positive test: NR  |
|               | Treatment characteristics:  |
|               | Type of antibiotic and length of treatment: 250mg sulfadimethoxine twice daily for 1 week     |
|               | the regimen was repeated if bacteriuria persisted   |
|               | Control group: Received no medication until symptoms appeared                                 |
|               | Follow-up testing: Followed at weekly intervals until delivery; were re-tested at least once, |
|               | after the first course of treatment.  |
| Outcomes      | Benefits:   |
|               | Pyelonephritis: Clinical evidence of active infection, including acute symptoms of            |
|               | cystopyelitis; urine was tested at the time of the episode                                    |
|               | Harms: NR   |
| Notes         | Pyelonephritis after delivery was reported, but this was excluded from the present analysis   |

ASB: asymptomatic bacteriuria; GA: gestational age; mg: milligram(s); n: number; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; US: United States; wks: weeks

| Pathak, 1969 |  |
|--------------|--|
| Objective    | To determine the effect of short-term antibacterial therapy on eradication of bacteriuria  |
|              | during pregnancy, and its effects on pregnancy outcomes  |
| Methods      | Design: RCT; placebo-controlled  |
|              | Recruitment: Pregnant women attending antenatal clinics  |
|              | Inclusion criteria: Pregnant women ≤24 wks GA with confirmed bacteriuria on two consecutive tests  |
|              | Exclusion criteria: Confirmation of bacteriuria at >24 wks GA, blood pressure >130/90mmHg at the initial antenatal visit, did not re-attend after first examination (wrong dates or could not be traced), early abortions, clinical pyelonephritis, 'mentally defective' |
| Participants | Setting: University College Hospital and Kingston Public Hospital, Jamaica; urban  |
|              | Study period: NR   |
|              | Sample: n=178; treated (n=76); placebo (n=76)  |
|              | Mean age (SD), years: NR   |
|              | Risk factors:  |
|              | Sickle-cell trait: 18/24 (21.4%) in bacteriuric patients, incidence by group NR  |
|              | Urogenital anomalies: 9/50 (18%) of bacteriurics had abnormalities on postpartum intravenous pyelogram (1 bilateral hydroureter with hydronephrosis, 1 localized calyceal  |

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|                    | clubbing, 1 bifid pelvis, 2 had changes consistent with papillary necrosis, 4 showed evidence of chronic pyelonephritis).   |
|--------------------|---|
|                    | Length of follow-up: Until delivery (all) and 3-9 months postpartum for a subset  |
|                    | Loss to follow-up: n=26 (15%) lost; 12 (14%) treated (9 antibiotic received for positive serology, 3 defaulted from the clinic and could not be traced), 14 (16%) placebo (12 antibiotic received, 3 defaulted from the clinic)             |
| Interventions      | Screening characteristics:  |
|                    | Timing: NR; ≤24 wks GA  |
|                    | Urine collection: clean-voided urine sample   |
|                    | Urine testing method: NR  |
|                    | Criteria for a positive test: >10 <sup>5</sup> CFU/mL on two consecutive specimens  |
|                    | Treatment characteristics:  |
|                    | Type of antibiotic and length of treatment: 100mg nitrofurantoin twice daily for 3 wks;<br>patients who did not respond received 400mg nitrofurantoin daily for a further 4 days<br>Control group: Received placebo identical in appearance |
|                    | Follow-up testing: Retested at weekly intervals during treatment (or placebo), then every 2 wks until delivery, and a subset (n=69, 24 treated and 45 placebo) at 3-9 months postpartum   |
| Outcomes           | Benefits:<br>Pyelonephritis: ND   |
|                    | Harms: NR   |
| Notes              | Reported preterm birth/fetal loss only by bacteriuric status, not by treatment group.   |
| SB: asymptomati    | c bacteriuria; CFU: colony forming units per millilitre; GA: gestational age; mg: milligram; mmH  |
| nillimetre of merc | cury; n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD:   |
| tandard deviatior  | n; wks: weeks   |
| Thomsen, 1987      |   |

| Thomsen, 1987 |   |
|---------------|---|
| Objective     | To assess the effect of treatment for group-B streptococcal bacteriuria in pregnant women<br>on the incidence of preterm labour |
| Methods       | Design: RCT; placebo-controlled   |
|               | Recruitment: Pregnant women attending Statens Seruminstitut   |
|               | Inclusion criteria: Pregnant women 27-31 wks GA who were positive for group-B streptococcal bacteriuria                         |
|               | Exclusion criteria: NR; <27 or >31 wks GA   |
| Participants  | Setting: University Hospital, Denmark; urban  |
|               | Study period: October 1, 1984-October 1, 1986   |
|               | Sample: n=69; treated (n=37), placebo (n=32)  |
|               | Mean age, years: 28.1, similar for both groups  |
|               | Risk factors:   |

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|               | Ethnicity: All patients were white   |
|---------------|--|
|               | Socioeconomic status: Similar for both groups  |
|               | Length of follow-up: Until delivery (see notes)  |
|               | Loss to follow-up: None reported.  |
| Interventions | Screening characteristics:   |
|               | Timing: NR; 27-31 wks GA   |
|               | Urine collection: Midstream urine sample   |
|               | Urine testing method: Urine culture  |
|               | Criteria for a positive test: 10 <sup>2</sup> -10 <sup>6</sup> CFU/mL of group-B streptococci bacteria |
|               | Treatment characteristics:   |
|               | Type of antibiotic and length of treatment: 10 <sup>6</sup> IU penicillin 3 times daily for 6 days;    |
|               | treatment was repeated if bacteriuria persisted  |
|               | Control group: Received placebo tablets  |
|               | Follow-up testing: Retested weekly until delivery for persistent bacteriuria or recurrence             |
| Outcomes      | Benefits:  |
|               | Preterm delivery: <37 wks GA (mean wks GA for treated: 39.6, placebo: 36.2)                            |
|               | Neonatal sepsis: ND  |
|               | Harms: NR  |
| Notes         | Patients positive for streptococci at delivery were treated with 2g ampicillin intravenously           |
|               | followed by 1g intravenously every 4 hours from the start of labour. Infants were given                |
|               | ampicillin (50mg/kg) intramuscularly every 12 hours to avoid sepsis. Umbilical cord blood              |
|               | was tested from group-B streptococci and babies with positive cultures were treated for 6              |
|               | days. One infant tested positive for sepsis at 6 wks post-delivery.                                    |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram; GA: gestational age; IU: international unit; kg: kilogram; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; wks: weeks

| To investigate the effect of treatment of ASB in pregnancy on urine concentrating ability<br>and the development of symptomatic UTI<br>Design: RCT<br>Recruitment: Pregnant women attending their first antenatal visit<br>Inclusion criteria: Pregnant women <30 wks GA with significant ASB at the first antenatal |
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| and the development of symptomatic UTI<br>Design: RCT<br>Recruitment: Pregnant women attending their first antenatal visit   |
| Recruitment: Pregnant women attending their first antenatal visit  |
|  |
| Inclusion criteria: Pregnant women <30 wks GA with significant ASB at the first antenatal  |
| visit, confirmed by a second positive test within 10 days  |
| Exclusion criteria: NR   |
| Setting: Maternity Hospital and St. David's Hospital, Cardiff, Wales, England; urban   |
| Study period: 1967   |
| Sample: n=163; treated (n=85), untreated (n=78)  |
| Mean age (SE), years: 24.82 (0.49) for all bacteriurics, differences between groups NR   |
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|               | Risk factors: NR   |
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|               | Length of follow-up: Until 10 days postpartum  |
|               | Loss to follow-up: None reported   |
| Interventions | Screening characteristics:   |
|               | Timing: First antenatal visit; mean (SE) 20.78 (0.45) wks GA   |
|               | Urine collection: Clean-voided midstream urine sample  |
|               | Urine testing method: Urine culture  |
|               | Criteria for a positive test: >10 <sup>5</sup> gram-negative CFU/mL in at least two consecutive urine  |
|               | specimens; if the first specimen was positive, patients were recalled for a second specimen within 10 days   |
|               |  |
|               | Treatment characteristics:   |
|               | Type of antibiotic: 1g sulphadimidine 3 times daily for 7 days; if bacteriuria persisted, patients received 100mg nitrofurantoin twice daily for 7 days; if bacteriuria still persisted, patients received 250mg ampicillin 3 times daily for 7 days (ampicillin repeated as |
|               | necessary)   |
|               | Control group: received no treatment until symptoms presented  |
|               | Follow-up testing: Retested 2-3 wks after the first course of treatment, and each subsequent course of treatment   |
| Outcomes      | Benefits:  |
|               | Pyelonephritis: loin pain and tenderness with or without fever (no record of fever in antenatal patients)  |
|               | Harms: NR  |
| Notes         | The study also included a non-bacteriuric and a non-pregnant group. Data for pyelonephrit  |
|               | includes postpartum infections (n=6) because group assignment NR.  |

ASB: asymptomatic bacteriuria; CFU/mL: colony forming units per millilitre; g: gram(s); GA: gestational age; mg: milligram(s); n: number; NR: not reported; RCT: randomized controlled trial; SE: standard error; UTI: urinary tract infection; wks: weeks

| Wren, 1969   |  |
|--------------|--|
| Objective    | To evaluate the effect of treatment of pregnant women with ASB on the incidence of premature deliveries and other adverse pregnancy outcomes |
| Methods      | Design: Quasi-RCT  |
|              | Recruitment: Pregnant women booking at an antenatal clinic   |
|              | Inclusion criteria: Pregnant women with ASB at their first antenatal visit   |
|              | Exclusion criteria: NR   |
| Participants | Setting: Royal Hospital for Women, New South Wales, Australia; urban   |
|              | Study period: November 1968-December 1968  |
|              | Sample: n=183; treated (n=83), untreated (n=90)  |
|              | Mean age (SD): NR  |

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|               | Risk factors: NR  |  |  |  |  |  |  |  |  |
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|               | Length of follow-up: Until 6 wks postpartum   |  |  |  |  |  |  |  |  |
|               | Loss to follow-up: Of original n=183, 10 (5%) women lost; 2 sets of twins, 4 moved away and could not be traced, 3 received antibiotics before the trial started, 1 refused to take the treatment |  |  |  |  |  |  |  |  |
| Interventions | Screening characteristics:  |  |  |  |  |  |  |  |  |
|               | Timing: First antenatal visit   |  |  |  |  |  |  |  |  |
|               | Urine collection: Midstream urine sample  |  |  |  |  |  |  |  |  |
|               | Urine testing method: NR  |  |  |  |  |  |  |  |  |
|               | Criteria for a positive test: NR  |  |  |  |  |  |  |  |  |
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|               | Treatment characteristics:  |  |  |  |  |  |  |  |  |
|               | Type of antibiotic and length of treatment: Rotational therapy with 100mg nitrofurantoin  |  |  |  |  |  |  |  |  |
|               | twice daily for 2 wks, 250mg ampicillin 4 times daily for 1 week, 500mg sulphurazole 4 times  |  |  |  |  |  |  |  |  |
|               | daily for 4 wks, and nalidixic acid 4 times daily for 2 wks. Each new patient started with one  |  |  |  |  |  |  |  |  |
|               | of the four drugs, then rotated through the remaining drugs in order. Every 9 wks, patients   |  |  |  |  |  |  |  |  |
|               | began a new course of rotational therapy until 1-6 wks after delivery.  |  |  |  |  |  |  |  |  |
|               | Control group: Untreated until clinical evidence of UTI developed   |  |  |  |  |  |  |  |  |
|               | Follow-up testing: Patients were retested one per month when possible, until the last   |  |  |  |  |  |  |  |  |
| <u> </u>      | month of pregnancy  |  |  |  |  |  |  |  |  |
| Outcomes      | Benefits:   |  |  |  |  |  |  |  |  |
|               | Spontaneous abortion: ND; 'abortion'  |  |  |  |  |  |  |  |  |
|               | Perinatal mortality: Stillbirth and neonatal death  |  |  |  |  |  |  |  |  |
|               | Preterm delivery: <37 wks GA  |  |  |  |  |  |  |  |  |
|               | Low birth weight (reported as prematurity): <2501g  |  |  |  |  |  |  |  |  |
|               |   |  |  |  |  |  |  |  |  |
|               | Harms: NR   |  |  |  |  |  |  |  |  |
| Notes         | The study also included a control group of non-bacteriuric women.   |  |  |  |  |  |  |  |  |

ASB: asymptomatic bacteriuria; g: gram(s); GA: gestational age; mg: milligram(s); n: number; ND: not defined; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; UTI: urinary tract infection; wks: weeks

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## Supplement 5. Risk of bias (ROB) assessments for included studies

|          | 5 Summary of ROB for studies of screening effectiveness |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
|----------|---|---|------------------------------------|---------------------------|--|------------|--------------------------|--------------------|-----------------------|-------------------------------------|-------------------------------------|------------------------|------------|------------------------|
| о<br>7   | First Author,   | Selection                               |                                    |                           | Comparability Outcome  |            |                          |                    |                       | Total                               | Selective                           |                        |            |                        |
|          | Year  |   |                                    |                           |  |            |                          |                    |                       |                                     | Score <sup>a</sup>                  | Outcome                |            |                        |
| 8        | · cu.   |   |                                    |                           |  |            |                          |                    |                       |                                     | (max                                | Reporting <sup>b</sup> |            |                        |
| 9        |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        | 9)         | Reporting              |
| 10       |   |   | 1                                  |                           |  |            |                          |                    |                       | 1                                   | 1                                   |                        | 3)         |                        |
| 11       |   |   |                                    | a                         | t  |            |                          |                    |                       | Ż                                   |                                     |                        |            |                        |
| 12       |   | f                                       | ed                                 | un:                       | sta<br>is/   |            | rts                      |                    | e                     | lo<br>I                             | of                                  |                        |            |                        |
| 13       |   | t S                                     | SOC                                | SOC                       | at<br>irit   |            | рч                       |                    | lo                    | fo                                  | dņ                                  |                        |            |                        |
| 14       |   | Representativeness of<br>exposed cohort | Selection of non-exposed<br>cohort | Ascertainment of exposure | Outcome not present at start<br>of study (pyelonephritis/<br>other outcomes) |            | Comparability of cohorts |                    | Assessment of outcome | Adequacy of length of follow-<br>up | Adequacy of follow-up of<br>cohorts |                        |            |                        |
| 15       |   | vel                                     | έt                                 | of                        | ese<br>one   | _          | of                       | _                  | fo                    | sth 3                               | ts JIC                              | _                      |            |                        |
| 16       |   | ati<br>ed e                             | of non-<br>cohort                  | t                         | /elo   | Total      | Ξţ                       | Total              | to                    | up en                               | y of foll<br>cohorts                | Total                  |            |                        |
| 17       |   | ent<br>ose                              | of S                               | me                        | r o t  | Ĕ          | lidi                     | Ĕ                  | en                    | fl                                  |                                     | Ĕ                      |            |                        |
| 18       |   | x pe                                    | ion                                | i.                        | he r   |            | arg                      |                    | sm                    | 2                                   | Iac                                 |                        |            |                        |
| 19       |   | e                                       | sct                                | irte                      |  |            | du                       |                    | ses                   | nao                                 | nba                                 |                        |            |                        |
| 20       |   | Å                                       | ele.                               | sce                       | ofs  |            | l S                      |                    | As                    | edi                                 | Ade                                 |                        |            |                        |
| 20       |   |   | 0,                                 | Ā                         | ō  |            | -                        |                    |                       | Ad                                  | 1                                   |                        |            |                        |
| 21       | 0 / 1 4000  |   |                                    |                           | 0.14   |            |                          | 0                  |                       | -                                   |                                     |                        | 6          |                        |
| 23       | Gérard, 1983  | 1                                       | 1                                  | 0                         | 0/1  | 3          | 0                        | 0                  | 1                     | 1                                   | 1                                   | 3                      | 6          | Suspected <sup>c</sup> |
| 24       | Gratacós, 1994  | 1                                       | 1                                  | 0                         | 0/1  | 3          | 0                        | 0                  | 1                     | 1                                   | 1                                   | 3                      | 6          | Suspected <sup>d</sup> |
| 25       | Rhode, 2007   | 1                                       | 1                                  | 1                         | 0/1  | 4          | 1                        | 1                  | 1                     | 1                                   | 1                                   | 3                      | 8          | Suspected <sup>e</sup> |
| 26       | Uncu, 2002  | 1                                       | 1                                  | 1                         | 0/1  | 4          | 0                        | 0                  | 1                     | 1                                   | 0                                   | 2                      | 6          | Not                    |
| 20       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            | suspected <sup>f</sup> |
| 27       | aAssesse  | ed using t                              | the Newo                           | castle-Ot                 | tawa Qual  | ity Asses  | sment S                  | cale <sup>31</sup> |                       |                                     |                                     |                        |            |                        |
| 28<br>29 | <sup>b</sup> Assesse                                    | ed due to                               | concern                            | ı regardi                 | ng reportir  | ng bias ir | the stu                  | dies, but          | assessm               | ent not i                           | included                            | in the to              | otal score | č                      |
| 30       | Did not°  | report o                                | n fetal a                          | bnormal                   | ities  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
|          | <sup>d</sup> Did not                                    | report o                                | on sponta                          | aneous a                  | bortion, pe  | erinatal ı | mortality                | , preterr          | n deliver             | y or feta                           | l abnorn                            | nalities               |            |                        |
| 31       |   | -                                       | -                                  |                           | bortion, pe  |            |                          |                    |                       | -                                   |                                     |                        |            |                        |
| 32       |   | -                                       | -                                  |                           | ing fetal d  |            | -                        |                    |                       |                                     | orinatal                            | mortality              | ر)<br>ا    |                        |
| 33       | Reporte   | u on an i                               | outcome                            | .s, meruu                 | ing ictai u  |            | WEEKS                    | Ji gestati         |                       |                                     | crinatar                            | nortanty               | ()         |                        |
| 34       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 35       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 36       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 37       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 38       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 39       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 40       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 41       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 42       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 43       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 44       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 45       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 46       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 47       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 48       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 49       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 50       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 51       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 52       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 53       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 54       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 55       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 56       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 57       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 58       |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
| 50<br>59 |   |   |                                    |                           |  |            |                          |                    |                       |                                     |                                     |                        |            |                        |
|          |   |   | For pe                             | er reviev                 | w only - ht  | tp·//hmi   | open hr                  | ni com/s           | ite/ahou              | it/auidel                           | ines sht                            | ml                     |            |                        |
| 60       |   |   | i oi pe                            |                           | , only in  | ·P·// Drij | openior                  |                    | , 0000                | guide                               | cs.xiit                             |                        |            |                        |

| Domain   | Author's<br>judgement | Support for judgement  |
|--|-----------------------|--|
| Gérard, 1983 (cohort)  | J                     |  |
| Representativeness of the exposed cohort                                       | 1                     | Included all pregnant women who visited the clinic at <25 wks GA.  |
| Selection of the non-<br>exposed cohort  | 1                     | Formed retrospectively, pregnant women attending the clinic in th 10 previous months (before implementation of screening). |
| Ascertainment of exposure  | 0                     | Not reported.  |
| Outcome not present at<br>start of study<br>(pyelonephritis/other<br>outcomes) | 0/1                   | Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.                  |
| Comparability of the cohorts   | 0                     | No evidence of comparability.  |
| Assessment of outcome  | 1                     | Appear to have used a chart review.  |
| Adequacy of length of follow-up  | 1                     | Follow-up until delivery and for 3-6 months post-partum for those with ≥2 instances of asymptomatic bacteriuria.           |
| Adequacy of follow-up of cohorts   | 1                     | No loss to follow-up.  |
| Selective outcome<br>reporting <sup>b</sup>                                    | suspected             | Did not report on fetal abnormalities.   |
| Total score (maximum 10)   | 6                     | 4  |
| Gratacós, 1944 (cohort)  |                       |  |
| Representativeness of the<br>exposed cohort                                    | 1                     | All pregnant women presenting to the clinic at <25 wks GA betwee<br>January 1991 and December 1992.                        |
| Selection of the non-<br>exposed cohort  | 1                     | Women who visited the same clinic in years (January 1987 to December 1990) before implementation of the screening program  |
| Ascertainment of exposure  | 0                     | Not reported.  |
| Outcome not present at<br>start of study<br>(pyelonephritis/other<br>outcomes) | 0/1                   | Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study.                  |
| Comparability of the<br>cohorts  | 0                     | No evidence of comparability.  |
| Assessment of outcome  | 1                     | Used a chart review – 'was recorded for 6 years'.  |
| Adequacy of length of follow-up  | 1                     | Followed-up until delivery.  |
| Adequacy of follow-up of cohorts   | 1                     | 10 (6.9%) lost to follow-up.   |
| Selective outcome reporting <sup>b</sup>                                       | suspected             | Did not report on spontaneous abortion, perinatal mortality, prete<br>delivery or fetal abnormalities.                     |
| Total score (maximum 10)   | 6                     |  |
| Rhode, 2007 (cohort)   |                       |  |
| Representativeness of the<br>exposed cohort                                    | 1                     | All pregnant women who enrolled for care and delivered after Aug 15, 2002.   |
| Selection of the non-<br>exposed cohort  | 1                     | All pregnant women who enrolled for care at the same practice an delivered before August 15, 2002.                         |

| Domain   | Author's<br>judgement | Support for judgement   |
|--|-----------------------|---|
| Ascertainment of exposure  | 1                     | Used delivery records.  |
| Outcome not present at<br>start of study<br>(pyelonephritis/other<br>outcomes) | 0/1                   | Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study. |
| Comparability of the<br>cohorts  | 1                     | Compared 10 demographic factors, showing that groups were simil   |
| Assessment of outcome  | 1                     | Used a chart review.  |
| Adequacy of length of follow-up  | 1                     | Followed-up until delivery of the patient left the practice.  |
| Adequacy of follow-up of cohorts   | 1                     | 112 (4.6%) lost to follow-up.   |
| Selective outcome reporting <sup>b</sup>                                       | suspected             | Did not report on spontaneous abortion, perinatal mortality or feta abnormalities.                        |
| Total score (maximum 10)   | 8                     |   |
| Uncu, 2002 (cohort)  |                       |   |
| Representativeness of the<br>exposed cohort                                    | 1                     | All pregnant women <32 wks GA seen at an antenatal outpatient clinic.                                     |
| Selection of the non-<br>exposed cohort  | 1                     | Women who visited the clinic prior to the start of the screening stu                                      |
| Ascertainment of exposure  | 1                     | Used delivery records.  |
| Outcome not present at<br>start of study<br>(pyelonephritis/other<br>outcomes) | 0/1                   | Not ascertained for pyelonephritis, other outcomes could not have been present at the start of the study. |
| Comparability of the<br>cohorts  | 0                     | No evidence of comparability.   |
| Assessment of outcome  | 1                     | Used delivery records.  |
| Adequacy of length of follow-up  | 1                     | Follow-up until post-delivery.  |
| Adequacy of follow-up of<br>cohorts  | 0                     | Not reported.   |
| Selective outcome  | not                   | Reported on all outcomes, including fetal death >20 wks GA (eligibl                                       |
| reporting <sup>b</sup>   | suspected             | for perinatal mortality).   |
| Total score (maximum 10)   | 6                     |   |

<sup>a</sup>Assessed using the Newcastle-Ottawa Quality Assessment Scale

<sup>b</sup>Assessed due to concern regarding reporting bias in the studies, but assessment not included in the total score

| Si | ummary of RC | DB for studies of | women's outco | ome valuation |
|----|--------------|-------------------|---------------|---------------|
|    |              |                   |               |               |

| First<br>Author,<br>Year | Did the study address a clearly focused question /<br>issue? | Is the research method (study design) appropriate<br>for answering the research question? | Is the method of selection of the subjects clearly described? | Could the way the sample was obtained introduce<br>bias? | Was the sample of subjects representative of the population to which the findings will be referred? | Was the sample size based on pre-study<br>considerations of<br>statistical power? | Was a satisfactory response rate achieved? | Are the measurements (questionnaires) likely to be<br>valid and reliable? | Was the statistical significance assessed? | Are confidence intervals given for the main results? | Could there be confounding factors that haven't<br>been<br>accounted for? | Can the results be applied to your organization? |
|--------------------------|--|---|---|--|---|---|--|---|--|--|---|--|
| Butters, 1990            | 1  | 1   | 1   | 2  | 1   | 2   | 1  | 2   | 1  | 3  | 1   | 1  |
| Kazemier, 2015           | 2  | 2   | 1   | 3  | 1   | 2   | 2  | 2   | 3  | 3  | 2   | 3  |
| Lupattelli, 2014         | 1  | 1   | 1   | 1  | 1   | 2   | 2  | 2   | 1  | 1  | 3   | 1  |
| Mashayekhi, 2009         | 1  | 1   | 1   | 1  | 1   | 2   | 2  | 2   | 1  | 3  | 1   | 1  |
| Nordeng, 2010            | 1  | 1   | 1   | 1  | 1   | 2   | 2  | 2   | 1  | 3  | 2   | 1  |
| Sanz, 2000               | 1  | 1   | 3   | 2  | 1   | 2   | 2  | 2   | 1  | 3  | 1   | 1  |
| Sharma, 2006             | 1  | 1   | 3   | 2  | 1   | 2   | 2  | 1   | 1  | 3  | 1   | 1  |
| Twigg, 2016              | 1  | 1   | 1   | 1  | 1   | 2   | 2  | 1   | 1  | 3  | 1   | 1  |

<sup>a</sup>Assessed using a tool developed by the Center for Evidence-based Management<sup>32</sup> for cross-sectional studies (surveys)

1=Yes, 2=Can't Tell, 3=No

| Domain   | Author's   | Support for judgement  |
|--|------------|--|
|  | judgement* |  |
| Butters, 1990 (cross-sectional survey                                |            |  |
| Clearly focused question/issue                                       | 1          | Awareness of the effects of commonly used drug   |
|  |            | cigarettes and alcohol on the fetus  |
| Appropriate research method  | 1          | Cross-sectional survey of women in postnatal wa  |
| (study design)   |            |  |
| Selection of subjects clearly  | 1          | Provides inclusion and exclusion criteria, outlines  |
| described  |            | selection methods  |
| Sampling method introduces bias                                      | 2          | Sampling was not random, may be consecutive  |
| Sample of subjects representative                                    | 1          | Included women who were recently post-partum   |
| of the population  |            |  |
| Sample size based on pre-study                                       | 2          | Not reported   |
| considerations of statistical power                                  |            |  |
| Satisfactory response rate   | 1          | Response rate was 87%  |
| Questionnaires are likely to be                                      | 2          | Validation of survey questions was not reported  |
| valid and reliable   | Ā          |  |
| Statistical significance assessed                                    | 1          | Chi-square analysis  |
| Confidence intervals for main  |            |  |
| results  | 3          | No confidence intervals reported   |
|  |            |  |
| Confounding factors not accounted                                    | 1          | Confounders were not addressed with study des  |
| for  |            | or analysis  |
| Applicability of the results   | 1          | Identifies areas for further education in this   |
|  |            | population   |
| outcomes obtained/reported in cros<br>Clearly focused question/issue | -          | <ul> <li>bort with embedded treatment RCT; valuation of</li> <li>To assess maternal and neonatal consequences of</li> </ul>  |
| clearly locused question/issue                                       | 2          | treating and not treating asymptomatic bacterium   |
|  |            | in pregnancy; however, no direct examination of  |
|  |            | outcome valuation set out in protocol or study   |
|  |            | methods  |
| Appropriate research method  | 2          | Appears to be cross-sectional for information  |
| Appropriate research method (study design)                           | <u> </u>   | regarding why eligible women did not consent to  |
| (study design)   |            |  |
| Soloction of cubicate closely  | 1          | participate in treatment trial   |
| Selection of subjects clearly  | 1          | Clear inclusion and exclusion criteria for screenin  |
| described  |            | cohort and treatment RCT, with study flow  |
| <u> </u>   |            | documented   |
| Sampling method introduces bias                                      | 3          | Various clinics, hospitals and ultrasound centres  |
|  |            | the Netherlands  |
| Sample of subjects representative                                    | 1          | Women 18 years or older with singleton pregnar   |
| of the population  |            | without symptoms of urinary tract infection.   |
| Sample size based on pre-study                                       | 2          | Sample size estimates reported in statistical anal   |
| considerations of statistical power                                  |            | but none specified for cross-section of women for  |
| considerations of statistical power                                  |            | outcome valuation  |
|  |            | A ut have all all wat ways and was a water an a stift as lly   |
|  | 2          | Authors did not report response rate specifically  |
|  | 2          |  |
| Satisfactory response rate   | 2          | cross-section of women who declined treatment  |
|  | 2          | cross-section of women who declined treatment<br>255 ASB-positive women, 163 received no treatm  |
|  | 2          | cross-section of women who declined treatment<br>255 ASB-positive women, 163 received no treatment<br>(of whom 155 did not want treatment for specifi  |
|  | 2          | cross-section of women who declined treatment<br>255 ASB-positive women, 163 received no treatm<br>(of whom 155 did not want treatment for specifi<br>reason), but authors do not report if those who  |
|  | 2          | Authors did not report response rate specifically<br>cross-section of women who declined treatment.<br>255 ASB-positive women, 163 received no treatm<br>(of whom 155 did not want treatment for specific<br>reason), but authors do not report if those who<br>participated in treatment trial were asked/provid<br>reason(s) |

| Questionnaires are likely to be valid and reliable                   | 2      | Validation of reason(s) for dissenting not reported |
|--|--------|---|
| Statistical significance assessed                                    | 3      | Fisher's exact test for outcomes from screening     |
|  |        | cohort and treatment trial; no significance for     |
|  |        | outcome valuation data                              |
| Confidence intervals for main  | 3      | CI's reported for outcomes from screening cohort    |
| results  |        | and treatment trial; no Cl's for outcome valuation  |
|  |        | data  |
| Confounding factors not accounted                                    | 2      | Assessed confounders for outcomes from screening    |
| for  |        | cohort and treatment trial, but not for outcome     |
|  |        | valuation data                                      |
| Applicability of the results   | 3      | Medication avoidance for asymptomatic conditions    |
|  |        | in pregnancy among Dutch women acknowledged b       |
|  |        | study authors to align with Dutch guidelines (not   |
|  |        | routinely screening and treating women with ASB);   |
|  |        | may be more applicable for the Netherlands but no   |
|  |        | for Canada where routine screening and treatment    |
|  | 4      | is standing practice                                |
| Lupattelli, 2014 (cross-sectional surv                               | /ey)   |   |
| Clearly focused question/issue                                       | 1      | Association of health literacy and risk perception  |
| Appropriate research method  | 1      | Cross-sectional survey of pregnant women            |
| (study design)   |        |   |
| Selection of subjects clearly  | 1      | Self-selection, voluntary internet survey           |
| described  |        |   |
| Sampling method introduces bias                                      | 1      | Informal sampling method – self-selection was not   |
|  |        | random or consecutive                               |
| Sample of subjects representative                                    | 1      | Pregnant women with internet access                 |
| of the population  |        |   |
| Sample size based on pre-study                                       | 2      | Not reported  |
| considerations of statistical power                                  |        |   |
| Satisfactory response rate   | 2      | Large n, no response rate reported                  |
| Questionnaires are likely to be                                      | 2      | Validation of survey questions was not reported     |
| valid and reliable   |        |   |
| Statistical significance assessed                                    | 1      | Mann-Whitney U test, Spearman's rank correlation    |
| -  |        | coefficient, logistic regression                    |
| Confidence intervals for main  | 1      | Reported in Table 3                                 |
| results  |        |   |
| Confounding factors not accounted                                    | 3      | Adjusted for confounders in statistical analysis    |
| for  |        |   |
| Applicability of the results   | 1      | Health literacy is significantly associated with    |
|  |        | adherence to pharmacotherapy in pregnant womer      |
| Mashayekhi, 2009 (cross-sectional s                                  | urvey) | · · · · · ·   |
| Clearly focused question/issue                                       | 1      | Awareness of pregnant women on the effects of       |
|  |        | drugs during pregnancy                              |
| Appropriate research method  | 1      | Cross-sectional survey of pre and postnatal women   |
| (study design)   |        | -/  |
| Selection of subjects clearly  | 1      | Reports selection methods                           |
| described  | -      |   |
|  | 1      | Sampling was not random or consecutive              |
| Sampling method introduces bias                                      |        |   |
| Sampling method introduces bias<br>Sample of subjects representative | 1      | Included pre and postnatal women in hospital ward   |

| Sample size based on pre-study considerations of statistical power | 2   | Not reported  |
|--|-----|---|
| Satisfactory response rate   | 2   | Large n, no response rate reported  |
| Questionnaires are likely to be<br>valid and reliable              | 2   | Validation of survey questions was not reported                               |
| Statistical significance assessed                                  | 1   | Chi-square, Student's t-test, Pearson correlation ANOVA                       |
| Confidence intervals for main results                              | 3   | Not reported  |
| Confounding factors not accounted for                              | 1   | Confounders were not addressed with study de or analysis                      |
| Applicability of the results                                       | 1   | Identifies roles for pharmacists in education of population                   |
| Nordeng, 2010 (cross-sectional surve                               | ey) |   |
| Clearly focused question/issue                                     | 1   | Women's perception of risk during pregnancy                                   |
| Appropriate research method (study design)                         | 1   | Cross-sectional survey of pregnant women and mothers                          |
| Selection of subjects clearly described                            | 1   | Self-selection, voluntary internet survey                                     |
| Sampling method introduces bias                                    | 1   | Informal sampling method – self-selection was random or consecutive           |
| Sample of subjects representative of the population                | 1   | Pregnant women and young mothers (child less<br>5 years) with internet access |
| Sample size based on pre-study considerations of statistical power | 2   | Not reported  |
| Satisfactory response rate   | 2   | Large n, no response rate reported  |
| Questionnaires are likely to be valid and reliable                 | 2   | Validation of survey questions was not reported                               |
| Statistical significance assessed                                  | 1   | Linear regression, ANOVA, Student's t-test                                    |
| Confidence intervals for main results                              | 3   | Confidence intervals were available in graph for only                         |
| Confounding factors not accounted for                              | 2   | Addressed in limitations  |
| Applicability of the results                                       | 1   | Indicates women overestimate risks and more education in this area is needed. |
| Sanz, 2000 (cross-sectional)                                       | •   |   |
| Clearly focused question/issue                                     | 1   | Drug utilization in pregnant women  |
| Appropriate research method<br>(study design)                      | 1   | Cross sectional, visual analogue scale  |
| Selection of subjects clearly described                            | 3   | Selection methods are not reported for all populations                        |
| Sampling method introduces bias                                    | 2   | Not reported for all populations  |
| Sample of subjects representative of the population                | 1   | Pregnant women attending out-patient clinic at<br>hospital                    |
| Sample size based on pre-study considerations of statistical power | 2   | Not reported  |
| Satisfactory response rate   | 2   | Small n, no response rate reported  |
| Questionnaires are likely to be valid and reliable                 | 2   | Validation of VAS questions was not reported                                  |
| Statistical significance assessed                                  | 1   | Mann-Whitney U, Kruskal Wallis, Chi-squared                                   |

| Confidence intervals for main results                              | 3  | Only in graph format   |
|--|----|--|
| Confounding factors not accounted for                              | 1  | Confounders were not addressed with study desig<br>or analysis   |
| Applicability of the results                                       | 1  | Pregnant women have high perceptions of teratogenic risk   |
| Sharma, 2006 (cross-sectional surve                                | v) |  |
| Clearly focused question/issue                                     | 1  | Drug utilization in pregnant women   |
| Appropriate research method<br>(study design)                      | 1  | Cross-sectional survey of pregnant women   |
| Selection of subjects clearly                                      | 3  | Selected from an antenatal clinic but no sampling  |
| described  |    | methods  |
| Sampling method introduces bias                                    | 2  | Not reported   |
| Sample of subjects representative of the population                | 1  | Pregnant women   |
| Sample size based on pre-study considerations of statistical power | 2  | Not reported   |
| Satisfactory response rate   | 2  | Large n, no response rate reported   |
| Questionnaires are likely to be                                    | 1  | Women's statements were confirmed through  |
| valid and reliable   |    | medical records when available   |
| Statistical significance assessed                                  | 1  | Chi-squared test   |
| Confidence intervals for main<br>results provided                  | 3  | Not reported   |
| Confounding factors not accounted                                  | 1  | Confounders were not addressed with study desig  |
| for  |    | or analysis  |
| Applicability of the results                                       | 1  | Education of women of child-bearing age regardin<br>benefits and harms of drug use during pregnancy in<br>needed |
| Twigg, 2016 (cross-sectional survey)                               |    |  |
| Clearly focused question/issue                                     | 1  | Risk perception of medications in pregnant women<br>and relationship with use                                    |
| Appropriate research method<br>(study design)                      | 1  | Cross-sectional survey of pregnant women and ne mothers  |
| Selection of subjects clearly described                            | 1  | Self-selection, voluntary internet survey  |
| Sampling method introduces bias                                    | 1  | Informal sampling method – self-selection was not random or consecutive  |
| Sample of subjects representative of the population                | 1  | Pregnant women or women <1 year post-natal wit<br>internet access  |
| Sample size based on pre-study considerations of statistical power | 2  | Not reported   |
| Satisfactory response rate   | 2  | Large n, no response rate reported   |
| Questionnaires are likely to be valid and reliable                 | 1  | Used validated BMQ-General questionnaire   |
| Statistical significance assessed                                  | 1  | Chi-square, Fisher's exact test, Mann-Whitney U,<br>Independent t-test   |
| Confidence intervals for main results                              | 3  | No confidence intervals for the main results, descriptive statistics only  |
| Confounding factors not accounted for                              | 1  | Adjustment for confounding not reported in desig<br>or analysis  |

| Applicability of the results | 1              | Medication use by pregnant women is impacted by<br>beliefs about risk   |
|------------------------------|----------------|---|
| * 1=Yes, 2=Can't Tell, 3=No  | symptomatic ba | Evidence-based Management for cross-sectional studies<br>acteriuria; BMQ: beliefs about medicine questionnaire; n:<br>al analogue scale |
|                              |                |   |
|                              |                |   |
|                              |                |   |
|                              |                |   |
|                              |                |   |
|                              |                |   |
|                              |                |   |
|                              |                |   |
|                              |                |   |

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| Study   | Sequence Generation                                | Allocation Concealment                              | Blinding of Participants<br>and Personnel <sup>1</sup> | Blinding of Outcome<br>Assessors <sup>1</sup>      | Incomplete Reporting <sup>2</sup>                   | Selective Reporting <sup>3</sup> | Other Bias <sup>4</sup>            | O <sup>v</sup><br>I F<br>Of<br>Bi |
|---|--|---|--|--|---|----------------------------------|------------------------------------|-----------------------------------|
| Brumfitt 1975   | •  |   |  | - `  | -   | •                                |                                    |                                   |
| Elder 1966  |  |   |  |  |   |                                  |                                    |                                   |
| Elder 1971  |  |   |  |  |   |                                  |                                    |                                   |
| Foley 1987  |  |   |  |  |   |                                  |                                    |                                   |
| Furness 1975  |  |   |  |  |   |                                  |                                    |                                   |
| Gold 1966   |  |   |  |  |   |                                  |                                    |                                   |
| Kass 1960   |  |   |  |  |   |                                  |                                    |                                   |
| Kazemier 2015   |  |   |  |  |   |                                  |                                    |                                   |
| Kincaid-Smith 1965  |  |   |  |  |   |                                  |                                    |                                   |
| Little 1966   |  |   |  |  |   |                                  |                                    |                                   |
| Mulla 1960  |  |   |  |  |   |                                  |                                    |                                   |
| Pathak 1969   |  |   |  |  |   |                                  |                                    |                                   |
| Thomsen 1987  |  |   |  |  |   |                                  |                                    |                                   |
| Williams 1969   |  |   |  |  |   |                                  |                                    |                                   |
| Wren 1969   |  |   |  |  |   |                                  |                                    |                                   |
| between groups<br><sup>3</sup> For the selective<br>undetected or no<br><sup>4</sup> Assessed as: Lo  | e reporting do<br>ot highly susp                   | omain, a defa<br>ected                              |  |  |   |                                  |                                    |                                   |
| detected such as<br>randomized, or k<br>this domain.<br>* Assessed as: Lo<br>domains are asse<br>Legend:<br>Low risk<br>Unclear risk<br>High risk | : participant o<br>blocked rando<br>bw if all doma | characteristic<br>omization in tr<br>ins are assess | s (baseline iml<br>rials without b<br>red as low, Un   | balances), stu<br>linding); Unc<br>clear if at lea | udy design cha<br>lear risk of bia<br>st one domair | aracteristics (<br>as assessmen  | crossover, clus<br>t not applicabl | ter-<br>e for                     |
|   |  |   |  |  |   |                                  |                                    |                                   |
|   |  |   |  |  |   |                                  |                                    |                                   |

| Domain                   | Author's<br>judgement | Support for judgement  |
|--------------------------|-----------------------|--|
| Brumfitt, 1975 (RCT)     |                       |  |
| Random sequence          | Unclear               | No description of the sequence generation process, how women       |
| generation               |                       | were assigned to treatment or placebo, unequal numbers in          |
| 5                        |                       | treatment and placebo groups.                                      |
| Allocation               | Unclear               | No information provided to judge.                                  |
| concealment              |                       |  |
| Blinding of participants | Low                   | "were given placebo under double-blind conditions". Method not     |
| and personnel            |                       | described in sufficient detail. Objective outcomes.                |
| Blinding of outcome      | Low                   | "were given placebo under double-blind conditions". Method not     |
| assessment               | LOW                   | described in sufficient detail. Objective outcomes.                |
| Incomplete outcome       | High                  | Inconsistencies in total number of women not explained (number of  |
| data                     | nign                  | <2500g babies provided for 413/326 bacteriuric women); results no  |
| uala                     |                       | provided for pyelonephritis for all women in treated group (only   |
|                          |                       |  |
| Calaatina a di           |                       | subset).   |
| Selective reporting      | High                  | Results not provided for pyelonephritis for all women allocated to |
|                          |                       | treatment.   |
| Other bias               | Low                   | Insufficient information to judge.                                 |
| Overall risk of bias     | High                  |  |
| Elder, 1966 (RCT)        |                       |  |
| Random sequence          | Unclear               | "a random sequence". Insufficient information to judge.            |
| generation               |                       |  |
| Allocation               | Unclear               | No information provided to judge.                                  |
| concealment              |                       |  |
| Blinding of participants | Low                   | "double-blind trial"; no information provided to judge. Objective  |
| and personnel            |                       | outcomes.  |
| Blinding of outcome      | Low                   | "double-blind trial"; no information provided to judge. Objective  |
| assessment               |                       | outcomes.  |
| Incomplete outcome       | Low                   | Information provided on women lost to follow-up, reasonably        |
| data                     | 2011                  | balanced between groups.   |
| Selective reporting      | High                  | Result not provided for pyelonephritis for all participants; no    |
| Selective reporting      | i ligit               | pregnancy outcomes (GA, birthweight).                              |
| Otherhies                | Low                   |  |
| Other bias               | Low                   | Insufficient information to judge.                                 |
| Overall risk of bias     | High                  |  |
| Elder, 1971 (CCT)        | 1                     |  |
| Random sequence          | High                  | "alternate bacteriuricwere assigned."                              |
| generation               |                       |  |
| Allocation               | High                  | Participants were allocated by alternation.                        |
| concealment              |                       |  |
| Blinding of participants | Unclear               | "identical-appearing placebo"; insufficient information to judge.  |
| and personnel            |                       |  |
| Blinding of outcome      | Unclear               | "identical-appearing placebo"; insufficient information to judge.  |
| assessment               |                       |  |
| Incomplete outcome       | Unclear               | Insufficient information to judge.                                 |
| data                     |                       |  |
| Selective reporting      | Unclear               | Unable to judge; twin deliveries were excluded.                    |
| Other bias               | Low                   | Insufficient information to judge.                                 |
| Overall risk of bias     |                       |  |
|                          | High                  |  |

| Domain                   | Author's<br>judgement | Support for judgement   |
|--------------------------|-----------------------|---|
| Random sequence          | Low                   | Allocated to treatment or no treatment by "toss of a coin".         |
| generation               |                       |   |
| Allocation               | Unclear               | No information to judge.  |
| concealment              |                       |   |
| Blinding of participants | Unclear               | No description of any attempt at blinding; not placebo-controlled.  |
| and personnel            |                       | Objective outcomes.   |
| Blinding of outcome      | Unclear               | No description of any attempt at blinding; not placebo-controlled.  |
| assessment               |                       | Objective outcomes.   |
| Incomplete outcome       | Unclear               | Loss to follow-up: 19%; no reasons provided for missing outcome     |
| data                     |                       | data.   |
| Selective reporting      | High                  | No pregnancy outcomes (GA, birthweight).                            |
| Other bias               | Low                   | Insufficient information to judge.                                  |
| Overall risk of bias     | High                  |   |
| Furness, 1975 (RCT)      | 8                     |   |
| Random sequence          | Unclear               | "by random allocation"; no additional information to judge.         |
| generation               |                       |   |
| Allocation               | Unclear               | No information to judge.  |
| concealment              | Undicut               |   |
| Blinding of participants | Unclear               | Not placebo-controlled. Objective outcomes.                         |
| and personnel            | Uncicul               |   |
| Blinding of outcome      | Unclear               | No information to judge.  |
| assessment               | Uncical               | No mornation to judge.  |
| Incomplete outcome       | High                  | 20/226 women withdrawn from trial, no details provided. All wome    |
| data                     | i ligit               | included in outcome of pyelonephritis, 17% loss to follow-up or low |
| Gata                     |                       | birthweight and GA at delivery.                                     |
| Selective reporting      | Unclear               | Unable to separate incidence of pyelonephritis during pregnancy an  |
| Sciective reporting      | Uncical               | puerperium; results combined.                                       |
| Other bias               | Low                   | Insufficient information to judge.                                  |
| Overall risk of bias     | High                  |   |
| Gold, 1966 (CCT)         | 111g11                |   |
| Random sequence          | High                  | Women allocated to treatment based on study number: odd numbe       |
| generation               | i ligit               | treatment, even number control.                                     |
| Allocation               | High                  | Allocated to treatment based on study number.                       |
| concealment              | i ligit               | Anocated to treatment based on study humber.                        |
| Blinding of participants | Unclear               | Placebo-controlled; no further details provided. Objective outcomes |
| and personnel            | Unclear               | racebo-controlled, no further details provided. Objective outcomes  |
| Blinding of outcome      | Unclear               | No information to judge. Objective outcomes.                        |
| assessment               | Unclear               | No mormation to judge. Objective outcomes.                          |
| Incomplete outcome       | Low                   | Does not appear to be any loss to follow-up.                        |
| data                     |                       |   |
| Selective reporting      | Unclear               | No definition provided for prematurity.                             |
| Other bias               |                       | Insufficient information to judge.                                  |
| Overall risk of bias     | Low                   |   |
|                          | High                  |   |
| Kass, 1960 (CCT)         | High                  | "alternate women received a placebe"                                |
| Random sequence          | High                  | "alternate women received a placebo".                               |
| generation               | Liel                  |   |
| Allocation               | High                  | Allocation based on alternation: "alternate women received a        |
| concealment              |                       | placebo".   |

| Domain                     | Author's<br>judgement | Support for judgement   |
|----------------------------|-----------------------|---|
| Blinding of participants   | Low                   | Placebo was used and "the nature of the treatment was not known to  |
| and personnel              |                       | the patient or to the attending obstetrical staff".   |
| Blinding of outcome        | Unclear               | Although a placebo was used, no further details are provided on   |
| assessment                 |                       | blinding of outcome assessment. Objective outcomes.   |
| Incomplete outcome         | Unclear               | 40 (21%) women were not enrolled either because they were >32   |
| data                       |                       | weeks GA before treatment could be started (n=30), or already   |
|                            |                       | received treatment for symptomatic infection (n=10). Loss to follow-  |
|                            |                       | up: 23 (11%) for pyelonephritis and low birthweight, no details   |
|                            |                       | provided; 69 (34%) for long-term persistent bacteriuria.  |
| Selective reporting        | Unclear               | 3 women had subsequent pregnancy and were reassigned to their   |
|                            |                       | original treatment group included in the analysis. In 5 placebo   |
|                            |                       | patients, symptomatic disease was assumed but no symptoms were  |
|                            |                       | documented. Not all women in symptomatic group were confirmed   |
|                            |                       | to have fever. Women treated for infections other than that in the  |
|                            |                       | urinary tract were included in the symptomatic group if they had  |
| Otherhize                  | 1                     | cleared their bacteriuria.  |
| Other bias                 | Low                   | Insufficient information to judge.  |
| Overall risk of bias       | High                  |   |
| Kazemier, 2015 (RCT)       | 1                     | Deaders excise monthin 1.1 vetics, computer, concreted list with  |
| Random sequence            | Low                   | Random assignment in 1:1 ratio; computer-generated list with  |
| generation<br>Allocation   | Low                   | random block sizes of 2/4/6 participants.<br>Women, treating physicians and researchers remained unaware of |
| concealment                | Low                   | bacteriuria status and treatment allocation. Central allocation -   |
| conceannent                |                       | unmasking of treatment allocation was possible by 24h telephone   |
|                            |                       | service.  |
| Blinding of participants   | Low                   | Double-blinded. Women, treating physicians and researchers  |
| and personnel              | 2011                  | remained unaware of bacteriuria status and treatment allocation.  |
|                            |                       | Objective outcomes.   |
| Blinding of outcome        | Low                   | Outcomes recorded by participants on questionnaires, and from data  |
| assessment                 |                       | provided by hospitals and midwives up to 6 weeks post-delivery.   |
| Incomplete outcome         | Low                   | ITT and dropout rate <10% (12/255 ASB-positive)   |
| data                       |                       |   |
| Selective reporting        | Low                   | Cost-effectiveness was outlined in protocol but not reported in final                                       |
| 1 0                        |                       | study methods or results.   |
| Other bias                 | Low                   | No other sources of bias identified.  |
| Overall risk of bias       | Low                   |   |
| Kincaid-Smith, 1965 (RCT)  | •                     |   |
| Random sequence            | Unclear               | No description of sequence generation process.  |
| generation                 |                       |   |
| Allocation                 | Low                   | "a code of instructions to the pharmacist ensured that the trial  |
| concealment                |                       | remained double-blind despitealterations in therapeutic regimen".   |
| Blinding of participants   | Low                   | "a code of instructions to the pharmacist ensured that the trial  |
| and personnel              |                       | remained double-blind despitealterations in therapeutic regimen".   |
| Blinding of outcome        | Low                   | "a code of instructions to the pharmacist ensured that the trial  |
| assessment                 |                       | remained double-blind despitealterations in therapeutic regimen".   |
| Incomplete outcome<br>data | Unclear               | 240 women initially identified as bacteriuric; no information available                                     |
|                            |                       | on 55 (23%) women randomized to treatment but not included in the   |
|                            |                       | analysis because of poor compliance (attended infrequently or failed  |
|                            |                       | to take tablets continuously).  |
| Selective reporting        | Unclear               | Insufficient information to judge.  |

| Domain                                    | Author's<br>judgement | Support for judgement  |
|---|-----------------------|--|
| Other bias                                | Low                   | Insufficient information to judge.   |
| Overall risk of bias                      | Unclear               |  |
| Little, 1966 (RCT)                        |                       |  |
| Random sequence                           | Unclear               | No information to judge.   |
| generation                                |                       |  |
| Allocation<br>concealment                 | Unclear               | Allocation to treatment or control was drawn for "a pool of sealed<br>envelopes containing a slip of paper", but there was no information<br>provided to ensure appropriate safeguards to prevent investigators<br>being aware of the treatment group. |
| Blinding of participants                  | Unclear               | Participants in the control group "were given placebo"; no further   |
| and personnel                             |                       | details provided. Objective outcomes.  |
| Blinding of outcome                       | Unclear               | No information to judge. Objective outcomes.   |
| assessment                                |                       |  |
| Incomplete outcome<br>data                | Low                   | No missing outcome data.   |
| Selective reporting                       | Unclear               | Insufficient information to judge.   |
| Other bias                                | Low                   | Insufficient information to judge.   |
| Overall risk of bias                      | Unclear               |  |
| Mulla, 1960 (RCT)                         |                       |  |
| Random sequence<br>generation             | Unclear               | No description of sequence generation process.   |
| Allocation                                | Unclear               | Women were "randomly divided into two groups"; no other details  |
| concealment                               |                       | provided   |
| Blinding of participants<br>and personnel | Unclear               | Not placebo-controlled. Objective outcomes.  |
| Blinding of outcome assessment            | Unclear               | No information to judge. Objective outcomes.   |
| Incomplete outcome<br>data                | Low                   | No missing outcome data.   |
| Selective reporting                       | High                  | No definition for outcome of cystopyelitis; no pregnancy outcomes (GA, birthweight).   |
| Other bias                                | Low                   | Insufficient information to judge.   |
| Overall risk of bias                      | High                  |  |
| Pathak, 1969 (RCT)                        |                       |  |
| Random sequence<br>generation             | Unclear               | "on a random basis". Insufficient information provided to permit further judgement.  |
| Allocation<br>concealment                 | Unclear               | Method of concealment not described.   |
| Blinding of participants<br>and personnel | Unclear               | No information to judge.   |
| Blinding of outcome<br>assessment         | Unclear               | No information to judge.   |
| Incomplete outcome<br>data                | Low                   | Missing outcome data balanced; reasons similar and unlikely to hav introduced bias.  |
| Selective reporting                       | High                  | No pregnancy outcomes (GA, birthweight).   |
| Other bias                                | Low                   | Insufficient information to judge.   |
| Overall risk of bias                      | High                  |  |

| Domain                                  | Author's<br>judgement | Support for judgement   |
|---|-----------------------|---|
| Random sequence                         | Unclear               | Described as "randomly allocated" but no description of the             |
| generation                              |                       | sequence generation process.  |
| Allocation                              | Unclear               | Method of concealment of allocation not described.                      |
| concealment                             |                       |   |
| Blinding of participants                | Unclear               | Placebo-controlled, described as "double-blinded" but no additional     |
| and personnel                           |                       | data. Objective outcomes.   |
| Blinding of outcome                     | Unclear               | Described as "double-blinded" but no specific information provided      |
| assessment                              |                       | to ensure outcome assessment was blinded. Objective outcomes.           |
| Incomplete outcome                      | Low                   | No missing outcome data.  |
| data                                    |                       |   |
| Selective reporting                     | Unclear               | Insufficient information to judge.                                      |
| Other bias                              | Low                   | Insufficient information to judge.                                      |
| Overall risk of bias                    | Unclear               |   |
| Williams, 1969 (RCT)                    |                       |   |
| Random sequence<br>generation           | Unclear               | "allocation at random"; no additional information to judge.             |
| Allocation                              | Unclear               | No information to judge.  |
| concealment<br>Blinding of participants | Unclear               | No blinding, outcome may have been influenced by lack of blinding.      |
| and personnel                           | Unclear               | No treatment group was given antibiotics to take if symptoms of         |
| and personner                           |                       | infection developed. Objective outcomes.                                |
| Blinding of outcome                     | Unclear               | No blinding; assessment of outcome (pyelonephritis) may have beer       |
| assessment                              | Uncical               | influenced by knowledge of treatment allocation. Objective              |
|   |                       | outcomes.   |
| Incomplete outcome                      | Unclear               | No explanation for unequal group sizes; no information provided on      |
| data                                    |                       | any missing data. An unknown number of women in the control             |
|   |                       | group were given antibiotic treatment if they developed symptoms of     |
|   |                       | UTI.  |
| Selective reporting                     | High                  | No pregnancy outcomes (GA, birthweight).                                |
| Other bias                              | Low                   | Insufficient information to judge.                                      |
| Overall risk of bias                    | High                  |   |
| Wren, 1969 (CCT)                        |                       |   |
| Random sequence<br>generation           | High                  | Women "were divided into two groups, alternate patients being treated". |
| Allocation                              | High                  | Women "were divided into two groups, alternate patients being           |
| concealment                             | -                     | treated".   |
| Blinding of participants                | Unclear               | No blinding; knowledge of treatment group may have influenced           |
| and personnel                           |                       | outcome; women in untreated group who developed clinical UTI            |
|   |                       | (33/90) were given antibiotics at the choice of the obstetrician,       |
|   |                       | continued to delivery in 50% of cases. Objective outcomes.              |
| Blinding of outcome                     | Unclear               | No blinding; however, outcome of birthweight unlikely to be             |
| assessment                              |                       | influenced by lack of blinding.   |
| Incomplete outcome<br>data              | Low                   | 10 (6%) women not included in outcomes: 2 sets of twins excluded,       |
|   |                       | moved and 2 could not be traced, 3 delivered before antibiotics cou     |
|   |                       | be started, 1 refused treatment.  |
| Selective reporting                     | Unclear               | Insufficient information to judge; outcome of pyelonephritis not        |
| -10                                     |                       | reported.   |
| Other bias                              | Low                   | Insufficient information to judge.                                      |
| Overall risk of bias                    | High                  |   |

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<sup>a</sup>Assessed using the Cochrane Risk of Bias tool ASB: asymptomatic bacteriuria; g: gram(s); GA: gestational age; UTI: urinary tract infection

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#### Supplement 6. GRADE Summary of Findings & Evidence Profiles tables & forest plots

#### Evidence Set 1. Table 1.1 GRADE Summary of Findings – Benefits and harms of screening compared to no screening

#### Screening compared to no screening for asymptomatic bacteriuria in pregnant women

Patient or population: asymptomatic bacteriuria in pregnant women

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: screening

**Comparison**: no screening

| Outcomes                | Anticipated a<br>effects <sup>*</sup> (95% |  | Relative<br>effect<br>(95% CI) | № of<br>participants<br>(studies)    | Quality of<br>the<br>evidence  | Comments  |
|-------------------------|--|--|--------------------------------|--------------------------------------|--------------------------------|---|
|                         | Risk with no screening                     | Risk with screening  |                                |                                      | (GRADE)                        |   |
| Maternal<br>mortality   | 0 per 1,000                                | <b>0 per 1,000</b><br>(0 to 0)   | not<br>estimable               | (0 studies)                          | -                              | No study reported on maternal mortality.  |
| Maternal sepsis         | 0 per 1,000                                | <b>0 per 1,000</b><br>(0 to 0)   | not<br>estimable               | (0 studies)                          | -                              | No study reported on maternal sepsis.   |
| Pyelonephritis          | Median                                     |  | <b>RR 0.28</b> (0.15 to        | 5659<br>(3                           | ⊕○○○<br>VERY LOW <sup>1,</sup> | We are very uncertain ab the effects of screening o                             |
|                         | 18 per 1,000                               | <b>13 fewer</b><br><b>per 1,000</b><br>(from 8<br>fewer to 16<br>fewer)  | 0.54)                          | observational<br>studies)            | a                              | pyelonephritis.   |
| Perinatal<br>mortality  | Median                                     |  | <b>RR 1.21</b> (0.01 to        | 724<br>(2                            | ⊕○○○<br>VERY LOW <sup>1,</sup> | We are very uncertain ab the effects of screening o                             |
|                         | 19 per 1,000                               | <b>4 more per</b><br><b>1,000</b><br>(from 19<br>fewer to<br>1,000 more) | 102.93)                        | observational<br>studies)            | Ь                              | perinatal mortality.  |
| Spontaneous<br>abortion | 55 per 1,000                               | <b>2 fewer per</b><br><b>1,000</b><br>(from 32<br>fewer to 70<br>more)   | <b>RR 0.96</b> (0.41 to 2.27)  | 370<br>(1<br>observational<br>study) |                                | We are very uncertain ab<br>the effects of screening o<br>spontaneous abortion. |

| Screening compared to no screening for asymptomatic bacteriuria in pregnant women |
|---|
|---|

#### Patient or population: asymptomatic bacteriuria in pregnant women

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: screening

Comparison: no screening

|  | k with no<br>eening | Risk with screening   | (95% CI)                      | (studies)                            | evidence<br>(GRADE)                 | Comments   |
|--|---------------------|---|-------------------------------|--------------------------------------|-------------------------------------|--|
|  |                     | Ū   |                               |                                      | χ- γ                                |  |
| Neonatal sepsis 0 pe   | er 1,000            | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable              | (0 studies)                          | -                                   | No study reported on neonatal sepsis.  |
| Preterm delivery Med   | dian                |   | <b>RR 8.70</b> (0.32 to       | 722<br>(2                            | ⊕○○○<br>VERY LOW <sup>1,</sup>      | We are very uncertain abo<br>the effects of screening on                         |
| 13 p   | per 1,000           | <b>102 more</b><br><b>per 1,000</b><br>(from 9<br>fewer to<br>1,000 more) | 240.07)                       | observational<br>studies)            | d                                   | preterm delivery.  |
| Low birthweight 0 pe   | er 1,000            | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable              | (0 studies)                          | -                                   | No study reported on low birthweight.  |
| Maternal serious<br>harm(s) 0 pe   | er 1,000            | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable              | (0 studies)                          | 2                                   | No study reported on maternal serious harms.                                     |
| Neonatal serious<br>harm: fetal<br>abnormalities 11 g                      | per 1,000           | <b>5 more per</b><br><b>1,000</b><br>(from 8<br>fewer to 85<br>more)      | <b>RR 1.50</b> (0.25 to 8.87) | 372<br>(1<br>observational<br>study) | ⊕⊖⊖⊖<br>VERY LOW <sup>1,</sup><br>e | We are very uncertain abo<br>the effects of screening on<br>fetal abnormalities. |
| *The risk in the interverse group and the relative CI: Confidence interval | e effect of t       | the intervention  |                               | •                                    | d on the assun                      | ned risk in the comparison   |

Screening compared to no screening for asymptomatic bacteriuria in pregnant women

#### Patient or population: asymptomatic bacteriuria in pregnant women

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: screening

Comparison: no screening

|   | Anticipated a<br>effects <sup>*</sup> (95%   |   | Relative<br>effect<br>(95% Cl)   | № of<br>participants<br>(studies)  | Quality of<br>the<br>evidence   | Comments  |
|---|--|---|--|--|---|---|
|   | Risk with no screening   | Risk with screening   |  |  | (GRADE)   |   |
| High quality:<br>Moderate qua<br>estimate of th<br>Low quality:<br>estimate of th<br>Very low qual  | e effect, but there<br>Dur confidence in t<br>le effect  | ent that the<br>erately confic<br>is a possibili<br>he effect est<br>little confide   | lent in the effe<br>ty that it is sub<br>imate is limite   | ect estimate: The<br>ostantially differe<br>d: The true effec  | e true effect is<br>ent<br>t may be subs  | of the effect<br>likely to be close to the<br>stantially different from the<br>likely to be substantially   |
| <sup>1</sup> The imprecisi  | ion domain is asse   | ssed using G  | RADE guidanc   | e <sup>42</sup> relevant for   | systematic rev  | views as follows: when  |
| •   | nation size (OIS) cr<br>efit or important l  |   | -  |  | •   | no effect, consideration of 1.25).  |
| - I I ···   | <b>1</b> 1 1 1 <b>0</b>  |   | -  |  |   |   |
| Uncu 2001) rep<br>level data. Furt<br>with: 1) no der<br>analyses for ris<br>therefore dow  | ported this outcom<br>ther downgrading f<br>monstration of com<br>k factors or other   | ne (n=5,659).<br>From low to v<br>nparability be<br>patient chara<br>e <b>cision</b> is not   | Quality of evid<br>very low is war<br>etween screen<br>acteristics. The<br>warranted. Th   | dence is downgra<br>ranted due to se<br>ing and no scree<br>optimal informa  | aded from hig<br>rious <b>risk of b</b><br>ning groups, a<br>ation size is m  | érard 1983, Gratacós 1994<br>h to low due to observatio<br><b>ilas</b> across studies associat<br>and 2) no adjustment to<br>et (sample size >5600),<br>to warrant downgrading fo |
| Uncu 2001) rep<br>level data. Furt<br>with: 1) no der<br>analyses for ris<br>therefore dow<br><b>inconsistency</b> ,<br><b>Perinatal mort</b><br>2001) reported<br>Further downg<br>demonstration<br>factors or othe<br>mortality. Furt | borted this outcom<br>ther downgrading f<br>monstration of com<br>k factors or other<br>ingrading for impre-<br>indirectness, or of<br>ality [b] → Very Lo<br>tality [b] → Very Lo | te (n=5,659).<br>From low to very a patient characteristics, and sub-<br>crision is not<br>ther consider<br>ow Quality E<br>ality of evider<br>overy low is very low is very<br>fistics, and sub-<br>swarranted for | Quality of evid<br>very low is war<br>etween screen<br>acteristics. The<br>warranted. The<br><b>rations</b> .<br><b>vidence:</b> Two<br>nce is downgr<br>warranted due<br>ening and no<br>spected report<br>for <b>imprecision</b> | dence is downgra<br>ranted due to se<br>ing and no scree<br>optimal informa<br>ere were no seri<br>non-concurrent<br>aded from high to<br>screening groups<br>ting bias as two<br>n due to optimal | aded from hig<br>rious <b>risk of b</b><br>ning groups, a<br>ation size is me<br>ous concerns<br>cohort studies<br>to low due to<br>of <b>bias</b> across s<br>s, and 2) no ac<br>studies did no<br>information s | h to low due to observatio<br><b>lias</b> across studies associat<br>and 2) no adjustment to<br>et (sample size >5600),   |

factors or other patient characteristics, and suspected reporting bias as two studies did not report on spontaneous abortion. Only one study provided data on spontaneous abortion, so this warrants downgrading for **inconsistency**. Further downgrading for **imprecision** is warranted due to low event rates (total of 20) without optimal information size. There were no serious concerns to warrant downgrading for **indirectness** or **other considerations**.

**Preterm delivery [d]** → **Very Low Quality Evidence:** Two non-concurrent cohort studies (n=722; Gérard 1983, Uncu 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on preterm delivery. Further downgrading is warranted for imprecision for inadequate sample size and optimal information size not being met (total of 38 events). There were no serious concerns to warrant downgrading for inconsistency, indirectness or other considerations. 

**Neonatal serious harm: fetal abnormalities (harm)**  $[e] \rightarrow Very Low Quality Evidence: One non-concurrent cohort study$ reported this outcome (n=370; Uncu 2001). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as three studies did not report on fetal abnormalities. Only one study provided data on this outcome so this warrants downgrading for inconsistency. Further downgrading for imprecision is warranted due to the optimal information size not being met for rare events. There were no serious concerns to warrant downgrading for indirectness or other considerations. 

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### Evidence Set 1. Table 1.2 GRADE Evidence Profile – Benefits and harms of screening compared to no screening

Question: Screening compared to no screening for asymptomatic bacteriuria in pregnant women

Setting: Any primary or clinical care setting providing care to pregnant women

| Risk of<br>bias | Inconsistency | Indirectness           | Imprecision<br>1                   | Other<br>considerations                    | screening                                       | no<br>screening | Relative<br>(95% Cl)<br>not<br>estimable | Absolute<br>(95% CI)   | -   | CRITICAL   |
|-----------------|---------------|------------------------|------------------------------------|--|---|-----------------|--|--|---|--|
|                 |               |                        | C/                                 |  |   |                 |  |  | -   | CRITICAL   |
|                 |               |                        | 90×                                |  |   |                 |  |  | -   | CRITICAL   |
|                 |               | 1                      |                                    |  |   |                 | estimable                                |  |   | CRITICAL   |
|                 |               | 1                      |                                    |  |   |                 |  |  |   |  |
|                 |               |                        |                                    | 0  |   |                 | not<br>estimable                         |  | -   | CRITICAL   |
|                 | 1             | J                      | <u> </u>                           | 1  |   |                 |  | <u></u>  |   |  |
| I serious       | not serious   | not serious            | serious                            | none                                       | 10/2008<br>(0.5%)                               | 1.8%            | <b>RR 0.28</b> (0.15 to 0.54)            | <b>13 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 8<br>fewer to<br>16<br>fewer) | ⊕⊖⊖⊖<br>VERY<br>LOW <sup>1, a</sup>                             | CRITICAL   |
|                 | Il serious    | Il serious not serious | Il serious not serious not serious | Il serious not serious not serious serious | Il serious not serious not serious serious none |                 |  | (0.5%) (0.15 to  | (0.5%) (0.15 to per<br>0.54) 1,000<br>(from 8<br>fewer to<br>16 | (0.5%) (0.15 to per VERY<br>0.54) 1,000 LOW <sup>1, a</sup><br>(from 8<br>fewer to<br>16 |

| Quality          | assessment               | assessment № of patients Effect |               |              |             |                         |                 |                  |                                 |   | Quality                             | Importance |
|------------------|--------------------------|---------------------------------|---------------|--------------|-------------|-------------------------|-----------------|------------------|---------------------------------|---|-------------------------------------|------------|
| Nº of<br>studies | Study design             | Risk of<br>bias                 | Inconsistency | Indirectness | Imprecision | Other<br>considerations | screening       | no<br>screening  | Relative<br>(95% Cl)            | Absolute<br>(95% Cl)  |                                     |            |
| 2                | observational<br>studies | serious                         | not serious   | not serious  | serious     | none                    | 6/349<br>(1.7%) | 1.9%             | <b>RR 1.21</b> (0.01 to 102.93) | <b>4 more</b><br><b>per</b><br><b>1,000</b><br>(from 19<br>fewer to<br>1,000<br>more) | ⊕⊖⊖⊖<br>VERY<br>LOW <sup>1, b</sup> | CRITICAL   |
| Spontan          | eous abortion            | L                               | •             |              | I           |                         |                 |                  |                                 | •   |                                     |            |
| 1                | observational<br>studies | serious                         | serious       | not serious  | serious     | none                    | 9/170<br>(5.3%) | 11/200<br>(5.5%) | <b>RR 0.96</b> (0.41 to 2.27)   | <b>2 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 32<br>fewer to<br>70<br>more)   | ⊕⊖⊖⊖<br>VERY<br>LOW <sup>1, c</sup> | CRITICAL   |
| Neonata          | al sepsis                | <u> </u>                        | 1             | I            |             | I                       |                 |                  |                                 | 1   | I                                   | 1          |
| 0                |                          |                                 |               |              |             |                         |                 | J                | not<br>estimable                |   | -                                   | CRITICAL   |
|                  | delivery                 | <u> </u>                        | ļ             | <u> </u>     | I           | Į                       | <u> </u>        | <u> </u>         |                                 | <u> </u>  | <u> </u>                            | <u> </u>   |

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| Quality         | assessment               |                 |               |              |             |                         | Nº of patio      | ents            | Effect                                |  | Quality                             | Importance |
|-----------------|--------------------------|-----------------|---------------|--------------|-------------|-------------------------|------------------|-----------------|---------------------------------------|--|-------------------------------------|------------|
| № of<br>studies | Study design             | Risk of<br>bias | Inconsistency | Indirectness | Imprecision | Other<br>considerations | screening        | no<br>screening | Relative<br>(95% CI)                  | Absolute<br>(95% Cl)   |                                     |            |
| 2               | observational<br>studies | serious         | not serious   | not serious  | serious     | none                    | 33/347<br>(9.5%) | 1.3%            | <b>RR 8.70</b><br>(0.32 to<br>240.07) | <b>102</b><br><b>more</b><br><b>per</b><br><b>1,000</b><br>(from 9<br>fewer to<br>1,000<br>more) | ⊕⊖⊖⊖<br>VERY<br>LOW <sup>1, d</sup> | CRITICAL   |
| Low birt        | thweight                 |                 |               |              |             |                         |                  |                 |                                       |  |                                     |            |
| 0               |                          |                 |               |              |             | 0.                      |                  |                 | not<br>estimable                      |  | -                                   | IMPORTAN   |
| Materna         | al serious harm(         | s)              | <u> </u>      | ļ            | <u> </u>    |                         | <u> </u>         | <u>,</u>        |                                       |  | <u>,</u>                            |            |
| 0               |                          |                 |               |              |             |                         | C                | 51              | not<br>estimable                      |  | -                                   | CRITICAL   |
| Neonata         | al serious harm:         | fetal abn       | ormalities    |              |             |                         |                  |                 |                                       |  |                                     |            |
| 1               | observational<br>studies | serious         | serious       | not serious  | serious     | none                    | 3/186<br>(1.6%)  | 2/186<br>(1.1%) | <b>RR 1.50</b> (0.25 to 8.87)         | <b>5 more</b><br><b>per</b><br><b>1,000</b><br>(from 8<br>fewer to<br>85                         | ⊕⊖⊖⊖<br>VERY<br>LOW <sup>1, e</sup> | CRITICAL   |

CI: Confidence interval; RR: Risk ratio

<sup>1</sup> The imprecision domain is assessed using GRADE guidance<sup>42</sup> relevant for systematic reviews as follows: when optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25).

 Pyelonephritis [a] → Very Low Quality Evidence: Three non-concurrent cohort studies (Gérard 1983, Gratacós 1994, Uncu 2001) reported this outcome (n=5,659). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics. The optimal information size is met (sample size >5600), therefore downgrading for imprecision is not warranted. There were no serious concerns to warrant downgrading for inconsistency, indirectness, or other considerations.

Perinatal mortality [b] → Very Low Quality Evidence: Two non-concurrent cohort studies (n=724; Gérard 1983, Uncu 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on perinatal mortality. Further downgrading is warranted for imprecision due to optimal information size not being met with a small sample size. There were no serious concerns to warrant downgrading for inconsistency, indirectness or other considerations.

Spontaneous abortion [c] → Very Low Quality Evidence: One non-concurrent cohort study reported this outcome (n=370; Gérard 1983). Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on spontaneous abortion. Only one study provided data on spontaneous abortion, so this warrants downgrading for inconsistency. Further downgrading for imprecision is warranted due to low event rates (total of 20) without optimal information size. There were no serious concerns to warrant downgrading for indirectness or other considerations.

Preterm delivery [d] → Very Low Quality Evidence: Two non-concurrent cohort studies (n=722; Gérard 1983, Uncu 2001) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for risk factors or other patient characteristics, and suspected reporting bias as two studies did not report on preterm delivery. Further downgrading is warranted for imprecision for inadequate sample size and optimal information size not being met (total of 38 events). There were no serious concerns to warrant downgrading for inconsistency, indirectness or other considerations.

Neonatal serious harm: fetal abnormalities [e] → Very Low Quality Evidence: One non-concurrent cohort study reported this outcome (n=370; Uncu 2001).
Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious risk
of bias across studies associated with: 1) no demonstration of comparability between screening and no screening groups, and 2) no adjustment to analyses for
risk factors or other patient characteristics, and suspected reporting bias as three studies did not report on fetal abnormalities. Only one study provided data on
this outcome so this warrants downgrading for inconsistency. Further downgrading for imprecision is warranted due to the optimal information size not being
met for rare events. There were no serious concerns to warrant downgrading for indirectness or other considerations.

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## Evidence Set 1. Forest Plots 1.1-1.5 – Benefits and harms of screening compared to no screening

| Outcome  |   |  |   |   |  | o. of   | No. of  |      | Effect size                          |   |
|--|---|--|---|---|--|---|---|------|--------------------------------------|---|
|  |   |  |   |   |  | udies   | participant   |      | (Risk Ratio; M-H, R                  | andom, 95%Cl)   |
| 1.1 Pyelonepl  |   |  |   |   | 3  |   | 5659  |      | 0.28 [0.15, 0.54]                    |   |
| 1.2 Perinatal  | -   |  |   |   | 2  |   | 724   |      | 1.21 [0.01, 102.93]                  |   |
| note: Gérard   |   |  |   |   |  |   |   |      |                                      |   |
| 1.3 Spontane   |   |  |   |   | 1  |   | 370   |      | 0.96 [0.41, 2.27]                    |   |
| note: 1 study  |   | •  |   | 7-21 w  |  |   |   |      |                                      |   |
| 1.4 Preterm c  |   |  |   |   | 2  |   | 722   |      | 8.70 [0.32, 240.07]                  |   |
| 1.5 Neonatal   |   |  |   |   |  |   | 372   |      | 1.50 [0.25, 8.87]<br>ber; wks: weeks |   |
| 1.1 Pyelonephritis   | 5   |  |   |   |  |   |   |      |                                      |   |
|  | Screenin  |  | No scree  | nina  |  | Die   | k Ratio   |      | Dick                                 | Ratio   |
| Study or Subgroup  | Events T  |  |   | _   | Weight   |   | ndom, 95% Cl  |      |                                      | om, 95% Cl  |
| Gratacos 1994  | 9 1   |  | 60  | 3265  | 86.3%  |   | 80 [0.15, 0.60]   |      |                                      |   |
| Gérard 1983  |   | 170  | 3   | 200   | 4.8%   | 0.1   | 7 [0.01, 3.23]  | •    |                                      | <u> </u>  |
| Uncu 2001  | 1   | 186  | 4   | 186   | 8.8%   | 0.2   | 25 [0.03, 2.22]   |      |                                      |   |
| Total (95% CI)   | 2   | 2008   |   | 3651  | 100.0%   | 0.2   | 8 [0.15, 0.54]  |      | •                                    |   |
| Total events   | 10  |  | 67  |   |  |   |   |      | •                                    |   |
| Heterogeneity: Tau <sup>2</sup> =  |   |  |   | = 0.93)   | ; I² = 0%  |   |   | 0.01 | 0.1                                  | <br>1 10  |
| Test for overall effect:   | : Z = 3.80 (P :   | = 0.0  | 001)  |   |  |   |   | 0.01 |                                      | Favours no screenin                                   |
|  |   |  |   |   |  |   |   |      |                                      |   |
| 1.2 Perinatal mort   | tality (>=2   | 0 wl   | ks GA)  |   |  |   |   |      |                                      |   |
|  | Screenin  | Ig   | No scree  | _   | Maiabé   |   | k Ratio   |      |                                      | Ratio   |
| Study or Subgroup  | Screenin<br>Events T  | ig<br>Fotal  | No scree<br>Events  | Total   |  | M-H, Rai  | ndom, 95% Cl  |      |                                      | Ratio<br>om, 95% Cl                                   |
|  | Screenin<br>Events T<br>5   | ıg   | No scree  | _   | Weight<br>47.5%<br>52.5%   | M-H, Rar<br>12.74   |   |      |                                      |   |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001  | Screenin<br>Events T<br>5<br>1  | ig<br>Total<br>163<br>186  | No scree<br>Events<br>O   | Total<br>189<br>186                                     | 47.5%<br>52.5%   | M-H, Rar<br>12.74  <br>0.1  | ndom, 95% Cl<br>[0.71, 228.74]<br>4 [0.02, 1.15]  |      |                                      |   |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)  | Screenin<br>Events T<br>5<br>1  | ig<br>Fotal<br>163   | No scree<br>Events<br>0<br>7  | Total<br>189<br>186                                     | 47.5%  | M-H, Rar<br>12.74  <br>0.1  | ndom, 95% Cl<br>[0.71, 228.74]  |      |                                      |   |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events  | Screenin<br>Events T<br>5<br>1  | ig<br>T <u>otal</u><br>163<br>186<br><b>349</b>  | No scree<br>Events<br>0<br>7<br>7   | Total<br>189<br>186<br>375                              | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21 [</b>                                       | ndom, 95% Cl<br>[0.71, 228.74]<br>4 [0.02, 1.15]  |      | M-H, Rand                            | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)  | Screenin<br>Events T<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup> =   | ig<br>163<br>186<br><b>349</b><br>= 6.25   | No scree<br>Events<br>0<br>7<br>7<br>5, df = 1 (P   | Total<br>189<br>186<br>375                              | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21 [</b>                                       | ndom, 95% Cl<br>[0.71, 228.74]<br>4 [0.02, 1.15]  |      | M-H, Rand                            | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =   | Screenin<br>Events T<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup> =   | ig<br>163<br>186<br><b>349</b><br>= 6.25   | No scree<br>Events<br>0<br>7<br>7<br>5, df = 1 (P   | Total<br>189<br>186<br>375                              | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21 [</b>                                       | ndom, 95% Cl<br>[0.71, 228.74]<br>4 [0.02, 1.15]  |      | M-H, Rand<br>                        | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =   | Screenin<br>Events T<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup> =   | ig<br>163<br>186<br><b>349</b><br>= 6.25   | No scree<br>Events<br>0<br>7<br>7<br>5, df = 1 (P   | Total<br>189<br>186<br>375                              | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21 [</b>                                       | ndom, 95% Cl<br>[0.71, 228.74]<br>4 [0.02, 1.15]  |      | M-H, Rand                            | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:   | Screenin<br>Events T<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup> =<br>: Z = 0.08 (P  | 19<br>163<br>186<br><b>349</b><br>= 6.26<br>= 0.9  | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)  | Total<br>189<br>186<br><b>375</b><br>= 0.01)            | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21 [</b>                                       | ndom, 95% Cl<br>[0.71, 228.74]<br>4 [0.02, 1.15]  | 0.01 | M-H, Rand<br>                        | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =   | Screenin<br>Events T<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup> =<br>: Z = 0.08 (P  | 19<br>163<br>186<br><b>349</b><br>= 6.26<br>= 0.9  | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)  | Total<br>189<br>186<br><b>375</b><br>= 0.01)            | 47.5%<br>52.5%<br><b>100.0%</b>  | M-H, Rar<br>12.74  <br>0.1<br><b>1.21 [</b>                                       | ndom, 95% Cl<br>[0.71, 228.74]<br>4 [0.02, 1.15]  |      | M-H, Rand                            | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:   | Screenin<br>Events T<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup> =<br>: Z = 0.08 (P  | rotal<br>163<br>186<br><b>349</b><br>= 6.25<br>= 0.9   | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)  | Total<br>189<br>186<br><b>375</b><br>= 0.01)            | 47.5%<br>52.5%<br><b>100.0%</b>  | <u>M-H, Rar</u><br>12.74  <br>0.1<br><b>1.21  </b>                                | ndom, 95% Cl<br>[0.71, 228.74]<br>4 [0.02, 1.15]  | 0.01 | M-H, Rand                            | om, 95% Cl  |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:   | Screening<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup> =<br>: Z = 0.08 (P<br>abortion (<<br>Screening<br>Events T   | ng<br><u>Fotal</u><br>163<br>186<br><b>349</b><br>= 6.25<br>= 0.9<br><b>&lt;20</b><br>   | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)<br>wks GA)<br>No scree                             | Total<br>189<br>186<br><b>375</b><br>= 0.01)            | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>z</sup> = 84%                            | <u>M-H, Ran</u><br>12.74  <br>0.1<br><b>1.21  </b>                                | ndom, 95% Cl<br>[0.71, 228.74]<br>4 [0.02, 1.15]<br>0.01, 102.93]   | 0.01 | M-H, Rand                            | om, 95% Cl<br>10<br>Favours no screenin               |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.3 Spontaneous a  | Screening<br>5<br>1<br>6<br>= 8.67; Chi <sup>2</sup> =<br>: Z = 0.08 (P<br>abortion (<<br>Screening<br>Events T   | ng<br>fotal<br>163<br>186<br><b>349</b><br>= 6.25<br>= 0.9   | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)<br>wks GA)<br>No scree                             | Total<br>189<br>186<br>375<br>= 0.01)<br>ening<br>Total | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>z</sup> = 84%                            | <u>M-H, Ran</u><br>12.74<br>0.1<br><b>1.21</b> [                                  | ndom, 95% CI<br>(0.71, 228.74)<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>k Ratio                                    |      | M-H, Rand                            | om, 95% Cl<br>10<br>Favours no screenin               |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983  | Screening           Events         T           5         1           6         8.67; Chi² =           : Z = 0.08 (P =         2           abortion (         Screening           Events         T           9         9                                       | ng<br><u>Fotal</u><br>163<br>186<br><b>349</b><br>= 6.25<br>= 0.9<br><b>&lt;20</b><br><u>rotal</u><br>170                        | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)<br>wks GA)<br>No scree<br>Events                   | Total<br>189<br>186<br>375<br>= 0.01)<br>= 0.01)        | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Ran</u><br>12.74<br>0.1<br><b>1.21</b> [<br>0.9<br><u>M-H, Ran</u><br>0.9 | ndom, 95% CI<br>(0.71, 228.74)<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>k Ratio<br>ndom, 95% CI<br>36 [0.41, 2.27] | 0.01 | M-H, Rand                            | om, 95% Cl<br>10<br>Favours no screenin               |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.3 Spontaneous a<br>Study or Subgroup   | Screening           Events         T           5         1           6         8.67; Chi² =           : Z = 0.08 (P =         2           abortion (         Screening           Events         T           9         9                                       | ng<br><u>Fotal</u><br>163<br>186<br><b>349</b><br>= 6.25<br>= 0.9<br><b>&lt;20</b><br>   | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)<br>wks GA)<br>No scree<br>Events                   | Total<br>189<br>186<br>375<br>= 0.01)<br>= 0.01)        | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br>Weight                  | <u>M-H, Ran</u><br>12.74<br>0.1<br><b>1.21</b> [<br>0.9<br><u>M-H, Ran</u><br>0.9 | ndom, 95% CI<br>(0.71, 228.74)<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>k Ratio<br>ndom, 95% CI                    | 0.01 | M-H, Rand                            | om, 95% Cl<br>10<br>Favours no screenin               |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events<br>Heterogeneity: Not ag                             | Screening           Events         T           5         1           6         8.67; Chi² =           : Z = 0.08 (P)         Abortion (           Screening         P           Events         T           9         9           pplicable         9          | rg<br><u>Fotal</u><br>163<br>186<br><b>349</b><br>= 6.25<br>= 0.9<br><b>&lt;20</b><br><u>rotal</u><br>170<br><b>170</b>          | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)<br>wks GA)<br>No scree<br>Events<br>11<br>11       | Total<br>189<br>186<br>375<br>= 0.01)<br>= 0.01)        | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Ran</u><br>12.74<br>0.1<br><b>1.21</b> [<br>0.9<br><u>M-H, Ran</u><br>0.9 | ndom, 95% CI<br>(0.71, 228.74)<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>k Ratio<br>ndom, 95% CI<br>36 [0.41, 2.27] |      | M-H, Rand                            | om, 95% Cl<br>10<br>Favours no screenin<br>om, 95% Cl |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events  | Screening           Events         T           5         1           6         8.67; Chi² =           : Z = 0.08 (P)         Abortion (           Screening         P           Events         T           9         9           pplicable         9          | rg<br><u>Fotal</u><br>163<br>186<br><b>349</b><br>= 6.25<br>= 0.9<br><b>&lt;20</b><br><u>rotal</u><br>170<br><b>170</b>          | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)<br>wks GA)<br>No scree<br>Events<br>11<br>11       | Total<br>189<br>186<br>375<br>= 0.01)<br>= 0.01)        | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Ran</u><br>12.74<br>0.1<br><b>1.21</b> [<br>0.9<br><u>M-H, Ran</u><br>0.9 | ndom, 95% CI<br>(0.71, 228.74)<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>k Ratio<br>ndom, 95% CI<br>36 [0.41, 2.27] | 0.01 | M-H, Rand                            | Ratio<br>om, 95% Cl<br>Favours no screenir            |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events<br>Heterogeneity: Not ag                             | Screening           Events         T           5         1           6         8.67; Chi² =           : Z = 0.08 (P)         Abortion (           Screening         P           Events         T           9         9           pplicable         9          | rg<br><u>Fotal</u><br>163<br>186<br><b>349</b><br>= 6.25<br>= 0.9<br><b>&lt;20</b><br><u>rotal</u><br>170<br><b>170</b>          | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)<br>wks GA)<br>No scree<br>Events<br>11<br>11       | Total<br>189<br>186<br>375<br>= 0.01)<br>= 0.01)        | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Ran</u><br>12.74<br>0.1<br><b>1.21</b> [<br>0.9<br><u>M-H, Ran</u><br>0.9 | ndom, 95% CI<br>(0.71, 228.74)<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>k Ratio<br>ndom, 95% CI<br>36 [0.41, 2.27] |      | M-H, Rand                            | om, 95% CI<br>10<br>Favours no screenin<br>om, 95% CI |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events<br>Heterogeneity: Not ag<br>Test for overall effect: | Screening           Events         T           5         1           6         8.67; Chi² =           2 = 0.08 (P)         0           abortion (         Screening           Events         T           9         9           pplicable         2 = 0.09 (P) | rg<br><u>Fotal</u><br>163<br>186<br><b>349</b><br>= 6.25<br>= 0.9<br><b>&lt;20</b><br><b>fotal</b><br>170<br><b>170</b><br>= 0.9 | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)<br>wks GA)<br>No scree<br>Events<br>11<br>11<br>3) | Total<br>189<br>186<br>375<br>= 0.01)<br>= 0.01)        | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Ran</u><br>12.74<br>0.1<br><b>1.21</b> [<br>0.9<br><u>M-H, Ran</u><br>0.9 | ndom, 95% CI<br>(0.71, 228.74)<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>k Ratio<br>ndom, 95% CI<br>36 [0.41, 2.27] |      | M-H, Rand                            | om, 95% Cl<br>10<br>Favours no screenin<br>om, 95% Cl |
| Study or Subgroup<br>Gérard 1983<br>Uncu 2001<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.3 Spontaneous a<br>Study or Subgroup<br>Gérard 1983<br>Total (95% CI)<br>Total events<br>Heterogeneity: Not ag                             | Screening           Events         T           5         1           6         8.67; Chi² =           2 = 0.08 (P)         0           abortion (         Screening           Events         T           9         9           pplicable         2 = 0.09 (P) | rg<br><u>Fotal</u><br>163<br>186<br><b>349</b><br>= 6.25<br>= 0.9<br><b>&lt;20</b><br><b>fotal</b><br>170<br><b>170</b><br>= 0.9 | No scree<br>Events<br>0<br>7<br>5, df = 1 (P<br>3)<br>wks GA)<br>No scree<br>Events<br>11<br>11<br>3) | Total<br>189<br>186<br>375<br>= 0.01)<br>= 0.01)        | 47.5%<br>52.5%<br><b>100.0%</b><br>; I <sup>2</sup> = 84%<br><u>Weight</u><br>100.0% | <u>M-H, Ran</u><br>12.74<br>0.1<br><b>1.21</b> [<br>0.9<br><u>M-H, Ran</u><br>0.9 | ndom, 95% CI<br>(0.71, 228.74)<br>4 [0.02, 1.15]<br>0.01, 102.93]<br>k Ratio<br>ndom, 95% CI<br>36 [0.41, 2.27] |      | M-H, Rand                            | Ratio<br>om, 95% Cl<br>Favours no screenin            |

|        |                                   | Screen   | ing     | No scree | ening   |                        | Risk Ratio           | Risk Ratio                             |
|--------|-----------------------------------|----------|---------|----------|---------|------------------------|----------------------|--|
| 1      | Study or Subgroup                 | Events   | Total   | Events   | Total   | Weight                 | M-H, Random, 95% Cl  | M-H, Random, 95% Cl                    |
| 2      | Gérard 1983                       | 11       | 161     | 5        | 189     | 57.5%                  | 2.58 [0.92, 7.28]    | <b>⊢_∎</b>                             |
| 3      | Uncu 2001                         | 22       | 186     | 0        | 186     | 42.5%                  | 45.00 [2.75, 736.39] | <b>∎</b> →                             |
| 4<br>5 | Total (95% CI)                    |          | 347     |          | 375     | 100.0%                 | 8.70 [0.32, 240.07]  |  |
| 6      | Total events                      | 33       |         | 5        |         |                        |                      |  |
| 7      | Heterogeneity: Tau <sup>2</sup> = | •        |         |          | = 0.02) | ; I <sup>z</sup> = 80% |                      |  |
| 8      | Test for overall effect:          | Z=1.28 ( | P = 0.2 | :0)      |         |                        |                      | Favours screening Favours no screening |
| 9      |                                   |          |         |          |         |                        |                      |  |

#### 1.5 Neonatal serious harm: fetal abnormalities

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| Study or Subgroup                     | Screening        |         | screening  | Moint     | Risk Ratio                               | Risk Ratio   |
|---------------------------------------|------------------|---------|------------|-----------|--|--|
| Study or Subgroup<br>Uncu 2001        | Events To<br>3 1 | 86      |            | 100.0%    | M-H, Random, 95% Cl<br>1.50 [0.25, 8.87] |  |
|                                       |                  |         |            |           |  |  |
| Total (95% CI)                        | 1                | 86      | 186        | 100.0%    | 1.50 [0.25, 8.87]                        |  |
| Total events<br>Heterogeneity: Not ap | 3<br>anlicable   |         | 2          |           |  |  |
| Test for overall effect:              | :Z = 0.45 (P =   | 0.65)   |            |           |  | 0.01 0.1 10 10<br>Favours screening Favours no screening |
|                                       |                  |         |            |           |  | Favours screening Favours no screening                   |
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#### Evidence Set 2. Table 2.1 GRADE Summary of Findings - Benefits and harms of frequent screening compared to onetime screening Frequent screening compared to one-time screening for asymptomatic bacteriuria Patient or population: asymptomatic bacteriuria **Setting**: Any primary clinical care setting providing care to pregnant women 10 Intervention: frequent screening 11 12 Comparison: one-time screening 13 14 Anticipated absolute Quality of Outcomes Relative Nº of Comments 15 effects<sup>\*</sup> (95% CI) effect participants the 16 17 (95% CI) (studies) evidence 18 (GRADE) **Risk with** Risk 19 one-time difference 20 screening with 21 22 frequent 23 screening 24 25 **Pyelonephritis** 0 fewer per RR 1.09 1952 $\oplus \bigcirc \bigcirc \bigcirc$ We are very uncertain about 26 27 1,000 (0.27 to (1 VERY LOW 1, the effects of frequent 28 4 per 1,000 (from 3 4.35) observational <sup>a</sup> screening compared to one-29 fewer to 13 time screening on study) 30 more) pyelonephritis. 31 32 33 28 more per RR 1.57 $\Theta \cap \cap O$ Preterm delivery 1952 We are very uncertain about 34 1,000 VERY LOW <sup>1,</sup> the effects of frequent (1.11 to (1 35 49 per 1,000 (from 5 2.23) observational <sup>b</sup> screening compared to one-36 time screening on preterm more to 60 study) 37 38 more) delivery. 39 40 \*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison 41 group and the **relative effect** of the intervention (and its 95% CI). 42 43 44 CI: Confidence interval; RR: Risk ratio 45 46 **GRADE Working Group grades of evidence** 47 48 High quality: We are very confident that the true effect lies close to that of the estimate of the effect 49 Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the 50 estimate of the effect, but there is a possibility that it is substantially different 51 Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the 52 estimate of the effect 53 Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially 54 55 different from the estimate of effect 56 57 58 <sup>1</sup> The imprecision domain is assessed using GRADE guidance<sup>42</sup> relevant for systematic reviews as follows: when 59

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optimal information size (OIS) criterion is met, and the 95% confidence interval overlaps no effect, consideration of important benefit or important harm will be assessed using a relative risk of 1.0 (0.75 to 1.25).

CI: Confidence interval; RR: Risk ratio

**Pyelonephritis [a]**  $\rightarrow$  **Very Low Quality Evidence:** One non-concurrent cohort study (n=1952; Rhode 2007) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to serious **risk of bias** associated with: 1) no demonstration that pyelonephritis was not present at start of study, 2) no demonstration of comparability between frequent and one-time screening groups, and 3) no adjustment to analyses to account for risk factors or other patient characteristics. Only one study provided data for this outcome so downgrading is warranted for **inconsistency**. Further downgrading is warranted for **indirectness** as the women are predominantly medically underserved, Hispanic and receiving care from a midwifery clinic, with a high rate of gestational diabetes (9%). The optimal information size is not met (8 events) with sample size (n=1952), therefore this warrants downgrading for **imprecision**. There were no serious concerns to warrant downgrading for **other considerations**.

Preterm delivery [b] -> Very Low Quality Evidence: One non-concurrent cohort study (n=1952; Rhode 2007) reported this outcome. Quality of evidence is downgraded from high to low due to observational level data. Further downgrading from low to very low is warranted due to very serious risk of bias associated with: 1) no demonstration of comparability between frequent and one-time screening groups, 2) no adjustment to analyses to account for risk factors or other patient characteristics, and 3) suspected reporting bias among outcomes reported by studies (did not report on spontaneous abortion, perinatal mortality or fetal abnormalities). Only one study provided data for this outcome so downgrading is warranted for **inconsistency**. Further downgrading is warranted for **indirectness** as the women are predominantly medically underserved, Hispanic and receiving care from a midwifery clinic, with a high rate of gestational diabetes (9%). The event rate is low (122 events) without meeting optimal information size, so this is downgraded for **imprecision**. There were no serious concerns to warrant downgrading for **other considerations**. 

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#### Evidence Set 3. Table 3.1 GRADE Summary of Findings – Benefits and harms of treatment compared to no treatment

### Treatment compared to no treatment for asymptomatic bacteriuria

Patient or population: asymptomatic bacteriuria

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: treatment

Comparison: no treatment

| Outcomes                | Anticipated a effects <sup>*</sup> (95% |   | Relative<br>effect<br>(95% CI) | № of<br>participants<br>(studies) | Quality of<br>the<br>evidence  | Comments  |
|-------------------------|---|---|--------------------------------|-----------------------------------|--------------------------------|---|
|                         | Risk with no<br>treatment               | Risk with<br>treatment  |                                |                                   | (GRADE)                        |   |
| Maternal<br>mortality   | 0 per 1,000                             | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable               | (0 studies)                       | -                              | No study reported on maternal mortality.                |
| Maternal sepsis         | 0 per 1,000                             | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable               | (0 studies)                       | -                              | No study reported on maternal sepsis.                   |
| Pyelonephritis          | Median                                  |   | <b>RR 0.24</b> (0.13 to        | 2017<br>(12 RCTs)                 | ⊕⊕○○<br>LOW <sup>1, a</sup>    | There may be a reduction in pyelonephritis from         |
|                         | 232 per<br>1,000                        | <b>176 fewer</b><br><b>per 1,000</b><br>(from 137<br>fewer to 202<br>fewer) | 0.41)                          |                                   |                                | treatment.  |
| Perinatal<br>mortality  | Median                                  |   | <b>RR 0.96</b> (0.27 to        | 1104<br>(6 RCTs)                  | ⊕○○○<br>VERY LOW <sup>1,</sup> | We are very uncertain about the effects of treatment on |
| ,<br>,                  | 40 per 1,000                            | <b>2 fewer per</b><br><b>1,000</b><br>(from 29<br>fewer to 97<br>more)      | 3.39)                          | (2)                               | b                              | perinatal mortality.                                    |
| Spontaneous<br>abortion | Median                                  |   | <b>RR 0.60</b> (0.11 to        | 379<br>(2 RCTs)                   | ⊕○○○<br>VERY LOW <sup>1,</sup> | We are very uncertain about the effects of treatment on |
|                         | 33 per 1,000                            | <b>13 fewer</b><br><b>per 1,000</b><br>(from 30<br>fewer to 70<br>more)     | 3.10)                          | 、)                                | c                              | spontaneous abortion.                                   |

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|     |             |             | ,         |                   |                     |                 |

#### Treatment compared to no treatment for asymptomatic bacteriuria

#### Patient or population: asymptomatic bacteriuria

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: treatment

#### **Comparison**: no treatment

| Outcomes                    | Anticipated a effects <sup>*</sup> (95% |  | Relative<br>effect<br>(95% CI) | № of<br>participants<br>(studies) | Quality of<br>the<br>evidence  | Comments  |  |  |
|-----------------------------|---|--|--------------------------------|-----------------------------------|--------------------------------|---|--|--|
|                             | Risk with no<br>treatment               | Risk with<br>treatment   |                                |                                   | (GRADE)                        |   |  |  |
| Neonatal sepsis             | Median                                  |  | <b>RR 0.22</b> (0.01 to        | 154<br>(2 RCTs)                   | ⊕○○○<br>VERY LOW <sup>1,</sup> | We are very uncertain about the effects of treatment on |  |  |
|                             | 22 per 1,000                            | <b>17 fewer</b><br><b>per 1,000</b><br>(from 22<br>fewer to 79<br>more)  | 4.54)                          |                                   | d                              | neonatal sepsis.  |  |  |
| Preterm delivery            | Median                                  |  | <b>RR 0.57</b> (0.21 to        | 533<br>(4 RCTs)                   | ⊕○○○<br>VERY LOW <sup>1,</sup> | We are very uncertain about the effects of treatment on |  |  |
|                             | 158 per<br>1,000                        | <b>68 fewer</b><br><b>per 1,000</b><br>(from 125<br>fewer to 88<br>more) | 1.56)                          | ien (                             | e                              | preterm delivery.                                       |  |  |
| Low birth weight            | Median                                  |  | <b>RR 0.63</b><br>(0.45 to     | 1522<br>(7 RCTs)                  | ⊕○○○<br>LOW <sup>1, f</sup>    | There may be a reduction i low birth weight from        |  |  |
|                             | 118 per<br>1,000                        | <b>44 fewer</b><br><b>per 1,000</b><br>(from 12<br>fewer to 65<br>fewer) | 0.90)                          | ,                                 |                                | treatment.  |  |  |
| Maternal serious<br>harm(s) | 0 per 1,000                             | <b>0 per 1,000</b><br>(0 to 0)   | not<br>estimable               | (0 studies)                       | -                              | No study reported on maternal serious harms.            |  |  |
|                             | Median                                  |  |                                |                                   |                                |   |  |  |

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## Treatment compared to no treatment for asymptomatic bacteriuria

#### Patient or population: asymptomatic bacteriuria

Setting: Any primary or clinical care setting providing care to pregnant women

Intervention: treatment

**Comparison**: no treatment

| Outcomes  | Anticipated a effects <sup>*</sup> (95%             |   | Relative<br>effect<br>(95% CI)       | № of<br>participants<br>(studies) | Quality of<br>the<br>evidence       | Comments   |
|---|---|---|--------------------------------------|-----------------------------------|-------------------------------------|--|
|   | Risk with no<br>treatment                           | Risk with<br>treatment  | ``´                                  |                                   | (GRADE)                             |  |
| Neonatal serious<br>harm: fetal<br>abnormalities              | 19 per 1,000  | <b>9 fewer per</b><br><b>1,000</b><br>(from 15<br>fewer to 8<br>more) | <b>RR 0.49</b><br>(0.17 to<br>1.43)  | 821<br>(4 RCTs)                   | ⊕○○○<br>VERY LOW <sup>1,</sup><br>g | We are very uncertain a<br>the effects of treatment<br>harms (fetal abnormaliti          |
| Neonatal serious<br>harm: hemolytic<br>anemia                 | 0 per 1,000   | <b>0 per 1,000</b><br>(0 to 0)  | not<br>estimable                     | 265<br>(1 RCT)                    | ⊕⊖⊖⊖<br>VERY LOW <sup>1,</sup>      | We are very uncertain a the effects of treatment harms (hemolytic anemi                  |
| estimate of the ef  | : We are mode<br>fect, but there<br>confidence in t | rately confide<br>is a possibility                                    | nt in the effect<br>that it is subst | estimate: The<br>antially differe | true effect is l<br>ent             | ikely to be close to the<br>antially different from the                                  |
| estimate of the ef<br>Very low quality:<br>different from the | We have very  |   | ce in the effect                     | estimate: The                     | true effect is li                   | ikely to be substantially  |
| •   |   | 0   | 0                                    |                                   | •                                   | iews as follows: when<br>no effect, consideration o                                      |
| important benefit   |   | -   |                                      |                                   | •                                   | -  |
| <b>CI:</b> Confidence inte                                    | erval; <b>RR:</b> Risk r                            | atio  |                                      |                                   |                                     |  |
| Gold 1966, Kass 19  | 60, Kazemier 2                                      | 015, Kincaid-S  | Smith 1965, Litt                     | le 1966, Mulla                    | 1960, Pathak                        | 71, Foley 1987, Furness 19<br>1969, Williams 1969)<br>e due to serious <b>risk of bi</b> |
|   |   |   |                                      |                                   | 0                                   |  |

associated with use of alternation for sequence generation (Elder 1971, Gold 1966, Kass 1960), inadequate allocation concealment (Elder 1971, Gold 1966, Kass 1960), and incomplete reporting (Brumfitt 1975, Furness 1975). This body of evidence on treatment effectiveness is downgraded from moderate to low for indirectness due to studies that did not explicitly include asymptomatic women (only 3 studies included exclusively asymptomatic women; Kazemier 2015, Mulla 1960, and Williams 1969), and studies that included high-risk women (Elder 1971, Kincaid-Smith 1965, Little 1966, and Pathak 1969). The optimal information size criterion is met (control group event rate=20%; total number of events=253) with an adequate sample size (n=2,017), and the confidence interval (0.13 to 0.41) indicates there may be important benefit; therefore, downgrading is not warranted for imprecision. There were no concerns with inconsistency or other considerations to warrant further downgrading. 10

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11 Perinatal mortality [b] → Very Low Quality Evidence: Six trials (n=1,104; Elder 1971, Kass 1960, Kazemier 2015, Kincaid-12 13 Smith 1965, Little 1966, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate 14 due to serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Kass 1960, Wren 15 1969), and inadequate allocation concealment (Elder 1971, Kass 1960). This body of evidence on treatment 16 effectiveness is downgraded for indirectness due to studies that did not explicitly include asymptomatic women as well 17 as studies that included high-risk women. Further downgrading is warranted for **imprecision** due to the samples size not 18 19 being met for optimal information size criterion (37 events). There were no concerns to warrant downgrading for 20 inconsistency or other considerations. 21

22 Spontaneous abortion [c]→ Very Low Quality Evidence: Two trials (n=379; Furness 1975, Wren 1969) reported this 23 outcome. Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of 24 alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969) and incomplete 25 reporting (Furness 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that 26 did not explicitly include exclusively asymptomatic women. The sample size is inadequate with optimal information size 27 28 not met (10 events) to warrant downgrading twice from low to very low for imprecision. There were no concerns to 29 warrant downgrading for inconsistency or other considerations. 30

31 Neonatal sepsis [d] → Very Low Quality Evidence: Two trials (n=154; Kazemier 2015, Thomsen 1987) reported this 32 outcome. Quality of evidence is downgraded for indirectness due to studies that did not explicitly include exclusively 33 asymptomatic women. The sample size (<2000) is not met with only 2 events to warrant downgrading twice for 34 imprecision. There were no concerns to warrant downgrading for risk of bias, inconsistency or other considerations. 35

36 **Preterm delivery [e]** → Very Low Quality Evidence: Four trials (n=533; Furness 1975, Kazemier 2015, Thomsen 1987, 37 38 Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated 39 with use of alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969), and 40 incomplete reporting (Furness 1975). There is substantial heterogeneity (I<sup>2</sup>=70%) with point estimates on both sides of 41 the line of no effect to warrant downgrading for inconsistency. Downgrading from moderate to low for indirectness is 42 warranted due to studies that did not explicitly include exclusively asymptomatic women. There were no concerns to 43 warrant downgrading for imprecision or other considerations. 44 45

Low birth weight [f] → Low Quality Evidence: Seven trials (n=1,522; Brumfitt 1975, Elder 1971, Kass 1960, Kazemier 46 47 2015, Kincaid-Smith 1965, Little 1966, Wren 1969) reported this outcome. Quality of evidence is downgraded from high 48 to moderate for serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Kass 1960, 49 Wren 1969), inadequate allocation concealment (Elder 1971, Kass 1960, Wren 1969), and incomplete reporting (Brumfitt 50 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly 51 include exclusively asymptomatic women as well as studies that included high-risk women. The optimal information size 52 53 was not quite met (<2000 patients and <200 events), but we did not think the concerns were serious enough to 54 downgrade for this outcome for imprecision. There were no concerns to warrant downgrading for inconsistency or 55 other considerations. 56

57 **Neonatal serious harm: fetal abnormalities [g]**  $\rightarrow$  Very Low Quality Evidence: Four trials (n=821; Elder 1971, Furness 58 1975, Kazemier 2015, Little 1966) reported this outcome. Quality of evidence is downgraded from high to moderate for 59 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 60

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serious risk of bias associated with use of alternation for sequence generation (Elder 1971), inadequate allocation concealment (Elder 1971), and incomplete reporting (Furness 1975). Downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women as well as studies that included high-risk women. Further downgrading from low to very low for imprecision is warranted due to optimal information size (sample size of 821) not being met for rare events. There were no concerns to warrant downgrading for inconsistency or other considerations. 

**Neonatal serious harm: hemolytic anemia [h]**  $\rightarrow$  **Very Low Quality Evidence:** One trial (n=265; Elder 1971) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation and inadequate allocation concealment. Only one study provided data for this outcome so downgrading from moderate to low for inconsistency is warranted. Further downgrading from low to very low is warranted for indirectness due the study not explicitly including exclusively asymptomatic women as well as studies that included high-risk women. Due to optimal information size (sample size of 265) not being met for rare events, downgrading twice is warranted for imprecision. There were no concerns to warrant downgrading for other considerations. 

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#### Evidence Set 3. Table 3.1 GRADE Evidence Profile – Benefits and harms of treatment compared to no treatment

Question: Treatment compared to no treatment for asymptomatic bacteriuria

Setting: Any primary or clinical care setting providing care to pregnant women

#### Bibliography:

| Quality          | assessment           |                 |               |                  |                  |                         | № of patie        | nts             | Effect                              |   | Quality                         | Importance |
|------------------|----------------------|-----------------|---------------|------------------|------------------|-------------------------|-------------------|-----------------|-------------------------------------|---|---------------------------------|------------|
| Nº of<br>studies | Study<br>design      | Risk of<br>bias | Inconsistency | Indirectness     | Imprecision<br>1 | Other<br>considerations | treatment         | no<br>treatment | Relative<br>(95% Cl)                | Absolute<br>(95% Cl)  |                                 |            |
| Materna          | al mortality         |                 |               |                  |                  |                         | <u> </u>          |                 |                                     | <u> </u>  |                                 |            |
| 0                |                      |                 |               | N                | 00               |                         |                   |                 | not<br>estimable                    |   | -                               | CRITICAL   |
| Materna          | al sepsis            | Ι               |               |                  |                  |                         | I                 | 1               | L                                   | 1   | I                               | 1          |
| 0                |                      |                 |               |                  |                  | 16                      |                   |                 | not<br>estimable                    |   | -                               | CRITICAL   |
| Pyelone          | phritis              | <u></u>         | <u></u>       |                  |                  | Į                       |                   | 1               | <u> </u>                            | 1   |                                 | 1          |
| 12               | randomised<br>trials | serious         | not serious   | serious          | not serious      | none                    | 55/1023<br>(5.4%) | 23.2%           | <b>RR 0.24</b><br>(0.13 to<br>0.41) | <b>176</b><br><b>fewer</b><br><b>per</b><br><b>1,000</b><br>(from<br>137<br>fewer to<br>202<br>fewer) | ⊕⊕⊖<br>⊖<br>LOW <sup>1, a</sup> | CRITICAL   |
| Perinata         | I mortality          |                 |               |                  |                  |                         |                   |                 |                                     |   |                                 |            |
|                  |                      |                 | Fc            | or peer review o | nly - http://bm  | ijopen.bmj.com/si       | te/about/gui      | delines.xhtml   |                                     |   |                                 |            |

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| Quanty           | assessment           |                 |               |              |                 |                         | Nº of patie      | nts             | Effect                              |  | Quality                                 | Importance |
|------------------|----------------------|-----------------|---------------|--------------|-----------------|-------------------------|------------------|-----------------|-------------------------------------|--|---|------------|
| Nº of<br>studies | Study<br>design      | Risk of<br>bias | Inconsistency | Indirectness | Imprecision     | Other<br>considerations | treatment        | no<br>treatment | Relative<br>(95% CI)                | Absolute<br>(95% Cl)   |   |            |
| 6                | randomised<br>trials | serious         | not serious   | serious      | serious         | none                    | 16/529<br>(3.0%) | 4.0%            | <b>RR 0.96</b><br>(0.27 to<br>3.39) | <b>2 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 29<br>fewer to<br>97<br>more)  | ⊕⊖⊖<br>⊖<br>VERY<br>LOW <sup>1, b</sup> | CRITICAI   |
| Spontan          | eous abortior        | 1               | 1             |              |                 | 1                       | I                | 1               | 1                                   |  | I                                       | 1          |
| 2                | randomised<br>trials | serious         | not serious   | serious      | very<br>serious | none                    | 4/222<br>(1.8%)  | 3.3%            | <b>RR 0.60</b> (0.11 to 3.10)       | <b>13 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 30<br>fewer to<br>70<br>more) | ⊕⊖⊖<br>⊖<br>VERY<br>LOW <sup>1, c</sup> | CRITICAI   |
| Neonata          | al sepsis            |                 |               |              |                 |                         |                  |                 | <u> </u>                            |  |   | <u> </u>   |
| 2                | randomised<br>trials | not<br>serious  | not serious   | serious      | very<br>serious | none                    | 0/77<br>(0.0%)   | 2.2%            | <b>RR 0.22</b> (0.01 to 4.54)       | <b>17 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 22<br>fewer to<br>79<br>more) | ⊕⊖⊖<br>⊖<br>VERY<br>LOW <sup>1, d</sup> | CRITICAL   |

| trials       Image: serious se | Quality a | assessment      |             |               |                  |                  |                   | Nº of patie  | nts           | Effect   |  | Quality    | Importance |
|--|-----------|-----------------|-------------|---------------|------------------|------------------|-------------------|--------------|---------------|----------|--|------------|------------|
| trials       Image: serious       serious       (11.4%)       (0.21 to 1.56)       per 1,000       VERY LOW 1.e         Low birth weight       Image: serious       not serious       serious       not serious       none       64/769       11.8%       RR 0.63       44 fewer per per 1,000       (0.45 to 0.90)       per 1,000       (0.45 to 0.90)       0.90)       1.000       (1.4%)       Image: Description of trials  |           | -               |             | Inconsistency | Indirectness     |                  |                   | treatment    |               |          |  |            |            |
| 7       randomised trials       serious       not serious       not serious       none       64/769 (8.3%)       11.8%       RR 0.63 (0.45 to 0.90)       44 fewer per 1,000 (from 12 fewer to 65 fewer)       IMPORTATION         Maternal serious harm(s)       0  |           |                 | serious     | serious       | not serious      | •                | none              |              | 15.8%         | (0.21 to | <b>per</b><br><b>1,000</b><br>(from<br>125<br>fewer to<br>88 | O<br>VERY  | CRITICAL   |
| trials       Image: serious harm(s)         0       Image: serious harm(s)             0       Image: not serious harm(s)             0       Image: not serious harm(s)   | Low birt  | h weight        |             |               |                  |                  |                   |              | L             |          | L  |            | L          |
| 0 Not - CRITICAL estimable   |           |                 | serious     | not serious   | serious          | not serious      | none              |              | 11.8%         | (0.45 to | <b>per</b><br><b>1,000</b><br>(from 12<br>fewer to<br>65     | $\bigcirc$ | IMPORTAN   |
| estimable  | Materna   | al serious harr | n(s)        |               | <u></u>          |                  | Į                 | <u>.</u>     |               | <u>.</u> | <u> </u>   | <u> </u>   | 1          |
| Neonatal serious harm: fetal abnormalities   | 0         |                 |             |               |                  |                  |                   |              |               |          |  | -          | CRITICAL   |
|  | Neonata   | Il serious harn | n: fetal al | onormalities  | 1                |                  | 1                 | <u> </u>     | I             | <u> </u> | I  | <u> </u>   | 1          |
|  |           |                 |             | Fc            | or peer review o | only - http://bm | ijopen.bmj.com/si | te/about/gui | delines.xhtml |          |  |            |            |

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| Quality          | assessment                              |                 |               |              |                 |                         | № of patie      | nts             | Effect                              |   | Quality                                 | Importance |
|------------------|---|-----------------|---------------|--------------|-----------------|-------------------------|-----------------|-----------------|-------------------------------------|---|---|------------|
| Nº of<br>studies | Study<br>design                         | Risk of<br>bias | Inconsistency | Indirectness | Imprecision     | Other<br>considerations | treatment       | no<br>treatment | Relative<br>(95% Cl)                | Absolute<br>(95% CI)  |   |            |
| 4                | randomised<br>trials                    |                 |               | serious      | very<br>serious | none                    | 4/425<br>(0.9%) | 1.9%            | <b>RR 0.49</b><br>(0.17 to<br>1.43) | <b>9 fewer</b><br><b>per</b><br><b>1,000</b><br>(from 15<br>fewer to<br>8 more) | ⊕⊖⊖<br>⊖<br>VERY<br>LOW <sup>1, g</sup> | CRITICAL   |
| 1                | al serious harn<br>randomised<br>trials | [               |               | serious      | very<br>serious | none                    | 0/122<br>(0.0%) | 0/143<br>(0.0%) | not<br>estimable                    |   | ⊕<br>○<br>VERY<br>LOW <sup>1, h</sup>   | CRITICAL   |

#### 1.25).

CI: Confidence interval; RR: Risk ratio

Pyelonephritis, overall [a] → Low Quality Evidence: Twelve trials (Brumfitt 1975, Elder 1971, Foley 1987, Furness 1975, Gold 1966, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Mulla 1960, Pathak 1969, Williams 1969) reported this outcome (n=2,017). Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Gold 1966, Kass 1960), inadequate allocation concealment (Elder 1971, Gold 1966, Kass 1960), and incomplete reporting (Brumfitt 1975, Furness 1975). This body of evidence on treatment effectiveness is downgraded from moderate to low for indirectness due to studies that did not explicitly include asymptomatic women (only 3 studies included exclusively asymptomatic women; Kazemier 2015, Mulla 1960, and Williams 1969), and studies that included high-risk women (Elder 1971, Kincaid-Smith 1965, Little 1966, and Pathak 1969). The optimal information size criterion is met (control group event rate=20%; total number of events=253) with an adequate sample size (n=2,017), and the confidence interval (0.13 to 0.41) indicates there may be important benefit; therefore, downgrading is not warranted for imprecision. There were no concerns with inconsistency or other considerations to warrant further downgrading.

Perinatal mortality [b] → Very Low Quality Evidence: Six trials (n=1,104; Elder 1971, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Wren 1969)
 reported this outcome. Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of alternation for sequence

generation (Elder 1971, Kass 1960, Wren 1969), and inadequate allocation concealment (Elder 1971, Kass 1960). This body of evidence on treatment effectiveness is downgraded for **indirectness** due to studies that did not explicitly include asymptomatic women as well as studies that included high-risk women. Further downgrading is warranted for **imprecision** due to the samples size not being met for optimal information size criterion (37 events). There were no concerns to warrant downgrading for **inconsistency** or **other considerations**.

Spontaneous abortion [c]→ Very Low Quality Evidence: Two trials (n=379; Furness 1975, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate due to serious risk of bias associated with use of alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969) and incomplete reporting (Furness 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women. The sample size is inadequate with optimal information size not met (10 events) to warrant downgrading twice from low to very low for imprecision. There were no concerns to warrant downgrading for inconsistency or other considerations.

Neonatal sepsis [d] → Very Low Quality Evidence: Two trials (n=154; Kazemier 2015, Thomsen 1987) reported this outcome. Quality of evidence is downgraded for indirectness due to studies that did not explicitly include exclusively asymptomatic women. The sample size (<2000) is not met with only 2 events to warrant downgrading twice for imprecision. There were no concerns to warrant downgrading for risk of bias, inconsistency or other considerations.

Preterm delivery [e] → Very Low Quality Evidence: Four trials (n=533; Furness 1975, Kazemier 2015, Thomsen 1987, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation (Wren 1969), inadequate allocation concealment (Wren 1969), and incomplete reporting (Furness 1975). There is substantial heterogeneity (I<sup>2</sup>=70%) with point estimates on both sides of the line of no effect to warrant downgrading for inconsistency. Downgrading from moderate to low for indirectness is warranted due to studies that did not explicitly include exclusively asymptomatic women. There were no concerns to warrant downgrading for imprecision or other considerations.

Low birth weight [f] → Low Quality Evidence: Seven trials (n=1,522; Brumfitt 1975, Elder 1971, Kass 1960, Kazemier 2015, Kincaid-Smith 1965, Little 1966, Wren 1969) reported this outcome. Quality of evidence is downgraded from high to moderate for serious risk of bias associated with use of alternation for sequence generation (Elder 1971, Kass 1960, Wren 1969), inadequate allocation concealment (Elder 1971, Kass 1960, Wren 1969), and incomplete reporting (Brumfitt 1975). Further downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women as well as studies that included high-risk women. The optimal information size was not quite met (<2000 patients and <200 events), but we did not think the concerns were serious enough to downgrade for this outcome for imprecision. There were no concerns to warrant downgrading for inconsistency or other considerations.

Neonatal serious harm: fetal abnormalities [g] → Very Low Quality Evidence: Four trials (n=821; Elder 1971, Furness 1975, Kazemier 2015, Little 1966) reported this outcome. Quality of evidence is downgraded from high to moderate for serious risk of bias associated with use of alternation for sequence generation (Elder 1971), inadequate allocation concealment (Elder 1971), and incomplete reporting (Furness 1975). Downgrading from moderate to low is warranted for indirectness due to studies that did not explicitly include exclusively asymptomatic women as well as studies that included high-risk women. Further downgrading from low to very low for imprecision is warranted due to optimal information size (sample size of 821) not being met for rare events. There were no concerns to warrant downgrading for inconsistency or other considerations.

Neonatal serious harm: hemolytic anemia [h] → Very Low Quality Evidence: One trial (n=265; Elder 1971) reported this outcome. Quality of evidence is downgraded from high to moderate for risk of bias associated with use of alternation for sequence generation and inadequate allocation concealment. Only one study provided data for this outcome so downgrading from moderate to low for inconsistency is warranted. Further downgrading from low to very low is warranted for indirectness due the study not explicitly including exclusively asymptomatic women as well as studies that included high-risk women. Due to For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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optimal information size (sample size of 265) not being met for rare events, downgrading twice is warranted for imprecision. There were no concerns to warrant downgrading for other considerations. For beer review only

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| Outcome   | No. of  | No. of       | Effect size                      |
|---|---------|--------------|----------------------------------|
|   | studies | participants | (Risk Ratio; M-H, Random, 95%CI) |
| 3.1 Pyelonephritis  | 12      | 2017         | 0.24 [0.13, 0.41]                |
| 3.2 Perinatal mortality (≥20 wks, including intrauterine                                      | 6       | 1104         | 0.96 [0.27, 3.39]                |
| demise, stillbirth, early neonatal death)   |         |              |                                  |
| 3.3 Spontaneous abortion (<20 wks)  | 2       | 379          | 0.60 [0.11, 3.10]                |
| 3.4 Neonatal sepsis   | 2       | 154          | 0.22 [0.01, 4.54]                |
| 3.5 Preterm delivery (<38 wks)  | 4       | 533          | 0.57 [0.21, 1.56]                |
| 3.6 Low birth weight (≤2500g; SGA <10 <sup>th</sup> percentile & <5 <sup>th</sup> percentile) | 7       | 1522         | 0.63 [0.45, 0.90]                |
| 3.7 Neonatal serious harm: fetal abnormalities  | 4       | 821          | 0.49 [0.17, 1.43]                |
| 3.8 Neonatal serious harm: hemolytic anemia   | 1       | 265          | Not estimable                    |

#### Evidence Set 3: Forest Plots 3.1-3.8 - KQ4: Benefits and harms of treatment compared to no treatment

CI: confidence interval; g: grams; M-H: Mantel-Haenszel; No.: number; SGA: small for gestational age; wks: weeks

#### 3.1 Pyelonephritis

|                                   | Treatm                 | ent                 | No treatment or p      | lacebo                                     |        | Risk Ratio          | Risk Ratio  |
|-----------------------------------|------------------------|---------------------|------------------------|--|--------|---------------------|---|
| Study or Subgroup                 | Events                 | Total               | Events                 | Total                                      | Weight | M-H, Random, 95% Cl | I M-H, Random, 95% CI                                     |
| Brumfitt 1975                     | 9                      | 87                  | 20                     | 86   | 12.8%  | 0.44 [0.21, 0.92]   | ]   |
| Elder 1971                        | 4                      | 133                 | 27                     | 148  | 10.6%  | 0.16 [0.06, 0.46]   | ]   |
| Foley 1987                        | 3                      | 100                 | 3                      | 120  | 7.1%   | 1.20 [0.25, 5.82]   | ]   |
| Furness 1975                      | 23                     | 139                 | 17                     | 67   | 14.1%  | 0.65 [0.37, 1.14]   | ]   |
| Gold 1966                         | 0                      | 35                  | 2                      | 30   | 2.9%   | 0.17 [0.01, 3.45]   | ] ←   |
| Kass 1960                         | 1                      | 93                  | 26                     | 98   | 5.4%   | 0.04 [0.01, 0.29]   | ] ←   |
| Kazemier 2015                     | 0                      | 40                  | 1                      | 45   | 2.6%   | 0.37 [0.02, 8.93]   | ]   |
| Kincaid-Smith 1965                | 2                      | 61                  | 20                     | 55   | 8.0%   | 0.09 [0.02, 0.37]   | ]   |
| Little 1966                       | 4                      | 124                 | 35                     | 141  | 10.7%  | 0.13 [0.05, 0.36]   | ]   |
| Mulla 1960                        | 1                      | 50                  | 12                     | 50   | 5.3%   | 0.08 [0.01, 0.62]   | ]   |
| Pathak 1969                       | 3                      | 76                  | 17                     | 76   | 9.4%   | 0.18 [0.05, 0.58]   | ]   |
| Williams 1969                     | 5                      | 85                  | 18                     | 78   | 11.2%  | 0.25 [0.10, 0.65]   | ]   |
| Total (95% CI)                    |                        | 1023                |                        | 994  | 100.0% | 0.24 [0.13, 0.41]   | ▲ I   |
| Total events                      | 55                     |                     | 198                    |  |        |                     |   |
| Heterogeneity: Tau <sup>2</sup> = | 0.49; Chi <sup>a</sup> | <sup>2</sup> = 27.6 | i9, df = 11 (P = 0.004 | 4); <b>I<sup>2</sup> =</b> 60 <sup>4</sup> | %      |                     |   |
| Test for overall effect:          | Z = 5.09 (I            | P < 0.0             | 0001)                  |  |        |                     | 0.01 0.1 1 10 1<br>Favours treatment Favours no treatment |
|                                   |                        |                     |                        |  |        |                     |   |

#### **3.2** Perinatal mortality

|                                   | Treatm                 | nent                | No treatment or pla     | acebo          |        | Risk Ratio          |      | Risk                       | Ratio                     |             |
|-----------------------------------|------------------------|---------------------|-------------------------|----------------|--------|---------------------|------|----------------------------|---------------------------|-------------|
| Study or Subgroup                 | Events                 | Total               | Events                  | Total          | Weight | M-H, Random, 95% Cl |      | M-H, Rando                 | om, 95% Cl                |             |
| Elder 1971                        | 6                      | 128                 | 2                       | 145            | 21.2%  | 3.40 [0.70, 16.54]  |      | _                          |                           |             |
| Kass 1960                         | 0                      | 93                  | 7                       | 98             | 12.1%  | 0.07 [0.00, 1.21]   | ←    | •                          | -                         |             |
| Kazemier 2015                     | 1                      | 40                  | 0                       | 45             | 10.5%  | 3.37 [0.14, 80.36]  |      |                            |                           |             |
| Kincaid-Smith 1965                | 4                      | 61                  | 4                       | 56             | 23.4%  | 0.92 [0.24, 3.50]   |      |                            |                           |             |
| Little 1966                       | 5                      | 124                 | 2                       | 141            | 20.8%  | 2.84 [0.56, 14.39]  |      |                            |                           |             |
| Wren 1969                         | 0                      | 83                  | 6                       | 90             | 12.0%  | 0.08 [0.00, 1.46]   | •    | •                          | <u> </u>                  |             |
| Total (95% CI)                    |                        | 529                 |                         | 575            | 100.0% | 0.96 [0.27, 3.39]   |      |                            |                           |             |
| Total events                      | 16                     |                     | 21                      |                |        |                     |      |                            |                           |             |
| Heterogeneity: Tau <sup>2</sup> = | 1.29; Chi <sup>a</sup> | <sup>2</sup> = 11.4 | 2, df = 5 (P = 0.04); f | <b>≈</b> = 56% |        |                     | L    |                            | 10                        | 400         |
| Test for overall effect:          | Z = 0.06 (             | P = 0.9             | 6)                      |                |        |                     | 0.01 | 0.1 1<br>Favours treatment | I 10<br>Favours no treatr | 100<br>ment |

#### 3.3 Spontaneous abortion

| Study or Subgroup  | Treatm<br>Events |     | No treatment or p<br>Events |       | Weight | Risk Ratio<br>M-H, Random, 95% Cl |           | Risk Ratio<br>M-H, Random, 95% C     | I                |            |
|--|------------------|-----|-----------------------------|-------|--------|-----------------------------------|-----------|--------------------------------------|------------------|------------|
| Furness 1975   | 2                | 139 | 0                           | 67    | 26.3%  | 2.43 [0.12, 49.89]                |           |                                      |                  |            |
| Wren 1969  | 2                | 83  | 6                           | 90    | 73.7%  | 0.36 [0.08, 1.74]                 |           |                                      |                  |            |
| Total (95% CI)   |                  | 222 |                             | 157   | 100.0% | 0.60 [0.11, 3.10]                 |           |                                      |                  |            |
| Total events   | 4                |     | 6                           |       |        |                                   |           |                                      |                  |            |
| Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect |                  |     |                             | ²=17% |        |                                   | L<br>0.01 | 0.1 1<br>Favours treatment Favours r | 10<br>no treatme | 100<br>ent |

#### 3.4 Neonatal sepsis

|                          | Treatm       | ent      | No treatment or placebo |        | Risk Ratio          | Risk Ratio                             |
|--------------------------|--------------|----------|-------------------------|--------|---------------------|--|
| Study or Subgroup        | Events       | Total    | Events Total            | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl                    |
| Kazemier 2015            | 0            | 40       | 2 45                    | 100.0% | 0.22 [0.01, 4.54]   |  |
| Thomsen 1987             | 0            | 37       | 0 32                    |        | Not estimable       |  |
| Total (95% CI)           |              | 77       | 77                      | 100.0% | 0.22 [0.01, 4.54]   |  |
| Total events             | 0            |          | 2                       |        |                     |  |
| Heterogeneity: Not ap    | pplicable    |          |                         |        |                     |  |
| Test for overall effect: | : Z = 0.97 ( | (P = 0.3 | (3)                     |        |                     | Favours treatment Favours no treatment |
| 3.5 Preterm de           | livery       |          |                         |        |                     |  |
|                          | Treatm       | ent      | No treatment or placebo |        | Risk Ratio          | Risk Ratio                             |

#### 3.5 Preterm delivery

|                                   | Treatm       | ient               | No treatment or pla                  | acebo |        | Risk Ratio          |      | Risk Ratio   |    |
|-----------------------------------|--------------|--------------------|--------------------------------------|-------|--------|---------------------|------|--|----|
| Study or Subgroup                 | Events       | Total              | Events                               | Total | Weight | M-H, Random, 95% CI |      | M-H, Random, 95% Cl                                  |    |
| Furness 1975                      | 24           | 139                | 10                                   | 67    | 32.4%  | 1.16 [0.59, 2.28]   |      | _ <b></b>  |    |
| Kazemier 2015                     | 3            | 40                 | 2                                    | 45    | 17.9%  | 1.69 [0.30, 9.59]   |      |  |    |
| Thomsen 1987                      | 2            | 37                 | 12                                   | 32    | 21.7%  | 0.14 [0.03, 0.60]   |      |  |    |
| Wren 1969                         | 5            | 83                 | 15                                   | 90    | 28.1%  | 0.36 [0.14, 0.95]   |      |  |    |
| Total (95% CI)                    |              | 299                |                                      | 234   | 100.0% | 0.57 [0.21, 1.56]   |      |  |    |
| Total events                      | 34           |                    | 39                                   |       |        |                     |      |  |    |
| Heterogeneity: Tau <sup>2</sup> = | = 0.70; Chi  | <sup>2</sup> = 9.8 | 5, df = 3 (P = 0.02); I <sup>2</sup> | = 70% |        |                     | L    |  | -  |
| Test for overall effect           | : Z = 1.10 ( | (P = 0.2           | 7)                                   |       |        |                     | 0.01 | 0.1 1 10 1<br>Favours treatment Favours no treatment | 00 |

#### 3.6 Low birthweight

|                                   | Treatm    | ient                | No treatment or pl                  | acebo |        | Risk Ratio          | Risk Ratio  |
|-----------------------------------|-----------|---------------------|-------------------------------------|-------|--------|---------------------|---|
| Study or Subgroup                 | Events    | Total               | Events                              | Total | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl                                       |
| Brumfitt 1975                     | 18        | 235                 | 21                                  | 178   | 23.0%  | 0.65 [0.36, 1.18]   |   |
| Elder 1971                        | 15        | 133                 | 15                                  | 145   | 19.4%  | 1.09 [0.55, 2.14]   | _ <b>_</b>  |
| Kass 1960                         | 7         | 93                  | 21                                  | 98    | 14.8%  | 0.35 [0.16, 0.79]   |   |
| Kazemier 2015                     | 1         | 40                  | 4                                   | 45    | 2.5%   | 0.28 [0.03, 2.41]   |   |
| Kincaid-Smith 1965                | 9         | 61                  | 12                                  | 56    | 15.5%  | 0.69 [0.31, 1.51]   |   |
| Little 1966                       | 10        | 124                 | 13                                  | 141   | 15.4%  | 0.87 [0.40, 1.92]   |   |
| Wren 1969                         | 4         | 83                  | 14                                  | 90    | 9.3%   | 0.31 [0.11, 0.90]   |   |
| Total (95% CI)                    |           | 769                 |                                     | 753   | 100.0% | 0.63 [0.45, 0.90]   | •   |
| Total events                      | 64        |                     | 100                                 |       |        |                     |   |
| Heterogeneity: Tau <sup>2</sup> = | 0.04; Chi | <sup>2</sup> = 7.52 | . df = 6 (P = 0.28); I <sup>2</sup> | = 20% |        | ŀ                   |   |
| Test for overall effect:          |           |                     |                                     |       |        | l                   | 0.01 0.1 1 10 1<br>Favours treatment Favours no treatment |

#### 3.7 Neonatal serious harm: fetal abnormalities

|                                   | Treatm       | nent                 | No treatment or p       | lacebo |        | Risk Ratio          |      | Ris                     | k Ratio     |           |           |
|-----------------------------------|--------------|----------------------|-------------------------|--------|--------|---------------------|------|-------------------------|-------------|-----------|-----------|
| Study or Subgroup                 | Events       | Total                | Events                  | Total  | Weight | M-H, Random, 95% Cl |      | M-H, Ran                | dom, 95% C  |           |           |
| Elder 1971                        | 2            | 122                  | 6                       | 143    | 46.4%  | 0.39 [0.08, 1.90]   |      |                         | +           |           |           |
| Furness 1975                      | 0            | 139                  | 1                       | 67     | 11.4%  | 0.16 [0.01, 3.92]   | ←    | •                       |             |           |           |
| Kazemier 2015                     | 0            | 40                   | 1                       | 45     | 11.5%  | 0.37 [0.02, 8.93]   |      | •                       |             |           |           |
| Little 1966                       | 2            | 124                  | 2                       | 141    | 30.7%  | 1.14 [0.16, 7.95]   |      |                         | •           |           |           |
| Total (95% CI)                    |              | 425                  |                         | 396    | 100.0% | 0.49 [0.17, 1.43]   |      | -                       |             |           |           |
| Total events                      | 4            |                      | 10                      |        |        |                     |      |                         |             |           |           |
| Heterogeneity: Tau <sup>2</sup> = | = 0.00; Chi  | i <sup>2</sup> = 1.2 | 9, df = 3 (P = 0.73); l | ²=0%   |        |                     |      |                         | -           | 10        | 100       |
| Test for overall effect           | : Z = 1.31 ( | (P = 0.1             | 9)                      |        |        |                     | 0.01 | 0.1<br>Favours treatmen | t Favours r | o treatme | 100<br>nt |

#### 3.8 Neonatal serious harm: hemolytic anemia

| Study or Subgroup       | Treatm<br>Events |       | No treatment or pl<br>Events |     | Weight | Risk Ratio<br>M-H, Random, 95% Cl |         |                   | Ratio<br>om, 95% Cl |
|-------------------------|------------------|-------|------------------------------|-----|--------|-----------------------------------|---------|-------------------|---------------------|
| Elder 1971              | 0                | 122   |                              | 143 | weight | Not estimable                     |         | m-n, Kanu         | 557 61              |
| Total (95% CI)          |                  | 122   |                              | 143 |        | Not estimable                     |         |                   |                     |
| Total events            | 0                | 122   | 0                            | 145 |        | Notestimable                      |         |                   |                     |
| Heterogeneity: Not a    |                  |       | U                            |     |        |                                   | <b></b> |                   | · · · · ·           |
| Test for overall effect |                  | cable |                              |     |        |                                   | 0.01    | 0.1               | i1'0                |
|                         |                  | 04010 |                              |     |        |                                   |         | Favours treatment | Favours no treatmen |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |
|                         |                  |       |                              |     |        |                                   |         |                   |                     |

# Evidence Set 3. Forest Plots for Subgroup Analyses 3.1.1-3.1.4 – KQ4: Benefits and harms of treatment compared to no treatment

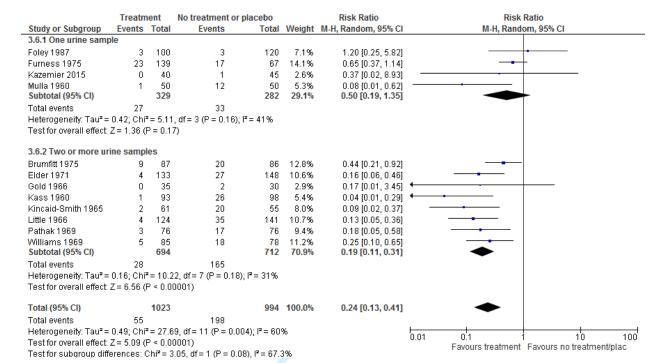
| Outcome   | No. of       | No. of             | Effect size                      |
|---|--------------|--------------------|----------------------------------|
|   | studies      | participants       | (Risk Ratio; M-H, Random, 95%CI) |
| 3.1 Pyelonephritis (overall)  | 12           | 2017               | 0.24 [0.13, 0.41]                |
| 3.1.1 Subgroup analysis: no. of urine samples before con              | firming bact | eriuria and giving | treatment                        |
| One urine sample  | 4            | 611                | 0.50 [0.19, 1.35]                |
| Two or more urine samples   | 8            | 1406               | 0.19 [0.11, 0.31]                |
| 3.1.2 Subgroup analysis: testing for persistent bacteriuria           | 3            | ·                  |                                  |
| Tested for persistent bacteriuria during pregnancy                    | 8            | 1352               | 0.26 [0.15, 0.45]                |
| Testing for persistent bacteriuria post-delivery only                 | 1            | 206                | 0.65 [0.37, 1.14]                |
| Testing for persistent bacteriuria during pregnancy and post-delivery | 3            | 459                | 0.11 [0.05, 0.25]                |
| 3.1.3 Subgroup analysis: follow-up                                    |              | •                  |                                  |
| Follow-up until delivery or puerperium (≤6 wks post-<br>delivery)     | 9            | 1558               | 0.31 [0.18, 0.54]                |
| Follow-up until >6 wks post-delivery                                  | 3            | 459                | 0.11 [0.05, 0.25]                |

CI: confidence interval; M-H: Mantel-Haenszel; No.: number; wks: weeks

#### 3.1 Pyelonephritis (overall)

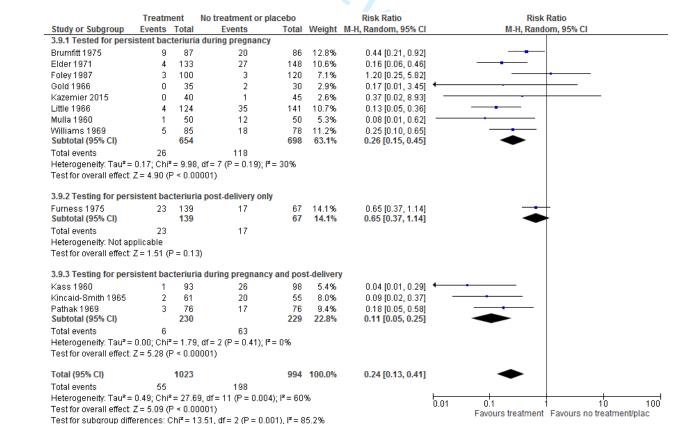
|                                   | Treatm                 |                     | No treatment or p     |                          |        | Risk Ratio          | Risk Ratio          |
|-----------------------------------|------------------------|---------------------|-----------------------|--------------------------|--------|---------------------|---------------------|
| Study or Subgroup                 | Events                 | Total               | Events                | Total                    | Weight | M-H, Random, 95% Cl | M-H, Random, 95% Cl |
| Brumfitt 1975                     | 9                      | 87                  | 20                    | 86                       | 12.8%  | 0.44 [0.21, 0.92]   |                     |
| Elder 1971                        | 4                      | 133                 | 27                    | 148                      | 10.6%  | 0.16 [0.06, 0.46]   |                     |
| Foley 1987                        | 3                      | 100                 | 3                     | 120                      | 7.1%   | 1.20 [0.25, 5.82]   |                     |
| Furness 1975                      | 23                     | 139                 | 17                    | 67                       | 14.1%  | 0.65 [0.37, 1.14]   |                     |
| Gold 1966                         | 0                      | 35                  | 2                     | 30                       | 2.9%   | 0.17 [0.01, 3.45]   | <b>←</b>            |
| Kass 1960                         | 1                      | 93                  | 26                    | 98                       | 5.4%   | 0.04 [0.01, 0.29]   | ← →                 |
| Kazemier 2015                     | 0                      | 40                  | 1                     | 45                       | 2.6%   | 0.37 [0.02, 8.93]   |                     |
| Kincaid-Smith 1965                | 2                      | 61                  | 20                    | 55                       | 8.0%   | 0.09 [0.02, 0.37]   |                     |
| Little 1966                       | 4                      | 124                 | 35                    | 141                      | 10.7%  | 0.13 [0.05, 0.36]   |                     |
| Mulla 1960                        | 1                      | 50                  | 12                    | 50                       | 5.3%   | 0.08 [0.01, 0.62]   |                     |
| Pathak 1969                       | 3                      | 76                  | 17                    | 76                       | 9.4%   | 0.18 [0.05, 0.58]   |                     |
| Williams 1969                     | 5                      | 85                  | 18                    | 78                       | 11.2%  | 0.25 [0.10, 0.65]   | <b>_</b>            |
| Total (95% CI)                    |                        | 1023                |                       | 994                      | 100.0% | 0.24 [0.13, 0.41]   | ◆                   |
| Total events                      | 55                     |                     | 198                   |                          |        |                     |                     |
| Heterogeneity: Tau <sup>2</sup> = | 0.49; Chi <sup>a</sup> | <sup>2</sup> = 27.6 | i9, df = 11 (P = 0.00 | (4); I <sup>z</sup> = 60 | %      |                     | 0.01 0.1 1 10       |

#### 3.1.1 Pyelonephritis subgroup: number of urine samples at each screening visit\*



\*The additional culture(s) was used to confirm levels of bacteriuria.

#### 3.1.2 Pyelonephritis subgroup: timing of testing for persistent bacteriuria



4 5

## 3.1.3 Pyelonephritis subgroup: duration of follow-up

| 6  |   |                       |                            |                            |                |  |   |
|----|---|-----------------------|----------------------------|----------------------------|----------------|--|---|
| 7  |   | Treatment             | No treatment or            | placebo                    |                | Risk Ratio                             | Risk Ratio                                  |
|    | Study or Subgroup   | Events Tota           | il Events                  | Total                      |                | M-H, Random, 95% Cl                    |   |
| 8  | 3.5.1 Follow-up to deli   |                       |                            |                            |                |  |   |
| 9  | Brumfitt 1975<br>Elder 1971                                     | 98<br>413             |                            |                            | 12.8%<br>10.6% | 0.44 [0.21, 0.92]<br>0.16 [0.06, 0.46] |   |
| 10 | Foley 1987  | 3 10                  |                            | 140                        | 7.1%           | 1.20 [0.25, 5.82]                      |   |
| 11 | Furness 1975  | 23 13                 |                            | 67                         | 14.1%          | 0.65 [0.37, 1.14]                      |   |
| 12 | Gold 1966   | 0 3                   |                            | 30                         | 2.9%           | 0.17 [0.01, 3.45]                      | •   |
| 13 | Kazemier 2015<br>Little 1966                                    | 0 4<br>4 12           |                            | 45<br>141                  | 2.6%<br>10.7%  | 0.37 [0.02, 8.93]<br>0.13 [0.05, 0.36] |   |
| 14 | Mulla 1960  | 1 5                   |                            | 50                         | 5.3%           | 0.08 [0.01, 0.62]                      |   |
| 15 | Williams 1969   | 58                    | 5 18                       | 78                         | 11.2%          | 0.25 [0.10, 0.65]                      |   |
|    | Subtotal (95% CI)   | 79                    |                            | 765                        | 77.2%          | 0.31 [0.18, 0.54]                      | •   |
| 16 | Total events<br>Heterogeneity: Tau <sup>2</sup> =               | 49<br>0 33: ⊂bi≩ – 17 | 135<br>17 df = 9 (P = 0.03 | N- 12 - 5206               |                |  |   |
| 17 | Test for overall effect: 2                                      |                       |                            | 0,1 = 33.0                 |                |  |   |
| 18 |   |                       |                            |                            |                |  |   |
| 19 | 3.5.3 Follow-up until >   | -                     | -                          |                            |                |  |   |
| 20 | Kass 1960<br>Kincaid-Smith 1965                                 | 19<br>26              |                            | 98<br>55                   | 5.4%<br>8.0%   |  |   |
| 21 | Pathak 1969   | 3 7                   |                            | 76                         | 9.4%           | 0.18 [0.05, 0.58]                      |   |
|    | Subtotal (95% CI)   | 23                    |                            | 229                        | 22.8%          | 0.11 [0.05, 0.25]                      | ◆   |
| 22 | Total events  | 6                     | 63                         |                            |                |  |   |
| 23 | Heterogeneity: Tau <sup>2</sup> =                               |                       |                            | l≝=0%                      |                |  |   |
| 24 | Test for overall effect: 2                                      | ∠ – 0.26 (F ≤ U.      | 00001)                     |                            |                |  |   |
| 25 | Total (95% CI)  | 102                   | 3                          | 994                        | 100.0%         | 0.24 [0.13, 0.41]                      | ◆   |
| 26 | Total events  | 55                    | 198                        |                            |                |  |   |
| 27 | Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect: J |                       |                            | 104); I <sup>2</sup> = 609 | %              |  | 0.01 0.1 1 10 100                           |
| 28 | Test for subgroup diffe   |                       |                            | )4),  ² = 76.4             | 1%             |  | Favours treatment Favours no treatment/plac |
|    |   |                       |                            |                            |                |  |   |
| 29 |   |                       |                            |                            |                |  |   |
| 30 |   |                       |                            |                            |                |  |   |
| 31 |   |                       |                            |                            |                |  |   |
| 32 |   |                       |                            |                            |                |  |   |
| 33 |   |                       |                            |                            |                |  |   |
| 34 |   |                       |                            |                            |                |  |   |
| 35 |   |                       |                            |                            |                |  |   |
|    |   |                       |                            |                            |                |  |   |
| 36 |   |                       |                            |                            |                |  |   |
| 37 |   |                       |                            |                            |                |  |   |
| 38 |   |                       |                            |                            |                |  |   |
| 39 |   |                       |                            |                            |                |  |   |
| 40 |   |                       |                            |                            |                |  |   |
| 41 |   |                       |                            |                            |                |  |   |
| 42 |   |                       |                            |                            |                |  |   |
|    |   |                       |                            |                            |                |  |   |
| 43 |   |                       |                            |                            |                |  |   |
| 44 |   |                       |                            |                            |                |  |   |
| 45 |   |                       |                            |                            |                |  |   |
| 46 |   |                       |                            |                            |                |  |   |
| 47 |   |                       |                            |                            |                |  |   |
| 48 |   |                       |                            |                            |                |  |   |
| 49 |   |                       |                            |                            |                |  |   |
|    |   |                       |                            |                            |                |  |   |
| 50 |   |                       |                            |                            |                |  |   |
| 51 |   |                       |                            |                            |                |  |   |
| 52 |   |                       |                            |                            |                |  |   |
| 53 |   |                       |                            |                            |                |  |   |
| 54 |   |                       |                            |                            |                |  |   |
| 55 |   |                       |                            |                            |                |  |   |
| 56 |   |                       |                            |                            |                |  |   |
|    |   |                       |                            |                            |                |  |   |
| 57 |   |                       |                            |                            |                |  |   |
| 58 |   |                       |                            |                            |                |  |   |
| 59 |   |                       |                            |                            |                |  |   |
| 60 |   | For pee               | r review only              | - http://                  | bmjop          | oen.bmj.com/site                       | e/about/guidelines.xhtml                    |
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# Supplement 7. Funnel Plot Asymmetry Test for outcome of pyelonephritis for treatment

# PRISMA 2009 Checklist

| Section/topic                      | #  | Checklist item  | Reported on page #                   |
|------------------------------------|----|---|--------------------------------------|
| TITLE                              |    |   |                                      |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.   | Title page                           |
| ABSTRACT                           |    |   |                                      |
| Structured summary                 | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | p. 2                                 |
| INTRODUCTION                       |    |   |                                      |
| Rationale                          | 3  | Describe the rationale for the review in the context of what is already known.  | р. З                                 |
| Objectives                         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | p. 3-4                               |
| METHODS                            |    |   |                                      |
| Protocol and registration          | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.   | Abstract;<br>p.4;<br>Supplement<br>1 |
| Eligibility criteria               | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | p. 4;<br>Supplement<br>3             |
| Information sources                | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | p. 4                                 |
| Search                             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.   | Supplement<br>2                      |
| Study selection                    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).   | p. 4-5                               |
| Data collection process            | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | p. 5                                 |
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.   | p. 4-5<br>Supplemen<br>3             |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | p. 5                                 |

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# **PRISMA 2009 Checklist**

| Summary measures     | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | р. 5 |
|----------------------|----|--|------|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis. | р. 5 |

|                               |    | Page 1 of 2  | Dan - (                                     |
|-------------------------------|----|--|---|
| Section/topic                 | #  | Checklist item   | Reported<br>on page #                       |
| Risk of bias across studies   | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).   | p. 4-5                                      |
| Additional analyses           | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.   | р. 5-6                                      |
| RESULTS                       |    |  |   |
| Study selection               | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | p. 6;<br>Figure 1                           |
| Study characteristics         | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.   | p. 6;<br>Table 1;<br>Supplement             |
| Risk of bias within studies   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | p. 7-11;<br>Supplement<br>5                 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | p. 7-11;<br>Table 2;<br>Supplement<br>4 & 6 |
| Synthesis of results          | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | p. 9-12;<br>Table 2;<br>Supplement<br>6     |
| Risk of bias across studies   | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | p.7-11;<br>Supplement<br>5                  |
| Additional analysis           | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).<br>For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml       | p. 9-10<br>Supplement<br>6 & 7              |



## **PRISMA 2009 Checklist**

| DISCUSSION          |    |  |          |
|---------------------|----|--|----------|
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | p. 13    |
| Limitations         | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                        |          |
| Conclusions         | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | р. 13-14 |
| FUNDING             |    |  |          |
| Funding             | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.   | p.15-16  |

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17 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. 18 doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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