Antibiotics for treating bacterial vaginosis in pregnancy (Review)

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ABSTRACT

Background
Bacterial vaginosis is an imbalance of the normal vaginal flora with an overgrowth of anaerobic bacteria and a lack of the normal lactobacillary flora. Bacterial vaginosis during pregnancy has been associated with poor perinatal outcome and, in particular, preterm birth (PTB). Identification and treatment may reduce the risk of PTB and its consequences.

Objectives
To assess the effects of antibiotic treatment of bacterial vaginosis in pregnancy.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (May 2006).

Selection criteria
Randomized trials comparing antibiotic treatment with placebo or no treatment, or comparing two or more antibiotic regimens in pregnant women with bacterial vaginosis or intermediate vaginal flora.

Data collection and analysis
Two review authors assessed trials and extracted data independently. We contacted study authors for additional information.

Main results
We included fifteen trials of good quality, involving 5888 women. Antibiotic therapy was effective at eradicating bacterial vaginosis during pregnancy (Peto odds ratio (OR) 0.17, 95% confidence interval (CI) 0.15 to 0.20; 10 trials, 4357 women). Treatment did not reduce the risk of PTB before 37 weeks (Peto OR 0.91, 95% CI 0.78 to 1.06; 15 trials, 5888 women), or the risk of preterm prelabour rupture of membranes (PPROM) (Peto OR 0.88, 95% CI 0.61 to 1.28; four trials, 2579 women). However, treatment before 20 weeks' gestation may reduce the risk of preterm birth less than 37 weeks (Peto OR 0.63, 95% CI 0.48 to 0.84; five trials, 2387 women). In women with a previous PTB, treatment did not affect the risk of subsequent PTB (Peto OR 0.83, 95% CI 0.59 to 1.17, five trials of 622); however, it may decrease the risk of PPROM (Peto OR 0.14, 95% CI 0.05 to 0.38) and low birthweight (Peto OR 0.31, 95% CI 0.13 to 0.75)(two trials, 114 women). In women with abnormal vaginal flora (intermediate flora or bacterial vaginosis) treatment may reduce the risk of PTB before 37 weeks (Peto OR 0.51, 95% CI 0.32 to 0.81; two trials, 894 women). Clindamycin did not reduce the risk of PTB before 37 weeks (Peto OR 0.80, 95% CI 0.60 to 1.05; six trials, 2406 women).

Authors' conclusions
Antibiotic treatment can eradicate bacterial vaginosis in pregnancy. This review provides little evidence that screening and treating all pregnant women with asymptomatic bacterial vaginosis will prevent PTB and its consequences. However, there is some suggestion that treatment before 20 weeks' gestation may reduce the risk of PTB. This needs to be further verified by future trials.

PLAIN LANGUAGE SUMMARY

Antibiotics during pregnancy for overgrowth of abnormal bacteria in the birth canal does not reduce the risk of babies being born too early

Bacteria are normally present in the birth canal and are useful in maintaining the health of the vagina. However, if the numbers of abnormal bacteria increase, this may cause an unpleasant discharge and may cause some babies to be born too early. The review of 15 trials, involving 5888 women, found that antibiotics given to pregnant women reduced this overgrowth of bacteria, but did not reduce the numbers of babies who were born too early. The effect of earlier treatment needs to be studied in further trials.

BACKGROUND

Bacterial vaginosis is an imbalance of vaginal flora caused by a reduction of the normal lactobacillary bacteria, and a heavy overgrowth of mixed anaerobic flora including Gardnerella vaginalis, Mycoplasma hominis and Mobiluncus species. Why these organisms multiply, many of which are normally present in small numbers in the vagina, while the usually prevalent lactobacilli decrease, is not clear. The role of hydrogen peroxide-producing lactobacilli appears to be important in preventing overgrowth of anaerobes in normal vaginal flora (Hillier 1993). Bacterial vaginosis does not appear to be sexually transmitted but may be associated with sexual activity.

Bacterial vaginosis is often asymptomatic but may result in a vaginal discharge which can be grey in colour with a characteristic 'fishy' odour. It is not associated with vaginal mucosal inflammation and rarely causes vulval itch.

The classical diagnosis of bacterial vaginosis is confirmed by fulfilling three out of four criteria (Amsel 1983). These are (i) a vaginal pH greater than 4.7, (ii) the presence of 'clue cells' on a Gram stain or wet mount of the vaginal discharge, (iii) the presence of a thin homogenous discharge and (iv) the release of a fishy odour when potassium hydroxide is added to a sample of the discharge. The use of these criteria for diagnosis, however, is complex and time consuming. Use of a Gram stain of a vaginal swab with semi-quantification of the microbial flora has high sensitivity and specificity and is an accepted alternative method which has been used in many studies (Nugent 1991). Scoring systems which weight low numbers or the absence of lactobacilli and large numbers of Gram negative/Gram variable bacilli are routinely used in the clinical laboratory for the diagnosis of bacterial vaginosis from a Gram stain. Clue cells may be present but are not mandatory. The Nugent classification includes an "intermediate" group of women with abnormal genital tract colonisation (reduced lactobacilli and intermediate flora) which may be a transition stage on the way to fully fledged bacterial vaginosis.

Natural history in pregnancy

Bacterial vaginosis is present in up to 20% of women during pregnancy (Lamont 1993). The majority of these cases will be asymptomatic. The natural history of bacterial vaginosis is such that it may spontaneously resolve without treatment although most women identified as having bacterial vaginosis in early pregnancy are likely to have persistent infection later in pregnancy (Hay 1994).

There is now a substantial body of evidence associating bacterial vaginosis in pregnancy with poor perinatal outcome, in particular an increased risk of preterm birth (Hay 1994a; Hillier 1995; Kurki 1992; McGregor 1990), with potential neonatal sequelae due to prematurity. There is also evidence associating intermediate flora with adverse pregnancy outcome (Hay 1994a). Whilst a number of other genital micro-organisms such as Escherichia coli, Listeria monocytogenes and viridans streptococci may be involved in chorioamnionitis, carriage of these organisms during early to mid pregnancy has not been associated with an increased risk of preterm labour. Although maternal carriage of group B streptococcus increases the risk of neonatal sepsis due to this organism, there is conflicting evidence about whether carriage during pregnancy increases the risk of preterm birth. Infections during pregnancy for which there is good evidence of an increased risk of preterm birth and preterm prelabour rupture of the membranes, include asymptomatic bacteriuria, Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis and bacterial vaginosis. The opportunity therefore exists to reduce the preterm birth rate by treatment of these infections during pregnancy.

Bacterial vaginosis is relatively common, even in populations of women at low risk of adverse events and, as it is amenable to treatment (Burtin 1995; Fischbach 1993; McDonald 1994), identification during pregnancy and treatment may present a rare opportunity to reduce the preterm birth rate, and resulting risk of prematurity to the newborn. Such treatment may also reduce other adverse perinatal outcomes such as postpartum infection. However, the question of why bacterial vaginosis is associated with preterm birth in some women but not in others remains unanswered and the exact mechanism by which the organisms associated with bacterial vaginosis may effect the initiation of preterm labour remains unclear. Recent evidence indicates individual susceptibility to preterm birth or intrauterine infection, or both, may be increased by the presence of specific gene polymorphisms (Annells 2004; Annells 2005; Simhan 2003; Witkin 2003). Hence the results of randomized controlled trials of treatment are needed

to provide more direct evidence of the role of bacterial vaginosis in preterm birth.

OBJECTIVES

To determine whether the use of antibiotics for bacterial vaginosis in pregnancy can:
(a) improve maternal symptoms;
(b) decrease incidence of adverse perinatal outcomes.

To determine, if antibiotics are helpful, which antibiotic regimens are most effective.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomized controlled trials that compare (i) one antibiotic regimen with placebo or no treatment or (ii) two or more alternative antibiotic regimens in pregnant women with bacterial vaginosis (however defined).

Types of participants

Women of any age, at any stage of pregnancy with a diagnosis of bacterial vaginosis regardless of method of diagnosis (detected because of symptoms or asymptomatic as part of a screening programme). Co-infection with other sexually transmitted infections is not a reason to exclude a study from the review.

Types of intervention

Any antibiotic (any dosage regimen, any route of administration) compared with either placebo or no treatment.
Any two antibiotic regimens compared.

Types of outcome measures

The outcome measures in this review are as follows.

(A) Maternal symptoms
(i) Clinical report by women of failure of symptoms to improve;
(ii) failure to eradicate bacterial vaginosis on examination (failure to achieve 'microbiological cure');
(iii) incidence of fever during labour or delivery;
(iv) incidence of chorioamnionitis treated with antibiotics;
(v) incidence of postpartum fever;
(vi) incidence of postpartum uterine infection;
(vii) incidence of pregnancy loss up to 24 weeks' gestation (late miscarriage).

(B) Neonatal outcomes

Clinical
(viii) Perinatal death including stillbirth after 24 weeks' gestation and neonatal death, up to 28 days after birth;
(ix) severe neonatal morbidity (moderate to severe respiratory distress syndrome - defined as any ventilatory support, intraventricular haemorrhage, necrotising enterocolitis, chronic lung disease);
(x) neonatal sepsis (defined as definite symptoms or positive cultures from a sterile site - positive culture of gastric aspirates alone will not be sufficient);
(xi) incidence of preterm prelabour rupture of membranes;
(xii) birth less than 37 weeks' gestation;
(xiii) birth less than 34 weeks' gestation;
(xiv) birth less than 32 weeks' gestation;
(xv) incidence of low birthweight (however defined);
(xvi) cerebral palsy at childhood follow up;
(xvii) moderate/severe visual impairment at childhood follow up;
(xviii) moderate/severe hearing impairment at childhood follow up;

Economic
(xxii) Admission to neonatal unit;
(xxiii) total duration of ventilatory support.

(C) Maternal side-effects
(xxiv) Side-effects sufficient to stop or change treatment;
(xxv) other side-effects not sufficient to stop or change treatment.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (May 2006).

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) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

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 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

We applied no language restrictions. We searched cited references from retrieved articles for additional studies and reviewed abstracts and letters to the editor to identify randomized controlled trials that have not been published. We also reviewed editorials, indicating expert opinion, to identify and ensure that no key studies were missed for inclusion in this review.

METHODS OF THE REVIEW

We selected all potential trials for eligibility according to the criteria specified in the protocol. Each of the authors independently abstracted the information necessary for the review from the report and, where necessary, we sought additional information from the authors.

We assessed all trials for methodological quality using the standard Cochrane criteria. As there are a sufficient number of trials in the review, we stratified the trials by quality to explore the robustness of the findings. We calculated summary Peto odds ratios when appropriate (ie there was no evidence of significant heterogeneity) using the Cochrane Review Manager software (RevMan 2003).

Stratified analysis
As there are sufficient trials in the review, the comparisons are stratified to explore the effect of the intervention on the outcomes by the following factors:
(1) oral versus vaginal antibiotics;
(2) women with a previous preterm birth;
(3) women with intermediate flora/bacterial vaginosis;
(4) clindamycin versus placebo treatment;
(5) treatment before 20 weeks' gestation.

It was not possible to stratify results into symptomatic versus asymptomatic bacterial vaginosis because in most trials, women with symptoms were treated with antibiotics and were therefore excluded.

DESCRIPTION OF STUDIES

Fifteen trials, involving 5888 women, are included. *See* table of 'Characteristics of included studies' for details.

Five trials used oral metronidazole alone, one used oral metronidazole plus erythromycin, one oral clindamycin, one ampicillin, one vaginal metronidazole gel, while six used intravaginal clindamycin. Ten trials performed microbiological follow up and seven trials gave a second course of treatment (four only if bacterial vaginosis was not eradicated). One trial compared different antibiotic regimens (once daily versus twice daily vaginal metronidazole).

Two trials which used intermediate vaginal flora (Nugent score four to six) as well as bacterial vaginosis as the basis for recruitment have been included as a separate comparison.

For details of excluded studies, *see* table of 'Characteristics of excluded studies'.

METHODOLOGICAL QUALITY

Overall the quality of the trials was good. All but two of the trials were placebo controlled (one compared once daily versus twice daily regimens, although this was not completed (Porter 2001) and one compared treatment with no treatment (Guaschino 2003). One trial (Duff 1991) did not provide pregnancy outcome data. Eleven trials reported losses to follow up. The description of the interventions was good and the main outcome of all the trials was well described.

However, the interventions differed (oral, intravaginal, metronidazole, clindamycin) as did the timing of the intervention during pregnancy.

Two trials did not report an intention-to-treat analysis (Kiss 2004; Morales 1994). The Morales trial (Morales 1994) excluded women who were not compliant with the treatment allocated (6% of the total trial cohort). Two trials recruited women considered to be at risk of preterm labour on the basis of their past history of spontaneous preterm birth. They were allocated antibiotic or placebo and the results were stratified by whether they did or did not have bacterial vaginosis at that visit (the results of which were available after randomization) (Hauth 1995; Vermeulen 1999). Although this is not ideal, it is unlikely that any selection bias resulted from this process. In addition, in the latter trial only 11 women in each group had bacterial vaginosis. Another trial (Odendaal 2002) included primigravidae from the general population and women with a history of preterm birth or midtrimester miscarriage, or both. A further trial (McDonald 1997) included women with bacterial vaginosis or women with a heavy growth of Gardnerella vaginalis. Women with bacterial vaginosis have been included in this review. In the largest study to date (NICHD MFMU 2000), 1919 women were enrolled from the general population between 18 to 24 weeks, although in some women treatment was delayed up to eight weeks after the detection of bacterial vaginosis, at which time one-quarter of the women in each group had a negative test for bacterial vaginosis. This high rate of spontaneous resolution may have reduced any measurable effect of antibiotic treatment on adverse pregnancy outcomes. A second study from this trial (NICHD MFMU 2001) has now been included containing data not included in the 2000 publication, ie women with Trichomonas and bacterial vaginosis. Two recent trials included women with reduced lactobacilli and intermediate flora as well as those with bacterial vaginosis (Lamont 2003; Ugwumadu 2003). These have been included because of evidence that women with intermediate vaginal flora are also at higher risk of preterm birth (Hay 1994a).

In women with a previous preterm birth, the design of the trials varied. In two trials, women with a previous preterm birth were randomized and a subgroup of them had bacterial vaginosis

(Hauth 1995; Vermeulen 1999). In a third trial, women with bacterial vaginosis were randomized and a subgroup of them had experienced a previous preterm birth (McDonald 1997). The fourth trial did not perform an intention-to-treat analysis (Morales 1994). The fifth trial (Odendaal 2002) enrolled women with a previous preterm birth or a previous midtrimester miscarriage as a separate arm of the trial. In the largest trial (NICHD MFMU 2000) a subgroup of 210 women had a previous preterm birth. (In another trial (Ugwumadu 2003) a subgroup of 74 had a previous preterm birth, however, because the data included late miscarriages and data for elective preterm births were not available, this study was not included here.) In the recent trial added in this update (Kiss 2004), a large number of women were excluded from the analysis; randomization was performed on all enrolled women and a subanalysis of women with bacterial vaginosis was performed.

In two trials (Lamont 2003, Ugwumadu 2003) women with intermediate flora or bacterial vaginosis were considered to have abnormal genital tract flora and were randomized without distinction. These have been put into a separate sixth category for evaluation.

RESULTS

Fifteen trials involving 5888 women were included. The available evidence from these trials suggests that antibiotic treatment given to women with bacterial vaginosis in pregnancy is highly effective at eradicating bacterial vaginosis infection (Peto odds ratio (OR) 0.17, 95% confidence interval (CI) 0.15 to 0.20, 10 trials of 4357 women). There was significant heterogeneity between trials in this 'failure of test of cure' comparison, but using random-effects analysis makes very little difference to the result (Peto OR 0.14, 95% CI 0.08 to 0.25). The effect size is similar whether the antibiotic is given orally or vaginally, although there was no direct head to head comparison of oral versus vaginal treatment (Peto OR 0.15, 95% CI 0.13 to 0.17, seven trials of 3244 women and Peto OR 0.27, 95% CI 0.21 to 0.35, three trials of 1113 women).

There was no statistically significant decrease in the risk of preterm birth less than 37 weeks' gestation for any treatment versus no treatment or placebo (Peto OR 0.91, 95% CI 0.78 to 1.06, 15 trials of 5888 women). There was also no evidence of an effect on birth before 34 weeks' (Peto OR 1.22, 95% CI 0.67 to 2.19, five trials of 851 women), nor for an effect on birth before 32 weeks (Peto OR 1.14, 95% CI 0.76 to 1.70, four trials of 3565 women). The effect of treatment on the incidence of low birthweight suggests no difference (Peto OR 0.95, 95% CI 0.77 to 1.17, seven trials of 4107 women). Antibiotics were not associated with a decrease in the risk of preterm prelabour rupture of membranes (Peto OR 0.88, 95% CI 0.61 to 1.28 four trials of 2579 women), and there was significant heterogeneity between trials. Using random-effects analysis makes little difference to the result (Peto OR 0.71, 95% CI 0.25 to 1.97).

Very few perinatal deaths were reported and only one trial (NICHD MFMU 2000 unpublished) reported substantive measures of neonatal morbidity or economic outcomes such as health service utilisation.

Stratified analyses were possible for (a) whether the antibiotic treatment was oral or vaginal (b) whether the women had experienced a previous preterm birth and (c) whether the woman had intermediate vaginal flora (including bacterial vaginosis), (d) clindamycin treatment (e) treatment before 20 weeks' gestation.

(a) Oral and vaginal antibiotics

Vaginal antibiotics appear to have no effect on any measure of preterm birth: Peto OR 0.88, 95% CI 0.64 to 1.21 for birth less than 37 weeks (five trials of 1921 women); Peto OR 1.79, 95% CI 0.81 to 3.98 for birth less than 32 weeks (one trial of 681 women); and Peto OR 1.14, 95% CI 0.75 to 1.74 for low birthweight (three trials of 1181 women). Oral antibiotics were not associated with an effect on birth less than 37 weeks (Peto OR 0.90, 95% CI 0.75 to 1.08, eight trials of 4069 women, with significant heterogeneity between the studies), nor on preterm prelabour rupture of membranes (Peto OR 0.80, 95% CI 0.54 to 1.19, three trials of 2479 women), birth less than 34 weeks (Peto OR 1.30, 95% CI 0.72 to 2.35, three trials of 819 women), less than 32 weeks (Peto OR 0.98, 95% CI 0.61 to 1.55, three trials of 2884 women) or low birthweight (Peto OR 0.89, 95% CI 0.70 to 1.13, four trials of 2926 women).

(b) Women with a previous preterm birth

In women with a previous preterm birth, the use of antibiotics was associated with a statistically significant decreased risk of preterm prelabour rupture of membranes (Peto OR 0.14, 95% CI 0.05 to 0.38, two trials of 114 women), and low birthweight (Peto OR 0.31, 95% CI 0.13 to 0.75, two trials of 114 women). There is no evidence of an effect on birth less than 37 weeks (Peto OR 0.83, 95% CI 0.59 to 1.17, five trials of 622 women, with significant heterogeneity between these trials), birth less than 34 weeks (Peto OR 1.21, 95% CI 0.59 to 2.49, four trials of 257 women) nor on birth less than 32 weeks (Peto OR 0.49, 95% CI 0.05 to 5.08, one trial of 34 women).

(c) Intermediate flora including bacterial vaginosis

In two trials of 894 women with abnormal vaginal flora (intermediate flora or bacterial vaginosis), the use of antibiotics (one trial used oral clindamycin, the other vaginal) was associated with a statistically significant decreased risk of preterm birth less than 37 weeks (Peto OR 0.51, 95% CI 0.32 to 0.81). However, there was no difference in other outcome measures such as preterm birth less than 32 weeks or low birthweight, etc.

(d) Clindamycin (oral or vaginal) treatment

Although Clindamycin may have more antimicrobial activity than metronidazole against Mobiluncus species (these are often present in bacterial vaginosis), in six trials of 2406 women clindamycin was effective against bacterial vaginosis (Peto OR 0.14, 95% CI

0.12 to 0.18) but did not significantly lower the preterm birth rate before 37 weeks (Peto OR 0.80, 95% CI 0.60 to 1.05).

(e) Treatment before 20 weeks' gestation
In five trials of 2387 women who were treated before 20 weeks' gestation, the use of antibiotics was associated with a statistically significant decreased risk of preterm birth less than 37 weeks (Peto OR 0.63, 95% CI 0.48 to 0.84).

The one trial of 94 women comparing once daily with twice daily vaginal metronidazole did not show a difference in gestation of birth or low birthweight.

The addition of further data from the NICHD MFMU study has enlarged the meta-analysis of the impact of antibiotic treatment on neonatal sepsis and mortality. However, no significant decrease in neonatal sepsis was found.

Side-effects with the drug regimens included in the trials seem to be uncommon (although not reported in many of the studies), and they do not appear to result in large numbers of women having to stop treatment.

DISCUSSION

There is now a substantial body of evidence that associates bacterial vaginosis in pregnancy with a poor perinatal outcome, in particular an increased risk of preterm birth. This strong association between bacterial vaginosis and preterm birth has led many researchers and clinicians to believe that bacterial vaginosis may be the cause of preterm birth in these women.

The results of trials that treat bacterial vaginosis in pregnancy, however, are not encouraging. Previously, there was some suggestion, albeit based on small numbers of women, that antibiotic treatment on bacterial vaginosis in pregnancy can reduce the risk of preterm prelabour rupture of membranes. However, with the addition of three trials (Guaschino 2003; NICHD MFMU 2000; NICHD MFMU 2001), the association has weakened. There is some suggestion that identification and treatment of women with a previous preterm birth, who have asymptomatic bacterial vaginosis in pregnancy, may result in a decrease in the risk of subsequent low birthweight infant and preterm prelabour rupture of membranes. An earlier Cochrane review containing three trials of high risk women suggested an association between antibiotic treatment and a decreased risk of preterm birth, but with the addition of two recent trials (NICHD MFMU 2000; Odendaal 2002), no such association persists. (The relevant data on low birthweight and preterm prelabour rupture of membranes were not available for these recent studies, and the previous associations with low birthweight and preterm prelabour rupture of membranes remain). The basis for enrolment in Odendaal's trial included both previous midtrimester miscarriage and preterm birth (Odendaal 2002).

The two recent trials of women with abnormal vaginal flora, ie intermediate flora or bacterial vaginosis (Lamont 2003; Ugwumadu 2003), showed significant association with preterm birth less than 37 weeks' gestation, which the authors postulate may be due to the earlier gestation of treatment in both these studies (13 to 20 weeks (Lamont 2003) and 12 to 22 weeks, mean 15.6 (Ugwumadu 2003)). When analysed as a separate category, antibiotic treatment of abnormal flora resulted in a significant decrease in preterm birth. However, their inclusion in meta-analysis of all the trials has not made a substantial difference to the overall picture.

The results of the five trials (Kekki 1999; Kiss 2004; Lamont 2003; Morales 1994; NICHD MFMU 2000) in which women were treated before 20 weeks' gestation are encouraging, showing a significant association between treatment and preterm birth less than 37 weeks. However this finding needs to be further verified by future trials as there have been no head to head comparisons of early versus late treatment. The only trial large enough to stratify their results by early or later treatment failed to show any difference in effect when comparing earlier versus later treatment, although it could be argued that even in the early group, treatment was not started early enough.

Additional information on neonatal sepsis from the large NICHD MFMU trial has now been included in the analysis but provides no evidence of a reduction in neonatal sepsis.

Significant heterogeneity was found in several analyses - in the 'failure of cure' analysis this is probably due to differences in the timing of the test of cure and the method for determining test of cure. Also trials in this review have used several different methods of diagnosing bacterial vaginosis or abnormal genital flora (Amsel or clinical criteria, Gram stain criteria, and abnormal flora Nugent score 4-10. In the outcome 'preterm birth less than 37 weeks' heterogeneity occurred in the high-risk population subgroup, but not in the general population. This may be due to the variation in criteria for determining high-risk status. The heterogeneity seen in the oral antibiotics comparison of 'preterm birth less than 37 weeks' is similarly due to inclusion of a high risk study (Morales 1994).

Limitations of the trials
The trial protocols differ in a number of ways such as the method for diagnosing bacterial vaginosis, timing of screening, timing of treatment, and the period between screening and treatment. Most trials have tested treatment in the second trimester; some as late as 28 weeks' gestation. This may be too late to prevent ascending infection and may be one of the main reasons for the observed lack of a statistically significant effect on the preterm birth rates. The five studies in which women were treated before 20 weeks (Kekki 1999; Kiss 2004; Lamont 2003; Morales 1994; NICHD MFMU 2000 subgroup) showed a decrease in risk of preterm birth. Secondly, the efficacy of antibiotic treatment in long-term eradication of bacterial vaginosis is at best 80%. The subgroups of women in whom bacterial vaginosis was successfully eradicated,

and those with recurring bacterial vaginosis, need to be identified and studied more closely in future trials.

Most trials have concentrated on the timing of birth and have made the assumption that the later in gestation a baby is born, the greater are its chances of disability-free survival. This may not be the case, however. Neonatal wellbeing and measures of maternal postpartum morbidity were each reported by two trials. However, the majority of outcomes we considered important for this review were not mentioned.

Since the first publication of the earlier Cochrane review in 1998 (Brocklehurst 1998), the number of women in this meta analysis has trebled, largely due to the inclusion of the NICHD MFMU 2000 and NICHD MFMU 2001 studies with 2132 women. This fourth review has increased the trial numbers by 586. Although there is still no evidence that screening and treating all women with bacterial vaginosis in the antenatal period will have a major impact on the consequences of preterm birth, there is now a suggestion that early treatment may be more effective.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence to date does not suggest any benefit in screening and treating all pregnant women for asymptomatic bacterial vaginosis to prevent preterm birth. The lack of a significant effect despite large numbers of women in the included trials may be due to many differences within the trials regarding diagnosis, timing of treatment and antibiotic choice. In considering the implications for clinical practice it should be remembered, however, that women with symptomatic bacterial vaginosis were generally absent from these trials due to treatment of their symptoms with antibiotics. These women, especially those with recurrent or persistent bacterial vaginosis, may be at highest risk of associated adverse outcomes. Unfortunately, from studies to date we know almost nothing about the impact of these interventions on the health of the baby.

At the present time, there seems little justification for initiating a policy of screening for asymptomatic bacterial vaginosis in pregnancy. Any impact may be dependent upon early detection and treatment.

Implications for research

The consequences of preterm birth to the individuals concerned and the health services are of major importance. Any intervention with the potential to decrease the risk of mortality and morbidity associated with neonatal immaturity, therefore, needs prompt and appropriate evaluation so that any benefits may be maximised. The focus of current research is to identify those subgroups of pregnant women who are at highest risk for adverse sequelae of bacterial vaginosis. These subgroups include women with recurrent or persistent bacterial vaginosis. Individual susceptibility to preterm birth may also be increased by the presence of specific gene polymorphisms, producing a heightened inflammatory response to vaginal or intrauterine infection. In addition, recent findings suggest future studies may need to focus on earlier detection and treatment of bacterial vaginosis in the first trimester of pregnancy, or better still, preconception.

What then remains to be demonstrated is that a policy for screening and treatment for asymptomatic bacterial vaginosis in pregnancy can reduce substantive measures of morbidity associated with neonatal immaturity, and that this results in cost savings to families and the health services. Large trials are needed which can determine the effect of a screening programme on neonatal mortality and major measures of morbidity such as intracranial damage and chronic lung disease. For example, in the NICHD MFMU trial, to reduce the incidence of neonatal morbidity by 25% (1.9% to 1.4%) with 90% power, significant at the 5% level, would require recruitment of at least 28,000 women.

If the detection and treatment of bacterial vaginosis can be shown to improve neonatal outcome, further trials will be necessary to determine the most effective antibiotic regimen.

FEEDBACK

Klebanoff, October 2005

Summary

I have a couple of minor technical corrections. First, the NICHD trial (NICHD MFMU 2000) randomized women from 16 to 24 weeks, not from 18 to 24 weeks. In fact, these women were randomized not much later than those in Ugwumadu 2003.

Second, women with bacterial vaginosis plus Trichomonas were not eligible for the NICHD study included in this review. However, they were randomized into a parallel NICHD Trichomonas study .[1] In that study, we presented results separately for women who had Trichomonas only and women who had Trichomonas plus bacterial vaginosis. Since many other bacterial vaginosis trials did not screen for Trichomonas, and therefore probably randomized some women who had both, there is no reason to exclude such women recruited to our second study from your review.

Finally, our original draft of the paper for NICHD MFMU 2000 included data on neonatal mortality and morbidity. This table was removed at the request of the NEJM Editor. If you wish, I can investigate whether we can provide you with this additional data.

Reference

[1] Klebanoff MA, Carey JC, Hauth JC, Hillier SL, Nugent RP, Thom EA, et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic Trichomonas vaginalis infection. N Engl J Med. 2001;345:487-93.

(Summary of comments from Mark Klebanoff, October 2005)

Author's reply

Thank you very much for your comments. We have addressed each of your points in this update as follows:
(1) the information about NICHD MFMU 2000 is now correct, women were enrolled between 16 to 24 weeks;
(2) we have included the published data from the NICHD Trichomonas study (NICHD MFMU 2001);
(3) data from NICHD MFMU 2000 on neonatal mortality and morbidity supplied by the authors have been included.

(Summary of response from Helen McDonald, November 2006)

Contributors

Mark Klebanoff

POTENTIAL CONFLICT OF INTEREST

Helen McDonald is the author of one of the included trials in this review.

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Professor Mary Hannah, Women's College Hospital, University of Toronto, Ontario, Canada: co-author on the first review.
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Internal sources of support

- Women's and Children's Hospital, North Adelaide AUSTRALIA

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Duff 1991**
Methods	"Adaptive randomization plan using a biased-can technique which balanced the groups after every 6 enrollees."
Participants	Women were screened for BV at 15-25 weeks' gestation. BV diagnosed on Gram stain (Nugents criteria). Exclusions: penicillin allergy, antimicrobial use within 2 weeks of enrolment, anticipated movement away from area, inability to speak English, diabetes, cervical cerclage, multiple pregnancy, hypertension on treatment, pregnancy-induced hypertension, fetal anomalies.
Interventions	Amoxycillin 500 mg x 3/day for 14 days or matching placebo.
Outcomes	"Test-of-cure" 2 weeks after treatment complete, at 34-36 weeks and at admission in labour; preterm delivery; low birthweight; premature rupture of membranes; neonatal sepsis; maternal infection.

Characteristics of included studies (*Continued*)

Notes	At randomization 54 antibiotic group vs 54 placebo. Loss to follow up - 7/54 (13%) in amoxycillin group, 9/54 (17%) in placebo group.
Allocation concealment	A – Adequate

Study	**Guaschino 2003**
Methods	Phoned to randomization centre - randomization lists stratified for centre.
Participants	Pregnant women between 14-25 weeks with asymptomatic BV.
Interventions	Intravaginal clindamycin 2% cream once daily for 7 days, vs no treatment.
Outcomes	Preterm delivery < 37 weeks. Low BW, PROM
Notes	At randomization 49 antibiotic vs 51 no treatment. Not blinded. No placebo. 10.7% lost to follow up, 6 in each group.
Allocation concealment	C – Inadequate

Study	**Hauth 1995**
Methods	Blocked randomization scheme of 2:1 generated by investigational drug service.
Participants	Pregnant women at 22-24 weeks' gestation with history of previous preterm delivery or who weighed < 50 kg in current pregnancy. All women were screened for BV (diagnosed by Amsels criteria). Exclusions: allergies to metronidazole or erythromycin, uncertain gestational age, multiple pregnancy, prior vaginal bleeding, medical complications, any antibiotic use in the previous 4 weeks, co-infection with gonorrhoea, trichomonas or vaginal candida.
Interventions	Metronidazole 250 mg x 3/day for 7 days plus erythromycin base 333 mg x 3/day for 14 days or matching placebo. Treatment repeated if BV still present at "test-of-cure". Rx mean 27.6 weeks.
Outcomes	"Test-of-cure" 2 to 4 weeks after treatment; preterm delivery before 37 weeks.
Notes	All women who were enrolled in the trial were treated with antibiotics/placebo at trial entry regardless of whether they had BV - this formed a post-randomization stratification. BV positive women - 176 antibiotic vs 87 placebo. Loss to follow up for the whole trial cohort - 7/176 (4%) in antibiotic group, 1/87 (1%) in placebo group. Data not provided for the subset with bacterial vaginosis.
Allocation concealment	B – Unclear

Study	**Joesoef 1995**
Methods	Random-number generator in balanced blocks of 6. Stratified by centre.
Participants	Pregnant women screened at 14-26 weeks for BV (Nugents criteria). Exclusions: allergy to clindamycin, medical condition associated with preterm delivery (hypertension, multiple pregnancy, diabetes etc), previous tocolytic treatment, previous steroid treatment, antibiotics in 2 weeks before trial entry, age < 15 years, uterine or fetal abnormalities or incompetent cervix.
Interventions	Clindamycin cream 2% - 5 g intravaginally at bedtime for 7 days or matching placebo. 43% enrolled @ less than 20 weeks.
Outcomes	"Test-of-cure" 2 weeks after completion of treatment and again after 34 weeks; preterm delivery < 37 and < 32 weeks; low birthweight (< 2500 g).
Notes	At randomization 340 antibiotic vs 341 placebo. Loss to follow up - 64/745 (9%).

Characteristics of included studies (*Continued*)

Allocation concealment	A – Adequate

Study	**Kekki 1999**
Methods	Block randomization within each centre (3 centres). Allocation in sealed envelopes. Double blinded.
Participants	Pregnant women with BV (screened at 10-17 weeks, using Spiegel's criteria). Exclusions: multiple pregnancy, history of preterm birth, induced/spontaneous abortion, move to another city.
Interventions	2% vaginal clindamycin cream (single course) for 7 days or matching placebo for 7 days. Randomized @ 12-19 weeks.
Outcomes	"Test-of-cure" 1 week after treatment; spontaneous preterm delivery < 37 weeks' gestation; peripartum infectious morbidity (postpartum endometritis, postpartum sepsis, caesarian section wound infection, episiotomy infection necessitating antibiotic treatment).
Notes	At randomization 187 antibiotic vs 188 placebo. No dropouts, but 35 attended only 1 follow up visit. 21 (6%) given additional topical treatment for symptomatic BV. Intention-to-treat analysis.
Allocation concealment	A – Adequate

Study	**Kiss 2004**
Methods	Computer-generated randomization list.
Participants	Pregnant women at 15-19 weeks' gestation all screened for BV (Nugents criteria) Exclusions: subjective complaints of vaginal infection, multiple pregnancy.
Interventions	2% vaginal clindamycin cream for 6 days, given 7-10 days after diagnosis. (12-19 weeks). No treatment for control group. Retreated if still present @ follow up.
Outcomes	Preterm birth < 37 weeks, intrauterine death, miscarriage, bw < 2500, < 2000 ,< 1500 and < 1000 g.
Notes	Not intention-to-treat. 274 excluded from analysis post randomization leaving 177 antibiotic vs 179 placebo. Lost to follow up 8 in BV group and 13 in controls.
Allocation concealment	A – Adequate

Study	**Lamont 2003**
Methods	Computerised block randomization (block size 10).
Participants	Asymptomatic pregnant women 13-20 weeks with BV or intermediate flora by Nugent's criteria. Excluded women with sensitivity to clindamycin; history of antibiotic-related colitis; inflammatory bowel disease or frequent periodic diarrhoea.
Interventions	5 g of 2% clindamycin intravaginal cream (+ 100 mg) or placebo for 3 nights. In addition 7 extra days if vaginal swab still positive (BV/intermediate flora) at visit 2.
Outcomes	Preterm birth < 37 weeks; low birthweight, very low birthweight, stillborn.
Notes	Intent-to-treat analysis. 30 did not return for visit 2 in clindamycin group, and 11 in the placebo group, leaving 208 antibiotic vs 201 placebo.
Allocation concealment	D – Not used

Study	**McDonald 1997**
Methods	Random-number tables in balanced blocks of 16 for each centre.
Participants	Pregnant women at 18 weeks' gestation with BV or Gardnerella vaginalis.

Characteristics of included studies (*Continued*)

	Exclusions: multiple pregnancy, age < 17 years, in-vitro fertilisation, allergy to metronidazole, symptomatic BV requiring treatment, ruptured membranes, cervical cerclage, diabetes, placenta previa, antibiotic treatment for vaginitis within 2 weeks of trial entry, inability to attend before 28 weeks, language difficulties.
Interventions	Metronidazole 400 mg x 2/day for 2 days at 24 weeks' gestation or matching placebo. If repeat swabs remained positive at 28 weeks' gestation a further course of treatment was given.
Outcomes	Preterm birth < 37 weeks; preterm premature rupture of the membranes; stratified by previous history of preterm delivery.
Notes	The women included in this review were the subset of women with bacterial vaginosis, (56% of total trial cohort). Women with a heavy growth of Gardnerella but no bacterial vaginosis have not been included. Loss to follow up - 10/439 (2%) metronidazole group, 12/440 (3%) placebo group. Leaving BV positive randomized to 242 antibiotic vs 238 placebo Additional information supplied by investigator.
Allocation concealment	A – Adequate

Study	**Morales 1994**
Methods	Random-number tables.
Participants	Pregnant women with a previous preterm delivery who were screened for BV at 13-20 weeks (Amsels criteria). Exclusions: trichomonas infection, medical complications, cocaine use, previous preterm delivery due to intrauterine infection or incompetent cervix, antibiotic use during 2 weeks prior to trial entry, lethal fetal abnormality, 2nd trimester bleeding, asymptomatic bacteriuria on initial screen.
Interventions	Metronidazole 250 mg x 3/day for 7 days or matching vitamin C placebo.
Outcomes	Admission for preterm labour; preterm birth (< 34 and < 37 weeks); low birthweight (< 2500 g); preterm rupture of membranes.
Notes	Not intention-to-treat analysis - women were excluded from the analysis if they failed to complete the assigned treatment - 6/94 women in total (6%). Loss to follow up - 5/94 in total (5%). Leaving 44 antibiotic vs 36 placebo.
Allocation concealment	A – Adequate

Study	**NICHD MFMU 2000**
Methods	Computer-generated randomization, with stratification according to clinical centre.
Participants	Pregnant women at 16-23 + 6 weeks with asymptomatic BV (not TV+) (screened at 8-22 + 6 weeks) gestation. Excluded: multifetal gestation; allergy to metronidazole; current abuse of ethanol; antibiotic treatment within previous 14 days; intention to receive antenatal care or deliver at location where no follow up possible; planned antibiotic treatment before delivery; current/planned Cx cerclage; preterm labour before screening; current/planned tocolytic treatment; fetal death/known life-threatening anomaly; medical illnesses requiring long-term/intermittent drug treatment: if received any antibiotics between screening and study treatment, if time between screening and randomization exceeded 8 weeks, or if tests for syphilis or chlamydia were positive.
Interventions	8 x 250 mg dose oral metronidazole or placebo plus repeat dose in 48 hours (@ 16-23 + 6 weeks' gestation). Second treatment at 24-30 weeks' gestation.
Outcomes	"Test-of-cure" at least 14 days after initial visit and before second treatment; gestational age at delivery; birthweight; pPROM (at least 1 hr); clinical intra-amniotic infection; postpartum endometritis; neonatal sepsis; use of tocolytic drugs; visits and admissions to hospital; preterm labour.

Characteristics of included studies (*Continued*)

Notes	Low recruitment response - only 29% BV+ women were enrolled. 10% did not return for follow up visit, leaving 953 antibiotic vs 966 placebo. Unpublished data on neonatal morbidity and admission to a neonatal unit were supplied by the authors.
Allocation concealment	C – Inadequate

Study	**NICHD MFMU 2001**
Methods	Computer-generated randomization, with stratification according to clinical centre, based on Trichomonas positive result.
Participants	Pregnant women at 16-23 + 6 weeks with positive culture for trichomonas vaginalis plus asymptomatic BV (screened at 8-22 + 6 weeks' gestation). Excluded: multifetal gestation; allergy to metronidazole; current abuse of ethanol; antibiotic treatment within previous 14 days; intention to receive antenatal care or deliver at location where no follow up possible; planned antibiotic treatment before delivery; current/planned Cx cerclage; preterm labour before screening; current/planned tocolytic treatment; fetal death/known life-threatening anomaly; medical illnesses requiring long-term/intermittent drug treatment: if received any antibiotics between screening and study treatment, if time between screening and randomization exceeded 8 weeks, or if tests for syphilis or chlamydia were positive.
Interventions	8 x 250 mg dose oral metronidazole or placebo plus repeat dose in 48 hours. Second treatment at 24-30 weeks gestation
Outcomes	Preterm delivery; birthweight; antibiotics prescribed after randomization;hospital admissions for preterm labour or PPROM; tocolysis; preterm rupture of membranes; clinical intra-amniotic infection; postpartum endometritis; suspected or confirmed neonatal sepsis.
Notes	Parallel study to NICHD MFMU 2000 assessing Met vs placebo for those with positive trichomonas. Subgroup that had BV plus trichomonas analysed. 119 antibiotic vs 113 placebo.
Allocation concealment	A – Adequate

Study	**Odendaal 2002**
Methods	Blocked randomization using computer, but not done separately for 2 groups.
Participants	2 groups of women with BV (Spiegel's criteria): primigravidae at first antenatal visit, between 15 and 26 weeks' gestation; women with a previous preterm labour/midtrimester miscarriage. Exclusions: multiple pregnancy; known cervical incompetence.
Interventions	Oral metronidazole 400 mg twice daily for 2 days and if still BV positive after 4 weeks, repeat treatment course, or placebo containing 100 mg vitamin C at matching times.
Outcomes	"Test-of-cure" 4 weeks after; preterm delivery < 37, < 34, < 28 weeks' gestation; birthweight; intrauterine death; neonatal death; perinatal death; 5-minute Apgar score.
Notes	Women with a history of taking antibiotics within the previous 2 weeks had enrolment postponed for 2 weeks. Lost to follow up participants not separated into treatment/placebo. Intention-to-treat analysis of 128 antibiotic vs 127 placebo.
Allocation concealment	A – Adequate

Study	**Porter 2001**
Methods	Randomization method unknown.
Participants	Pregnant women with BV at 12 to 28 weeks' gestation (3 out of 4 Amsel criteria confirmed by Nugent's and Spiegel's criteria).
Interventions	Once daily vs twice daily vaginal metronidazole gel (0.75%) for 5 days (no placebo). Repeat treatment if positive at follow up.

Outcomes	"Test-of-cure" at unknown time after treatment; gestation at delivery; birthweight; 1-min and 5-min Apgar scores; caesarean section rate; spontaneous rupture of membranes; intra-amniotic infection; endometritis; bladder infection.
Notes	Study not yet completed. 186 out of 194 delivered at his point. No further publication of data.
Allocation concealment	B – Unclear

Study	**Ugwumadu 2003**
Methods	Computer-generated randomization. Allocation blinded until after data analysis.
Participants	Pregnant women (12-22 weeks) with asymptomatic intermediate flora (Nugent score 4-6) or BV (Nugent 7-10).
Interventions	Oral clindamycin 300 mg or placebo twice daily for 5 days.
Outcomes	Spontaneous preterm birth (> or = 24 to < 37 weeks and late miscarriage (> or = 13 weeks but < 24 weeks). Death in utero. "Test of cure" at 14 days post AB or placebo, NICU admission, BW < 2500, BW < 1500.
Notes	Intention-to-treat analysis. 9 women lost to follow up, leaving 244 antibiotic vs 241 placebo. PTB stratified by Nugent score 1-10, previous PTB, and race.
Allocation concealment	A – Adequate

Study	**Vermeulen 1999**
Methods	Blocks of 4 stratified by centre and by BV.
Participants	Pregnant women with a history of spontaneous preterm birth in preceding pregnancy. Exclusions: multiple pregnancy, major fetal congenital anomalies, previous preterm birth associated with hypertension or pre-eclampsia, placental disorders, congenital uterine anomalies, maternal diseases or allergy to clindamycin.
Interventions	2% clindamycin vaginal cream or placebo daily for 7 days at 26 weeks and again at 32 weeks.
Outcomes	Spontaneous preterm delivery < 37 weeks; admission for threatened preterm labour; neonatal infectious morbidity; infectious morbidity associated with sepsis; pneumonia.
Notes	Treated all high-risk women with and without BV. Low sample size: needed 566 but enrolled 168. Only 11 BV positive women in antibiotic group vs 11 placebo. Intention-to-treat analysis.
Allocation concealment	B – Unclear

AB: antibiotic
BV: bacterial vaginosis
BW: birthweight
Cx: cervix
hr: hour
MET: metronidazole
min: minutes
NICU: neonatal intensive care unit
pPROM: preterm premature rupture of membranes
PROM: premature rupture of membranes
PTB: preterm birth
TV: Trichomonas vaginalis
vs: versus

Characteristics of excluded studies

Study	**Reason for exclusion**
Andrews 2005	Women not pregnant at randomization and treatment plus women not specifically screened for bacterial vaginosis.

Characteristics of excluded studies (*Continued*)

Goldenberg 2006	Studied 3120 HIV+ and 600 HIV- women. No pregnancy outcomes for bacterial vaginosis positive women.
Hawkinson 1966	Study conducted before diagnostic criteria for bacterial vaginosis were established.
Hitti 2002	No pregnancy-outcome data.
Holst 1990	Not a randomized trial. Not an evaluation of an antibiotic regimen.
Klebanoff 2004	Study of regression of asymptomatic BV. No pregnancy outcome data.
Leitich 2003	Meta-analysis of existing studies.
McGregor 1994	This was a two phase observational trial (phase 1 - examination for BV and micro-organisms: phase 2 - treatment for infected women) and is not a randomized placebo-controlled trial.
Neri 1993	Intervention agent yoghurt. Did not fulfil entry criteria for review.
Paternoster 2004	Intervention not antibiotic.
Rosnes 2002	No evaluation of pregnancy outcome.
Shennan 2006	No outcomes for women with bacterial vaginosis.
Steyn 2003	Not an evaluation of an antibiotic regimen.
Thiagarajan 1998	No evaluation of pregnancy outcome.
Ugwumadu 1999	No usable data available, trial report in abstract form only.
Yudin 2002	No evaluation of pregnancy outcome.
Yudin 2003	No evaluation of pregnancy outcome.

BV: bacterial vaginosis

ANALYSES

Comparison 01. Any antibiotic versus placebo/no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure of test of cure	10	4357	Peto Odds Ratio 95% CI	0.17 [0.15, 0.20]
02 Postpartum infection	2	618	Peto Odds Ratio 95% CI	0.67 [0.39, 1.17]
03 Perinatal death	3	2666	Peto Odds Ratio 95% CI	0.96 [0.53, 1.73]
04 Incidence of preterm prelabour rupture of membranes	4	2501	Peto Odds Ratio 95% CI	1.10 [0.74, 1.63]
05 Preterm birth < 37 weeks	15	5888	Peto Odds Ratio 95% CI	0.91 [0.78, 1.06]
06 Preterm birth < 34 weeks	5	851	Peto Odds Ratio 95% CI	1.22 [0.67, 2.19]
07 Preterm birth < 32 weeks	4	3565	Peto Odds Ratio 95% CI	1.14 [0.76, 1.70]
08 Incidence of low birthweight	7	4107	Peto Odds Ratio 95% CI	0.95 [0.77, 1.17]
09 Neonatal sepsis	3	2345	Peto Odds Ratio 95% CI	1.40 [0.45, 4.36]
10 Side-effects sufficient to stop treatment	3	1450	Peto Odds Ratio 95% CI	1.57 [0.95, 2.59]
11 Side-effects not sufficient to stop treatment	3	1340	Peto Odds Ratio 95% CI	1.33 [0.73, 2.42]
12 Severe neonatal morbidity	1	1917	Peto Odds Ratio 95% CI	0.96 [0.50, 1.84]
13 Admission to neonatal unit	2	2383	Peto Odds Ratio 95% CI	1.11 [0.87, 1.41]

Comparison 02. Oral antibiotics versus placebo/no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure of test of cure	7	3244	Peto Odds Ratio 95% CI	0.15 [0.13, 0.17]
02 Postpartum uterine infection	1	243	Peto Odds Ratio 95% CI	2.69 [0.37, 19.30]
03 Perinatal death	3	2656	Peto Odds Ratio 95% CI	0.94 [0.52, 1.70]
04 Incidence of preterm prelabour rupture of membranes	3	2479	Peto Odds Ratio 95% CI	0.80 [0.54, 1.19]
05 Preterm birth < 37 weeks	8	4069	Peto Odds Ratio 95% CI	0.90 [0.75, 1.08]
06 Preterm birth < 34 weeks	3	819	Peto Odds Ratio 95% CI	1.30 [0.72, 2.35]
07 Preterm birth < 32 weeks	3	2884	Peto Odds Ratio 95% CI	0.98 [0.61, 1.55]
08 Incidence of low birthweight	4	2926	Peto Odds Ratio 95% CI	0.89 [0.70, 1.13]
09 Neonatal sepsis	2	2323	Peto Odds Ratio 95% CI	1.40 [0.45, 4.36]
10 Side-effects sufficient to stop treatment	2	965	Peto Odds Ratio 95% CI	1.30 [0.69, 2.47]
11 Side-effects not sufficient to stop treatment	2	965	Peto Odds Ratio 95% CI	1.47 [0.73, 2.99]
12 Severe neonatal morbidity	1	1917	Peto Odds Ratio 95% CI	0.96 [0.50, 1.84]
13 Admission to a neonatal unit	2	2383	Peto Odds Ratio 95% CI	1.11 [0.87, 1.41]

Comparison 03. Vaginal antibiotics versus placebo/no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure of test of cure	3	1113	Peto Odds Ratio 95% CI	0.27 [0.21, 0.35]
02 Postpartum uterine infection	1	375	Peto Odds Ratio 95% CI	0.60 [0.34, 1.07]
03 Perinatal death	1	409	Peto Odds Ratio 95% CI	0.35 [0.05, 2.52]
04 Incidence of preterm prelabour rupture of membranes	1	100	Peto Odds Ratio 95% CI	2.52 [0.69, 9.25]
05 Preterm birth < 37 weeks	5	1921	Peto Odds Ratio 95% CI	0.88 [0.64, 1.21]
06 Preterm birth < 34 weeks	1	22	Peto Odds Ratio 95% CI	1.00 [0.06, 17.12]
07 Preterm birth < 32 weeks	1	681	Peto Odds Ratio 95% CI	1.79 [0.81, 3.98]
08 Incidence of low birthweight	3	1181	Peto Odds Ratio 95% CI	1.14 [0.75, 1.74]
09 Neonatal sepsis	2	431	Peto Odds Ratio 95% CI	1.17 [0.58, 2.39]
10 Side-effects not sufficient to stop treatment	1	375	Peto Odds Ratio 95% CI	1.01 [0.32, 3.17]

Comparison 04. Previous preterm delivery: antibiotics versus placebo/no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure of test of cure	2	201	Peto Odds Ratio 95% CI	0.11 [0.06, 0.19]
02 Postpartum uterine infection	1	15	Peto Odds Ratio 95% CI	Not estimable
03 Perinatal death	2	155	Peto Odds Ratio 95% CI	3.64 [0.86, 15.45]
04 Incidence of preterm prelabour rupture of membranes	2	114	Peto Odds Ratio 95% CI	0.14 [0.05, 0.38]
05 Preterm delivery < 37 weeks	5	622	Peto Odds Ratio 95% CI	0.83 [0.59, 1.17]
06 Preterm delivery < 34 weeks	4	257	Peto Odds Ratio 95% CI	1.21 [0.59, 2.49]
07 Preterm delivery < 32 weeks	1	34	Peto Odds Ratio 95% CI	0.49 [0.05, 5.08]
08 Incidence of low birthweight	2	114	Peto Odds Ratio 95% CI	0.31 [0.13, 0.75]

09 Neonatal sepsis	2	52	Peto Odds Ratio 95% CI	Not estimable

Comparison 05. Single daily dose versus double daily dose vaginal antibiotic

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Postpartum uterine infection	1	94	Peto Odds Ratio 95% CI	3.08 [0.42, 22.59]
02 Preterm delivery < 37 weeks	1	94	Peto Odds Ratio 95% CI	0.40 [0.11, 1.39]
03 Incidence of low birthweight	1	94	Peto Odds Ratio 95% CI	1.25 [0.49, 3.20]

Comparison 06. Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure of test of cure	1	462	Peto Odds Ratio 95% CI	0.04 [0.03, 0.05]
02 Perinatal death	2	894	Peto Odds Ratio 95% CI	0.50 [0.10, 2.48]
03 Preterm birth < 37 weeks	2	894	Peto Odds Ratio 95% CI	0.51 [0.32, 0.81]
04 Preterm birth < 32 weeks	1	485	Peto Odds Ratio 95% CI	1.49 [0.53, 4.16]
05 Incidence of low birthweight	2	876	Peto Odds Ratio 95% CI	0.95 [0.59, 1.52]
06 Late miscarriage	1	485	Peto Odds Ratio 95% CI	0.25 [0.08, 0.79]
07 Side-effects sufficient to stop or change treatment	1	485	Peto Odds Ratio 95% CI	2.11 [0.94, 4.71]
08 Admission to neonatal unit	1	466	Peto Odds Ratio 95% CI	0.73 [0.39, 1.39]

Comparison 07. Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure of test of cure	4	1575	Peto Odds Ratio 95% CI	0.14 [0.12, 0.18]
02 Postpartum uterine infection	1	375	Peto Odds Ratio 95% CI	0.60 [0.34, 1.07]
03 Perinatal death	2	894	Peto Odds Ratio 95% CI	0.50 [0.10, 2.48]
04 Incidence of preterm prelabour rupture of membranes	1	100	Peto Odds Ratio 95% CI	2.52 [0.69, 9.25]
05 Preterm birth < 37 weeks	6	2406	Peto Odds Ratio 95% CI	0.80 [0.60, 1.05]
06 Preterm birth < 34 weeks	1	22	Peto Odds Ratio 95% CI	1.00 [0.06, 17.12]
07 Preterm birth < 32 weeks	2	1166	Peto Odds Ratio 95% CI	1.67 [0.89, 3.14]
08 Incidence of low birthweight	4	1648	Peto Odds Ratio 95% CI	1.03 [0.73, 1.45]
09 Neonatal sepsis	2	431	Peto Odds Ratio 95% CI	1.17 [0.58, 2.39]
10 Side-effects sufficient to stop or change treatment	1	485	Peto Odds Ratio 95% CI	2.11 [0.94, 4.71]
11 Late miscarriage	1	485	Peto Odds Ratio 95% CI	0.25 [0.08, 0.79]
12 Admission to neonatal unit	1	466	Peto Odds Ratio 95% CI	0.73 [0.39, 1.39]

Comparison 08. Treatment at less than 20 weeks' gestation

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Failure of test of cure	2	442	Peto Odds Ratio 95% CI	0.21 [0.14, 0.30]
02 Postpartum uterine infection	1	375	Peto Odds Ratio 95% CI	0.60 [0.34, 1.07]
03 Incidence of preterm prelabour rupture of membranes	1	80	Peto Odds Ratio 95% CI	0.14 [0.04, 0.44]
04 Preterm birth less than 37 weeks	5	2387	Peto Odds Ratio 95% CI	0.63 [0.48, 0.84]

05 Preterm birth less than 34 weeks' gestation	1	80	Peto Odds Ratio 95% CI	0.39 [0.07, 2.07]
06 Incidence of low birthweight	2	489	Peto Odds Ratio 95% CI	0.79 [0.44, 1.41]
07 Side-effects not sufficient to stop treatment	1	375	Peto Odds Ratio 95% CI	1.01 [0.32, 3.17]

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Pregnancy Complications, Infectious [*drug therapy]; Premature Birth [*prevention & control]; Randomized Controlled Trials; Vaginosis, Bacterial [*drug therapy]

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Antibiotics for treating bacterial vaginosis in pregnancy
Authors	McDonald HM, Brocklehurst P, Gordon A
Contribution of author(s)	Helen McDonald (HM), as the new contact author from 2003, was responsible for performing searches; personal communications with researchers; extracted and entered data; revised text and responded to comments, etc, for the second and third reviews. HM is the guarantor for the review. Peter Brocklehurst, as contact author for the first review, was primarily responsible for writing the text, responding to comments, etc. As co-author for the second and third reviews, he reviewed studies and contributed to the revised text. Adrienne Gordon, co-author for the third review, reviewed studies, extracted data, performed double entry of data, restructured tables, and contributed to the revised text for the third review.
Issue protocol first published	1997/3
Review first published	1998/4
Date of most recent amendment	15 November 2006
Date of most recent SUBSTANTIVE amendment	25 September 2006
What's New	September 2006 (1) Search updated May 2006. (2) Addition of co-author Dr Adrienne Gordon. (3) Addition of extra neonatal data in NICHD MFMU 2000 study. (4) Addition of three new studies (NICHD MFMU 2001 with parallel data to NICHD MFMU 2000; Lamont 2003; Kiss 2004). (5) Analysis of clindamycin trials. (6) Analysis of abnormal vaginal flora trials (recruited on the basis of Nugent score 4-10). (7) Analysis of treatment at less than 20 weeks' gestation.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author

Date new studies found and included/excluded	30 May 2006
Date authors' conclusions section amended	22 June 2004
Contact address	Dr Adrienne Gordon Neonatal Fellow Royal Prince Alfred Hospital Missenden Road Sydney NSW 2050 AUSTRALIA E-mail: adrienne.gordon@email.cs.nsw.gov.au Tel: 00 61 2 9515 6111 Fax: 00 61 2 9550 4375
DOI	10.1002/14651858.CD000262.pub3
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Editorial group code	HM-PREG

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 01 Failure of test of cure

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 01 Failure of test of cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Duff 1991	23/39	34/42		1.7	0.35 [0.14, 0.91]
Guaschino 2003	8/33	11/37		1.4	0.76 [0.27, 2.17]
Hauth 1995	53/176	71/87		5.7	0.13 [0.08, 0.21]
Joesoef 1995	49/340	151/341		13.8	0.24 [0.17, 0.33]
Kekki 1999	62/181	119/181		8.9	0.28 [0.19, 0.43]
McDonald 1997	39/197	88/202		8.5	0.34 [0.22, 0.51]
Morales 1994	5/44	31/36		1.9	0.05 [0.02, 0.12]
NICHD MFMU 2000	188/845	538/859		40.7	0.19 [0.16, 0.23]

(*Continued* . . .)

(... *Continued*)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Odendaal 2002	39/128	90/127		6.2	0.20 [0.12, 0.33]
Ugwumadu 2003	22/231	214/231		11.3	0.04 [0.03, 0.05]
Total (95% CI)	2214	2143		100.0	0.17 [0.15, 0.20]
Total events: 488 (Treatment), 1347 (Control)					
Test for heterogeneity chi-square=109.60 df=9 p=<0.0001 I^2 =91.8%					
Test for overall effect z=27.93 p<0.00001					

Analysis 01.02. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 02 Postpartum infection

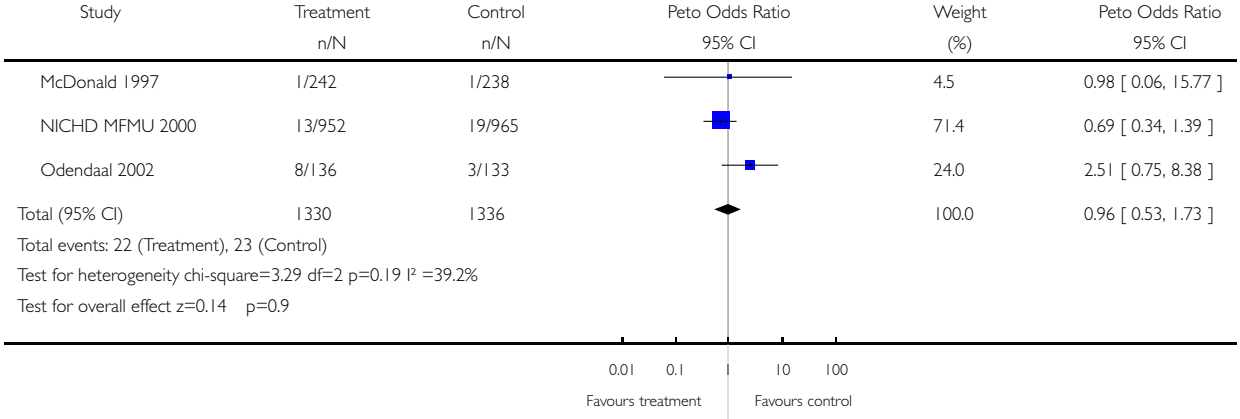
Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 02 Postpartum infection

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Kekki 1999	21/187	33/188		92.1	0.60 [0.34, 1.07]
McDonald 1997	3/123	1/120		7.9	2.69 [0.37, 19.30]
Total (95% CI)	310	308		100.0	0.67 [0.39, 1.17]
Total events: 24 (Treatment), 34 (Control)					
Test for heterogeneity chi-square=2.05 df=1 p=0.15 I^2 =51.1%					
Test for overall effect z=1.40 p=0.2					

Analysis 01.03. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 03 Perinatal death



Analysis 01.04. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 04 Incidence of preterm prelabour rupture of membranes

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 04 Incidence of preterm prelabour rupture of membranes

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 General population					
Guaschino 2003	7/49	3/51		9.3	2.52 [0.69, 9.25]
McDonald 1997	6/242	10/238		15.9	0.59 [0.22, 1.59]
NICHD MFMU 2000	40/953	36/966		74.8	1.13 [0.72, 1.79]
Subtotal (95% CI)	1244	1255		100.0	1.10 [0.74, 1.63]
Total events: 53 (Treatment), 49 (Control)					
Test for heterogeneity chi-square=3.11 df=2 p=0.21 I^2 =35.6%					
Test for overall effect z=0.46 p=0.6					
02 High-risk population					
× Morales 1994	0/1	0/1		0.0	Not estimable
Subtotal (95% CI)	1	1		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	1245	1256		100.0	1.10 [0.74, 1.63]
Total events: 53 (Treatment), 49 (Control)					
Test for heterogeneity chi-square=3.11 df=2 p=0.21 I^2 =35.6%					
Test for overall effect z=0.46 p=0.6					

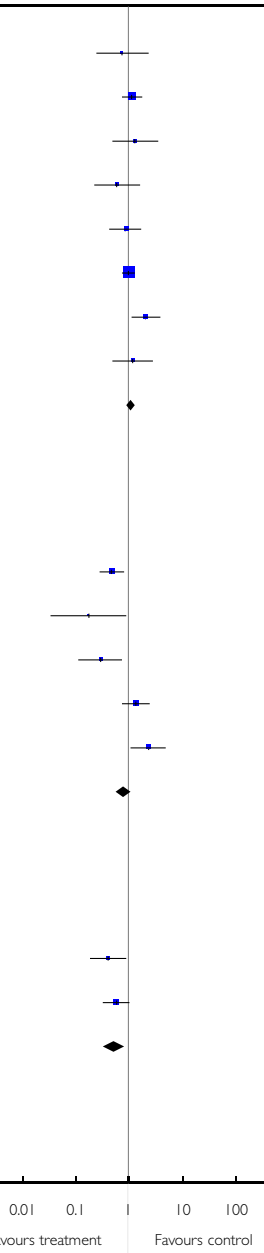
Analysis 01.05. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 05 Preterm birth < 37 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 05 Preterm birth < 37 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 General population					
Guaschino 2003	6/49	8/51		1.9	0.75 [0.24, 2.32]
Joesoef 1995	51/340	46/341		13.0	1.13 [0.74, 1.74]
Kekki 1999	9/187	7/188		2.4	1.30 [0.48, 3.55]
Kiss 2004	6/177	10/179		2.4	0.60 [0.22, 1.63]
McDonald 1997	16/242	18/238		5.0	0.87 [0.43, 1.74]
NICHD MFMU 2000	116/953	121/966		32.5	0.97 [0.74, 1.27]
NICHD MFMU 2001	31/119	16/113		5.9	2.08 [1.10, 3.94]
Odendaal 2002	12/66	13/82		3.2	1.18 [0.50, 2.79]
Subtotal (95% CI)	2133	2158		66.4	1.06 [0.87, 1.28]
Total events: 247 (Treatment), 239 (Control)					
Test for heterogeneity chi-square=6.94 df=7 p=0.44 I^2 =0.0%					
Test for overall effect z=0.55 p=0.6					
02 High-risk population					
Hauth 1995	54/172	42/86		8.4	0.48 [0.28, 0.81]
McDonald 1997	1/17	6/17		0.9	0.17 [0.03, 0.90]
Morales 1994	8/44	16/36		2.6	0.29 [0.11, 0.76]
NICHD MFMU 2000	30/101	26/109		6.5	1.35 [0.73, 2.48]
Odendaal 2002	30/70	12/51		4.2	2.33 [1.10, 4.96]
Subtotal (95% CI)	404	299		22.6	0.78 [0.56, 1.08]
Total events: 123 (Treatment), 102 (Control)					
Test for heterogeneity chi-square=21.75 df=4 p=0.0002 I^2 =81.6%					
Test for overall effect z=1.49 p=0.1					
03 Intermediate flora and bacterial vaginosis					
Lamont 2003	8/208	19/201		4.0	0.40 [0.19, 0.88]
Ugwumadu 2003	19/244	31/241		7.0	0.58 [0.32, 1.04]
Subtotal (95% CI)	452	442		11.0	0.51 [0.32, 0.81]
Total events: 27 (Treatment), 50 (Control)					
Test for heterogeneity chi-square=0.52 df=1 p=0.47 I^2 =0.0%					
Test for overall effect z=2.84 p=0.005					



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Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	2989	2899		100.0	0.91 [0.78, 1.06]
Total events: 397 (Treatment), 391 (Control)					
Test for heterogeneity chi-square=38.34 df=14 p=0.0005 I^2 =63.5%					
Test for overall effect z=1.20 p=0.2					

Analysis 01.06. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 06 Preterm birth < 34 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 06 Preterm birth < 34 weeks

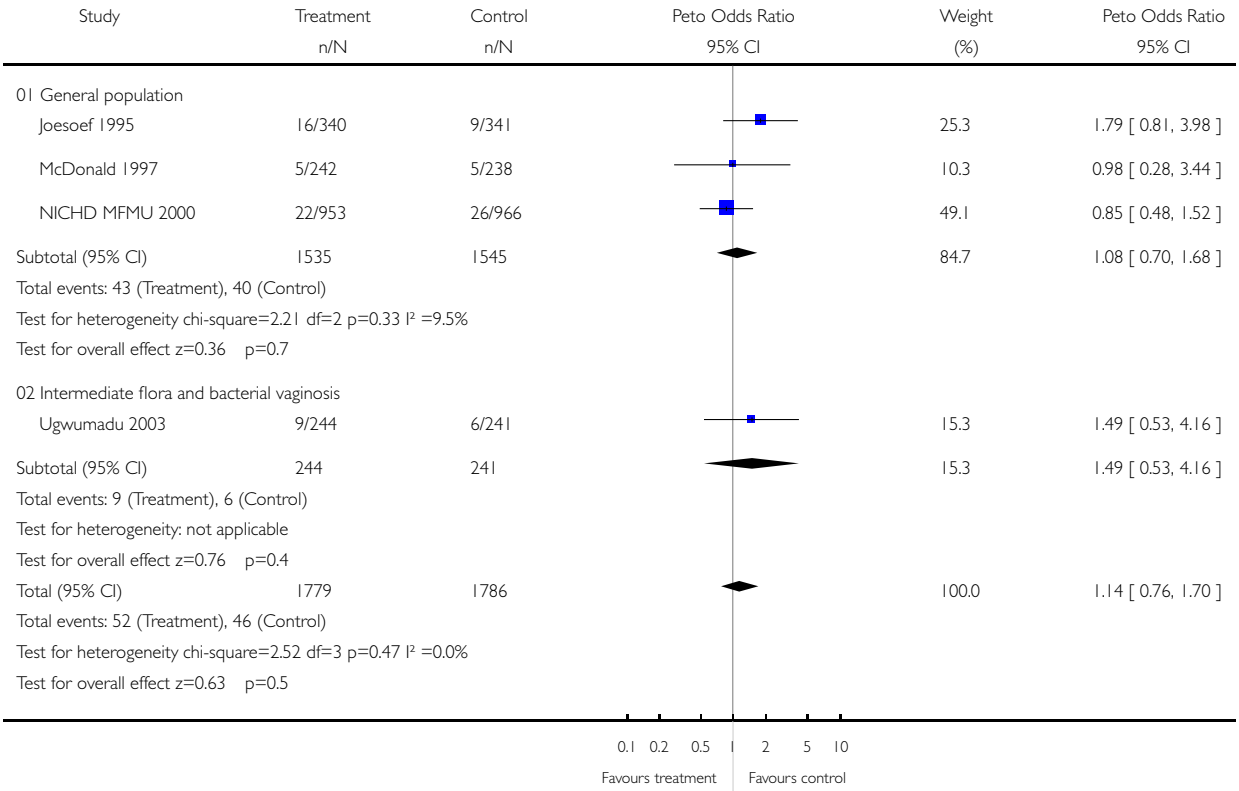
Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 General population					
McDonald 1997	7/242	6/238		28.7	1.15 [0.38, 3.46]
Odendaal 2002	2/66	4/82		13.0	0.62 [0.12, 3.21]
Subtotal (95% CI)	308	320		41.6	0.95 [0.38, 2.37]
Total events: 9 (Treatment), 10 (Control)					
Test for heterogeneity chi-square=0.37 df=1 p=0.54 I^2 =0.0%					
Test for overall effect z=0.11 p=0.9					
02 High-risk women					
Morales 1994	2/44	4/36		12.6	0.39 [0.07, 2.07]
Odendaal 2002	17/70	6/51		41.5	2.24 [0.90, 5.60]
Vermeulen 1999	1/11	1/11		4.3	1.00 [0.06, 17.12]
Subtotal (95% CI)	125	98		58.4	1.45 [0.67, 3.14]
Total events: 20 (Treatment), 11 (Control)					
Test for heterogeneity chi-square=3.31 df=2 p=0.19 I^2 =39.5%					
Test for overall effect z=0.94 p=0.3					
Total (95% CI)	433	418		100.0	1.22 [0.67, 2.19]
Total events: 29 (Treatment), 21 (Control)					
Test for heterogeneity chi-square=4.15 df=4 p=0.39 I^2 =3.7%					
Test for overall effect z=0.65 p=0.5					

Analysis 01.07. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 07 Preterm birth < 32 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 07 Preterm birth < 32 weeks

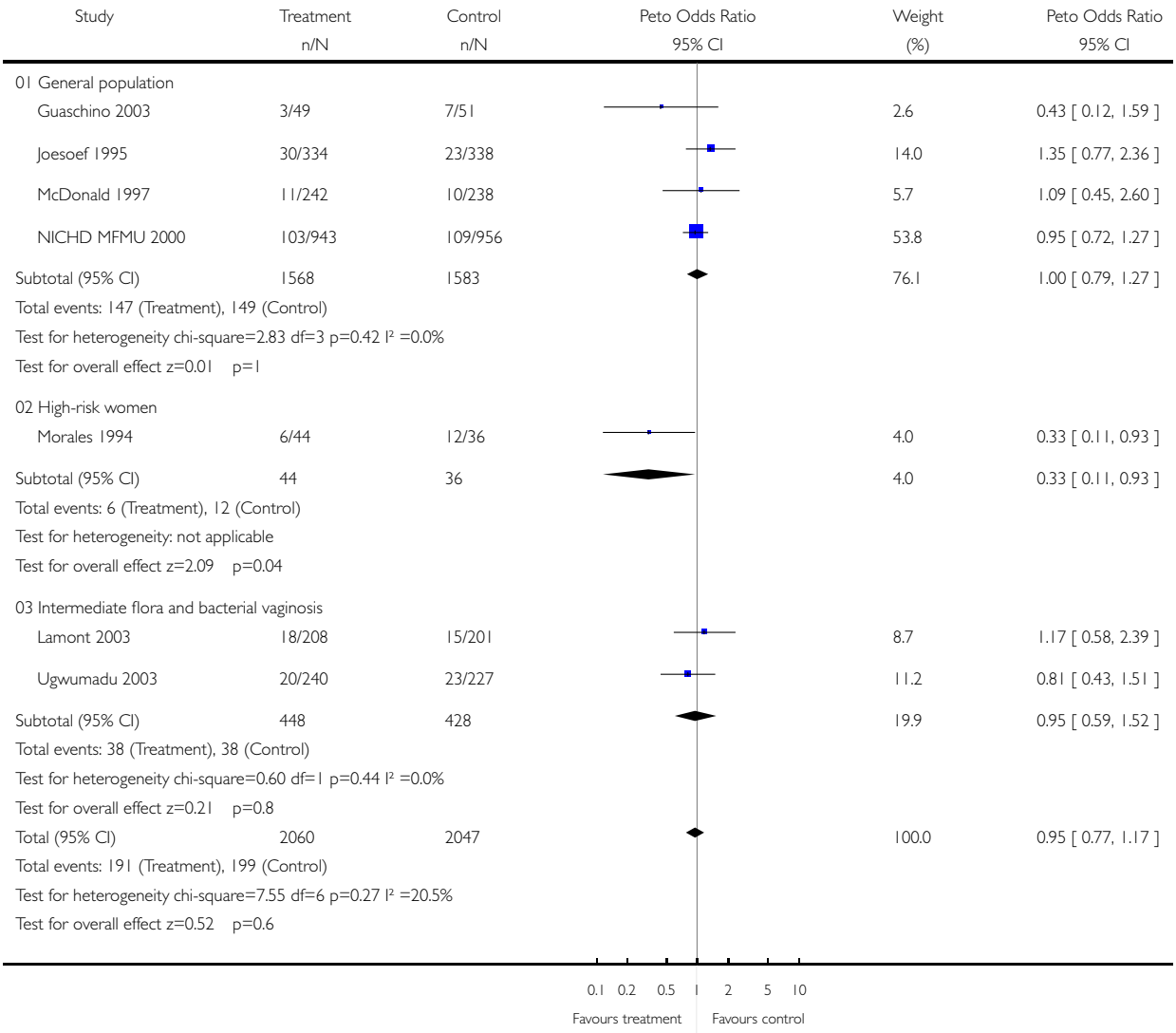


Analysis 01.08. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 08 Incidence of low birthweight

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 08 Incidence of low birthweight



Analysis 01.09. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 09 Neonatal sepsis

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 09 Neonatal sepsis

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	1/208	1/198		16.7	0.95 [0.06, 15.28]
NICHD MFMU 2000	6/952	4/965		83.3	1.52 [0.44, 5.25]
× Vermeulen 1999	0/11	0/11		0.0	Not estimable
Total (95% CI)	1171	1174		100.0	1.40 [0.45, 4.36]

Total events: 7 (Treatment), 5 (Control)

Test for heterogeneity chi-square=0.09 df=1 p=0.76 I^2 =0.0%

Test for overall effect z=0.58 p=0.6

Analysis 01.10. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 10 Side-effects sufficient to stop treatment

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 10 Side-effects sufficient to stop treatment

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Duff 1991	3/54	3/54		9.3	1.00 [0.19, 5.15]
McDonald 1997	19/429	14/428		51.9	1.37 [0.68, 2.74]
Ugwumadu 2003	17/244	8/241		38.8	2.11 [0.94, 4.71]
Total (95% CI)	727	723		100.0	1.57 [0.95, 2.59]

Total events: 39 (Treatment), 25 (Control)

Test for heterogeneity chi-square=0.96 df=2 p=0.62 I^2 =0.0%

Test for overall effect z=1.76 p=0.08

Analysis 01.11. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 11 Side-effects not sufficient to stop treatment

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 11 Side-effects not sufficient to stop treatment

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Duff 1991	14/54	14/54		49.3	1.00 [0.42, 2.36]
Kekki 1999	6/187	6/188		27.4	1.01 [0.32, 3.17]
McDonald 1997	8/429	2/428		23.3	3.35 [0.96, 11.66]
Total (95% CI)	670	670		100.0	1.33 [0.73, 2.42]
Total events: 28 (Treatment), 22 (Control)					
Test for heterogeneity chi-square=2.77 df=2 p=0.25 I^2 =27.8%					
Test for overall effect z=0.92 p=0.4					

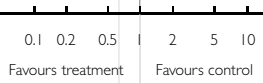
Analysis 01.12. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 12 Severe neonatal morbidity

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 12 Severe neonatal morbidity

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
NICHD MFMU 2000	18/952	19/965		100.0	0.96 [0.50, 1.84]
Total (95% CI)	952	965		100.0	0.96 [0.50, 1.84]
Total events: 18 (Treatment), 19 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.12 p=0.9					



Analysis 01.13. Comparison 01 Any antibiotic versus placebo/no treatment, Outcome 13 Admission to neonatal unit

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 01 Any antibiotic versus placebo/no treatment

Outcome: 13 Admission to neonatal unit

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
NICHD MFMU 2000	146/952	128/965		86.2	1.18 [0.92, 1.53]
Ugwumadu 2003	18/238	23/228		13.8	0.73 [0.39, 1.39]
Total (95% CI)	1190	1193		100.0	1.11 [0.87, 1.41]
Total events: 164 (Treatment), 151 (Control)					
Test for heterogeneity chi-square=1.88 df=1 p=0.17 I^2 =46.9%					
Test for overall effect z=0.85 p=0.4					

Analysis 02.01. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 01 Failure of test of cure

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

Outcome: 01 Failure of test of cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Duff 1991	23/39	34/42		2.2	0.35 [0.14, 0.91]
Hauth 1995	53/176	71/87		7.5	0.13 [0.08, 0.21]
McDonald 1997	39/197	88/202		11.1	0.34 [0.22, 0.51]
Morales 1994	5/44	31/36		2.5	0.05 [0.02, 0.12]
NICHD MFMU 2000	188/845	538/859		53.5	0.19 [0.16, 0.23]
Odendaal 2002	39/128	90/127		8.2	0.20 [0.12, 0.33]
Ugwumadu 2003	22/231	214/231		14.9	0.04 [0.03, 0.05]
Total (95% CI)	1660	1584		100.0	0.15 [0.13, 0.17]
Total events: 369 (Treatment), 1066 (Control)					
Test for heterogeneity chi-square=89.50 df=6 p=<0.0001 I^2 =93.3%					
Test for overall effect z=26.28 p<0.00001					

Analysis 02.02. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 02 Postpartum uterine infection

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

Outcome: 02 Postpartum uterine infection

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	3/123	1/120		100.0	2.69 [0.37, 19.30]
Total (95% CI)	123	120		100.0	2.69 [0.37, 19.30]
Total events: 3 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.98 p=0.3					

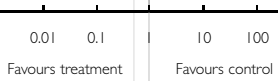
Analysis 02.03. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 03 Perinatal death

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

Outcome: 03 Perinatal death

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	1/242	1/238		4.5	0.98 [0.06, 15.77]
NICHD MFMU 2000	13/952	19/965		71.5	0.69 [0.34, 1.39]
Odendaal 2002	8/136	3/123		24.0	2.32 [0.70, 7.77]
Total (95% CI)	1330	1326		100.0	0.94 [0.52, 1.70]
Total events: 22 (Treatment), 23 (Control)					
Test for heterogeneity chi-square=2.90 df=2 p=0.23 I^2 =31.0%					
Test for overall effect z=0.20 p=0.8					



Analysis 02.04. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 04 Incidence of preterm prelabour rupture of membranes

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

Outcome: 04 Incidence of preterm prelabour rupture of membranes

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	6/242	10/238		15.5	0.59 [0.22, 1.59]
Morales 1994	2/44	12/36		11.6	0.14 [0.04, 0.44]
NICHD MFMU 2000	40/953	36/966		73.0	1.13 [0.72, 1.79]
Total (95% CI)	1239	1240		100.0	0.80 [0.54, 1.19]
Total events: 48 (Treatment), 58 (Control)					
Test for heterogeneity chi-square=11.39 df=2 p=0.003 I^2 =82.4%					
Test for overall effect z=1.10 p=0.3					

Analysis 02.05. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 05 Preterm birth < 37 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

Outcome: 05 Preterm birth < 37 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Hauth 1995	54/172	42/86		11.8	0.48 [0.28, 0.81]
Kiss 2004	6/177	10/179		3.3	0.60 [0.22, 1.63]
McDonald 1997	16/242	18/238		6.9	0.87 [0.43, 1.74]
Morales 1994	8/44	16/36		3.7	0.29 [0.11, 0.76]
NICHD MFMU 2000	116/953	121/966		45.4	0.97 [0.74, 1.27]
NICHD MFMU 2001	31/119	16/113		8.2	2.08 [1.10, 3.94]
Odendaal 2002	42/136	25/123		10.9	1.73 [0.99, 3.02]
Ugwumadu 2003	19/244	31/241		9.8	0.58 [0.32, 1.04]
Total (95% CI)	2087	1982		100.0	0.90 [0.75, 1.08]
Total events: 292 (Treatment), 279 (Control)					
Test for heterogeneity chi-square=25.89 df=7 p=0.0005 I^2 =73.0%					
Test for overall effect z=1.16 p=0.2					

Analysis 02.06. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 06 Preterm birth < 34 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

Outcome: 06 Preterm birth < 34 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	7/242	6/238		28.8	1.15 [0.38, 3.46]
Morales 1994	2/44	4/36		12.6	0.39 [0.07, 2.07]
Odendaal 2002	19/136	10/123		58.6	1.80 [0.83, 3.88]
Total (95% CI)	422	397		100.0	1.30 [0.72, 2.35]

Total events: 28 (Treatment), 20 (Control)

Test for heterogeneity chi-square=2.71 df=2 p=0.26 I^2 =26.2%

Test for overall effect z=0.88 p=0.4

Analysis 02.07. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 07 Preterm birth < 32 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

Outcome: 07 Preterm birth < 32 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	5/242	5/238		13.8	0.98 [0.28, 3.44]
NICHD MFMU 2000	22/953	26/966		65.8	0.85 [0.48, 1.52]
Ugwumadu 2003	9/244	6/241		20.5	1.49 [0.53, 4.16]
Total (95% CI)	1439	1445		100.0	0.98 [0.61, 1.55]

Total events: 36 (Treatment), 37 (Control)

Test for heterogeneity chi-square=0.86 df=2 p=0.65 I^2 =0.0%

Test for overall effect z=0.10 p=0.9

Analysis 02.08. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 08 Incidence of low birthweight

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

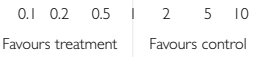
Outcome: 08 Incidence of low birthweight

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	11/242	10/238		7.7	1.09 [0.45, 2.60]
Morales 1994	6/44	12/36		5.3	0.33 [0.11, 0.93]
NICHD MFMU 2000	103/943	109/956		72.0	0.95 [0.72, 1.27]
Ugwumadu 2003	20/240	23/227		14.9	0.81 [0.43, 1.51]
Total (95% CI)	1469	1457		100.0	0.89 [0.70, 1.13]

Total events: 140 (Treatment), 154 (Control)

Test for heterogeneity chi-square=4.00 df=3 p=0.26 I^2 =25.0%

Test for overall effect z=0.97 p=0.3



Analysis 02.09. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 09 Neonatal sepsis

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

Outcome: 09 Neonatal sepsis

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	1/208	1/198		16.7	0.95 [0.06, 15.28]
NICHD MFMU 2000	6/952	4/965		83.3	1.52 [0.44, 5.25]
Total (95% CI)	1160	1163		100.0	1.40 [0.45, 4.36]

Total events: 7 (Treatment), 5 (Control)

Test for heterogeneity chi-square=0.09 df=1 p=0.76 I^2 =0.0%

Test for overall effect z=0.58 p=0.6

Analysis 02.10. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 10 Side-effects sufficient to stop treatment

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

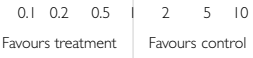
Outcome: 10 Side-effects sufficient to stop treatment

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Duff 1991	3/54	3/54		15.3	1.00 [0.19, 5.15]
McDonald 1997	19/429	14/428		84.7	1.37 [0.68, 2.74]
Total (95% CI)	483	482		100.0	1.30 [0.69, 2.47]

Total events: 22 (Treatment), 17 (Control)

Test for heterogeneity chi-square=0.12 df=1 p=0.73 I^2 =0.0%

Test for overall effect z=0.81 p=0.4



Analysis 02.11. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 11 Side-effects not sufficient to stop treatment

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

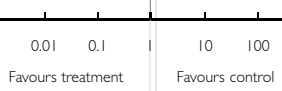
Outcome: 11 Side-effects not sufficient to stop treatment

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Duff 1991	14/54	14/54		67.9	1.00 [0.42, 2.36]
McDonald 1997	8/429	2/428		32.1	3.35 [0.96, 11.66]
Total (95% CI)	483	482		100.0	1.47 [0.73, 2.99]

Total events: 22 (Treatment), 16 (Control)

Test for heterogeneity chi-square=2.46 df=1 p=0.12 I^2 =59.4%

Test for overall effect z=1.08 p=0.3



Analysis 02.12. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 12 Severe neonatal morbidity

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

Outcome: 12 Severe neonatal morbidity

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
NICHD MFMU 2000	18/952	19/965		100.0	0.96 [0.50, 1.84]
Total (95% CI)	952	965		100.0	0.96 [0.50, 1.84]
Total events: 18 (Treatment), 19 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.12 p=0.9					

Analysis 02.13. Comparison 02 Oral antibiotics versus placebo/no treatment, Outcome 13 Admission to a neonatal unit

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 02 Oral antibiotics versus placebo/no treatment

Outcome: 13 Admission to a neonatal unit

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
NICHD MFMU 2000	146/952	128/965		86.2	1.18 [0.92, 1.53]
Ugwumadu 2003	18/238	23/228		13.8	0.73 [0.39, 1.39]
Total (95% CI)	1190	1193		100.0	1.11 [0.87, 1.41]
Total events: 164 (Treatment), 151 (Control)					
Test for heterogeneity chi-square=1.88 df=1 p=0.17 I^2 =46.9%					
Test for overall effect z=0.85 p=0.4					

Analysis 03.01. Comparison 03 Vaginal antibiotics versus placebo/no treatment, Outcome 01 Failure of test of cure

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 03 Vaginal antibiotics versus placebo/no treatment

Outcome: 01 Failure of test of cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Guaschino 2003	8/33	11/37		5.7	0.76 [0.27, 2.17]
Joesoef 1995	49/340	151/341		57.5	0.24 [0.17, 0.33]
Kekki 1999	62/181	119/181		36.9	0.28 [0.19, 0.43]
Total (95% CI)	554	559		100.0	0.27 [0.21, 0.35]

Total events: 119 (Treatment), 281 (Control)

Test for heterogeneity chi-square=4.40 df=2 p=0.11 I^2 =54.6%

Test for overall effect z=10.24 p<0.00001

Analysis 03.02. Comparison 03 Vaginal antibiotics versus placebo/no treatment, Outcome 02 Postpartum uterine infection

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 03 Vaginal antibiotics versus placebo/no treatment

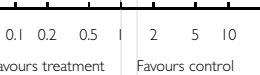
Outcome: 02 Postpartum uterine infection

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Kekki 1999	21/187	33/188		100.0	0.60 [0.34, 1.07]
Total (95% CI)	187	188		100.0	0.60 [0.34, 1.07]

Total events: 21 (Treatment), 33 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=1.74 p=0.08



Analysis 03.03. Comparison 03 Vaginal antibiotics versus placebo/no treatment, Outcome 03 Perinatal death

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 03 Vaginal antibiotics versus placebo/no treatment

Outcome: 03 Perinatal death

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Lamont 2003	1/208	3/201		100.0	0.35 [0.05, 2.52]
Total (95% CI)	208	201		100.0	0.35 [0.05, 2.52]
Total events: 1 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.04 p=0.3					

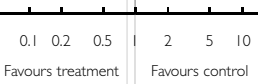
Analysis 03.04. Comparison 03 Vaginal antibiotics versus placebo/no treatment, Outcome 04 Incidence of preterm prelabour rupture of membranes

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 03 Vaginal antibiotics versus placebo/no treatment

Outcome: 04 Incidence of preterm prelabour rupture of membranes

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Guaschino 2003	7/49	3/51		100.0	2.52 [0.69, 9.25]
Total (95% CI)	49	51		100.0	2.52 [0.69, 9.25]
Total events: 7 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.39 p=0.2					



Analysis 03.05. Comparison 03 Vaginal antibiotics versus placebo/no treatment, Outcome 05 Preterm birth < 37 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 03 Vaginal antibiotics versus placebo/no treatment

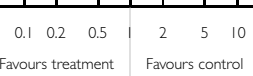
Outcome: 05 Preterm birth < 37 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Guaschino 2003	6/49	8/51		8.0	0.75 [0.24, 2.32]
Joesoef 1995	51/340	46/341		55.0	1.13 [0.74, 1.74]
Kekki 1999	9/187	7/188		10.1	1.30 [0.48, 3.55]
Kiss 2004	6/177	10/179		10.1	0.60 [0.22, 1.63]
Lamont 2003	8/208	19/201		16.7	0.40 [0.19, 0.88]
Total (95% CI)	961	960		100.0	0.88 [0.64, 1.21]

Total events: 80 (Treatment), 90 (Control)

Test for heterogeneity chi-square=6.38 df=4 p=0.17 I^2 =37.3%

Test for overall effect z=0.81 p=0.4



Analysis 03.06. Comparison 03 Vaginal antibiotics versus placebo/no treatment, Outcome 06 Preterm birth < 34 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 03 Vaginal antibiotics versus placebo/no treatment

Outcome: 06 Preterm birth < 34 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Vermeulen 1999	1/11	1/11		100.0	1.00 [0.06, 17.12]
Total (95% CI)	11	11		100.0	1.00 [0.06, 17.12]

Total events: 1 (Treatment), 1 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=0.00 p=1

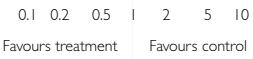
Analysis 03.07. Comparison 03 Vaginal antibiotics versus placebo/no treatment, Outcome 07 Preterm birth < 32 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 03 Vaginal antibiotics versus placebo/no treatment

Outcome: 07 Preterm birth < 32 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Joesoef 1995	16/340	9/341		100.0	1.79 [0.81, 3.98]
Total (95% CI)	340	341		100.0	1.79 [0.81, 3.98]
Total events: 16 (Treatment), 9 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.43 p=0.2					



Analysis 03.08. Comparison 03 Vaginal antibiotics versus placebo/no treatment, Outcome 08 Incidence of low birthweight

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 03 Vaginal antibiotics versus placebo/no treatment

Outcome: 08 Incidence of low birthweight

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Guaschino 2003	3/49	7/51		10.3	0.43 [0.12, 1.59]
Joesoef 1995	30/334	23/338		55.3	1.35 [0.77, 2.36]
Lamont 2003	18/208	15/201		34.4	1.17 [0.58, 2.39]
Total (95% CI)	591	590		100.0	1.14 [0.75, 1.74]
Total events: 51 (Treatment), 45 (Control)					
Test for heterogeneity chi-square=2.48 df=2 p=0.29 I^2 =19.3%					
Test for overall effect z=0.63 p=0.5					

Analysis 03.09. Comparison 03 Vaginal antibiotics versus placebo/no treatment, Outcome 09 Neonatal sepsis

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 03 Vaginal antibiotics versus placebo/no treatment

Outcome: 09 Neonatal sepsis

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Lamont 2003	18/208	15/201		100.0	1.17 [0.58, 2.39]
× Vermeulen 1999	0/11	0/11		0.0	Not estimable
Total (95% CI)	219	212		100.0	1.17 [0.58, 2.39]
Total events: 18 (Treatment), 15 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.44 p=0.7					

Analysis 03.10. Comparison 03 Vaginal antibiotics versus placebo/no treatment, Outcome 10 Side-effects not sufficient to stop treatment

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 03 Vaginal antibiotics versus placebo/no treatment

Outcome: 10 Side-effects not sufficient to stop treatment

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Kekki 1999	6/187	6/188		100.0	1.01 [0.32, 3.17]
Total (95% CI)	187	188		100.0	1.01 [0.32, 3.17]
Total events: 6 (Treatment), 6 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					

Analysis 04.01. Comparison 04 Previous preterm delivery: antibiotics versus placebo/no treatment, Outcome 01 Failure of test of cure

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 04 Previous preterm delivery: antibiotics versus placebo/no treatment

Outcome: 01 Failure of test of cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Morales 1994	5/44	31/36		40.1	0.05 [0.02, 0.12]
Odendaal 2002	21/70	37/51		59.9	0.18 [0.09, 0.38]
Total (95% CI)	114	87		100.0	0.11 [0.06, 0.19]
Total events: 26 (Treatment), 68 (Control)					
Test for heterogeneity chi-square=4.96 df=1 p=0.03 I^2 =79.8%					
Test for overall effect z=7.77 p<0.00001					

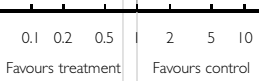
Analysis 04.02. Comparison 04 Previous preterm delivery: antibiotics versus placebo/no treatment, Outcome 02 Postpartum uterine infection

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 04 Previous preterm delivery: antibiotics versus placebo/no treatment

Outcome: 02 Postpartum uterine infection

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× McDonald 1997	0/9	0/6		0.0	Not estimable
Total (95% CI)	9	6		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 04.03. Comparison 04 Previous preterm delivery: antibiotics versus placebo/no treatment, Outcome 03 Perinatal death

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 04 Previous preterm delivery: antibiotics versus placebo/no treatment

Outcome: 03 Perinatal death

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× McDonald 1997	0/17	0/17		0.0	Not estimable
Odendaal 2002	7/70	1/51		100.0	3.64 [0.86, 15.45]
Total (95% CI)	87	68		100.0	3.64 [0.86, 15.45]

Total events: 7 (Treatment), 1 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=1.75 p=0.08

Analysis 04.04. Comparison 04 Previous preterm delivery: antibiotics versus placebo/no treatment, Outcome 04 Incidence of preterm prelabour rupture of membranes

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 04 Previous preterm delivery: antibiotics versus placebo/no treatment

Outcome: 04 Incidence of preterm prelabour rupture of membranes

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	0/17	3/17		19.6	0.12 [0.01, 1.23]
Morales 1994	2/44	12/36		80.4	0.14 [0.04, 0.44]
Total (95% CI)	61	53		100.0	0.14 [0.05, 0.38]

Total events: 2 (Treatment), 15 (Control)

Test for heterogeneity chi-square=0.01 df=1 p=0.90 I^2 =0.0%

Test for overall effect z=3.80 p=0.0001

Analysis 04.05. Comparison 04 Previous preterm delivery: antibiotics versus placebo/no treatment, Outcome 05 Preterm delivery < 37 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 04 Previous preterm delivery: antibiotics versus placebo/no treatment

Outcome: 05 Preterm delivery < 37 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Hauth 1995	47/121	32/56		29.5	0.48 [0.25, 0.90]
McDonald 1997	1/17	6/17		4.4	0.17 [0.03, 0.90]
Morales 1994	8/44	16/36		13.1	0.29 [0.11, 0.76]
NICHD MFMU 2000	30/101	26/109		32.0	1.35 [0.73, 2.48]
Odendaal 2002	30/70	12/51		20.9	2.33 [1.10, 4.96]
Total (95% CI)	353	269		100.0	0.83 [0.59, 1.17]

Total events: 116 (Treatment), 92 (Control)

Test for heterogeneity chi-square=20.59 df=4 p=0.0004 I^2 =80.6%

Test for overall effect z=1.05 p=0.3

Analysis 04.06. Comparison 04 Previous preterm delivery: antibiotics versus placebo/no treatment, Outcome 06 Preterm delivery < 34 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 04 Previous preterm delivery: antibiotics versus placebo/no treatment

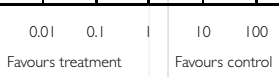
Outcome: 06 Preterm delivery < 34 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	1/17	3/17		12.4	0.33 [0.04, 2.60]
Morales 1994	2/44	4/36		18.9	0.39 [0.07, 2.07]
Odendaal 2002	17/70	6/51		62.3	2.24 [0.90, 5.60]
Vermeulen 1999	1/11	1/11		6.5	1.00 [0.06, 17.12]
Total (95% CI)	142	115		100.0	1.21 [0.59, 2.49]

Total events: 21 (Treatment), 14 (Control)

Test for heterogeneity chi-square=5.03 df=3 p=0.17 I^2 =40.4%

Test for overall effect z=0.51 p=0.6



Analysis 04.07. Comparison 04 Previous preterm delivery: antibiotics versus placebo/no treatment, Outcome 07 Preterm delivery < 32 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 04 Previous preterm delivery: antibiotics versus placebo/no treatment

Outcome: 07 Preterm delivery < 32 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	1/17	2/17		100.0	0.49 [0.05, 5.08]
Total (95% CI)	17	17		100.0	0.49 [0.05, 5.08]

Total events: 1 (Treatment), 2 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=0.60 p=0.6

Analysis 04.08. Comparison 04 Previous preterm delivery: antibiotics versus placebo/no treatment, Outcome 08 Incidence of low birthweight

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 04 Previous preterm delivery: antibiotics versus placebo/no treatment

Outcome: 08 Incidence of low birthweight

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
McDonald 1997	2/17	6/17		31.1	0.28 [0.06, 1.34]
Morales 1994	6/44	12/36		68.9	0.33 [0.11, 0.93]
Total (95% CI)	61	53		100.0	0.31 [0.13, 0.75]

Total events: 8 (Treatment), 18 (Control)

Test for heterogeneity chi-square=0.03 df=1 p=0.87 I^2 =0.0%

Test for overall effect z=2.62 p=0.009

Analysis 04.09. Comparison 04 Previous preterm delivery: antibiotics versus placebo/no treatment, Outcome 09 Neonatal sepsis

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 04 Previous preterm delivery: antibiotics versus placebo/no treatment

Outcome: 09 Neonatal sepsis

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× McDonald 1997	0/14	0/16		0.0	Not estimable
× Vermeulen 1999	0/11	0/11		0.0	Not estimable
Total (95% CI)	25	27		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 05.01. Comparison 05 Single daily dose versus double daily dose vaginal antibiotic, Outcome 01 Postpartum uterine infection

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 05 Single daily dose versus double daily dose vaginal antibiotic

Outcome: 01 Postpartum uterine infection

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Porter 2001	3/45	1/49		100.0	3.08 [0.42, 22.59]
Total (95% CI)	45	49		100.0	3.08 [0.42, 22.59]
Total events: 3 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.10 p=0.3					

Analysis 05.02. Comparison 05 Single daily dose versus double daily dose vaginal antibiotic, Outcome 02 Preterm delivery < 37 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 05 Single daily dose versus double daily dose vaginal antibiotic

Outcome: 02 Preterm delivery < 37 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Porter 2001	3/45	8/49		100.0	0.40 [0.11, 1.39]
Total (95% CI)	45	49		100.0	0.40 [0.11, 1.39]
Total events: 3 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.45 p=0.1					

Analysis 05.03. Comparison 05 Single daily dose versus double daily dose vaginal antibiotic, Outcome 03 Incidence of low birthweight

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 05 Single daily dose versus double daily dose vaginal antibiotic

Outcome: 03 Incidence of low birthweight

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Porter 2001	12/45	11/49		100.0	1.25 [0.49, 3.20]
Total (95% CI)	45	49		100.0	1.25 [0.49, 3.20]
Total events: 12 (Treatment), 11 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.47 p=0.6					

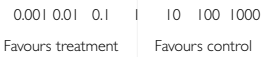
Analysis 06.01. Comparison 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment, Outcome 01 Failure of test of cure

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment

Outcome: 01 Failure of test of cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Ugwumadu 2003	22/231	214/231		100.0	0.04 [0.03, 0.05]
Total (95% CI)	231	231		100.0	0.04 [0.03, 0.05]
Total events: 22 (Treatment), 214 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=17.85 p<0.00001					



Analysis 06.02. Comparison 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment, Outcome 02 Perinatal death

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment

Outcome: 02 Perinatal death

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Lamont 2003	1/208	3/201		66.5	0.35 [0.05, 2.52]
Ugwumadu 2003	1/244	1/241		33.5	0.99 [0.06, 15.84]
Total (95% CI)	452	442		100.0	0.50 [0.10, 2.48]
Total events: 2 (Treatment), 4 (Control)					
Test for heterogeneity chi-square=0.35 df=1 p=0.55 I^2 =0.0%					
Test for overall effect z=0.85 p=0.4					

Analysis 06.03. Comparison 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment, Outcome 03 Preterm birth < 37 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment

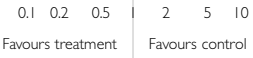
Outcome: 03 Preterm birth < 37 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Lamont 2003	8/208	19/201		36.0	0.40 [0.19, 0.88]
Ugwumadu 2003	19/244	31/241		64.0	0.58 [0.32, 1.04]
Total (95% CI)	452	442		100.0	0.51 [0.32, 0.81]

Total events: 27 (Treatment), 50 (Control)

Test for heterogeneity chi-square=0.52 df=1 p=0.47 I^2 =0.0%

Test for overall effect z=2.84 p=0.005



Analysis 06.04. Comparison 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment, Outcome 04 Preterm birth < 32 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment

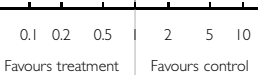
Outcome: 04 Preterm birth < 32 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Ugwumadu 2003	9/244	6/241		100.0	1.49 [0.53, 4.16]
Total (95% CI)	244	241		100.0	1.49 [0.53, 4.16]

Total events: 9 (Treatment), 6 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=0.76 p=0.4



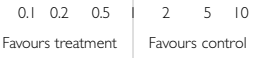
Analysis 06.05. Comparison 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment, Outcome 05 Incidence of low birthweight

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment

Outcome: 05 Incidence of low birthweight

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Lamont 2003	18/208	15/201		43.7	1.17 [0.58, 2.39]
Ugwumadu 2003	20/240	23/227		56.3	0.81 [0.43, 1.51]
Total (95% CI)	448	428		100.0	0.95 [0.59, 1.52]
Total events: 38 (Treatment), 38 (Control)					
Test for heterogeneity chi-square=0.60 df=1 p=0.44 I^2 =0.0%					
Test for overall effect z=0.21 p=0.8					



Analysis 06.06. Comparison 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment, Outcome 06 Late miscarriage

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment

Outcome: 06 Late miscarriage

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Ugwumadu 2003	2/244	10/241		100.0	0.25 [0.08, 0.79]
Total (95% CI)	244	241		100.0	0.25 [0.08, 0.79]
Total events: 2 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.36 p=0.02					

Analysis 06.07. Comparison 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment, Outcome 07 Side-effects sufficient to stop or change treatment

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment

Outcome: 07 Side-effects sufficient to stop or change treatment

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Ugwumadu 2003	17/244	8/241		100.0	2.11 [0.94, 4.71]
Total (95% CI)	244	241		100.0	2.11 [0.94, 4.71]
Total events: 17 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.81 p=0.07					

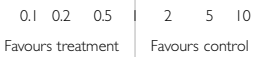
Analysis 06.08. Comparison 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment, Outcome 08 Admission to neonatal unit

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 06 Intermediate flora/bacterial vaginosis: antibiotics versus placebo/no treatment

Outcome: 08 Admission to neonatal unit

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Ugwumadu 2003	18/238	23/228		100.0	0.73 [0.39, 1.39]
Total (95% CI)	238	228		100.0	0.73 [0.39, 1.39]
Total events: 18 (Treatment), 23 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.96 p=0.3					



Analysis 07.01. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 01 Failure of test of cure

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome: 01 Failure of test of cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Guaschino 2003	8/33	11/37		3.9	0.76 [0.27, 2.17]
Joesoef 1995	49/340	151/341		39.1	0.24 [0.17, 0.33]
Kekki 1999	62/181	119/181		25.1	0.28 [0.19, 0.43]
Ugwumadu 2003	22/231	214/231		32.0	0.04 [0.03, 0.05]
Total (95% CI)	785	790		100.0	0.14 [0.12, 0.18]

Total events: 141 (Treatment), 495 (Control)

Test for heterogeneity chi-square=84.24 df=3 p=<0.0001 I^2 =96.4%

Test for overall effect z=18.54 p<0.00001

Analysis 07.02. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 02 Postpartum uterine infection

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome: 02 Postpartum uterine infection

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Kekki 1999	21/187	33/188		100.0	0.60 [0.34, 1.07]
Total (95% CI)	187	188		100.0	0.60 [0.34, 1.07]

Total events: 21 (Treatment), 33 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=1.74 p=0.08

Analysis 07.03. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 03 Perinatal death

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome: 03 Perinatal death

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Lamont 2003	1/208	3/201		66.5	0.35 [0.05, 2.52]
Ugwumadu 2003	1/244	1/241		33.5	0.99 [0.06, 15.84]
Total (95% CI)	452	442		100.0	0.50 [0.10, 2.48]
Total events: 2 (Treatment), 4 (Control)					
Test for heterogeneity chi-square=0.35 df=1 p=0.55 I^2 =0.0%					
Test for overall effect z=0.85 p=0.4					

Analysis 07.04. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 04 Incidence of preterm prelabour rupture of membranes

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome: 04 Incidence of preterm prelabour rupture of membranes

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Guaschino 2003	7/49	3/51		100.0	2.52 [0.69, 9.25]
Total (95% CI)	49	51		100.0	2.52 [0.69, 9.25]
Total events: 7 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.39 p=0.2					

Analysis 07.05. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 05 Preterm birth < 37 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

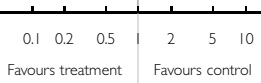
Outcome: 05 Preterm birth < 37 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Guaschino 2003	6/49	8/51		6.2	0.75 [0.24, 2.32]
Joesoef 1995	51/340	46/341		42.4	1.13 [0.74, 1.74]
Kekki 1999	9/187	7/188		7.8	1.30 [0.48, 3.55]
Kiss 2004	6/177	10/179		7.8	0.60 [0.22, 1.63]
Lamont 2003	8/208	19/201		12.9	0.40 [0.19, 0.88]
Ugwumadu 2003	19/244	31/241		22.9	0.58 [0.32, 1.04]
Total (95% CI)	1205	1201		100.0	0.80 [0.60, 1.05]

Total events: 99 (Treatment), 121 (Control)

Test for heterogeneity chi-square=7.89 df=5 p=0.16 I^2 =36.6%

Test for overall effect z=1.59 p=0.1



Analysis 07.06. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 06 Preterm birth < 34 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome: 06 Preterm birth < 34 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Vermeulen 1999	1/11	1/11		100.0	1.00 [0.06, 17.12]
Total (95% CI)	11	11		100.0	1.00 [0.06, 17.12]

Total events: 1 (Treatment), 1 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=0.00 p=1

Analysis 07.07. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 07 Preterm birth < 32 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

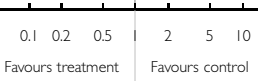
Outcome: 07 Preterm birth < 32 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Joesoef 1995	16/340	9/341		62.3	1.79 [0.81, 3.98]
Ugwumadu 2003	9/244	6/241		37.7	1.49 [0.53, 4.16]
Total (95% CI)	584	582		100.0	1.67 [0.89, 3.14]

Total events: 25 (Treatment), 15 (Control)

Test for heterogeneity chi-square=0.08 df=1 p=0.78 I^2 =0.0%

Test for overall effect z=1.60 p=0.1



Analysis 07.08. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 08 Incidence of low birthweight

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome: 08 Incidence of low birthweight

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Guaschino 2003	3/49	7/51		7.1	0.43 [0.12, 1.59]
Joesoef 1995	30/334	23/338		38.4	1.35 [0.77, 2.36]
Lamont 2003	18/208	15/201		23.9	1.17 [0.58, 2.39]
Ugwumadu 2003	20/240	23/227		30.7	0.81 [0.43, 1.51]
Total (95% CI)	831	817		100.0	1.03 [0.73, 1.45]

Total events: 71 (Treatment), 68 (Control)

Test for heterogeneity chi-square=3.31 df=3 p=0.35 I^2 =9.2%

Test for overall effect z=0.16 p=0.9

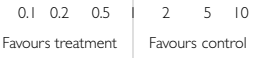
Analysis 07.09. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 09 Neonatal sepsis

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome: 09 Neonatal sepsis

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Lamont 2003	18/208	15/201		100.0	1.17 [0.58, 2.39]
× Vermeulen 1999	0/11	0/11		0.0	Not estimable
Total (95% CI)	219	212		100.0	1.17 [0.58, 2.39]
Total events: 18 (Treatment), 15 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.44 p=0.7					



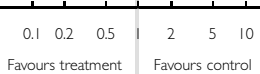
Analysis 07.10. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 10 Side-effects sufficient to stop or change treatment

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome: 10 Side-effects sufficient to stop or change treatment

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Ugwumadu 2003	17/244	8/241		100.0	2.11 [0.94, 4.71]
Total (95% CI)	244	241		100.0	2.11 [0.94, 4.71]
Total events: 17 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.81 p=0.07					



Analysis 07.11. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 11 Late miscarriage

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome: 11 Late miscarriage

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Ugwumadu 2003	2/244	10/241		100.0	0.25 [0.08, 0.79]
Total (95% CI)	244	241		100.0	0.25 [0.08, 0.79]
Total events: 2 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.36 p=0.02					

Analysis 07.12. Comparison 07 Clindamycin (oral or vaginal) versus placebo/no treatment, Outcome 12 Admission to neonatal unit

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 07 Clindamycin (oral or vaginal) versus placebo/no treatment

Outcome: 12 Admission to neonatal unit

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Ugwumadu 2003	18/238	23/228		100.0	0.73 [0.39, 1.39]
Total (95% CI)	238	228		100.0	0.73 [0.39, 1.39]
Total events: 18 (Treatment), 23 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.96 p=0.3					

Analysis 08.01. Comparison 08 Treatment at less than 20 weeks' gestation, Outcome 01 Failure of test of cure

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 08 Treatment at less than 20 weeks' gestation

Outcome: 01 Failure of test of cure

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Kekki 1999	62/181	119/181		82.1	0.28 [0.19, 0.43]
Morales 1994	5/44	31/36		17.9	0.05 [0.02, 0.12]
Total (95% CI)	225	217		100.0	0.21 [0.14, 0.30]
Total events: 67 (Treatment), 150 (Control)					
Test for heterogeneity chi-square=12.13 df=1 p=0.0005 I^2 =91.8%					
Test for overall effect z=8.23 p<0.00001					

Analysis 08.02. Comparison 08 Treatment at less than 20 weeks' gestation, Outcome 02 Postpartum uterine infection

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 08 Treatment at less than 20 weeks' gestation

Outcome: 02 Postpartum uterine infection

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Kekki 1999	21/187	33/188		100.0	0.60 [0.34, 1.07]
Total (95% CI)	187	188		100.0	0.60 [0.34, 1.07]
Total events: 21 (Treatment), 33 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.74 p=0.08					

Analysis 08.03. Comparison 08 Treatment at less than 20 weeks' gestation, Outcome 03 Incidence of preterm prelabour rupture of membranes

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 08 Treatment at less than 20 weeks' gestation

Outcome: 03 Incidence of preterm prelabour rupture of membranes

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Morales 1994	2/44	12/36		100.0	0.14 [0.04, 0.44]
Total (95% CI)	44	36		100.0	0.14 [0.04, 0.44]
Total events: 2 (Treatment), 12 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.35 p=0.0008					

Analysis 08.04. Comparison 08 Treatment at less than 20 weeks' gestation, Outcome 04 Preterm birth less than 37 weeks

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 08 Treatment at less than 20 weeks' gestation

Outcome: 04 Preterm birth less than 37 weeks

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 General population					
Kekki 1999	9/187	7/188		7.8	1.30 [0.48, 3.55]
Kiss 2004	6/177	10/179		7.8	0.60 [0.22, 1.63]
NICHD MFMU 2000	71/545	77/522		64.8	0.87 [0.61, 1.23]
Subtotal (95% CI)	909	889		80.4	0.87 [0.64, 1.19]
Total events: 86 (Treatment), 94 (Control)					
Test for heterogeneity chi-square=1.16 df=2 p=0.56 I^2 =0.0%					
Test for overall effect z=0.88 p=0.4					
02 High-risk population					
Morales 1994	8/144	16/36		6.8	0.04 [0.01, 0.10]
Subtotal (95% CI)	144	36		6.8	0.04 [0.01, 0.10]
Total events: 8 (Treatment), 16 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=6.12 p<0.00001					
03 Intermediate flora and bacterial vaginosis					
Lamont 2003	8/208	19/201		12.8	0.40 [0.19, 0.88]
Subtotal (95% CI)	208	201		12.8	0.40 [0.19, 0.88]

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Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total events: 8 (Treatment), 19 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.28 p=0.02					
Total (95% CI)	1261	1126	◆	100.0	0.63 [0.48, 0.84]
Total events: 102 (Treatment), 129 (Control)					
Test for heterogeneity chi-square=34.36 df=4 p=<0.0001 I^2 =88.4%					
Test for overall effect z=3.20 p=0.001					

Analysis 08.05. Comparison 08 Treatment at less than 20 weeks' gestation, Outcome 05 Preterm birth less than 34 weeks' gestation

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 08 Treatment at less than 20 weeks' gestation

Outcome: 05 Preterm birth less than 34 weeks' gestation

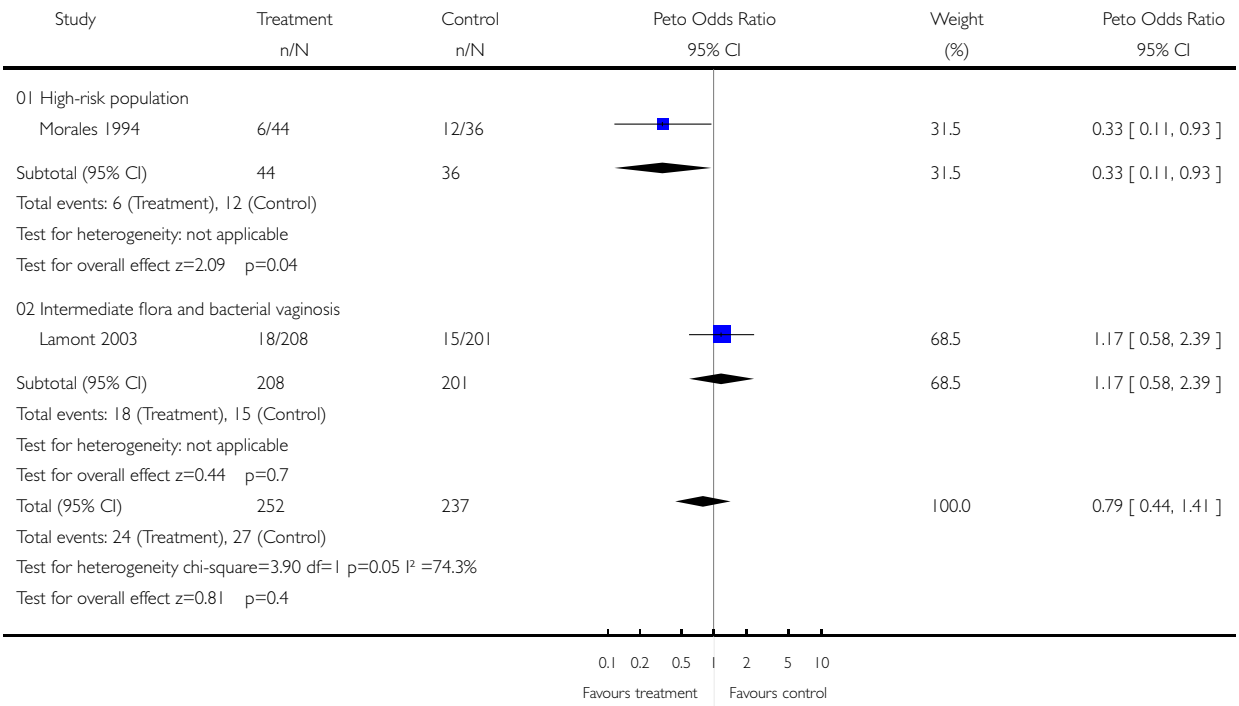
Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 High-risk population					
Morales 1994	2/44	4/36	■	100.0	0.39 [0.07, 2.07]
Total (95% CI)	44	36	◆	100.0	0.39 [0.07, 2.07]
Total events: 2 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.10 p=0.3					

Analysis 08.06. Comparison 08 Treatment at less than 20 weeks' gestation, Outcome 06 Incidence of low birthweight

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 08 Treatment at less than 20 weeks' gestation

Outcome: 06 Incidence of low birthweight



Analysis 08.07. Comparison 08 Treatment at less than 20 weeks' gestation, Outcome 07 Side-effects not sufficient to stop treatment

Review: Antibiotics for treating bacterial vaginosis in pregnancy

Comparison: 08 Treatment at less than 20 weeks' gestation

Outcome: 07 Side-effects not sufficient to stop treatment