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Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity (Review)

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[Intervention Review]

Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity

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ABSTRACT

Background

Several studies have suggested that prophylactic antibiotics given during pregnancy improved maternal and perinatal outcomes, while others have shown no benefit and some have reported adverse effects.

Objectives

To determine the effect of prophylactic antibiotics on maternal and perinatal outcomes during the second and third trimester of pregnancy for all women or women at risk of preterm delivery.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2015) and reference lists of retrieved articles.

Selection criteria

Randomised controlled trials comparing prophylactic antibiotic treatment with placebo or no treatment for women in the second or third trimester of pregnancy before labour.

Data collection and analysis

We assessed trial quality and extracted data.

Main results

The review included eight randomised controlled trials. Approximately 4300 women were recruited to detect the effect of prophylactic antibiotic administration on pregnancy outcomes.

Primary outcomes

Antibiotic prophylaxis did not reduce the risk of preterm prelabour rupture of membranes (risk ratio (RR) 0.31; 95% confidence interval (CI) 0.06 to 1.49 (one trial, 229 women), *low quality evidence*) or preterm delivery (RR 0.88; 95% CI 0.72 to 1.09 (six trials, 3663 women), high*quality evidence*). However, preterm delivery was reduced in the subgroup of pregnant women with a previous preterm birth who had

bacterial vaginosis (BV) during the current pregnancy (RR 0.64; 95% CI 0.47 to 0.88 (one trial, 258 women)), but there was no reduction in the subgroup of pregnant women with previous preterm birth without BV during the pregnancy (RR 1.08; 95% CI 0.66 to 1.77 (two trials, 500 women)). A reduction in the risk of postpartum endometritis (RR 0.55; 95% CI 0.33 to 0.92 (one trial, 196 women)) was observed in high-risk pregnant women (women with a history of preterm birth, low birthweight, stillbirth or early perinatal death) and in all women (RR 0.53; 95% CI 0.35 to 0.82 (three trials, 627 women), *moderate quality evidence*). There was no difference in low birthweight (RR 0.86; 95% CI 0.53 to 1.39 (four trials; 978 women)) or neonatal sepsis (RR 11.31; 95% CI 0.64 to 200.79) (one trial, 142 women)); and blood culture confirming sepsis was not reported in any of the studies.

Secondary outcomes

Antibiotic prophylaxis reduced the risk of prelabour rupture of membranes (RR 0.34; 95% CI 0.15 to 0.78 (one trial, 229 women), *low quality evidence*) and gonococcal infection (RR 0.35; 95% CI 0.13 to 0.94 (one trial, 204 women)). There were no differences observed in other secondary outcomes (congenital abnormality; small-for-gestational age; perinatal mortality), whilst many other secondary outcomes (e.g. intrapartum fever needing treatment with antibiotics) were not reported in included trials.

Regarding the route of antibiotic administration, vaginal antibiotic prophylaxis during pregnancy did not prevent infectious pregnancy outcomes. The overall risk of bias was low, except that incomplete outcome data produced high risk of bias in some studies. The quality of the evidence using GRADE was assessed as low for preterm prelabour rupture of membranes, high for preterm delivery, moderate for postpartum endometritis, low for prelabour rupture of membranes, and very low for chorioamnionitis. Intrapartum fever needing treatment with antibiotics was not reported in any of the included studies.

Authors' conclusions

Antibiotic prophylaxis did not reduce the risk of preterm prelabour rupture of membranes or preterm delivery (apart from in the subgroup of women with a previous preterm birth who had bacterial vaginosis). Antibiotic prophylaxis given during the second or third trimester of pregnancy reduced the risk of postpartum endometritis, term pregnancy with pre-labour rupture of membranes and gonococcal infection when given routinely to all pregnant women. Substantial bias possibly exists in the review's results because of a high rate of loss to follow-up and the small numbers of studies included in each of our analyses. There is also insufficient evidence on possible harmful effects on the baby. Therefore, we conclude that there is not enough evidence to support the use of routine antibiotics during pregnancy to prevent infectious adverse effects on pregnancy outcomes.

PLAIN LANGUAGE SUMMARY

Antibiotic prophylaxis during the second and third trimester in pregnancy to reduce adverse pregnancy outcomes and morbidity

Antibiotics are administered to pregnant women during the second and third trimester of pregnancy (before labour) to prevent bacteria in the vagina and cervix affecting the pregnancy. Infection by some infectious organisms in a woman’s genital tract can cause health problems for the mother and her baby, and has been associated with preterm births. This review of eight randomised trials involved approximately 4300 women in their second or third trimester. We found that antibiotics did not reduce the risk of preterm prelabour rupture of the membranes (one trial, *low quality of evidence*), or the risk of preterm birth (six trials, high*quality of evidence*). Preterm delivery was reduced in pregnant women who had a previous preterm birth and an imbalance of bacteria in the vagina (bacterial vaginosis) during the current pregnancy. There was no reduction in preterm delivery in pregnant women with previous preterm birth without a bacterial imbalance during the current pregnancy (two trials). Postpartum endometritis, or infection of the uterus following birth, was reduced overall (three trials, *moderate quality of evidence*), as well as in a trial of high-risk women who had a previous preterm birth (one trial, *moderate quality of evidence*). No reduction in neonatal illness was observed. Outcomes of interest were available in trials with high losses to follow-up. We could not estimate the side effects of antibiotics since side effects were rare; however, antibiotics may still have serious side effects on women and their babies.

There is, therefore, no justification to give antibiotics to all pregnant women during the second or third trimester to prevent adverse infectious effects on pregnancy outcomes.

Summary of findings for the main comparison. Prophylactic antibiotics versus placebo for preventing infectious morbidity and mortality

Prophylactic antibiotics versus placebo for preventing infectious morbidity and mortality

Population: women in the second or third trimester of pregnancy before labour and delivery
Settings: hospitals in Kenya, Belgium, USA, India, The Netherlands
Intervention: prophylactic antibiotics versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Prophylactic antibiotics versus placebo				
Preterm prelabour rupture of membranes	**Study population**		**RR 0.31** (0.06 to 1.49)	229 (1 study)	⊕⊕⊝⊝ **low** [1,2]	
	84 per 1000	**60 per 1000** (16 to 224)				
	Moderate					
	55 per 1000	**40 per 1000** (10 to 147)				
Prelabour rupture of membranes	**Study population**		**RR 0.34** (0.15 to 0.78)	229 (1 study)	⊕⊕⊝⊝ **low** [2,3]	
	173 per 1000	**59 per 1000** (26 to 135)				
	Moderate					
	173 per 1000	**59 per 1000** (26 to 135)				
Preterm delivery	**Study population**		**RR 0.88** (0.72 to 1.09)	3663 (6 studies)	⊕⊕⊕⊕ high	
	155 per 1000	**150 per 1000** (127 to 178)				
	Moderate					
	101 per 1000	**98 per 1000**				

		(83 to 116)				
Chorioamnionitis	**Study population**		**RR 0.62** (0.10 to 3.62)	229 (1 study)	⊕⊖⊖⊖ **very low** [1,2,3]	
	27 per 1000	**17 per 1000** (3 to 99)				
	Moderate					
	27 per 1000	**17 per 1000** (3 to 98)				
Puerperal sepsis/postpartum endometritis	**Study population**		**RR 0.53** (0.35 to 0.82)	627 (3 studies)	⊕⊕⊕⊖ **moderate** [4]	
	161 per 1000	**85 per 1000** (56 to 132)				
	Moderate					
	104 per 1000	**55 per 1000** (36 to 85)				
Intrapartum fever needing treatment with antibiotics	Not estimable			(0 study)	See comment	This outcome was not reported in any of the included studies.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in the footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Wide confidence interval crossing the line of no effect, few events & small sample size.
[2] One study with design limitations.
[3] Few events and small sample size.
[4] Small sample size.

BACKGROUND

Description of the condition

Female genital tract infection can be caused by various organisms and could be due to acquisition, overgrowth, or ascending of the normal flora from the lower genital tract into the uterine cavity.

Maternal genital tract infection or colonisation by some infectious organisms can cause maternal and perinatal mortality and morbidity. Preterm delivery is the most common cause of perinatal morbidity and mortality in the world. Moreover, prematurity is implicated in at least two-thirds of early infant deaths (Cunningham 1997).

A large number of medical and demographic factors have been implicated in the aetiology of preterm birth. These can be categorised into four groups:

1. medical and obstetric complications (e.g. hypertensive disorders, placental haemorrhage);
2. lifestyle factors (e.g. cigarette smoking, poor nutrition);
3. amniotic fluid infection caused by a variety of micro-organisms located in the genital tract;
4. cervical incompetence.

Approximately one-third of preterm births have been associated with chorioamniotic infection (Lettieri 1993). Many micro-organisms have been suggested as the cause of preterm prelabour rupture of membranes, preterm labour, or both; for example, bacterial vaginosis, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Ureaplasma urealyticum*, *Chlamydia trachomatis* and Group B streptococci (Braun 1971; Gravett 1986; Hardy 1984; Hillier 1995; Regan 1981). Case detection and treatment in pregnant women is problematic and expensive, emphasising the need for other strategies. Considering the association between preterm births and infection, prophylactic antibiotics seem to be a logical strategy for preventing preterm births, although the effectiveness of prophylactic antibiotics for which population should be given is still not clear (e.g., all women or only high-risk women).

Description of the intervention

Antibiotic prophylaxis is used for prevention of infection and reduces the risk of sequelae of infection. Antibiotics used for prophylaxis should be initiated before documented infection. Antibiotic use during pregnancy is not without possible risk. Long-term follow-up of children whose mothers were randomly allocated to antibiotics versus placebo for suspected preterm labour with intact membranes were found to have an increased risk of cerebral palsy at seven years of age (Kenyon 2008).

How the intervention might work

Infections and related complications in pregnancy and childbirth are potentially preventable. However, the appropriate intervention is yet to be identified. Routine antenatal detection and treatment of infections, especially in countries with a high prevalence, would seem the most reasonable approach. Limited laboratory facilities make this strategy unrealistic in low-resource settings. Diagnosis algorithms, including clinical signs and symptoms, and behavioural patterns, are sometimes used for quick identification of infections for prompt care. Unfortunately, despite the fact that this approach may be useful in countries with limited resources, diagnostic algorithms have low sensitivity, predictive values and validity. In a situation where realistic options are few, a strategy of routine antibiotic prophylaxis might be a worthwhile alternative.

Why it is important to do this review

The available body of literature on prophylactic antibiotics in pregnancy has yielded conflicting results. While some studies demonstrated that prophylactic antibiotic administration in pregnancy improved maternal and perinatal morbidity and mortality, other studies could not confirm this finding (Eschenbach 1991; McCormack 1987; Morales 1994; Newton 1989; Oleszczuk 2000; Romero 1988; Romero 1993). It is in view of this uncertainty that there is a need for a systematic review of the results of randomised controlled trials of antibiotic prophylaxis in pregnancy.

OBJECTIVES

To determine whether the routine administration of prophylactic antibiotics in the second or third trimester of pregnancy for all women or women at risk of preterm delivery reduces adverse pregnancy and infant outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) including cluster-RCTs were eligible for inclusion. Quasi-RCTs were not eligible for inclusion.

Types of participants

Women in the second or third trimester of pregnancy before labour and delivery. We included routine prophylaxis for all women and prophylaxis for women with high risk of preterm birth. High risk was defined as women at risk of preterm delivery, for example, having a previous spontaneous preterm delivery, history of having an infant with a low birthweight, having bacterial vaginosis (BV) in the current pregnancy, or a pre-pregnancy weight less than 50 kg. We excluded trials in which antibiotics were given to women for treatment purposes or if they had a positive test for fetal fibronectin (fFN) as the trial entry criteria.

Types of interventions

Prophylactic prenatal antibiotics versus placebo or no treatment. We excluded interventions at intrapartum.

Types of outcome measures

Primary outcomes are directly related to infectious morbidity/mortality.

Primary outcomes

Maternal outcomes

1. Preterm prelabour rupture of membranes (membrane rupture before gestational age of 37 weeks and before labour)
2. Preterm delivery
3. Puerperal sepsis/postpartum endometritis, wound infection, urinary tract infection

Neonatal outcomes

1. Low birthweight

2. Clinical neonatal sepsis
3. Blood culture confirming sepsis

Secondary outcomes

Maternal outcomes

1. Prelabour rupture of membranes (membrane rupture after gestational age of 37 weeks but before labour)
2. Chorioamnionitis
3. Intrapartum fever needing treatment with antibiotics
4. Serious maternal complications of puerperal infection (requiring laparotomy for infection or hysterectomy), death
5. Gonococcal cervicitis (postpartum detected) (not prespecified)
6. Maternal side effects of antibiotic prophylaxis, such as allergy, gastrointestinal tract disturbance, etc
7. Duration of hospital stay
8. Satisfaction with care
9. Compliance with medication regimens, such as taking all medication according to doctor's instructions

Neonatal outcomes

1. Mean gestational age
2. Admission to neonatal intensive care unit
3. Mean birthweight
4. Ophthalmia neonatorum
5. Congenital abnormality
6. Small-for-gestational age
7. Abnormal neurological development
8. Perinatal mortality
9. Childhood allergies
10. Childhood gastrointestinal problems
11. Childhood functional impairment
12. Childhood cerebral palsy

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 April 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We searched the reference lists of all retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review,*see* Thinkhamrop 2015a.

For this second update in 2015, we used the following methods when assessing the trials identified by the updated search.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. We entered data into Review Manager software (RevMan 2014) and checked for accuracy.

When information regarding any of the above was unclear, we planned to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving the third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);

- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence

For this update, we assessed the quality of the evidence using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following key outcomes for the main comparison.

Maternal outcomes

1. Preterm prelabour rupture of membranes (membrane rupture before gestational age of 37 weeks and before labour)
2. Prelabour rupture of membranes (membrane rupture after gestational age of 37 weeks but before labour)
3. Preterm delivery
4. Chorioamnionitis
5. Intrapartum fever needing treatment with antibiotics
6. Puerperal sepsis/postpartum endometritis, wound infection, urinary tract infection

We used GRADEprofiler (GRADEpro 2014) to import data from Review Manager 5.3 (RevMan 2014) in order to create a 'Summary of findings' table. We produced a summary of the intervention effect and a measure of quality for each of the above outcomes using the GRADE approach. The GRADE approach uses five considerations

(study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

We used the mean difference if outcomes were measured in the same way between trials. If necessary, we planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We intended to include cluster-randomised controlled trials (RCTs) in the analyses along with individually-randomised trials. Although we could not find any cluster-RCTs for this version of the review. In future updates, if identified, we will adjust their sample sizes using the methods described in the *Handbook [Section 16.3.4 or 16.3.6]* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-RCTs and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We would also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

We planned to exclude cross-over design since it is unlikely to be a valid study design for this review.

Other unit of analysis issues

We planned to exclude outcomes for multiple pregnancies since there is a different mechanism for preterm labour.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. Had we identified substantial heterogeneity (above 30%), we planned to explore it by prespecified subgroup analysis.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

Where there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

Where we identified substantial heterogeneity, we investigated it using subgroup analyses. We considered whether an overall summary was meaningful, and if it was, we used random-effects analysis to produce it.

We carried out subgroup analyses on the high-risk group: that is, the group of pregnant women who may be at risk of having the primary outcomes, including those with a history of preterm delivery, a history of genital tract and urinary tract infection.

For the previous update (Thinkhamrop 2015a), 'high risk' was defined as women who had a previous spontaneous preterm delivery, history of low birthweight, a diagnosis of bacterial vaginosis (BV) in the current pregnancy (BV identified after enrolment and antibiotics used only for prophylaxis before knowing if the participant had BV or not), or a pre-pregnancy weight less than 50 kg.

All outcomes were used in subgroup analyses.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We did not conduct sensitivity analysis in this version of the review. In future updates, we plan to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result.

RESULTS

Description of studies

Results of the search

We searched up to 30 April 2015 and assessed at total of 46 reports of 20 trials. In this 2015 update, we included eight trials (Gichangi 1997; Hauth 1995; McGregor 1990; Paul 1997; Sen 2005; Temmerman 1995; Van den Broek 2009; Vermeulen 1999) and excluded 11 trials (Andrews 2003; Andrews 2006; Audebert 1989; Goldenberg 2006; Gray 2001; Larsson 2006; Luntamo 2010; Peters 1995; Shennan 2006; Tripathi 2008; Unger 2015). We have grouped Rathjen 2010, a previously ongoing report, under the newly excluded trial (Unger 2015). One study is ongoing (Hoffman 2013).

In this 2015 update, we have included a previously excluded trial (Van den Broek 2009). In this trial there are two interventions (azithromycin prophylaxis for preterm labour and sulphadoxine-pyrimethamine as an antimalarial prophylaxis). However, the antimalarial prophylaxis was given to all recruited women and so the trial meets our inclusion criteria for antibiotic prophylaxis (azithromycin compared with placebo). In the previous update (Thinkhamrop 2015a), we excluded two previously included studies (Lin 2005; Shennan 2006), because the trials included pregnant women with positive fetal fibronectin using antibiotic for treatment but not for prophylaxis. Lin 2005 is an additional report of the excluded trial Andrews 2003. Two previously excluded studies are now incorporated into the excluded trial Goldenberg 2006 and one previously excluded study (Kurtzman 2008) is now incorporated into the excluded trial Shennan 2006. One previously ongoing study (Ashorn 2006) is now incorporated in the newly excluded trial Luntamo 2010.

Included studies

Eight trials (nine reports) met the inclusion criteria for this review. For a detailed description of the included studies, *see* Characteristics of included studies. Three of the studies (Hauth 1995; McGregor 1990; Vermeulen 1999), were conducted in high-income countries (USA, Netherlands) while the other five (Gichangi 1997; Paul 1997; Sen 2005; Temmerman 1995, Van den Broek 2009) were reports from low- and middle-income countries (Kenya, India, Malawi). Three trials (Gichangi 1997; Hauth 1995; Vermeulen 1999), enrolled only high-risk pregnant women. All studies adequately described the characteristics of the women admitted into the study.

The antibiotics used in these studies were oral erythromycin, azithromycin, metronidazole, cephalexin, cefetamet-pivoxil, and parenteral ceftriaxone, and clindamycin vaginal cream.

The earliest of the studies reviewed was published in 1990, five others were published from 1995 to 1999, one in 2005, and the latest one was published in 2009.

Excluded studies

We excluded 11 trials (36 reports) for the following reasons.

1. Antibiotic administration took place during the first half of the pregnancy and not during the second and third trimesters of pregnancy, which is the focus of this review (Audebert 1989; Gray 2001; Larsson 2006).
2. One study focused on twin gestation, which has a higher risk of adverse pregnancy outcome with some different mechanisms from single pregnancy (Peters 1995).
3. Antibiotics were administered before the current pregnancy, when the women were not pregnant (Andrews 2006).
4. Antibiotics were given prenatally and during labour, which was not relevant to the review's objective to assess the effect of prophylactic antibiotics given prenatally (Goldenberg 2006).
5. The study compared one intervention with another intervention without a placebo/no treatment arm (Luntamo 2010; Unger 2015).
6. Antibiotic usage was for treatment after having identified the infection, not for prophylaxis (Andrews 2003; Shennan 2006; Tripathi 2008).

For a detailed description of the excluded studies,*see* Characteristics of excluded studies. Trials with more than one report can be found in the reference list of the excluded studies.

Risk of bias in included studies

See Figure 1 and Figure 2 for a summary of all 'Risk of bias' assessments.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

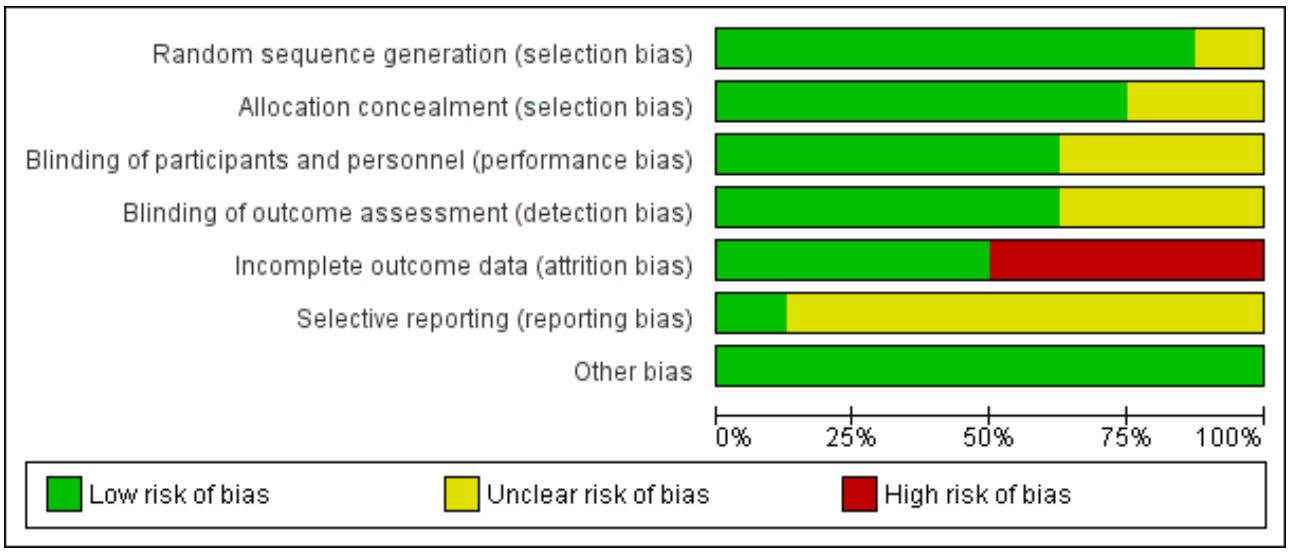
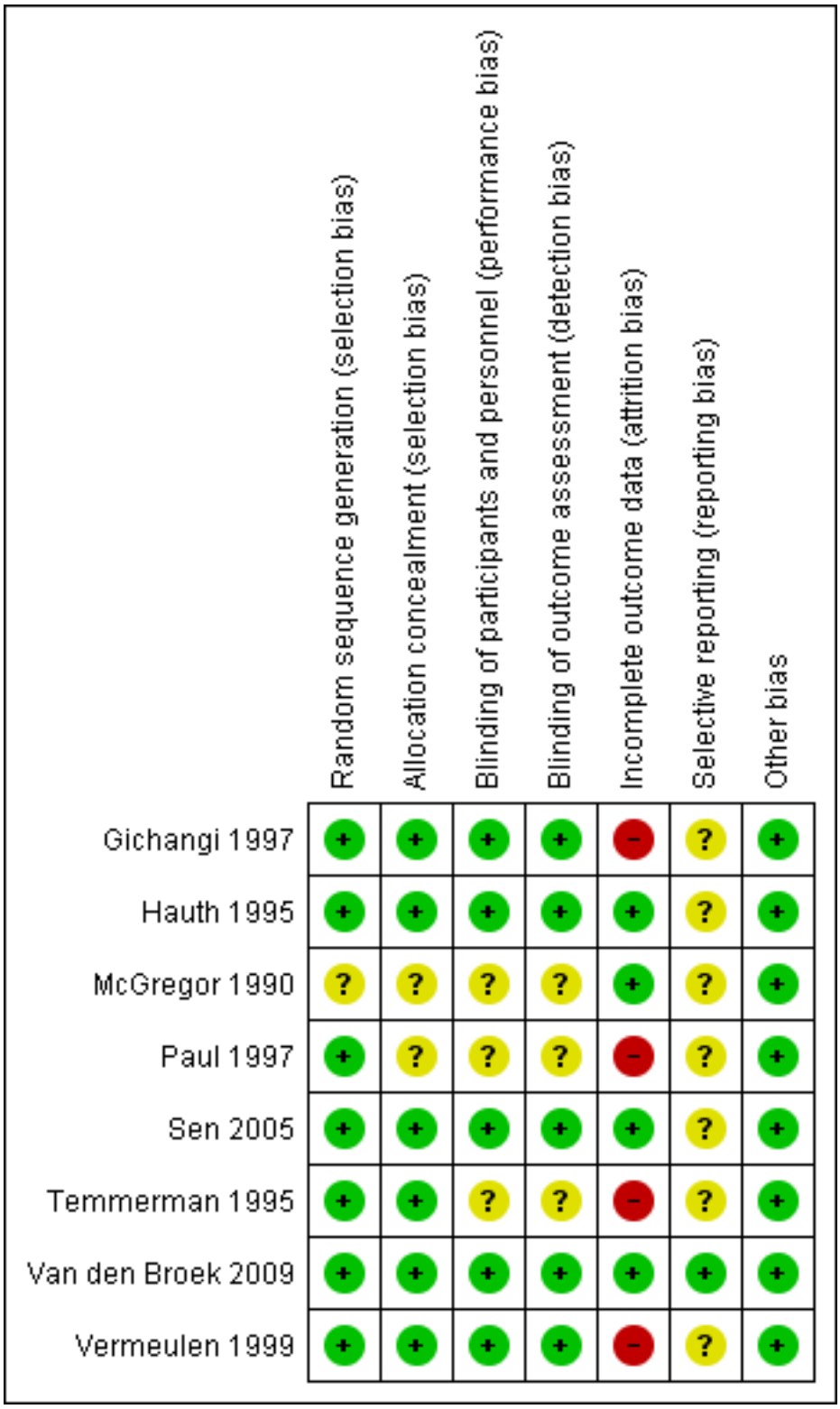


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



For the detailed information on methods, *see* Characteristics of included studies.

Allocation

The methodological quality of the trials based on selection bias (method of randomisation, allocation concealment) was mainly adequate. Only two studies had unclear allocation

concealment (McGregor 1990; Paul 1997) and one unclear methods of randomisation (McGregor 1990).

Blinding

Eight studies were described as being double-blind randomised trials, although three studies had no information on methods for blinding in the study reports (McGregor 1990; Paul 1997; Temmerman 1995). Outcome assessors were blind to treatment groups in five studies (Gichangi 1997; Hauth 1995; Sen 2005; Van den Broek 2009; Vermeulen 1999).

Incomplete outcome data

One study (Temmerman 1995) had a high drop-out rate (166 (41.5%) out of 400 women enrolled). The losses for some outcomes were higher than the figures given in the characteristics of included studies tables (Gichangi 1997; Temmerman 1995). This might have influenced the results. However, there was no evidence that these drop-outs occurred preferentially in one or the other arm of the trial. There were high drop-out rates in the other studies too (Gichangi 1997 21%; Paul 1997 22%; Vermeulen 1999 15.5%). These high loss rates might have the potential to introduce bias. Fours studies were assessed as low risk of bias, due to few drop-outs with reasons given (Hauth 1995; McGregor 1990; Sen 2005; Van den Broek 2009).

Selective reporting

We cannot assess reporting bias of most included studies since we did not have the studies' protocols in seven trials. Only one trial protocol was available online (Van den Broek 2009).

Other potential sources of bias

We did not identify any other potential sources of bias in the included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Prophylactic antibiotics versus placebo for preventing infectious morbidity and mortality

We included eight randomised controlled trials with a total of approximately 4300 women to evaluate the effect of prophylactic antibiotic administration in the second or third trimester on pregnancy outcomes. We found many studies on the topic of antibiotic use to prevent preterm delivery, but unlike the included studies, these studies focused on antibiotic treatment given after there was evidence of infection or complications of pregnancy; for example, detection of bacterial vaginosis (BV) or prelabour rupture of membranes before administration of antibiotics. These studies were therefore identified as trials of treatment and not prophylaxis. Publication of the included studies took place over more than 15 years (1990 to 2009). Three trials with a total of 1019 women (Gichangi 1997; Hauth 1995; Vermeulen 1999) enrolled only high-risk pregnant women. 'High risk' was defined as women who had a previous spontaneous preterm delivery, history of low birthweight, a diagnosis of BV in the current pregnancy (BV identified after enrolment and antibiotics used only for prophylaxis before knowing if the participant had BV or not). or a pre-pregnancy weight less than 50 kg. Seven studies used oral antibiotics: erythromycin alone (McGregor 1990; Paul 1997); erythromycin plus metronidazole (Hauth 1995); cefetamet-pivoxil (Gichangi 1997); or a combination of metronidazole and cephalexin (Sen 2005), and azithromycin (Van den Broek 2009). One study used ceftriaxone intramuscular injection (Temmerman 1995); and one used clindamycin vaginal cream application (Vermeulen 1999).

The subgroup analysis was conducted for outcomes of preterm delivery (Analysis 1.2), preterm delivery in all high-risk pregnancies (Analysis 1.3), puerperal sepsis (Analysis 1.4), low birthweight (Analysis 1.5), mean birthweight (Analysis 1.12), and perinatal mortality (Analysis 1.15).

The interaction was significant between the subgroups in preterm delivery in all high-risk pregnancies (P = 0.08) (Analysis 1.3), and low birthweight (P = 0.04) (Analysis 1.5). There was no significant interaction identified in the other analyses (Analysis 1.2; Analysis 1.4; Analysis 1.12; Analysis 1.15).

Prophylactic antibiotics versus placebo

Primary outcomes

Studies of antibiotic prophylaxis during the second or third trimester (ranging from 14 to 34 weeks of gestational age) in pregnant women reported the primary outcomes of interest as the following: preterm prelabour rupture of membranes, preterm delivery, postpartum endometritis, low birthweight and neonatal sepsis. Blood culture confirming sepsis was not reported in any of the studies.

Antibiotic prophylaxis did not reduce the risk of preterm prelabour rupture of membranes (average risk ratio (RR) 0.31; 95% confidence interval (CI) 0.06 to 1.49 (one trial, 229 women) Analysis 1.1) or preterm delivery (average RR 0.88; 95% CI 0.72 to 1.09 (six trials, 3663 women) Analysis 1.2 all women; average RR 0.97; 95% CI 0.82 to 1.15 (four trials, 2905 women) Analysis 1.2.1 unselected women). However, preterm delivery was reduced in the subgroup of pregnant women with a previous preterm birth who had BV during the current pregnancy (average RR 0.64, 95% CI 0.47 to 0.88; one trial, 258 women, subgroup differences P = 0.08; Analysis 1.3.1), but there was no reduction in the subgroup of pregnant women with previous preterm birth without BV during the pregnancy (average RR 1.08; 95% CI 0.66 to 1.77 (two trials, 500 women) Analysis 1.3,2), or in the whole group of high-risk women (average RR 0.89; 95% CI 0.58 to 1.36 (two trials, 758 women) Analysis 1.3), and a difference between these subgroups of high-risk women was observed (Test for subgroup differences: $Chi^2 = 3.11$, df = 1 (P = 0.08), $I^2 = 67.8\%$).

A reduction in the risk of postpartum endometritis (RR 0.55; 95% CI 0.33 to 0.92 (one trial, 196 women)) was observed in high-risk pregnant women (women with a history of preterm birth, low birthweight, stillbirth or early perinatal death) Analysis 1.4,2, and in all women (RR 0.53; 95% CI 0.35 to 0.82 (three trials, 627 women) Analysis 1.4), but not in unselected women (RR 0.51; 95% CI 0.24 to 1.08 (two trials, 431 women) Analysis 1.4.1. There was no difference in low birthweight in all women (average RR 0.86; 95% CI 0.53 to 1.39 (four trials; 978 women) (Analysis 1.5), or unselected pregnant women (average RR 1.07; 95% CI 0.71 to 1.63 (three trials; 725 women) Analysis 1.5.1, although a difference was observed in high-risk women (average RR 0.57; 95% CI 0.37 to 0.88 (one trial; 253 women) Analysis 1.5.2 and a difference in subgroups observed (Test for subgroup differences: $Chi^2 = 4.22$, df = 1 (P = 0.04), $I^2 = 76.3\%$). There was no difference in neonatal sepsis (RR 11.31; 95% CI 0.64 to 200.79) (one trial, 142 women) Analysis 1.6, and blood culture confirming sepsis was not reported in any of the studies.

Secondary outcomes

A reduction was observed in preterm rupture of membranes (RR 0.34; 95% CI 0.15 to 0.78; one trial; 229 women; Analysis 1.7) and gonococcal infection (postpartum detected) (RR 0.35, 95% CI 0.13 to 0.94; one trial; 204 women; Analysis 1.9) in the group of women who received antibiotic prophylaxis. Other secondary outcomes did not show any significant effects (chorioamnionitis; compliance; mean gestational age; mean birthweight; congenital abnormality; small-for-gestational age; perinatal mortality). The included studies did not report any serious adverse effects of antibiotic prophylaxis, and no data were reported on some maternal outcomes that we had planned to assess, including intrapartum fever requiring treatment with antibiotics, serious maternal complications (puerperal infection requiring laparotomy for infection or hysterectomy; death), maternal side effects, duration of hospital stay and satisfaction with care. We observed a lack of data to assess congenital abnormality and perinatal mortality. We also found limited data to evaluate the effect of antibiotics on low birthweight in unselected women. There were four trials in this analysis: three reported on an unselected population and the other reported in a high-risk group, which had effects in opposite directions. We found no data on the following neonatal outcomes: admission to neonatal intensive care unit; ophthalmia neonatorum; and abnormal neurological development.

There was only one included study (Vermeulen 1999) that used vaginal application for antibiotic prophylaxis. It did not prevent infectious morbidity outcomes in terms of preterm delivery (average RR 1.47; 95% CI 0.81 to 2.67; 142 women) Analysis 1.2.4 and neonatal sepsis (RR 11.31; 95% CI 0.64 to 200.79; 142 women) Analysis 1.6.2.

One study (McGregor 1990) reported that compliance with medication was different between groups (73% in the treatment group versus 84% in the control group). In this trial, the treatment and control group received treatment bottles that looked identical, but which contained either an erythromycin base tablet or a placebo.

DISCUSSION

Summary of main results

The results of this review showed that antibiotic prophylaxis during the second or third trimester of pregnancy was effective in reducing risk of preterm delivery in pregnant women with bacterial vaginosis (BV) in the current pregnancy, prelabour rupture of membranes, postpartum endometritis and gonococcal infection (detected postpartum). However, some analyses are based on studies with high risk of bias or only one trial. Limited data showed that routine use of antibiotics during pregnancy might prevent infectious morbidity for the mother, but could not reduce neonatal morbidity and mortality. We could not estimate the side effects of prophylactic antibiotics from these data, since side effects from prophylactic antibiotics are rare events.

Overall completeness and applicability of evidence

None of the included studies reported on preterm labour, serious maternal complications of puerperal infection requiring laparotomy, maternal side effects of antibiotic prophylaxis (severe side effect), duration of hospitalisation, satisfaction with care, blood culture confirming neonatal sepsis or opthalmia neonatorum. However, these outcomes are not the outcomes we expected when evaluating the effectiveness of the intervention. Some included studies reported the expected outcomes, such as preterm delivery, preterm prelabour rupture of membranes, prelabour rupture of membranes, chorioamnionitis, puerperal sepsis, postpartum endometritis, mean gestational age, low birthweight, admission to neonatal intensive care unit and perinatal mortality. Nevertheless, the power of the available studies is inadequate to provide conclusions about some rare but serious outcomes such as chorioamnionitis, intrapartum fever requiring antibiotic treatment, neonatal sepsis, admission to the intensive neonatal care unit and perinatal mortality. However, an ongoing study (Hoffman 2013) plans to enrol 1726 women which, once completed, might add more power to the assessment of these rare outcomes.

Quality of the evidence

Overall, the methodological quality of the included trials was satisfactory. Of the eight trials included, six described methods which were at low risk for selection bias, five were at low risk for performance bias, and four had low risk of incomplete outcome data. However, some outcomes of interest were only available in trials with high risk of incomplete outcome data and high rate of loss to follow-up. Furthermore, most outcomes of interest were found in only one to two studies, meaning that the sample size might not be large enough to demonstrate key differences.

The rate of loss to follow-up in the included studies was quite high (20% to 40%), especially for studies that reported on puerperal sepsis/postpartum endometritis. Since puerperal sepsis/postpartum endometritis had the significant beneficial effect of antibiotic prophylaxis administration during pregnancy, we are reluctant to recommend the use of this intervention due to this potential bias.

The quality of the evidence as assessed using GRADE was moderate for postpartum endometritis, and was downgraded due to a small sample size in one study. After including Van den Broek 2009 trial, the quality of evidence for preterm delivery was upgraded to high quality. Low-quality evidence was also observed for preterm prelabour rupture of membranes, and prelabour rupture of membranes due to small sample size, wide confidence intervals crossing the line of no effect, and the design limitations of one study. Very low quality of evidence was also found for chorioamnionitis due to the design limitations of one study, few events and small sample size and wide confidence intervals crossing the line of no effect. (Summary of findings for the main comparison).

Potential biases in the review process

Our search strategy was supported by the Pregnancy and Childbirth Review Group**.** All review authors contributed to assessing the appropriateness of inclusion or exclusion of studies, so potential bias in the review process is unlikely.

Agreements and disagreements with other studies or reviews

Most outcomes of interest in this review revealed no evidence of effectiveness of the intervention, with the same direction of effect as individual studies. However, those outcome assessments were

available in only one or two studies. Of the outcomes of interest that revealed evidence of effectiveness (preterm delivery in pregnant women with BV in the current pregnancy, prelabour rupture of membranes, postpartum endometritis and postpartum detection of gonococcal infection), only postpartum endometritis had three included studies relevant to our analysis, while two of these three individual studies showed no significant effectiveness.

AUTHORS' CONCLUSIONS

Implications for practice

Routine use of antibiotic prophylaxis in pregnant women during the second and third trimester could prevent maternal infectious morbidity by reducing postpartum endometritis. We observed risk reduction in preterm delivery only in pregnant women with bacterial vaginosis (BV) during the current pregnancy, but there was a lack of evidence showing any benefits for neonatal morbidity and mortality. We also noted a possible substantial bias in the review's results due to a high rate of loss to follow-up. The evidence is not strong enough to support routine use of antibiotics in the second and third trimester to prevent infectious complications.

Implications for research

The results of this review suggest that antibiotic prophylaxis might only be effective in reducing maternal puerperal infection. Due to limited data, we could not evaluate any benefits for neonatal morbidity and mortality. In addition, data were lacking on some health outcomes such as short- and long-term effects on children. Therefore, there is a need for further studies to address these missing gaps in the evidence.

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As part of the pre-publication editorial process, this review update has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser (previous update, Thinkhamrop 2015a).

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REFERENCES

References to studies included in this review

Gichangi 1997 *{published data only}*

Gichangi PB, Ndinya-Achola JO, Ombete J, Nagelkerke NJ, Temmerman M. Antimicrobial prophylaxis in pregnancy: a randomized placebo-controlled trial with cefetamet-pivoxil in pregnant women with a poor obstetric history. *American Journal of Obstetrics and Gynecology* 1997;**177**:680-4.

Hauth 1995 *{published data only}*

Hauth JC, Goldenberg LR, Andrews WW, DuBard MB, Copper RL. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *New England Journal of Medicine* 1995;**333**:1732-6.

McGregor 1990 *{published data only}*

McGregor JA, French JI, Richter R, Vuchetich M, Bachus V, Franco-Buff A, et al. Prospective, double-blinded, randomized, placebo-controlled trial of short-course erythromycin (E) base in women at high risk for preterm birth. Proceedings of the Society for Gynecologic Investigation; 1988. 1988.

* McGregor JA, French JI, Richter R, Vuchetich M, Bachus V, Seo K, et al. Cervicovaginal microflora and pregnancy outcome: results of a double-blind, placebo-controlled trial of erythromycin treatment. *American Journal of Obstetrics and Gynecology* 1990;**163**:1580-91.

Paul 1997 *{published data only}*

Paul VK, Singh M, Buckshee K. Erythromycin treatment of pregnant women to reduce the incidence of low birth weight and preterm deliveries. *International Journal of Gynecology & Obstetrics* 1998;**62**:87-8.

Sen 2005 *{published data only}*

Sen A, Mahalanabis D, Mukhopadhyay S, Chakrabarty K, Singh AK, Bisai S, et al. Routine use of antimicrobials by pregnant Indian women does not improve birth outcome: a randomized controlled trial. *Journal of Health, Population & Nutrition* 2005;**23**(3):236-44.

Temmerman 1995 *{published data only}*

Temmerman M, Njagi E, Nagelkerke N, Ndinya-Achola J, Plummer FA, Meheus A. Mass antimicrobial treatment in pregnancy, a randomized, placebo-controlled trial in a population with high rates of sexually transmitted diseases. *Journal of Reproductive Medicine* 1995;**40**:176-80.

Van den Broek 2009 *{published data only}*

van den Broek NR, White SA, Goodall M, Ntonya C, Kayira E, Kafulafula G, et al. The APPLe study: a randomized, community-based, placebo-controlled trial of azithromycin for the prevention of preterm birth, with meta-analysis. *PLoS Medicine* 2009;**6**(12):e1000191.

Vermeulen 1999 *{published data only}*

Vermeulen GM, Bruinse HW. Prophylactic administration of clindamycin 2% vaginal cream to reduce the incidence of spontaneous preterm birth in women with an increased recurrence risk: a randomised placebo-controlled double-blind trial. *British Journal of Obstetrics and Gynaecology* 1999;**106**:652-7.

References to studies excluded from this review

Andrews 2003 *{published data only}*

* Anderson B, Zhao Y, Andrews WW, Dudley DJ, Sibai B, Iams JD, et al. Effect of antibiotic exposure on Nugent score among pregnant women with and without bacterial vaginosis. *Obstetrics & Gynecology* 2011;**117**(4):844-9.

Andrews WW, Sibai BM, Thom EA, Dudley D, Ernest JM, McNellis D, et al. Randomized clinical trial of metronidazole plus erythromycin to prevent spontaneous preterm delivery in fetal fibronectin-positive women. *Obstetrics & Gynecology* 2003;**101**(5 Pt 1):847-55.

Hendler I, Andrews WW, Carey CJ, Klebanoff MA, Noble WD, Sibai BM, et al. The relationship between resolution of asymptomatic bacterial vaginosis and spontaneous preterm birth in fetal fibronectin-positive women. *American Journal of Obstetrics and Gynecology* 2007;**197**(5):488.e1-488.e5.

Lin M, for the NICHD MFMU Network. Impact of quantitative fetal fibronectin (FFN) change of efficacy of antibiotic vs. placebo treatment of asymptomatic FFN positive women to prevent subsequent preterm birth [abstract]. *American Journal of Obstetrics and Gynecology* 2005;**193**(6 Suppl):S56.

Ramsey P. Relationship of midtrimester fetal fibronectin (FFN) concentration to antibiotic efficacy for the prevention of spontaneous preterm birth in asymptomatic FFN positive women [abstract]. *American Journal of Obstetrics and Gynecology* 2004;**191**(6 Suppl 1):S11.

Andrews 2006 *{published data only}*

Andrews W, Goldenberg R, Hauth J, Cliver S. Interconceptional antibiotics to prevent spontaneous preterm birth (SPTB): a randomized trial [abstract]. *American Journal of Obstetrics and Gynecology* 2003;**189**(6 Suppl 1):s57.

* Andrews WW, Goldenberg RL, Hauth JC, Cliver SP, Copper R, Conner M. Interconceptional antibiotics to prevent spontaneous preterm birth: a randomized clinical trial. *American Journal of Obstetrics and Gynecology* 2006;**194**(3):617-23.

Tita A, Cliver S, Goepfert A, Goldenberg R, Conner M, Andrews W. Impact of interconceptional antibiotics on the "endometrial flora". *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1):S17.

Tita A, Cliver S, Goepfert A, Goldenberg R, Conner M, Andrews W. Interconceptional antibiotics and preterm delivery: subgroup analyses. *American Journal of Obstetrics and Gynecology* 2006;**195**(6 Suppl 1):S76.

Tita AT, Cliver SP, Goepfert AR, Conner M, Goldenberg RL, Hauth JC, et al. Impact of interconception antibiotics on the endometrial microbial flora. *American Journal of Obstetrics and Gynecology* 2007;**196**(3):226.e1-226.e6.

Tita AT, Cliver SP, Goepfert AR, Conner M, Goldenberg RL, Hauth JC, et al. Clinical trial of interconceptional antibiotics to prevent preterm birth: subgroup analyses and possible adverse antibiotic-microbial interaction. *American Journal of Obstetrics and Gynecology* 2007;**197**(4):367.e1-6.

Audebert 1989 *{published data only}*

Audebert AJM. Use of polygynax in pregnant women for preventing cervico-vaginal infections. *Revue Francaise de Gynecologie et d Obstetrique* 1989;**84**:287-90.

Goldenberg 2006 *{published data only}*

Aboud S, Msamanga G, Read JS, Wang L, Mfalila C, Sharma U, et al. Effect of prenatal and perinatal antibiotics on maternal health in Malawi, Tanzania, and Zambia. *International Journal of Gynecology & Obstetrics* 2009;**107**(3):202-7.

Goldenberg R, Andrews W, Taha T, Fawzi W, Brown E. HIVNET 024: fetal fibronectin (FFN), preterm birth (PTB) and mother to child transmission of HIV (MTCT) in African women with HIV [abstract]. *American Journal of Obstetrics and Gynecology* 2005;**193**(6 Suppl):S52.

Goldenberg R, Mudenda V, Brown E, Taha T, Kaaya E. HIVNET 024: neutrophilic and mononuclear placental infiltration, antibiotics and outcome in an African population [abstract]. *American Journal of Obstetrics and Gynecology* 2005;**193**(6 Suppl):S188.

Goldenberg R, Taha T, Hoffman I, Fawzi W, Mwatha A. HPTN 024: antibiotics do not prevent preterm birth (PTB) in an HIV-infected African population [abstract]. *American Journal of Obstetrics and Gynecology* 2005;**193**(6 Suppl):S3.

* Goldenberg RL, Mudenda V, Read JS, Brown ER, Sinkala M, Kamiza S, et al. HPTN 024 study: histologic chorioamnionitis, antibiotics and adverse infant outcomes in a predominantly HIV-1-infected African population. *American Journal of Obstetrics & Gynecology* 2006;**195**(4):1065-74.

Goldenberg RL, Mwatha A, Read JS, Adeniyi-Jones S, Sinkala M, Msmanga G, et al. The HPTN 024 study: the efficacy of antibiotics to prevent chorioamnionitis and preterm birth. *American Journal of Obstetrics and Gynecology* 2006;**194**(3):650-61.

Kafulafula G, Mwatha A, Chen YQ, Aboud S, Martinson F, Hoffman I, et al. Intrapartum antibiotic exposure and early neonatal, morbidity, and mortality in Africa. *Pediatrics* 2009;**124**(1):e137-44.

Stringer E, Read JS, Hoffman I, Valentine M, Aboud S, Goldenberg RL. Treatment of trichomoniasis in pregnancy in sub-Saharan Africa does not appear to be associated with low birth weight or preterm birth. *South African Medical Journal* 2010;**100**(1):58-64.

Taha TE, Brown ER, Hoffman IF, Fawzi W, Read JS, Sinkala M, et al. A phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission. *AIDS* 2006;**20**(9):1313-21.

Gray 2001 *{published data only}*

* Gray RH, Wabwire-Mangen F, Kigozi G, Sewankambo NK, Serwadda D, Moulton LH, et al. Randomized trial of presumptive sexually transmitted disease therapy during pregnancy in Rakai, Uganda. *American Journal of Obstetrics & Gynecology* 2001;**185**:1209-17.

Kigozi GG, Brahmbhatt H, Wabwire-Mangen F, Wawer MJ, Serwadda D, Sewankambo N, et al. Treatment of trichomonas in pregnancy and adverse outcomes of pregnancy: a subanalysis of a randomized trial in Rakai, Uganda. *American Journal of Obstetrics and Gynecology* 2003;**189**:1398-400.

Larsson 2006 *{published data only}*

Larsson PG, Fahraeus L, Carlsson B, Jakobsson T, Forsum U, the premature study group of the southeast health care region of Sweden. Late miscarriage and preterm birth after treatment with clindamycin: a randomised consent design study according to Zelen. *BJOG: an international journal of obstetrics and gynaecology* 2006;**113**(6):629-37.

Luntamo 2010 *{published data only}*

Ashorn P. Gestational sulfadoxine-pyrimethamine and azithromycin treatment to prevent preterm birth (ongoing trial). ClinicalTrials.gov (http://clinicaltrials.gov/) (accessed 21 March 2006) 2006.

Luntamo M, Kulmala T, Cheung YB, Maleta K, Ashorn P. The effect of antenatal monthly sulphadoxine-pyrimethamine, alone or with azithromycin, on foetal and neonatal growth faltering in Malawi: a randomised controlled trial. *Tropical Medicine & International Health* 2013;**18**(4):386-97.

* Luntamo M, Kulmala T, Mbewe B, Cheung YB, Maleta K, Ashorn P. Effect of repeated treatment of pregnant women with sulfadoxine- pyrimethamine and azithromycin on preterm delivery in Malawi: a randomized controlled trial. *American Journal of Tropical Medicine and Hygiene* 2010;**83**(6):1212-20.

Peters 1995 *{published data only}*

Peter MT, Brown CEL, Buam A, Risser R. Randomized, double-blind, placebo-controlled trial of amoxycillin/clavulanic acid to prevent preterm delivery in twin gestation. *Infectious Diseases in Obstetrics and Gynecology* 1995;**3**:158-63.

Shennan 2006 *{published data only}*

Kurtzman J, Chandiramani M, Briley A, Poston L, Shennan A. Minimal quantitative levels of fetal fibronectin (1-49 NG/ML) at 24-27 weeks are associated with an increased risk of recurrent preterm delivery in asymptomatic patients with prior preterm birth. *American Journal of Obstetrics and Gynecology* 2008;**199**(6 Suppl 1):S47.

Kurtzman J, Chandiramani M, Briley A, Poston L, Shennan A. Quantitative fetal fibronectin screening at 24 weeks substantially discriminates the risk of recurrent preterm delivery in asymptomatic patients with prior preterm birth. *American Journal of Obstetrics and Gynecology* 2008;**199**(6 Suppl 1):S10.

* Shennan A, Crawshaw S, Briley A, Hawken J, Seed P, Jones G, et al. A randomised controlled trial of metronidazole

for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET study. *BJOG: an international journal of obstetrics and gynaecology* 2006;**113**(1):65-74.

Thompson C. Taken before their time. *Nursing Times* 2002;**98**(3):29.

Tripathi 2008 *{published data only}*

Gupta S, Tripathi R, Singh N, Bhalla P, Ramji S, Mala YM. Pregnancy outcome in asymptomatic women with abnormal vaginal flora without any treatment and after treatment with vaginal clindamycin and clotrimazole: a randomised controlled trial. *South African Journal of Obstetrics and Gynaecology* 2013;**19**(2):35-8.

* Tripathi R, Gupta S, Bhalla P, Mala YM, Tyagi S, Ramji S. Maternal and fetal outcome in patients with abnormal vaginal flora after treatment with vaginal clindamycin in early pregnancy. *BJOG: an international journal of obstetrics and gynaecology* 2008;**115**(s1):161.

Unger 2015 *{published data only}*

Rathjen P. Intermittent preventive treatment with azithromycin-containing regimens in pregnant women in Papua New Guinea (IPTp in PNG). ClinicalTrials.gov (http://clinicaltrials.gov) [accessed April 2013) 2010.

* Unger HW, Ome-Kaius M, Wangnapi RA, Umbers AJ, Hanieh S, Suen CS, et al. Sulphadoxine-pyrimethamine plus azithromycin for the prevention of low birthweight in Papua New Guinea: a randomised controlled trial. *BMC Medicine* 2015;**13**(1):9.

References to ongoing studies

Hoffman 2013 *{published data only}*

Hoffman M. Clindamycin to reduce preterm birth in a low resource setting. ClinicalTrials.gov (accessed 21 May 2013) 2013.

Additional references

Ashorn 2006

Ashorn P. Gestational sulfadoxine-pyrimethamine and azithromycin treatment to prevent preterm birth (ongoing trial). ClinicalTrials.gov (http://clinicaltrials.gov/) (accessed 21 March 2006) 2006.

Braun 1971

Braun P, Lee Y, Klein JO, Marcy M, Klein TA, Charles D. Birth weight and genital mycoplasma in pregnancy. *New England Journal of Medicine* 1971;**284**:167-74.

Cunningham 1997

Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC, Hankins GDV, et al. Williams Obstetrics. 20th Edition. Norwalk, CT: Appleton & Lange, 1997.

Eschenbach 1991

Eschenbach DA, Nugent RP, Rao VA, Cotch MF, Gibbs RS, Lipscomb KA, et al. A randomized placebo controlled trial of erythromycin for the treatment of ureaplasma urealyticum in preventing premature delivery. *American Journal of Obstetrics and Gynecology* 1991;**164**:734-42.

GRADEpro 2014 [Computer program]

McMaster University. GRADEpro. [Computer program on www.gradepro.org]. Version 2014. McMaster University, 2014.

Gravett 1986

Gravett MG, Nelson HP, DeRouen T, Critchlow C, Eschenbach DA, Holmes KK. Independent associations of bacterial vaginosis and chlamydia trachomatis infection with adverse pregnancy outcome. *JAMA* 1986;**256**:1899-905.

Hardy 1984

Hardy PH, Nell EE, Spence MR, Hardy JB, Graham DA, Rosenbaum RC. Prevalence of six sexually transmitted disease agents among pregnant innercity adolescents and pregnancy outcome. *Lancet* 1984;**8**:333-7.

Higgins 2011

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hillier 1995

Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, et al. Association between bacterial vaginosis and preterm delivery of low-birth weight infant. *New England Journal of Medicine* 1995;**333**:1737-42.

Kenyon 2008

Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. *Lancet* 2008;**372**(9646):1319-27.

Kurtzman 2008

Kurtzman J, Chandiramani M, Briley A, Poston L, Shennan A. Quantitative fetal fibronectin screening at 24 weeks substantially discriminates the risk of recurrent preterm delivery in asymptomatic patients with prior preterm birth. *American Journal of Obstetrics and Gynecology* 2008;**199**(6 Suppl 1):S10.

Lettieri 1993

Lettieri L, Vintzileos AM, Rodis JF, Albini SM, Saladia CM. Does idiopathic preterm labor resulting in preterm birth exist?. *American Journal of Obstetrics and Gynecology* 1993;**168**:1480-5.

Lin 2005

Lin M, for the NICHD MFMU Network. Impact of quantitative fetal fibronectin (FFN) change of efficacy of antibiotic vs. placebo treatment of asymptomatic FFN positive women to prevent subsequent preterm birth [abstract]. *American Journal of Obstetrics and Gynecology* 2005;**193**(6 Suppl):S56.

McCormack 1987

McCormack WM, Rosner B, Lee YH, Munoz A, Kass CD. Effect on birth weight of erythromycin in treatment of pregnant women. *Obstetrics & Gynecology* 1987;**69**:202-7.

Morales 1994

Morales JW, Schorr S, Albritton J. Effect of metronidazole in patients with preterm birth in preceding pregnancy and bacterial vaginosis: a placebo controlled double blind study. *Obstetrics & Gynecology* 1994;**171**:345-9.

Newton 1989

Newton ER, Dinsmoor MJ, Gibbs RS. A randomised blinded placebo controlled trial of antibiotics in idiopathic preterm labour. *Obstetrics & Gynecology* 1989;**74**:562-6.

Oleszczuk 2000

Oleszczuk JJ, Keith LG. Vaginal infection: prophylaxis and perinatal outcome-a review of the literature. *International Journal of Fertility* 2000;**45**(6):358-67.

Rathjen 2010

Rathjen P. Intermittent preventive treatment with azithromycin-containing regimens in pregnant women in Papua New Guinea (IPTp in PNG). ClinicalTrials.gov (http://clinicaltrials.gov) [accessed April 2013) 2010.

Regan 1981

Regan JA, Chao S, James SL. Premature rupture of membranes, preterm delivery, and group B streptococcal colonization of mothers. *American Journal of Obstetrics and Gynecology* 1981;**141**:184-6.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Romero 1988

Romero R, Mazor M. Infection and preterm labor. *Clinical Obstetrics and Gynecology* 1988;**31**:553-83.

Romero 1993

Romero R, Sibai B, Caritis S, Paul R, Depp R, Rosen M, et al. Antibiotic treatment of preterm labour with intact membranes: a multicenter randomised double blinded controlled trial. *American Journal of Obstetrics and Gynecology* 1993;**169**:764-74.

Schunemann 2009

Schunemann HJ. GRADE: from grading the evidence to developing recommendations. A description of the system and a proposal regarding the transferability of the results of clinical research to clinical practice [GRADE: Von der Evidenz zur Empfehlung. Beschreibung des Systems und Losungsbeitrag zur Ubertragbarkeit von Studienergebnissen]. *Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen* 2009;**103**(6):391-400.

References to other published versions of this review

Thinkhamrop 2002

Thinkhamrop J, Hofmeyr GJ, Adetoro O, Lumbiganon P. Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality. *Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD002250]

Thinkhamrop 2015a

Thinkhamrop J, Hofmeyer GJ, Adetoro O, Lumbiganon P, Ota E. Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity. *Cochrane Database of Systematic Reviews* 2015, Issue 1. [DOI: 10.1002/14651858.CD002250.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Gichangi 1997

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	320 pregnant women during GA 28 to 32 wks with a history of LBW (less than 2500 g), stillbirth or early perinatal death. (High risk.)
Interventions	Treatment group received a single dose of 2 g cefetamet-pivoxil and the control group received a placebo. There was no information on the appearance of the placebo tablet.
Outcomes	A total of 253 of 320 women delivered in the study centre. Out of these 253 women, there were 134 in the treatment group and 119 in the placebo group. The mean birthweight in the treatment group was higher than in the placebo group.
Notes	Nairobi, Kenya and Ghent, Belgium. November 1995 to February 1996. 83% of the treatment group and 74% of the placebo group delivered at the study centre, the rest were delivered elsewhere and could not be traced for follow-up.

Gichangi 1997 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The authors mentioned that they use randomised allocation.
Allocation concealment (selection bias)	Low risk	The patients were randomised by means of sealed envelopes into either the intervention group or placebo group.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women were enrolled by one investigator who was blinded to the study medication, and the women received a single oral dose of 2 g of cefetamet-pivoxil or a placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The persons who assessed the outcomes did not know to which group the women were assigned.
Incomplete outcome data (attrition bias) All outcomes	High risk	83% of the treatment group and 74% of the placebo group delivered at the study centre, the rest delivered elsewhere and could not be traced for follow-up.
Selective reporting (reporting bias)	Unclear risk	Unknown.
Other bias	Low risk	None.

Hauth 1995

Methods	A 2:1 double-blind, randomised, placebo-controlled trial.
Participants	The study randomised 624 pregnant women during GA 22 to 24 weeks, who were at risk of preterm delivery due to having had a previous preterm delivery or a pre-pregnancy weight of less than 50 kg. 433 were in the treatment group and 191 were in the placebo group. (High risk.)
Interventions	The treatment group were given 250 mg metronidazole 3 times a day for 7 days, and erythromycin 333 mg 3 times a day for 14 days, while an identical preparation containing lactose was given to the placebo group.
Outcomes	26% of the trial group delivered preterm, as compared with 68% of the placebo group.
Notes	Birmingham, Alabama. May 1989 to December 1993. 8 participants were lost to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was used for allocation.
Allocation concealment (selection bias)	Low risk	Our Investigational Drug Service generated a blocked randomisation scheme in a ratio of 2:1 (i.e., 2 women were assigned to the study treatment for every 1 woman assigned to placebo), with blocks of randomly chosen sizes. At 22

Hauth 1995 *(Continued)*

		to 24 weeks' gestation (mean, 22.9), each woman was assigned to take either metronidazole (250 mg 3 times a day for 7 days) and erythromycin base (333 mg 3 times a day for 14 days) or an identical-appearing placebo containing a lactose filler.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All the women were seen every 2 weeks for antepartum care by the same nursing team, and the importance of adherence to treatment was emphasised. Pills were counted at each visit, and each woman kept a log of medications. If a woman's compliance was less than 80%, she was counselled again about the importance of taking the pills. All follow-up visits were scheduled for the same day of the week, but women who presented at unscheduled times still received care from the same nursing team. Patients who missed their regular clinic visits were called on the telephone and seen at the next convenient time.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessment was a hard outcome (delivery before 37 weeks).
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 of 624 pregnant women were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Unknown.
Other bias	Low risk	None.

McGregor 1990

Methods	Double-blind, placebo-controlled trial.
Participants	235 pregnant women during GA 26 to 30 weeks. (Unselected pregnant women.)
Interventions	They were given identical prepared bottles and tablets that were either erythromycin base 333 mg or placebo taking 1 tablet 3 times a day for 1 week.
Outcomes	229 of 235 women were analysed. Prelabour rupture of membranes occurred less frequently (P < 0.01) among women who received erythromycin (6%) versus placebo (16%).
Notes	Denver, Colorado and Seattle, Washington. October 1985 to August 1988. 4 participants were lost to follow-up. Only 73% of women randomised to receive erythromycin, and 84% of women who receive placebo completed 4 or more days of study treatment (P = 0.04)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	There was no information about randomisation in the article.
Allocation concealment (selection bias)	Unclear risk	There was no information about allocation concealment.

McGregor 1990 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There was no information about blinding to the participant and attending physicians.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was no information about blinding to whom assess the outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 of 235 participants were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Unknown.
Other bias	Low risk	None.

Paul 1997

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	437 pregnant women during gestational age 26 to 34 weeks. (Unselected pregnant women.)
Interventions	The treatment group received erythromycin sterate 500 mg and placebo (no description of placebo tablet) in the control group twice a day for 6 wks.
Outcomes	Of the 437 women enrolled in the trial, 219 were in the erythromycin group and 218 in the placebo group. There were no differences in their mean birthweight, incidence of LBW or incidence of preterm delivery in the treatment and control groups.
Notes	29 participants were lost to follow-up. 66 participants dropped out with a specified reason.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The participants were randomised to receive tablets of either erythromycin stearate 500 mg or placebo twice a day.
Allocation concealment (selection bias)	Unclear risk	Not mentioned in the trial report.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in the trial report.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned in the trial report.
Incomplete outcome data (attrition bias)	High risk	Of the 437 participants, 29 participants were lost to follow-up. 66 participants dropped out with a specified reason.

Paul 1997 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Unknown.
Other bias	Low risk	None.

Sen 2005

Methods	A non-placebo, randomised controlled trial.
Participants	224 pregnant women in their second trimester (between 14 and 24 weeks) were recruited during February to July 2001.
Interventions	Women in the intervention group were treated with a course of antimicrobials and provided with iron-folic acid tablets and women in the control group received iron-folic acid tablets only. A combination of metronidazole and cephalexin was used for antimicrobial therapy.
Outcomes	112 women in the intervention group and 112 women in the control group were analysed to assess the pregnancy outcomes.
Notes	Only 170 of the total 224 enrolled women were analysed. The study was conducted among pregnant women attending the antenatal clinic of a government hospital in Kolkata, India, that serves the urban poor.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised into intervention and control groups.
Allocation concealment (selection bias)	Low risk	Allocation to treatment or control according to the randomisation was sealed in serial-numbered envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physicians who evaluated the women and their babies were blinded to the treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physicians who evaluated the women and their babies were blinded to the treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 224 participants, 112 women were allocated to the intervention group and 112 women to the control group. Only 89 participants in the intervention group and 81 in the control group were analysed to assess pregnancy outcomes.
Selective reporting (reporting bias)	Unclear risk	Unknown.
Other bias	Low risk	None.

Temmerman 1995

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	400 pregnant women during GA 28 to 32 wks. (Unselected pregnant women.)
Interventions	Single dose of 250 mg ceftriaxone IM versus placebo 3.5 mL 0.9% NaCl IM.
Outcomes	Mean birthweight in the ceftriaxone group 153 g higher than in the placebo group, i.e. 3209 versus 3056 (P = 0.01).
Notes	Nairobi, Kenya. 60% of the treatment group and 57% of the placebo group were delivered at the study centre; the rest were delivered elsewhere. 166 participants were lost to follow-up.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised by means of sealed envelopes into treatment and control groups.
Allocation concealment (selection bias)	Low risk	Patients were randomised by means of sealed envelopes into treatment and control groups.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned in the trial report.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned in the trial report.
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 400 participants, 60% of the treatment group and 57% of the placebo group delivered at the study centre; the rest delivered elsewhere. 166 participants were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Unknown.
Other bias	Low risk	None.

Van den Broek 2009

Methods	A randomised controlled trial.
Participants	Pregnant women, gestational age less than 24 weeks, in three rural and one peri-urban antenatal clinic in Southern Malawi.
Interventions	Recruited women were randomly allocated to receive either 1g azithromycin or placebo at both 16-24 and 28-32 wks. of gestation. All women received iron tablets daily 60 mg + 0.25 mg folic acid and antimalarial prophylaxis (two doses of Fansidar: 500 mg sulphadoxine with 25 mg phrimethamine).

Van den Broek 2009 *(Continued)*

Outcomes	Preterm delivery, mean gestational age at delivery, mean birthweight, perinatal mortality, maternal malaria and anaemia.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation schedule was prepared by a statistician not involved in the trial analysis using a random generation procedure with variable block size to assign to treatments equally within each block of consecutive numbers.
Allocation concealment (selection bias)	Low risk	The azithromycin and placebo treatments allocated were provided in identical capsules and packed in pairs of sealed envelopes for each individual study number, according to the randomised schedule, by staff who were not involved in the conduct of the trial. The randomisation schedule was placed in sealed envelopes and not disclosed to anyone involved in the trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participant and the midwives who allocated the random numbers were blinded to the study assignment. At no time during the study was there cause to unblind the treatment allocation for any of the participants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study staff were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: intervention group 1096 (95.4%); control group 1087 (94.7%). Both groups balanced and few drop-outs with reasons.
Selective reporting (reporting bias)	Low risk	Trial protocol was available online at doi: 10.1371/journal.pmed.1000191.s001
Other bias	Low risk	None known.

Vermeulen 1999

Methods	Randomised, double-blind, placebo-controlled trial.
Participants	168 pregnant women during GA 26 to 32 wks with a history of preterm delivery in the preceding pregnancy (high risk).
Interventions	Clindamycin 2% vaginal cream, or placebo (identical-looking cream), applied daily for 7 days.
Outcomes	142 of 168 enrolled women were analysed. No difference was found in overall preterm birth between the treatment and the control groups.
Notes	12 hospitals in The Netherlands January 1, 1994 to December 31, 1996. The lost to follow-up rate, or incomplete medication taken, was 13 out of 83 in the treatment group and 13 out of 85 in the placebo group.

Risk of bias

Vermeulen 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed in blocks of 4 and was stratified by centre and by bacterial vaginosis.
Allocation concealment (selection bias)	Low risk	A research co-ordinator allocated medication or placebo using a pre-determined randomisation list so that care providers were blinded to medication and the presence of bacterial vaginosis.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participating women collected their medication at the pharmaceutical department of each hospital. The medication, or an identical looking placebo, had to be applied for seven days intravaginally at 26 and 32 weeks of gestation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The care providers were blinded to medication and the presence of bacterial vaginosis.
Incomplete outcome data (attrition bias) All outcomes	High risk	The lost to follow-up rate or incomplete medication taken was 13 out of 83 in the treatment group and 13 out of 85 in the placebo group.
Selective reporting (reporting bias)	Unclear risk	Unknown.
Other bias	Low risk	None.

GA: gestational age
IM: intramuscular
LBW: low birthweight
NaCl: sodium chloride
wks: weeks

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andrews 2003	The study included pregnant women with positive fetal fibronectin. The authors mentioned in the study's objective that they planned to estimate the antibiotic treatment effects in asymptomatic women with a positive cervical or vaginal fetal fibronectin test to reduce the risk of spontaneous preterm delivery. Fetal fibronectin is a placental and membrane protein that is a unique epitope of the fibronectins. One hypothesis holds that intrauterine infection causes disruption of the extracellular choriodecidual basement membrane, causing leakage of fetal fibronectin into cervical or vaginal secretions, in which it can then be detected. This might imply that antibiotic usage in this situation is for treatment not for prophylaxis.
Andrews 2006	Prophylactic antibiotics were administered during the interpregnancy interval in non-pregnant women with a prior early (< 34 weeks') spontaneous preterm birth, and not during the second and third trimesters, which is the objective of this review.
Audebert 1989	A randomised study designed to assess the efficacy of Polygynax in preventing vaginal infections at the start of pregnancy. However, the study outcomes assessment was only on the eradication rate of vaginal infection. They did not assess the pregnancy outcomes for mothers and newborns.
Goldenberg 2006	Prophylactic antibiotics were given prenatally and during labour, which was not relevant to the review's objective to assess the effect of prophylactic antibiotics given prenatally.

Study	Reason for exclusion
Gray 2001	Pregnant women were enrolled at varying gestations, and treatment could not be provided on a fixed schedule during pregnancy. In this trial, the intervention was given to 529 women in the first half of gestation and to 851 women in the second half of gestation. This is unlikely to have introduced bias to the comparison between randomisation arms because the trimester of enrolment was similar in the two arms. Nevertheless, the variable timing of treatment during pregnancy may have reduced the efficacy of antibiotics on adverse pregnancy outcomes, especially if the antibiotic prophylaxis was given in the first trimester.
Larsson 2006	Participants recruited for prophylactic antibiotics were between 10 and 14 weeks of gestational age, which was not relevant to the review's objective to assess the effect of antibiotic prophylaxis given in the second or third trimester.
Luntamo 2010	We planned to include only studies that compared any intervention with placebo or no treatment arm. However, this study compared 3 treatment arms without a placebo arm.
Peters 1995	The objective of this study was to determine whether prophylactic treatment with oral broad-spectrum antimicrobial therapy improves pregnancy outcomes in twin gestations. The perinatal morbidity and mortality in twin gestations is higher than in singleton gestations because of an increased incidence of preterm labour, which is mainly due to mechanical distention of the uterus, or is combined with other factors.
Shennan 2006	This study randomised pregnant women with positive fetal fibronectin, who were screened for fetal fibronectin at 24 and 27 weeks' gestation, to receive a week's course of oral metronidazole or placebo. Women who received a positive test received antibiotics. Antibiotic usage in this situation is considered a form of treatment rather than prophylaxis.
Tripathi 2008	This study assessed antibiotic treatment effects on pregnancy outcomes in pregnant women with abnormal vaginal flora, which was not relevant to our objective to assess antibiotic prophylaxis (not as a treatment of a documented infection).
Unger 2015	The trial had two treatment arms. The intervention arm women received three courses of sulphadoxine-pyrimethamine and azithromycin.The women assigned to the control arm received one course of sulphadoxine-pyrimethamine and chloroquin. Since there is no placebo arm this study does not meet the review inclusion criteria.

Characteristics of ongoing studies *[ordered by study ID]*

Hoffman 2013

Trial name or title	Clindamycin to reduce preterm birth in a low resource setting [official title: Clindamycin to reduce preterm birth in a low resource setting: A randomized placebo-controlled trial]
Methods	A randomised placebo-controlled trial in pregnant women between 13-20 gestational weeks with an elevated vaginal pH ≥ 5 (evidence of this type of infection), will be randomised to 300 mg oral clindamycin 2 times per day for 5-days administered at 13-20 weeks of gestation or placebo (starch).
Participants	Pregnant women between 13-20 gestational weeks with an elevated vaginal pH ≥ 5.
Interventions	300 mg oral clindamycin two times per day for 5-days administered at 13-20 weeks of gestation or placebo (starch).
Outcomes	Preterm birth prior to 37 weeks.

Hoffman 2013 *(Continued)*	Preterm birth prior to 34 weeks. Late miscarriage. Low birthweight. Very low birthweight. Neonatal complications through 42 days after delivery. Maternal complications through 42 days postpartum. The utility of vaginal pH tests for identification of women at elevated risk for preterm delivery.
Starting date	April 2013.
Contact information	ClinicalTrials.gov (accessed 21 May 2013) 2013 Contact: Mrutyunjaya Bellad, MD, mbbellad@hotmail.com Contact: Shivaprasad Goudar, MD, sgoudar@jnmc.edu
Notes	Estimated primary completion date: August 2015 (final data collection date for primary outcome measure).

Hb: haemoglobin
IPTp: intermittent preventive treatment in pregnancy
LLIN: long-lasting insecticidal nets
(S)AE: (serious) adverse event
SP: sulfadoxine-pyrimethamine

DATA AND ANALYSES

Comparison 1. Prophylactic antibiotics versus placebo

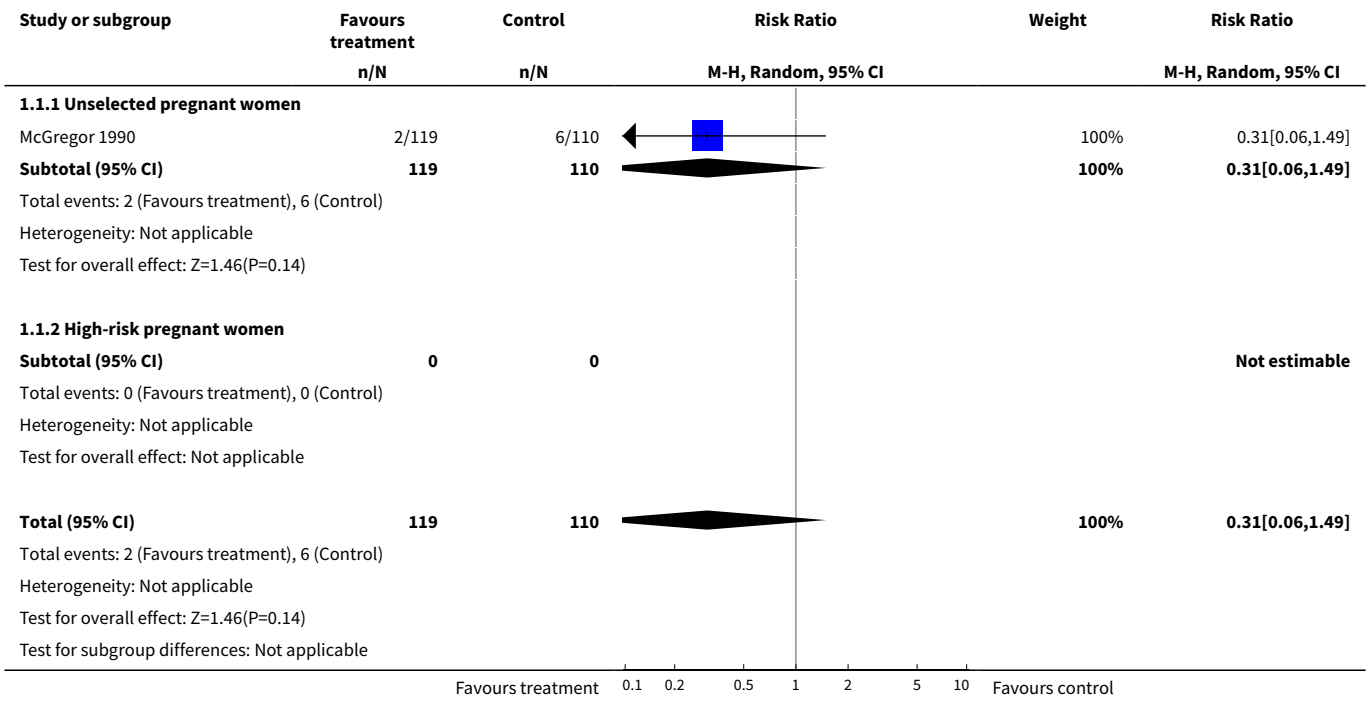
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm prelabour rupture of membranes	1	229	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.06, 1.49]
1.1 Unselected pregnant women	1	229	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.06, 1.49]
1.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Preterm delivery	6	3663	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.72, 1.09]
2.1 Unselected pregnant women	4	2905	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.82, 1.15]
2.2 High-risk pregnant women with BV and weight before pregnancy less than 50 kg	1	81	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.18, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 High-risk pregnant women with BV and weight before pregnancy more than 50 kg	1	177	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.49, 0.93]
2.4 High-risk pregnant women with previous preterm delivery	2	500	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.66, 1.77]
3 Preterm delivery in all high-risk pregnancy	2	758	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.58, 1.36]
3.1 High-risk pregnant women with BV and weight before pregnancy less than 50 kg or greater than 50 kg	1	258	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.47, 0.88]
3.2 High-risk pregnant women with previous preterm delivery	2	500	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.66, 1.77]
4 Puerperal sepsis/postpartum endometritis	3	627	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.35, 0.82]
4.1 Unselected pregnant women	2	431	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.24, 1.08]
4.2 High-risk pregnant women; history of preterm delivery, LBW < 2500 g, stillbirth or early perinatal death	1	196	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.33, 0.92]
5 Low birthweight	4	978	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.53, 1.39]
5.1 Unselected pregnant women	3	725	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.71, 1.63]
5.2 High-risk pregnant women; history of preterm delivery, LBW < 2500 g, still birth or early neonatal death	1	253	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.37, 0.88]
6 Neonatal sepsis	1	142	Risk Ratio (M-H, Fixed, 95% CI)	11.31 [0.64, 200.79]
6.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 High-risk pregnant women; with previous preterm delivery	1	142	Risk Ratio (M-H, Fixed, 95% CI)	11.31 [0.64, 200.79]
7 Prelabour rupture of membranes	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.15, 0.78]
7.1 Unselected pregnant women	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.15, 0.78]
7.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Chorioamnionitis	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.10, 3.62]
8.1 Unselected pregnant women	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.10, 3.62]
8.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Gonococcal infection; postpartum detected (not prespecified)	1	204	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.13, 0.94]
9.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 High-risk pregnant women	1	204	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.13, 0.94]
10 Compliance	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 1.00]
10.1 Unselected pregnant women	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 1.00]
10.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Mean gestational age (weeks)	1	253	Mean Difference (IV, Fixed, 95% CI)	0.70 [0.01, 1.39]
11.1 Unselected pregnant women	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 High-risk pregnant women	1	253	Mean Difference (IV, Fixed, 95% CI)	0.70 [0.01, 1.39]
12 Mean birthweight	4	978	Mean Difference (IV, Random, 95% CI)	41.60 [-78.20, 161.40]
12.1 Unselected pregnant women	3	725	Mean Difference (IV, Random, 95% CI)	9.08 [-123.61, 141.77]
12.2 High-risk pregnant women	1	253	Mean Difference (IV, Random, 95% CI)	155.0 [6.22, 303.78]
13 Congenital abnormality	2	463	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.20, 11.14]
13.1 Unselected pregnant women	2	463	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.20, 11.14]
13.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

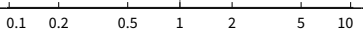
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Small-for-gestational age	1	229	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.42, 3.96]
14.1 Unselected pregnant women	1	229	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.42, 3.96]
14.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Perinatal mortality	4	2710	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.57, 1.20]
15.1 Perinatal mortality in unselected women	2	2315	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.57, 1.23]
15.2 High-risk pregnant women with history of preterm delivery, LBW < 2500 g, stillbirth or perinatal death	1	253	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.13, 2.18]
15.3 High-risk pregnant women with previous preterm delivery	1	142	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.13, 74.46]

Analysis 1.1. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 1 Preterm prelabour rupture of membranes.



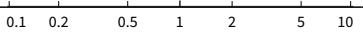
Analysis 1.2. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 2 Preterm delivery.

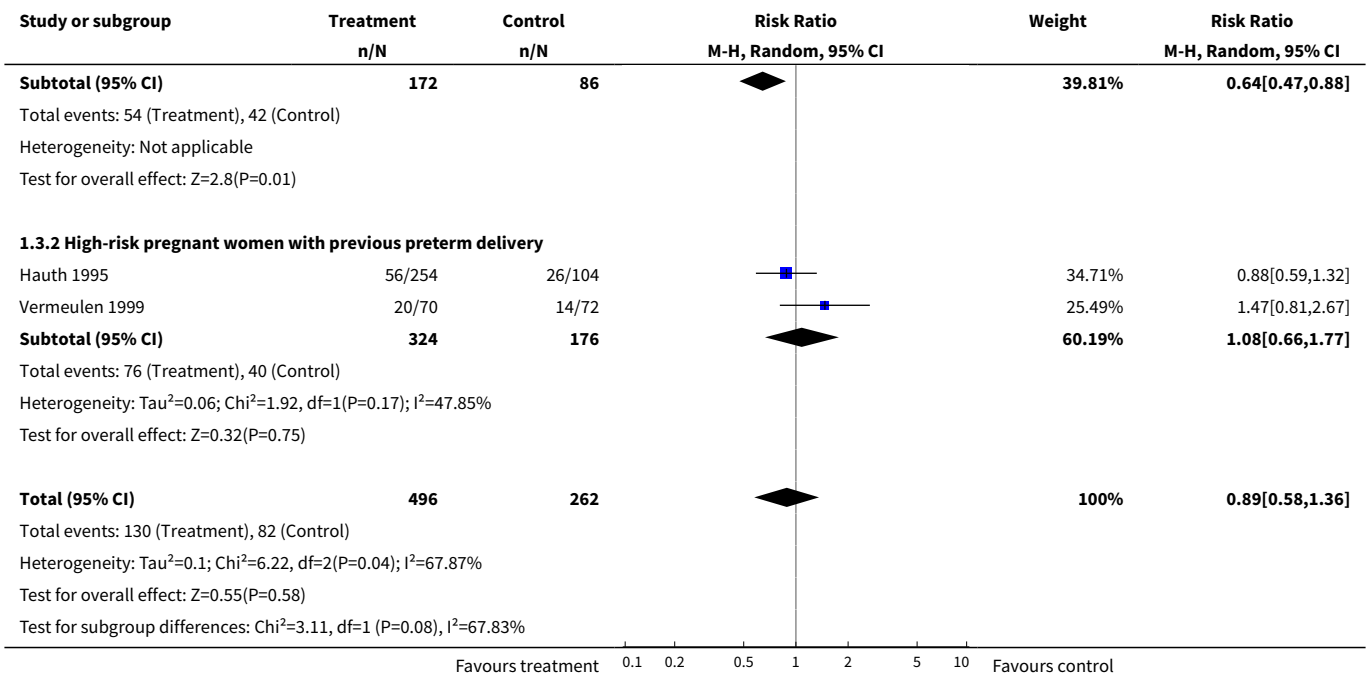
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Unselected pregnant women					
McGregor 1990	8/119	9/110		4.7%	0.82[0.33,2.05]
Paul 1997	21/159	17/164		9.43%	1.27[0.7,2.32]
Sen 2005	6/89	8/81		3.92%	0.68[0.25,1.88]
Van den Broek 2009	184/1096	189/1087		30.24%	0.97[0.8,1.16]
Subtotal (95% CI)	**1463**	**1442**		**48.29%**	**0.97[0.82,1.15]**
Total events: 219 (Treatment), 223 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.38, df=3(P=0.71); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					
1.2.2 High-risk pregnant women with BV and weight before pregnancy less than 50 kg					
Hauth 1995	7/51	10/30		5.31%	0.41[0.18,0.97]
Subtotal (95% CI)	**51**	**30**		**5.31%**	**0.41[0.18,0.97]**
Total events: 7 (Treatment), 10 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.04(P=0.04)					
1.2.3 High-risk pregnant women with BV and weight before pregnancy more than 50 kg					
Hauth 1995	47/121	32/56		20.8%	0.68[0.49,0.93]
Subtotal (95% CI)	**121**	**56**		**20.8%**	**0.68[0.49,0.93]**
Total events: 47 (Treatment), 32 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.38(P=0.02)					
1.2.4 High-risk pregnant women with previous preterm delivery					
Hauth 1995	56/254	26/104		16.11%	0.88[0.59,1.32]
Vermeulen 1999	20/70	14/72		9.49%	1.47[0.81,2.67]
Subtotal (95% CI)	**324**	**176**		**25.6%**	**1.08[0.66,1.77]**
Total events: 76 (Treatment), 40 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=1.92, df=1(P=0.17); I^2=47.85%					
Test for overall effect: Z=0.32(P=0.75)					
Total (95% CI)	**1959**	**1704**		**100%**	**0.88[0.72,1.09]**
Total events: 349 (Treatment), 305 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=11.07, df=7(P=0.14); I^2=36.79%					
Test for overall effect: Z=1.14(P=0.25)					
Test for subgroup differences: Chi^2=7.52, df=1 (P=0.06), I^2=60.12%					



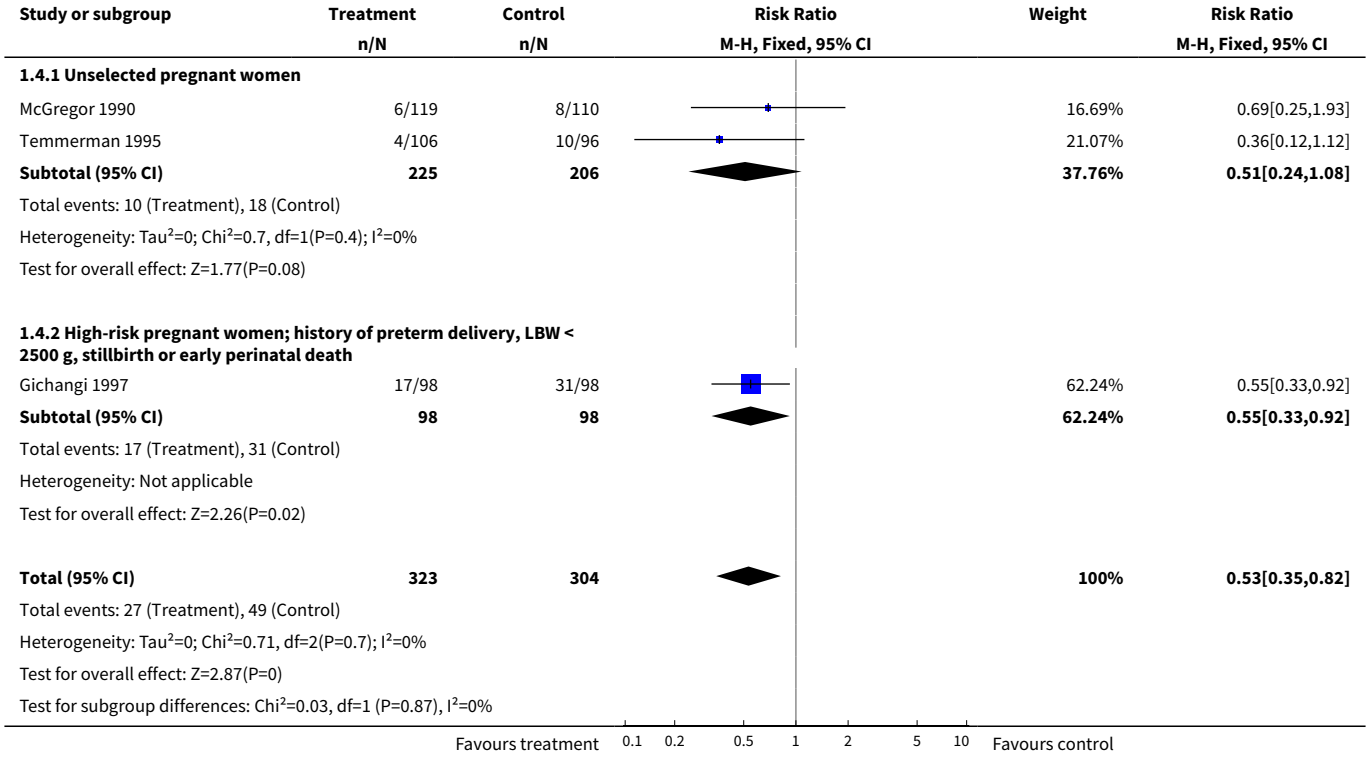
Analysis 1.3. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 3 Preterm delivery in all high-risk pregnancy.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 High-risk pregnant women with BV and weight before pregnancy less than 50 kg or greater than 50 kg					
Hauth 1995	54/172	42/86		39.81%	0.64[0.47,0.88]



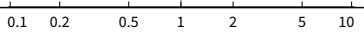


Analysis 1.4. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 4 Puerperal sepsis/postpartum endometritis.



Analysis 1.5. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 5 Low birthweight.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Unselected pregnant women					
Paul 1997	34/157	28/164		28.09%	1.27[0.81,1.99]
Sen 2005	37/89	28/81		30.02%	1.2[0.82,1.77]
Temmerman 1995	5/125	10/109		13.41%	0.44[0.15,1.24]
Subtotal (95% CI)	**371**	**354**		**71.52%**	**1.07[0.71,1.63]**
Total events: 76 (Treatment), 66 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=3.59, df=2(P=0.17); I^2=44.36%					
Test for overall effect: Z=0.33(P=0.74)					
1.5.2 High-risk pregnant women; history of preterm delivery, LBW < 2500 g, still birth or early neonatal death					
Gichangi 1997	25/134	39/119		28.48%	0.57[0.37,0.88]
Subtotal (95% CI)	**134**	**119**		**28.48%**	**0.57[0.37,0.88]**
Total events: 25 (Treatment), 39 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.53(P=0.01)					
Total (95% CI)	**505**	**473**		**100%**	**0.86[0.53,1.39]**
Total events: 101 (Treatment), 105 (Control)					
Heterogeneity: Tau^2=0.16; Chi^2=10.44, df=3(P=0.02); I^2=71.26%					
Test for overall effect: Z=0.62(P=0.54)					
Test for subgroup differences: Chi^2=4.22, df=1 (P=0.04), I^2=76.32%					



Favours treatment — Favours control

Analysis 1.6. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 6 Neonatal sepsis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Unselected pregnant women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.6.2 High-risk pregnant women; with previous preterm delivery					
Vermeulen 1999	5/70	0/72		100%	11.31[0.64,200.79]
Subtotal (95% CI)	**70**	**72**		**100%**	**11.31[0.64,200.79]**
Total events: 5 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.65(P=0.1)					
Total (95% CI)	**70**	**72**		**100%**	**11.31[0.64,200.79]**
Total events: 5 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.65(P=0.1)					
Test for subgroup differences: Not applicable					

Favours treatment — Favours control

Analysis 1.7. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 7 Prelabour rupture of membranes.

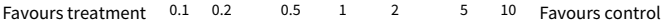
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Unselected pregnant women					
McGregor 1990	7/119	19/110		100%	0.34[0.15,0.78]
Subtotal (95% CI)	**119**	**110**		**100%**	**0.34[0.15,0.78]**
Total events: 7 (Treatment), 19 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.55(P=0.01)					
1.7.2 High-risk pregnant women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**119**	**110**		**100%**	**0.34[0.15,0.78]**
Total events: 7 (Treatment), 19 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.55(P=0.01)					
Test for subgroup differences: Not applicable					

Analysis 1.8. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 8 Chorioamnionitis.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Unselected pregnant women					
McGregor 1990	2/119	3/110		100%	0.62[0.1,3.62]
Subtotal (95% CI)	**119**	**110**		**100%**	**0.62[0.1,3.62]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
1.8.2 High-risk pregnant women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**119**	**110**		**100%**	**0.62[0.1,3.62]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
Test for subgroup differences: Chi^2=0, df=1 (P<0.0001), I^2=100%					

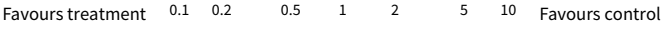
Analysis 1.9. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 9 Gonococcal infection; postpartum detected (not prespecified).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Unselected pregnant women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.9.2 High-risk pregnant women					
Gichangi 1997	5/103	14/101		100%	0.35[0.13,0.94]
Subtotal (95% CI)	**103**	**101**		**100%**	**0.35[0.13,0.94]**
Total events: 5 (Treatment), 14 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.09(P=0.04)					
Total (95% CI)	**103**	**101**		**100%**	**0.35[0.13,0.94]**
Total events: 5 (Treatment), 14 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.09(P=0.04)					
Test for subgroup differences: Not applicable					



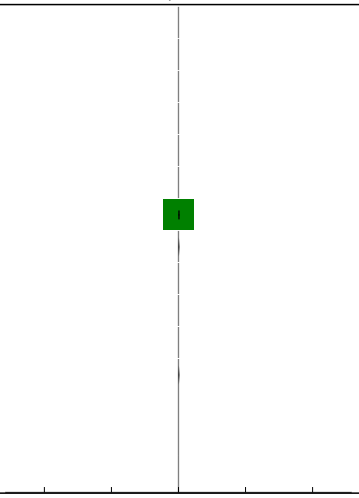
Analysis 1.10. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 10 Compliance.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 Unselected pregnant women					
McGregor 1990	87/119	92/110		100%	0.87[0.76,1]
Subtotal (95% CI)	**119**	**110**		**100%**	**0.87[0.76,1]**
Total events: 87 (Treatment), 92 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.93(P=0.05)					
1.10.2 High-risk pregnant women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**119**	**110**		**100%**	**0.87[0.76,1]**
Total events: 87 (Treatment), 92 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.93(P=0.05)					
Test for subgroup differences: Not applicable					



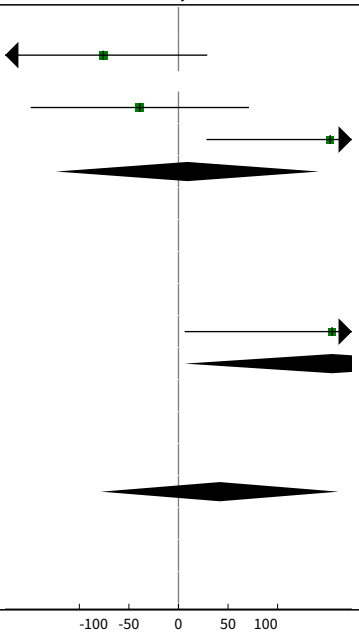
Analysis 1.11. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 11 Mean gestational age (weeks).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.11.1 Unselected pregnant women							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.11.2 High-risk pregnant women							
Gichangi 1997	134	37.9 (2.7)	119	37.2 (2.9)		100%	0.7[0.01,1.39]
Subtotal * **	**134**		**119**			**100%**	**0.7[0.01,1.39]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.98(P=0.05)							
Total * **	**134**		**119**			**100%**	**0.7[0.01,1.39]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.98(P=0.05)							
Test for subgroup differences: Not applicable							



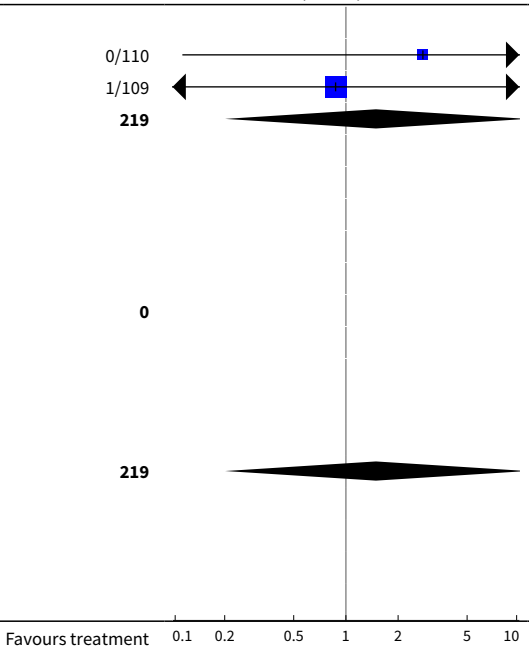
Analysis 1.12. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 12 Mean birthweight.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.12.1 Unselected pregnant women							
Paul 1997	157	2811.5 (476)	164	2887.5 (484)		26.81%	-76[-181.03,29.03]
Sen 2005	89	2545 (374)	81	2584 (358)		26.28%	-39[-149.07,71.07]
Temmerman 1995	125	3209 (463)	109	3056 (505)		24.71%	153[28.2,277.8]
Subtotal * **	**371**		**354**			**77.8%**	**9.08[-123.61,141.77]**
Heterogeneity: Tau^2=10407.97; Chi^2=8.27, df=2(P=0.02); I^2=75.8%							
Test for overall effect: Z=0.13(P=0.89)							
1.12.2 High-risk pregnant women							
Gichangi 1997	134	2927 (555)	119	2772 (642)		22.2%	155[6.22,303.78]
Subtotal * **	**134**		**119**			**22.2%**	**155[6.22,303.78]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.04(P=0.04)							
Total * **	**505**		**473**			**100%**	**41.6[-78.2,161.4]**
Heterogeneity: Tau^2=11065.42; Chi^2=11.82, df=3(P=0.01); I^2=74.63%							
Test for overall effect: Z=0.68(P=0.5)							
Test for subgroup differences: Chi^2=2.06, df=1 (P=0.15), I^2=51.42%							



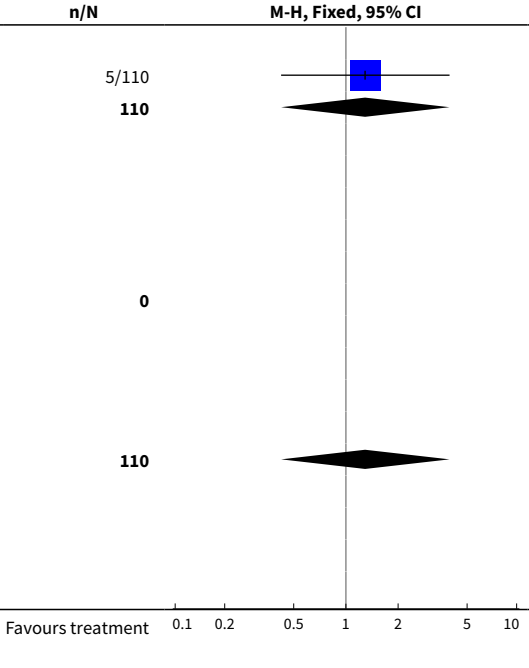
Analysis 1.13. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 13 Congenital abnormality.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.13.1 Unselected pregnant women					
McGregor 1990	1/119	0/110		32.72%	2.78[0.11,67.41]
Temmerman 1995	1/125	1/109		67.28%	0.87[0.06,13.78]
Subtotal (95% CI)	**244**	**219**		**100%**	**1.49[0.2,11.14]**
Total events: 2 (Treatment), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=0.39(P=0.69)					
1.13.2 High-risk pregnant women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**244**	**219**		**100%**	**1.49[0.2,11.14]**
Total events: 2 (Treatment), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=0.39(P=0.69)					
Test for subgroup differences: Not applicable					

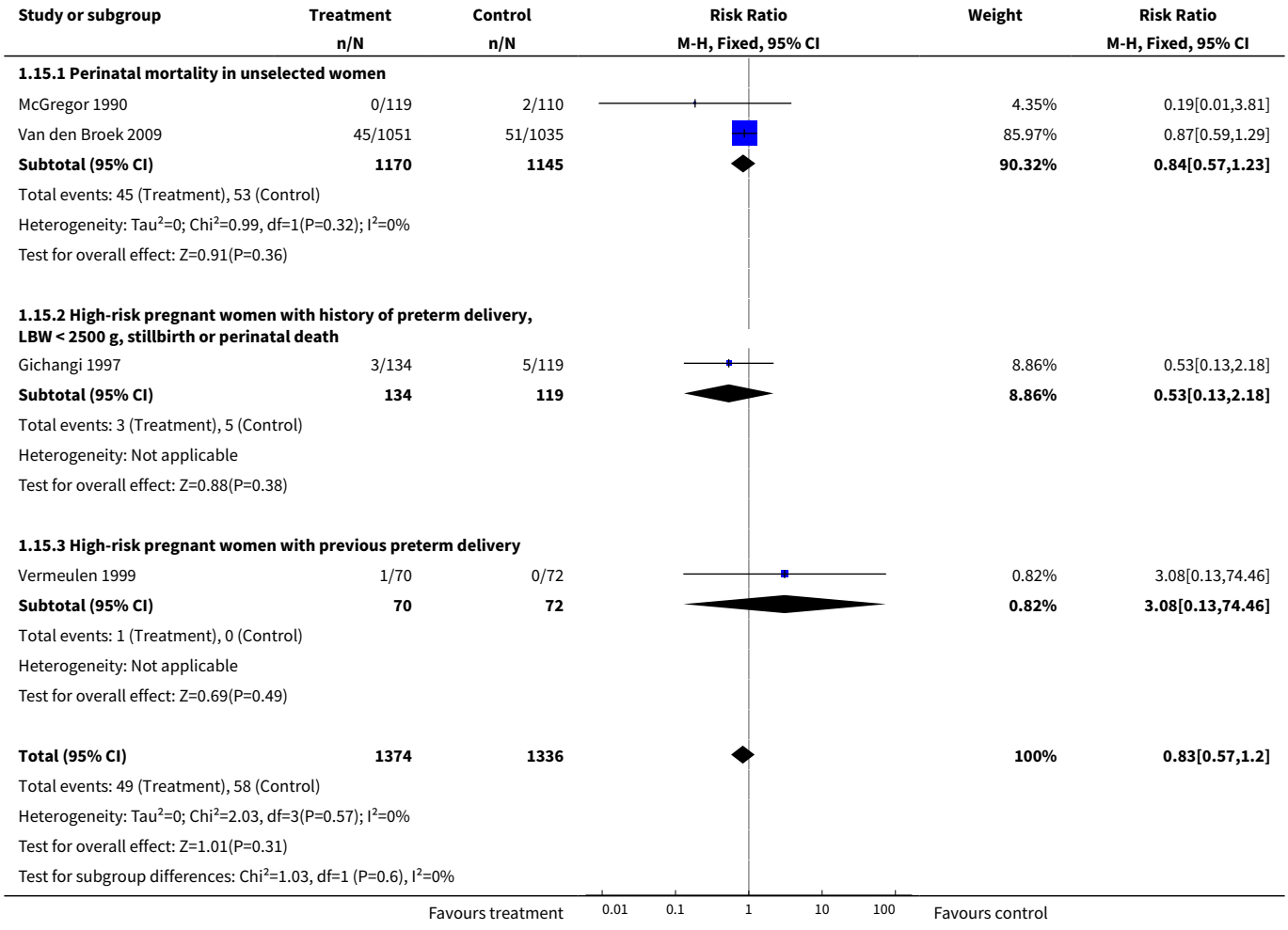


Analysis 1.14. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 14 Small-for-gestational age.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 Unselected pregnant women					
McGregor 1990	7/119	5/110		100%	1.29[0.42,3.96]
Subtotal (95% CI)	**119**	**110**		**100%**	**1.29[0.42,3.96]**
Total events: 7 (Treatment), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.45(P=0.65)					
1.14.2 High-risk pregnant women					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**119**	**110**		**100%**	**1.29[0.42,3.96]**
Total events: 7 (Treatment), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.45(P=0.65)					
Test for subgroup differences: Not applicable					



Analysis 1.15. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 15 Perinatal mortality.



WHAT'S NEW

Date	Event	Description
30 April 2015	New citation required but conclusions have not changed	Review updated. This update now includes eight studies. At the last update the review included seven studies. The review's conclusions remain unchanged.
30 April 2015	New search has been performed	Search updated. One trial previously excluded (Van den Broek 2009), after further scrutiny, has now been included. One trial (Unger 2015) previously an ongoing study (published in Rathjen 2010) has been excluded. Please note that blinding has now been divided into two assessments: 1. Blinding of participants and personnel (performance bias); and 2. Blinding of outcome assessors (detection bias) - tables have been updated. A 'Summary of findings' table has been incorporated.

HISTORY

Protocol first published: Issue 3, 2000
Review first published: Issue 4, 2002

Date	Event	Description
30 August 2009	New search has been performed	New search conducted in June 2009 which identified 11 new studies. We have included three (Lin 2005a; Sen 2005; Shennan 2006a) and excluded eight (Andrews 2006; Audebert 1989; Goldenberg 2006; Goldenberg 2005b; Kurtzman 2008; Larsson 2006; Tripathi 2008). One is ongoing (Ashorn 2006a). Another new search on 2 September 2010 identified four new reports (Aboud 2009; Kafulafula 2009; Stringer 2010a; Van den Broek 2009a). These trials will be incorporated into the next update of this review.
5 March 2008	Amended	Converted to new review format.
29 February 2004	New search has been performed	February 2004: search repeated, identifying one new report of an existing excluded study.

CONTRIBUTIONS OF AUTHORS

For this update, June 2015, J Thinkhamrop extracted data, analysed and interpreted the data, drafted and approved the final version of the update review. P Lumbiganon, GJ Hofmeyr and O Adetoro commented and approved the final version. E Ota verified the data, evaluated the quality of the data and summarised findings.

For the second version of this review (Thinkhamrop 2015a), J Thinkhamrop conducted the literature search under the supervision of the Pregnancy and Childbirth Group's Trials Search Co-ordinator, extracted data, analysed and interpreted the data, drafted and approved the final version of the update review. P Lumbiganon extracted and interpreted the data, and approved the final version of the review. GJ Hofmeyr and O Adetoro commented and approved the final version. E Ota verified the data, evaluated the quality of the data and summarised findings.

For the first version of this review (Thinkhamrop 2002), GJ Hofmeyr and O Adetoro prepared the original protocol, commented on the draft of the review and approved the final version of the review. J Thinkhamrop revised the protocol, conducted the literature search, analysed and interpreted the data, drafted and approved the final version of the review. P Lumbiganon revised the protocol, interpreted the data, drafted and approved the final version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Khon Kaen University, Thailand.
- University of the Witwatersrand, South Africa.
- Ogun State University, Nigeria.

External sources

- Thailand Research Fund/Senior Research Scholar, Thailand.
- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have performed subgroup analysis for pregnancies with previous preterm delivery and bacterial vaginosis in the current pregnancy; this subgroup analysis was not prespecified in our protocol.

The outcome of gonococcal infection detected postpartum was not prespecified in our protocol.

The title was changed for the previous update (Thinkhamrop 2015a) to: Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Endometritis [*prevention & control]; Fetal Membranes, Premature Rupture [prevention & control]; Fetal Weight [drug effects]; Pregnancy Outcome; Pregnancy Trimester, Second; Pregnancy Trimester, Third; Pregnancy, High-Risk; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic; Vaginosis, Bacterial [complications] [drug therapy]

MeSH check words

Female; Humans; Pregnancy