Antibiotics for preterm rupture of membranes (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

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Status: *Commented*

This record should be cited as:
Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of membranes. *Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD001058. DOI: 10.1002/14651858.CD001058.

This version first published online: 22 April 2003 in Issue 2, 2003.
Date of most recent substantive amendment: 24 January 2003

ABSTRACT

Background
Premature birth carries substantial neonatal morbidity and mortality. One cause, associated with preterm rupture of membranes (pROM), is often subclinical infection. Maternal antibiotic therapy might lessen infectious morbidity and delay labour, but could suppress labour without treating underlying infection.

Objectives
To evaluate the immediate and long-term effects of administering antibiotics to women with pROM before 37 weeks, on maternal infectious morbidity, fetal and neonatal morbidity and mortality, and longer-term childhood development.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group trials register (August 2004).

Selection criteria
Randomised controlled trials comparing antibiotic administration with placebo that reported clinically relevant outcomes were included. In addition, trials, in which no placebo was used, were included for the outcome of perinatal death alone.

Data collection and analysis
We extracted data from each report without blinding of either the results or the treatments that women received. We sought unpublished data from a number of authors.

Main results
Twenty-two trials involving over 6000 women and their babies were included.

The use of antibiotics following pROM is associated with a statistically significant reduction in chorioamnionitis (relative risk (RR) 0.57, 95% confidence interval (CI) 0.37 to 0.86). There was a reduction in the numbers of babies born within 48 hours (RR 0.71, 95% CI 0.58 to 0.87) and seven days of randomisation (RR 0.80, 95% CI 0.71 to 0.90). The following markers of neonatal morbidity were reduced: neonatal infection (RR 0.68, 95% CI 0.53 to 0.87), use of surfactant (RR 0.83, 95% CI 0.72 to 0.96), oxygen therapy (RR 0.88, 95% CI 0.81 to 0.96), and abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.82, 95% CI 0.68 to 0.98). Co-amoxiclav was associated with an increased risk of neonatal necrotising enterocolitis (RR 4.60, 95% CI 1.98 to 10.72).

Authors' conclusions
Antibiotic administration following pROM is associated with a delay in delivery and a reduction in major markers of neonatal morbidity. These data support the routine use of antibiotics in pPROM.

The choice as to which antibiotic would be preferred is less clear as, by necessity, fewer data are available. Co-amoxiclav should be avoided in women at risk of preterm delivery because of the increased risk of neonatal necrotising enterocolitis. From the available evidence, erythromycin would seem a better choice.

PLAIN LANGUAGE SUMMARY

Certain antibiotics given to women with early broken waters will improve babies' health

Babies born too soon are more likely to suffer ill health in the early days and sometimes throughout life. Early labour and birth (before 37 weeks) may be due to undetected infection. The review found that certain antibiotics given to women, when their waters break early, increase the time babies stay in the womb. They reduced infection and the number of babies with potential development problems, but did not save more babies. One antibiotic (co-amoxiclav) increased the number of babies with a rare condition of inflammation of the bowel. The antibiotic recommended for women whose waters break early is erythromycin.

BACKGROUND

Despite socio-economic improvements and the development of a large range of therapeutic interventions, little progress has been made in reducing the incidence of preterm birth in recent decades. In industrialised countries the proportion of births before 37 weeks remains at 6% to 8%. About one third of these is associated with preterm prelabour rupture of membranes (pPROM) (Mercer 1995). This is thus an important problem, which places both mother and child at risk of infection, preterm delivery and the complications of prematurity. Whatever the consequences, the experience is often traumatic and painful for mothers and their families.

The causes of pROM are multifactorial. Infection appears to have an important role, either as a cause or as a consequence of pROM. Some organisms may produce collagenases, mucinases and proteases which weaken the amnion and chorion and may lead to pROM. On the other hand, infection may occur secondary to membrane rupture. Ascending infection may lead to occult deciduitis, intra-amniotic infection or fetal infection.

A possible mechanism for the link between infection and preterm delivery is bacterial stimulation of the biosynthesis of prostaglandins, either directly via phospholipase A2 and C (Bejar 1981), or indirectly via substances such as interleukin-1, tumour necrosis factor and platelet activating factor, all of which may be found in infected amniotic fluid (Yoon 2000).

Attention has been directed at the management of women once pPROM has occurred as risk assessment strategies have not been useful in its prediction.

In theory, antibiotic therapy might improve outcome by two processes. Prevention or treatment of infection may, firstly, reduce maternal or fetal infectious morbidity. Secondly, it may delay the progression to preterm birth described above. This may reduce the neonatal consequences of prematurity.

In general, prolongation of pregnancy would be expected to improve subsequent child development by reducing the effects of prematurity. However, it is plausible that maternal antibiotic therapy may suppress the stimulation of labour without effectively treating fetal infection. Such prolongation of intrauterine infection may have adverse consequences for the health of the baby. Uncertainty concerning the benefits of prolonging pregnancy in the presence of pPROM is heightened by the findings of two observational studies (Murphy 1995; Spinillo 1995). Both showed a positive correlation between the duration of rupture of membranes and the risk of cerebral palsy or other neurodevelopmental impairment.

There may, in theory, be differences in the effects of different antibiotics. For example, macrolide antibiotics such as clindamycin and erythromycin, which reduce bacterial virulence, may have advantages over the beta lactam antibiotics (co-amoxiclav, cephalosporins) which, by destroying bacteria, release endotoxins and prostaglandins and may worsen outcomes (McGregor 1997). Thus, separate comparisons of these antibiotics are included in the review. The use of antibiotics for women with preterm labour with intact membranes is addressed by another review (King 2002).

OBJECTIVES

To assess the effects of administering antibiotics to women with preterm rupture of membranes on fetal and neonatal morbidity and mortality, maternal infectious morbidity and mortality, and long-term childhood development.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We considered all randomised, controlled comparisons of antibiotic administration versus placebo, given to women with preterm rupture of membranes, for inclusion in this review. For the unambiguous and important outcome of perinatal death alone, trials were included in the review that were randomised but not placebo controlled. Trials that used quasi-randomisation were excluded. Trials where the method of randomisation was not specified in detail were included in the expectation that their inclusion in this review would encourage the authors to make available further information on the method of randomisation. Trials where non-randomised cohorts were amalgamated with randomised participants were excluded if the results of the randomised participants

were not reported separately. Trials in which postrandomisation exclusions occurred were included provided there was no evidence that these occurred preferentially in one or other arm of the trials. Studies were excluded where outcomes for over 20% of participants were not reported.

Types of participants

Women with preterm (less than 37 weeks) rupture of the membranes.

Types of intervention

Any antibiotic versus placebo
All penicillins (excluding co-amoxiclav) versus placebo
Beta lactam antibiotics versus placebo
Macrolide antibiotics versus placebo
Co-amoxiclav versus erythromycin
All penicillins (except co-amoxiclav) versus erythromycin
Antibiotic versus no antibiotic - perinatal death only (all included trials)
Antibiotic versus no treatment (no placebo) - perinatal death only
Different treatment regimens of same antibiotic

Types of outcome measures

Maternal death
Serious maternal morbidity (e.g. septicaemia, need for intensive care, organ failure, need for ventilation, need for hysterectomy)
Major maternal adverse drug reaction
Maternal infection after delivery prior to discharge
Chorioamnionitis
Caesarean section
Days from randomisation to birth
Days from birth to discharge from hospital
Birth within 48 hours
Birth within seven days
Birth before 37 weeks
Birthweight
Birthweight less than 2500 grams
Need for intensive care
Days in neonatal intensive care unit
Neonatal infection including pneumonia
Positive neonatal blood culture
Necrotising enterocolitis
Respiratory distress syndrome
Treatment with surfactant
Days of ventilation
Days of oxygen therapy
Oxygen treatment greater than 28 days
Oxygen treatment greater than 36 weeks' postconceptual age
Neonatal encephalopathy
Major cerebral abnormality on ultrasound prior to discharge
Serious disability (as defined by trial authors) after two years
Perinatal death or death before discharge from hospital

For the sake of readability, we only present those outcome measures with included data.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group trials register (August 2004).

The Cochrane Pregnancy and Childbirth Group's trials register is maintained by the Trials Search Co-ordinator and contains trials identified from:
1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. monthly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness search of a further 37 journals.

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

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

METHODS OF THE REVIEW

All trials identified by the methods described in the search strategy were scrutinised by the reviewers. We processed included trial data as described in Alderson 2004. We evaluated trials under consideration for inclusion and methodological quality. There was no blinding of authorship. We assigned quality scores for concealment of allocation to each trial, using the criteria described in section six of the Cochrane Reviewers' Handbook (Alderson 2004): A = adequate; B = unclear; C = inadequate; D = not used.

We excluded trials that proved on closer examination not to be true randomised trials. We analysed outcomes on an intention to treat basis.

We extracted and double entered data. Wherever possible, we sought unpublished data from the investigator. Where outcomes were published in the form of percentages or graphs, the number of events were calculated. Where maternal outcomes were presented, numerators and denominators were calculated based on the

number of mothers. Babies from multiple pregnancies have been treated as a single unit, with the worst outcome among the babies included in analyses. Of the 22 trials included, 12 only randomised singletons. Of the seven remaining, two did not state whether multiples were included. Of the five trials that included multiples, two specified how they had analysed the data (Kenyon 2001; Mercer 1997) and both used the worst outcomes in any baby.

We tested for heterogeneity between trial results using a standard chi-squared test. For dichotomous data, we calculated the relative risk and for continuous variables, the weighted mean difference; in both cases, we reported 95% confidence intervals.

DESCRIPTION OF STUDIES

The search identified 33 trials; 22 are included in the review, involving over 6000 women and their babies, and 18 excluded. Of the trials included, the majority were small with the exception of Kenyon 2001, which randomised 4826 women, and Mercer 1997, which randomised 614 women. Women were recruited between 20 and 37 weeks of gestation and inclusion criteria varied from clinicians definition of pPROM to amniocentesis being done as part of an infection screen (Mercer 1992). The majority of women were not in active labour. Ten trials tested broad spectrum penicillins either alone or in combination (Almeida 1996; Cox 1995; Ernest 1994; Grable 1996; Johnston 1990; Kenyon 2001; Kurki 1992; Lockwood 1993; Mercer 1997; Svare 1997). Five tested macrolide antibiotics (erythromycin) either alone or in combination (Garcia 1995; Kenyon 2001; McGregor 1991; Mercer 1992; Mercer 1997) and one tested clindamycin and gentamycin (Ovalle Salas 1997). The duration of treatment varied between two doses (Kurki 1992) and 10 days (Kenyon 2001) with five trials opting for a maximum of seven days of treatment (Almeida 1996; McGregor 1991; Mercer 1997; Ovalle Salas 1997; Svare 1997). Four trials treated women until delivery (Ernest 1994; Garcia 1995; Johnston 1990; Mercer 1992). In five of the trials, women were treated with oral antibiotic alone (Almeida 1996; Garcia 1995; Kenyon 2001; McGregor 1991; Mercer 1992). In two of the trials, women were treated with intravenous antibiotic alone (Kurki 1992; Lockwood 1993). In six of the trials, women were treated with a combination of intravenous and oral antibiotics (Cox 1995; Ernest 1994; Johnston 1990; Mercer 1997; Ovalle Salas 1997; Svare 1997).

Outcome measures chosen concerned maternal infection, prolongation of pregnancy and various measures of neonatal mortality and morbidity. Only one study had undertaken follow up past discharge from hospital (Kurki 1992) but the results are not reported by treatment group but by duration of membrane rupture.

The six non-placebo controlled but randomised studies, which contributed data to the outcome measure perinatal death alone, were: Amon 1988; Camli 1997; Christmas 1992; Magwali 1999; Morales 1989; Owen 1993.

For details of included and excluded studies, *see* 'Table of included studies' and 'Table of excluded studies'.

METHODOLOGICAL QUALITY

Most trials (with the exception of Mercer 1997 and Kenyon 2001) included small numbers of women.

The method of randomisation was clearly described in all trials with the exception of Amon 1988, Cox 1995 and Ovalle Salas 1997. All trials had matched placebos and were blinded apart from the six non-placebo controlled studies described above. No detail on losses to follow up or exclusions were available from two trials (Cox 1995; Johnston 1990).

RESULTS

Twenty-two trials involving over 6000 women and their babies were included.

Initial analysis using a fixed effect model showed significant heterogeneity in the comparisons of any antibiotic and all penicillins versus placebo. Because of this and that the nature of the antibiotics varied in these groups, we applied a random effects model for all outcomes in these comparisons.

Any antibiotic versus placebo

There were 14 trials included in the review, which randomised over 6000 women and their babies. The use of antibiotics following preterm rupture of membranes (pROM) is associated with a statistically significant reduction in chorioamnionitis (relative risk (RR) 0.57, 95% confidence interval (CI) 0.37 to 0.86) (12 trials/1669 women). There were no reports of major adverse drug reactions. There was a significant reduction in the numbers of babies born within 48 hours (RR 0.71, 95% CI 0.58 to 0.87) (seven trials/5927 babies) and seven days (RR 0.80, 95% CI 0.71 to 0.90) (six trials/5860 babies) of randomisation. Neonatal infection (RR 0.68, 95% CI 0.53 to 87) (11 trials/1575 babies) was statistically significantly reduced in the babies whose mothers received antibiotics as was the numbers of babies requiring oxygen therapy overall (RR 0.88, 95% CI 0.81 to 0.96) (one trial/4809 babies). Only one trial (Kenyon 2001) assessed the use of surfactant and it found a statistically significant reduction (RR 0.83, 95% CI 0.72 to 0.96) (one trial/4809 babies). The babies in the treatment groups spent less time in neonatal intensive care 5.05 days (weighted mean difference (WMD) -5.05, 95% CI -9.77 to -0.33) (three trials/225 babies) and their birthweight was greater by 51 g (WMD 51.53, 95% CI 11.61 to 91.44) (13 trials/6480 babies). There was a significant reduction in the number of babies with an abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.82, 95% CI 0.68 to 0.98) (12 trials/6294 babies). Overall, there was no evidence of adverse effect.

Any penicillin (except co-amoxiclav) versus placebo
Six trials, which randomised over 600 women, were included (Almeida 1996; Ernest 1994; Grable 1996; Johnston 1990; Kurki 1992; Lockwood 1993). A statistically significant reduction in the numbers of women developing chorioamnionitis (RR 0.29, 95% Cl 0.11 to 0.77) (five trials/512 women) was found. Birth was delayed at 48 hours (RR 0.41, 95% CI 0.25 to 0.66) (three trials/220 babies) and seven days (RR 0.68, 95% Cl 0.56 to 0.82) (three trials/220 babies). There was a statistically significant reduction in the numbers of babies who developed neonatal infection (RR 0.33, 95% Cl 0.14 to 0.81) (four trials/416 babies), had positive blood cultures (RR 0.18, 95% Cl 0.05 to 0.68) (two trials/195 babies) and had major cerebral abnormality on ultrasound before discharge (RR 0.49, 95% CI 0.25 to 0.97) (three trials/267 babies).

Co-amoxiclav (Beta lactam antibiotics) versus placebo
Two trials, which randomised nearly 2500 women, were included (Cox 1995; Kenyon 2001). There was a statistically significant reduction in the number of babies born within 48 hours (RR 0.75, 95% CI 0.67 to 0.84) (one trial/2430 babies) and seven days (RR 0.91, 95% CI 0.85 to 0.97) (one trial/2430 babies) of randomisation. However, there was a highly significant increase in the numbers of babies with necrotising enterocolitis (RR 4.60, 95% CI 1.98 to 10.72) (two trials/2492 babies) in the co-amoxiclav treatment group.

Erythromycin (macrolide antibiotics) versus placebo
Four trials (Garcia 1995; Kenyon 2001; McGregor 1991; Mercer 1992), which randomised 2750 women, were included. For babies whose mothers had macrolide antibiotics, there was a significant reduction in the number of babies born within 48 hours (RR 0.84, 95% CI 0.76 to 0.93) (two trials/2635 babies), requiring oxygen therapy (RR 0.87, 95% CI 0.78 to 0.98) (one trial/2415 babies) and with a positive blood culture (RR 0.70, CI 0.52 to 0.94) (one trial/2415 babies).

Erythromycin versus co-amoxiclav
One trial (Kenyon 2001) was included, involving 2415 women. Delivery within 48 hours was less common after co-amoxiclav (RR 1.14, 95% CI 1.02 to 1.28) but the difference was not statistically significant at seven days. There was no significant difference in any index of neonatal morbidity except for necrotising enterocolitis, which was statistically significantly less frequent after erythromycin (RR 0.46, 95% CI 0.23 to 0.94).

No statistically significant reduction in perinatal mortality prior to discharge from hospital could be found when additional data were included from the six studies that were randomised but not placebo controlled (RR 0.87 95% CI 0.72 to 1.05) (19 trials/6982 babies).

Differing regimens
Two trials (Lewis 2003; Segel 2003) compared three versus seven day regimens of ampicillin treatment (130 women). From the limited available outcome data, there was no obvious disadvantage to the three day regimen.

DISCUSSION

This review shows that routine antibiotic administration to women with pROM reduces maternal and neonatal morbidity. This does not translate into a statistically significant reduction in perinatal mortality. Most trials, however, report fewer deaths in the treatment group and the summary result shows a trend towards a beneficial effect. All randomised trials were included in the evaluation of perinatal death as this outcome is unlikely to be influenced by knowledge of the treatment allocation. Such a clear reduction in major markers of maternal and neonatal morbidity when antibiotics are administered makes a reduction in death possible, even if the result was statistically non-significant from pooling of available data.

By far the largest trial included is UK MRC ORACLE (Kenyon 2001), which randomised 4826 women. The significant increase in neonatal necrotising enterocolitis found in this trial is plausible since co-amoxiclav is known to select for Enterobacter, Citrobacter and Pseudomonas (Hoy 2001). One suggested mechanism of pathogenesis of neonatal necrotising enterocolitis is abnormal microbial colonisation of the intestinal tract by one or a few species unhindered by competitors. Co-amoxiclav, because of its range of activity and effectiveness, can facilitate such colonisation. Furthermore, the immature gut is able to absorb exotoxins produced intact, resulting in mucosal damage and the initiation of necrotising enterocolitis.

Particularly in the light of UK MRC ORACLE's finding of reduced abnormal cerebral ultrasound scans before discharge from hospital, it is important that long term follow up is undertaken. The UK MRC ORACLE Children Study will follow up at seven years old those babies randomised within the UK to the MRC ORACLE trial. The study will be completed in 2008.

AUTHORS' CONCLUSIONS

Implications for practice

Antibiotic treatment following pPROM is associated with a statistically significant delay in women giving birth and reductions in major markers of neonatal morbidity (although not perinatal mortality). This delay in delivery would allow sufficient time for prophylactic prenatal corticosteroids to take effect (Crowley 2001). These data support the routine use of antibiotics in this clinical situation. The increase in the numbers of babies who developed neonatal necrotising enterocolitis with the prescription of prenatal co-amoxiclav mean that this antibiotic is best avoided in women at risk of preterm delivery. On the basis of the available evidence erythromycin appears the antibiotic of choice.

Implications for research

Further evaluation of the long-term outcome on health and development of children following this intervention is important. In the future there is the possibility that comparative studies may be conducted should there be developments in the pharmacology of antibiotics.

FEEDBACK

Shapiro, March 2003

Summary

The ORACLE study accounts for the vast majority of women included in this review, 4826 out of around 6000 women. ORACLE did not have a stopping rule, so that one cannot gauge why the study was stopped when it was. Were repeated statistical tests done? The impression, unfortunately, is that the study may have been stopped when a significant result was obtained. If so, this makes the "significant" conclusions untenable.

Author's reply

Thank you for your comments. The Medical Research Council (UK) ORACLE Trial had both a Steering Group and a Data Monitoring Committee. The Data Monitoring Committee agreed terms of reference before the start of the Study. These were documented in the trial protocol, as follows:
"The independent Data Monitoring Committee (chairman: Professor Adrian Grant, Aberdeen; members: Professor Forrester Cockburn, Glasgow; Mr Richard Gray, Oxford; Professor Charles Rodeck, London) will conduct interim analyses of morbidity and mortality among all trial participants. The Trial Director and Steering Group will be informed if at any time the randomised comparisons in this study have provided both (i) proof beyond reasonable doubt of a difference in a major endpoint between the study and control groups, and (ii) evidence that would be expected to alter substantially the choice of treatment for patients whose doctors are, in the light of the evidence from the other randomised trials, substantially uncertain whether to recommend antibiotics. Exact criteria of "proof beyond reasonable doubt" are not specified, but members of the committee have expressed sympathy with the view that it should generally involve a difference of at least three standard deviations in a major endpoint. Using this criterion has the practical advantage that the exact number of interim analyses is of little importance, and so no fixed schedule is proposed."

The Committee met annually throughout trial recruitment, and for the last time in June 1999. At that time the conditions for discontinuation had not been met so it was decided to carry on until funding ceased. Recruitment closed on 31st May 2000, as this allowed time for the last women to deliver, data to be chased and cleaned, analysis to be undertaken and reports prepared for publication.

[Summary of response from Sara Kenyon, May 2003]

Contributors

Summary of comment from Mervyn Shapiro, March 2003.

POTENTIAL CONFLICT OF INTEREST

Sara Kenyon was the Co-ordinator of the ORACLE Trial, which was included in this review.

ACKNOWLEDGEMENTS

We acknowledge assistance with the review from Justus Hofmeyr, David Taylor, Ann Blackburn and Rebecca Smyth.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- University of Liverpool UK
- University of Geneva SWITZERLAND
- Leicester Royal Infirmary UK

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** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Almeida 1996
Methods	Randomised double blind placebo controlled trial. Randomisation based on random numbers tables with blocks providing 1:1 ratio and balancing every 6 women. Randomisation conducted in pharmacy.
Participants	110 women 30-36 weeks pregnant with clinically evident rupture of the membranes, not in labour. Exclusions: on antibiotics already. Not stated if multiple pregnancy included.
Interventions	Amoxicillin 75 g 3 x daily or placebo for 7 days or until delivery.
Outcomes	Stay in hospital, type of delivery, fetal outcome, birthweight, duration of interval between membrane rupture and delivery, duration of delivery from the beginning of the active stage of dilatation to expulsion, proportion of newborns requiring neonatal ward care and duration of stay of such newborns in the neonatal ward.
Notes	Joint venture between Mozambique (where women were recruited), Sweden and Norway. Data (apart from birthweight and caesarean section rates in the paper) supplied additionally by authors.
Allocation concealment	A – Adequate

Study	Amon 1988
Methods	Randomised trial. No mention of method of randomisation. Not placebo controlled or blinded.
Participants	82 women treatment 43 control 39. Inclusions: 20-34 weeks pregnant. pPROM confirmed by sterile speculum. Singleton pregnancy only.
Interventions	Treatment group: ampicillin 1 gm IV every 6 hours for 24 hours. Maintained on oral 500 mg ampicillin 6 hourly until delivery. In labour they were recommenced on 1 gm intravenous ampicillin.
Outcomes	Death only included.
Notes	
Allocation concealment	B – Unclear

Study	Camli 1997
Methods	Randomised trial-no mention of the method of randomisation.
Participants	31 women with premature rupture of the membranes between 28-34 weeks gestation. pPROM confirmed by speculum. Exclusions: women who go into active labour within 24 hours or who need induction of labour. Multiple pregnancy and fetal malformations. Women with serious medical conditions or who need antibiotic treatment for a known infection. Women who have received antibiotics in the last 10 days or who are allergic to penicillin.
Interventions	Treatment group oral Ampicillin 1 gm 4 x daily. No placebo arm or tocolysis used.
Outcomes	Death only included.
Notes	
Allocation concealment	B – Unclear

Study	Christmas 1992
Methods	Randomised trial. Using sequentially numbered sealed envelopes. Not placebo controlled or blinded. The control group received IV fluids without antibiotics for first 24 hours.

Characteristics of included studies (*Continued*)

Participants	94 women randomised 48 treatment, 46 control. Inclusions: singleton pregnancies 20-34 weeks with pPROM confirmed by sterile speculum. Exclusions: penicillin allergy. Prior antibiotic therapy. Clinical evidence of intraamniotic infection. Evidence of labour or fetal distress.
Interventions	Treatment: 24 hours IV ampicillin 2 g every 6 hours for 4 doses; gentamycin 90 mg loading dose 60 mg every 8 hours for 3 doses. Then oral amoxicillin + clavulanic acid. 500 mg 3 x day for 7 days. Control IV fluids without antibiotics for 24 hours.
Outcomes	Death only included.
Notes	
Allocation concealment	A – Adequate

Study	**Cox 1995**
Methods	Randomised controlled trial.
Participants	62 women pPROM between 24 and 29 weeks pregnant. Not stated whether multiple pregnancy included.
Interventions	Co-amoxiclav 3 gm 6 hourly for 4 doses then co-amoxiclav 500 mg 6 hourly for 5 days or matching placebo.
Outcomes	Prolongation of pregnancy. Neonatal mortality and morbidity.
Notes	Data extracted from abstract only. Further data requested from Dr Cox but not made available. Study took place between May 1991 and April 1994 in Dallas, Texas.
Allocation concealment	B – Unclear

Study	**Ernest 1994**
Methods	Randomised double blind placebo controlled trial. A table of random numbers was used. Drugs and placebo were prepared by research nurses. The authors specify that participants and caregivers were blinded as to group.
Participants	148 women at 21-37 weeks with premature rupture of the membranes preterm confirmed with positive nitrazine test and 'ferning' of amniotic fluid or by seeing vaginal pool of amniotic fluid from os. No tocolytics or steroids given. Multiple pregnancies included. Exclusions are not clearly stated.
Interventions	4 hourly IV 1 million units benzylpenicillin for 12-24 hours - oral 250 mg penicillin twice daily before delivery or a matched placebo.
Outcomes	Latency period, infection complications and neonatal outcomes studies. Data on death not included.
Notes	Study conducted from March 2 1989 to May 29 1991, in a single site (North Carolina, USA). 148 women. 71 placebo. 77 treatment. 4 women were excluded because of protocol violation in placebo arm (antibiotics given).
Allocation concealment	A – Adequate

Study	**Garcia 1995**
Methods	Randomised double blind placebo controlled trial.
Participants	60 singleton pregnancy women. Preterm PROM under 36 weeks pregnant. Ruptured membranes confirmed by sterile speculum examination, ferning test and nitrazine test. No steroids or tocolytics given after randomisation. Exclusions: > 37/40. Discrepancy of over 2 standard deviations between scan and dates EDD

Characteristics of included studies (*Continued*)

	Bleeding Contractions Fetal distress Fetal malformation Fetal death Chorioamnionitis on admission Antibiotics given during previous 10 days.
Interventions	Erythromycin 500 mg 6 hourly orally until delivery. Matched placebo given until delivery.
Outcomes	Maternal morbidity. Neonatal mortality and morbidity.
Notes	60 women recruited during 1992 from single centre in Madrid, Spain. No losses to follow up. Paper in Spanish and data extracted with help from Dr Pigem.
Allocation concealment	A – Adequate

Study	**Grable 1996**
Methods	60 women randomised to double blind placebo controlled trial. Randomisation based on random numbers tables with blocks providing 1:1 ratio and balancing every 6 women. Randomisation conducted in pharmacy.
Participants	60 women randomised. Inclusions <= 35 weeks with documented pPROM. Exclusions: digital examination of cx, non-reassuring stress test, presence of chorioamnionitis, abruptio placenta, pre-eclampsia, multiple pregnancy and penicillin allergy.
Interventions	IV ampicillin 2 gm every 6 hours for 24 hours followed by 500 mg oral ampicillin until delivery or discharge. Matched placebos.
Outcomes	Maternal morbidity. Neonatal mortality and morbidity.
Notes	Study divided into GBS positive and negative patients. Unclear whether clinician knew of positive culture.
Allocation concealment	A – Adequate

Study	**Johnston 1990**
Methods	Randomised double-blind placebo controlled trial. Randomisation table generated by consecutive coin toss, the randomisation schedule kept in pharmacy.
Participants	85 women randomised. Inclusions: mothers with singleton gestations between 20-34 weeks with pPROM confirmed by sterile speculum for pooling, ferning and nitrazine paper testing. Exclusions: penicillin allergy, taking antibiotics at the time of pPROM, had fever > 100.4 degrees Fahrenheit, had signs of chorioamnionitis, were in active labour (defined by 3 or more contractions per 10 minute period for 1 hour or presented with cervical dilatation > 3 cm confirmed at the time of sterile speculum. Fetal indications for exclusion were the presence of fetal distress, defined as repetitive late deceleration or sustained bradycardia, or congenital abnormality on ultrasound.
Interventions	IV mezlocillin for 48 hours followed by oral ampicillin until delivery or matched (IV + oral) placebo. No doses noted. After randomisation no tocolytic steroids given. Study drugs discontinued if infection diagnosed.
Outcomes	Not clearly defined other than maternal or perinatal morbidity and mortality. Outcomes looked at included length of pregnancy, maternal infectious morbidity, mode of delivery. Neonatal outcomes - stillbirth, neonatal death, birthweight Apgar, cord pH, positive blood culture, RDS, IVH, NEC, NICU stay over 30 days.
Notes	Single centre - University Medical Centre - Jacksonville Florida. 85 women randomised. All women had infection screen on admission. No digital examination allowed.

	No comment as to losses to follow up or recruitment period.
Allocation concealment	A – Adequate

Study	**Kenyon 2001**
Methods	Randomised double-blind placebo controlled trial.
Participants	4826 women under 37 weeks pregnant with preterm rupture of membranes. Multiple pregnancies included.
Interventions	Co-amoxiclav 375 mg QDS, erythromycin 250 mg QDS orally for 10 days or until delivery matched placebo (2 x 2 factorial design).
Outcomes	Primary outcome: neonatal death or abnormal brain scans on discharge from hospital or oxygenation at 36 weeks postconceptual age. Secondary outcomes include prolongation of pregnancy, neonatal infection, respiratory outcomes.
Notes	Multicentre trial (161 centres, 135 in the UK). Randomised 4826 women. 2 women lost to follow up and 15 women were excluded due to protocol violations. 4809 women analysed. For twin pregnancies adverse outcomes were considered present if one twin affected. Consumers involved in drawing up of protocol and information for women.
Allocation concealment	A – Adequate

Study	**Kurki 1992**
Methods	Randomised double blind placebo controlled trial.
Participants	101 women randomised between 23-36 weeks pregnant with visible leakage of amniotic fluid who did not go into labour within 12 hours of admission. Sterile speculum, digital examination and infection screening was performed on admission. Multiple pregnancies included.
Interventions	2 doses of IV penicillin (5 mu) or matched placebo.
Outcomes	Prolongation of pregnancy. Infection, neonatal morbidity and mortality. Long-term development at 2 years.
Notes	Department of Obstetrics and Gynaecology, Helsinki, Finland. No mention of where the study was conducted. Sealed envelope randomisation. Results in 76 women not randomised but admitted during the same period are also reported.
Allocation concealment	A – Adequate

Study	**Lewis 2003**
Methods	Randomised trial looking at 3 or 7 days antibiotic therapy. Randomised using table of arbitrary numbers in blocks of 10. Indicator cards placed in sealed envelopes which were sequentially numbered and stored on an area away from the enrolment site.
Participants	84 singleton pregnancies were randomised between 24-34 weeks gestation. Exclusions included known infection, absence of cervical cerclage, not penicillin allergic. Corticosteroids given to all participants.
Interventions	Ampicillin-sulbactam 3 g intravenously every six hours for either 3 or 7 days.
Outcomes	Primary outcome was latency period between membrane rupture and delivery. Infection and neonatal morbidity and mortality.
Notes	3 study sites in Tennessee USA.
Allocation concealment	A – Adequate

Study	**Lockwood 1993**
Methods	Randomised double blind placebo controlled trial.

Characteristics of included studies (*Continued*)

Participants	75 women randomised with a single fetus at 24-34 completed weeks (accurate gestational age), admitted with pROM. No digital examination unless active labour. Women had infection screening. Exclusions: abruption, lethal fetal abnormalities clinical chorioamnionitis, maternal illness, diabetes, PIH, lupus, severe maternal disease, fetal growth retardation, fetal distress, cervical cerclage, active herpes. Women having received antibiotics for existing infection were also excluded.
Interventions	Piperacillin 3 gm IV 6 hourly 72 hours or placebo.
Outcomes	Prolongation of pregnancy. Neonatal outcomes.
Notes	Recruitment in 3 centres (USA) from January 1987 to January 1992. 75 women were randomised (treatment 38, placebo 37). 3 babies (1 in the experimental group and 2 in controls) were lost to follow up.
Allocation concealment	A – Adequate

Study	**Magwali 1999**
Methods	Randomised trial not placebo controlled. Randomisation by opening sealed consecutive opaque envelopes in admission room.
Participants	171 women randomised 84 in treatment group 87 in no treatment group. Inclusion pROM 26-36 weeks gestation drainage of liquor confirmed by sterile speculum. Exclusions: clinical signs of chorioamnionitis, multiple pregnancy, those with any contraindication to continuing the pregnancy and those who had just completed a course of antibiotics for another reason.
Interventions	Co-amoxiclav for 5 days. No mention of daily frequency or mg of drugs.
Outcomes	Death only included.
Notes	
Allocation concealment	A – Adequate

Study	**McGregor 1991**
Methods	Randomised double blind placebo controlled trial. Computer generated random number list. Sequentially numbered bottles.
Participants	65 women with singleton pregnancies. Women between 23-34 completed weeks' gestation with premature rupture of membranes. Sterile speculum. No corticosteroids administered. Exclusions: active labour, presence of maternal or fetal complication to necessitate delivery (fetal distress, prolapsed cord, pregnancy-induced hypertension, abruptio placentae) placenta praevia, cervical cerclage, known infection requiring antibiotic treatment, use of vaginal or oral antibiotics in last 2 weeks, presence of known uterine or fetal abnormality, history of vaginal bleeding in last month, serious existing maternal disease, history of allergy or intolerance to erythromycin.
Interventions	Erythromycin 333 mg 3 x daily or placebo 7 days or until active labour started.
Outcomes	Prolongation of pregnancy. Maternal and neonatal infectious morbidity.
Notes	July 1986-June 1988 University Hospital Denver 65 women recruited (10 excluded) 55 analysed - (28 treatment, 27 placebo). No replies received to letter requesting breakdown between stillbirths and neonatal deaths and asking if Blanco's paper has ever been published.
Allocation concealment	A – Adequate

Study	**Mercer 1992**
Methods	Randomised double blind placebo controlled trial.

	Computerized random number tables. Administered by the pharmacy. Stratified at 30 weeks gestational age.
Participants	Inclusions: 220 women 20-34/6 weeks pregnant with pPROM - sterile speculum and evaluation of cervix. Amniocentesis done for infection screen. Multiple pregnancies included. Exclusions: pPROM > 72 hours duration, cervical dilatation > 4 cm, progressive labour, vaginal bleeding, temperature 99 degrees Fahrenheit or greater, active infection requiring antibiotic therapy, antibiotic therapy within 1 week prior to admission, active hepatic disease, erythromycin allergy, cervical cerclage or medical condition requiring delivery. IUGR (< 10 centile), congenital abnormalities, evidence of fetal distress, unsuccessful tocolysis on admission for preterm labour.
Interventions	Oral 333 mg erythromycin. 8 hourly from randomisation to delivery with matched placebo.
Outcomes	Not clearly stated. Prolongation of pregnancy. Reduction of infectious morbidity.
Notes	Single centre (Memphis, Tennessee, USA). March 1989-August 1990. Women had infection screen before randomisation. 220 randomised, (treatment 106, placebo 114) 3 lost to follow up.
Allocation concealment	A – Adequate

Study	**Mercer 1997**
Methods	Randomised double blind placebo controlled trial. Urn randomisation scheme (a procedure to increase the likelihood of obtaining an equal number of subjects in each arm), stratified by centre.
Participants	614 women with pPROM at 24-32 weeks' gestation. Inclusion criteria: membrane rupture within 36 hours of randomisation; cervical dilatation 3 cm or less on usual examination; < 5 contractions in 6 minutes. Exclusion criteria: non-reassuring, fetal testing; vaginal bleeding; maternal or fetal indication for delivery, cervical cerclage in place, antibiotics within the last 5 days, corticosteroids within last 7 days, allergy to penicillin or erythromycin; maternal infection or medical disease, ultrasound evidence of placenta praevia, fetal weight < 10 th centile for gestational age, malformation. Previous successful tocolysis was not an exclusion criterion. Tocolysis and corticosteroids were prohibited after randomisation.
Interventions	Ampicillin 2 g 6 hourly and erythromycin 250 mg 6 hourly IV for 48 hours, then oral amoxacillin 250 mg every 8 hours and erythromycin 333 mg 8 hourly for 5 days and a matching placebo regimen.
Outcomes	Composite primary outcome included pregnancies complicated by at least one of the following: fetal or infant death, respiratory distress, severe intraventricular haemorrhage, stage 2 or 3 necrotising enterocolitis, or sepsis within 72 hours of birth. These perinatal morbidities were also assessed separately and pregnancy prolongation assessed. For twin pregnancies adverse outcomes considered present if one twin affected.
Notes	11 centres - USA. February 1992-January 1995. 1867 women screened. 804 eligible. 614 agreed to participate. 29 twin gestations. Group B Strep positive: 118/614. 3 women lost to follow up.
Allocation concealment	A – Adequate

Study	**Morales 1989**
Methods	Randomised trial not placebo controlled. RCT of antenatal steroids + ampicillin. 4 groups - GP1 - neither, GP2 steroids only, GP3 antibiotic only, GP4 both. Randomised by using sealed envelopes into one of groups.

Characteristics of included studies (*Continued*)

Participants	Randomised: 41 = GP1, 43 = GP2, 37 = GP3, 44 = GP4. Inclusion criteria 26-34 weeks pregnant singleton gestation. pROM confirmed by sterile speculum L/S ratio less than 2.0. Exclusions: In labour within 12 hours of randomisation women with uterine tenderness, foul smelling lochia or fetal tachycardia on admission, women allergic to penicillin, with congenital abnormality with L/S ratio greater than 2.0 or not obtained.
Interventions	2 g IV ampicillin every 6 hours until results of cervical cultures negative.
Outcomes	Death only included.
Notes	
Allocation concealment	A – Adequate

Study	**Ovalle Salas 1997**
Methods	Randomised double blind placebo controlled trial. No comment as to method of randomisation.
Participants	88 women. Inclusions: women with pPROM 24-34 weeks, pPROM diagnosed with sterile speculum-pooling, ferning and nitrazine tests. No digital examination performed. Exclusions: labour, significant haemorrhage, abruptio placentae, use of antibiotics within 30 days before screening for study, fetal anomaly or death, multiple gestation, documented allergy to clindamycin or gentamicin, uterine abnormality, presence of IUCD, fetal distress, clinical chorioamnionitis, maternal medical complications necessitating delivery or any condition precluding expectant management and intrauterine growth retardation (< 10 th centile for gestational age).
Interventions	Clindamycin 600 mg IV every 6 hours for 48 hours + 4 mg/kg/day gentamycin IV for 48 hours followed by Clindamycin 300 mg orally every 6 hours for 5 days + gentamycin 2 mg/kg/day IM every 12 hours for 5 days. Matching placebo.
Outcomes	Prolongation of pregnancy, maternal infection related morbidity, birthweight, neonatal morbidity and admission to neonatal intensive care unit.
Notes	November 1990-September 1994. 3 sites: 2 Chile, 1 USA. Women had infection screen. 88 women randomised (Treatment 42, Control 46). 1 lost to follow up in placebo arm. Trial stopped after intermediate evaluation showed treatment group had better outcome.
Allocation concealment	B – Unclear

Study	**Owen 1993**
Methods	Randomised not placebo controlled. Randomised using sealed opaque envelopes determined by computer algorithm.
Participants	118 randomised 1 lost to follow up. 59 treatment 58 controls. Inclusions 24 to 34 weeks' gestation. pPROM confirmed by speculum. Exclusions in labour, clinical evidence of infection suspected fetal compromise, membrane rupture over 2 days, fetal abnormality, antibiotics in last 7 days, multiple pregnancy, cervical cerclage, prompt delivery required.
Interventions	IV 1 gm ampicillin 6 hourly for 24 hours then 500 mg ampicillin orally every 6 hours. If allergic to penicillin 500 mg erythromycin used 6 hourly. Treatment continued with delivery or diagnosis of chorioamnionitis.
Outcomes	Death only included.
Notes	

Characteristics of included studies (*Continued*)

Allocation concealment	A – Adequate

Study	**Segel 2003**
Methods	Randomised double blind placebo controlled trial of 3 or 7 days treatment. Pharmacy provided randomisation with a computer generated random number table in blocks of 4.
Participants	48 women randomised: 24 in each arm-analysis on 23 in each arm. Women 24-33 weeks with clinically confirmed ruptured membranes. Exclusions included penicillin allergy, active labour, suspected infection, multiple pregnancy, known medical maternal or fetal problems and exposure to antibiotics within 1 week before admission.
Interventions	For first 48 hours all women recieved parenteral ampicillin 2 g every 6 hours. Women were then randomly selected to recieve either 3 or 7 days oral ampicillin. Women allocated the 3 day course recieved a matching placebo.
Outcomes	Primary outcome of prolongation of pregnancy for at least 7 days. Secondary outcomes included rated of chorioamnionitis, postpartum endometritis and neonatal morbidity and mortality.
Notes	Study took place between September 1999 - December 2001 Pennsylvania USA.
Allocation concealment	A – Adequate

Study	**Svare 1997**
Methods	Randomised double blind placebo controlled trial. Block randomisation done using computer generated numbers.
Participants	67 women randomised. 26 + 0 - 33 + 6 rupture of membranes, leakage of amniotic fluid at vaginal speculum examination. Preceding onset of uterine contractions. Singleton pregnancies.
Interventions	Ampicillin 2 gm IV 6 hourly. 24 hours - pivampicillin 500 g orally 8 hourly for 7 days plus IV metronidazole 500 mg every eight hours for 24 hours, followed by metronidazole 400 mg orally every eight hours for 7 days or identical placebo.
Outcomes	Latency period from admission - delivery. Gestational age at delivery. Preterm delivery less than 37/40 maternal - neonatal infection birthweight.
Notes	October 1991-April 1994. 6 centres around Copenhagen. 67 women randomised. 30 antibiotics. 37 placebo. Data sent from Mr Svare and extracted from PhD thesis.
Allocation concealment	A – Adequate

cx: cervix
EDD: expected date of delivery
GP: group
IM: intramuscular
IUCD: intrauterine contraceptive device
IUGR: intrauterine growth retardation
IV: intravenous
IVH: intraventricular haemorrhage
NEC: necrotising enterocolitis
NICU: neonatal intensive care unit
PIH: pregnancy induced hypertension
pPROM: preterm prelabour rupture of membranes
PROM: premature rupture of membranes
QDS: four times per day
RDS: respiratory distress syndrome

Characteristics of excluded studies

Study	Reason for exclusion
Blanco 1993	Abstract only - data requested. Following comments received during the publication of this review in 2004 we have written to Brian Mercer who included this data in a Lancet review in 1995 and James McGregor who was listed as an author.
Carroll 2000	Abstract only containing no usable data (p values only).
Debodinance 1990	Randomised trial of antibiotic treatment (mezlocillin) for women with pPROM. Not placebo controlled and no clinical outcomes reported. Mortality data requested from author.
Dunlop 1986	Study of 48 women with pPROM 26 to 34 weeks of pregnancy, given either oral ritodrine or cephalexin or both or neither (factorial design) - not placebo controlled. No concealment of allocation for some participants (Latin Square method).
Fortunato 1990	Study which investigated active versus passive management of women with pPROM. Fifty-five women were recruited when admitted and given antibiotics. The control group were women who presented with pPROM. 1985-1987 before use of active protocol. Excluded as not double blinded, randomised or controlled.
Julien 2002	Study compared antibiotic versus placebo only after 48 hour intravenous antibiotic treatment to all.
Lebherz 1963	Double blind randomised controlled trial of 1912 women but no mention of gestation at recruitment.
Lewis 1995	Study comparing treatment of women with PROM at 25 to 35 weeks' gestation in a randomised blinded trial comparing ampicillin-suibactum with ampicillin: ie comparison of similar antibiotics - so excluded, because did not fulfil selection criteria for interventions compared.
Lewis 1996	This is a randomised trial of corticosteroids in women with preterm PROM after a minimum of 12 hours ampicillin sulbactam. Seventy-seven women were enrolled. No statistically significant difference in latency period was noted. Neonatal and maternal infectious morbidity were similar. A significant reduction in the incidence of RDS, 18.4% versus 43.6%, was observed in the steroid group.
Lovett 1997	Double blind placebo controlled trial of 112 women with pPROM 23 to 25 weeks' gestation to receive ampicillin/ sulbactam or ampicillin or placebo. Excluded because of a high rate of exclusions (52/164: 32%). Further information has been requested from the authors.
Matsuda 1993a	Comparative study; not placebo controlled.
Matsuda 1993b	Prospective study, not randomised, of conservative versus aggressive management of women with pPROM. Aggressive management: IV antibiotics + tocolytics. Conservative management consisted of bedrest only.
Mbu 1998	Allocation by alternation.
McCaul 1992	Double blind placebo controlled trial of 84 women with pPROM (19 to 34 weeks pregnant) who received ampicillin or placebo. 112 randomised - 12 non-compliant so excluded and 26 removed from study (does not add up). Letter sent to Mr McCaul to get excluded women's data; in the meantime, excluded.
Norri 1991	Abstract only - does not say whether study was placebo controlled nor could any publication be found.
Ovalle 2002	Randomised placebo controlled study looking at chorioamnionitis. No clear details of method of randomisation. 100 women recruited-71 analysed-excluded as large number lost to follow-up.
Spitzer 1993	Comparison of neonatal infection rates in 2 groups of women, with pPROM. Both groups were treated with tocolytic and steroid therapy. The first group was given antibiotic therapy continuously from onset of pPROM until delivery. The second group received antibiotic therapy for the first 3 days after pPROM and for a 3 day period around each successive dose of corticosteroids. The study was neither randomised, nor placebo controlled or blinded.
Svare 1996	Abstract only - data requested. No usable data.

RDS: respiratory distress syndrome

IV: intravenous
pPROM: preterm prelabour rupture of membranes
PROM: premature rupture of membranes

ANALYSES

Comparison 01. Any antibiotic versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Maternal death	4	873	Relative Risk (Random) 95% CI	Not estimable
02 Serious maternal morbidity	0	0	Relative Risk (Random) 95% CI	Not estimable
03 Major adverse drug reaction	4	5597	Relative Risk (Random) 95% CI	Not estimable
04 Maternal infection after delivery prior to discharge	5	5657	Relative Risk (Random) 95% CI	0.82 [0.48, 1.39]
05 Chorioamnionitis	12	1669	Relative Risk (Random) 95% CI	0.57 [0.37, 0.86]
06 Caesarean section	12	6423	Relative Risk (Random) 95% CI	0.96 [0.88, 1.05]
07 Days from randomisation to birth	0	0	Weighted Mean Difference (Random) 95% CI	Not estimable
08 Days from birth till discharge of mother	0	0	Weighted Mean Difference (Random) 95% CI	Not estimable
09 Birth within 48 hours of randomisation	7	5927	Relative Risk (Random) 95% CI	0.71 [0.58, 0.87]
10 Birth within 7 days of randomisation	6	5860	Relative Risk (Random) 95% CI	0.80 [0.71, 0.90]
11 Birth before 37 weeks' gestation	3	4931	Relative Risk (Random) 95% CI	1.00 [0.97, 1.03]
12 Birthweight	13	6480	Weighted Mean Difference (Random) 95% CI	51.53 [11.61, 91.44]
13 Birthweight < 2500 g	2	4876	Relative Risk (Random) 95% CI	1.00 [0.96, 1.04]
14 Neonatal intensive care	4	5023	Relative Risk (Random) 95% CI	0.98 [0.85, 1.13]
15 Days in neonatal intensive care unit	3	225	Weighted Mean Difference (Random) 95% CI	-5.05 [-9.77, -0.33]
16 Neonatal infection including pneumonia	11	1575	Relative Risk (Random) 95% CI	0.68 [0.53, 0.87]
17 Positive neonatal blood culture	4	5071	Relative Risk (Random) 95% CI	0.50 [0.21, 1.19]
18 Neonatal necrotising enterocolitis	10	6124	Relative Risk (Random) 95% CI	1.14 [0.66, 1.97]
19 Neonatal respiratory distress syndrome	11	6182	Relative Risk (Random) 95% CI	0.95 [0.83, 1.10]
20 Treatment with surfactant	1	4809	Relative Risk (Random) 95% CI	0.83 [0.72, 0.96]
21 Number of babies requiring ventilation	2	4924	Relative Risk (Random) 95% CI	0.90 [0.80, 1.02]
22 Number of babies requiring oxygen therapy	1	4809	Relative Risk (Random) 95% CI	0.88 [0.81, 0.96]
23 Neonatal oxygenation > 28 days	4	5597	Relative Risk (Random) 95% CI	0.75 [0.53, 1.06]
24 Oxygen treatment > 36 weeks postconceptual age	1	4809	Relative Risk (Random) 95% CI	0.91 [0.70, 1.17]
25 Neonatal encephalopathy	1	60	Relative Risk (Random) 95% CI	Not estimable
26 Major cerebral abnormality on ultrasound before discharge	12	6294	Relative Risk (Random) 95% CI	0.82 [0.68, 0.98]
27 Serious childhood disability at approximately 2 years	0	0	Relative Risk (Random) 95% CI	Not estimable

28 Perinatal death/death before discharge	13	6411	Relative Risk (Random) 95% CI	0.90 [0.74, 1.10]

Comparison 02. All penicillins(excluding co-amoxiclav) versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Maternal death	2	195	Relative Risk (Random) 95% CI	Not estimable
02 Serious maternal morbidity	0	0	Relative Risk (Random) 95% CI	Not estimable
03 Major adverse drug reaction	1	110	Relative Risk (Random) 95% CI	Not estimable
04 Maternal infection after delivery prior to discharge	1	110	Relative Risk (Random) 95% CI	0.03 [0.00, 0.23]
05 Chorioamnionitis	5	512	Relative Risk (Random) 95% CI	0.29 [0.11, 0.77]
06 Caesarean section	5	511	Relative Risk (Random) 95% CI	1.00 [0.71, 1.41]
07 Days from randomisation to birth	0	0	Weighted Mean Difference (Random) 95% CI	Not estimable
08 Days from birth till discharge of mother	0	0	Weighted Mean Difference (Random) 95% CI	Not estimable
09 Birth within 48 hours of randomisation	3	220	Relative Risk (Random) 95% CI	0.41 [0.25, 0.66]
10 Birth within 7 days of randomisation	3	220	Relative Risk (Random) 95% CI	0.68 [0.56, 0.82]
11 Birth before 37 weeks' gestation	0	0	Relative Risk (Random) 95% CI	Not estimable
12 Birthweight	5	511	Weighted Mean Difference (Random) 95% CI	97.19 [2.90, 191.48]
13 Birthweight < 2500 g	0	0	Relative Risk (Random) 95% CI	Not estimable
14 Neonatal intensive care	0	0	Relative Risk (Random) 95% CI	Not estimable
15 Days in neonatal intensive care unit	1	85	Weighted Mean Difference (Random) 95% CI	0.50 [-12.33, 13.33]
16 Neonatal infection including pneumonia	4	416	Relative Risk (Random) 95% CI	0.33 [0.14, 0.81]
17 Positive neonatal blood culture	2	195	Relative Risk (Random) 95% CI	0.18 [0.05, 0.68]
18 Neonatal necrotising enterocolitis	2	157	Relative Risk (Random) 95% CI	1.25 [0.24, 6.43]
19 Neonatal respiratory distress syndrome	2	157	Relative Risk (Random) 95% CI	0.93 [0.55, 1.58]
20 Treatment with surfactant	0	0	Relative Risk (Random) 95% CI	Not estimable
21 Number of babies requiring ventilation	1	115	Relative Risk (Random) 95% CI	0.90 [0.38, 2.18]
22 Number of babies requiring oxygen therapy	0	0	Relative Risk (Random) 95% CI	Not estimable
23 Neonatal oxygenation > 28 days	1	110	Relative Risk (Random) 95% CI	0.10 [0.01, 1.75]
24 Oxygen treatment > 36 weeks postconceptual age	0	0	Relative Risk (Random) 95% CI	Not estimable
25 Neonatal encephalopathy	0	0	Relative Risk (Random) 95% CI	Not estimable
26 Major cerebral abnormality on ultrasound before discharge	3	267	Relative Risk (Random) 95% CI	0.49 [0.25, 0.97]
27 Serious childhood disability at approximately 2 years	0	0	Relative Risk (Random) 95% CI	Not estimable
28 Perinatal death/death before discharge	5	442	Relative Risk (Random) 95% CI	0.59 [0.30, 1.17]

Comparison 03. Co-amoxiclav versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Maternal death	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Serious maternal morbidity	0	0	Relative Risk (Fixed) 95% CI	Not estimable
03 Major adverse drug reaction	1	2430	Relative Risk (Fixed) 95% CI	Not estimable
04 Maternal infection after delivery prior to discharge	1	2430	Relative Risk (Fixed) 95% CI	0.93 [0.79, 1.08]
05 Chorioamnionitis	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Caesarean section	1	2430	Relative Risk (Fixed) 95% CI	0.95 [0.83, 1.07]
08 Days from birth till discharge of mother	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Birth within 48 hours of randomisation	1	2430	Relative Risk (Fixed) 95% CI	0.75 [0.67, 0.84]
10 Birth within 7 days of randomisation	1	2430	Relative Risk (Fixed) 95% CI	0.91 [0.85, 0.97]
11 Birth before 37 weeks' gestation	1	2430	Relative Risk (Fixed) 95% CI	1.00 [0.97, 1.03]
12 Birthweight	2	2492	Weighted Mean Difference (Fixed) 95% CI	8.26 [-49.84, 66.36]
13 Birthweight < 2500 g	1	2430	Relative Risk (Fixed) 95% CI	1.01 [0.96, 1.06]
14 Neonatal intensive care	2	2492	Relative Risk (Fixed) 95% CI	0.98 [0.94, 1.03]
15 Days in neonatal intensive care unit	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
16 Neonatal infection including pneumonia	1	62	Relative Risk (Fixed) 95% CI	0.33 [0.01, 7.88]
17 Positive neonatal blood culture	1	2430	Relative Risk (Fixed) 95% CI	0.83 [0.63, 1.10]
18 Neonatal necrotising enterocolitis	2	2492	Relative Risk (Fixed) 95% CI	4.60 [1.98, 10.72]
19 Neonatal respiratory distress syndrome	2	2492	Relative Risk (Fixed) 95% CI	0.95 [0.82, 1.09]
20 Treatment with surfactant	1	2430	Relative Risk (Fixed) 95% CI	0.85 [0.71, 1.02]
21 Number of babies requiring ventilation	1	2430	Relative Risk (Fixed) 95% CI	0.91 [0.79, 1.06]
22 Number of babies requiring oxygen therapy	1	2430	Relative Risk (Fixed) 95% CI	0.89 [0.80, 1.00]
23 Neonatal oxygenation > 28 days	1	2430	Relative Risk (Fixed) 95% CI	0.99 [0.77, 1.27]
24 Oxygen treatment > 36 weeks postconceptual age	1	2430	Relative Risk (Fixed) 95% CI	0.92 [0.67, 1.27]
25 Neonatal encephalopathy	0	0	Relative Risk (Fixed) 95% CI	Not estimable
26 Major cerebral abnormality on ultrasound before discharge	2	2492	Relative Risk (Fixed) 95% CI	0.78 [0.55, 1.10]
27 Serious childhood disability at approximately 2 years	0	0	Relative Risk (Fixed) 95% CI	Not estimable
28 Perinatal death/death before discharge	2	2492	Relative Risk (Fixed) 95% CI	0.93 [0.70, 1.25]

Comparison 04. Erythromycin versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Maternal death	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Serious maternal morbidity	0	0	Relative Risk (Fixed) 95% CI	Not estimable
03 Major adverse drug reaction	1	2415	Relative Risk (Fixed) 95% CI	Not estimable
04 Maternal infection after delivery prior to discharge	2	2475	Relative Risk (Fixed) 95% CI	0.95 [0.82, 1.11]
05 Chorioamnionitis	3	332	Relative Risk (Fixed) 95% CI	1.00 [0.63, 1.60]
06 Caesarean section	3	2692	Relative Risk (Fixed) 95% CI	0.99 [0.88, 1.12]
07 Days from randomisation to birth	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Days from birth till discharge of mother	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Birth within 48 hours of randomisation	2	2635	Relative Risk (Fixed) 95% CI	0.84 [0.76, 0.93]
10 Birth within 7 days of randomisation	2	2635	Relative Risk (Fixed) 95% CI	0.95 [0.90, 1.01]
11 Birth before 37 weeks' gestation	2	2470	Relative Risk (Fixed) 95% CI	0.99 [0.96, 1.03]
12 Birthweight	4	2750	Weighted Mean Difference (Fixed) 95% CI	13.18 [-42.39, 68.75]
13 Birthweight < 2500 g	1	2415	Relative Risk (Fixed) 95% CI	1.01 [0.96, 1.06]
14 Neonatal intensive care	1	2415	Relative Risk (Fixed) 95% CI	0.98 [0.93, 1.03]
15 Days in neonatal intensive care unit	1	55	Weighted Mean Difference (Fixed) 95% CI	-5.00 [-13.12, 3.12]
16 Neonatal infection including pneumonia	3	334	Relative Risk (Fixed) 95% CI	0.79 [0.45, 1.37]
17 Positive neonatal blood culture	1	2415	Relative Risk (Fixed) 95% CI	0.70 [0.52, 0.94]
18 Neonatal necrotising enterocolitis	3	2688	Relative Risk (Fixed) 95% CI	1.00 [0.56, 1.80]
19 Neonatal respiratory distress syndrome	4	2746	Relative Risk (Fixed) 95% CI	0.94 [0.82, 1.09]
20 Treatment with surfactant	1	2415	Relative Risk (Fixed) 95% CI	0.83 [0.70, 1.00]
21 Number of babies requiring ventilation	1	2415	Relative Risk (Fixed) 95% CI	0.91 [0.79, 1.06]
22 Number of babies requiring oxygen therapy	1	2415	Relative Risk (Fixed) 95% CI	0.87 [0.78, 0.98]
23 Neonatal oxygenation > 28 days	1	2415	Relative Risk (Fixed) 95% CI	0.85 [0.65, 1.10]
24 Oxygen treatment > 36 weeks postconceptual age	1	2415	Relative Risk (Fixed) 95% CI	0.89 [0.65, 1.23]
25 Neonatal encephalopathy	1	60	Relative Risk (Fixed) 95% CI	Not estimable
26 Major cerebral abnormality on ultrasound before discharge	4	2748	Relative Risk (Fixed) 95% CI	0.92 [0.67, 1.26]
27 Serious childhood disability at approximately 2 years	0	0	Relative Risk (Fixed) 95% CI	Not estimable
28 Perinatal death/death before discharge	4	2750	Relative Risk (Fixed) 95% CI	0.89 [0.67, 1.18]

Comparison 05. Erythromycin versus co-amoxiclav

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Maternal death	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Serious maternal morbidity	0	0	Relative Risk (Fixed) 95% CI	Not estimable
03 Major adverse drug reaction	1	2395	Relative Risk (Fixed) 95% CI	Not estimable
04 Maternal infection after delivery prior to discharge	1	2395	Relative Risk (Fixed) 95% CI	1.02 [0.87, 1.20]
05 Chorioamnionitis	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Caesarean section	1	2395	Relative Risk (Fixed) 95% CI	1.02 [0.90, 1.16]
07 Days from randomisation to birth	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Days from birth till discharge of mother	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Birth within 48 hours of randomisation	1	2395	Relative Risk (Fixed) 95% CI	1.14 [1.02, 1.28]
10 Birth within 7 days of randomisation	1	2395	Relative Risk (Fixed) 95% CI	1.06 [0.99, 1.13]
11 Birth before 37 weeks' gestation	1	2395	Relative Risk (Fixed) 95% CI	0.99 [0.96, 1.03]
12 Birthweight	1	2395	Weighted Mean Difference (Fixed) 95% CI	19.00 [-41.92, 79.92]
13 Birthweight < 2500 g	1	2395	Relative Risk (Fixed) 95% CI	1.00 [0.95, 1.05]
14 Neonatal intensive care	1	2395	Relative Risk (Fixed) 95% CI	1.00 [0.95, 1.05]
15 Days in neonatal intensive care unit	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
16 Neonatal infection including pneumonia	0	0	Relative Risk (Fixed) 95% CI	Not estimable
17 Positive neonatal blood culture	1	2395	Relative Risk (Fixed) 95% CI	0.84 [0.62, 1.15]
18 Neonatal necrotising enterocolitis	1	2395	Relative Risk (Fixed) 95% CI	0.46 [0.23, 0.94]
19 Neonatal respiratory distress syndrome	1	2395	Relative Risk (Fixed) 95% CI	0.99 [0.84, 1.16]
20 Treatment with surfactant	1	2395	Relative Risk (Fixed) 95% CI	0.98 [0.81, 1.19]
21 Number of babies requiring ventilation	1	2395	Relative Risk (Fixed) 95% CI	1.00 [0.86, 1.17]
22 Number of babies requiring oxygen therapy	1	2395	Relative Risk (Fixed) 95% CI	0.98 [0.87, 1.10]
23 Neonatal oxygenation > 28 days	1	2395	Relative Risk (Fixed) 95% CI	0.86 [0.66, 1.12]
24 Oxygen treatment > 36 weeks postconceptual age	1	2395	Relative Risk (Fixed) 95% CI	0.97 [0.70, 1.34]
25 Neonatal encephalopathy	0	0	Relative Risk (Fixed) 95% CI	Not estimable
26 Major cerebral abnormality on ultrasound before discharge	1	2395	Relative Risk (Fixed) 95% CI	1.10 [0.74, 1.63]
27 Serious childhood disability at approximately 2 years	0	0	Relative Risk (Fixed) 95% CI	Not estimable
28 Perinatal death/death before discharge	1	2395	Relative Risk (Fixed) 95% CI	0.90 [0.66, 1.23]

Comparison 07. Antibiotics versus no antibiotic

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Perinatal death/death before discharge	19	6982	Relative Risk (Random) 95% CI	0.87 [0.72, 1.05]

Comparison 08. Antibiotics versus no treatment (no placebo)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Perinatal death/death before discharge	6	571	Relative Risk (Random) 95% CI	0.69 [0.41, 1.14]

Comparison 09. 3 versus 7 day ampicillin regimens

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Maternal death	0	0	Relative Risk (Random) 95% CI	Not estimable
02 Serious maternal morbidity	0	0	Relative Risk (Random) 95% CI	Not estimable
03 Major adverse drug reaction	0	0	Relative Risk (Random) 95% CI	Not estimable
04 Maternal infection after delivery prior to discharge	1	84	Relative Risk (Random) 95% CI	1.25 [0.36, 4.33]
05 Chorioamnionitis	1	84	Relative Risk (Random) 95% CI	0.73 [0.33, 1.63]
06 Caesarean section	1	84	Relative Risk (Random) 95% CI	1.18 [0.72, 1.91]
07 Days from randomisation to birth	0	0	Weighted Mean Difference (Random) 95% CI	Not estimable
08 Days from birth till discharge of mother	0	0	Weighted Mean Difference (Random) 95% CI	Not estimable
09 Birth within 48 hours of randomisation	1	84	Relative Risk (Random) 95% CI	1.14 [0.46, 2.87]
10 Birth within 7 days of randomisation	1	84	Relative Risk (Random) 95% CI	1.00 [0.70, 1.42]
11 Birth before 37 weeks' gestation	0	0	Relative Risk (Random) 95% CI	Not estimable
12 Birthweight	0	0	Weighted Mean Difference (Random) 95% CI	Not estimable
13 Birthweight < 2500 g	0	0	Relative Risk (Random) 95% CI	Not estimable
14 Neonatal intensive care	1	84	Relative Risk (Random) 95% CI	1.00 [0.84, 1.19]
15 Days in neonatal intensive care unit	0	0	Weighted Mean Difference (Random) 95% CI	Not estimable
16 Neonatal infection including pneumonia	0	0	Relative Risk (Random) 95% CI	Not estimable
17 Positive neonatal blood culture	0	0	Relative Risk (Random) 95% CI	Not estimable
18 Neonatal necrotising enterocolitis	2	130	Relative Risk (Random) 95% CI	0.43 [0.07, 2.86]
19 Neonatal respiratory distress syndrome	2	130	Relative Risk (Random) 95% CI	0.96 [0.62, 1.49]
20 Treatment with surfactant	0	0	Relative Risk (Random) 95% CI	Not estimable
21 Number of babies requiring ventilation	0	0	Relative Risk (Random) 95% CI	Not estimable
22 Number of babies requiring oxygen therapy	0	0	Relative Risk (Random) 95% CI	Not estimable

23 Neonatal oxygenation > 28 days	0	0	Relative Risk (Random) 95% CI	Not estimable
24 Oxygen treatment > 36 weeks postconceptual age	0	0	Relative Risk (Random) 95% CI	Not estimable
25 Neonatal encephalopathy	0	0	Relative Risk (Random) 95% CI	Not estimable
26 Neonatal intraventricular haemorrhage	2	130	Relative Risk (Random) 95% CI	0.33 [0.04, 3.12]
27 Serious childhood disability at approximately 2 years	0	0	Relative Risk (Random) 95% CI	Not estimable
28 Perinatal death/death before discharge	2	130	Relative Risk (Random) 95% CI	0.40 [0.05, 2.94]

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Delivery, Obstetric; Fetal Membranes, Premature Rupture [*drug therapy]; Infant, Newborn; Infant, Premature; Infant, Premature, Diseases [prevention & control]; Macrolides; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Antibiotics for preterm rupture of membranes
Authors	Kenyon S, Boulvain M, Neilson J
Contribution of author(s)	Sara Kenyon identified the relevant trials, abstracted the data and wrote the text of the review. Michel Boulvain and Jim Neilson checked the extracted data and helped write the review.
Issue protocol first published	1998/2
Review first published	1998/2
Date of most recent amendment	11 November 2004
Date of most recent SUBSTANTIVE amendment	24 January 2003
What's New	September 2004 This update includes comparisons between different treatment durations (Lewis 2003; Segal 2003) and adds data to the outcome of 'death alone' from a non-placebo controlled trial (Camli 1997). January 2003 The revised title clarifies the inclusion of women who had evidence of uterine activity at randomisation to a trial. The text has been extensively revised. No new data from placebo-controlled, randomised trials have been included since the previous update, but further analysis has been undertaken in an attempt to assess the effectiveness and safety of individual antibiotic agents. New data have been included on the single outcome of perinatal death from non-placebo (but randomised) controlled trials.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author

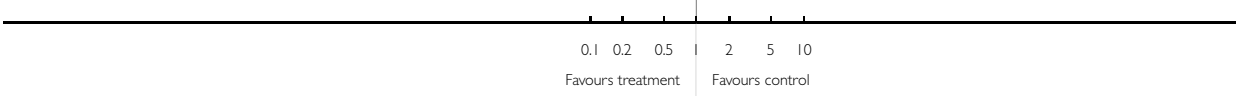
Date new studies found and included/excluded	31 August 2004
Date authors' conclusions section amended	Information not supplied by author
Contact address	Ms Sara Kenyon Senior Research Fellow Division of Reproductive Sciences ORACLE Centre 22-28 Princess Road West PO Box 65 Leicester LE2 7LX UK E-mail: oracle@le.ac.uk Tel: +44 116 2525476 Fax: +44 116 2523154
DOI	10.1002/14651858.CD001058
Cochrane Library number	CD001058
Editorial group	Cochrane Pregnancy and Childbirth Group
Editorial group code	HM-PREG

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Any antibiotic versus placebo, Outcome 01 Maternal death

Review: Antibiotics for preterm rupture of membranes
Comparison: 01 Any antibiotic versus placebo
Outcome: 01 Maternal death

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Almeida 1996	0/59	0/51		0.0	Not estimable
× Johnston 1990	0/40	0/45		0.0	Not estimable
× Mercer 1997	0/299	0/312		0.0	Not estimable
× Svare 1997	0/30	0/37		0.0	Not estimable
Total (95% CI)	428	445		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 01.03. Comparison 01 Any antibiotic versus placebo, Outcome 03 Major adverse drug reaction

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 03 Major adverse drug reaction

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Almeida 1996	0/59	0/51		0.0	Not estimable
× Kenyon 2001	0/3584	0/1225		0.0	Not estimable
× Mercer 1997	0/299	0/312		0.0	Not estimable
× Svare 1997	0/30	0/37		0.0	Not estimable
Total (95% CI)	3972	1625		0.0	Not estimable

Total events: 0 (Treatment), 0 (Control)

Test for heterogeneity: not applicable

Test for overall effect: not applicable

Analysis 01.04. Comparison 01 Any antibiotic versus placebo, Outcome 04 Maternal infection after delivery prior to discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 04 Maternal infection after delivery prior to discharge

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	1/59	27/51		6.2	0.03 [0.00, 0.23]
Garcia 1995	8/30	7/30		19.0	1.14 [0.47, 2.75]
Kenyon 2001	686/3584	262/1225		39.1	0.89 [0.79, 1.02]
Mercer 1997	33/299	36/312		31.2	0.96 [0.61, 1.49]
Svare 1997	2/30	1/37		4.5	2.47 [0.23, 25.91]
Total (95% CI)	4002	1655		100.0	0.82 [0.48, 1.39]

Total events: 730 (Treatment), 333 (Control)

Test for heterogeneity chi-square=12.80 df=4 p=0.01 I^2 =68.8%

Test for overall effect z=0.75 p=0.5

Analysis 01.05. Comparison 01 Any antibiotic versus placebo, Outcome 05 Chorioamnionitis

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 05 Chorioamnionitis

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	3/59	21/51		7.6	0.12 [0.04, 0.39]
Ernest 1994	3/77	9/67		6.8	0.29 [0.08, 1.03]
Garcia 1995	3/30	1/30		3.0	3.00 [0.33, 27.23]
Grable 1996	4/31	8/29		8.0	0.47 [0.16, 1.39]
Johnston 1990	3/40	16/45		7.5	0.21 [0.07, 0.67]
Kurki 1992	1/50	7/51		3.4	0.15 [0.02, 1.14]
Lockwood 1993	10/35	10/37		11.3	1.06 [0.50, 2.23]
McGregor 1991	7/28	6/27		9.2	1.13 [0.43, 2.92]
Mercer 1992	18/105	22/112		13.3	0.87 [0.50, 1.53]
Mercer 1997	69/299	101/312		16.3	0.71 [0.55, 0.93]
Ovalle Salas 1997	2/42	11/45		5.7	0.19 [0.05, 0.83]
Svare 1997	6/30	5/37		8.1	1.48 [0.50, 4.38]
Total (95% CI)	826	843		100.0	0.57 [0.37, 0.86]

Total events: 129 (Treatment), 217 (Control)

Test for heterogeneity chi-square=27.51 df=11 p=0.004 I^2 =60.0%

Test for overall effect z=2.65 p=0.008

Analysis 01.06. Comparison 01 Any antibiotic versus placebo, Outcome 06 Caesarean section

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

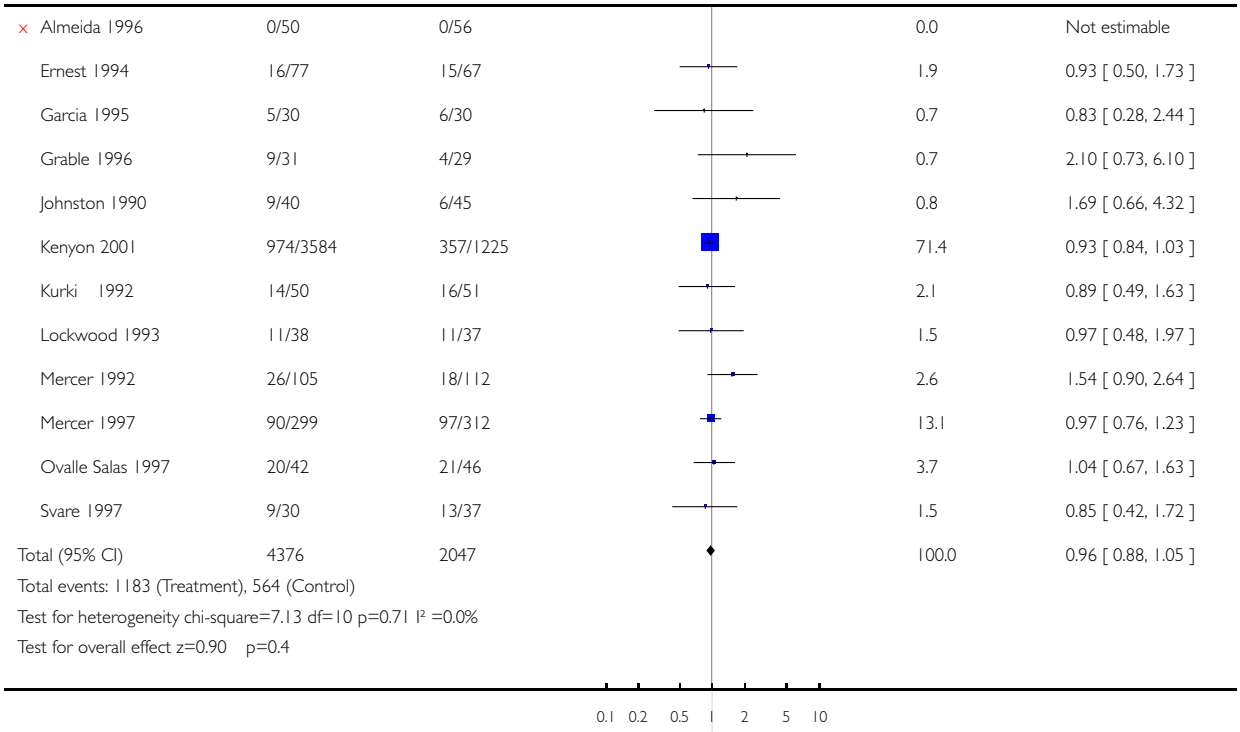
Outcome: 06 Caesarean section

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Almeida 1996	0/50	0/56		0.0	Not estimable
Ernest 1994	16/77	15/67		1.9	0.93 [0.50, 1.73]
Garcia 1995	5/30	6/30		0.7	0.83 [0.28, 2.44]
Grable 1996	9/31	4/29		0.7	2.10 [0.73, 6.10]
Johnston 1990	9/40	6/45		0.8	1.69 [0.66, 4.32]
Kenyon 2001	974/3584	357/1225		71.4	0.93 [0.84, 1.03]
Kurki 1992	14/50	16/51		2.1	0.89 [0.49, 1.63]
Lockwood 1993	11/38	11/37		1.5	0.97 [0.48, 1.97]
Mercer 1992	26/105	18/112		2.6	1.54 [0.90, 2.64]
Mercer 1997	90/299	97/312		13.1	0.97 [0.76, 1.23]
Ovalle Salas 1997	20/42	21/46		3.7	1.04 [0.67, 1.63]
Svare 1997	9/30	13/37		1.5	0.85 [0.42, 1.72]
Total (95% CI)	4376	2047		100.0	0.96 [0.88, 1.05]

Total events: 1183 (Treatment), 564 (Control)

Test for heterogeneity chi-square=7.13 df=10 p=0.71 I^2 =0.0%

Test for overall effect z=0.90 p=0.4



Analysis 01.07. Comparison 01 Any antibiotic versus placebo, Outcome 07 Days from randomisation to birth

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 07 Days from randomisation to birth

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Total (95% CI)	0	0		0.0	Not estimable

Test for heterogeneity: not applicable

Test for overall effect: not applicable

Analysis 01.08. Comparison 01 Any antibiotic versus placebo, Outcome 08 Days from birth till discharge of mother

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 08 Days from birth till discharge of mother

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.09. Comparison 01 Any antibiotic versus placebo, Outcome 09 Birth within 48 hours of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 09 Birth within 48 hours of randomisation

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Grable 1996	3/31	12/29		2.8	0.23 [0.07, 0.75]
Johnston 1990	1/40	6/45		0.9	0.19 [0.02, 1.49]
Kenyon 2001	1153/3584	498/1225		36.4	0.79 [0.73, 0.86]
Lockwood 1993	12/38	24/37		10.7	0.49 [0.29, 0.82]
Mercer 1992	37/106	57/114		19.7	0.70 [0.51, 0.96]
Mercer 1997	82/299	114/312		25.4	0.75 [0.59, 0.95]
Svare 1997	8/30	6/37		4.1	1.64 [0.64, 4.22]
Total (95% CI)	4128	1799		100.0	0.71 [0.58, 0.87]
Total events: 1296 (Treatment), 717 (Control)					
Test for heterogeneity chi-square=12.11 df=6 p=0.06 I^2 =50.5%					
Test for overall effect z=3.32 p=0.0009					

Analysis 01.10. Comparison 01 Any antibiotic versus placebo, Outcome 10 Birth within 7 days of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 10 Birth within 7 days of randomisation

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Grable 1996	17/31	21/29		6.9	0.76 [0.51, 1.12]
Johnston 1990	22/40	37/45		9.6	0.67 [0.49, 0.91]
Kenyon 2001	2067/3584	775/1225		29.1	0.91 [0.87, 0.96]
Lockwood 1993	22/38	33/37		10.4	0.65 [0.48, 0.87]
Mercer 1992	77/106	94/114		20.9	0.88 [0.76, 1.02]
Mercer 1997	166/299	229/312		23.1	0.76 [0.67, 0.85]
Total (95% CI)	4098	1762		100.0	0.80 [0.71, 0.90]
Total events: 2371 (Treatment), 1189 (Control)					
Test for heterogeneity chi-square=15.36 df=5 p=0.009 I^2 =67.4%					
Test for overall effect z=3.72 p=0.0002					

Analysis 01.11. Comparison 01 Any antibiotic versus placebo, Outcome 11 Birth before 37 weeks' gestation

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 11 Birth before 37 weeks' gestation

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Kenyon 2001	3049/3584	1041/1225		96.9	1.00 [0.97, 1.03]
× McGregor 1991	28/28	27/27		0.0	Not estimable
Svare 1997	27/30	34/37		3.1	0.98 [0.84, 1.14]
Total (95% CI)	3642	1289		100.0	1.00 [0.97, 1.03]
Total events: 3104 (Treatment), 1102 (Control)					
Test for heterogeneity chi-square=0.08 df=1 p=0.78 I^2 =0.0%					
Test for overall effect z=0.03 p=1					

Analysis 01.12. Comparison 01 Any antibiotic versus placebo, Outcome 12 Birthweight

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 12 Birthweight

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Almeida 1996	50	2094.00 (459.00)	56	2045.00 (462.00)		5.0	49.00 [-126.58, 224.58]
Cox 1995	31	1282.00 (409.00)	31	1305.00 (413.00)		3.7	-23.00 [-227.61, 181.61]
Ernest 1994	77	1896.00 (556.00)	67	1808.00 (716.00)		3.5	88.00 [-123.70, 299.70]
Garcia 1995	30	2022.00 (607.00)	30	2170.00 (799.70)		1.2	-148.00 [-507.26, 211.26]
Johnston 1990	40	1897.00 (600.00)	45	1587.00 (592.00)		2.4	310.00 [56.05, 563.95]
Kenyon 2001	3584	2103.00 (764.00)	1225	2072.00 (769.00)		44.0	31.00 [-18.80, 80.80]
Kurki 1992	50	2124.00 (390.00)	51	2090.00 (516.00)		4.8	34.00 [-144.16, 212.16]
Lockwood 1993	38	1837.00 (759.00)	37	1697.00 (581.00)		1.7	140.00 [-165.42, 445.42]
McGregor 1991	28	1638.50 (530.80)	27	1741.40 (444.00)		2.3	-102.90 [-361.17, 155.37]
Mercer 1992	106	1771.00 (653.00)	114	1817.00 (637.00)		5.3	-46.00 [-216.66, 124.66]
Mercer 1997	299	1549.00 (497.00)	312	1457.00 (508.00)		21.3	92.00 [12.31, 171.69]
Ovalle Salas 1997	42	1849.00 (458.40)	43	1645.00 (521.40)		3.6	204.00 [-4.58, 412.58]
Svare 1997	30	1962.00 (712.00)	37	1838.00 (785.00)		1.2	124.00 [-235.02, 483.02]
Total (95% CI)	4405		2075			100.0	51.53 [11.61, 91.44]

Test for heterogeneity chi-square=12.62 df=12 p=0.40 I^2 =4.9%

Test for overall effect z=2.53 p=0.01

Analysis 01.13. Comparison 01 Any antibiotic versus placebo, Outcome 13 Birthweight < 2500 g

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 13 Birthweight < 2500 g

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Kenyon 2001	2581/3584	880/1225		96.9	1.00 [0.96, 1.04]
Svare 1997	24/30	31/37		3.1	0.95 [0.76, 1.20]
Total (95% CI)	3614	1262		100.0	1.00 [0.96, 1.04]

Total events: 2605 (Treatment), 911 (Control)

Test for heterogeneity chi-square=0.17 df=1 p=0.68 I^2 =0.0%

Test for overall effect z=0.05 p=1

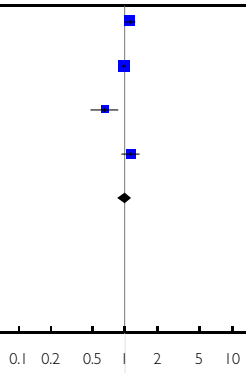
Analysis 01.14. Comparison 01 Any antibiotic versus placebo, Outcome 14 Neonatal intensive care

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 14 Neonatal intensive care

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cox 1995	31/31	28/31		29.3	1.11 [0.99, 1.24]
Kenyon 2001	2502/3584	880/1225		34.9	0.97 [0.93, 1.01]
Ovalle Salas 1997	23/42	37/43		14.2	0.64 [0.47, 0.86]
Svare 1997	27/30	30/37		21.7	1.11 [0.91, 1.35]
Total (95% CI)	3687	1336		100.0	0.98 [0.85, 1.13]
Total events: 2583 (Treatment), 975 (Control)					
Test for heterogeneity chi-square=14.59 df=3 p=0.002 I^2 =79.4%					
Test for overall effect z=0.29 p=0.8					



Analysis 01.15. Comparison 01 Any antibiotic versus placebo, Outcome 15 Days in neonatal intensive care unit

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 15 Days in neonatal intensive care unit

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Johnston 1990	40	12.30 (35.90)	45	11.80 (21.90)		13.5	0.50 [-12.33, 13.33]
McGregor 1991	28	9.50 (10.50)	27	14.50 (18.90)		33.8	-5.00 [-13.12, 3.12]
Ovalle Salas 1997	42	6.70 (9.12)	43	13.20 (19.70)		52.7	-6.50 [-13.00, 0.00]
Total (95% CI)	110		115			100.0	-5.05 [-9.77, -0.33]
Test for heterogeneity chi-square=0.91 df=2 p=0.63 I^2 =0.0%							
Test for overall effect z=2.10 p=0.04							

Analysis 01.16. Comparison 01 Any antibiotic versus placebo, Outcome 16 Neonatal infection including pneumonia

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 16 Neonatal infection including pneumonia

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cox 1995	0/31	1/31		0.6	0.33 [0.01, 7.88]
Ernest 1994	0/77	2/67		0.7	0.17 [0.01, 3.57]
Garcia 1995	4/30	5/30		4.2	0.80 [0.24, 2.69]
Johnston 1990	3/40	11/45		4.3	0.31 [0.09, 1.02]
Kurki 1992	0/57	1/58		0.6	0.34 [0.01, 8.15]
Lockwood 1993	2/37	4/35		2.3	0.47 [0.09, 2.42]
McGregor 1991	1/24	1/27		0.8	1.13 [0.07, 17.02]
Mercer 1992	14/109	19/114		15.2	0.77 [0.41, 1.46]
Mercer 1997	46/299	67/312		53.5	0.72 [0.51, 1.01]
Ovalle Salas 1997	7/42	7/43		6.7	1.02 [0.39, 2.67]
Svare 1997	7/30	16/37		11.1	0.54 [0.26, 1.14]
Total (95% CI)	776	799		100.0	0.68 [0.53, 0.87]
Total events: 84 (Treatment), 134 (Control)					
Test for heterogeneity chi-square=4.56 df=10 p=0.92 I^2 =0.0%					
Test for overall effect z=3.04 p=0.002					

Analysis 01.17. Comparison 01 Any antibiotic versus placebo, Outcome 17 Positive neonatal blood culture

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 17 Positive neonatal blood culture

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	2/59	10/51		22.1	0.17 [0.04, 0.75]
Johnston 1990	0/40	2/45		7.3	0.22 [0.01, 4.54]
Kenyon 2001	233/3584	100/1225		59.5	0.80 [0.64, 1.00]
Svare 1997	1/30	2/37		11.1	0.62 [0.06, 6.48]
Total (95% CI)	3713	1358		100.0	0.50 [0.21, 1.19]
Total events: 236 (Treatment), 114 (Control)					
Test for heterogeneity chi-square=4.76 df=3 p=0.19 I^2 =37.0%					
Test for overall effect z=1.56 p=0.1					

Analysis 01.18. Comparison 01 Any antibiotic versus placebo, Outcome 18 Neonatal necrotising enterocolitis

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 18 Neonatal necrotising enterocolitis

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cox 1995	5/31	0/31		3.3	11.00 [0.63, 190.79]
Grable 1996	1/31	1/29		3.6	0.94 [0.06, 14.27]
Johnston 1990	2/40	3/45		7.8	0.75 [0.13, 4.26]
Kenyon 2001	55/3584	6/1225		20.0	3.13 [1.35, 7.26]
Lockwood 1993	2/37	0/35		3.0	4.74 [0.24, 95.33]
McGregor 1991	2/26	4/27		8.8	0.52 [0.10, 2.60]
Mercer 1992	8/106	12/114		19.7	0.72 [0.31, 1.69]
Mercer 1997	24/299	27/312		28.1	0.93 [0.55, 1.57]
Ovalle Salas 1997	0/42	1/43		2.7	0.34 [0.01, 8.14]
Svare 1997	0/30	1/37		2.8	0.41 [0.02, 9.68]
Total (95% CI)	4226	1898		100.0	1.14 [0.66, 1.97]
Total events: 99 (Treatment), 55 (Control)					
Test for heterogeneity chi-square=13.26 df=9 p=0.15 I^2 =32.2%					
Test for overall effect z=0.47 p=0.6					

Analysis 01.19. Comparison 01 Any antibiotic versus placebo, Outcome 19 Neonatal respiratory distress syndrome

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 19 Neonatal respiratory distress syndrome

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Cox 1995	27/31	21/31		15.1	1.29 [0.97, 1.70]
Garcia 1995	7/30	6/30		2.0	1.17 [0.44, 3.06]
Grable 1996	6/31	9/29		2.3	0.62 [0.25, 1.53]
Johnston 1990	6/40	11/45		2.3	0.61 [0.25, 1.51]
Kenyon 2001	719/3584	266/1225		28.0	0.92 [0.82, 1.05]
Lockwood 1993	23/37	20/35		10.0	1.09 [0.74, 1.59]
McGregor 1991	15/26	15/25		7.6	0.96 [0.61, 1.52]
Mercer 1992	27/106	24/114		7.0	1.21 [0.75, 1.96]
Mercer 1997	121/299	152/312		22.9	0.83 [0.69, 0.99]
Ovalle Salas 1997	4/42	13/43		1.8	0.32 [0.11, 0.89]
Svare 1997	3/30	3/37		0.8	1.23 [0.27, 5.67]
Total (95% CI)	4256	1926		100.0	0.95 [0.83, 1.10]

Total events: 958 (Treatment), 540 (Control)

Test for heterogeneity chi-square=14.98 df=10 p=0.13 I^2 =33.3%

Test for overall effect z=0.63 p=0.5

Analysis 01.20. Comparison 01 Any antibiotic versus placebo, Outcome 20 Treatment with surfactant

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 20 Treatment with surfactant

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Kenyon 2001	526/3584	217/1225		100.0	0.83 [0.72, 0.96]
Total (95% CI)	3584	1225		100.0	0.83 [0.72, 0.96]

Total events: 526 (Treatment), 217 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=2.56 p=0.01

Analysis 01.21. Comparison 01 Any antibiotic versus placebo, Outcome 21 Number of babies requiring ventilation

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 21 Number of babies requiring ventilation

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Kenyon 2001	749/3584	283/1225		98.2	0.90 [0.80, 1.02]
Kurki 1992	8/57	9/58		1.8	0.90 [0.38, 2.18]
Total (95% CI)	3641	1283		100.0	0.90 [0.80, 1.02]
Total events: 757 (Treatment), 292 (Control)					
Test for heterogeneity chi-square=0.00 df=1 p=1.00 I^2 =0.0%					
Test for overall effect z=1.65 p=0.1					

Analysis 01.22. Comparison 01 Any antibiotic versus placebo, Outcome 22 Number of babies requiring oxygen therapy

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 22 Number of babies requiring oxygen therapy

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Kenyon 2001	1125/3584	436/1225		100.0	0.88 [0.81, 0.96]
Total (95% CI)	3584	1225		100.0	0.88 [0.81, 0.96]
Total events: 1125 (Treatment), 436 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.75 p=0.006					

Analysis 01.23. Comparison 01 Any antibiotic versus placebo, Outcome 23 Neonatal oxygenation > 28 days

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 23 Neonatal oxygenation > 28 days

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	0/59	4/51		1.4	0.10 [0.01, 1.75]
Kenyon 2001	299/3584	114/1225		57.7	0.90 [0.73, 1.10]
Mercer 1997	39/299	64/312		39.8	0.64 [0.44, 0.92]
Svare 1997	0/30	1/37		1.1	0.41 [0.02, 9.68]
Total (95% CI)	3972	1625		100.0	0.75 [0.53, 1.06]
Total events: 338 (Treatment), 183 (Control)					
Test for heterogeneity chi-square=4.88 df=3 p=0.18 I^2 =38.5%					
Test for overall effect z=1.64 p=0.1					

Analysis 01.24. Comparison 01 Any antibiotic versus placebo, Outcome 24 Oxygen treatment > 36 weeks postconceptual age

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 24 Oxygen treatment > 36 weeks postconceptual age

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Kenyon 2001	202/3584	76/1225		100.0	0.91 [0.70, 1.17]
Total (95% CI)	3584	1225		100.0	0.91 [0.70, 1.17]
Total events: 202 (Treatment), 76 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.74 p=0.5					

Analysis 01.25. Comparison 01 Any antibiotic versus placebo, Outcome 25 Neonatal encephalopathy

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 25 Neonatal encephalopathy

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Garcia 1995	0/30	0/30		0.0	Not estimable
Total (95% CI)	30	30		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.26. Comparison 01 Any antibiotic versus placebo, Outcome 26 Major cerebral abnormality on ultrasound before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 26 Major cerebral abnormality on ultrasound before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	0/59	1/51		0.4	0.29 [0.01, 6.94]
Cox 1995	7/31	8/31		4.5	0.88 [0.36, 2.12]
Garcia 1995	2/30	1/30		0.6	2.00 [0.19, 20.90]
× Grable 1996	0/31	0/29		0.0	Not estimable
Johnston 1990	5/40	14/45		4.1	0.40 [0.16, 1.02]
Kenyon 2001	142/3584	61/1225		41.2	0.80 [0.59, 1.07]
Lockwood 1993	5/37	7/35		3.2	0.68 [0.24, 1.93]
McGregor 1991	5/26	1/27		0.8	5.19 [0.65, 41.50]
Mercer 1992	11/106	14/114		6.4	0.85 [0.40, 1.78]
Mercer 1997	57/299	68/312		35.8	0.87 [0.64, 1.20]
Ovalle Salas 1997	3/42	7/43		2.1	0.44 [0.12, 1.58]
Svare 1997	3/30	1/37		0.7	3.70 [0.41, 33.77]
Total (95% CI)	4315	1979		100.0	0.82 [0.68, 0.98]
Total events: 240 (Treatment), 183 (Control)					
Test for heterogeneity chi-square=9.32 df=10 p=0.50 I^2 =0.0%					
Test for overall effect z=2.12 p=0.03					

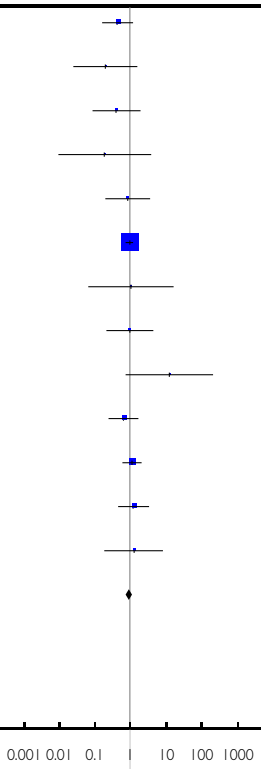
Analysis 01.28. Comparison 01 Any antibiotic versus placebo, Outcome 28 Perinatal death/death before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 01 Any antibiotic versus placebo

Outcome: 28 Perinatal death/death before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	5/59	10/51		4.0	0.43 [0.16, 1.18]
Cox 1995	1/31	5/31		0.9	0.20 [0.02, 1.61]
Garcia 1995	2/30	5/30		1.7	0.40 [0.08, 1.90]
Grable 1996	0/31	2/29		0.5	0.19 [0.01, 3.75]
Johnston 1990	3/40	4/45		2.0	0.84 [0.20, 3.54]
Kenyon 2001	226/3584	82/1225		68.3	0.94 [0.74, 1.20]
Kurki 1992	1/57	1/58		0.5	1.02 [0.07, 15.88]
Lockwood 1993	3/37	3/35		1.7	0.95 [0.20, 4.38]
McGregor 1991	6/28	0/27		0.5	12.55 [0.74, 212.52]
Mercer 1992	6/106	10/114		4.3	0.65 [0.24, 1.71]
Mercer 1997	19/299	18/312		10.4	1.10 [0.59, 2.06]
Ovalle Salas 1997	7/42	6/43		4.0	1.19 [0.44, 3.26]
Svare 1997	2/30	2/37		1.1	1.23 [0.18, 8.25]
Total (95% CI)	4374	2037		100.0	0.90 [0.74, 1.10]
Total events: 281 (Treatment), 148 (Control)					
Test for heterogeneity chi-square=10.88 df=12 p=0.54 I^2 =0.0%					
Test for overall effect z=1.00 p=0.3					



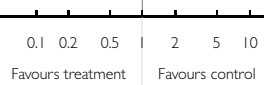
Analysis 02.01. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 01 Maternal death

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 01 Maternal death

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Almeida 1996	0/59	0/51		0.0	Not estimable
× Johnston 1990	0/40	0/45		0.0	Not estimable
Total (95% CI)	99	96		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



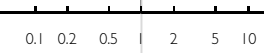
Analysis 02.03. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 03 Major adverse drug reaction

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 03 Major adverse drug reaction

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Almeida 1996	0/59	0/51		0.0	Not estimable
Total (95% CI)	59	51		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 02.04. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 04 Maternal infection after delivery prior to discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 04 Maternal infection after delivery prior to discharge

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	1/59	27/51		100.0	0.03 [0.00, 0.23]
Total (95% CI)	59	51		100.0	0.03 [0.00, 0.23]
Total events: 1 (Treatment), 27 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.44 p=0.0006					

Analysis 02.05. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 05 Chorioamnionitis

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 05 Chorioamnionitis

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	3/59	21/51		21.0	0.12 [0.04, 0.39]
Ernest 1994	3/77	9/67		19.8	0.29 [0.08, 1.03]
Johnston 1990	3/40	16/45		21.0	0.21 [0.07, 0.67]
Kurki 1992	1/50	7/51		12.8	0.15 [0.02, 1.14]
Lockwood 1993	10/35	10/37		25.3	1.06 [0.50, 2.23]
Total (95% CI)	261	251		100.0	0.29 [0.11, 0.77]
Total events: 20 (Treatment), 63 (Control)					
Test for heterogeneity chi-square=13.74 df=4 p=0.008 I^2 =70.9%					
Test for overall effect z=2.49 p=0.01					

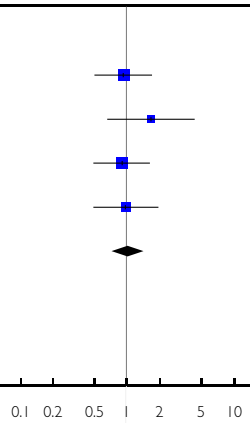
Analysis 02.06. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 06 Caesarean section

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 06 Caesarean section

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Almeida 1996	0/50	0/56		0.0	Not estimable
Ernest 1994	16/77	15/67		30.3	0.93 [0.50, 1.73]
Johnston 1990	9/40	6/45		13.3	1.69 [0.66, 4.32]
Kurki 1992	14/50	16/51		32.5	0.89 [0.49, 1.63]
Lockwood 1993	11/38	11/37		23.9	0.97 [0.48, 1.97]
Total (95% CI)	255	256		100.0	1.00 [0.71, 1.41]
Total events: 50 (Treatment), 48 (Control)					
Test for heterogeneity chi-square=1.39 df=3 p=0.71 I^2 =0.0%					
Test for overall effect z=0.02 p=1					



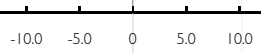
Analysis 02.07. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 07 Days from randomisation to birth

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 07 Days from randomisation to birth

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 02.08. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 08 Days from birth till discharge of mother

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 08 Days from birth till discharge of mother

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 02.09. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 09 Birth within 48 hours of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 09 Birth within 48 hours of randomisation

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Grable 1996	3/31	12/29		16.9	0.23 [0.07, 0.75]
Johnston 1990	1/40	6/45		5.4	0.19 [0.02, 1.49]
Lockwood 1993	12/38	24/37		77.7	0.49 [0.29, 0.82]
Total (95% CI)	109	111		100.0	0.41 [0.25, 0.66]
Total events: 16 (Treatment), 42 (Control)					
Test for heterogeneity chi-square=2.04 df=2 p=0.36 I^2 =1.8%					
Test for overall effect z=3.65 p=0.0003					

Analysis 02.10. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 10 Birth within 7 days of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 10 Birth within 7 days of randomisation

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Grable 1996	17/31	21/29		23.0	0.76 [0.51, 1.12]
Johnston 1990	22/40	37/45		36.2	0.67 [0.49, 0.91]
Lockwood 1993	22/38	33/37		40.8	0.65 [0.48, 0.87]
Total (95% CI)	109	111		100.0	0.68 [0.56, 0.82]
Total events: 61 (Treatment), 91 (Control)					
Test for heterogeneity chi-square=0.40 df=2 p=0.82 I² =0.0%					
Test for overall effect z=4.03 p=0.00005					

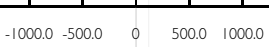
Analysis 02.12. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 12 Birthweight

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 12 Birthweight

Study	Treatment N	Mean(SD)	Control N	Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Almeida 1996	50	2094.00 (459.00)	56	2045.00 (462.00)		28.8	49.00 [-126.58, 224.58]
Ernest 1994	77	1896.00 (556.00)	67	1808.00 (716.00)		19.8	88.00 [-123.70, 299.70]
Johnston 1990	40	1897.00 (600.00)	45	1587.00 (592.00)		13.8	310.00 [56.05, 563.95]
Kurki 1992	50	2124.00 (390.00)	51	2090.00 (516.00)		28.0	34.00 [-144.16, 212.16]
Lockwood 1993	38	1837.00 (759.00)	37	1697.00 (581.00)		9.5	140.00 [-165.42, 445.42]
Total (95% CI)	255		256			100.0	97.19 [2.90, 191.48]
Test for heterogeneity chi-square=3.55 df=4 p=0.47 I² =0.0%							
Test for overall effect z=2.02 p=0.04							



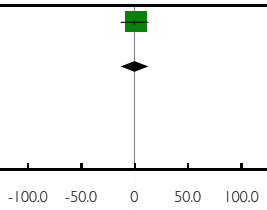
Analysis 02.15. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 15 Days in neonatal intensive care unit

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 15 Days in neonatal intensive care unit

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Johnston 1990	40	12.30 (35.90)	45	11.80 (21.90)		100.0	0.50 [-12.33, 13.33]
Total (95% CI)	40		45			100.0	0.50 [-12.33, 13.33]
Test for heterogeneity: not applicable							
Test for overall effect z=0.08 p=0.9							



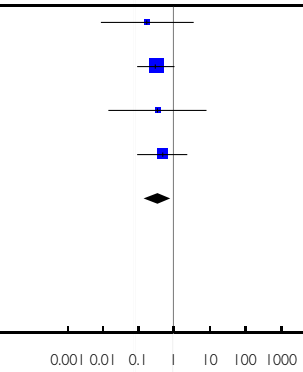
Analysis 02.16. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 16 Neonatal infection including pneumonia

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 16 Neonatal infection including pneumonia

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Ernest 1994	0/77	2/67		8.6	0.17 [0.01, 3.57]
Johnston 1990	3/40	11/45		54.2	0.31 [0.09, 1.02]
Kurki 1992	0/57	1/58		7.8	0.34 [0.01, 8.15]
Lockwood 1993	2/37	4/35		29.4	0.47 [0.09, 2.42]
Total (95% CI)	211	205		100.0	0.33 [0.14, 0.81]
Total events: 5 (Treatment), 18 (Control)					
Test for heterogeneity chi-square=0.37 df=3 p=0.95 I^2 =0.0%					
Test for overall effect z=2.42 p=0.02					



Analysis 02.17. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 17 Positive neonatal blood culture

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 17 Positive neonatal blood culture

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	2/59	10/51		80.7	0.17 [0.04, 0.75]
Johnston 1990	0/40	2/45		19.3	0.22 [0.01, 4.54]
Total (95% CI)	99	96		100.0	0.18 [0.05, 0.68]
Total events: 2 (Treatment), 12 (Control)					
Test for heterogeneity chi-square=0.02 df=1 p=0.88 I^2 =0.0%					
Test for overall effect z=2.53 p=0.01					

Analysis 02.18. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 18 Neonatal necrotising enterocolitis

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 18 Neonatal necrotising enterocolitis

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Johnston 1990	2/40	3/45		72.3	0.75 [0.13, 4.26]
Lockwood 1993	2/37	0/35		27.7	4.74 [0.24, 95.33]
Total (95% CI)	77	80		100.0	1.25 [0.24, 6.43]
Total events: 4 (Treatment), 3 (Control)					
Test for heterogeneity chi-square=1.12 df=1 p=0.29 I^2 =10.4%					
Test for overall effect z=0.27 p=0.8					

Analysis 02.19. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 19 Neonatal respiratory distress syndrome

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 19 Neonatal respiratory distress syndrome

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Johnston 1990	6/40	11/45		26.5	0.61 [0.25, 1.51]
Lockwood 1993	23/37	20/35		73.5	1.09 [0.74, 1.59]
Total (95% CI)	77	80		100.0	0.93 [0.55, 1.58]
Total events: 29 (Treatment), 31 (Control)					
Test for heterogeneity chi-square=1.48 df=1 p=0.22 I^2 =32.2%					
Test for overall effect z=0.25 p=0.8					

Analysis 02.21. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 21 Number of babies requiring ventilation

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 21 Number of babies requiring ventilation

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Kurki 1992	8/57	9/58		100.0	0.90 [0.38, 2.18]
Total (95% CI)	57	58		100.0	0.90 [0.38, 2.18]
Total events: 8 (Treatment), 9 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.22 p=0.8					

Analysis 02.23. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 23 Neonatal oxygenation > 28 days

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 23 Neonatal oxygenation > 28 days

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	0/59	4/51		100.0	0.10 [0.01, 1.75]
Total (95% CI)	59	51		100.0	0.10 [0.01, 1.75]
Total events: 0 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.58 p=0.1					

Analysis 02.26. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 26 Major cerebral abnormality on ultrasound before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 26 Major cerebral abnormality on ultrasound before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	0/59	1/51		4.6	0.29 [0.01, 6.94]
Johnston 1990	5/40	14/45		53.6	0.40 [0.16, 1.02]
Lockwood 1993	5/37	7/35		41.8	0.68 [0.24, 1.93]
Total (95% CI)	136	131		100.0	0.49 [0.25, 0.97]
Total events: 10 (Treatment), 22 (Control)					
Test for heterogeneity chi-square=0.64 df=2 p=0.72 I^2 =0.0%					
Test for overall effect z=2.05 p=0.04					

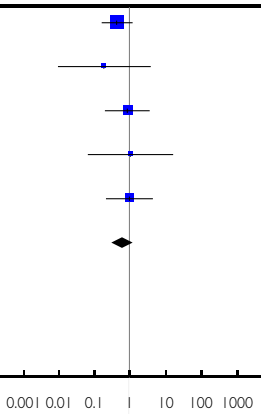
Analysis 02.28. Comparison 02 All penicillins(excluding co-amoxiclav) versus placebo, Outcome 28 Perinatal death/death before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 02 All penicillins(excluding co-amoxiclav) versus placebo

Outcome: 28 Perinatal death/death before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	5/59	10/51		46.1	0.43 [0.16, 1.18]
Grable 1996	0/31	2/29		5.2	0.19 [0.01, 3.75]
Johnston 1990	3/40	4/45		22.7	0.84 [0.20, 3.54]
Kurki 1992	1/57	1/58		6.2	1.02 [0.07, 15.88]
Lockwood 1993	3/37	3/35		19.9	0.95 [0.20, 4.38]
Total (95% CI)	224	218		100.0	0.59 [0.30, 1.17]
Total events: 12 (Treatment), 20 (Control)					
Test for heterogeneity chi-square=1.69 df=4 p=0.79 I^2 =0.0%					
Test for overall effect z=1.50 p=0.1					



Analysis 03.03. Comparison 03 Co-amoxiclav versus placebo, Outcome 03 Major adverse drug reaction

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 03 Major adverse drug reaction

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Kenyon 2001	0/1205	0/1225		0.0	Not estimable
Total (95% CI)	1205	1225		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 03.04. Comparison 03 Co-amoxiclav versus placebo, Outcome 04 Maternal infection after delivery prior to discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 04 Maternal infection after delivery prior to discharge

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	239/1205	262/1225		100.0	0.93 [0.79, 1.08]
Total (95% CI)	1205	1225		100.0	0.93 [0.79, 1.08]
Total events: 239 (Treatment), 262 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.95 p=0.3					

Analysis 03.06. Comparison 03 Co-amoxiclav versus placebo, Outcome 06 Caesarean section

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 06 Caesarean section

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	332/1205	357/1225		100.0	0.95 [0.83, 1.07]
Total (95% CI)	1205	1225		100.0	0.95 [0.83, 1.07]
Total events: 332 (Treatment), 357 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.87 p=0.4					

Analysis 03.08. Comparison 03 Co-amoxiclav versus placebo, Outcome 08 Days from birth till discharge of mother

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 08 Days from birth till discharge of mother

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 03.09. Comparison 03 Co-amoxiclav versus placebo, Outcome 09 Birth within 48 hours of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 09 Birth within 48 hours of randomisation

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	367/1205	498/1225		100.0	0.75 [0.67, 0.84]
Total (95% CI)	1205	1225		100.0	0.75 [0.67, 0.84]
Total events: 367 (Treatment), 498 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=5.20 p<0.00001					

Analysis 03.10. Comparison 03 Co-amoxiclav versus placebo, Outcome 10 Birth within 7 days of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 10 Birth within 7 days of randomisation

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	695/1205	775/1225		100.0	0.91 [0.85, 0.97]
Total (95% CI)	1205	1225		100.0	0.91 [0.85, 0.97]
Total events: 695 (Treatment), 775 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.81 p=0.005					

Analysis 03.11. Comparison 03 Co-amoxiclav versus placebo, Outcome 11 Birth before 37 weeks' gestation

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 11 Birth before 37 weeks' gestation

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	1025/1205	1041/1225		100.0	1.00 [0.97, 1.03]
Total (95% CI)	1205	1225		100.0	1.00 [0.97, 1.03]
Total events: 1025 (Treatment), 1041 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.06 p=1					

Analysis 03.12. Comparison 03 Co-amoxiclav versus placebo, Outcome 12 Birthweight

Review: Antibiotics for preterm rupture of membranes

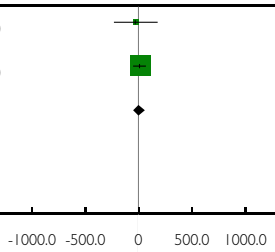
Comparison: 03 Co-amoxiclav versus placebo

Outcome: 12 Birthweight

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Cox 1995	31	1282.00 (409.00)	31	1305.00 (413.00)		8.1	-23.00 [-227.61, 181.61]
Kenyon 2001	1205	2083.00 (755.00)	1225	2072.00 (769.00)		91.9	11.00 [-49.59, 71.59]
Total (95% CI)	1236		1256			100.0	8.26 [-49.84, 66.36]

Test for heterogeneity chi-square=0.10 df=1 p=0.75 I^2 =0.0%

Test for overall effect z=0.28 p=0.8



Analysis 03.13. Comparison 03 Co-amoxiclav versus placebo, Outcome 13 Birthweight < 2500 g

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 13 Birthweight < 2500 g

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	877/1205	880/1225		100.0	1.01 [0.96, 1.06]
Total (95% CI)	1205	1225		100.0	1.01 [0.96, 1.06]

Total events: 877 (Treatment), 880 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=0.52 p=0.6

Analysis 03.14. Comparison 03 Co-amoxiclav versus placebo, Outcome 14 Neonatal intensive care

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 14 Neonatal intensive care

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1995	31/31	28/31		3.1	1.11 [0.99, 1.24]
Kenyon 2001	848/1205	880/1225		96.9	0.98 [0.93, 1.03]
Total (95% CI)	1236	1256		100.0	0.98 [0.94, 1.03]

Total events: 879 (Treatment), 908 (Control)

Test for heterogeneity chi-square=4.08 df=1 p=0.04 I^2 =75.5%

Test for overall effect z=0.66 p=0.5

Analysis 03.15. Comparison 03 Co-amoxiclav versus placebo, Outcome 15 Days in neonatal intensive care unit

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 15 Days in neonatal intensive care unit

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 03.16. Comparison 03 Co-amoxiclav versus placebo, Outcome 16 Neonatal infection including pneumonia

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 16 Neonatal infection including pneumonia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1995	0/31	1/31		100.0	0.33 [0.01, 7.88]
Total (95% CI)	31	31		100.0	0.33 [0.01, 7.88]
Total events: 0 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					

Analysis 03.17. Comparison 03 Co-amoxiclav versus placebo, Outcome 17 Positive neonatal blood culture

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 17 Positive neonatal blood culture

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	82/1205	100/1225		100.0	0.83 [0.63, 1.10]
Total (95% CI)	1205	1225		100.0	0.83 [0.63, 1.10]
Total events: 82 (Treatment), 100 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.27 p=0.2					

Analysis 03.18. Comparison 03 Co-amoxiclav versus placebo, Outcome 18 Neonatal necrotising enterocolitis

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 18 Neonatal necrotising enterocolitis

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1995	5/31	0/31		7.8	11.00 [0.63, 190.79]
Kenyon 2001	24/1205	6/1225		92.2	4.07 [1.67, 9.91]
Total (95% CI)	1236	1256		100.0	4.60 [1.98, 10.72]

Total events: 29 (Treatment), 6 (Control)

Test for heterogeneity chi-square=0.43 df=1 p=0.51 I^2 =0.0%

Test for overall effect z=3.54 p=0.0004

Analysis 03.19. Comparison 03 Co-amoxiclav versus placebo, Outcome 19 Neonatal respiratory distress syndrome

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 19 Neonatal respiratory distress syndrome

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1995	27/31	21/31		7.4	1.29 [0.97, 1.70]
Kenyon 2001	241/1205	266/1225		92.6	0.92 [0.79, 1.08]
Total (95% CI)	1236	1256		100.0	0.95 [0.82, 1.09]

Total events: 268 (Treatment), 287 (Control)

Test for heterogeneity chi-square=4.74 df=1 p=0.03 I^2 =78.9%

Test for overall effect z=0.73 p=0.5

Analysis 03.20. Comparison 03 Co-amoxiclav versus placebo, Outcome 20 Treatment with surfactant

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 20 Treatment with surfactant

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	182/1205	217/1225		100.0	0.85 [0.71, 1.02]
Total (95% CI)	1205	1225		100.0	0.85 [0.71, 1.02]
Total events: 182 (Treatment), 217 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.73 p=0.08					

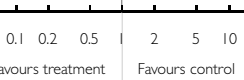
Analysis 03.21. Comparison 03 Co-amoxiclav versus placebo, Outcome 21 Number of babies requiring ventilation

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 21 Number of babies requiring ventilation

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	254/1205	283/1225		100.0	0.91 [0.79, 1.06]
Total (95% CI)	1205	1225		100.0	0.91 [0.79, 1.06]
Total events: 254 (Treatment), 283 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.20 p=0.2					



Analysis 03.22. Comparison 03 Co-amoxiclav versus placebo, Outcome 22 Number of babies requiring oxygen therapy

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 22 Number of babies requiring oxygen therapy

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	383/1205	436/1225		100.0	0.89 [0.80, 1.00]
Total (95% CI)	1205	1225		100.0	0.89 [0.80, 1.00]
Total events: 383 (Treatment), 436 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.98 p=0.05					

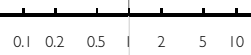
Analysis 03.23. Comparison 03 Co-amoxiclav versus placebo, Outcome 23 Neonatal oxygenation > 28 days

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 23 Neonatal oxygenation > 28 days

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	111/1205	114/1225		100.0	0.99 [0.77, 1.27]
Total (95% CI)	1205	1225		100.0	0.99 [0.77, 1.27]
Total events: 111 (Treatment), 114 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.08 p=0.9					



Analysis 03.24. Comparison 03 Co-amoxiclav versus placebo, Outcome 24 Oxygen treatment > 36 weeks postconceptual age

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 24 Oxygen treatment > 36 weeks postconceptual age

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	69/1205	76/1225		100.0	0.92 [0.67, 1.27]
Total (95% CI)	1205	1225		100.0	0.92 [0.67, 1.27]
Total events: 69 (Treatment), 76 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.50 p=0.6					

Analysis 03.26. Comparison 03 Co-amoxiclav versus placebo, Outcome 26 Major cerebral abnormality on ultrasound before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 26 Major cerebral abnormality on ultrasound before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1995	7/31	8/31		11.7	0.88 [0.36, 2.12]
Kenyon 2001	46/1205	61/1225		88.3	0.77 [0.53, 1.11]
Total (95% CI)	1236	1256		100.0	0.78 [0.55, 1.10]
Total events: 53 (Treatment), 69 (Control)					
Test for heterogeneity chi-square=0.07 df=1 p=0.79 I^2 =0.0%					
Test for overall effect z=1.41 p=0.2					

Analysis 03.28. Comparison 03 Co-amoxiclav versus placebo, Outcome 28 Perinatal death/death before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 03 Co-amoxiclav versus placebo

Outcome: 28 Perinatal death/death before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1995	1/31	5/31		5.8	0.20 [0.02, 1.61]
Kenyon 2001	79/1205	82/1225		94.2	0.98 [0.73, 1.32]
Total (95% CI)	1236	1256		100.0	0.93 [0.70, 1.25]
Total events: 80 (Treatment), 87 (Control)					
Test for heterogeneity chi-square=2.19 df=1 p=0.14 I^2 =54.3%					
Test for overall effect z=0.45 p=0.6					

Analysis 04.03. Comparison 04 Erythromycin versus placebo, Outcome 03 Major adverse drug reaction

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 03 Major adverse drug reaction

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Kenyon 2001	0/1190	0/1225		0.0	Not estimable
Total (95% CI)	1190	1225		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

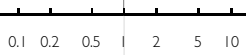
Analysis 04.04. Comparison 04 Erythromycin versus placebo, Outcome 04 Maternal infection after delivery prior to discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 04 Maternal infection after delivery prior to discharge

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Garcia 1995	8/30	7/30		2.6	1.14 [0.47, 2.75]
Kenyon 2001	241/1190	262/1225		97.4	0.95 [0.81, 1.11]
Total (95% CI)	1220	1255		100.0	0.95 [0.82, 1.11]
Total events: 249 (Treatment), 269 (Control)					
Test for heterogeneity chi-square=0.17 df=1 p=0.68 I^2 =0.0%					
Test for overall effect z=0.63 p=0.5					



Analysis 04.05. Comparison 04 Erythromycin versus placebo, Outcome 05 Chorioamnionitis

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 05 Chorioamnionitis

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Garcia 1995	3/30	1/30		3.5	3.00 [0.33, 27.23]
McGregor 1991	7/28	6/27		21.5	1.13 [0.43, 2.92]
Mercer 1992	18/105	22/112		75.0	0.87 [0.50, 1.53]
Total (95% CI)	163	169		100.0	1.00 [0.63, 1.60]
Total events: 28 (Treatment), 29 (Control)					
Test for heterogeneity chi-square=1.24 df=2 p=0.54 I^2 =0.0%					
Test for overall effect z=0.01 p=1					

Analysis 04.06. Comparison 04 Erythromycin versus placebo, Outcome 06 Caesarean section

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 06 Caesarean section

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Garcia 1995	5/30	6/30		1.6	0.83 [0.28, 2.44]
Kenyon 2001	335/1190	357/1225		93.8	0.97 [0.85, 1.10]
Mercer 1992	26/105	18/112		4.6	1.54 [0.90, 2.64]
Total (95% CI)	1325	1367		100.0	0.99 [0.88, 1.12]

Total events: 366 (Treatment), 381 (Control)

Test for heterogeneity chi-square=2.83 df=2 p=0.24 I^2 =29.5%

Test for overall effect z=0.15 p=0.9

Analysis 04.07. Comparison 04 Erythromycin versus placebo, Outcome 07 Days from randomisation to birth

Review: Antibiotics for preterm rupture of membranes

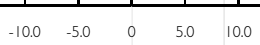
Comparison: 04 Erythromycin versus placebo

Outcome: 07 Days from randomisation to birth

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable

Test for heterogeneity: not applicable

Test for overall effect: not applicable



Analysis 04.08. Comparison 04 Erythromycin versus placebo, Outcome 08 Days from birth till discharge of mother

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 08 Days from birth till discharge of mother

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 04.09. Comparison 04 Erythromycin versus placebo, Outcome 09 Birth within 48 hours of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 09 Birth within 48 hours of randomisation

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	414/1190	498/1225		89.9	0.86 [0.77, 0.95]
Mercer 1992	37/106	57/114		10.1	0.70 [0.51, 0.96]
Total (95% CI)	1296	1339		100.0	0.84 [0.76, 0.93]
Total events: 451 (Treatment), 555 (Control)					
Test for heterogeneity chi-square=1.42 df=1 p=0.23 I^2 =29.7%					
Test for overall effect z=3.49 p=0.0005					

Analysis 04.10. Comparison 04 Erythromycin versus placebo, Outcome 10 Birth within 7 days of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 10 Birth within 7 days of randomisation

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	725/1190	775/1225		89.4	0.96 [0.90, 1.02]
Mercer 1992	77/106	94/114		10.6	0.88 [0.76, 1.02]
Total (95% CI)	1296	1339		100.0	0.95 [0.90, 1.01]
Total events: 802 (Treatment), 869 (Control)					
Test for heterogeneity chi-square=1.26 df=1 p=0.26 I^2 =20.7%					
Test for overall effect z=1.58 p=0.1					

Analysis 04.11. Comparison 04 Erythromycin versus placebo, Outcome 11 Birth before 37 weeks' gestation

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 11 Birth before 37 weeks' gestation

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	1006/1190	1041/1225		100.0	0.99 [0.96, 1.03]
× McGregor 1991	28/28	27/27		0.0	Not estimable
Total (95% CI)	1218	1252		100.0	0.99 [0.96, 1.03]
Total events: 1034 (Treatment), 1068 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.30 p=0.8					

Analysis 04.12. Comparison 04 Erythromycin versus placebo, Outcome 12 Birthweight

Review: Antibiotics for preterm rupture of membranes

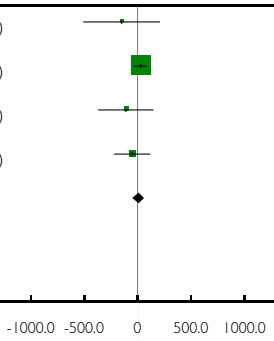
Comparison: 04 Erythromycin versus placebo

Outcome: 12 Birthweight

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Garcia 1995	30	2022.00 (607.00)	30	2170.00 (799.70)		2.4	-148.00 [-507.26, 211.26]
Kenyon 2001	1190	2104.00 (766.00)	1225	2072.00 (769.00)		82.4	32.00 [-29.23, 93.23]
McGregor 1991	28	1638.50 (530.80)	27	1741.40 (444.00)		4.6	-102.90 [-361.17, 155.37]
Mercer 1992	106	1771.00 (653.00)	114	1817.00 (637.00)		10.6	-46.00 [-216.66, 124.66]
Total (95% CI)	1354		1396			100.0	13.18 [-42.39, 68.75]

Test for heterogeneity chi-square=2.37 df=3 p=0.50 I^2 =0.0%

Test for overall effect z=0.46 p=0.6



Analysis 04.13. Comparison 04 Erythromycin versus placebo, Outcome 13 Birthweight < 2500 g

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

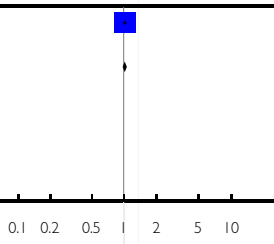
Outcome: 13 Birthweight < 2500 g

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	863/1190	880/1225		100.0	1.01 [0.96, 1.06]
Total (95% CI)	1190	1225		100.0	1.01 [0.96, 1.06]

Total events: 863 (Treatment), 880 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=0.38 p=0.7



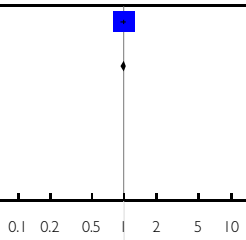
Analysis 04.14. Comparison 04 Erythromycin versus placebo, Outcome 14 Neonatal intensive care

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 14 Neonatal intensive care

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	836/1190	880/1225		100.0	0.98 [0.93, 1.03]
Total (95% CI)	1190	1225		100.0	0.98 [0.93, 1.03]
Total events: 836 (Treatment), 880 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.86 p=0.4					



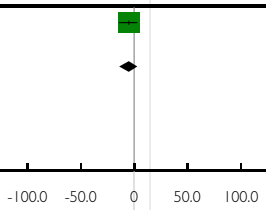
Analysis 04.15. Comparison 04 Erythromycin versus placebo, Outcome 15 Days in neonatal intensive care unit

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 15 Days in neonatal intensive care unit

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
McGregor 1991	28	9.50 (10.50)	27	14.50 (18.90)		100.0	-5.00 [-13.12, 3.12]
Total (95% CI)	28		27			100.0	-5.00 [-13.12, 3.12]
Test for heterogeneity: not applicable							
Test for overall effect z=1.21 p=0.2							



Analysis 04.16. Comparison 04 Erythromycin versus placebo, Outcome 16 Neonatal infection including pneumonia

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 16 Neonatal infection including pneumonia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Garcia 1995	4/30	5/30		20.4	0.80 [0.24, 2.69]
McGregor 1991	1/24	1/27		3.8	1.13 [0.07, 17.02]
Mercer 1992	14/109	19/114		75.8	0.77 [0.41, 1.46]
Total (95% CI)	163	171		100.0	0.79 [0.45, 1.37]
Total events: 19 (Treatment), 25 (Control)					
Test for heterogeneity chi-square=0.07 df=2 p=0.96 I^2 =0.0%					
Test for overall effect z=0.83 p=0.4					

Analysis 04.17. Comparison 04 Erythromycin versus placebo, Outcome 17 Positive neonatal blood culture

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 17 Positive neonatal blood culture

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	68/1190	100/1225		100.0	0.70 [0.52, 0.94]
Total (95% CI)	1190	1225		100.0	0.70 [0.52, 0.94]
Total events: 68 (Treatment), 100 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.35 p=0.02					

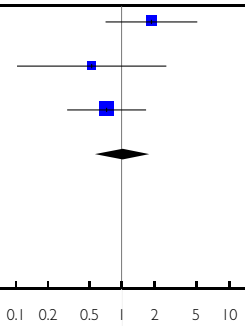
Analysis 04.18. Comparison 04 Erythromycin versus placebo, Outcome 18 Neonatal necrotising enterocolitis

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 18 Neonatal necrotising enterocolitis

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	11/1190	6/1225		27.6	1.89 [0.70, 5.09]
McGregor 1991	2/26	4/27		18.3	0.52 [0.10, 2.60]
Mercer 1992	8/106	12/114		54.0	0.72 [0.31, 1.69]
Total (95% CI)	1322	1366		100.0	1.00 [0.56, 1.80]
Total events: 21 (Treatment), 22 (Control)					
Test for heterogeneity chi-square=2.80 df=2 p=0.25 I^2 =28.5%					
Test for overall effect z=0.01 p=1					



Analysis 04.19. Comparison 04 Erythromycin versus placebo, Outcome 19 Neonatal respiratory distress syndrome

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 19 Neonatal respiratory distress syndrome

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Garcia 1995	7/30	6/30		2.0	1.17 [0.44, 3.06]
Kenyon 2001	236/1190	266/1225		85.5	0.91 [0.78, 1.07]
McGregor 1991	15/26	15/25		5.0	0.96 [0.61, 1.52]
Mercer 1992	27/106	24/114		7.5	1.21 [0.75, 1.96]
Total (95% CI)	1352	1394		100.0	0.94 [0.82, 1.09]
Total events: 285 (Treatment), 311 (Control)					
Test for heterogeneity chi-square=1.38 df=3 p=0.71 I^2 =0.0%					
Test for overall effect z=0.81 p=0.4					

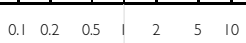
Analysis 04.20. Comparison 04 Erythromycin versus placebo, Outcome 20 Treatment with surfactant

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 20 Treatment with surfactant

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	176/1190	217/1225		100.0	0.83 [0.70, 1.00]
Total (95% CI)	1190	1225		100.0	0.83 [0.70, 1.00]
Total events: 176 (Treatment), 217 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.94 p=0.05					



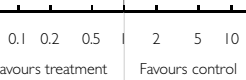
Analysis 04.21. Comparison 04 Erythromycin versus placebo, Outcome 21 Number of babies requiring ventilation

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 21 Number of babies requiring ventilation

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	251/1190	283/1225		100.0	0.91 [0.79, 1.06]
Total (95% CI)	1190	1225		100.0	0.91 [0.79, 1.06]
Total events: 251 (Treatment), 283 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.19 p=0.2					



Analysis 04.22. Comparison 04 Erythromycin versus placebo, Outcome 22 Number of babies requiring oxygen therapy

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 22 Number of babies requiring oxygen therapy

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	370/1190	436/1225		100.0	0.87 [0.78, 0.98]
Total (95% CI)	1190	1225		100.0	0.87 [0.78, 0.98]
Total events: 370 (Treatment), 436 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.34 p=0.02					

Analysis 04.23. Comparison 04 Erythromycin versus placebo, Outcome 23 Neonatal oxygenation > 28 days

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 23 Neonatal oxygenation > 28 days

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	94/1190	114/1225		100.0	0.85 [0.65, 1.10]
Total (95% CI)	1190	1225		100.0	0.85 [0.65, 1.10]
Total events: 94 (Treatment), 114 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.23 p=0.2					

Analysis 04.24. Comparison 04 Erythromycin versus placebo, Outcome 24 Oxygen treatment > 36 weeks postconceptual age

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 24 Oxygen treatment > 36 weeks postconceptual age

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	66/1190	76/1225		100.0	0.89 [0.65, 1.23]
Total (95% CI)	1190	1225		100.0	0.89 [0.65, 1.23]
Total events: 66 (Treatment), 76 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.69 p=0.5					

Analysis 04.25. Comparison 04 Erythromycin versus placebo, Outcome 25 Neonatal encephalopathy

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 25 Neonatal encephalopathy

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Garcia 1995	0/30	0/30		0.0	Not estimable
Total (95% CI)	30	30		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 04.26. Comparison 04 Erythromycin versus placebo, Outcome 26 Major cerebral abnormality on ultrasound before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 26 Major cerebral abnormality on ultrasound before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Garcia 1995	2/30	1/30		1.3	2.00 [0.19, 20.90]
Kenyon 2001	50/1190	61/1225		79.5	0.84 [0.59, 1.22]
McGregor 1991	5/26	1/27		1.3	5.19 [0.65, 41.50]
Mercer 1992	11/106	14/114		17.8	0.85 [0.40, 1.78]
Total (95% CI)	1352	1396		100.0	0.92 [0.67, 1.26]
Total events: 68 (Treatment), 77 (Control)					
Test for heterogeneity chi-square=3.34 df=3 p=0.34 I^2 =10.2%					
Test for overall effect z=0.54 p=0.6					

Analysis 04.28. Comparison 04 Erythromycin versus placebo, Outcome 28 Perinatal death/death before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 04 Erythromycin versus placebo

Outcome: 28 Perinatal death/death before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Garcia 1995	2/30	5/30		5.2	0.40 [0.08, 1.90]
Kenyon 2001	70/1190	82/1225		84.2	0.88 [0.65, 1.20]
McGregor 1991	6/28	0/27		0.5	12.55 [0.74, 212.52]
Mercer 1992	6/106	10/114		10.0	0.65 [0.24, 1.71]
Total (95% CI)	1354	1396		100.0	0.89 [0.67, 1.18]
Total events: 84 (Treatment), 97 (Control)					
Test for heterogeneity chi-square=4.80 df=3 p=0.19 I^2 =37.5%					
Test for overall effect z=0.79 p=0.4					

Analysis 05.03. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 03 Major adverse drug reaction

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 03 Major adverse drug reaction

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Kenyon 2001	0/1190	0/1205		0.0	Not estimable
Total (95% CI)	1190	1205		0.0	Not estimable
Total events: 0 (Erythromycin), 0 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 05.04. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 04 Maternal infection after delivery prior to discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 04 Maternal infection after delivery prior to discharge

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	241/1190	239/1205		100.0	1.02 [0.87, 1.20]
Total (95% CI)	1190	1205		100.0	1.02 [0.87, 1.20]
Total events: 241 (Erythromycin), 239 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.26 p=0.8					

Analysis 05.06. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 06 Caesarean section

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 06 Caesarean section

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	335/1190	332/1205		100.0	1.02 [0.90, 1.16]
Total (95% CI)	1190	1205		100.0	1.02 [0.90, 1.16]
Total events: 335 (Erythromycin), 332 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.33 p=0.7					

Analysis 05.07. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 07 Days from randomisation to birth

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 07 Days from randomisation to birth

Study	Erythromycin N Mean(SD)	Co-amoxiclav N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 05.08. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 08 Days from birth till discharge of mother

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 08 Days from birth till discharge of mother

Study	Erythromycin N Mean(SD)	Co-amoxiclav N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 05.09. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 09 Birth within 48 hours of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 09 Birth within 48 hours of randomisation

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	414/1190	367/1205		100.0	1.14 [1.02, 1.28]
Total (95% CI)	1190	1205		100.0	1.14 [1.02, 1.28]
Total events: 414 (Erythromycin), 367 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.26 p=0.02					

Analysis 05.10. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 10 Birth within 7 days of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

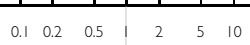
Outcome: 10 Birth within 7 days of randomisation

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	725/1190	695/1205		100.0	1.06 [0.99, 1.13]
Total (95% CI)	1190	1205		100.0	1.06 [0.99, 1.13]

Total events: 725 (Erythromycin), 695 (Co-amoxiclav)

Test for heterogeneity: not applicable

Test for overall effect z=1.62 p=0.1



Analysis 05.11. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 11 Birth before 37 weeks' gestation

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

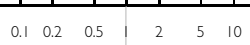
Outcome: 11 Birth before 37 weeks' gestation

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	1006/1190	1025/1205		100.0	0.99 [0.96, 1.03]
Total (95% CI)	1190	1205		100.0	0.99 [0.96, 1.03]

Total events: 1006 (Erythromycin), 1025 (Co-amoxiclav)

Test for heterogeneity: not applicable

Test for overall effect z=0.36 p=0.7



Analysis 05.12. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 12 Birthweight

Review: Antibiotics for preterm rupture of membranes

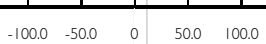
Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 12 Birthweight

Study	Erythromycin N	Erythromycin Mean(SD)	Co-amoxiclav N	Co-amoxiclav Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Kenyon 2001	1190	2102.00 (766.00)	1205	2083.00 (755.00)		100.0	19.00 [-41.92, 79.92]
Total (95% CI)	1190		1205			100.0	19.00 [-41.92, 79.92]

Test for heterogeneity: not applicable

Test for overall effect z=0.61 p=0.5



Analysis 05.13. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 13 Birthweight < 2500 g

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 13 Birthweight < 2500 g

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	863/1190	877/1205		100.0	1.00 [0.95, 1.05]
Total (95% CI)	1190	1205		100.0	1.00 [0.95, 1.05]
Total events: 863 (Erythromycin), 877 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.14 p=0.9					

Analysis 05.14. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 14 Neonatal intensive care

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 14 Neonatal intensive care

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	836/1190	848/1205		100.0	1.00 [0.95, 1.05]
Total (95% CI)	1190	1205		100.0	1.00 [0.95, 1.05]
Total events: 836 (Erythromycin), 848 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.06 p=0.9					

Analysis 05.15. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 15 Days in neonatal intensive care unit

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 15 Days in neonatal intensive care unit

Study	Erythromycin N Mean(SD)	Co-amoxiclav N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 05.17. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 17 Positive neonatal blood culture

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 17 Positive neonatal blood culture

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	68/1190	82/1205		100.0	0.84 [0.62, 1.15]
Total (95% CI)	1190	1205		100.0	0.84 [0.62, 1.15]
Total events: 68 (Erythromycin), 82 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.10 p=0.3					

Analysis 05.18. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 18 Neonatal necrotising enterocolitis

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 18 Neonatal necrotising enterocolitis

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	11/1190	24/1205		100.0	0.46 [0.23, 0.94]
Total (95% CI)	1190	1205		100.0	0.46 [0.23, 0.94]
Total events: 11 (Erythromycin), 24 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.12 p=0.03					

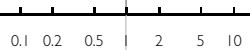
Analysis 05.19. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 19 Neonatal respiratory distress syndrome

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 19 Neonatal respiratory distress syndrome

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	236/1190	241/1205		100.0	0.99 [0.84, 1.16]
Total (95% CI)	1190	1205		100.0	0.99 [0.84, 1.16]
Total events: 236 (Erythromycin), 241 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.10 p=0.9					



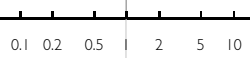
Analysis 05.20. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 20 Treatment with surfactant

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 20 Treatment with surfactant

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	176/1190	182/1205		100.0	0.98 [0.81, 1.19]
Total (95% CI)	1190	1205		100.0	0.98 [0.81, 1.19]
Total events: 176 (Erythromycin), 182 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.22 p=0.8					



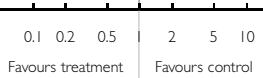
Analysis 05.21. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 21 Number of babies requiring ventilation

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 21 Number of babies requiring ventilation

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	251/1190	254/1205		100.0	1.00 [0.86, 1.17]
Total (95% CI)	1190	1205		100.0	1.00 [0.86, 1.17]
Total events: 251 (Erythromycin), 254 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					



Analysis 05.22. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 22 Number of babies requiring oxygen therapy

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 22 Number of babies requiring oxygen therapy

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	370/1190	383/1205		100.0	0.98 [0.87, 1.10]
Total (95% CI)	1190	1205		100.0	0.98 [0.87, 1.10]
Total events: 370 (Erythromycin), 383 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.36 p=0.7					

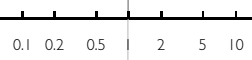
Analysis 05.23. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 23 Neonatal oxygenation > 28 days

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 23 Neonatal oxygenation > 28 days

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	94/1190	111/1205		100.0	0.86 [0.66, 1.12]
Total (95% CI)	1190	1205		100.0	0.86 [0.66, 1.12]
Total events: 94 (Erythromycin), 111 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.15 p=0.3					

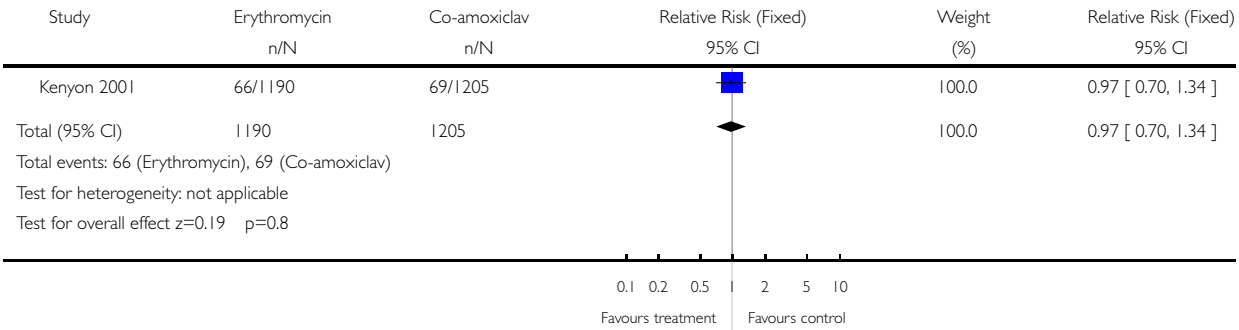


Analysis 05.24. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 24 Oxygen treatment > 36 weeks postconceptual age

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 24 Oxygen treatment > 36 weeks postconceptual age

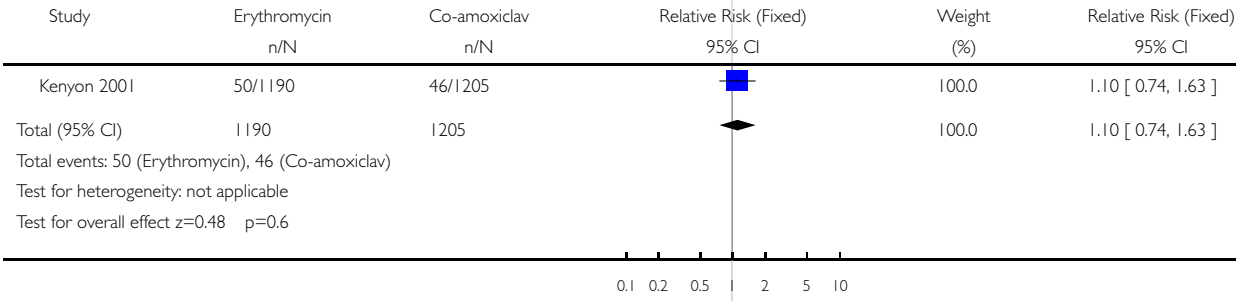


Analysis 05.26. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 26 Major cerebral abnormality on ultrasound before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 26 Major cerebral abnormality on ultrasound before discharge



Analysis 05.28. Comparison 05 Erythromycin versus co-amoxiclav, Outcome 28 Perinatal death/death before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 05 Erythromycin versus co-amoxiclav

Outcome: 28 Perinatal death/death before discharge

Study	Erythromycin n/N	Co-amoxiclav n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kenyon 2001	70/1190	79/1205		100.0	0.90 [0.66, 1.23]
Total (95% CI)	1190	1205		100.0	0.90 [0.66, 1.23]
Total events: 70 (Erythromycin), 79 (Co-amoxiclav)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					

Analysis 07.01. Comparison 07 Antibiotics versus no antibiotic, Outcome 01 Perinatal death/death before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 07 Antibiotics versus no antibiotic

Outcome: 01 Perinatal death/death before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Almeida 1996	5/59	10/51		3.5	0.43 [0.16, 1.18]
Amon 1988	2/43	6/39		1.5	0.30 [0.06, 1.41]
Camli 1997	3/15	4/16		2.0	0.80 [0.21, 3.00]
Christmas 1992	1/48	3/46		0.7	0.32 [0.03, 2.96]
Cox 1995	1/31	5/31		0.8	0.20 [0.02, 1.61]
Garcia 1995	2/30	5/30		1.4	0.40 [0.08, 1.90]
Grable 1996	0/31	2/29		0.4	0.19 [0.01, 3.75]
Johnston 1990	3/40	4/45		1.7	0.84 [0.20, 3.54]
Kenyon 2001	226/3584	82/1225		59.1	0.94 [0.74, 1.20]
Kurki 1992	1/57	1/58		0.5	1.02 [0.07, 15.88]
Lockwood 1993	3/37	3/35		1.5	0.95 [0.20, 4.38]
Magwali 1999	8/82	11/86		4.8	0.76 [0.32, 1.80]
McGregor 1991	6/28	0/27		0.4	12.55 [0.74, 212.52]
Mercer 1992	6/106	10/114		3.7	0.65 [0.24, 1.71]
Mercer 1997	19/299	18/312		9.0	1.10 [0.59, 2.06]

(*Continued . . .*)

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Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Morales 1989	5/42	3/37		1.9	1.47 [0.38, 5.73]
Ovalle Salas 1997	7/42	6/43		3.5	1.19 [0.44, 3.26]
Owen 1993	4/59	7/58		2.6	0.56 [0.17, 1.82]
Svare 1997	2/30	2/37		1.0	1.23 [0.18, 8.25]
Total (95% CI)	4663	2319		100.0	0.87 [0.72, 1.05]
Total events: 304 (Treatment), 182 (Control)					
Test for heterogeneity chi-square=14.79 df=18 p=0.68 I^2 =0.0%					
Test for overall effect z=1.46 p=0.1					

Analysis 08.01. Comparison 08 Antibiotics versus no treatment (no placebo), Outcome 01 Perinatal death/death before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 08 Antibiotics versus no treatment (no placebo)

Outcome: 01 Perinatal death/death before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Amon 1988	2/43	6/39		11.0	0.30 [0.06, 1.41]
Camli 1997	3/15	4/16		15.0	0.80 [0.21, 3.00]
Christmas 1992	1/48	3/46		5.3	0.32 [0.03, 2.96]
Magwali 1999	8/82	11/86		35.5	0.76 [0.32, 1.80]
Morales 1989	5/42	3/37		14.1	1.47 [0.38, 5.73]
Owen 1993	4/59	7/58		19.0	0.56 [0.17, 1.82]
Total (95% CI)	289	282		100.0	0.69 [0.41, 1.14]
Total events: 23 (Treatment), 34 (Control)					
Test for heterogeneity chi-square=2.97 df=5 p=0.70 I^2 =0.0%					
Test for overall effect z=1.45 p=0.1					

Analysis 09.04. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 04 Maternal infection after delivery prior to discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 04 Maternal infection after delivery prior to discharge

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Lewis 2003	5/42	4/42		100.0	1.25 [0.36, 4.33]
Total (95% CI)	42	42		100.0	1.25 [0.36, 4.33]
Total events: 5 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.35 p=0.7					

Analysis 09.05. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 05 Chorioamnionitis

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 05 Chorioamnionitis

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Lewis 2003	8/42	11/42		100.0	0.73 [0.33, 1.63]
Total (95% CI)	42	42		100.0	0.73 [0.33, 1.63]
Total events: 8 (Treatment), 11 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.78 p=0.4					

Analysis 09.06. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 06 Caesarean section

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 06 Caesarean section

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Lewis 2003	20/42	17/42		100.0	1.18 [0.72, 1.91]
Total (95% CI)	42	42		100.0	1.18 [0.72, 1.91]
Total events: 20 (Treatment), 17 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.66 p=0.5					

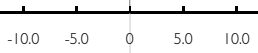
Analysis 09.07. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 07 Days from randomisation to birth

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 07 Days from randomisation to birth

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



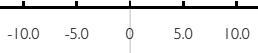
Analysis 09.08. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 08 Days from birth till discharge of mother

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 08 Days from birth till discharge of mother

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



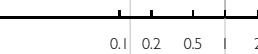
Analysis 09.09. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 09 Birth within 48 hours of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 09 Birth within 48 hours of randomisation

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Lewis 2003	8/42	7/42		100.0	1.14 [0.46, 2.87]
Total (95% CI)	42	42		100.0	1.14 [0.46, 2.87]
Total events: 8 (Treatment), 7 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.28 p=0.8					



Analysis 09.10. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 10 Birth within 7 days of randomisation

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 10 Birth within 7 days of randomisation

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Lewis 2003	25/42	25/42		100.0	1.00 [0.70, 1.42]
Total (95% CI)	42	42		100.0	1.00 [0.70, 1.42]
Total events: 25 (Treatment), 25 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					

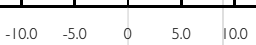
Analysis 09.12. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 12 Birthweight

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 12 Birthweight

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 09.14. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 14 Neonatal intensive care

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 14 Neonatal intensive care

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Lewis 2003	36/42	36/42		100.0	1.00 [0.84, 1.19]
Total (95% CI)	42	42		100.0	1.00 [0.84, 1.19]
Total events: 36 (Treatment), 36 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					

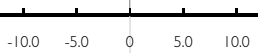
Analysis 09.15. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 15 Days in neonatal intensive care unit

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 15 Days in neonatal intensive care unit

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 09.18. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 18 Neonatal necrotising enterocolitis

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 18 Neonatal necrotising enterocolitis

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Lewis 2003	1/42	2/42		64.0	0.50 [0.05, 5.31]
Segel 2003	0/23	1/23		36.0	0.33 [0.01, 7.78]
Total (95% CI)	65	65		100.0	0.43 [0.07, 2.86]
Total events: 1 (Treatment), 3 (Control)					
Test for heterogeneity chi-square=0.04 df=1 p=0.84 I^2 =0.0%					
Test for overall effect z=0.87 p=0.4					

Analysis 09.19. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 19 Neonatal respiratory distress syndrome

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

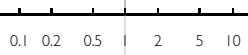
Outcome: 19 Neonatal respiratory distress syndrome

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Lewis 2003	14/42	15/42		55.5	0.93 [0.52, 1.68]
Segel 2003	10/23	10/23		44.5	1.00 [0.52, 1.93]
Total (95% CI)	65	65		100.0	0.96 [0.62, 1.49]

Total events: 24 (Treatment), 25 (Control)

Test for heterogeneity chi-square=0.02 df=1 p=0.88 I^2 =0.0%

Test for overall effect z=0.17 p=0.9



Analysis 09.26. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 26 Neonatal intraventricular haemorrhage

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 26 Neonatal intraventricular haemorrhage

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Lewis 2003	0/42	1/42		49.6	0.33 [0.01, 7.96]
Segel 2003	0/23	1/23		50.4	0.33 [0.01, 7.78]
Total (95% CI)	65	65		100.0	0.33 [0.04, 3.12]

Total events: 0 (Treatment), 2 (Control)

Test for heterogeneity chi-square=0.00 df=1 p=1.00 I^2 =0.0%

Test for overall effect z=0.96 p=0.3

Analysis 09.28. Comparison 09 3 versus 7 day ampicillin regimens, Outcome 28 Perinatal death/death before discharge

Review: Antibiotics for preterm rupture of membranes

Comparison: 09 3 versus 7 day ampicillin regimens

Outcome: 28 Perinatal death/death before discharge

Study	Treatment n/N	Control n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Lewis 2003	1/42	1/42		53.0	1.00 [0.06, 15.47]
Segel 2003	0/23	3/23		47.0	0.14 [0.01, 2.62]
Total (95% CI)	65	65		100.0	0.40 [0.05, 2.94]

Total events: 1 (Treatment), 4 (Control)

Test for heterogeneity chi-square=0.94 df=1 p=0.33 I^2 =0.0%

Test for overall effect z=0.90 p=0.4