PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Asymptomatic Bacteriuria in Pregnancy: Systematic Reviews of Screening and Treatment Effectiveness and Patient Preferences
AUTHORS	Wingert, Aireen; Pillay, Jennifer; Sebastianski, Meghan; Gates, Michelle; Featherstone, Robin; Shave, Kassi; Vandermeer, Ben; Hartling, Lisa

VERSION 1 – REVIEW

REVIEWER	Peng-Hui Wang Department of Obstetrics and Gynecology, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan
REVIEW RETURNED	20-Jan-2018

GENERAL COMMENTS	Manuscript No. BMJ Open 2017 021347, entitled “Asymptomatic Bacteriuria in Pregnancy: Systematic Reviews of Screening and Treatment Effectiveness and Patient Preferences ”. This was a systematic reviews of screening and treatment effectiveness and patient preferences and the authors performed a systematic review and found that evidence on screening effectiveness was considered very low quality. Women have conflicting opinions about the antibiotics treatment during pregnancy. However, it is consistent with current guideline suggestion to show that the use of antibiotics treatment might be beneficial on the reduction of acute pyelonephritis during pregnancy. Current study is valuable and interesting. Some comments are shown below. 1. The aim of the current study is relatively complicated. Success of screening strategy might result in the decision of treatment or not. The authors’ result seemed to argue the need of screening policy. However, treatment of “these women after screening” seemed to show some benefits on these pregnant women due to reduction of risk of pyelonephritis and possible lower birth weight. But the authors found “conflicted attitude” of pregnant women for the antibiotics treatment. Although it is interesting and the interaction between each seemed to be conflicting in the current study. The authors should carefully present their data. 2. Although quality of enrolled studies might not good, the relative risk of pyelonephritis and of low birth weight seemed to be significantly different. The “power” of terms to study the occurrence of pyelonephritis during pregnancy is much more strong than that of terms to the study target—low birth weight. The authors should consider the difference between two.

	3. If the quality of all articles did not reach to “accepted” levels the authors claimed, this article failed to add any new information to change the current understanding in the management of pregnant women with asymptomatic bacteria. Therefore, if the screening strategy is not effective, it is hard to evaluate whether the benefits of treatment for these patients. 4. In overall, it is a hard work of the current study. Much more precise or clear definition for the aims of the current study might be needed.

REVIEWER	Judith Rukweza University of Zimbabwe, College of Health Sciences, Zimbabwe
REVIEW RETURNED	10-Feb-2018

GENERAL COMMENTS	The systematic review was well searched and presented.

REVIEWER	Caroline Schneeberger Academic Medical Center, Amsterdam, the Netherlands
REVIEW RETURNED	18-Mar-2018

GENERAL COMMENTS	First of all I would like to compliment the authors with their work. The review is very comprehensive. Especially the focus of the review on ‘the benefits and harms of screening’ and ‘the women’s outcome valuation’ are innovative and clinically relevant. This review provides insight in the knowledge gaps currently present concerning the topic screening for asymptomatic bacteriuria in pregnancy in the broader sense. For that alone it is important that this review will be available. Suggestions Page 6 lines 10-18: I would suggest to add the total number of included studies at the end of the paragraph. Page 7 Table 1 ‘summary of included studies for screening and treatment effectiveness’: The table is not easy to read. For example: - The headings (e.g. population characteristics) are not always clear or comprehensive - How should we interpret the following “≥105 CFU/mL (≥108 CFU/mL)” Regarding treatment details: “treatment after sensitivity testing (3)” Does this mean that in the other study (number 4) no information is provided concerning treatment? Or concerning susceptibility testing? Page 9, lines 35-39 “Studies that followed women beyond six weeks after delivery found a greater reduction in pyelonephritis”. How can this be explained and how does this affect the choice to introduce (or maintain) a screening program for ASB during pregnancy? Conclusion & discussion page 12-13: the authors do not mention the fact that most studies are performed in the sixties, seventies and eighties while the midwifery and obstetric care was completely different. During the last decades many new techniques are introduced and applied in the routine care of pregnant women such as the use of ultrasound. The ultrasound is used among

	other things to determine the gestational age. Uncertainty about the gestational age before the introduction of the ultrasound affects the outcome preterm delivery in 'older' studies. Appendix (and discussion): In some of the studies the definition of asymptomatic bacteriuria seems to be missing (e.g. Wren 1969). Could the authors elaborate (more) on the effect of this missing information in the discussion. And the same for studies that included low colony counts of GBS such as Thomsen 1987.

REVIEWER	Siobhan P. Brown University of Washington, United States of America
REVIEW RETURNED	15-May-2018

GENERAL COMMENTS	The manuscript reports the results of several meta-analyses of bacteriuria in pregnancy. The paper is well written, the methods clearly described, and the interpretation consistent with the results. The statistical methods used are appropriate for the study, and clearly and thoroughly explained. I found only a handful of potential typos: P. 11, line 78: The CI for low birth weight doesn't contain the point estimate. Is there a typo here? P. 61, line 27-28: It looks like you have provided the quartiles rather than the SE? P. 65, lines 3-7: The Mann-Whitney U test is not generally considered a test of difference of means. It certainly shouldn't have been used to test both the difference of means and of medians. Was the error in the original paper, or is this a typo? P. 87: The column header "Was the sample size based on pre-study considerations of…" is cut off.

REVIEWER	Thomas E. Finucane Emeritus, Johns Hopkins University, USA
REVIEW RETURNED	07-Jul-2018

GENERAL COMMENTS	The authors reference evidence that ASB is present in 2 – 10% of ambulatory premenopausal women and that prevalence is higher still in pregnant women. They study whether intervening on this common, asymptomatic lab abnormality is beneficial. They find mainly decades-old low quality trials. The biological plausibility that treatment for so common a 'condition' would exceed benefit seems low. Billions of women have had ASB during pregnancy without treatment, over the eons prior to antibiotic development and now around the world in under-resourced settings. I, a geriatrician, am unaware of a public health burden developing from ASB in pregnant women in these settings where no one gets or has gotten antibiotics. Finding an association between ASB and harm is no evidence of need to treat. For example, "an observational study of 1,497 individuals undergoing joint replacement found asymptomatic bacteriuria in 12%. At 1-year follow-up the, rate of prosthetic joint infection was three times as high in individuals with bacteriuria (4.3%) as in those without (1.4%) (P < .001), but antibiotic treatment of bacteriuria did not reduce the risk of infection …" [Finucane TE. J Am Geratr Soc 2017] and "microorganisms

	isolated in prosthetic joint infections were not the same as those in preoperative urine cultures in any patient with asymptomatic bacteriuria." [Sousa R, Mu~noz-Mahamud E, Quayle J. Is asymptomatic bacteriuria a risk factor for prosthetic joint infection? Clin Infect Dis 2014;59:41–47]. ASB here seems to be no more than a biomarker, a measure of vulnerability/frailty. The authors offer further caveats. Although they seem to make a strong causal inference, they conclude that the risk/benefit calculus remains uncertain: "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),2, 4 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. ADDIN EN.CITE 2, 4, 5" I couldn't figure out why screening programs not linked to treatment could be beneficial and fear I am missing something. Their definition of ASB is based on "significant quantitative counts" But the significance of "significant bacteriuria" remains uncertain, threshold colony counts have ranged from 102 to 105, and the construct has not been shown to identify patients who are more likely to achieve net benefit from antibiotic treatment. Further, the authors themselves cite an article entitled "Urine is not sterile…" [Hilt. Author's ref] which uses modern diagnostic techniques to show that most, perhaps all people have bacteriuria most, perhaps all the time. To base diagnostic decisions on results of standard agar-based cultures is to assume that any bacteria that are difficult to identify may safely be ignored. Treatment led to a sharp reduction in pyelonephritis but no reduction, and perhaps an increase, in mortality. Could this be because treatment cleared the bacteriuria, consequently rendering pyelonephritis an untenable diagnosis? The diagnosis depends on pain in "flank" or "loin", areas that are ill-defined in non-pregnant people and in pregnant patients may offer an even broader target when uncertain clinicians need a diagnosis in order to start antibiotics. But even with "flank pain" there must be bacteriuria. I very strongly disagree with the authors view that "the anticipation of a large RR reduction for pyelonephritis appears to limit the clinical equipoise necessary to conduct RCTs on screening for ASB…" The authors do go on to justify randomization but the case should be made far more strongly in the era of the microbiome. Harm from antibiotic treatment is ever more obviously harmful to complex, stable, regulated, generally beneficial microbiomes. Disrupting the fantastic interactions between fetus and mother does not seem to me fully justified by the results of biased, low-quality trials from half a century ago. What we have is no longer equipoise – it is ignorance. I would vote very strongly for high-quality RCTs that are sensitive to the risks of treatment and very careful about the diagnosis of pyelonephritis, reduction of which seems to be the main putative benefit of giving antibiotics to pregnant women.a I am not qualified to comment on the statistical methods but they are clearly and convincingly (to me) described.

VERSION 1 – AUTHOR RESPONSE
Authors' Responses to Reviewers' Comments

Comment	Response	Reference
Reviewer 1		
R1. General Comment This was a systematic reviews of screening and treatment effectiveness and patient preferences and the authors performed a systematic review and found that evidence on screening effectiveness was considered very low quality. Women have conflicting opinions about the antibiotics treatment during pregnancy. However, it is consistent with current guideline suggestion to show that the use of antibiotics treatment might be beneficial on the reduction of acute pyelonephritis during pregnancy. Current study is valuable and interesting.	Thank you for your comment. No edits required.	Not applicable
R1.1 The aim of the current study is relatively complicated. Success of screening strategy might result in the decision of treatment or not. The authors' result seemed to argue the need of screening policy. However, treatment of "these women after screening" seemed to show some benefits on these pregnant women due to reduction of risk of pyelonephritis and possible lower birth weight. But the authors found "conflicted attitude" of pregnant women for the antibiotics treatment. Although it is interesting and	Thank you for your comment. We can appreciate the complexity of multiple objectives and systematic reviews of the present study, including the nuances between screening and treatment. Due to limitations to word count we had omitted some explanation of our review process (as outlined in our protocol) although it seems essential to provide some more detail for the manuscript, and avoid confusion. We have clarified the approach undertaken for screening program effectiveness compared to (as linked/indirect	Background (p.3)

the interaction between each seemed to be conflicting in the current study. The authors should carefully present their data.	evidence) treatment effectiveness, in the Background: "The findings from this review were used by the Canadian Task Force on Preventive Health Care (CTFPHC) – supplemented by consultations with patients on outcome valuation and by information from stakeholders and other sources on issues of feasibility, acceptability, costs/resources, and equity – to inform recommendations about screening for ASB to support primary health care providers in delivery preventive care (available at http://www.cmaj.ca/content/190/27/E823). A staged approach to the research questions was used, beginning with an examination of direct evidence on the effectiveness of screening programs and of women's outcome valuation: 1) What are the benefits and harms of screening compared with no screening, or different screening methods or algorithms, for ASB in pregnancy? Screening is a program, not only a test. Screening therefore includes a series of events initiated by systematically offering a test to diagnose ASB in all pregnant women, with subsequent decisions about and adherence to treatment protocols and any other follow-up activities. 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? If there was insufficient quality of evidence from screening effectiveness and women's outcome valuation for the CTFPHC to make a recommendation, an examination of treatment effectiveness (one key component of a screening program) is planned: 3) What are the benefits and harms of antibiotic treatment compared with placebo or no treatment for ASB in pregnancy? Evidence from studies of treatment effectiveness would provide linked evidence on the clinical effectiveness of screening programs, and is one critical component of a screening program." We did find conflicting evidence on women's attitudes regarding antibiotic use in pregnancy, where some did not want to use antibiotics in pregnancy due to perceived harm on the baby, while others did not consider antibiotics to pose a risk to the mother or baby. We presented the evidence as such in our findings and the end user (Canadian Task Force) considered all the evidence when making their recommendation.	
R1.2 Although quality of enrolled studies might not good, the relative risk of pyelonephritis and of low birth weight seemed to be significantly	The effect estimate for pyelonephritis (treatment effectiveness) was 0.24 (95% CI 0.13, 0.41), based on low quality evidence from 12 studies (2017 participants). The effect estimate	Results, treatment effectiveness (p.9)

different. The “power” of terms to study the occurrence of pyelonephritis during pregnancy is much more strong than that of terms to the study target—low birth weight. The authors should consider the difference between two.	for low birth weight (≤2500g) was 0.63 (95% CI 0.45, 0.90), based on low quality evidence from 7 studies (1522 participants). We are unclear what the reviewer means by “power of terms to study occurrence of pyelonephritis…much more strong than that of terms to…low birth weight”. If the reviewer is referring to the sample size differences between pyelonephritis and low birth weight, this was taken into account in the GRADE assessment for imprecision which considers the number of patients and number of events; both outcomes were not downgraded for this domain. Furthermore, we have reported the results for each outcome individually; while each outcome was statistically significant, no attempt was made to compare the effect sizes of these two outcomes.	
R1.3 If the quality of all articles did not reach to “accepted” levels the authors claimed, this article failed to add any new information to change the current understanding in the management of pregnant women with asymptomatic bacteria. Therefore, if the screening strategy is not effective, it is hard to evaluate whether the benefits of treatment for these patients.	Thank you for raising this point. We did not identify reviews of the effectiveness of screening programs. Published literature has focused mainly on treatment of ASB. Therefore, while the quality of the evidence was generally low to very low for screening and treatment effectiveness, and insufficient for women’s valuation of benefits and harms of screening, undertaking the current review was needed to identify the available evidence to date in all of the three key areas.	See Response to Reviewer R1.1

	Moreover, this information provided the basis for the Canadian Task Force to make recommendations. The review updates evidence on screening for bacteriuria in pregnancy which has not been revisited by the Task Force since 1993; the review identifies low quality of evidence underlying this long standing standard of prenatal care that potentially helps women and their children without reported serious adverse harms from antibiotics and warrants continuation of the practice, while calling upon researchers to address gaps in evidence. The evidence from studies of screening effectiveness did not show that screening was ineffective. The few studies that contributed to this body of evidence (4 cohort studies) had several quality assessment domains that were downgraded due to serious concerns, thereby providing us with high uncertainty about the true effects (benefits or harms) of screening. We have clarified the approach undertaken to examine effectiveness of screening programs compared to effectiveness of treatment in our response above (R1.1).	
R1.4 In overall, it is a hard work of the current study. Much more precise or clear definition for the aims of the	Thank you for your comment. We have clarified the approach undertaken for all questions, as described in the response to R1.1.	Background (p.3);

current study might be needed.		
Reviewer 2		
R2. General Comment The systematic review was well searched and presented.	Thank you for your comment. No edits required.	Not applicable
Reviewer 3		
R3. General Comment First of all I would like to compliment the authors with their work. The review is very comprehensive. Especially the focus of the review on 'the benefits and harms of screening' and 'the women's outcome valuation' are innovative and clinically relevant. This review provides insight in the knowledge gaps currently present concerning the topic screening for asymptomatic bacteriuria in pregnancy in the broader sense. For that alone it is important that this review will be available.	Thank you for your comment and underscoring the value of this work. No edits required.	Not applicable
R3.1 Page 6 lines 10-18: I would suggest to add the total number of included studies at the end of the paragraph.	Thank you for your suggestion. We have added: "A total of 25 unique studies were included in the review."	Results (p.6)
R3.2 Page 7 Table 1 'summary of included studies for screening and treatment effectiveness': The table is not easy to read. For	We have made the following changes to make Table 1 clearer and easier to read: - Added subheadings for each group of summary	Table 1 (Summary of included studies)

example: - The headings (e.g. population characteristics) are not always clear or comprehensive - How should we interpret the following "≥105 CFU/mL (≥108 CFU/mL)" Regarding treatment details: "treatment after sensitivity testing (3)" Does this mean that in the other study (number 4) no information is provided concerning treatment? Or concerning susceptibility testing?	data (e.g., Timing of screening, Urine testing method, Timing/frequency of testing for persistent bacteriuria); - Added "not reported (NR)" to capture missing data; - Separated testing follow-up (timing/frequency of testing for persistent bacteriuria) from outcomes follow-up (timing of outcome assessment). We included two equivalent unit representations of bacterial colony count considered significant ≥10^5 CFU/mL and ≥10^8 CFU/L (note distinction between mL vs. L) as clinicians reported that bacterial counts from urine cultures were conventionally reported in litre (CFU/L) within the Canadian context, compared to milliliter (CFU/mL) commonly found among publications from the US or elsewhere. We have added "Criteria for positive test: ≥10^5 CFU/mL (≥10^8 CFU/L)" to specify what this measurement refers to. One study (Rhode et al) did not provide information regarding treatment or susceptibility testing. The remaining studies (Gérard et al, Gratacós et al, and Uncu et al) reported treating women based on antibiotic sensitivity testing. We have revised this for clarity to: "Protocol for antibiotic treatment: based on antibiotic-sensitivity testing", and included "NR (1)" to capture missing data.	

R3.3 Page 9, lines 35-39 “Studies that followed women beyond six weeks after delivery found a greater reduction in pyelonephritis”. How can this be explained and how does this affect the choice to introduce (or maintain) a screening program for ASB during pregnancy?	The finding of greater reduction in pyelonephritis among women who were followed up beyond six weeks post-delivery may be due to the development of pyelonephritis during the post-delivery phase in some (untreated) women, thereby showing a greater treatment effect. The effect of this finding on the maintenance or introduction of a screening program may be to suggest a longer follow-up period to prevent later development of bacteriuria (or re-infection) and pyelonephritis, and any adverse maternal effects. However, the main concern regarding development of pyelonephritis **during** pregnancy is any potential adverse effects on the infant (e.g., preterm delivery, low birth weight). We cautiously interpret these subgroup analyses, since the follow-up information was based on between-study (non-randomized) comparisons and not within-study comparisons. We have added the following to the Discussion: “The finding of a greater reduction in pyelonephritis among women who were followed up beyond postpartum suggests that a longer follow-up period within a screening program may prevent later development of bacteriuria (and subsequent pyelonephritis) when there is concern regarding adverse maternal effects.”	Results, treatment effectiveness (p.9); Discussion (p.13)

R3.4 Conclusion & discussion page 12-13: the authors do not mention the fact that most studies are performed in the sixties, seventies and eighties while the midwifery and obstetric care was completely different. During the last decades many new techniques are introduced and applied in the routine care of pregnant women such as the use of ultrasound. The ultrasound is used among other things to determine the gestational age. Uncertainty about the gestational age before the introduction of the ultrasound affects the outcome preterm delivery in 'older' studies.	Thank you for raising this point. We agree that the majority of studies pre-dated current obstetric practices that may improve the ascertainment of maternal and neonatal outcomes. We have added the following sentence to the Conclusions & Discussion: "The majority of studies were published in the 1960s to 1980s, pre-dating current obstetric practices having, for example, better recognition of risk factors for urinary tract infections and other pregnancy complications, prompt treatment of symptoms, a broader range of antibiotic options, and improved ascertainment of maternal and neonatal outcomes."	Conclusions & Discussion, Limitations of evidence base and review (p.12)
R3.5 Appendix (and discussion): In some of the studies the definition of asymptomatic bacteriuria seems to be missing (e.g. Wren 1969). Could the authors elaborate (more) on the effect of this missing information in the discussion. And the same for studies that included low colony counts of GBS such as Thomsen 1987.	Thank you for your suggestion. We have added to the Limitations: "While most studies used a urine culture to detect ASB, criteria for defining a positive test were not always clear or reported. One study only included women positive for group B streptococcus with a lower range criterion for bacteriuria warranting treatment (with many samples considered contaminated specimens, rather than ASB). Inclusion of these studies may have biased effects	Conclusions & Discussion, Limitations of evidence base and review (p.12); Supplement 4 (Characteristics of included studies); Table 1 (Summary of included studies)

	of screening programs and treatment for some outcomes." We have added clarity to the numbers in Table 1.	
Reviewer 4		
R4. General Comment The manuscript reports the results of several meta-analyses of bacteriuria in pregnancy. The paper is well written, the methods clearly described, and the interpretation consistent with the results. The statistical methods used are appropriate for the study, and clearly and thoroughly explained.	Thank you for your positive comments regarding our work. No edits required.	Not applicable
R4.1 I found only a handful of potential typos: P. 11, line 78: The CI for low birth weight doesn't contain the point estimate. Is there a typo here? P. 61, line 27-28: It looks like you have provided the quartiles rather than the SE?	Thank you for pointing these out. There doesn't appear to be line 78 on page 11, and the maximum number of lines is 60 per page. The only CIs in the manuscript for this outcome (RR 0.63; 95% CI 0.45, 0.90; I^2=20%; ARR 4.4%; NNT 23, 95% CI 15, 85) do contain the point estimate. Thank you for pointing this out. This refers to the gestational age data for Kazemier et al, for women's outcome valuation. This has been revised to:	Supplement: Characteristics of included studies on women's outcome valuation

P. 65, lines 3-7: The Mann-Whitney U test is not generally considered a test of difference of means. It certainly shouldn't have been used to test both the difference of means and of medians. Was the error in the original paper, or is this a typo?	"Median gestational age (wks + days at screening (IQR))". This refers to the study by Sanz et al reporting differences between groups (mean; median) on perceived teratogenic risk. The study authors used the Mann-Whitney U test and reported a table of means and a table of medians. We have revised the extracted outcomes to: "The mean value of the perceived teratogenic risk by non-pregnant women was higher than that perceived by pregnant women for erythromycin (55.6 vs. 38.7) and amoxicillin (49.3 vs. 40.4). 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) and amoxicillin (50.5 vs. 34.0). The Mann-Whitney U test showed a significant difference between groups for erythromycin and amoxicillin, respectively ($p<0.05$ vs. $p<0.001$, non-pregnant vs. pregnant women).	Supplement: Characteristics of included studies on women's outcome valuation
P. 87: The column header "Was the sample size based on pre-study considerations of…" is cut off.	Thank you for pointing this out. This refers to the table of summary of ROB for studies of women's outcome valuation, where this column header has been expanded to read "Was the sample size based on pre-study considerations of statistical power?"	Supplement: Summary of ROB for studies of women's outcome valuation
Reviewer 5		

R5. General Comment The authors reference evidence that ASB is present in 2 – 10% of ambulatory premenopausal women and that prevalence is higher still in pregnant women. They study whether intervening on this common, asymptomatic lab abnormality is beneficial. They find mainly decades-old low quality trials. The biological plausibility that treatment for so common a 'condition' would exceed benefit seems low. Billions of women have had ASB during pregnancy without treatment, over the eons prior to antibiotic development and now around the world in under-resourced settings. I, a geriatrician, am unaware of a public health burden developing from ASB in pregnant women in these settings where no one gets or has gotten antibiotics.	Thank you for your comment. The evidence is based on older studies, and we have added a sentence in the Conclusions & Discussion, as per response to reviewer above (R3.4). We report on the finding (albeit low quality evidence) that a reduction was found for pyelonephritis and low birth weight among comparative trials of treatment versus no treatment/placebo. Findings from controlled trials are usually acceptable for demonstrating causation. As per response to reviewer above (R1.3), we did not identify reviews of the effectiveness of screening programs, and published literature has focused mainly on treatment of ASB; therefore, we undertook the current work to systematically examine the effectiveness of screening programs, and of treatment, as well as women's outcome valuation. This was identified as a priority topic for the Canadian Task Force.	Conclusions & Discussion, Limitations of evidence base and review (p.12); See Responses to Reviewer (R3.4 and R1.3)
R5.1 Finding an association between ASB and harm is no evidence of need to treat. For example, "an observational study of 1,497 individuals undergoing joint replacement found asymptomatic bacteriuria in 12%. At 1-year follow-up the, rate of prosthetic joint infection was	Thank you for your comment. We found an association between treating ASB and a reduction in pyelonephritis and infant low birth weight. The decision to treat (or not) should be based on the balance of benefits (reduced maternal and neonatal morbidity) and harms (risk of adverse maternal and neonatal effects	Background (p.3); See Response to Reviewer (R1.1)

three times as high in individuals with bacteriuria (4.3%) as in those without (1.4%) (P < .001), but antibiotic treatment of bacteriuria did not reduce the risk of infection …" [Finucane TE. J Am Geratr Soc 2017] and "microorganisms isolated in prosthetic joint infections were not the same as those in preoperative urine cultures in any patient with asymptomatic bacteriuria." [Sousa R, Mu~noz-Mahamud E, Quayle J. Is asymptomatic bacteriuria a risk factor for prosthetic joint infection? Clin Infect Dis 2014;59:41–47]. ASB here seems to be no more than a biomarker, a measure of vulnerability/frailty. The authors offer further caveats. Although they seem to make a strong causal inference, they conclude that the risk/benefit calculus remains uncertain: "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),2, 4 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. ADDIN EN.CITE 2, 4, 5"	from antibiotic treatment), taking into account individual patient values. We cannot comment on studies of ASB among adults with prosthetic joint infection (e.g., whether ASB is a risk for, or surrogate marker of, prosthetic joint infection). We reported existing uncertainty around the direct clinical mechanisms/pathways of ASB and development of pyelonephritis, and of any subsequent morbidity.	

I couldn't figure out why screening programs not linked to treatment could be beneficial and fear I am missing something.	Treatment is a critical component of any screening program. We have clarified the approach undertaken to examine effectiveness of screening programs compared to effectiveness of treatment in our response above (R1.1). The studies we consider to evaluate "screening effectiveness" followed women until at least delivery such that the effects from treatment (as	

	per clinic protocol) would have been captured.	
R5.2 Their definition of ASB is based on “significant quantitative counts” But the significance of “significant bacteriuria” remains uncertain, threshold colony counts have ranged from 102 to 105, and the construct has not been shown to identify patients who are more likely to achieve net benefit from antibiotic treatment. Further, the authors themselves cite an article entitled “Urine is not sterile…” [Hilt. Author’s ref] which uses modern diagnostic techniques to show that most, perhaps all people have bacteriuria most, perhaps all the time. To base diagnostic decisions on results of standard agar-based cultures is to assume that any bacteria that are difficult to identify may safely be ignored.	Thank you for your comment. We recognize and report that acceptable bacterial count thresholds vary in clinical practice. The available evidence demonstrates that the quantitative urine culture is currently considered the gold (reference) standard for detecting ASB. This is consistent with consultations with clinical experts. Our review did not examine the accuracy of diagnostic tests since studies of screening program effectiveness and treatment effectiveness all used urine culture (or a culture-variant device), rather than other tests (e.g., point-of-care methods), to test for significant bacteriuria. In our discussion we note that future studies, having clinical outcomes, on enhanced culture protocols should be reviewed when available.	Introduction, issues to consider for screening tests (p.2); Conclusions & Discussion (p.14)
R5.3 Treatment led to a sharp reduction in pyelonephritis but no reduction, and perhaps an increase, in mortality. Could this be because treatment cleared the bacteriuria, consequently rendering pyelonephritis an untenable diagnosis? The diagnosis depends on pain in “flank” or “loin”, areas that are ill-defined in non-pregnant people and in	Evidence on treatment effectiveness showed that antibiotics produced a significant reduction in pyelonephritis (RR 0.24, 95% CI 0.13, 0.41; I^2=60%) but without significant difference on perinatal mortality (RR 0.96, 95% CI 0.27, 3.39; I^2=56%). The quality of evidence (e.g. precision) on mortality was too poor to make any conclusions (about direction or magnitude) or speculate on reasoning.	Conclusions & Discussion, Limitations of evidence base and review (p.14)

pregnant patients may offer an even broader target when uncertain clinicians need a diagnosis in order to start antibiotics. But even with "flank pain" there must be bacteriuria.	The definition of pyelonephritis varied when reported, among studies of screening (combinations of symptoms including fever, lumbar or flank pain, tenderness in costovertebral angle, dysuria) and treatment (combination of symptoms including fever or pyrexia, nausea, chills or rigours, vomiting, dysuria, frequency of urination, burning during urination, costovertebral tenderness, flank pain, and loin pain and/or tenderness). Two studies of screening effectiveness included a positive urine culture in addition to symptoms to define pyelonephritis. All studies of treatment effectiveness included women at study entry who were tested positive for bacteriuria. We agree that pyelonephritis is a clinical diagnosis with subjectivity. We have added to the Conclusions & Discussion: "Outcomes were defined variably among studies. There is a risk of bias due to subjectivity of outcomes ascertained by clinical diagnosis (e.g., pyelonephritis, when reported among studies, was defined using variable combinations of symptoms)."	
R5.4 I very strongly disagree with the authors view that "the anticipation of a large RR reduction for pyelonephritis appears to limit the clinical equipoise necessary to conduct RCTs on screening for ASB…" The authors do go on to justify randomization	Thank you for your comment. We have revised and added to the Conclusions & Discussion: "High quality RCTs of effectiveness of screening programs should be undertaken.	Conclusions & Discussion, Future Research (p.14).

but the case should be made far more strongly in the era of the microbiome. Harm from antibiotic treatment is ever more obviously harmful to complex, stable, regulated, generally beneficial microbiomes. Disrupting the fantastic interactions between fetus and mother does not seem to me fully justified by the results of biased, low-quality trials from half a century ago. What we have is no longer equipoise – it is ignorance. I would vote very strongly for high-quality RCTs that are sensitive to the risks of treatment and very careful about the diagnosis of pyelonephritis, reduction of which seems to be the main putative benefit of giving antibiotics to pregnant women.a	Current evidence provides uncertainty regarding: 1) applicability to current practice, 2) adequate collection and reporting of harms, and 3) modern and clearly defined outcomes. Because routine screening practices suggest limited clinical equipoise, contemporary studies using a pragmatic preference-based/tolerant screening trial design (e.g., those without a preference towards/against screening are randomized while others self-select one arm) should be adopted.”	
R5.5 I am not qualified to comment on the statistical methods but they are clearly and convincingly (to me) described.	Thank you for your comment. Our statistical methods are based on industry standards for systematic reviews.	Methods, data synthesis and analysis (p.4-5)

VERSION 2 – REVIEW

REVIEWER	Peng-Hui Wang Department of Obstetrics and Gynecology, Taipei Veterans General Hospital and Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan 11217.
REVIEW RETURNED	22-Aug-2018

GENERAL COMMENTS	great works and acceptable

REVIEWER	Siobhan P Brown University of Washington, United States of America

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GENERAL COMMENTS	I think this paper is ready for publication. No further questions or comments.