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Interventions for treating genital Chlamydia trachomatis infection in pregnancy (Review)

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Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

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A B S T R A C T

Background

Genital *Chlamydia trachomatis* (*C.trachomatis*) infection may lead to pregnancy complications such as miscarriage, preterm labour, low birthweight, preterm rupture of membranes, increased perinatal mortality, postpartum endometritis, chlamydial conjunctivitis and *C.trachomatis* pneumonia.This review supersedes a previous review on this topic.

Objectives

To establish the most efficacious and best-tolerated therapy for treatment of genital chlamydial infection in preventing maternal infection and adverse neonatal outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (26 June 2017) and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs) as well as studies published in abstract form assessing interventions for treating genital *C.trachomatis* infection in pregnancy. Cluster-RCTs were also eligible for inclusion but none were identified. Quasi-randomised trials and trials using cross-over design are not eligible for inclusion in this review.

Data collection and analysis

Two review authors independently assessed studies for inclusion, assessed trial quality and extracted the data using the agreed form. Data were checked for accuracy. Evidence was assessed using the GRADE approach.

Main results

We included 15 trials (involving 1754 women) although our meta-analyses were based on fewer numbers of studies/women. All of the included studies were undertaken in North America from 1982 to 2001. Two studies were low risk of bias in all domains, all other studies had varying risk of bias. Four other studies were excluded and one study is ongoing.

Eight comparisons were included in this review; three compared antibiotic (erythromycin, clindamycin, amoxicillin) versus placebo; five compared an antibiotic versus another antibiotic (erythromycin, clindamycin, amoxicillin, azithromycin). No study reported different antibiotic regimens.

Microbiological cure (primary outcome)

Antibiotics versus placebo: Erythromycin (average risk ratio (RR) 2.64, 95% confidence interval (CI) 1.60 to 4.38; two trials, 495 women; I^2 = 68%; *moderate-certainty evidence*), and clindamycin (RR 4.08, 95% CI 2.35 to 7.08; one trial, 85 women; *low-certainty evidence*) were associated with improved microbiological cure compared to a placebo control. In one very small trial comparing amoxicillin and placebo, the results were unclear, but the evidence was graded *very low* (RR 2.00, 95% CI 0.59 to 6.79; 15 women).

One antibiotic versus another antibiotic: Amoxicillin made little or no difference in microbiological cure in comparison to erythromycin (RR 0.97, 95% CI 0.93 to 1.01; four trials, 466 women; *high-certainty evidence*), probably no difference compared to clindamycin (RR 0.96, 95% CI 0.89 to 1.04; one trial, 101 women; *moderate-quality evidence*), and evidence is *very low certainty* when compared to azithromycin so the effect is not certain (RR 0.89, 95% CI 0.71 to 1.12; two trials, 144 women; *very low-certainty evidence*). Azithromycin versus erythromycin (average RR 1.11, 95% CI 1.00 to 1.23; six trials, 374 women; I^2 = 53%; *moderate-certainty evidence*) probably have similar efficacy though results appear to favour azithromycin. Clindamycin versus erythromycin (RR 1.06, 95% CI 0.97 to 1.15; two trials, 173 women; *low-certainty evidence*) may have similar numbers of women with a microbiological cure between groups.

Evidence was downgraded for design limitations, inconsistency, and imprecision in effect estimates.

Side effects of the treatment (maternal) (secondary outcome)

Antibiotics versus placebo: side effects including nausea, vomiting, and abdominal pain, were reported in two studies (495 women) but there was no clear evidence whether erythromycin was associated with more side effects than placebo and a high level of heterogeneity (I^2 = 78%) was observed (average RR 2.93, 95% CI 0.36 to 23.76). There was no clear difference in the number of women experiencing side effects when clindamycin was compared to placebo in one small study (5/41 versus 1/44) (RR 6.35, 95% CI 0.38 to 107.45, 62 women). The side effects reported were mostly gastrointestinal and also included resolving skin rashes.

One antibiotic versus another antibiotic: There was no clear difference in incidence of side effects (including nausea, vomiting, diarrhoea and abdominal pain) when amoxicillin was compared to azithromycin based on data from one small study (36 women) (RR 0.56, 95% CI 0.24 to 1.31).

However, amoxicillin was associated with fewer side effects compared to erythromycin with data from four trials (513 women) (RR 0.31, 95% CI 0.21 to 0.46; I^2 = 27%). Side effects included nausea, vomiting, diarrhoea, abdominal cramping, rash, and allergic reaction.

Both azithromycin (RR 0.24, 95% CI 0.17 to 0.34; six trials, 374 women) and clindamycin (RR 0.44, 95% CI 0.22 to 0.87; two trials, 183 women) were associated with a lower incidence of side effects compared to erythromycin. These side effects included nausea, vomiting, diarrhoea and abdominal cramping.

One small study (101 women) reported there was no clear difference in the number of women with side effects when amoxicillin was compared with clindamycin (RR 0.57, 95% CI 0.14 to 2.26; 107 women). The side effects reported included rash and gastrointestinal complaints.

Other secondary outcomes

Single trials reported data on repeated infections, preterm birth, preterm rupture of membranes, perinatal mortality and low birthweight and found no clear differences between treatments.

Many of this review's secondary outcomes were not reported in the included studies.

Authors' conclusions

Treatment with antibacterial agents achieves microbiological cure from *C. trachomatis* infection during pregnancy. There was no apparent difference between assessed agents (amoxicillin, erythromycin, clindamycin, azithromycin) in terms of efficacy (microbiological cure and repeat infection) and pregnancy complications (preterm birth, preterm rupture of membranes, low birthweight). Azithromycin and clindamycin appear to result in fewer side effects than erythromycin.

All of the studies in this review were conducted in North America, which may limit the generalisability of the results. In addition, study populations may differ in low-resource settings and these results are therefore only applicable to well-resourced settings. Furthermore, the trials in this review mainly took place in the nineties and early 2000's and antibiotic resistance may have changed since then.

Further well-designed studies, with appropriate sample sizes and set in a variety of settings, are required to further evaluate interventions for treating *C.trachomatis* infection in pregnancy and determine which agents achieve the best microbiological cure with the least side effects. Such studies could report on the outcomes listed in this review.

PLAIN LANGUAGE SUMMARY

Treatment of genital *Chlamydia trachomatis* infection in pregnancy

What is the issue?

This review aimed to assess whether the treatment of chlamydial infection during pregnancy cured the infection and prevented complications to the women and babies without causing side effects. This new review supersedes an earlier review on this topic.

Why is this important?

Chlamydia trachomatis is a bacterial infection which is sexually transmitted. It is more common in younger women. Women may have the infection without knowing it. In pregnant women, genital *Chlamydia trachomatis* can cause pregnancy complications such as preterm labour, preterm birth, premature rupture of the membranes, low birthweight of infants, and infection in the uterus after giving birth. Babies who acquire *Chlamydia trachomatis* during birth can develop infection of the lungs and the eyes.

Finding an effective treatment with minimal side effects is extremely important considering the complications that can occur with untreated *Chlamydia trachomatis* infection in pregnancy.

What evidence did we find?

We searched for evidence (June 2017) and included 15 studies in the review. The studies had a mixed risk of bias and were of limited quality, often with small numbers of participants. Three studies compared antibiotics (erythromycin, clindamycin, and amoxicillin) with placebo. The other studies compared different antibiotics with each other.

All of the studies reported on curing chlamydia, based on the elimination of the bacteria, with an antibiotic. Erythromycin (moderate-quality evidence from two studies, 495 women) and clindamycin (low-quality evidence from one study, 85 women) appeared to be more effective than placebo. The quality of the evidence for amoxicillin versus placebo (one study 15 women) was very low so we cannot be certain of the results.

When comparing different antibiotics with each other, no one antibiotic was substantially better than another at curing chlamydia in the studies that we examined: amoxicillin versus azithromycin (very low-quality evidence from two studies, 144 women), amoxicillin versus erythromycin (high-quality evidence from four studies, 466 women), azithromycin versus erythromycin (moderate-quality evidence from six studies, 374 women), clindamycin versus erythromycin (low-quality evidence from two studies, 173 women), amoxicillin versus clindamycin (moderate-quality evidence from one study, 101 women). Only single trials assessed repeated infections, preterm birth, preterm rupture of membranes, perinatal mortality and low birthweight and found there were no clear differences between the different types of antibiotics examined.

Side effects were more common with erythromycin (two studies, 495 women) and clindamycin (one study, 85 women) than with placebo. Amoxicillin resulted in fewer side effects than azithromycin (one study, 36 women) or erythromycin (four studies, 513 women), and azithromycin caused fewer side effects than erythromycin (six studies, 374 women). Amoxicillin and clindamycin produced a similar number of side effects in one study (107 women).

What does this mean?

Treatment of chlamydia infection with antibiotics appears to be effective during pregnancy. There is no clear difference between amoxicillin, erythromycin, clindamycin, azithromycin in curing the infection or preterm birth, preterm rupture of membranes, and low birthweight. Azithromycin and clindamycin appear to result in fewer side effects than erythromycin.

The included studies were all carried out in North America. Chlamydia testing remains a problem in low-resource settings because of its costs. We conclude that well-designed studies of appropriate sample size, in different settings, are needed to further assess the effects

of treatment of chlamydia infection in pregnancy. Resistance to the tested antibiotics could have changed since the studies included in this review were conducted. In particular, future research could report on the outcomes of focus in this review and target those antibiotics, such as amoxicillin and clindamycin, which may be effective in curing chlamydia with the least side effects.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Erythromycin compared to placebo for treating genital *Chlamydia trachomatis* **infection in pregnancy**

Patient or population: Pregnant women with a confirmed *Chlamydia trachomatis* infection
Setting: Obstetric Clinics, USA
Intervention: Erythromycin
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Erythromycin				
Microbiological cure	Study population		Average RR 2.64 (1.60 to 4.38)	495 (2 RCTs)	⊕⊕⊕◯ MODERATE [1] [2]	
	344 per 1000	908 per 1000 (550 to 1000)				

*The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Statistical Heterogeneity ($I^2 > 60\%$). (Inconsistency: -1)
[2] One included study has design limitations but contributed < 40% weight. (Not downgraded)

BACKGROUND

The prevalence of chlamydial infection in pregnancy is between 2% to 30% depending on the patient's age and risk factors (Berggren 2011; Much 1991). It is particularly common in women younger than 25 years of age (Walker 2012). Genital *Chlamydia trachomatis* (*C.trachomatis*) infection has been shown to be associated with pregnancy complications such as miscarriage (Nigro 2011), preterm labour (Pararas 2006; Rours 2011), low birthweight (Attenburrow 1985) and increased perinatal mortality (Silva 2011). There may also be an association with preterm rupture of membranes (Blas 2007) and postpartum endometritis (Ismail 1987). If the mother is untreated, 20% to 50% of newborn babies may develop chlamydial conjunctivitis (Kakar 2010), and another 10% to 20% may develop *C.trachomatis* pneumonia (Rours 2009). Vaginal birth is associated with the highest risk of transmission of chlamydial infection, however, there is a small risk of acquiring the infection even in infants born by caesarean section with premature rupture of membranes and intact membranes (Pammi 2012; Yu 2009).

Genital *C.trachomatis* infection is detected by nucleic acid amplification test (NAAT) on the specimens of genital secretions or urine. This test has replaced tissue culture of *C.trachomatis* (Jespersen 2005).

Description of the condition

Genital *C.trachomatis* infection is a common bacterial sexually transmitted infection. The majority of women infected with this bacteria are asymptomatic and, therefore, may be more likely to transmit the infection because they do not seek treatment for the infection, which may result in a longer duration of the infection. The sequelae of *C.trachomatis* genital infection range from cervicitis to pelvic inflammatory disease, perihepatitis, ectopic pregnancy and infertility (Zenilman 2012). We have described complications of pregnancy and diseases of newborn related to genital Chlamydia infection in the Background section above.

C.trachomatis is a small gram-negative intracellular bacterium with a two-phased life-cycle, which includes the form that infects new cells, (e.g. the small elementary body) and the active form (e.g. the reticulate body). The life-cycle is about two to three days, and, therefore, sustained high serum minimum inhibitory concentration of antimicrobial agents is needed to achieve eradication of the infection, which can be achieved by long-acting antimicrobials treatment or prolonged treatment. The incubation period of *C.trachomatis* infection varies between seven and 14 days (Zenilman 2012).

Description of the intervention

There are various treatment regimens for the management of chlamydial infection during pregnancy, however, there is no consensus on the most effective and safest option. In some, the hosts' immune system may even clear the infection.

According to the Centers for Disease Control and Prevention (CDC) guideline followed by many countries around the world, the recommended regimens for treatment of genital chlamydial infection in pregnancy are azithromycin (1 g orally given as a single dose) or amoxicillin (500 mg orally three times daily for seven days) (Workowski 2010). The alternative regimen according to the CDC guideline is erythromycin (500 mg or 250 mg orally four times daily for seven days), or erythromycin ethylsuccinate (800 mg orally four times daily for seven days, or 400 mg orally four times daily for 14 days) (Workowski 2010). Erythromycin is associated with a high degree of gastrointestinal side effects (primarily nausea) and the compliance may be an issue in such cases (Workowski 2010).

Women who present in labour but were not treated for a prior positive chlamydial test are advised to be treated immediately with one of the above regimens. However, such late treatment is unlikely to substantially decrease the risk of transmission of Chlamydia to the newborn.

Clindamycin is another alternative drug for treatment of genital *C.trachomatis* infection. Despite it being safe in pregnancy, clindamycin is not used widely due to its cost (Miller 2000).

Other antibiotics such as doxycycline, levofloxacin, ofloxacin, and erythromycin estolate are used for the treatment of genital *C.trachomatis* outside of pregnancy. These drugs are contraindicated in pregnancy and lactation (Workowski 2010).

Azithromycin is believed to be the superior agent in comparison to other antibiotics for treatment of chlamydial infection but new research has emerged suggesting that there is a higher failure rate with azithromycin treatment of chlamydial infection than previously believed (Schwebke 2011). One of the explanations for this recent finding is a higher sensitivity of NAAT in comparison to that previously used in the tissue culture as a test of cure (Handsfield 2011), although it does not explain the similar cure rates reported after doxycycline treatment with both of these tests. Another explanation for treatment failure is heterotopic resistance with high Chlamydia loads which leads to treatment failures (Horner 2006). Re-infection is also a cause of treatment failure (Horner 2006).

Cure rates of *C.trachomatis* in women who are pregnant are lower than in non-pregnant women. The reasons behind this is a generally higher failure rate of treatment with amoxicillin, which has been traditionally used for treatment of *C.trachomatis* infection during pregnancy. A test of cure has always been recommended for all pregnant women and is performed no earlier than three weeks after treatment is initiated (Workowski 2010).

The previous Cochrane review on interventions for treating genital *C.trachomatis* infection in pregnancy found that amoxicillin was as effective as erythromycin (odds ratio (OR) 0.54, 95% confidence

interval (CI) 0.28 to 1.02) (Brocklehurst 1998). Amoxycillin was found to be better tolerated than erythromycin (OR 0.16, 95% CI 0.09 to 0.30). Clindamycin and azithromycin were reported to be effective, however, the numbers of women included in trials were small (Brocklehurst 1998). New studies have been published in this area, therefore, it is important to update this review, which was done under new authorship.

How the intervention might work

Irradicating genital chlamydial infection during pregnancy with antibacterial drugs may lead to the following:

- treatment of symptoms and sequelae of genital chlamydial infection such as discharge, cervicitis, pelvic inflammatory disease, tubal disease and infertility;
- a decrease in perinatal complications such as preterm labour and early pregnancy loss, preterm rupture of membranes;
- a decrease in transmission of the infection to the fetus or newborn and, therefore, prevention of intrauterine infection, neonatal conjunctivitis and pneumonia during pregnancy;
- prevention of postpartum infection such as endometritis.

Why it is important to do this review

It is important to assess the different interventions for treating genital *C.trachomatis* in order to establish whether effective treatment of this infection improves perinatal outcomes and decreases maternal complications. This new review updates and replaces an earlier Cochrane review on this topic (Brocklehurst 1998).

OBJECTIVES

To establish the most efficacious and best-tolerated therapy for treatment of genital chlamydial infection in preventing maternal infection and adverse neonatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials. Cluster-randomised trials will be eligible for inclusion in this review in the future updates if identified. Quasi-randomised trials and trials using crossover design were not eligible for inclusion. We included studies published in abstract form.

Types of participants

Pregnant women with a confirmed *C.trachomatis* infection.

Types of interventions

- Any antibiotic versus no treatment or placebo for genital *C.trachomatis* infection in pregnancy
  - One antibiotic versus another antibiotic
  - Different antibacterial regimens

Types of outcome measures

Primary outcomes

- Microbiological cure - negative Chlamydia test at least three weeks after treatment of the mother

Secondary outcomes

A. Maternal

- Repeated infection
- Preterm labour
- Preterm birth
- Preterm rupture of membranes
- Chorioamnionitis
- Postpartum endometritis
- Sepsis
- Prolonged hospital stay of the mother
- Side effects of treatment
- Maternal satisfaction with treatment

B. Fetal/neonatal

- Perinatal mortality
- Neonatal conjunctivitis
- Neonatal pneumonia
- Fetal anomalies
- Low birthweight
- Apgar score less than seven at five minutes

C. Cost

- Cost of treatment

Search methods for identification of studies

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

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting their Information Specialist (26 June 2017).

The Register is a database containing over 23,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Pregnancy and Childbirth Group's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth Group in the Cochrane Library and select the 'Specialized Register' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

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

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Ongoing studies)

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (26 June 2017) for unpublished, planned and ongoing trial reports. The search terms we used are given in Appendix 1.

Searching other resources

We searched the reference lists of retrieved studies.
We did not apply any language or date restrictions.

Data collection and analysis

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

Selection of studies

Two review authors independently assessed all the potential studies identified as a result of the search strategy for inclusion. Two review authors assessed the quality and extracted the data using the agreed form. Discrepancies were resolved through discussion with a third review author when needed. We entered data into Review Manager software and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Studies published only in abstract form were included if they otherwise satisfied inclusion criteria. The authors of such studies were contacted if any additional information was required.

Data extraction and management

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

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

Assessment of risk of bias in included studies

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

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

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

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

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

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

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

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

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

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

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed methods used to blind outcome assessment as:
- low, high or unclear risk of bias.

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

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.
We assessed methods as:
- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

A cut-off point of 20% was used to assess the level of missing data as adequate for different outcomes.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:
- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

We described for each included study any important concerns we have about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:
- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

For this update , we assessed the quality of the evidence for all comparisons using the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence relating to the main outcome of microbiological cure.
We used GRADEpro GDT to import data from Review Manager 5.3 (RevMan 2014) to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious

inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

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

Continuous data

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

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials for inclusion in this version of the review. If we identify any cluster-randomised trials for inclusion in future updates, we will include them in our analyses along with individually-randomised trials. We will adjust their standard errors using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we will synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the studies and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will acknowledged heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Cross-over trials

This study design is not eligible for inclusion in this review.

Other unit of analysis issues

We identified the trials with more than two treatment groups and included each pair-wise comparison separately, but with shared intervention groups divided out approximately evenly among the comparisons. For dichotomous outcomes, both the number of events and the total number of patients were divided up. For continuous outcomes, only the total number of participants were divided up and the means and standard deviations left unchanged (*Cochrane Handbook for Systematic Reviews of Interventions* 16.5.4).

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis (see Sensitivity analysis).

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

We would have excluded studies with more than 20% missing data.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T², I² and Chi² statistics. We regarded heterogeneity as substantial if the I² was greater than 30% and either the T² was greater than zero, or there was a low P value (less than 0.10) in the Chi² test for heterogeneity.

Assessment of reporting biases

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

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing

between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

Where we used random-effects analyses, the results are presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We did not carry out ant of the planned subgroup analyses as the outcomes only had a few included trials. In future updates if we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We would consider carrying out the following subgroup analyses.

- Women with a first episode versus women with recurrent (previously treated in pregnancy) genital *C.trachomatis* infection
- Women in the first half (before 20 weeks) versus women in the second half (including 20 weeks and after 20 weeks) of pregnancy

The following outcome would be used in subgroup analysis.

- Microbiological cure negative Chlamydia test after treatment for the mother

We would have assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We would have reported the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test I² value.

Sensitivity analysis

Sensitivity analyses were not performed as there were no aspects of the review that may have affected the results, for example, the risk of bias associated with the quality of some of the included trials. We would have undertaken analysis of the primary outcome separately for trials with low risk of bias and high and unknown risk of bias (allocation concealment) if needed. Sensitivity analysis would have been carried out to explore the effects of random-effects analyses for outcomes with statistical heterogeneity. We would also have carried out sensitivity analysis to investigate the effect of the randomisation unit if we had included cluster-randomised controlled trials along with the individually-randomised trials.

R E S U L T S

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved 23 reports of 20 trials and we retrieved no other studies from other sources (see: Figure 1). We included 15 studies, excluded four, and one is ongoing (Okunola 2013).

Figure 1. Study flow diagram.
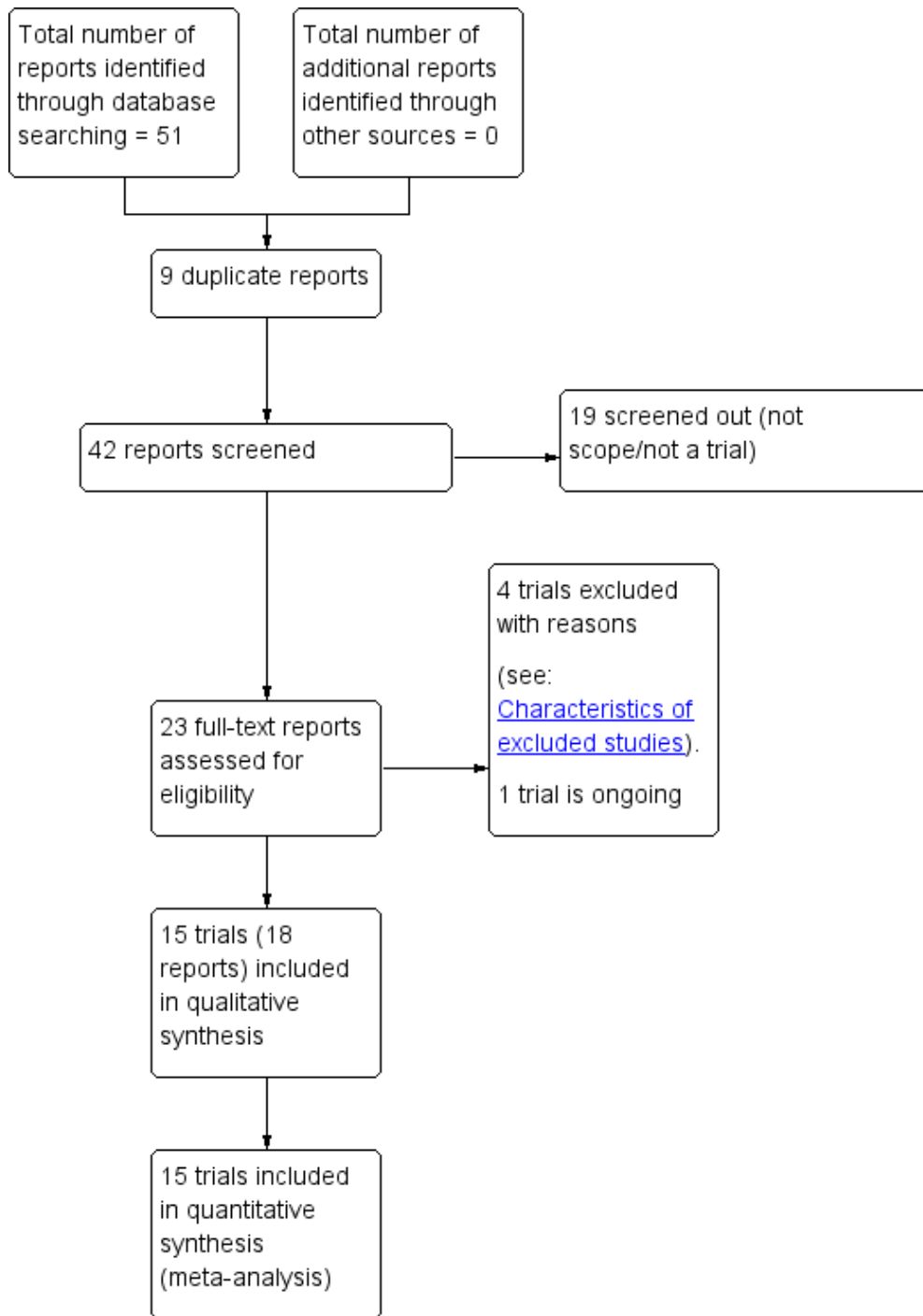
Included studies

We included 15 studies into the meta-analysis with a total of 1754 women. Meta-analyses were mostly based on fewer numbers of studies.

Methods

All the trials were randomised control trials of pregnant women with confirmed *Chlamydia trachomatis* (*C.trachomatis*) infection.

Populations and settings

All of the included studies were undertaken in North America (14 in USA and one in Canada). One study took place in 1982, and the rest took place in the nineties and early 2000s.

Interventions and comparisons

Two studies compared erythromycin and placebo (Alger 1991; Martin 1997). One study compared clindamycin and placebo (Alger 1991). One study compared amoxicillin versus placebo (Bell 1982). Two studies compared azithromycin and amoxicillin (Jacobson 2001; Kacmar 2001). Four studies compared amoxicillin and erythromycin (Alary 1994; Magat 1993; Silverman 1994; Turrentine 1995). Six studies compared erythromycin and azithromycin (Adair 1998; Bush 1994; Edwards 1996; Gunter 1996; Rosenn 1995; Wehbeh 1998). Two studies compared clindamycin and erythromycin (Alger 1991; Turrentine 1995). One study compared amoxicillin and clindamycin (Turrentine 1995).

Funding sources

Adair 1998, Edwards 1996, and Turrentine 1995 had drugs donated by a pharmaceutical company at no cost. Alger 1991 was funded by a grant from the Upjohn company.
Alary 1994 was funded by a grant from the National Health Research and Development Program. Kacmar 2001 was funded by a NIH grant. Martin 1997 was funded by a National Institute of Child Health and Human Development grant. Bell 1982 was supported by a US Public Health Service grant.
Wehbeh 1998 was funded by local departmental funds.
Bush 1994, Gunter 1996, Jacobson 2001, Magat 1993, Rosenn 1995, and Silverman 1994 did not disclose any funding sources.

Trial authors' declarations of interest

Declarations of interest were not mentioned in any of the included studies.

Excluded studies

Reasons for exclusion are as follows.

- El-Shourbagy 2011 - this study examines the rate of pre-eclampsia in groups of treated and non-treated *Chlamydia pneumoniae* infections in pregnancy.
- McGregor 1990 - this study included pregnant women with various genital tract infections and not only *Chlamydia trachomatis*. The data for *Chlamydia trachomatis* infection were not presented separately.
- Nadafi 2005 - this study included women with positive and negative Chlamydia test, it was a cohort study, sequence generation was not clear. The data for women with positive and negative Chlamydia test are presented together.
- Zulkarneev 1998 - this study was not a randomised controlled trial.

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
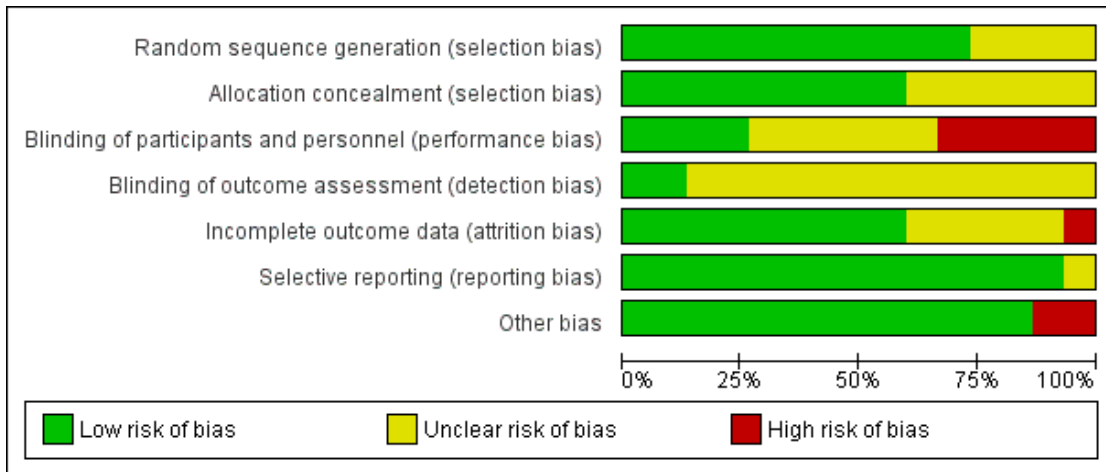
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Eleven studies had low risk of selection bias, e.g. three studies used number of blocks for allocation (Adair 1998; Alary 1994; Rosenn 1995), four studies used computer-generated randomisation for allocation (Bush 1994; Jacobson 2001; Martin 1997; Turrentine 1995), four studies used random number tables (Edwards 1996; Kacmar 2001; Magat 1993; Silverman 1994). Four studies had unclear risk of selection bias, e.g. allocation method was not described (Alger 1991; Bell 1982; Gunter 1996; Wehbeh 1998).

Nine studies had a low risk of bias for allocation sequence. Six used sealed opaque envelopes (Adair 1998; Bush 1994; Jacobson 2001; Kacmar 2001; Rosenn 1995; Silverman 1994). One study used identical treatment packs (Alary 1994). In two trials the medications were dispensed by the pharmacy to prevent the healthcare practitioners knowing which medication and which dose were allocated (Magat 1993; Turrentine 1995). There was an unclear risk in six studies as allocation concealment was not described (Alger 1991; Bell 1982; Edwards 1996; Gunter 1996; Martin 1997; Wehbeh 1998).

Blinding

Performance bias

Blinding of participants and personnel was performed four studies (Alary 1994; Alger 1991; Martin 1997; Turrentine 1995).

Five studies did not implement blinding of participants or personnel and were assessed as high risk (Adair 1998; Edwards 1996; Jacobson 2001; Magat 1993; Wehbeh 1998).

Six studies did not describe performance blinding (Bell 1982; Bush 1994; Gunter 1996; Kacmar 2001; Rosenn 1995; Silverman 1994).

Assessment bias

Blinding of outcome assessment was unclear in 13 studies (Adair 1998; Alger 1991; Bell 1982; Bush 1994; Edwards 1996; Gunter 1996; Jacobson 2001; Kacmar 2001; Magat 1993; Martin 1997; Rosenn 1995; Silverman 1994; Wehbeh 1998).

Assessment bias was assessed as low risk in two studies were staff taking cultures were blinded to treatment group (Alary 1994; Turrentine 1995).

Incomplete outcome data

No studies had significant attrition bias. All losses to follow-up were described. One study (Bell 1982) had high attrition for the final outcome reporting data for only 71% of participants. Five

studies are at unclear risk of attrition bias due to insufficient information given in the study report (Gunter 1996), and some unexplained loss to follow-up (Jacobson 2001; Kacmar 2001; Martin 1997; Silverman 1994).

Selective reporting

One study was published only in abstract form and states that it is an ongoing trial but no further information has been published (Gunter 1996). The remaining 14 studies were rated as being at low risk of reporting bias.

Other potential sources of bias

Two studies had unexplained different mean gestational ages in women in the two treatment arms (Edwards 1996; Magat 1993). The remaining 13 studies were assessed as being at a low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Erythromycin compared to placebo for treating genital *Chlamydia trachomatis* infection in pregnancy; **Summary of findings 2** Clindamycin compared to placebo for treating genital *Chlamydia trachomatis* infection in pregnancy; **Summary of findings 3** Amoxicillin compared to placebo for treating genital *Chlamydia trachomatis* infection in pregnancy; **Summary of findings 4** Amoxicillin compared to azithromycin for treating genital *Chlamydia trachomatis* infection in pregnancy; **Summary of findings 5** Amoxicillin compared to erythromycin for treating genital *Chlamydia trachomatis* infection in pregnancy; **Summary of findings 6** Azithromycin compared to erythromycin for treating genital *Chlamydia trachomatis* infection in pregnancy; **Summary of findings 7** Clindamycin compared to erythromycin for treating genital *Chlamydia trachomatis* infection in pregnancy; **Summary of findings 8** Amoxicillin compared to clindamycin for treating genital *Chlamydia trachomatis* infection in pregnancy

Erythromycin versus placebo (comparison 1)

Primary outcome

Microbiological cure

Erythromycin appears to improve microbiological cure in comparison to placebo (*moderate-certainty evidence*, Summary of findings

for the main comparison; (average risk ratio (RR) 2.64, 95% confidence interval (CI) 1.60 to 4.38; 495 women; studies = two; I² = 68%; Analysis 1.1)). There was evidence of substantial heterogeneity between the studies (I² = 68%) in effect size; both studies found erythromycin improved microbiological cure.

Secondary outcomes

Preterm birth

There was no clear difference in preterm births (RR 0.90, 95% CI 0.56 to 1.46; 405 women; studies = one; Analysis 1.2).

Preterm rupture of membranes

There was no clear difference in preterm rupture membranes between the treatment groups (RR 0.83, 95% CI 0.48 to 1.43; 389 women; studies = one; Analysis 1.3).

Side effects of treatment

We are uncertain if erythromycin results in a higher incidence of side effects when compared to placebo (average RR 2.93, 95% CI 0.36 to 23.76; 495 women; studies = two; I² = 78%; Analysis 1.4). There was substantial heterogeneity between the studies, I² = 78%. The side effects reported included nausea, appetite loss (Martin 1997), vomiting, diarrhoea, and abdominal pain (Alger 1991).

Perinatal mortality

There was no clear difference in perinatal deaths between the groups (RR 3.01, 95% CI 0.32 to 28.74; 405 women; studies = one; Analysis 1.5).

Low birthweight

There was no clear difference in low birthweight between the groups (RR 0.77, 95% CI 0.42 to 1.40; 400 women; studies = one; Analysis 1.6).

Other secondary outcomes

No studies assessed the other secondary outcomes.

Clindamycin versus placebo (comparison 2)

Primary outcome

Microbiological cure

Clindamycin appears to improve microbiological cure in comparison to placebo (*low-certainty evidence*, Summary of findings 2; (RR 4.08, 95% CI 2.35 to 7.08; 85 women; studies = one; Analysis 2.1)). One study (Alger 1991), which was funded by a pharmaceutical company contributed to this comparison.

Secondary outcomes

Side effects of treatment

There was no clear difference in side effects between the two groups (RR 5.37, 95% CI 0.65 to 44.01; 85 women; studies = one; Analysis 2.2). The side effects included a rash and mild gastrointestinal complaints including nausea and vomiting, abdominal pain, cramps and diarrhoea.

Other secondary outcomes

No studies assessed the other secondary outcomes.

Amoxicillin versus placebo (comparison 3)

Primary outcome

Microbiological cure

It is uncertain whether amoxicillin improves microbiological cure in comparison to placebo but the certainty of this evidence is *very low* (Summary of findings 3; (RR 2.00, 95% CI 0.59 to 6.79; 15 women; studies = one; Analysis 3.1)).

Secondary outcomes

No secondary outcomes were reported for this outcome in the included studies.

Amoxicillin versus azithromycin (comparison 4)

Primary outcome

Microbiological cure

It is uncertain whether amoxicillin improves or reduces microbiological cure in comparison to azithromycin because the certainty of this evidence is *very low* (Summary of findings 4; (RR 0.89, 95% CI 0.71 to 1.12; 144 women; studies = two; Analysis 4.1)).

Secondary outcomes

Repeated infection

There was no clear difference for the outcome of repeated infections between amoxicillin and azithromycin in the single included study (RR 0.42, 95% CI 0.02 to 9.55; 34 women; studies = one; Analysis 4.2).

Preterm birth

There was no clear difference in the incidence of preterm birth between amoxicillin and azithromycin (RR 1.17, 95% CI 0.43 to 3.20; 90 women; studies = one; Analysis 4.3).

Side effects of treatment

There was no clear difference in side effects between the two groups (RR 0.56, 95% CI 0.24 to 1.31; 36 women; studies = one; Analysis 4.4). Side effects reported included nausea, vomiting, diarrhoea and abdominal pain.

Other secondary outcomes

None were reported.

Amoxicillin versus erythromycin (comparison 5)

Primary outcome

Microbiological cure

Amoxicillin makes little or no difference to microbiological cure in comparison to erythromycin (*high-certainty evidence*, Summary of findings 5; (RR 0.97, 95% CI 0.93 to 1.01; 466 women; studies = 4; Analysis 5.1)).

Secondary outcomes

Side effects of treatment

Amoxicillin was associated with reduced incidence of side effects in comparison to erythromycin (RR 0.31, 95% CI 0.21 to 0.46; 513 women; studies = four; I² = 27%; Analysis 5.2). Side effects associated with erythromycin use included nausea, vomiting, diarrhoea, abdominal cramping, rash, and an allergic reaction.

Other secondary outcomes

None were reported.

Azithromycin versus erythromycin (comparison 6)

Primary outcome

Microbiological cure

It appears that azithromycin probably improves microbiological cure in comparison to erythromycin (*moderate-certainty evidence*, Summary of findings 6; (average RR 1.11, 95% CI 1.00 to 1.23; participants = 374; studies = six; I² = 53%; Analysis 6.1)), however, there was substantial heterogeneity between the included studies (I² = 53%) and the lower confidence interval just touches the line of no effect.

Secondary outcomes

Repeated infection

There was no clear difference between azithromycin and amoxicillin for the outcome of repeated infections (RR 1.37, 95% CI 0.32 to 5.73; 85 women; studies = one; Analysis 6.2).

Preterm birth

There was no clear difference in the rate of preterm birth between azithromycin and amoxicillin (RR 0.77, 95% CI 0.29 to 2.10; 126 women; studies = one; Analysis 6.3).

Preterm rupture of membranes

There was no clear difference for the outcome of preterm rupture of membranes between azithromycin and amoxicillin (RR 0.62, 95% CI 0.15 to 2.48; 126 women; studies = one; Analysis 6.4).

Side effects of treatment

Fewer women in the azithromycin group experienced side effects in comparison to women receiving erythromycin (RR 0.24, 95% CI 0.17 to 0.34; 374 women; studies = six; Analysis 6.5). These side effects were mostly gastrointestinal in origin and included nausea, vomiting, diarrhoea and abdominal cramping.

Other secondary outcomes

None were reported.

Clindamycin versus erythromycin (comparison 7)

Primary outcome

Microbiological cure

Clindamycin may make little or no difference on microbiological cure in comparison to erythromycin (*low-certainty evidence,* Summary of findings 7; (RR 1.06, 95% CI 0.97 to 1.15; 173 women; studies = two; Analysis 7.1)).

Secondary outcomes

Side effects of treatment

Women in the clindamycin group experienced less side effects in comparison to erythromycin (RR 0.44, 95% CI 0.22 to 0.87; 183 women; studies = two; Analysis 7.2). These side effects were mostly gastrointestinal in origin and included nausea, vomiting, diarrhoea and abdominal cramping.

Other secondary outcomes

None were reported.

Amoxicillin versus clindamycin (comparison 8)

Primary outcome

Microbiological cure

Amoxicillin probably makes little or no difference on microbiological cure in comparison to clindamycin (*moderate-certainty evidence*, Summary of findings 8; (RR 0.96, 95% CI 0.89 to 1.04; 101 women; studies = one; Analysis 8.1)).

Secondary outcomes

Side effects of treatment

There was no clear difference in number of side effects associated with amoxicillin and clindamycin (RR 0.57, 95% CI 0.14 to 2.26; 107 women; studies = one; Analysis 8.2). The side effects reported included rash and gastrointestinal complaints.

Other secondary outcomes

None were reported.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Clindamycin compared to placebo for treating genital *Chlamydia trachomatis* infection in pregnancy

Patient or population: Pregnant women with a confirmed *Chlamydia trachomatis* infection
Setting: Obstetric Clinic, USA
Intervention: Clindamycin
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Clindamycin**				
Microbiological cure	Study population		RR 4.08 (2.35 to 7.08)	85 (1 RCT)	⊕⊕◯◯ LOW [1][2]	
	227 per 1000	927 per 1000 (534 to 1000)				

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] The included study had design limitation (Design limitations: -1)
[2] Wide confidence interval and small sample size (Imprecision: -1)

Amoxicillin compared to placebo for treating genital *Chlamydia trachomatis* **infection in pregnancy**

Patient or population: Pregnant women with a confirmed *Chlamydia trachomatis* infection
Setting: USA
Intervention: Amoxicillin
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE) Comments
	Risk with placebo	**Risk with Amoxicillin**			
Microbiological cure	Study population		RR 2.00 (0.59 to 6.79)	15 (1 RCT)	⊕◯◯◯ VERY LOW [1][2]
	333 per 1000	667 per 1000 (197 to 1000)			

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] The included study had design limitation (Design limitations: -1)
[2] Wide confidence intervals crossing the line of no effect, few events, and small sample size (Imprecision: -2)

Amoxicillin compared to azithromycin for treating genital *Chlamydia trachomatis* **infection in pregnancy**

Patient or population: Pregnant women with a confirmed *Chlamydia trachomatis* infection
Setting: Prenatal clinics, USA
Intervention: Amoxicillin
Comparison: Azithromycin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with azithromycin	Risk with Amoxicillin				
Microbiological cure	Study population		RR 0.89 (0.71 to 1.12)	144 (2 RCTs)	⊕◯◯◯ VERY LOW [1][2]	
	716 per 1000	637 per 1000 (509 to 802)				

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] One study contributing to over 68% of weight to pooled analysis had some design limitations (Design limitations: -1)
[2] Wide confidence intervals crossing the line of no effect and small size (Imprecision: -2)

Amoxicillin compared to erythromycin for treating genital *Chlamydia trachomatis* **infection in pregnancy**

Patient or population: Pregnant women with a confirmed *Chlamydia trachomatis* infection
Setting: Obstetric centre or prenatal clinics in Canada, USA
Intervention: Amoxicillin
Comparison: Erythromycin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with erythromycin	Risk with Amoxicillin				
Microbiological cure	Study population		RR 0.97 (0.93 to 1.01)	466 (4 RCTs)	⊕⊕⊕⊕ HIGH	One study contributing to 24% of weight had some design limitation. (not downgraded)
	954 per 1000	925 per 1000 (887 to 963)				

*The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Azithromycin compared to erythromycin for treating genital *Chlamydia trachomatis* **infection in pregnancy**

Patient or population: Pregnant women with a confirmed *Chlamydia trachomatis* infection
Setting: Prenatal clinics, and university medical centres, USA
Intervention: Azithromycin
Comparison: erythromycin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with erythromycin	Risk with Azithromycin				
Microbiological cure	Study population		Average RR 1.11 (1.00 to 1.23)	374 (6 RCTs)	⊕⊕⊕◯ MODERATE [1][2]	
	825 per 1000	916 per 1000 (825 to 1000)				

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Most studies have design limitations (Design limitations: -1)
[2] Statistical heterogeneity at 53% ($I^2 < 60\%$) (not downgraded)

Clindamycin compared to erythromycin for treating genital *Chlamydia trachomatis* **infection in pregnancy**

Patient or population: Pregnant women with a confirmed *Chlamydia trachomatis* infection
Setting: Prenatal clinics, USA
Intervention: Clindamycin
Comparison: Erythromycin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with erythromycin	Risk with Clindamycin				
Microbiological cure	Study population		RR 1.06 (0.97 to 1.15)	173 (2 RCTs)	⊕⊕◯◯ LOW [1][2]	
	905 per 1000	959 per 1000 (878 to 1000)				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] One study contributing to over 40% of weight to pooled analysis had some design limitations (Design limitations: -1)
[2] Small sample size (Imprecision: -1)

Amoxicillin compared to clindamycin for treating genital *Chlamydia trachomatis* **infection in pregnancy**

Patient or population: Pregnant women with a confirmed *Chlamydia trachomatis* infection
Setting: Prenatal clinic, USA
Intervention: Amoxicillin
Comparison: Clindamycin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with clindamycin	**Risk with Amoxicillin**				
Microbiological cure	Study population		RR 0.96 (0.89 to 1.04)	101 (1 RCT)	⊕⊕⊕◯ MODERATE [1]	
	979 per 1000	940 per 1000 (871 to 1000)				

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] The pooled effect was based on one study with a small sample size (Imprecision: -1)

DISCUSSION

Summary of main results

Fifteen studies involving 1754 women were included in this review but our meta-analyses are based on fewer numbers of studies/ women. We excluded four studies and one study is ongoing.

Erythromycin (moderate-certainty evidence) and clindamycin (low-certainty evidence) were associated with a higher incidence of microbiological cure in comparison to placebo. Results were unclear in one very small study comparing amoxicillin placebo but the evidence was graded very-low certainty.

There is no clear difference in microbiological cure between the assessed agents compared to each other: amoxicillin versus azithromycin (very low-certainty evidence); amoxicillin versus erythromycin (high-certainty evidence); azithromycin versus erythromycin (moderate-certainty evidence); clindamycin versus erythromycin (low-certainty evidence); amoxicillin versus clindamycin (moderate-certainty evidence). There was no clear difference in repeat infections for amoxicillin versus azithromycin, or azithromycin versus erythromycin. Most secondary outcomes were not reported in any of the included studies.

Antibacterial treatment of genital *Chlamydia trachomatis (C.trachomatis)* infection was associated with side effects which were more common with the use of erythromycin and clindamycin than placebo as would be expected. Amoxicillin and clindamycin were associated with less side effects than azithromycin and erythromycin. Azithromycin caused less side effects than erythromycin. Side effects associated with erythromycin, azithromycin and clindamycin included nausea, vomiting, abdominal cramping and diarrhoea. Clindamycin use was occasionally associated with a non severe rash.

There were only a few studies that assessed the outcomes of preterm birth, preterm rupture of membranes and low birthweight. No studies assessed chorioamnionitis, postpartum endometritis, sepsis, prolonged hospital stay, maternal satisfaction, neonatal conjunctivitis, neonatal pneumonia, fetal anomalies, low birthweight and Apgar scores.

Overall completeness and applicability of evidence

All of the included studies were undertaken in North America (14 in USA and 1 in Canada) in 1982 and the mid to late nineties and early 2000s. Antibiotic resistance may have changed since these studies were performed. Study populations could differ in low-resource settings and the results are therefore only applicable to well-resourced settings. *C.trachomatis* testing remains a challenge in low-resource settings because of the cost, and the treatment of genital infection is still based on a syndromic approach (South African STI guideline 2015). There was little or no information on

the outcomes of preterm labour, preterm birth, preterm rupture of membranes, chorioamnionitis, postpartum endometritis, sepsis, prolonged hospital stay, maternal satisfaction with treatment, perinatal mortality, neonatal conjunctivitis, neonatal pneumonia, fetal anomalies, low birthweight, Apgar score less than seven at five minutes and cost of treatment.

Quality of the evidence

We assessed the included studies for risk of bias. Two studies (Alary 1994; Turrentine 1995) were assessed to be at low risk of bias in all domains. The remaining studies had varying risks of bias; blinding of participants and outcome assessors was unclear, not reported, or not attempted in most studies. We carried out formal assessments of quality of the evidence using GRADEpro for the review's primary outcome of microbiological cure. For this outcome, the evidence was graded from *very low* to *high certainty* for the different comparisons: amoxicillin versus placebo and versus azithromycin were graded *very low quality*; clindamycin versus placebo, and versus erythromycin were graded *low quality*; erythromycin versus placebo, azithromycin versus erythromycin, and amoxicillin versus clindamycin were graded *moderate quality*; amoxicillin versus erythromycin was graded *high quality*. Evidence was downgraded for limitations in study designs, inconsistency, and imprecision in effect estimates.

Potential biases in the review process

Evidence in this review was derived from studies identified in a detailed search process. Trials comparing interventions to treat *C. trachomatis* infection in pregnancy that have not been published may not have been identified. We attempted to minimise bias in the review process by having two review authors independently extract data.

Agreements and disagreements with other studies or reviews

We did not find any publications which included meta-analysis of published studies, but we have identified two recent reviews/ guidelines addressing the treatment of *C.trachomatis* during pregnancy.

CDC guidelines (CDC 2015) and the up-to-date review (Marrazzo 2016) recommends the treatment of *C.trachomatis* infection in pregnancy with azithromycin based on clinical practice as it is safe and effective. Recommended alternatives suggested by both documents are amoxicillin and erythromycin. A test of cure is recommended in pregnant women three to four weeks after treatment and again three months later. Resistance to amoxicillin is highlighted, however, it is referenced with respect to animal studies only. The review and guideline did not suggest clindamycin as

an alternative, but according to limited data from this review it could be considered as a treatment option.

AUTHORS' CONCLUSIONS

Implications for practice

The current evidence on individual antibiotic interventions for treating genital *Chlamydia trachomatis (C.trachomatis)* infection in pregnancy is limited - the largest meta-analysis in this review includes six studies involving 374 women, and most include only one or two studies. Clindamycin, erythromycin, and amoxicillin seem to be effective compared with placebo in achieving microbiological cure, however, the evidence related to amoxicillin is very low quality and we cannot be certain of this. There were no clear differences in microbiological cure between different antibiotics when compared against each other. Erythromycin was associated with more side effects than clindamycin, azithromycin, and amoxicillin, including nausea, vomiting, diarrhoea and abdominal cramps. The evidence related to effects of treatment on a number of maternal and most fetal outcomes is sparse.

Implications for research

Further well-designed studies of appropriate sample size are required to assess interventions for treating *C.trachomatis* infection in pregnancy with agents achieving the best microbiological cure and causing least side effects such as amoxicillin and clindamycin. The secondary outcomes in this review have been under-reported. Future research could assess these outcomes: repeated infection, preterm labour, preterm birth, preterm rupture of membranes, chorioamnionitis, postpartum endometritis, sepsis, prolonged hospital stay of the mother, maternal satisfaction with treatment, perinatal mortality, neonatal conjunctivitis, neonatal pneumonia, fetal anomalies, low birthweight, Apgar score less than seven at five minutes and cost of treatment. A network meta-analysis would be beneficial to compare agents which have not yet been compared directly. Future research is needed in low-resource settings were population characteristics, cost, and treatment approach may differ from the studies included in this review.

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* *Indicates the major publication for the study*

C H A R A C T E R I S T I C S   O F   S T U D I E S

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

Adair 1998

Methods	Randomised controlled trial.
Participants	106 pregnant women screened positive by a direct DNA probe for *Chlamydia trachomatis* were enrolled. Exclusion criteria included hypersensitivity to erythromycin or azithromycin, lack of desire to participate in the study, or gestational age at most 14 weeks. 85 women entered and completed the entire trial protocol. 42 were assigned to azithromycin and 43 were assigned to erythromycin
Interventions	Azithromycin 1 g oral slurry in a single dose or erythromycin base 500 mg orally 4 times daily for 7 days
Outcomes	Cure rate, repeated infection, side effects (nausea and vomiting)
Notes	In the azithromycin group, 9 were lost to follow-up, 2 were not pregnant, 1 was treated off protocol. In the erythromycin group, 7 were lost to follow-up, 2 were not pregnant, 1 was treated off protocol. 74.4% in the erythromycin group and 50% in the azithromycin group completed the protocol as prescribed within the 3-week period. This high rate of prolonged, unconfirmed test of cure could have resulted in higher positive tests of cure or possibly higher re-infection rates in the azithromycin group. Compliance in the azithromycin group was 97.6% and in the erythromycin group it was 53.5%. Patients with positive Chlamydia assays at the test of cure were treated with the alternative agent to the originally assigned agent. Sample size estimates suggested the need to enrol 120 patients Performed at Bowman Gray School of Medicine of Wake Forest University, North Carolina, USA **Sources of trial funding:** The drugs used in this study were supplied without charge by Pfizer, Incorporated, New York, New York **Declarations of interest:** Not reported. **Trial dates:** 1995 - 1997.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to treatment was made by random numbers in blocks of 20 by the program Rancode-Plus 3.1.1
Allocation concealment (selection bias)	Low risk	Allocation cards were placed in a sealed opaque envelope.

Adair 1998 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt was made to blind the investigators to treatment allocations after enrolment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	85 (80.2%) women completed the study. The number lost to follow-up was similar in both the groups
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Alary 1994

Methods	Randomised controlled trial.
Participants	210 women culture-positive for *Chlamydia trachomatis* were included. Exclusion criteria: allergy to either drug, treatment with antibiotics after the chlamydial culture was done, abortion or miscarriage, moving away from the study area or more than 38 weeks of gestation at diagnosis 11 were excluded from the final analysis (see below). Outcome data were available for 199 women. 100 were treated with amoxicillin 99 were treated with erythromycin.
Interventions	Amoxycillin 500 mg 3 times daily for 7 days versus erythromycin 500 mg 4 times daily for 7 days
Outcomes	Cure rate. SIde effects (gastrointestinal).
Notes	Urethral samples from sexual partners of positive patients were cultured, and doxycycline treatment (100 mg twice a day for 10 days) was given free of charge Eye, nose, pharyngeal, rectal and genital swabs were obtained in infants in the week after birth Patients unable to tolerate their medication were offered the alternative treatment. In these cases, second cervical and urethral samples were cultured and a doctor independent of the study allocated the alternative treatment without informing the patients, investigators or the responsible physicians what the first therapy had been 11 of the 210 enrolled women were excluded from the final analysis 6 (4 amoxicillin, 2 erythromycin) did not attend to any follow-up visits 1 (amoxicillin) received another antibiotic during the early phase of the trial 2 (erythromycin) delivered before any outcome measurements. In 2 women receiving erythromycin, treatment was interrupted by the physician because of side effects and the patients did not come for follow-up tests In the erythromycin group, 5 patients had a temporary treatment interruption due to

Alary 1994 (*Continued*)

severe side effects and 12 patients had to be stopped permanently

In the amoxicillin group, 1 had temporary treatment interruption and 1 permanent withdrawal due to side effects

Of the 13 patients who could not complete their treatment, 10 accepted an alternative treatment, and all but 1 were cured. Re-infection cannot be ruled out for this patient, since her regular sexual partner did not attend follow-up

Compliance was above 95% in both groups with exclusion of the 13 patients who could not complete their treatment because of side effects

Study performed in 9 obstetric centres in the province of Quebec, Canada

Sources of trial funding: Study was supported by a grant from the National Health Research and Development Program

Declarations of interest: Not reported.

Trial dates: January 1990 - April 1993.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each woman was randomly assigned treatment in a pre-determined order in blocks of 10
Allocation concealment (selection bias)	Low risk	Identical treatment packs were used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded. "The drugs were issued in identical capsules in similar blister packs. In the amoxycillin packs, to maintain double-blind nature of the project, the third daily dose was a placebo whereas other capsules contained 250 mg amoxycillin."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staff taking sample cultures after treatment termination were unaware of the treatment group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	After randomisation, only 5.6% women lost to follow-up, equally balanced across the two groups
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Alger 1991

Methods	Randomised controlled trial.
Participants	135 pregnant women with culture-positive endocervical *Chlamydia trachomatis* infection were enrolled. Data were available for 126. 40 women received erythromycin and a clindamycin placebo. 42 women received clindamycin and erythromycin placebo.

	44 received a placebo for both clindamycin and erythromycin.
Interventions	Clindamycin (450 mg), erythromycin (331 mg), placebo orally 4 times per day for 14 days
Outcomes	Cure rate, side effects.
Notes	Partners treated with doxycycline 100 mg orally twice a day for 7 days 9 participants were delivered at another hospital and were lost to follow-up Study was performed at the University of Maryland Obstetric Clinic, Baltimore, USA **Sources of trial funding:** Study was funded by a grant from the Upjohn company. **Declarations of interest:** Not reported. **Trial dates:** October 1985 - April 1998.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded. "Medications were dispensed in blister packs with each dose packaged sequentially in an individual cell, permitting accurate determination of the specific number and timing of missed doses."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	From table 3, it is clear that there was no missing data in the placebo group while the missing outcome data were balanced in numbers across the two interventions groups
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Bell 1982

Methods	Randomised controlled trial.
Participants	21 gravidas beyond the 24th week of pregnancy with *Chlamydial trachomatis* infection who were not allergic to penicillin. Only had outcomes for 15 participants 9 were in the amoxicillin group. 6 were in the placebo group.
Interventions	Amoxicillin 500 mg 3 times a day (11 participants) or placebo (10 participants)
Outcomes	Postpartum culture: 3/9 had positive culture in amoxicillin group. 4/6 had a positive culture in the placebo group
Notes	Amoxicillin group: 2 were lost to follow-up. Placebo: 1 was treated elsewhere with erythromycin, 2 were lost to follow-up and 1 died due to a cerebrovascular incident Site of the study was not stated but assumed to be performed at University of Washington, Seattle, USA **Sources of trial funding:** Study was supported by a US Public Health Service grant. **Declarations of interest:** Not reported. **Trial dates:** Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described, unlikely.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described, unlikely.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described, unlikely.
Incomplete outcome data (attrition bias) All outcomes	High risk	All participants accounted for but only 15/21 were assessed for final outcome (71%)
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Bush 1994

Methods	Randomised controlled trial.
Participants	30 pregnant women with positive cervical *Chlamydia trachomatis* screen analysed by direct DNA assay. 15 were randomised to azithromycin. 15 were randomised to erythromycin.
Interventions	Erythromycin 500 mg orally 4 times a day for 7 days versus azithromycin 1 g orally as a single dose
Outcomes	Cure rate, side effects.
Notes	In those intolerant to erythromycin, 500 mg 4 times daily the dosage was lowered to 250 mg 4 times daily. This occurred in 5 of the 15 erythromycin cases 1 of the patients treated with erythromycin who was intolerant got positive culture results after treatment, but was successfully treated with azithromycin Sexual partners were treated in the standard fashion with doxycycline, 100 mg orally twice a day for 7 days Site of study not directly described but assumed to be Willian Beaumont Army Medical Center, El Paso, Texas **Sources of trial funding:** No funding source was declared. **Declarations of interest:** Not reported. **Trial dates:** Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated number assignment.
Allocation concealment (selection bias)	Low risk	The women were assigned treatment in sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described, unlikely.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Edwards 1996

Methods	Randomised controlled trial.
Participants	140 pregnant women were enrolled. Patients were tested positive for *C.trachomatis* by DNA hybridisation from a cervical swab specimen. Exclusion criteria; allergy to or intolerance of either azithromycin or erythromycin 65 were randomised to azithromycin. 65 were randomised to erythromycin.
Interventions	Azithromycin orally 1 g taken orally at enrolment versus erythromycin 500 mg orally 4 times a day for 7 days
Outcomes	Cure rate, preterm birth, preterm rupture of membranes, side effects
Notes	Compliance for the azithromycin group was 100%. Compliance for the erythromycin group was 59.4%. All sexual partners were referred to the appropriate county health department for treatment Test of cure was repeated after 2 weeks. 62 of the 65 patients in the azithromycin group completed their post-treatment questionnaires, while 64 of the 65 patients in the erythromycin group completed the same form Study was undertaken at the Medical University of South Carolina, Charleston, USA **Sources of trial funding:** Sponsored by Pfizer pharmaceuticals. **Declarations of interest:** Not reported. **Trial dates:** April 1993 - July 1994.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done using a pre-established random number table
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No attempt was made to blind the study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, 3 in the azithromycin group and 1 in the erythromycin group
Selective reporting (reporting bias)	Low risk	No selective reporting noted.

Edwards 1996 (*Continued*)

Other bias	High risk	There was an unexplained significant difference in mean gestational age of 8.2 weeks between the 2 treatment groups (erythromycin 28.6 weeks; azithromycin 20.4 weeks)

Gunter 1996

Methods	Randomised controlled trial.
Participants	47 pregnant women with positive Gen-probe test for *C.trachomatis* were enrolled. Outcome data were available for 22 who were assigned to the azithromycin group and18 were assigned to the erythromycin group
Interventions	Erythromycin 500 mg 4 times a day for 7 days versus azithromycin powder 1 g orally once
Outcomes	Cure rate, side effects.
Notes	Treatment compliance was 100% in the azithromycin group and 44.5% in the erythromycin group Patients unable to tolerate original randomisation due to gastrointestinal side effects were allowed to cross-over to the opposite study medication 7 patients were excluded due to severe side effects from erythromycin and required cross-over to azithromycin Not directly stated but assumed that the study was undertaken at the Bowman Gray School of Medicine, Winston-Salem, NC, USA In published abstract it states it is an ongoing trial but no further publications were found **Sources of trial funding:** No funding source was declared. **Declarations of interest:** Not reported. **Trial dates:** Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk'
Selective reporting (reporting bias)	Unclear risk	States it is an ongoing trial but no further results have been published or presented
Other bias	Low risk	The study appears to be free of other sources of bias.

Jacobson 2001

Methods	Randomised controlled trial.
Participants	129 pregnant women with positive cervical *C.trachomatis* DNA test result were enrolled. Exclusion criteria included known allergy or hypersensitivity to amoxicillin, penicillin, or azithromycin; severe hyperemesis gravidarum at the time of entry; and concurrent use of an antibiotic with efficacy against *Chlamydia trachomatis* (fluoroquinolones, macrolides, clindamycin, tetracyclines, or sulphonamides) 110 completed the trial protocol. 55 were in the amoxicillin group and 55 were in the azithromycin group
Interventions	Amoxicillin 500 mg orally 3 times a day for 7 days versus azithromycin 1 g once
Outcomes	Cure rate, preterm birth.
Notes	The study was closed due to realisation that 3000 participants would be needed to complete it. The number of patients studied were too few. Data presented here include accrued cure rates for all patients studied Among the 19 women excluded from the analysis, 14 were lost to follow-up, (8 amoxicillin, 6 azithromycin) and 5 were involved in protocol violations (3 amoxicillin, 2 azithromycin) In the amoxicillin group, 3 patients were intolerant to treatment and in the azithromycin group, 6 patients were intolerant to treatment Only 35% of the subjects were seen within 7 days of the scheduled appointment for test of cure Study was undertaken in 2 university-based inner-city clinics in Milwaukee, USA **Sources of trial funding:** No funding source was declared. **Declarations of interest:** Not reported. **Trial dates:** Ocotber 1988 - February 2000.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was accomplished with a computer-generated random-number table in blocks of 10

Allocation concealment (selection bias)	Low risk	Treatment assignments were placed in sequentially numbered, opaque, sealed envelopes by staff not involved in enrolment, treatment, or evaluation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Assignments were not blinded, and there was no attempt to directly visualise patients taking their first dose of medication
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of the 19 women excluded from analysis, 14 were lost to follow-up (8 amoxicillin, 6 azithromycin), but no reasons were provided
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Kacmar 2001

Methods	Randomised controlled trial.
Participants	39 pregnant women. Routine Chlamydia screens using ligase chain reaction were performed on all patients attending Exclusion criteria: other infections requiring antibiotic therapy, known allergy or sensitivity to either amoxicillin or azithromycin, or gestational age greater than 33 weeks 19 received amoxicillin and 20 received azithromycin.
Interventions	Azithromycin 1 g orally as a single dose versus amoxicillin 500 mg orally 3 times a day for 7 days
Outcomes	Cure rate, repeated infection, side effects.
Notes	A referral for treatment was given to all partners of patients testing positive for Chlamydia, and patients were instructed to abstain from sexual intercourse until treatment was completed Compliance in the azithromycin group was 100%. Compliance in the amoxicillin group was 84%. A sample-size calculation was performed, showing that 50 patients would be needed for each treatment group, but due to limitations and difficulties with recruitment only 39 were enrolled in this trial The 1 positive test in the azithromycin group was in a patient who did not refer her partner for treatment, continued to have sexual intercourse and did not use a condom as recommended Totals in table 2 vary due to missing data. Study was undertaken at the Women and Infants Hospital prenatal clinic, Providence,

Kacmar 2001   (*Continued*)

<table>
<tr><td rowspan="4"></td><td>USA
Sources of trial funding: Funded by a NIH grant.
Declarations of interest: Not reported.
Trial dates: November 1998 - May 2000.</td></tr>
</table>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a random number sequence.
Allocation concealment (selection bias)	Low risk	Opaque envelopes were used for concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Four women in the amoxicillin group and one in the azithromycin group failed to return for follow-up test of cure and the reasons are not provided
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Magat 1993

Methods	Randomised controlled trial.
Participants	143 pregnant women with posItive culture for *Chlamydia trachomatis* enrolled before 36 weeks' gestation. Exlusion criteria: sensitivity to either study medication, persistent gastrointestinal symptoms or history of colitis or antibiotic therapy after screening and before enrolment 72 were randomised to amoxicillin and 71 to erythromycin.
Interventions	Erythromycin (500 mg 4 times daily for 7 days) and amoxicillin (500 mg 3 times a day for 7 days)
Outcomes	Cure rate, side effects of treatment.
Notes	Partners of all women received doxycycline (100 mg twice a day for 7 days) 15 in the erythromycin group were intolerant to the therapy. 1 woman in the amoxicillin group was intolerant to the therapy. In both groups, this intolerance to therapy was

developed the first or second day of treatment

Of the 15 who were intolerant to erythromycin, 11 were treated successfully with amoxicillin, 1 needed a further course of treatment, 2 refused further treatment and 1 was treated but not tested before delivery

2 of the 9 failures reported partner non-compliance with the doxycycline medication

Study was undertaken in by the University of Maryland School of Medicine, Baltimore, USA from October 1990 to August 1991

Sources of trial funding: No funding source was declared.

Declarations of interest: Not reported.

Trial dates: October 1990 - August 1991.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by pseudo-random number generator.
Allocation concealment (selection bias)	Low risk	The medications were dispensed by the hospital pharmacy to prevent the healthcare team from learning the assigned medication or dosage schedule
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	114 completed follow-up (80% completed the study). Missing data in the amoxicillin group: out of 72 enrolled, 8 women were excluded. 7 had no follow-up culture done before delivery. 5 of the 7 delivered before a test of cure was obtained; 1 woman was mistakenly entered into the study at 38.5 weeks; and the final woman was excluded because she was admitted with preterm labour and given erythromycin before the test of cure. 1 of the women had a allergic reaction and was also excluded. 64/72 finished treatment (88%) Missing data in the erythromycin group: out of 71 enrolled, 21 women were excluded. 6 women had no follow-up culture for test of cure. 4 of these 6 had delivered before a test of cure culture was obtained, 1 had a therapeutic abortion, and 1 moved out of the state. 15 were intolerant to erythromycin and were excluded. In conclusion 50/71 finished treatment (70%)
Selective reporting (reporting bias)	Low risk	No selective reporting noted.

Magat 1993 *(Continued)*

Other bias	High risk	There was an unexplained significant difference in the mean gestational age at entry between the amoxicillin group (24.0 ± 8.4 weeks) and the erythromycin group (20.8 ± 8.0 weeks)(P = .05).

Martin 1997

Methods	Randomised controlled trial.
Participants	414 pregnant women, between the 23rd and 26th week of pregnancy, who were diagnosed with positive reading of fluorescent isothiocyanate-conjugated *Chlamydia trachomatis*-specific monoclonal antibody were enrolled. Women were eligible if they were: more than 16 years old, were free of medical complications related to premature delivery, and were not taking selected medications. Women with positive screening cultures for *Neisseria gonorrhoeae* or > l0s micro-organisms/mL of urine were treated and thus ineligible for the trial 205 women were randomised to the erythromycin group. 209 women were randomised to the placebo group.
Interventions	Erythromycin 333 mg orally 3 times daily versus an identical placebo
Outcomes	Cure rate, preterm birth, preterm rupture of membranes, side effects, perinatal mortality, low birthweight
Notes	Trial participants with *Chlamydia trachomatis* were re-treated with doxycycline, tetracycline, or erythromycin immediately postpartum, regardless of which trial medication they received. Infants were either treated empirically after delivery or were followed, cultured at their first postnatal visit, and treated with antibiotics if indicated. Eligible women who agreed to participate in the clinical trial entered a week placebo run-in. Those who took less than two-thirds of the allotted placebo pills during the run-in, who did not return to the clinic or refused further participation were not randomised. Women identified as colonised with *Ureaplasma urealyticum,group B streptococci*, and/or *Chlamydia trachomatis* were considered for randomisation into the clinical trial. We included only the *Chlamydia trachomatis* results. The study have different amounts of missing data on different outcomes 25 erythromycin-treated and 23 placebo-treated women withdrew from the trial but were included in the intent-to-treat analysis. The primary outcome was measured mid-treatment. The 20% failure rate of erythromycin in our study suggests the dose is less than optimal, possibly due to the 40% increase in blood and extracellular volume in pregnancy acting to reduce serum and tissue drug levels Study was undertaken in 7 institutions utilising 6 antepartum clinics in Harlem Hospital, New York, Columbia University, New York, Louisiana State University and Tulane University, New Orleans, University of Oklahoma, Oklahoma City, University of Texas, San Antonio and University of Washington, Seattle, USA **Sources of trial funding:** This work was supported by contracts from the National Institute of Child Health and Human Development ant the National Institute of Allergy and Infectious Diseases

Martin 1997 *(Continued)*

	Declarations of interest: Not reported. **Trial dates:** November 1984 - March 1989.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Balanced randomisation scheme by Research Triangle Institute: computer randomised according to permuted-block procedure with random block sizes. (Reference 13)
Allocation concealment (selection bias)	Unclear risk	Not described. Identical placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	48 (11.6%) withdrew from the trial. Different amount of data missing in different aspects of outcomes
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Rosenn 1995

Methods	Randomised controlled trial.
Participants	48 pregnant women with positive culture of *Chlamydia trachomatis* were enrolled. 24 were randomised to receive erythromycin and 24 were randomised to receive azithromycin
Interventions	Azithromycin single dose 1 g orally versus erythromycin 500 mg 4 times daily for 7 days orally
Outcomes	Cure rate, side effects.
Notes	All partners received doxycycline 100 mg twice a day orally. Follow-up meeting 3 weeks after therapy. Compliance was then measured by pill count and the participants had filled out a questionnaire about: sexual activity, side effects and compliance. Azithromycin group compliance: 100%. Erythromycin group compliance: 61%. Study was undertaken at Thomas Jefferson University Hospital prenatal clinics, Philadel-

Rosenn 1995 *(Continued)*

phia, USA, from August 1994 to April 1995
Sources of trial funding: no funding source reported.
Declarations of interest: Not reported.
Trial dates: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block of 6 randomisation generated from a random-number table
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 were lost to follow-up (94% completed the study).
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Silverman 1994

Methods	Randomised controlled trial.
Participants	74 pregnant women with culture positive *Chlamydia trachomatis* infection. Excluded if the first prenatal visit was after 36 weeks, recent antibiotic use for another indication (within 14 days), and known allergy or sensitivity to either of the study medications 36 were treated with amoxicillin. 38 were treated with erythromycin.
Interventions	Amoxicillin 500 mg orally 3 times a day or erythromycin 500 mg orally 4 times daily for 7 days
Outcomes	Cure rate, side effects.
Notes	The women who did not cure from the first dosage were crossed over to the alternative treatment. These results are not included in our analysis Partners were treated with doxycycline 100 mg orally twice a day for 7 days Study was undertaken at Thomas Jefferson University Hospital prenatal clinics, Philadel-

Silverman 1994   *(Continued)*

phia, USA
Sources of trial funding: no funding source reported.
Declarations of interest: Not reported.
Trial dates: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block of 6 randomisation generated from a random-number table
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 women in each group were lost to follow-up and no reasons were provided
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Turrentine 1995

Methods	Randomised controlled trial.
Participants	168 pregnant women, < 36 weeks' gestation, with positive cervical *Chlamydia trachomatis* culture were enrolled. 56 received erythromycin, 57 received amoxicillin and 55 received clindamycin
Interventions	Erythromycin-base tablets 500 mg orally 4 times a day for 7 days, amoxicillin capsules 500 mg 2 times a day for 7 days or clindamycin tablets 600 mg orally 2 times a day for 10 days
Outcomes	Cure rate, side effects.
Notes	All sexual partners in the study was offered treatment with doxycycline 100 mg twice a day for 7 days. There were no statistically significant differences in age, racial distribution, gravidity, gestational age, or number of days to test-of-cure among the groups 6 women elected not to participate.

	8 patients were lost to follow-up, 3 in the erythromycin, 2 in the amoxicillin, and 3 in the clindamycin group, and were excluded from the analysis 5 women in the erythromycin group had severe side effects and discontinued the treatment In the amoxicillin group, 2 women had severe side effects and discontinued the treatment In the clindamycin group 2 women developed an allergic reaction to clindamycin and had to discontinue. 2 women had severe side effects to the treatment and discontinued 1 developed an allergic reaction to erythromycin and had to discontinue Study was undertaken by the University of Texas Health Science Center, Houston, USA **Sources of trial funding:** Pharmaceutical companies Parke-Davis, Lederle and Upjohn supplied the treatment medications **Declarations of interest:** Not reported. **Trial dates:** July 1991 - September 1993.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was accomplished by computer-generated assignment
Allocation concealment (selection bias)	Low risk	Unlabelled medications.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The unlabeled medications were dispensed by the hospital pharmacy to prevent the healthcare team from learning the assigned medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants had test of cure, assessors were still blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	148 (85%) completed the protocol. Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

Wehbeh 1998

Methods	Randomised controlled trial.
Participants	48 pregnant women screening positive for fluorescein-conjugated monoclonal antibody to*Chlamydia trachomatis* were enrolled. 17 received azithromycin and their partners received azithromycin, 10 received azithromycin and their partners received tetracycline and 21 received erythromycin and the partner received azithromycin

	For this analysis the azithromycin group was considered as one group (27 women) and was compared to the erythromycin group (21 women)
Interventions	3 groups. Single dose of azithromycin 1 g orally (partners got the same), erythromycin 500 mg orally 3 times a day for 7 days (partners got tetracycline) and single dose of azithromycin 1 g orally (partners got tetracycline)
Outcomes	Cure rate, side effects.
Notes	7-10 days after treatment started compliance was controlled by having a meeting with the couples. They were asked to bring their medication bottles and if it had at least 1 day of unused medications in it, the couple was considered non-compliant. Compliance rates: azithromycin: 92.6% (2 refused to participate after the randomisation) , erythromycin: 71.4%, tetracycline: 75%. There was no significant difference in age, gestational age at entry into the study or number of prior pregnancies between treatment groups. Only 12% in group 1 reported having sexual intercourse during the study period whilst 42.9% and 30% in group 2 and 3 did. Exact multiple logistic regression procedures was used to see if the treatment failure was due to reinfection from their sexual activity during the study. It showed no confounding of the observed treatment groups and is used as evidence that treatment failure is not due to reinfection of sexual partner The third treatment group was included in order to assess the efficacy of multidose course of tetracycline versus single-dose therapy with azithromycin, and to indirectly assess the possible reinfection of the pregnant women through sexual intercourse during the trial period. They considered that they did not need to make all the medications look the same and just placebo pills to make the azithromycin treatment identical to erythromycin because they thought compliance bias would be introduced Study was undertaken in a prenatal clinic located within a large urban medical centre with New York, USA **Sources of trial funding:** the trial was funded by local department funds. **Declarations of interest:** Not reported. **Trial dates:** Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	States all participants were unaware of the exact nature of the antibiotic treatment given to them but that no placebo was used

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 in the first study group refused medications (96% completed the study)
Selective reporting (reporting bias)	Low risk	No selective reporting noted.
Other bias	Low risk	The study appears to be free of other sources of bias.

g: gram
mg: milligram
mL: millilitre

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

Study	Reason for exclusion
El-Shourbagy 2011	This study examines the rate of pre-eclampsia in groups of treated and non-treated *Chlamydia pneumoniae* infections in pregnancy.
McGregor 1990	This study included pregnant women with various genital tract infections and not only *C.trachomatis*. The data for *C.trachomatis* infection were not presented separately.
Nadafi 2005	Not all participants of this trial had *C.trachomatis* infection, therefore, the study was excluded.
Zulkarneev 1998	This study was not a randomised controlled trial.

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

Okunola 2013

Trial name or title	Treatment of antenatal Chlamydia infection.
Methods	Randomised controlled trial. Open label.
Participants	Pregnant women at less than 36 weeks' gestation with positive *C.trachomatis* test on endocervical swab with rapid kit. Exlcuded with history of antibiotics in the last 2 weeks or low lying placenta, history of reaction to any of the drugs Plan to recruit 200 participants.

Interventions	Group 1 - amoxicillin 500 mg orally 3 times a day for a week Group 2 - erythromycin 500 mg 4 times a day for a week. Partners were treated with doxycycline for a week.
Outcomes	Completiion of course treatment. Microbiological cure. Side effects (nausea, diarrhoea, vomiting, loss of appetite)
Starting date	October 2013.
Contact information	Obafemi Awolowo University Teaching Hospital.
Notes	Clinical Trial identifier NCT01946256.

D A T A   A N D   A N A L Y S E S

Comparison 1.   Erythromycin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological cure	2	495	Risk Ratio (M-H, Random, 95% CI)	2.64 [1.60, 4.38]
2 Preterm birth	1	405	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.56, 1.46]
3 Preterm rupture of membranes	1	389	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.48, 1.43]
4 Side effects of treatment	2	495	Risk Ratio (M-H, Random, 95% CI)	2.93 [0.36, 23.76]
5 Perinatal mortality	1	405	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [0.32, 28.74]
6 Low birthweight	1	400	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.42, 1.40]

Comparison 2.   Clindamycin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological cure	1	85	Risk Ratio (M-H, Fixed, 95% CI)	4.08 [2.35, 7.08]
2 Side effects of treatment	1	85	Risk Ratio (M-H, Fixed, 95% CI)	5.37 [0.65, 44.01]

Comparison 3.   Amoxicillin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological cure	1	15	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.59, 6.79]

Comparison 4.   Amoxicillin versus azithromycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological cure	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.71, 1.12]
2 Repeated infection	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.02, 9.55]
3 Preterm birth	1	90	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.43, 3.20]
4 Side effects of treatment	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.24, 1.31]

Comparison 5. Amoxicillin versus erythromycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological cure	4	466	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.93, 1.01]
2 Side effects of treatment	4	513	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.21, 0.46]

Comparison 6. Azithromycin versus erythromycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological cure	6	374	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.00, 1.23]
2 Repeated infection	1	85	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.32, 5.73]
3 Preterm birth	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.29, 2.10]
4 Preterm rupture of membranes	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.15, 2.48]
5 Side effects of treatment	6	374	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.17, 0.34]

Comparison 7. Clindamycin versus erythromycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological cure	2	173	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.97, 1.15]
2 Side effects of treatment	2	183	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.22, 0.87]

Comparison 8. Amoxicillin versus clindamycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological cure	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.89, 1.04]
2 Side effects of treatment	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.14, 2.26]

Analysis 1.1. Comparison 1 Erythromycin versus placebo, Outcome 1 Microbiological cure.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 1 Erythromycin versus placebo

Outcome: 1 Microbiological cure

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Alger 1991	31/37	10/44		37.1 %	3.69 [2.10, 6.47]
Martin 1997	164/205	77/209		62.9 %	2.17 [1.80, 2.63]
Total (95% CI)	**242**	**253**		**100.0 %**	**2.64 [1.60, 4.38]**
Total events: 195 (Erythromycin), 87 (Placebo)					
Heterogeneity: Tau² = 0.10; Chi² = 3.08, df = 1 (P = 0.08); I² =68%					
Test for overall effect: Z = 3.78 (P = 0.00016)					
Test for subgroup differences: Not applicable					

0.2   0.5   1   2   5

Favours placebo   Favours erythomycin
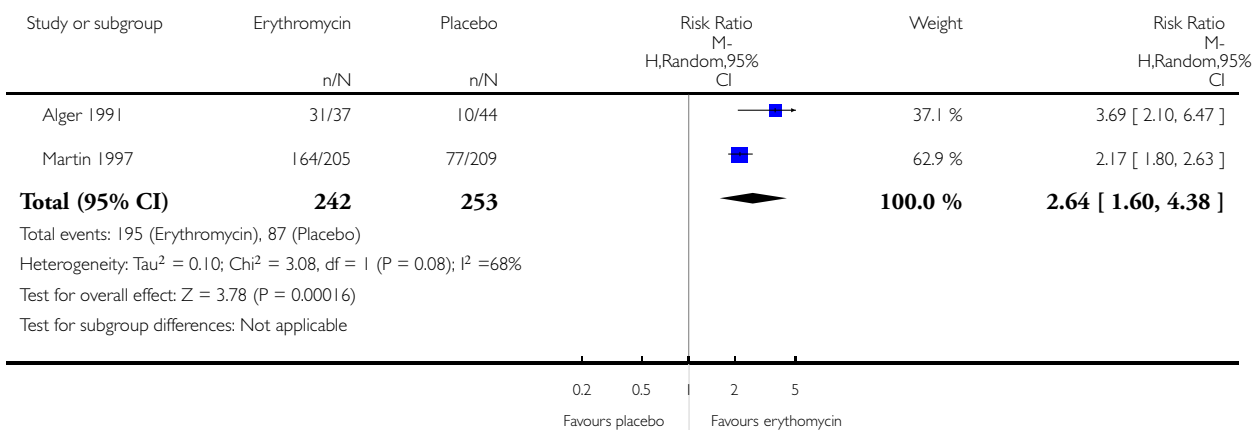
Analysis 1.2. Comparison 1 Erythromycin versus placebo, Outcome 2 Preterm birth.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 1 Erythromycin versus placebo

Outcome: 2 Preterm birth

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Martin 1997	27/202	30/203		100.0 %	0.90 [0.56, 1.46]
Total (95% CI)	**202**	**203**		**100.0 %**	**0.90 [0.56, 1.46]**
Total events: 27 (Erythromycin), 30 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.41 (P = 0.68)					
Test for subgroup differences: Not applicable					

0.01   0.1   1   10   100

Favours Erythromycin   Favours Placebo

Analysis 1.3. Comparison 1 Erythromycin versus placebo, Outcome 3 Preterm rupture of membranes.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 1 Erythromycin versus placebo

Outcome: 3 Preterm rupture of membranes

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Martin 1997	21/196	25/193		100.0 %	0.83 [0.48, 1.43]
Total (95% CI)	**196**	**193**		**100.0 %**	**0.83 [0.48, 1.43]**

Total events: 21 (Erythromycin), 25 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.49)

Test for subgroup differences: Not applicable

```
        0.01    0.1       1      10    100
        Favours Erythromycin   Favours Placebo
```

Analysis 1.4. Comparison 1 Erythromycin versus placebo, Outcome 4 Side effects of treatment.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 1 Erythromycin versus placebo

Outcome: 4 Side effects of treatment

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Alger 1991	9/37	1/44		39.0 %	10.70 [1.42, 80.62]
Martin 1997	113/205	90/209		61.0 %	1.28 [1.05, 1.56]
Total (95% CI)	**242**	**253**		**100.0 %**	**2.93 [0.36, 23.76]**

Total events: 122 (Erythromycin), 91 (Placebo)

Heterogeneity: Tau² = 1.86; Chi² = 4.47, df = 1 (P = 0.03); I² =78%

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable

```
        0.02    0.1       1      10    50
        Favours Erythromycin   Favours Placebo
```

Analysis 1.5. Comparison 1 Erythromycin versus placebo, Outcome 5 Perinatal mortality.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 1 Erythromycin versus placebo

Outcome: 5 Perinatal mortality

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Martin 1997	3/202	1/203		100.0 %	3.01 [0.32, 28.74]
Total (95% CI)	**202**	**203**		**100.0 %**	**3.01 [0.32, 28.74]**

Total events: 3 (Erythromycin), 1 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours Erythromycin   Favours Placebo

Analysis 1.6. Comparison 1 Erythromycin versus placebo, Outcome 6 Low birthweight.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 1 Erythromycin versus placebo

Outcome: 6 Low birthweight

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Martin 1997	17/201	22/199		100.0 %	0.77 [0.42, 1.40]
Total (95% CI)	**201**	**199**		**100.0 %**	**0.77 [0.42, 1.40]**

Total events: 17 (Erythromycin), 22 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours Erythromycin   Favours Placebo

Analysis 2.1.   Comparison 2 Clindamycin versus placebo, Outcome 1 Microbiological cure.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 2 Clindamycin versus placebo

Outcome: 1 Microbiological cure

Study or subgroup	Clindamycin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alger 1991	38/41	10/44		100.0 %	4.08 [2.35, 7.08]
Total (95% CI)	**41**	**44**		**100.0 %**	**4.08 [2.35, 7.08]**

Total events: 38 (Clindamycin), 10 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 4.99 (P < 0.00001)

Test for subgroup differences: Not applicable

```
        0.01    0.1     1     10    100
        Favours placebo      Favours clindamycin
```

Analysis 2.2.   Comparison 2 Clindamycin versus placebo, Outcome 2 Side effects of treatment.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 2 Clindamycin versus placebo

Outcome: 2 Side effects of treatment

Study or subgroup	Clindamycin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alger 1991	5/41	1/44		100.0 %	5.37 [0.65, 44.01]
Total (95% CI)	**41**	**44**		**100.0 %**	**5.37 [0.65, 44.01]**

Total events: 5 (Clindamycin), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Not applicable

```
        0.01    0.1     1     10    100
        Favours Clindamycin     Favours Placebo
```

Analysis 3.1. Comparison 3 Amoxicillin versus placebo, Outcome 1 Microbiological cure.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 3 Amoxicillin versus placebo

Outcome: 1 Microbiological cure

Study or subgroup	Amoxicillin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bell 1982	6/9	2/6		100.0 %	2.00 [0.59, 6.79]
Total (95% CI)	**9**	**6**		**100.0 %**	**2.00 [0.59, 6.79]**

Total events: 6 (Amoxicillin), 2 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10   100
        Favours placebo    Favours amoxicillin
```

Analysis 4.1. Comparison 4 Amoxicillin versus azithromycin, Outcome 1 Microbiological cure.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 4 Amoxicillin versus azithromycin

Outcome: 1 Microbiological cure

Study or subgroup	Amoxicillin n/N	Azithromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jacobson 2001	32/55	35/55		68.8 %	0.91 [0.68, 1.23]
Kacmar 2001	12/15	18/19		31.2 %	0.84 [0.64, 1.11]
Total (95% CI)	**70**	**74**		**100.0 %**	**0.89 [0.71, 1.12]**

Total events: 44 (Amoxicillin), 53 (Azithromycin)
Heterogeneity: Chi^2 = 0.18, df = 1 (P = 0.67); I^2 =0.0%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable

```
        0.5    0.7    1    1.5   2
        Favours Azithromycin   Favours Amoxicillin
```
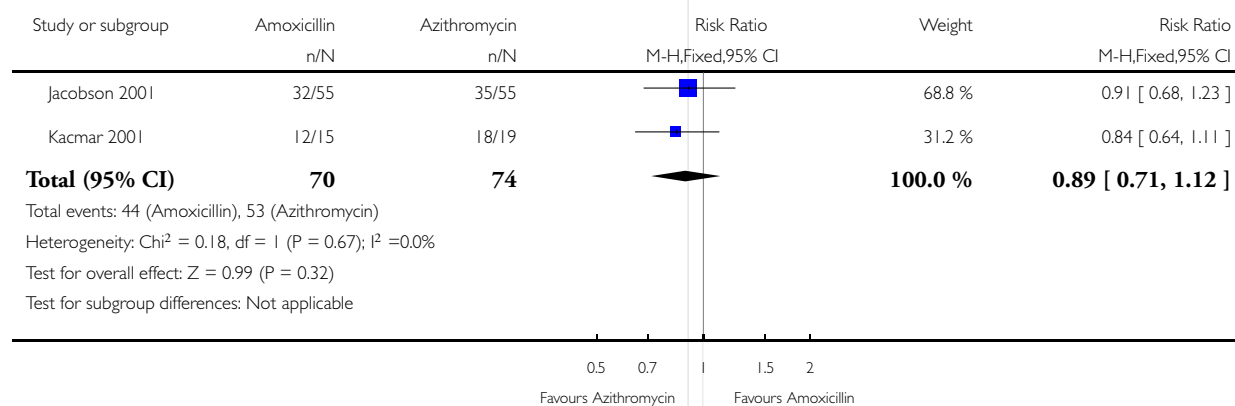
Analysis 4.2. Comparison 4 Amoxicillin versus azithromycin, Outcome 2 Repeated infection.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 4 Amoxicillin versus azithromycin

Outcome: 2 Repeated infection

Study or subgroup	Amoxicillin n/N	Azithromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kacmar 2001	0/15	1/19		100.0 %	0.42 [0.02, 9.55]
Total (95% CI)	**15**	**19**		**100.0 %**	**0.42 [0.02, 9.55]**

Total events: 0 (Amoxicillin), 1 (Azithromycin)
Heterogeneity: not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable

```
              0.01   0.1    1    10   100
          Favours Amoxicillin   Favours Azithromycin
```

Analysis 4.3. Comparison 4 Amoxicillin versus azithromycin, Outcome 3 Preterm birth.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 4 Amoxicillin versus azithromycin

Outcome: 3 Preterm birth

Study or subgroup	Amoxicillin n/N	Azithromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jacobson 2001	7/45	6/45		100.0 %	1.17 [0.43, 3.20]
Total (95% CI)	**45**	**45**		**100.0 %**	**1.17 [0.43, 3.20]**

Total events: 7 (Amoxicillin), 6 (Azithromycin)
Heterogeneity: not applicable
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable

```
              0.01   0.1    1    10   100
          Favours Amoxicillin   Favours Azithromycin
```

Analysis 4.4.   Comparison 4 Amoxicillin versus azithromycin, Outcome 4 Side effects of treatment.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 4 Amoxicillin versus azithromycin

Outcome: 4 Side effects of treatment

Study or subgroup	Amoxicillin n/N	Azithromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kacmar 2001	5/17	10/19		100.0 %	0.56 [0.24, 1.31]
Total (95% CI)	**17**	**19**		**100.0 %**	**0.56 [0.24, 1.31]**

Total events: 5 (Amoxicillin), 10 (Azithromycin)

Heterogeneity: not applicable

Test for overall effect: Z = 1.34 (P = 0.18)

Test for subgroup differences: Not applicable

```
        0.01    0.1    1    10    100
     Favours Amoxicillin   Favours Azithromycin
```

Analysis 5.1.   Comparison 5 Amoxicillin versus erythromycin, Outcome 1 Microbiological cure.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 5 Amoxicillin versus erythromycin
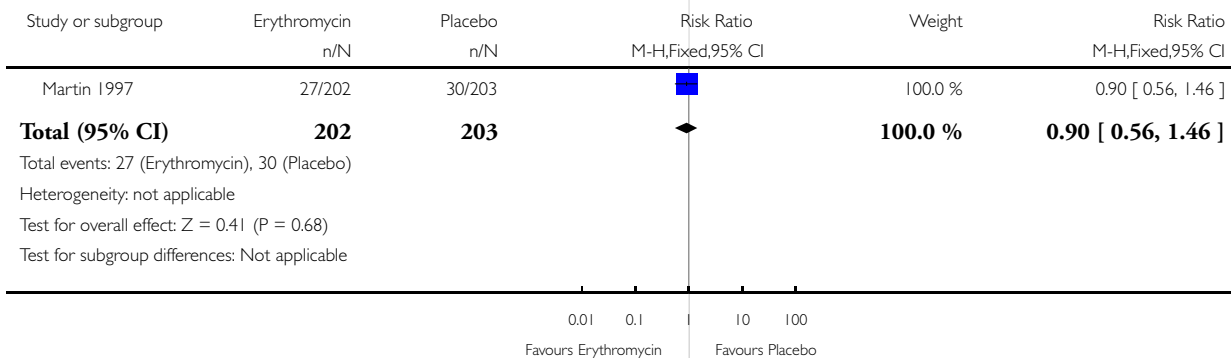
Outcome: 1 Microbiological cure

Study or subgroup	Amoxicillin n/N	Erythromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alary 1994	98/99	87/87		42.0 %	0.99 [0.96, 1.02]
Magat 1993	55/64	47/50		23.8 %	0.91 [0.81, 1.03]
Silverman 1994	28/34	27/32		12.6 %	0.98 [0.79, 1.21]
Turrentine 1995	50/53	45/47		21.5 %	0.99 [0.90, 1.08]
Total (95% CI)	**250**	**216**		**100.0 %**	**0.97 [0.93, 1.01]**

Total events: 231 (Amoxicillin), 206 (Erythromycin)

Heterogeneity: Chi^2 = 3.18, df = 3 (P = 0.36); I^2 =6%

Test for overall effect: Z = 1.34 (P = 0.18)

Test for subgroup differences: Not applicable

```
        0.5    0.7    1    1.5    2
     Favours Erythromycin   Favours Amoxicillin
```

Analysis 5.2.   Comparison 5 Amoxicillin versus erythromycin, Outcome 2 Side effects of treatment.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 5 Amoxicillin versus erythromycin
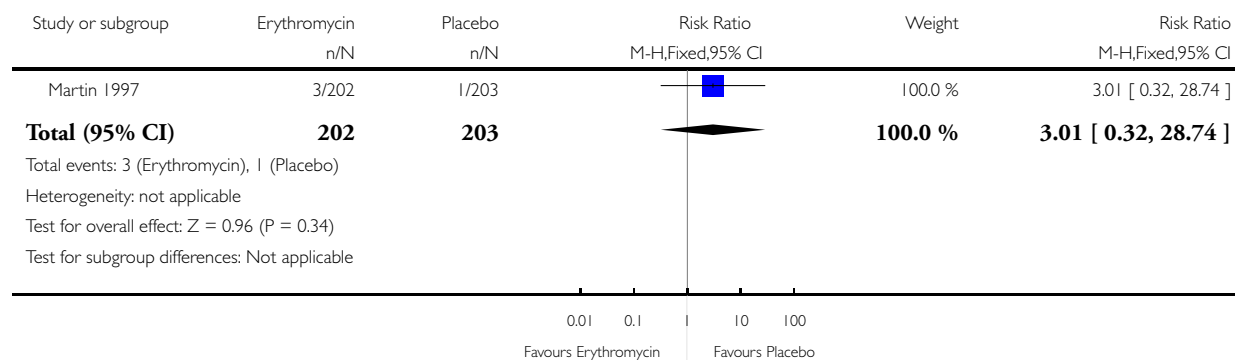
Outcome: 2 Side effects of treatment

Study or subgroup	Amoxicillin n/N	Erythromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Alary 1994	15/99	34/99		38.0 %	0.44 [0.26, 0.76]
Magat 1993	5/65	30/65		33.6 %	0.17 [0.07, 0.40]
Silverman 1994	5/39	12/38		13.6 %	0.41 [0.16, 1.04]
Turrentine 1995	3/55	13/53		14.8 %	0.22 [0.07, 0.74]
Total (95% CI)	**258**	**255**		**100.0 %**	**0.31 [0.21, 0.46]**

Total events: 28 (Amoxicillin), 89 (Erythromycin)

Heterogeneity: Chi² = 4.13, df = 3 (P = 0.25); I² =27%

Test for overall effect: Z = 5.89 (P < 0.00001)

Test for subgroup differences: Not applicable

0.2   0.5   1   2   5

Favours Amoxicillin   Favours Erythromycin

Analysis 6.1. Comparison 6 Azithromycin versus erythromycin, Outcome 1 Microbiological cure.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 6 Azithromycin versus erythromycin

Outcome: 1 Microbiological cure
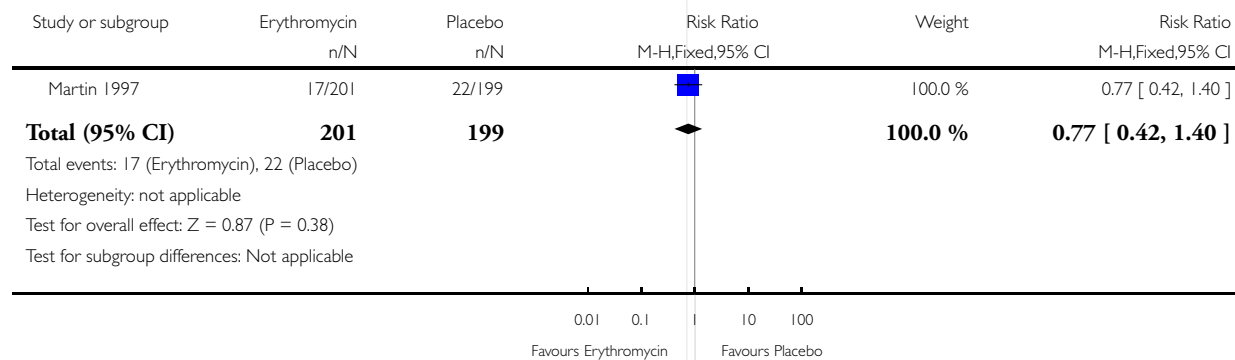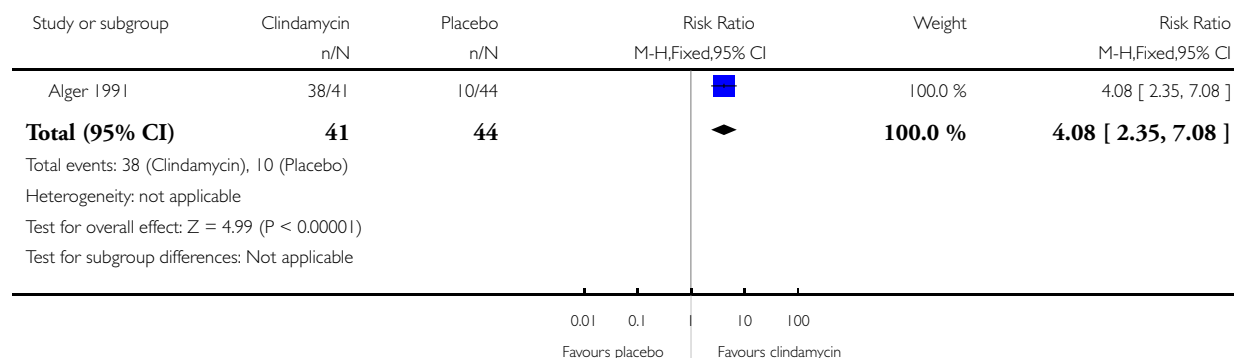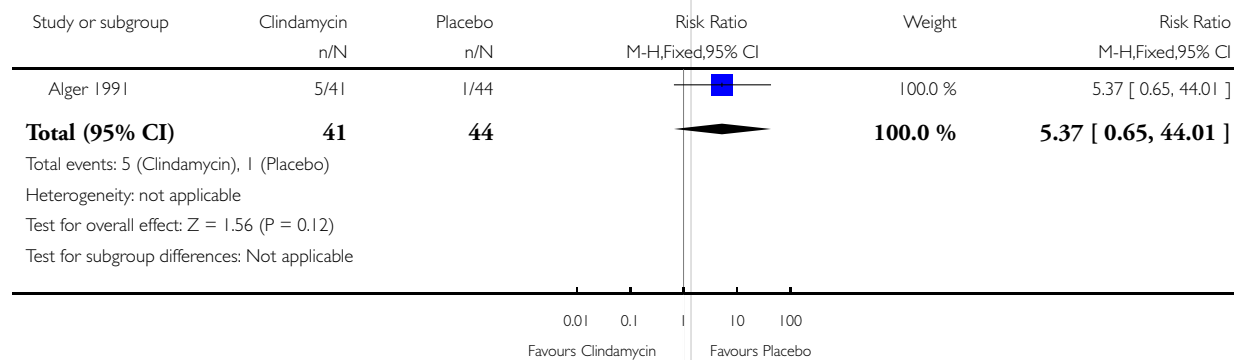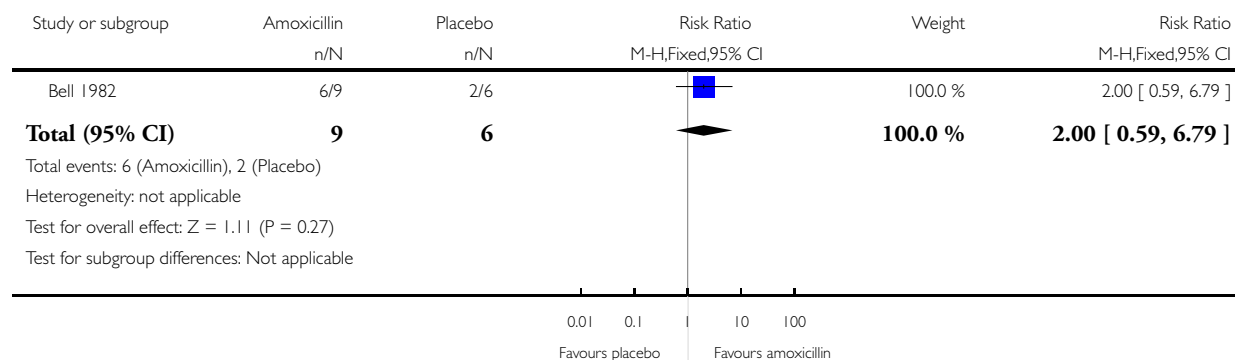
Study or subgroup	Azithromycin n/N	Erythromycin n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Adair 1998	37/42	40/43		20.9 %	0.95 [0.82, 1.09]
Bush 1994	15/15	14/15		16.6 %	1.07 [0.89, 1.28]
Edwards 1996	58/62	46/64		17.9 %	1.30 [1.10, 1.54]
Gunter 1996	22/22	17/18		20.1 %	1.06 [0.92, 1.23]
Rosenn 1995	21/23	17/22		11.0 %	1.18 [0.91, 1.53]
Wehbeh 1998	26/27	17/21		13.4 %	1.19 [0.95, 1.48]
Total (95% CI)	**191**	**183**		**100.0 %**	**1.11 [1.00, 1.23]**

Total events: 179 (Azithromycin), 151 (Erythromycin)

Heterogeneity: Tau^2 = 0.01; Chi^2 = 10.56, df = 5 (P = 0.06); I^2 =53%

Test for overall effect: Z = 1.87 (P = 0.061)

Test for subgroup differences: Not applicable

0.5　0.7　1　1.5　2

Favours Erythromycin　　　Favours Azithromycin

Analysis 6.2.   Comparison 6 Azithromycin versus erythromycin, Outcome 2 Repeated infection.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 6 Azithromycin versus erythromycin

Outcome: 2 Repeated infection
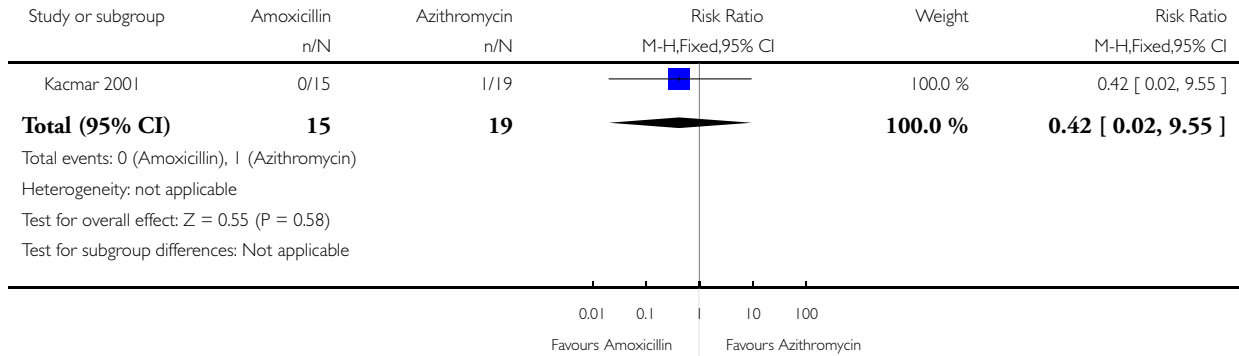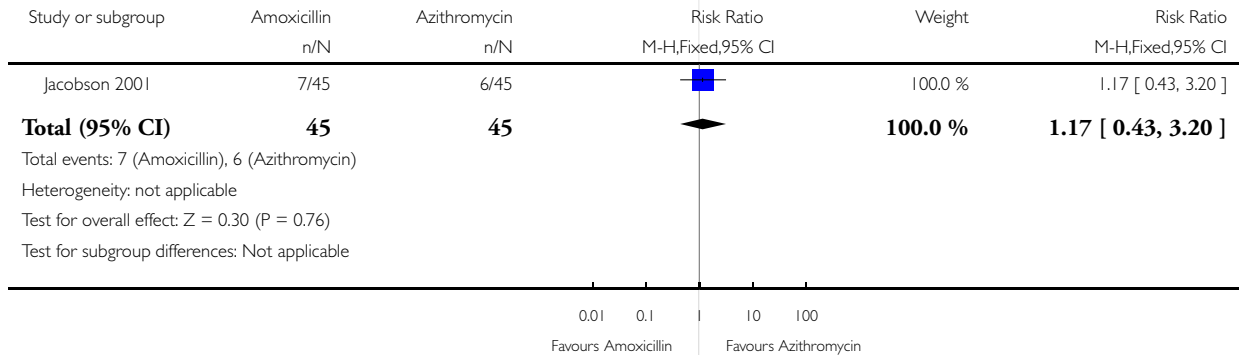
Study or subgroup	Azithromycin n/N	Erythromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Adair 1998	4/42	3/43		100.0 %	1.37 [0.32, 5.73]
Total (95% CI)	**42**	**43**		**100.0 %**	**1.37 [0.32, 5.73]**

Total events: 4 (Azithromycin), 3 (Erythromycin)
Heterogeneity: not applicable
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable

```
        0.01    0.1     1     10    100
       Favours Azithromycin   Favours Erythromycin
```

Analysis 6.3.   Comparison 6 Azithromycin versus erythromycin, Outcome 3 Preterm birth.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 6 Azithromycin versus erythromycin

Outcome: 3 Preterm birth

Study or subgroup	Azithromycin n/N	Erythromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Edwards 1996	6/62	8/64		100.0 %	0.77 [0.29, 2.10]
Total (95% CI)	**62**	**64**		**100.0 %**	**0.77 [0.29, 2.10]**

Total events: 6 (Azithromycin), 8 (Erythromycin)
Heterogeneity: not applicable
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable

```
        0.01    0.1     1     10    100
       Favours Azithromycin   Favours Erythromycin
```

Analysis 6.4. Comparison 6 Azithromycin versus erythromycin, Outcome 4 Preterm rupture of membranes.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

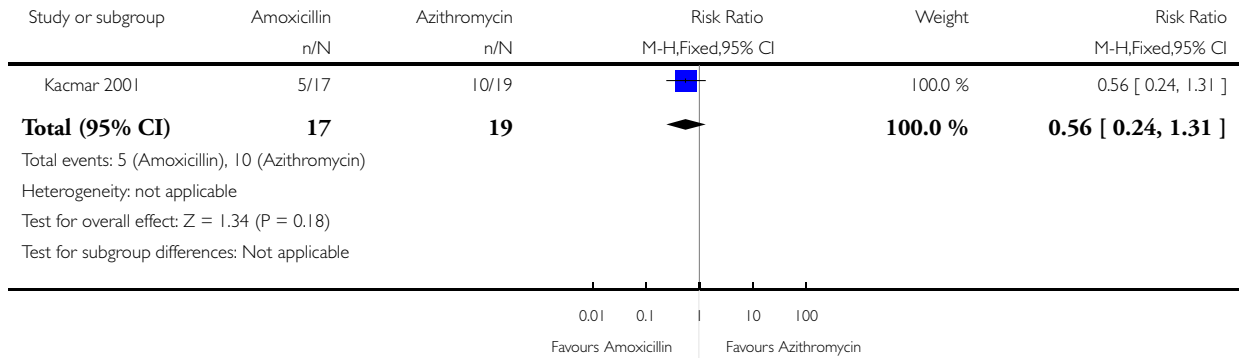Comparison: 6 Azithromycin versus erythromycin

Outcome: 4 Preterm rupture of membranes

Study or subgroup	Azithromycin n/N	Erythromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Edwards 1996	3/62	5/64		100.0 %	0.62 [0.15, 2.48]
Total (95% CI)	**62**	**64**		**100.0 %**	**0.62 [0.15, 2.48]**

Total events: 3 (Azithromycin), 5 (Erythromycin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Not applicable

0.01   0.1   1   10   100

Favours Azithromycin   Favours Erythromycin

Analysis 6.5.   Comparison 6 Azithromycin versus erythromycin, Outcome 5 Side effects of treatment.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 6 Azithromycin versus erythromycin
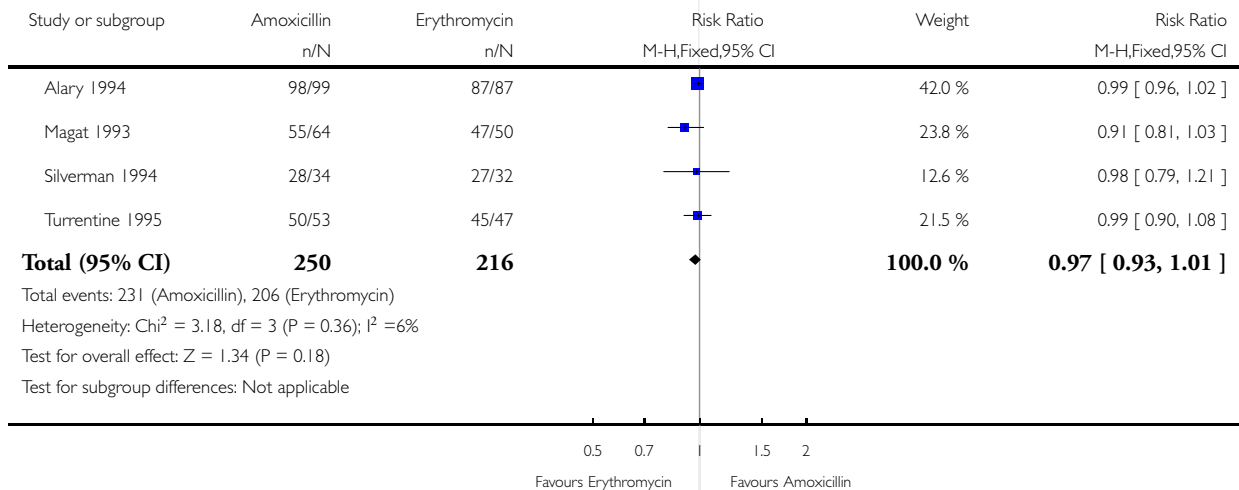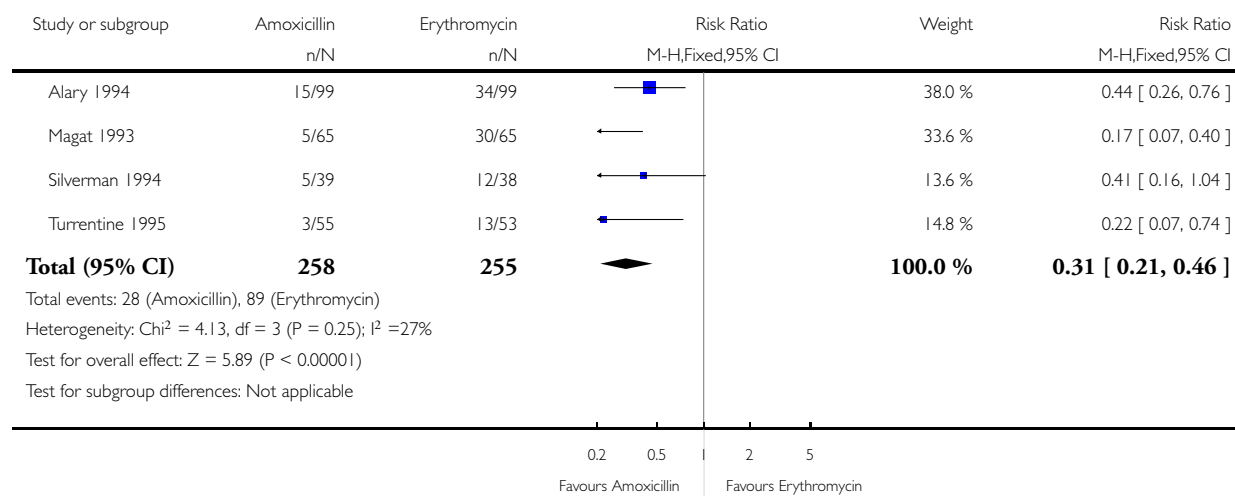
Outcome: 5 Side effects of treatment

Study or subgroup	Azithromycin n/N	Erythromycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Adair 1998	5/42	25/43		21.1 %	0.20 [0.09, 0.48]
Bush 1994	0/15	15/15		13.2 %	0.03 [0.00, 0.49]
Edwards 1996	12/62	42/64		35.2 %	0.29 [0.17, 0.51]
Gunter 1996	3/22	11/18		10.3 %	0.22 [0.07, 0.68]
Rosenn 1995	4/23	10/22		8.7 %	0.38 [0.14, 1.04]
Wehbeh 1998	4/27	12/21		11.5 %	0.26 [0.10, 0.69]
Total (95% CI)	**191**	**183**		**100.0 %**	**0.24 [0.17, 0.34]**

Total events: 28 (Azithromycin), 115 (Erythromycin)

Heterogeneity: Chi^2 = 3.71, df = 5 (P = 0.59); I^2 =0.0%

Test for overall effect: Z = 7.84 (P < 0.00001)

Test for subgroup differences: Not applicable

```
          0.01    0.1    1    10   100
       Favours Azithromycin    Favours Erythromycin
```
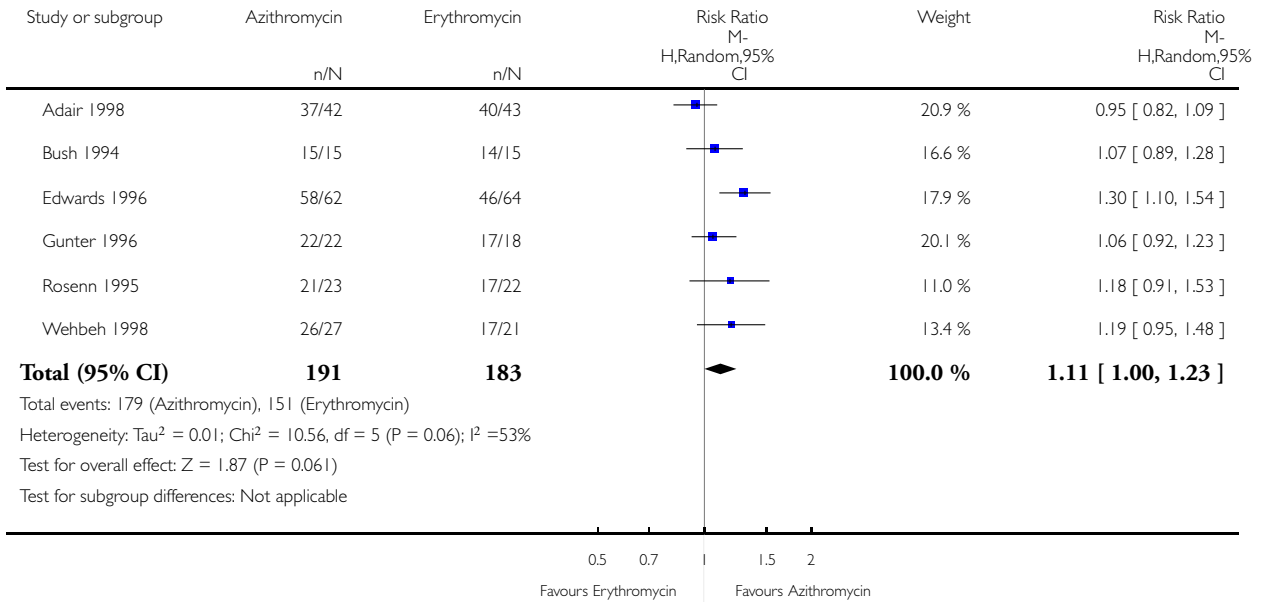
Analysis 7.1.   Comparison 7 Clindamycin versus erythromycin, Outcome 1 Microbiological cure.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 7 Clindamycin versus erythromycin

Outcome: 1 Microbiological cure
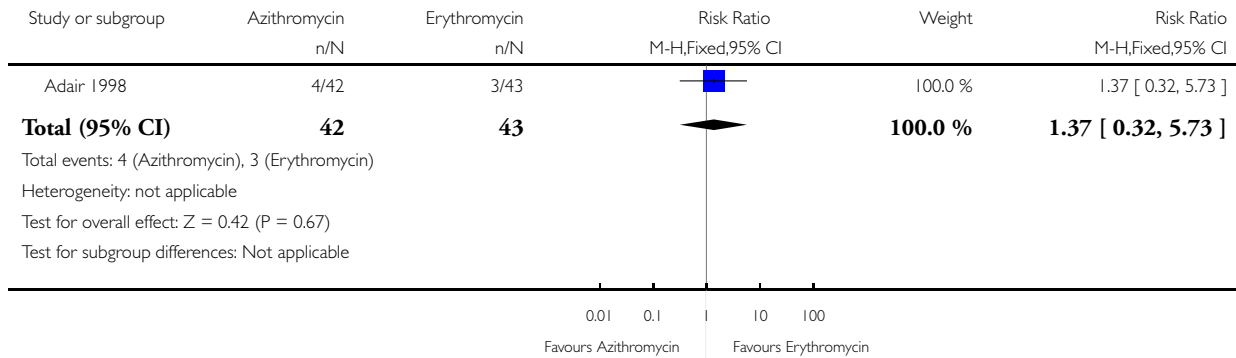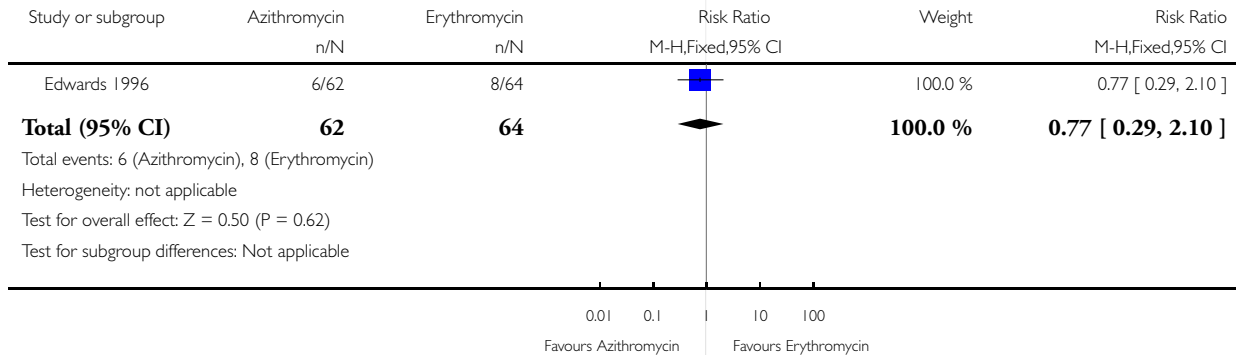
Study or subgroup	Clindamycin	Erythromycin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Alger 1991	38/41	31/37		41.7 %	1.11 [0.94, 1.31]
Turrentine 1995	47/48	45/47		58.3 %	1.02 [0.95, 1.10]
Total (95% CI)	**89**	**84**		**100.0 %**	**1.06 [0.97, 1.15]**

Total events: 85 (Clindamycin), 76 (Erythromycin)

Heterogeneity: Chi^2 = 1.09, df = 1 (P = 0.30); I^2 =8%

Test for overall effect: Z = 1.33 (P = 0.18)

Test for subgroup differences: Not applicable

```
        0.5    0.7    1    1.5    2
      Favours Erythromycin   Favours Clindamycin
```

Analysis 7.2.   Comparison 7 Clindamycin versus erythromycin, Outcome 2 Side effects of treatment.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

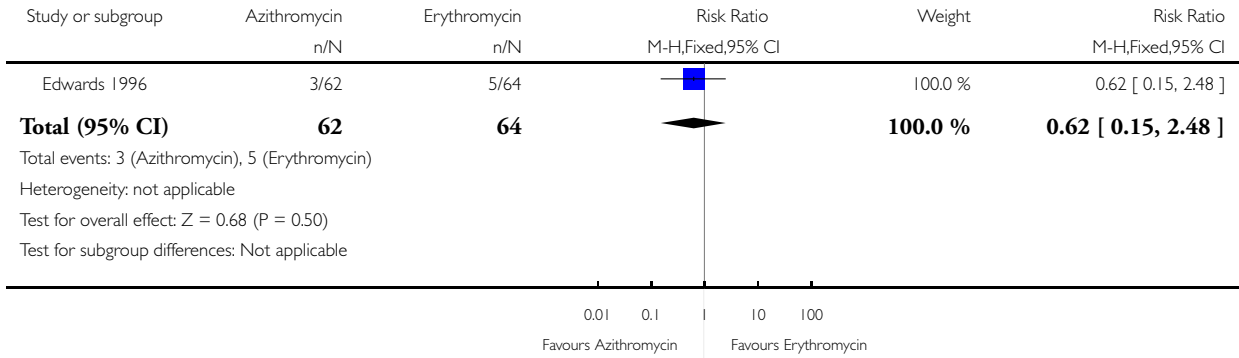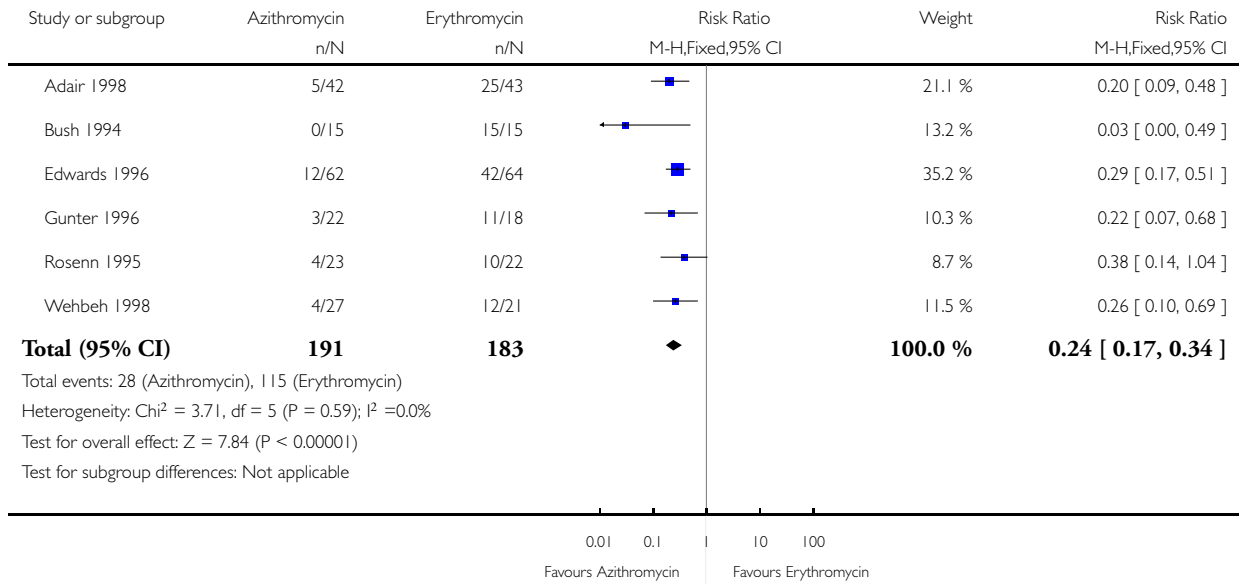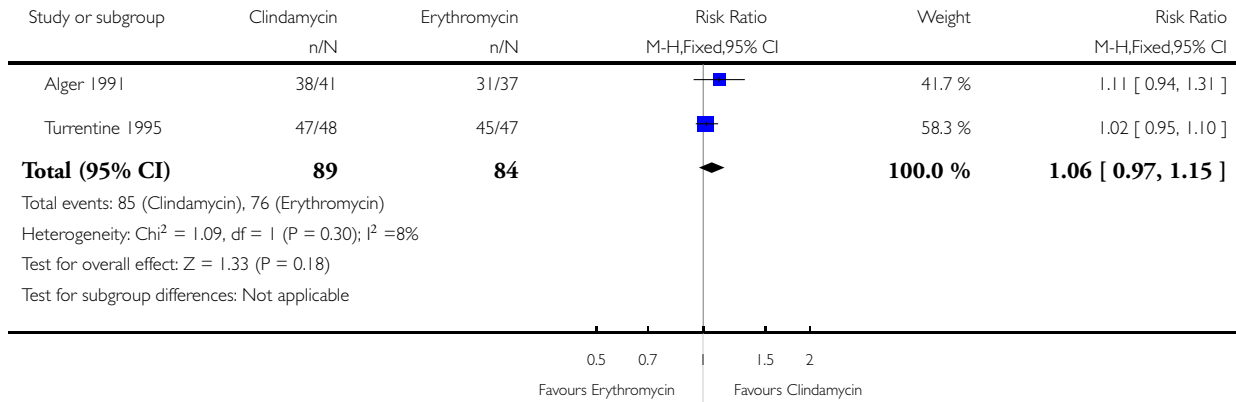Comparison: 7 Clindamycin versus erythromycin

Outcome: 2 Side effects of treatment

Study or subgroup	Clindamycin	Erythromycin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Alger 1991	5/41	9/37		42.4 %	0.50 [0.18, 1.36]
Turrentine 1995	5/52	13/53		57.6 %	0.39 [0.15, 1.02]
Total (95% CI)	**93**	**90**		**100.0 %**	**0.44 [0.22, 0.87]**

Total events: 10 (Clindamycin), 22 (Erythromycin)

Heterogeneity: Chi^2 = 0.12, df = 1 (P = 0.73); I^2 =0.0%

Test for overall effect: Z = 2.34 (P = 0.019)

Test for subgroup differences: Not applicable

```
        0.01    0.1    1    10    100
      Favours Clindamycin   Favours Erythromycin
```

Analysis 8.1. Comparison 8 Amoxicillin versus clindamycin, Outcome 1 Microbiological cure.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

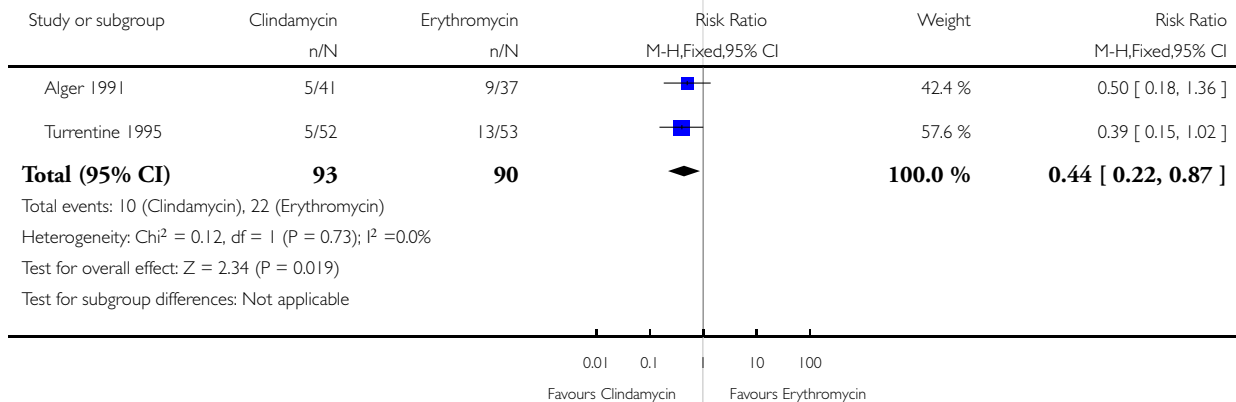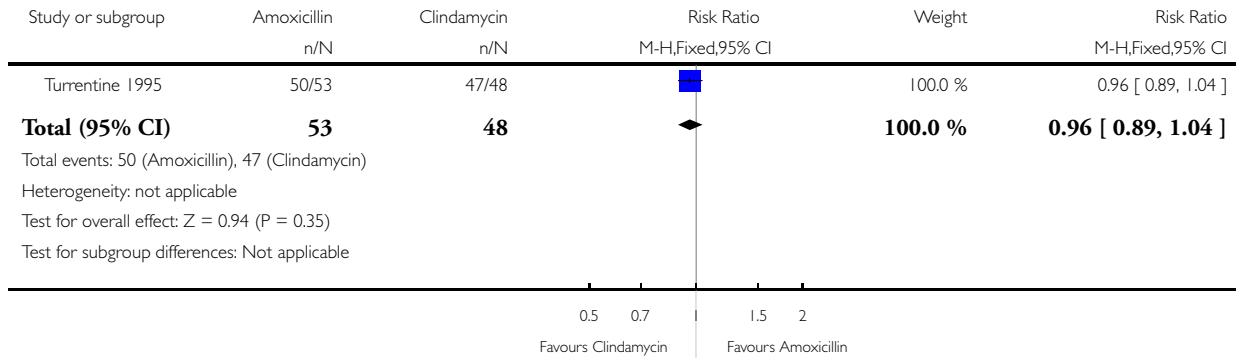Comparison: 8 Amoxicillin versus clindamycin

Outcome: 1 Microbiological cure

Study or subgroup	Amoxicillin n/N	Clindamycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Turrentine 1995	50/53	47/48		100.0 %	0.96 [0.89, 1.04]
Total (95% CI)	**53**	**48**		**100.0 %**	**0.96 [0.89, 1.04]**

Total events: 50 (Amoxicillin), 47 (Clindamycin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.94 (P = 0.35)

Test for subgroup differences: Not applicable

```
        0.5    0.7    1    1.5    2
   Favours Clindamycin    Favours Amoxicillin
```
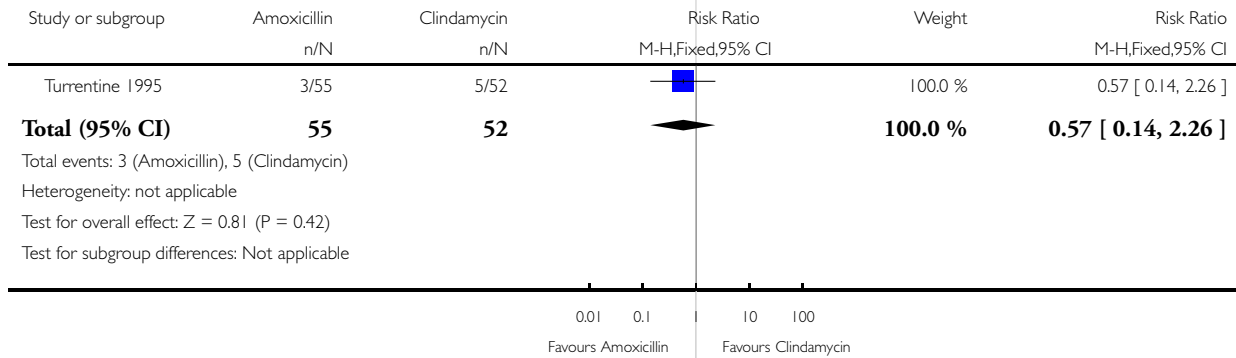
Analysis 8.2. Comparison 8 Amoxicillin versus clindamycin, Outcome 2 Side effects of treatment.

Review: Interventions for treating genital *Chlamydia trachomatis* infection in pregnancy

Comparison: 8 Amoxicillin versus clindamycin

Outcome: 2 Side effects of treatment

Study or subgroup	Amoxicillin n/N	Clindamycin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Turrentine 1995	3/55	5/52		100.0 %	0.57 [0.14, 2.26]
Total (95% CI)	**55**	**52**		**100.0 %**	**0.57 [0.14, 2.26]**

Total events: 3 (Amoxicillin), 5 (Clindamycin)

Heterogeneity: not applicable

Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: Not applicable

```
        0.01   0.1    1    10    100
   Favours Amoxicillin    Favours Clindamycin
```

APPENDICES

Appendix 1. Search terms for ClinicalTrials.gov and ICTRP

ClinicalTrials.gov
chlamydia AND pregnancy
chlamydia AND pregnant

CONTRIBUTIONS OF AUTHORS

Cathy Cluver and Natalia Novikova are the guarantors of the review. Natalia Novikova developed the protocol, provided clinical and methodological perspectives and drafted the review. Catherine Cluver provided general advice on the protocol, assisted with assessment of studies for inclusion into the meta-analysis, checked the trials for inclusion criteria, checked data entry, checked assessment of bias, performed the data analysis and edited the final versions of the review. David OA Eriksson and Kevin Bengtsson assessed the studies for inclusion into the meta-analysis, extracted the data and assisted with data analysis. Göran K Lingman checked the data and provided advice on the review.

DECLARATIONS OF INTEREST

Natalia Novikova: none known.

Catherine Cluver: none known.

David OA Eriksson: received a small travel scholarship from the international department of Lund University to finance some of the costs for travelling from Sweden to South Africa, to be a part of this review.

Kevin Bengtsson: received a small travel scholarship from the international department of Lund University to finance some of the costs for travelling from Sweden to South Africa, to be a part of this review.

Göran K Lingman: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are some differences between our published protocol (Novikova 2013) and the full review; these are outlined below.

- The contact person for the review has changed from Natalia Novikova to Cathy Cluver.

- We have updated our methods text to include the use of GRADE and we have included eight 'Summary of findings' tables.

- We have added the WHO International Clinical Trials Registry Platform (ICTRP) to sources searched.

NOTES

This new review updates and supersedes an earlier review on this topic by Brocklehurst 1998.

INDEX TERMS

Medical Subject Headings (MeSH)

*Chlamydia trachomatis; Amoxicillin [therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Azithromycin [therapeutic use]; Chlamydia Infections [*drug therapy]; Clindamycin [therapeutic use]; Erythromycin [therapeutic use]; Pregnancy Complications, Infectious [*drug therapy; microbiology]; Randomized Controlled Trials as Topic; Reproductive Tract Infections [*drug therapy]

MeSH check words

Female; Humans; Pregnancy