Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality (Review)

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[Intervention Review]

Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

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ABSTRACT

Background

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

Objectives

To determine the effect of prophylactic antibiotics during second and third trimester of pregnancy on maternal and perinatal outcomes.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (June 2009) and reference lists of articles. We updated this search on 2 September 2010 and added the results to the Awaiting classification section of the review.

Selection criteria

Randomized 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 nine randomized controlled trials. Eight trials recruited 2508 women to detect the effect of prophylactic antibiotic administration on pregnancy outcomes. One additional trial recruited 715 women but did not report on the outcomes of interest. Antibiotic prophylaxis reduced the risk of prelabour rupture of membranes (risk ratio (RR) 0.34; 95% confidence interval (CI) 0.15 to

0.78 (one trial, 229 women)). There was a reduction in risk of preterm delivery (RR 0.64; 95% CI 0.47 to 0.88, one trial, 258 women) in pregnant women with a previous preterm birth and had bacterial vaginosis (BV) during the current pregnancy, but there was no reduction in pregnant women with previous preterm birth without BV during pregnancy (RR 1.08; 95% CI 0.66 to 1.77; two trials, 500 women). There was reduction in the risk of postpartum endometritis (RR 0.55; 95% CI 0.33 to 0.92; one trial, 196 women) in all risk pregnant women (with/without previous preterm birth and had bacterial vaginosis (BV) during the current pregnancy). Regarding the route of antibiotic administration, vaginal antibiotic prophylaxis during pregnancy did not prevent infectious pregnancy outcomes.

Authors' conclusions

Antibiotic prophylaxis given during the second or third trimester of pregnancy reduces the risk of prelabour rupture of membranes and postpartum endometritis when given routinely to pregnant women. However there was also a possible substantial bias in the review's results because of a high rate of loss to follow up and small numbers of studies for each of our analyses. So we conclude that there is not enough evidence to recommend the use of routine antibiotics during pregnancy to prevent infectious adverse effect on pregnancy outcomes.

PLAIN LANGUAGE SUMMARY

Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Pregnant women can be given antibiotics during the second and third trimester of pregnancy (before labour) to prevent bacteria in the vagina and cervix affecting the pregnancy. Maternal genital tract infection or colonization by some infectious organisms can cause health problems for the mother and her baby. The review of eight randomized trials found that antibiotics reduce the risk of prelabour rupture of the membranes and the risk of preterm birth) only in pregnant women who had both a previous preterm birth and bacterial vaginosis during the current pregnancy. Infection of the uterus following birth (postpartum endometritis) was reduced. However, there was no reduction in neonatal morbidity and mortality. Our review is based on limited data as many of the analyses were based on small numbers of studies. There is therefore, no justification to give antibiotics to all pregnant women during second or third trimester to prevent adverse infectious effects on pregnancy outcomes.

BACKGROUND

Description of the condition

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

Maternal genital tract infection or colonization 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 wide number of medical and demographic factors have been implicated in the etiology of preterm birth. These can be categorized into four groups:

1. medical and obstetric complications (e.g. hypertensive disorders, placental hemorrhage);
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, emphasizing the need for other strategies.

Description of the intervention

Antibiotic prophylaxis is used for prevention of infection. Its usage reduces the risk of sequelae of infection. The antibiotic used for prophylaxis should be initiated before documented infection.

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 high prevalence, would be the most reasonable approach. Limited laboratory facilities make this strategy unrealistic in low-resource settings. Diagnosis algorithms, including clinical signs and symptoms and behavioral pattern, 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 randomized 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 reduces adverse pregnancy outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials. We excluded quasi-randomized trials.

Types of participants

Women in the second or third trimester of pregnancy before labour and delivery.

Types of interventions

Prophylactic antibiotics versus placebo or no treatment.

Types of outcome measures

Primary outcomes are directly related to infectious morbidity/mortality.

Primary outcomes

Maternal outcomes

1. Preterm labour;
2. preterm prelabour rupture of membranes (membrane rupture before gestational age of 37 weeks and before labour);
3. prelabour rupture of membranes (membrane rupture after gestational age of 37 weeks but before labour);
4. preterm delivery;
5. chorioamnionitis;
6. intrapartum fever needing treatment with antibiotics;
7. puerperal sepsis/postpartum endometritis, wound infection, urinary tract infection;
8. serious maternal complications of puerperal infection requiring laparotomy for infection, hysterectomy, death;
9. gonococcal cervicitis (postpartum detected).

Neonatal outcomes

1. Mean gestational age;
2. low birthweight;
3. mean birthweight;
4. clinical neonatal sepsis;
5. blood culture confirming sepsis.

Secondary outcomes

Maternal outcomes

1. Maternal side effects of antibiotic prophylaxis;
2. duration of hospital stay;
3. satisfaction with care;
4. compliance.

Neonatal outcomes

1. Admission to neonatal intensive care unit;
2. ophthalmia neonatorum;
3. congenital abnormality;
4. small-for-gestational age;
5. abnormal neurological development;
6. perinatal mortality.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (June 2009). We updated this search on 2 September 2010 and added the results to Studies awaiting classification for the authors to consider at the next update.

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

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

Details of the search strategies for CENTRAL and MEDLINE, 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 restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 1. For this update, we used the following methods when assessing the trials identified by the updated search.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (J Thinkhamrop and P Lumbiganon) extracted the data using the agreed form. We resolved discrepancies through discussion. We entered data into Review Manager software (RevMan 2008) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details. We assessed trials for eligibility according to the specified criteria. We extracted the following data from each publication:

1. information on the study setting (for example, country, type of population, and socio-economic status);
2. detailed description of the antibiotic regimen used (including type of drug, dose, frequency, and timing);
3. definition of the outcomes. We performed an 'intention-to-treat' analysis. We calculated a summary of the odds ratio using a fixed-effect model (where there was no significant heterogeneity among the trials);
4. effects of routine use of antibiotics during pregnancy in the allocated groups (unselected or unspecified risk; high risk or specified risks).

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 2008). We resolved any disagreement by discussion.

(1) Sequence generation (checking for possible selection bias)

We describe 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:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear.

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

We describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

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

(3) Blinding (checking for possible performance bias)

We describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized 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 was supplied by the trial authors, we re-included missing data in the analyses which we undertook. We assessed methods as:

- adequate (5% or less missing data);
- inadequate (more than 5% of missing data);
- unclear.

(5) Selective reporting bias

We describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.
We assessed the methods as:

- adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (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.

(6) Other sources of bias

We describe for each included study any important concerns we have about other possible sources of bias. We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2008). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Cotinuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We planned to use the standardized mean difference to combine trials that measure the same outcome, but use different methods.

Dealing with missing data

For included studies, we have noted levels of attrition. We have explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis if there were enough data.
For all outcomes we have carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomized to each group in the analyses. The denominator for each outcome in each trial would be the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (greater than 50%) we explored it by prespecified subgroup analysis.

Assessment of reporting biases

Where we suspected reporting bias (*see* 'Selective reporting bias' above), we attempted to contact study authors asking them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we have explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect (Mantel-Haenszel for categorical data, inverse variance for continuous data) meta-analysis for combining data where trials are examining the same intervention, and we judged the trials' populations and methods sufficiently similar. Where we suspected clinical or methodological heterogeneity among studies sufficient to suggest that treatment effects may differ between trials, we used random-effects (Mantel-Haenszel for categorical data, inverse variance for continuous data) meta-analysis.

If we identified substantial heterogeneity in a fixed-effect meta-analysis, we have noted this and repeated the analysis using a random-effects (Mantel-Haenszel for categorical data, inverse variance for continuous data) methods.

Subgroup analysis and investigation of heterogeneity

We carried out the following subgroup analysis: high-risk pregnant women were defined as having previous spontaneous preterm delivery, history of low birthweight (less than 2500 gm) or a prepregnancy weight less than 50 kg; or associated with bacterial vaginosis (BV) in the current pregnancy. This subgroup analysis was not prespecified in our protocol.

For fixed-effect meta-analyses we conducted subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. For random-effects meta-analyses we assessed differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality with poor quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

We identified 20 randomized controlled trials to assess the effect of antibiotics administration during pregnancy. We included nine, excluded 10 and classified one study as ongoing (Ashorn 2006) (*see* Characteristics of ongoing studies).

There are four reports in Studies awaiting classification which were identified by an updated search in September 2010. We will consider these at the next update.

Included studies

Nine trials met the inclusion criteria for this review. One of nine included trials (Lin 2005) reported no outcome of interest to the meta-analysis. For a detailed description of the included studies, *see* Characteristics of included studies. Four of the studies (Hauth 1995; McGregor 1990; Shennan 2006; Vermeulen 1999) were conducted in high-income countries (UK, USA, Netherlands) while the other four (Gichangi 1997; Paul 1997; Sen 2005; Temmerman 1995) were reports from low- and middle-income countries (Kenya, India). Four trials (Gichangi 1997; Hauth 1995; Shennan 2006; Vermeulen 1999) enrolled only high-risk pregnant women. All studies described adequately the characteristics of the women admitted into the study.

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

The earliest of the studies reviewed was published in 1990, four others were published in 1995 to 1997, and the latest one was published in 2006.

Excluded studies

We excluded 10 studies for the following reasons:

1. the 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;
2. the study looked at twin gestation, which has a higher risk of adverse pregnancy outcome with some different mechanisms from single pregnancy;
3. the antibiotics were administered before the current pregnancy when the women were not pregnant;
4. antibiotics were given prenatally and during labour, which was not relevant to the review's objective to assess effect of prophylactic antibiotics given prenatally.

For a detailed description of the excluded studies, *see* Characteristics of excluded studies.

Risk of bias in included studies

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

The methodological quality of the trials based on allocation concealment varied from adequate to unclear and inadequate. They were all placebo-controlled, double-blind randomized trials. 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.

Effects of interventions

We included eight randomized controlled trials with a total of 2508 women to evaluate the effect of prophylactic antibiotic administration in the second or third trimester on pregnancy outcomes. But one additional trial (Lin 2005) of 715 women was not analyzed since there was no outcome of interest in the published data. There were many studies of antibiotic use to prevent preterm delivery but, unlike the included studies, they were studies of 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. They were thus trials of treatment and not prophylaxis. The publication of the included studies took place over more than 10 years (1990 to 2006). Four trials with 1212 women (Gichangi 1997; Hauth 1995; Shennan 2006; Vermeulen 1999) enrolled only high-risk pregnant women. High risk was defined as women having a previous spontaneous preterm delivery, history of low birthweight, had BV in the current pregnancy (BV identified after enrolment and antibiotic only for prophylaxis before knowing if the participant had BV or not) or a prepregnancy weight less than 50 kg. Six studies used oral antibiotics: erythromycin alone (McGregor 1990; Paul 1997); erythromycin plus metronidazole (Hauth 1995); cefetamet-pivoxil (Gichangi 1997); combination of metronidazole and cephalexin (Sen 2005); and metronidazole alone (Shennan 2006). One study used ceftriaxone intramuscular injection (Temmerman 1995) and one used clindamycin vaginal cream application (Vermeulen 1999).

Primary outcomes

Studies of antibiotic prophylaxis during the second or third trimester (range 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, prelabour rupture of membranes, preterm delivery, chorioamnionitis, postpartum endometritis, low birthweight, mean birthweight.

There was only a significant risk reduction for prelabour rupture of membranes (risk ratio (RR) 0.34; 95% confidence interval (CI) 0.15 to 0.78; one trial, 229 women; Analysis 1.3). There was a risk reduction on postpartum endometritis (RR 0.53; 95% CI 0.35 to 0.82; three trials, 627 women; Analysis 1.8).

Results from trials for women specified as at high risk

High-risk group trials reported the following outcomes: preterm delivery, postpartum endometritis, gonococcal infection (postpartum detected), mean gestational age, low birthweight, mean birthweight, neonatal sepsis. Postpartum detected gonococcal infection is a non-prespecified outcome assessed.

There was a significant risk reduction in preterm delivery (RR 0.64; 95% CI 0.47 to 0.88; one trial; 258 women; Analysis 1.5) in pregnant women with previous preterm delivery and BV during their current pregnancy, but there was no risk reduction in pregnant women with previous preterm delivery without BV in their current pregnancy (RR 1.08; 95% CI 0.66 to 1.77; two trials, 500 women; Analysis 1.5). There was a risk reduction on postpartum endometritis (RR 0.55; 95% CI 0.33 to 0.92; one trial, 196 women; Analysis 1.8), gonococcal infection (postpartum detected) (RR 0.35; 95% CI 0.13 to 0.94; one trial, 204 women; Analysis 1.12) in pregnant women with a history of preterm delivery. There was also a marginally significant increase in mean gestational age (mean difference (MD) 0.70 weeks; 95% CI 0.01 to 1.39; one trial, 253 women; Analysis 1.15) in women with a previous low birthweight baby (less than 2500 gm). We did not prespecify these subgroup analyses in the protocol and therefore one should be cautious when interpreting these results. We also found limited data to evaluate the effect of antibiotics on low birthweight in unselected women. There were two trials in this analysis; one reported in unselected and the other reported in a high-risk group, which have effects in opposite directions. There were no data on blood culture confirming sepsis.

Secondary outcomes

The included studies did not report any serious adverse effects of antibiotic prophylaxis. There were no data reported on some maternal outcomes that we planned to assess, including preterm labour, intrapartum fever needing treatment with antibiotics, puerperal sepsis, wound infection, urinary tract infection, serious maternal complications (puerperal infection requiring laparotomy for infection, hysterectomy, death), maternal side effects, duration of hospital stay and satisfaction with care. There were limited

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 two trials in this analysis; one reported in unselected and the other reported in a high-risk group, which have effects in opposite directions. There were no data on the following neonatal outcomes: blood culture confirming sepsis; admission to neonatal intensive care unit; ophthalmia neon atorum; and abnormal neurological development. One study reported that compliance with medication was different between the 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

The results of this study 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 in the current pregnancy, prelabour rupture of membranes, postpartum endometritis and gonococcal infection (detected postpartum). However, our analyses are based on studies with high risk of bias or only one trial. The data demonstrated that routine use of antibiotics during pregnancy might prevent infectious morbidity for the mother, but could not reduce neonatal morbidity and mortality from the limited data. From the data, we cannot estimate the side effects of prophylactic antibiotics since they are rare events but they may have serious effects.

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 hospitalization, satisfaction with care, blood culture confirming neonatal sepsis or opthalmia neonatorum. However, these outcomes are not those expected when evaluating the effectiveness of the intervention. Some of the included studies reported the expected outcomes such as preterm delivery, preterm prelabour rupture of membranes, prelabour rupture membranes, chorioamnionitis, intrapartum fever needing antibiotic treatment, 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 needing antibiotic treatment, neonatal sepsis, admission to intensive neonatal care unit and perinatal mortality.

However, the ongoing Malawi trial (Ashorn 2006) is planned to be a large study and will add significant data when completed.

Quality of the evidence

The methodological quality of the nine included trials was satisfactory. Four of the eight included studies are randomized, double-blind, placebo-controlled trials with satisfactory methods of allocation concealment; the methods for four studies were unclear; and one study had inadequate information. The included studies were from both high-income and low- and middle-income countries. The sample size for unselected pregnant women might not be large enough to demonstrate differences for important uncommon outcomes.

Potential biases in the review process

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

AUTHORS' CONCLUSIONS

Implications for practice

Routine use of antibiotic prophylaxis in pregnant women during second and third trimester could prevent maternal infectious morbidity by reducing postpartum endometritis. For neonatal outcomes, there was risk reduction of preterm delivery only in pregnant women with bacterial vaginosis during the current pregnancy but there is absence of evidence of a benefit on neonatal morbidity and mortality. There was also a possible substantial bias in the review's results because of a high rate of loss to follow up. The evidence is not strong enough to recommend 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. With the limited data, it cannot evaluate the benefit on neonatal morbidity and mortality. Other than that, data on some health outcomes we would like to see are lacking. So we would suggest that there is a need for further studies to provide these missing gaps in the evidence.

ACKNOWLEDGEMENTS

We thank Dr Metin Gulmezoglu for his suggestions and encouragement to complete this review.

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.

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.

Lin 2005 *{published data only}*
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.

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.

Shennan 2006 *{published data only}*
* 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.

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.

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}*
* 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.
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.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.
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.

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 2005a ***{published data only}***
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.
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.

Goldenberg 2005b ***{published data only}***
Goldenberg R, Andrews W, Taha T, Fawzi W, Brown E. HIVNET 025: 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.

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.

Kurtzman 2008 ***{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.

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.

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.

Tripathi 2008 ***{published data only}***
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.

References to studies awaiting assessment

Aboud 2009 ***{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.

Kafulafula 2009 ***{published data only}***
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 2010 ***{published data only}***
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.

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.

References to ongoing studies

Ashorn 2006 *{published data only}*

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

Additional references

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.

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG editor (s). *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2001.

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.

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 2008

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. 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.

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.

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.

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 2008

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

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.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Gichangi 1997

Methods	Randomized, double-blind, placebo-controlled trial.
Participants	320 pregnant women during GA 28 to 32 wks with a history of LBW (less than 2500 gm), stillbirth or early perinatal death. (High risk.)
Interventions	Treatment group received a single dose of 2 gm 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 center. Out of the 253, 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 center, the rest were delivered elsewhere and could not be traced for follow up.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	The authors mentioned that they use randomized allocation.
Allocation concealment?	Unclear	Unclear.
Blinding? All outcomes	Unclear	The authors mentioned only that this study was double-blind but did have any detail who were blinded and if the outcome assessors were blind or not.
Incomplete outcome data addressed? All outcomes	No	83% of the treatment group and 74% of the placebo group delivered at the study center, the rest were delivered elsewhere and could not be traced for follow up.
Free of selective reporting?	Unclear	Unknown.
Free of other bias?	Yes	None.

Hauth 1995

Methods	A 2:1 double-blind, randomized, placebo-controlled trial.
Participants	624 pregnant women during GA 22 to 24 wks, at risk of preterm delivery because of previous preterm delivery or prepregnancy weight less than 50 kg, were randomized. 433 were in the treatment group and 191 were in the placebo group. (High risk.)
Interventions	Treatment group had 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 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomization was used for allocation.
Allocation concealment?	Yes	Adequate.
Blinding? All outcomes	Unclear	Not mentioned in the trial report.
Incomplete outcome data addressed? All outcomes	Yes	8 of 624 pregnant women were lost to follow up.
Free of selective reporting?	Unclear	Unknown.
Free of other bias?	Yes	None.

Lin 2005

Methods	Secondary analysis of a multicenter double blinded, placebo-controlled study.
Participants	715 asymptomatic pregnant women between 21-25 weeks' gestational age with positive cervicovaginal FFN $\geq$ 50 ng/mL.
Interventions	Women were randomized to either metronidazole 250 mg tid plus erythromycin 250 mg qid for 10 days or identical placebos.
Outcomes	Quantitative FFN was assessed at baseline and 2 weeks after treatment.
Notes	There was no outcome of interest in the study report.

Lin 2005 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomization was used.
Allocation concealment?	Unclear	Not mentioned in the trial report.
Blinding? All outcomes	Unclear	Not mentioned in the trial report.
Incomplete outcome data addressed? All outcomes	Unclear	Not mentioned in the trial report.
Free of selective reporting?	Unclear	Unknown.
Free of other bias?	Yes	None.

McGregor 1990

Methods	Randomized, double-blind, placebo-controlled trial.
Participants	235 pregnant women during GA 26 to 30 wks. (Unselected pregnant women.)
Interventions	They were given identical prepared bottles and tablets that were either erythromycin base 333 mg or placebo taking one tablet 3 times a day for 1 week.
Outcomes	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.

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomization was used.
Allocation concealment?	Yes	Adequate.
Blinding? All outcomes	Unclear	Not mentioned in the trial report.
Incomplete outcome data addressed? All outcomes	Yes	4 of 235 participants were lost to follow up

McGregor 1990 (*Continued*)

Free of selective reporting?	Unclear	Unknown.
Free of other bias?	Yes	None.

Paul 1997

Methods	Randomized, double-blind, placebo-controlled trial.
Participants	437 pregnant women during GA 26 to 34 wks. (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 437 women enrolled into the trial, there were 219 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 the control groups.
Notes	29 participants were lost to follow up. 66 participants dropped out with a specified reason.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomization was used.
Allocation concealment?	Unclear	Not mentioned in the trial report.
Blinding? All outcomes	Unclear	Not mentioned in the trial report.
Incomplete outcome data addressed? All outcomes	No	From 437 participants, 29 participants were lost to follow up. 66 participants dropped out with a specified reason.
Free of selective reporting?	Unclear	Unknown.
Free of other bias?	Yes	None.

Sen 2005

Methods	A non-placebo, randomized controlled trial.
Participants	224 pregnant women in their second trimester (between 14 and 24 weeks) were recruited during February to July 2001.
Interventions	The intervention group women were treated with a course of antimicrobials and provided with iron-folic acid tablets and the control group women 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 analyzed to assess the pregnancy outcomes.
Notes	The study was conduct among pregnant women attending the antenatal clinic of a government hospital in Kolkata, India, that serves the urban poor.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomization was used.
Allocation concealment?	Unclear	Not mentioned in the trial report.
Blinding? All outcomes	Unclear	Not mentioned in the trial report.
Incomplete outcome data addressed? All outcomes	Yes	From 224 participants, 112 women in the intervention group and 112 women in the control group were analyzed to assess the pregnancy outcomes.
Free of selective reporting?	Unclear	Unknown.
Free of other bias?	Yes	None.

Shennan 2006

Methods	Randomized, double-blind, placebo-controlled trial.
Participants	100 pregnant women with a known risk of preterm birth (singleton pregnancy with history of preterm birth or prelabour rupture of membranes before 37 weeks of gestation, previous late miscarriage during 16 to 24 weeks of gestation, uterine anatomical abnormality, cervical surgery prior to the index pregnancy or current cervical cerclage) who had positive fetal fibronectin during 23 to 27 weeks of gestation.
Interventions	The treatment group received metronidazole 400 mg tds (3 times a day) for 7 days, the control group received the identical placebo.

Shennan 2006 (*Continued*)

Outcomes	Gestation at birth, PPROM, onset of labour, mode of delivery, mean birthweight, neonatal outcomes.
Notes	1 case lost to follow up, 1 case of control group lack of data of delivery date.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization was used.
Allocation concealment?	Yes	Adequate.
Blinding? All outcomes	Unclear	Not mentioned in the trial report.
Incomplete outcome data addressed? All outcomes	Yes	From 100 participants, 1 case lost to follow up, 1 case of control group lack of data of delivery date.
Free of selective reporting?	Unclear	Unknown.
Free of other bias?	Yes	None.

Temmerman 1995

Methods	Randomized, 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 gm 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 center; the rest were delivered elsewhere. 166 participants were lost to follow up.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization was used.
Allocation concealment?	Yes	Adequate.

Temmerman 1995 (*Continued*)

Blinding? All outcomes	Unclear	Not mentioned in the trial report.
Incomplete outcome data addressed? All outcomes	No	Among 400 participants, 60% of the treatment group and 57% of the placebo group were delivered at the study center; the rest were delivered elsewhere. 166 participants were lost to follow up.
Free of selective reporting?	Unclear	Unknown.
Free of other bias?	Yes	None.

Vermeulen 1999

Methods	Randomized, 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	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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomization was used.
Allocation concealment?	No	Inadequate.
Blinding? All outcomes	Unclear	Not mentioned in the trial report.
Incomplete outcome data addressed? All outcomes	No	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.

Vermeulen 1999 (*Continued*)

Free of selective reporting?	Unclear	Unknown.
Free of other bias?	Yes	None.

FFN: fetal fibronectin
GA: gestational age
IM: intramuscular
LBW: low birthweight
NaCl: sodium chloride
PPROM: preterm prelabour rupture of membranes
qid: four times a day
tid: three times a day
wks: weeks

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

Study	Reason for exclusion
Andrews 2003	The prophylactic antibiotics administered during the interpregnancy interval in non-pregnant women with a prior early (< 34 weeks') spontaneous preterm birth, which was not relevant to the review's objective to assess in pregnant women.
Andrews 2006	The 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 randomized study designed to assess the efficacy of Polygynax in preventing vaginal infections at risks, at the start of pregnancy. However, this study outcomes assessment were only on the eradication rate of vaginal infection. They did not assess the pregnancy outcomes on the mothers and the newborns.
Goldenberg 2005a	The 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.
Goldenberg 2005b	There was no prophylactic antibiotic intervention in the study.
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 in the first half of gestation in 529 and second half in 851 women. This is unlikely to have biased the comparison between randomization arms because the trimester of enrollment was similar in the 2 arms. Nevertheless, the variable timing of treatment during pregnancy may have reduced the efficacy of antibiotic on adverse pregnancy outcomes.
Kurtzman 2008	The study compared the pregnancy outcomes in women with fetal fibronectin 0 and 1-49 ng/mL. The study's subjects did not receive any intervention.

(*Continued*)

Larsson 2006	The 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 effect of antibiotic prophylaxis given in second or third trimester.
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 combined with other factors.
Tripathi 2008	The study assessed the antibiotic treatment effects on pregnancy outcomes in pregnant women with abnormal vaginal flora which was not relevant to this review objective to assess the antibiotic prophylaxis (not treatment in documented infection).

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

Ashorn 2006

Trial name or title	Gestational sulfadoxine-pyrimethamine and azithromycin treatment to prevent preterm birth (official title: Lungwena antenatal intervention study, a single-center intervention trial in rural Malawi, testing maternal and infant health effects of presumptive intermittent treatment of pregnant women with sulfadoxine-pyrimethamine and azithromycin).
Methods	Randomized, single blind, placebo control, parallel assignment, safety/efficacy study.
Participants	A total of 1320 women at rural antenatal clinic after 14 but before 26 complete gestation weeks.
Interventions	One-third of the enrolled subjects were the control group, received standard care. Another third of the enrolled subjects received standard care and sulfadoxine-pyrimethamine monthly intervals. The final third received standard care and sulfadoxine-pyrimethamine monthly intervals and 2 doses of presumptive STI treatment with azithromycin.
Outcomes	The primary outcome measure is proportion of preterm births, anemia, parasitaemia during pregnancy, at delivery and at 1, 3, 6 months after delivery, gestational weight gain and morbidity and STI prevalence after delivery. Secondary child outcomes consist of proportion of babies with low birthweight, mean birthweight, growth in infancy and childhood, incidence of malnutrition in infancy and childhood, and mortality.
Starting date	December 2003.
Contact information	Principal investigator: Per Ashorn, MD, PhD, Study Director, University of Tampere, Medical School Kenneth M Maleta, MBBS, PhD, Principal investigator, University of Malawi College of Medicine Teija Kulmala, MD, PhD, Principal investigator, University of Tampere, School of Public Health.
Notes	

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 labour	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Preterm prelabour rupture of membranes	3	327	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.19, 2.67]
2.1 Unselected pregnant women	2	231	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.06, 1.49]
2.2 High-risk pregnant women	1	96	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.50, 2.91]
3 Prelabour rupture of membranes	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.15, 0.78]
3.1 Unselected pregnant women	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.15, 0.78]
3.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Preterm delivery	6	1416	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.33]
4.1 Unselected pregnant women	4	556	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.68, 1.85]
4.2 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]
4.3 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]
4.4 High-risk pregnant women with previous preterm delivery	3	602	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.84, 1.77]
5 Preterm delivery in all high-risk pregnancy	2	758	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.58, 1.36]
5.1 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]
5.2 High-risk pregnant women with previous preterm delivery	2	500	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.66, 1.77]
6 Chorioamnionitis	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.10, 3.62]
6.1 Unselected pregnant women	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.10, 3.62]

6.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Intrapartum fever needing antibiotic treatment	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.67, 1.43]
7.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 High-risk pregnant women	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.67, 1.43]
8 Puerperal sepsis/postpartum endometritis	3	627	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.35, 0.82]
8.1 Unselected pregnant women	2	431	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.24, 1.08]
8.2 High-risk pregnant women; history of preterm delivery, LBW < 2500 gm, stillbirth or early perinatal death	1	196	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.33, 0.92]
9 Serious maternal complications of puerperal infection requiring laparotomy for infection, hysterectomy, death	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Maternal side effects of antibiotic prophylaxis (severe side effects)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Duration of hospitalization	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
11.1 Unselected pregnant women	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
11.2 High-risk pregnant women	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12 Gonococcal infection; postpartum detected	1	204	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.13, 0.94]
12.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.2 High-risk pregnant women	1	204	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.13, 0.94]
13 Satisfaction with care	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
13.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Compliance	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 1.00]
14.1 Unselected pregnant women	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 1.00]

14.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Mean gestational age (weeks)	1	253	Mean Difference (IV, Fixed, 95% CI)	0.70 [0.01, 1.39]
15.1 Unselected pregnant women	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
15.2 High-risk pregnant women	1	253	Mean Difference (IV, Fixed, 95% CI)	0.70 [0.01, 1.39]
16 Low birthweight	4	907	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.51, 1.59]
16.1 Unselected pregnant women	2	555	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.30, 2.32]
16.2 High-risk pregnant women; history of preterm delivery, LBW < 2500 gm, still birth or early neonatal death	2	352	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.35, 2.53]
17 Mean birthweight	4	907	Mean Difference (IV, Random, 95% CI)	-44.96 [-267.16, 177.24]
17.1 Unselected pregnant women	2	555	Mean Difference (IV, Random, 95% CI)	-76.0 [-181.03, 29.03]
17.2 High-risk pregnant women	2	352	Mean Difference (IV, Random, 95% CI)	-73.14 [-574.54, 428.26]
18 Neonatal sepsis	1	142	Risk Ratio (M-H, Fixed, 95% CI)	11.31 [0.64, 200.79]
18.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.2 High-risk pregnant women; with previous preterm delivery	1	142	Risk Ratio (M-H, Fixed, 95% CI)	11.31 [0.64, 200.79]
19 Blood culture confirming sepsis	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
19.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20 Admission to neonatal intensive care unit	1	99	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.91, 2.25]
20.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
20.2 High-risk pregnant women	1	99	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.91, 2.25]
21 Opthalmia neonatorum	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
21.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
21.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
22 Congenital abnormality	2	463	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.20, 11.14]
22.1 Unselected pregnant women	2	463	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.20, 11.14]
22.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
23 Small-for-gestational age	1	229	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.42, 3.96]
23.1 Unselected pregnant women	1	229	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.42, 3.96]

23.2 High-risk pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
24 Abnormal neurological development	1	99	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [0.44, 10.66]
24.1 Unselected pregnant women	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
24.2 High-risk pregnant women	1	99	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [0.44, 10.66]
25 Perinatal mortality	4	723	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.31, 2.06]
25.1 Perinatal mortality in unselected women	1	229	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.81]
25.2 High-risk pregnant women with history of preterm delivery, LBW < 2500 gm, stillbirth or perinatal death	1	253	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.13, 2.18]
25.3 High-risk pregnant women with previous preterm delivery	2	241	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [0.44, 17.08]

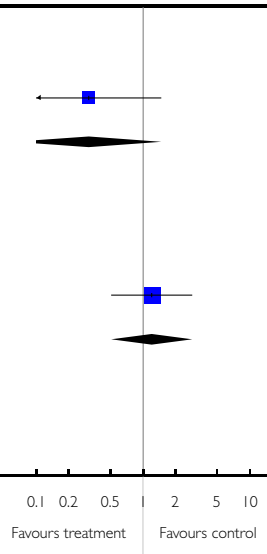
Analysis 1.2. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 2 Preterm prelabour rupture of membranes.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 2 Preterm prelabour rupture of membranes

Study or subgroup	Favours treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Unselected pregnant women				
Hauth 1995	0/1	0/1		0.0 [0.0, 0.0]
McGregor 1990	2/119	6/110		0.31 [0.06, 1.49]
Subtotal (95% CI)	**120**	**111**		**0.31 [0.06, 1.49]**
Total events: 2 (Favours treatment), 6 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.46 (P = 0.14)				
2 High-risk pregnant women				
Shennan 2006	10/52	7/44		1.21 [0.50, 2.91]
Subtotal (95% CI)	**52**	**44**		**1.21 [0.50, 2.91]**
Total events: 10 (Favours treatment), 7 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.42 (P = 0.67)				



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Study or subgroup	Favours treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**172**	**155**		**0.72 [0.19, 2.67]**
Total events: 12 (Favours treatment), 13 (Control)				
Heterogeneity: Tau^2 = 0.53; Chi^2 = 2.25, df = 1 (P = 0.13); I^2 =55%				
Test for overall effect: Z = 0.50 (P = 0.62)				

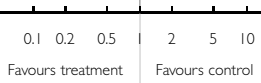
Analysis 1.3. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 3 Prelabour rupture of membranes.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 3 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 Unselected pregnant women					
McGregor 1990	7/119	19/110		100.0 %	0.34 [0.15, 0.78]
Subtotal (95% CI)	**119**	**110**		**100.0 %**	**0.34 [0.15, 0.78]**
Total events: 7 (Treatment), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.55 (P = 0.011)					
2 High-risk pregnant women					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**119**	**110**		**100.0 %**	**0.34 [0.15, 0.78]**
Total events: 7 (Treatment), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.55 (P = 0.011)					

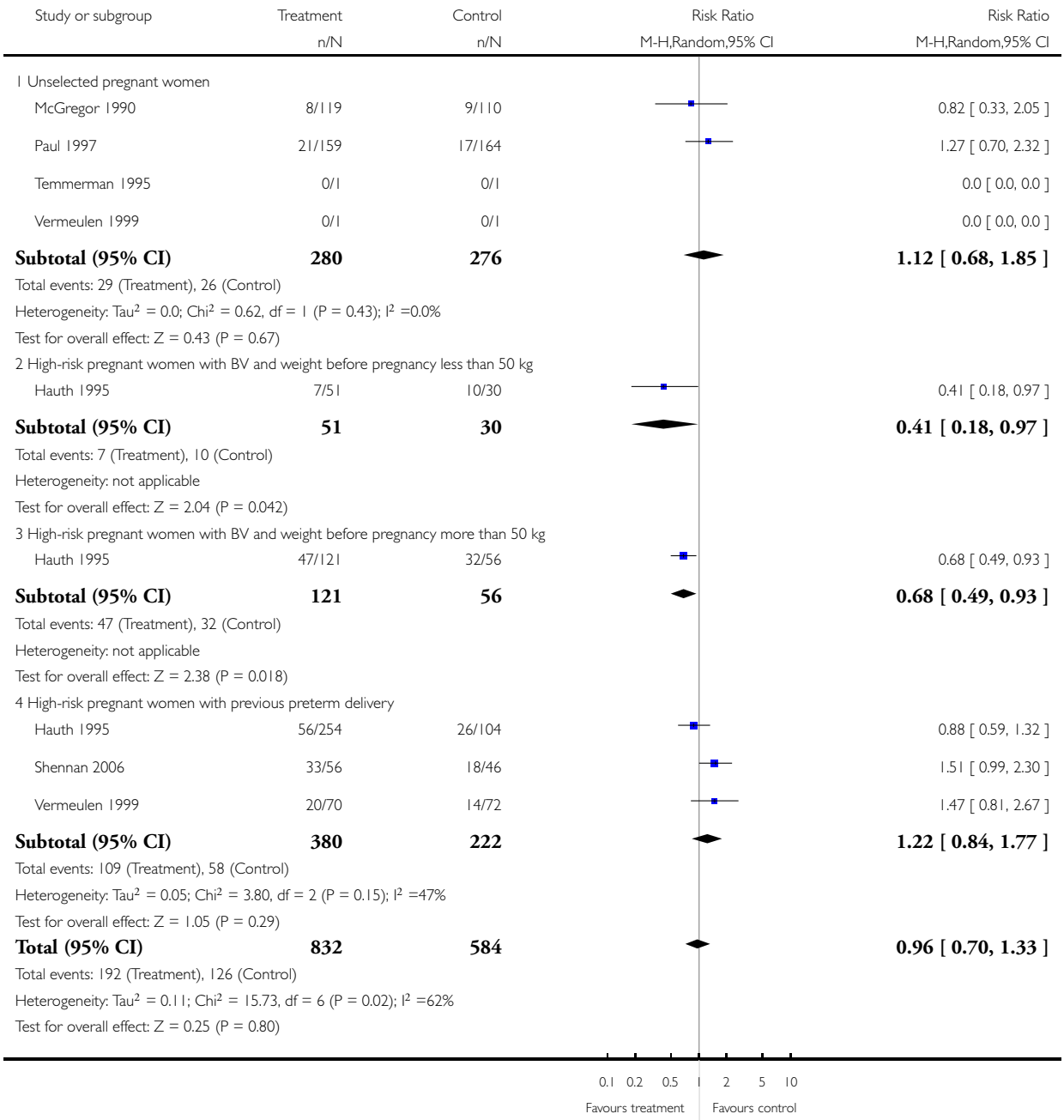


Analysis 1.4. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 4 Preterm delivery.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 4 Preterm delivery



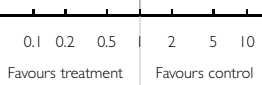
Analysis 1.5. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 5 Preterm delivery in all high-risk pregnancy.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 5 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 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		39.8 %	0.64 [0.47, 0.88]
Subtotal (95% CI)	**172**	**86**		**39.8 %**	**0.64 [0.47, 0.88]**
Total events: 54 (Treatment), 42 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.80 (P = 0.00511)					
2 High-risk pregnant women with previous preterm delivery					
Hauth 1995	56/254	26/104		34.7 %	0.88 [0.59, 1.32]
Vermeulen 1999	20/70	14/72		25.5 %	1.47 [0.81, 2.67]
Subtotal (95% CI)	**324**	**176**		**60.2 %**	**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 =48%					
Test for overall effect: Z = 0.32 (P = 0.75)					
Total (95% CI)	**496**	**262**		**100.0 %**	**0.89 [0.58, 1.36]**
Total events: 130 (Treatment), 82 (Control)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 6.22, df = 2 (P = 0.04); I^2 =68%					
Test for overall effect: Z = 0.55 (P = 0.58)					

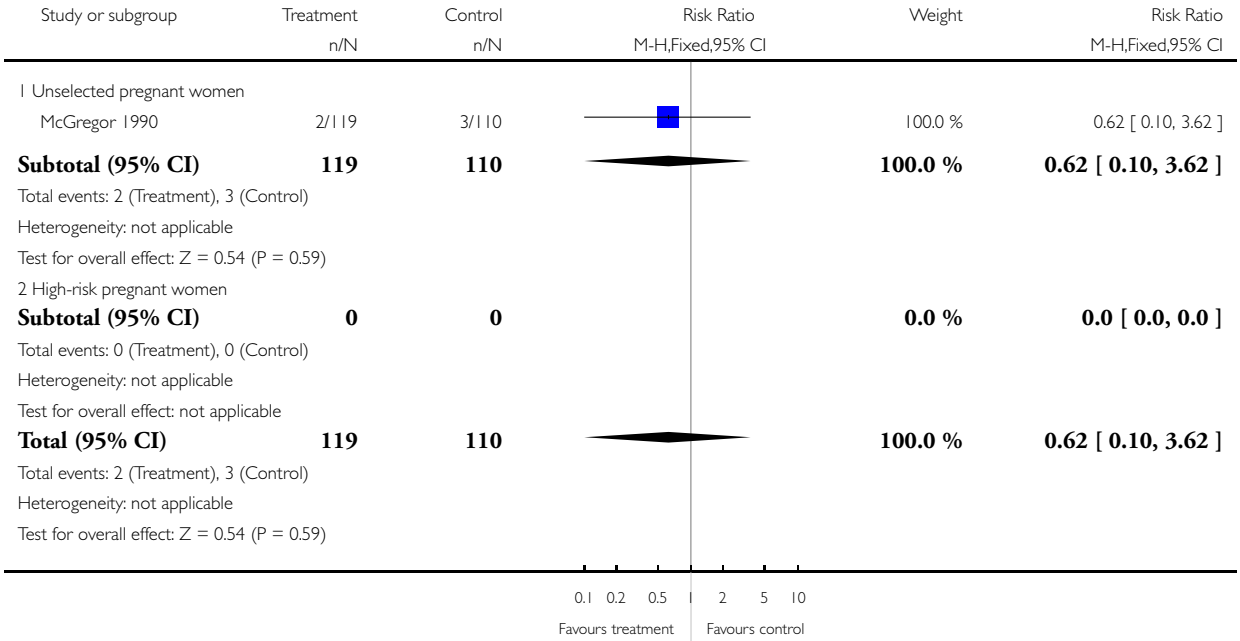


Analysis 1.6. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 6 Chorioamnionitis.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 6 Chorioamnionitis



Analysis 1.7. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 7 Intrapartum fever needing antibiotic treatment.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 7 Intrapartum fever needing antibiotic treatment

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 Unselected pregnant women					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High-risk pregnant women					
Shennan 2006	27/53	24/46		100.0 %	0.98 [0.67, 1.43]
Subtotal (95% CI)	**53**	**46**		**100.0 %**	**0.98 [0.67, 1.43]**
Total events: 27 (Treatment), 24 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.90)					
Total (95% CI)	**53**	**46**		**100.0 %**	**0.98 [0.67, 1.43]**
Total events: 27 (Treatment), 24 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.12 (P = 0.90)					

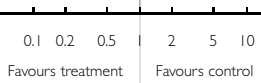
Analysis 1.8. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 8 Puerperal sepsis/postpartum endometritis.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 8 Puerperal sepsis/postpartum endometritis

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 Unselected pregnant women					
McGregor 1990	6/119	8/110		16.7 %	0.69 [0.25, 1.93]
Temmerman 1995	4/106	10/96		21.1 %	0.36 [0.12, 1.12]
Subtotal (95% CI)	**225**	**206**		**37.8 %**	**0.51 [0.24, 1.08]**
Total events: 10 (Treatment), 18 (Control)					
Heterogeneity: Chi^2 = 0.70, df = 1 (P = 0.40); I^2 =0.0%					
Test for overall effect: Z = 1.77 (P = 0.077)					
2 High-risk pregnant women; history of preterm delivery, LBW < 2500 gm, stillbirth or early perinatal death					
Gichangi 1997	17/98	31/98		62.2 %	0.55 [0.33, 0.92]
Subtotal (95% CI)	**98**	**98**		**62.2 %**	**0.55 [0.33, 0.92]**
Total events: 17 (Treatment), 31 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.26 (P = 0.024)					
Total (95% CI)	**323**	**304**		**100.0 %**	**0.53 [0.35, 0.82]**
Total events: 27 (Treatment), 49 (Control)					
Heterogeneity: Chi^2 = 0.71, df = 2 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 2.87 (P = 0.0041)					



Analysis 1.12. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 12 Gonococcal infection; postpartum detected.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 12 Gonococcal infection; postpartum detected

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 Unselected pregnant women					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High-risk pregnant women					
Gichangi 1997	5/103	14/101		100.0 %	0.35 [0.13, 0.94]
Subtotal (95% CI)	**103**	**101**		**100.0 %**	**0.35 [0.13, 0.94]**
Total events: 5 (Treatment), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.09 (P = 0.037)					
Total (95% CI)	**103**	**101**		**100.0 %**	**0.35 [0.13, 0.94]**
Total events: 5 (Treatment), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.09 (P = 0.037)					

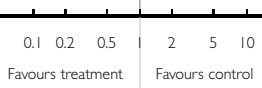
Analysis 1.14. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 14 Compliance.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 14 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 Unselected pregnant women					
McGregor 1990	87/119	92/110		100.0 %	0.87 [0.76, 1.00]
Subtotal (95% CI)	**119**	**110**		**100.0 %**	**0.87 [0.76, 1.00]**
Total events: 87 (Treatment), 92 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.054)					
2 High-risk pregnant women					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**119**	**110**		**100.0 %**	**0.87 [0.76, 1.00]**
Total events: 87 (Treatment), 92 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.054)					



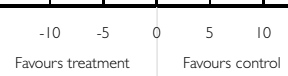
Analysis 1.15. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 15 Mean gestational age (weeks).

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 15 Mean gestational age (weeks)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Unselected pregnant women							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 High-risk pregnant women							
Gichangi 1997	134	37.9 (2.7)	119	37.2 (2.9)		100.0 %	0.70 [0.01, 1.39]
Subtotal (95% CI)	**134**		**119**			**100.0 %**	**0.70 [0.01, 1.39]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.98 (P = 0.048)							
Total (95% CI)	**134**		**119**			**100.0 %**	**0.70 [0.01, 1.39]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.98 (P = 0.048)							

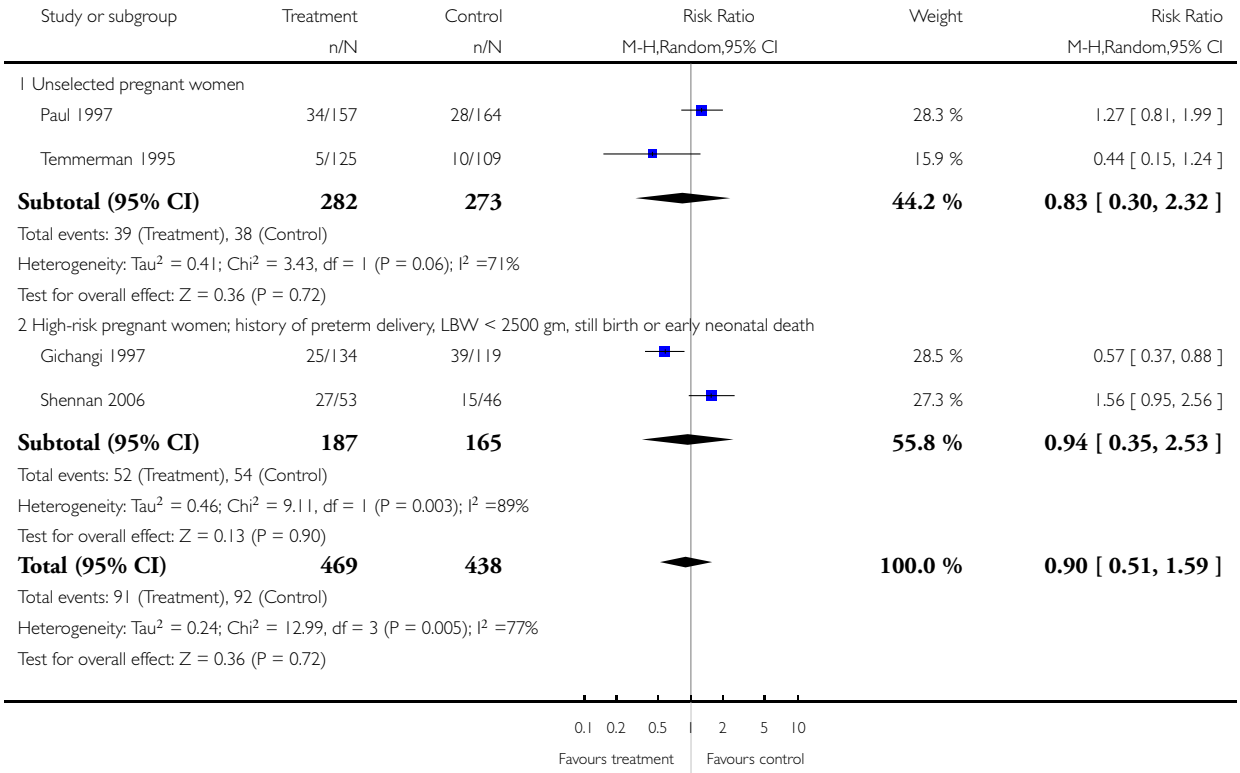


Analysis 1.16. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 16 Low birthweight.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 16 Low birthweight



Analysis 1.17. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 17 Mean birthweight.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 17 Mean birthweight

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Unselected pregnant women						
Paul 1997	157	2811.5 (476)	164	2887.5 (484)		-76.00 [-181.03, 29.03]
Temmerman 1995	125	3209 (0)	109	3056 (0)		0.0 [0.0, 0.0]
Subtotal (95% CI)	**282**		**273**			**-76.00 [-181.03, 29.03]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
2 High-risk pregnant women						
Gichangi 1997	134	2927 (555)	119	2772 (642)		155.00 [6.22, 303.78]
Shennan 2006	53	2360 (920)	46	2720 (960)		-360.00 [-731.90, 11.90]
Subtotal (95% CI)	**187**		**165**			**-73.14 [-574.54, 428.26]**
Heterogeneity: Tau^2 = 111729.07; Chi^2 = 6.35, df = 1 (P = 0.01); I^2 =84%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)	**469**		**438**			**-44.96 [-267.16, 177.24]**
Heterogeneity: Tau^2 = 27922.17; Chi^2 = 9.61, df = 2 (P = 0.01); I^2 =79%						
Test for overall effect: Z = 0.40 (P = 0.69)						

Analysis 1.18. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 18 Neonatal sepsis.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 18 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 Unselected pregnant women					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High-risk pregnant women; with previous preterm delivery					
Vermeulen 1999	5/70	0/72		100.0 %	11.31 [0.64, 200.79]
Subtotal (95% CI)	**70**	**72**		**100.0 %**	**11.31 [0.64, 200.79]**
Total events: 5 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.098)					
Total (95% CI)	**70**	**72**		**100.0 %**	**11.31 [0.64, 200.79]**
Total events: 5 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.65 (P = 0.098)					

Analysis 1.20. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 20 Admission to neonatal intensive care unit.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 20 Admission to neonatal intensive care unit

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 Unselected pregnant women					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High-risk pregnant women					
Shennan 2006	28/53	17/46		100.0 %	1.43 [0.91, 2.25]
Subtotal (95% CI)	**53**	**46**		**100.0 %**	**1.43 [0.91, 2.25]**
Total events: 28 (Treatment), 17 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.54 (P = 0.12)					
Total (95% CI)	**53**	**46**		**100.0 %**	**1.43 [0.91, 2.25]**
Total events: 28 (Treatment), 17 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.54 (P = 0.12)					

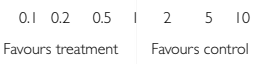
Analysis 1.22. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 22 Congenital abnormality.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 22 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 Unselected pregnant women					
McGregor 1990	1/119	0/110		32.7 %	2.78 [0.11, 67.41]
Temmerman 1995	1/125	1/109		67.3 %	0.87 [0.06, 13.78]
Subtotal (95% CI)	**244**	**219**		**100.0 %**	**1.49 [0.20, 11.14]**
Total events: 2 (Treatment), 1 (Control)					
Heterogeneity: Chi^2 = 0.29, df = 1 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 0.39 (P = 0.69)					
2 High-risk pregnant women					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**244**	**219**		**100.0 %**	**1.49 [0.20, 11.14]**
Total events: 2 (Treatment), 1 (Control)					
Heterogeneity: Chi^2 = 0.29, df = 1 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 0.39 (P = 0.69)					



Analysis 1.23. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 23 Small-for-gestational age.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 23 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 Unselected pregnant women					
McGregor 1990	7/119	5/110		100.0 %	1.29 [0.42, 3.96]
Subtotal (95% CI)	**119**	**110**		**100.0 %**	**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)					
2 High-risk pregnant women					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**119**	**110**		**100.0 %**	**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)					

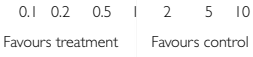
Analysis 1.24. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 24 Abnormal neurological development.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 24 Abnormal neurological development

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 Unselected pregnant women					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 High-risk pregnant women					
Shennan 2006	5/53	2/46		100.0 %	2.17 [0.44, 10.66]
Subtotal (95% CI)	**53**	**46**		**100.0 %**	**2.17 [0.44, 10.66]**
Total events: 5 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					
Total (95% CI)	**53**	**46**		**100.0 %**	**2.17 [0.44, 10.66]**
Total events: 5 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					

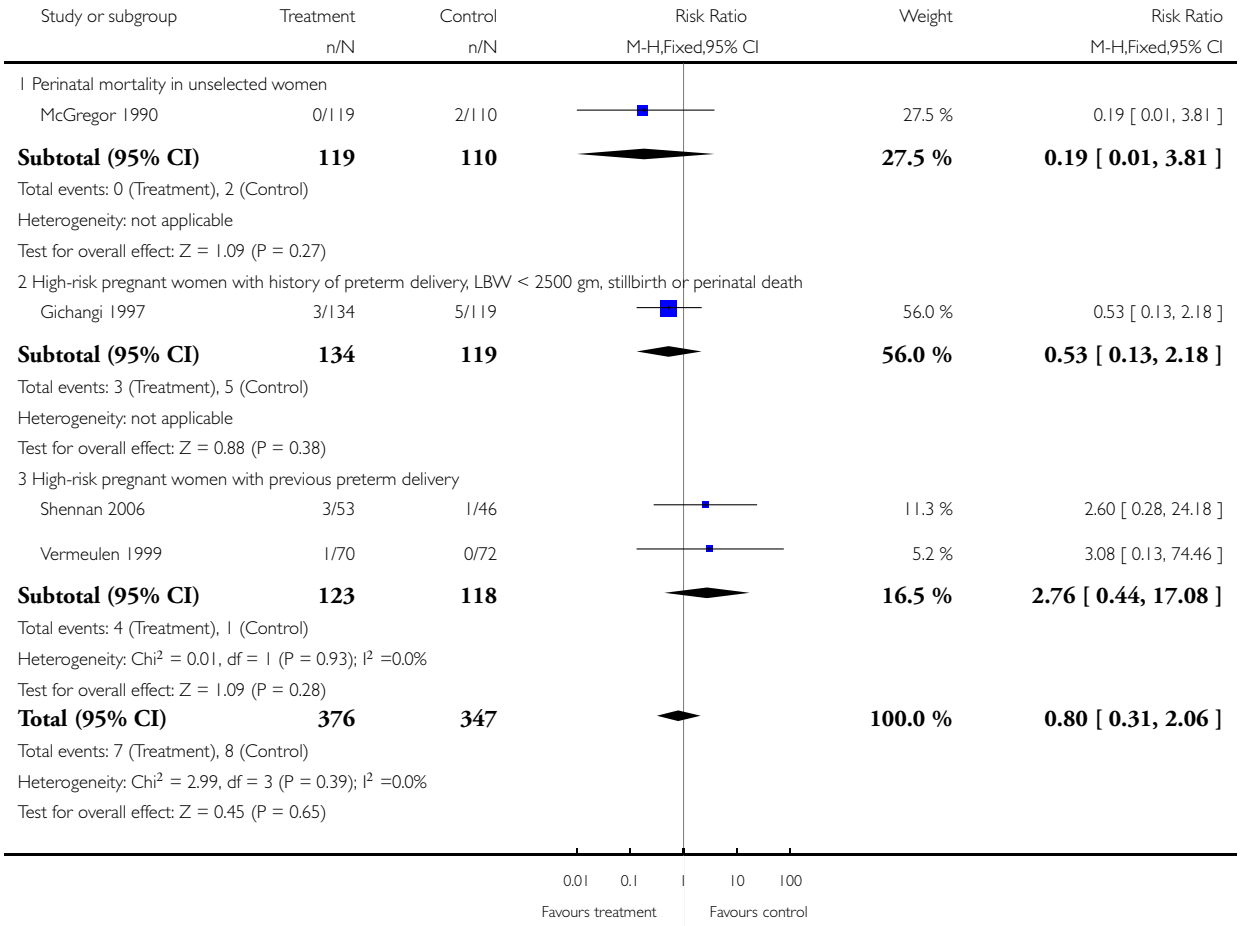


Analysis 1.25. Comparison 1 Prophylactic antibiotics versus placebo, Outcome 25 Perinatal mortality.

Review: Prophylactic antibiotic administration during second and third trimester in pregnancy for preventing infectious morbidity and mortality

Comparison: 1 Prophylactic antibiotics versus placebo

Outcome: 25 Perinatal mortality



APPENDICES

Appendix 1. Methods used to assess trials included in previous version of this review

We assessed trials for eligibility according to the specified criteria. We used the standard Cochrane criteria of allocation concealment (A = adequate; B = unclear; C = inadequate; D = allocation concealment was not used) to categorize the methodological quality of the trials. We noted whether the trials were placebo controlled, and collected information on the blinding of outcome assessment and loss to follow up.

We would have assessed the effect of trial quality in sensitivity analyses. We would have used Peto odds ratio and 95% confidence intervals to compare categorical data.

We extracted the following data from each publication:

(1) Information on the study setting (for example country, type of population, and socio-economic status).

(2) Detailed description of the antibiotic regimen used (including type of drug, dose, frequency, and timing).

(3) Definition of the outcomes. We performed an 'intention to treat' analysis. We calculated a summary of the odds ratio using a fixed effects model (where there was no significant heterogeneity among the trials).

(4) Effects of routine use of antibiotics during pregnancy in the allocated groups (unselected or unspecified risk; high risk or specified risks).

High-risk pregnant women were defined as previous spontaneous preterm delivery, history of low birth weight (< 2500 gm) or pre pregnancy weight less than 50 kg; or associate with bacterial vaginosis (BV) in that current pregnancy.

WHAT'S NEW

Last assessed as up-to-date: 30 August 2009.

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 2005; Sen 2005; Shennan 2006) and excluded eight (Andrews 2006; Audebert 1989; Goldenberg 2005a; Goldenberg 2005b; Kurtzman 2008; Larsson 2006; Tripathi 2008). One is ongoing (Ashorn 2006) . Another new search on 2 September 2010 identified four new reports (Aboud 2009; Kafulafula 2009; Stringer 2010; Van den Broek 2009). These trials will be incorporated into the next update of this review.

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 4, 2002

Date	Event	Description
5 March 2008	Amended	Converted to new review format.

(*Continued*)

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, J Thinkhamrop conducted the literature search under the supervision of the Pregnancy and Childbirth Group's Trials Search Co-ordinator, extracted data, analyzed 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 approve the final version.

For the first version of this review, 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, analyzed 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

- HRP-UNDP/UNFPA/WHO/World Bank Special Programme in Human Reproduction, Geneva, Switzerland.
- Thailand Research Fund/Senior Research Scholar, Thailand.

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 gonococcal infection, detected postpartum, was not prespecified in our protocol.

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

MeSH check words

Female; Humans; Pregnancy