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Prophylactic antibiotics for inhibiting preterm labour with intact membranes (Review)

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[Intervention Review]

Prophylactic antibiotics for inhibiting preterm labour with intact membranes

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ABSTRACT

Background

The aetiology of preterm birth is complex and there is evidence that subclinical genital tract infection influences preterm labour in some women but the role of prophylactic antibiotic treatment in the management of preterm labour is controversial. Since rupture of the membranes is an important factor in the progression of preterm labour, it is important to see if the routine administration of antibiotics confers any benefit or causes harm, prior to membrane rupture.

Objectives

To assess the effects of prophylactic antibiotics administered to women in preterm labour with intact membranes, on maternal and neonatal outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2013).

Selection criteria

Randomised trials that compared antibiotic treatment with placebo or no treatment for women in preterm labour (between 20 and 36 weeks' gestation) with intact membranes.

Data collection and analysis

Two review authors independently assessed trial eligibility, and undertook quality assessment and data extraction. We contacted study authors for additional information. Results are presented using risk ratio (RR) for categorical data and mean difference (MD) for data measured on a continuous scale with their respective 95% confidence intervals (CI). The number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH) was calculated where appropriate.

Main results

In this update (2013), with the addition of three trials (305 women), the large ORACLE II 2001 trial continues to dominate the results of this review. This review now includes a total of 14 studies randomising 7837 women. No significant difference was shown in perinatal or infant mortality for infants of women allocated to any prophylactic antibiotics compared with no antibiotics. However, an increase in neonatal deaths was shown for infants of women receiving any prophylactic antibiotics when compared with placebo (RR 1.57, 95% CI 1.03 to 2.40; NNTH 149, 95% CI 2500 to 61). No reduction in preterm birth or other clinically important short-term outcomes for the infant were shown.

Long-term child outcomes to seven years of age were available for infants in the UK enrolled in the ORACLE II trial. Comparing any antibiotics with placebo, a marginally non-statistically significant increase was shown in any functional impairment (RR 1.10, 95% CI 0.99 to 1.23) and cerebral palsy (CP) (RR 1.82, 95% CI 0.99 to 3.34). In subgroup analysis, CP was statistically significantly increased for infants of women allocated to macrolide and beta-lactam antibiotics combined compared with placebo (RR 2.83, 95% CI 1.02 to 7.88; NNTH 35, 95% CI 333 to 9).

Further, exposure to any macrolide antibiotics (including erythromycin alone or erythromycin plus co-amoxiclav) versus no macrolide antibiotics (including placebo and co-amoxiclav alone) was shown to increase neonatal death (RR 1.52, 95% CI 1.05 to 2.19; NNTH 139, 95% CI 1429 to 61), any functional impairment (RR 1.11, 95% CI 1.01 to 1.20; NNTH 24, 95% CI 263 to 13) and CP (RR 1.90, 95% CI 1.20 to 3.01; NNTH 64, 95% CI 286 to 29). Exposure to any beta-lactam (beta-lactam alone or in combination with macrolide antibiotics) versus no beta-lactam antibiotics resulted in more neonatal deaths (RR 1.51, 95% CI 1.06 to 2.15; NNTH 143, 95% CI 1250 to 63) and CP (RR 1.67, 95% CI 1.06 to 2.61; NNTH 79, 95% CI 909 to 33), however no difference was shown in functional impairment.

Maternal infection was reduced with the use of any prophylactic antibiotics compared with placebo (RR 0.74, 95% CI 0.63 to 0.86; NNTB 34, 95% CI 24 to 63) and any beta-lactam compared with no beta-lactam antibiotics (RR 0.80, 95% CI 0.69 to 0.92; NNTB 47, 95% CI 31 to 119). However, caution should be exercised with this finding due to the possibility of bias shown by funnel plot asymmetry. Any beta-lactam compared with no beta-lactam antibiotics was associated with an increase in maternal adverse drug reaction (RR 1.61, 95% CI 1.02 to 2.54; NNTH 17, 95% CI 526 to 7).

Authors' conclusions

This review did not demonstrate any benefit in important neonatal outcomes with the use of prophylactic antibiotics for women in preterm labour with intact membranes, although maternal infection may be reduced. Of concern, is the finding of short- and longer-term harm for children of mothers exposed to antibiotics. The evidence supports not giving antibiotics routinely to women in preterm labour with intact membranes in the absence of overt signs of infection.

Further research is required to develop sensitive markers of subclinical infection for women in preterm labour with intact membranes, as this is a group that might benefit from future novel interventions, including new modalities of antibiotic therapy. The results of this review demonstrate the need for future trials in the area of preterm birth to include assessment of long-term neurodevelopmental outcome.

PLAIN LANGUAGE SUMMARY

Prophylactic antibiotics for inhibiting preterm labour in women whose membranes are still intact

We found no benefit for the use of antibiotics for women going into labour too early, with their membranes still intact.

Maternal infection in the cervix or uterus may trigger preterm labour even if the infection does not cause symptoms (low grade infection). Preterm babies can have a range of complications, which often require admission to a neonatal intensive care unit, for example, because of breathing problems. Complications of being born early may result in death or longer-term disability such as chronic lung disease or cerebral palsy. Our systematic review of randomised trials, which included a total of 14 studies randomising 7837 women in preterm labour at a mean gestational age of 30 to 32 weeks compared routine administration of antibiotics before membrane rupture with placebo or no treatment for women without signs of infection. While antibiotics reduced the number of women who developed infections, they did not improve outcomes for the infant in terms of birth before 36 to 37 weeks, perinatal deaths or admission to neonatal intensive care or special care with serious illness. The review also found that antibiotic therapy was associated with an increase in neonatal deaths, functional impairment and cerebral palsy at seven years of age. The results of this review supports not giving antibiotics to women in threatened preterm labour with intact membranes who did not have clear signs of infection.

BACKGROUND

Preterm birth is a major contributor to the burden of perinatal mortality and morbidity (Lawn 2010). The rate of preterm birth has been increasing (Norman 2009; Tracy 2007), in both high- and low-middle income countries. For example, by 2005 it had risen in the USA from 9.5% in 1981 to 12.7% by 2005 (Hamilton 2006). Whilst increases in obstetric intervention have been implicated in rising rates of preterm birth (Henderson 2012; Norman 2009), the greatest proportion of preterm birth occurs as a consequence of spontaneous preterm labour in 40% to 45% of cases (Henderson 2012).

Little progress has been made over the last three decades in reducing the incidence of preterm birth despite a wide range of therapeutic interventions (Moutquin 1996; Muglia 2010). The initiation of parturition in humans is complex and still incompletely understood (Smith 2007). Of the pathways that play a role in the onset of labour, the three components that appear to be central to initiation and progression of labour are progesterone withdrawal, increasing oxytocin circulation and decidual activation (Romero 2006). Of these, decidual activation would seem to be the main pathway by which infection would play a role in preterm labour.

Such mechanisms may be acted upon directly though bacterial stimulation of prostaglandin synthesis or indirectly through a range of microbial endotoxins and inflammatory mediators (Bejar 1981). Infection may account for approximately 25% to 40% of spontaneous preterm birth (Goldenberg 2000). The presence of *Ureaplasma urealyticum* and *Mycoplasma spp*. have been detected in the amniotic fluid of women experiencing preterm birth (Yoon 2003). The presence of intra amniotic infection occurs more frequently with earlier gestational ages of preterm birth. The presence of the fetal inflammatory response is linked both to the onset of preterm labour and associated with an increased incidence of longer-term morbidity such as cerebral palsy and chronic lung disease (Yoon 2000).

While the contribution of subclinical genital tract infection to the aetiology of preterm birth is recognised, the role of antibiotic treatment in the management of preterm labour with intact membranes remains uncertain. While colonisation or the presence of bacteria, generally of low virulence, in the chorioamnion is common, this alone is insufficient to cause an inflammatory response to initiate preterm labour. As preterm prelabour rupture of the membranes has a major impact on the progression of preterm labour, we considered it important to assess the potential benefit of commencing prophylactic antibiotic therapy (usually given in addition to tocolysis) prior to membrane rupture.

It has also been hypothesised that the type of antibiotic may be important. Bacteriostatic antibiotics such as erythromycin have theoretical advantages over the beta-lactam antibiotics (penicillins, cephalosporins). The beta-lactams by destroying bacteria, release endotoxins which may increase local inflammatory mediators and adversely impact preterm birth (McGregor 1997). However, it has been suggested that erythromycin, through effects on the cardiovascular system, may lead to cerebral ischaemic events (Kallen 2005). Furthermore, the anaerobic organisms responsible for bacterial vaginosis (especially *Bacteroides* and *Mobiluncus spp*.) have been implicated in the aetiology of preterm labour. Antibiotics active against anaerobic organisms (such as clindamycin and metronidazole) may be more effective in prolonging gestation, but only if such organisms are present (Hauth 1995). Other genital tract infections such as trichomonas, chlamydia and gonorrhoea have been associated with an increased risk of preterm birth, although only when there is evidence of a maternal immune response in some instances (Sweet 1987).

This review examines the role of prophylactic antibiotics given to women in preterm labour with intact membranes. The use of antibiotics for treatment of preterm rupture of membranes is addressed in another review (Kenyon 2010).

OBJECTIVES

To assess the effects of prophylactic antibiotics administered to women in preterm labour with intact membranes on maternal, neonatal and longer-term outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised trials that compared outcomes for women and/or babies when prophylactic antibiotics were used in the routine management of preterm labour with intact membranes, with outcomes for controls (placebo or no treatment). Trials utilising a quasi-randomised method of allocation and cross-over randomised trials were excluded.

Types of participants

Women thought to be in preterm labour with intact membranes between 20 and 36 completed weeks of gestation. The diagnosis of preterm labour will be as defined by study investigators. This reflects usual clinical practice, strengthening the generalisability of the findings.

Types of interventions

Antibiotics administered either intravenously or orally in the management of preterm labour with intact membranes compared with no antibiotics (placebo or no treatment).

Types of outcome measures

Primary outcomes

For the infant/child

- Death (fetal, neonatal, or later death up to the time of follow-up).
- Major long-term infant neurosensory impairment.
- Death or major long-term infant neurosensory impairment.

For the woman

- Serious adverse outcome related to antibiotic treatment (respiratory arrest, cardiac arrest, death).

Secondary outcomes

For the infant/child

- Interval between randomisation and birth.
- Birth within 48 hours of randomisation.
- Birth within seven days of randomisation.
- Birth prior to 37 completed weeks.
- Birth prior to 34 completed weeks.
- Birth prior to 28 completed weeks.
- Gestational age at birth.
- Birthweight.
- Perinatal mortality
- Stillbirth.
- Neonatal death.
- Apgar score of less than seven at five minutes.
- Neonatal sepsis.
- Duration of mechanical ventilation.
- Respiratory distress syndrome.
- Necrotising enterocolitis.
- Retinopathy of prematurity (all stages).
- Retinopathy of prematurity (stages III and IV).
- Intraventricular haemorrhage (all grades).
- Intraventricular haemorrhage (grades 3 and 4).
- Cerebral cystic lesions (periventricular leukomalacia, porencephalic cysts).
- Chronic lung disease (infant receiving any respiratory support (supplemental oxygen or any form of assisted ventilation) for a chronic pulmonary disorder (i) on the day they reached 36 weeks' post menstrual age, and (ii) at 28 days postnatal age).
- Long-term neurosensory impairment (defined as moderate or severe cerebral palsy as defined by trialists; moderate or severe neurological impairment: developmental delay or intellectual impairment - developmental quotient or intelligence quotient less than two standard deviations (SD) below the mean; legal blindness; sensorineural deafness requiring hearing aids).

For the woman

- Maternal adverse drug reaction.
- Maternal infection - chorioamnionitis/amnionitis.
- Postpartum pyrexia.
- Adverse drug reaction requiring cessation of treatment.
- Admission to intensive care.
- Maternal death.

Health services use

- Length of maternal postnatal hospital stay.
- Length of neonatal postnatal hospital stay.

In this update, primary and secondary outcomes have been defined. Additional outcomes measures are included as primary outcomes. For the woman these are: serious adverse outcome related to antibiotic treatment (respiratory arrest, cardiac arrest, death); admission to intensive care; and maternal death; and for the infant/child, a composite measure of death (fetal, neonatal, or later death up to the time of follow-up) or major long-term infant neurosensory impairment. Further, the list of outcomes measures included in subgroup analyses are now restricted to those that are considered to be most clinically important as defined above.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2013).

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

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

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group. Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
We did not apply any language restrictions.

Data collection and analysis

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

Selection of studies

At least two review authors (V Flenady, G Hawley and O Stock) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third person.

Data extraction and management

The review authors used the standard methods of The Cochrane Collaboration and considered all potential trials for inclusion. Evaluation of methodological quality and data extraction were undertaken independently by at least two review authors (V Flenady, G Hawley and O Stock) in this update, as described in Higgins 2011.
We resolved discrepancies through discussion. We entered data into Review Manager software (RevMan 2012) and checked for accuracy.
When information was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

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

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

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

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

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

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

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

(3) Blinding (checking for possible performance bias)

We described for each included study, the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We provided information on whether the intended blinding was effective. Where blinding was not possible, we assessed whether the lack of blinding was likely to have introduced bias. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

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

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

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

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with

substantial departure of intervention received from that assigned at randomisation);

- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how the possibility of selective outcome reporting bias was examined by us and what we found. We assessed the methods as:

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

(6) Other sources of bias

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

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses- *see* Sensitivity analysis. However, this was not required due to the generally high quality of the included studies.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference as outcomes were measured in the same way between trials.

Unit of analysis issues

Multiarm studies

For the subgroup comparisons undertaken, to avoid double counting, we divided out data from the shared group approximately evenly among the comparisons as described in the *Cochrane Handbook* 16.5.4 (Higgins 2011). This was undertaken in the subgroup analyses for the ORACLE II trial (Kenyon 2001a).

Multiple pregnancy

The analysis in this review involves multiple pregnancies, therefore, wherever possible, analyses should be adjusted for clustering to take into account the non-independence of babies from the same pregnancy (Gates 2004). Treating babies from multiple pregnancies as if they are independent, when they are more likely to have similar outcomes than babies from different pregnancies, will overestimate the sample size and give confidence intervals that are too narrow. Each woman can be considered a cluster in multiple pregnancy, with the number of individuals in the cluster being equal to the number of fetuses in her pregnancy. Analysis using cluster trial methods allows calculation of relative risk and adjustment of confidence \intervals. Usually this will mean that the confidence intervals get wider. Although this may make little difference to the conclusion of a trial, it avoids misleading results in those trials where the difference may be substantial.

We planned to adjust for clustering in the analyses, wherever possible, and to use the inverse variance method for adjusted analyses, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, due to insufficient information in the included trials, we were not able to adjust our analyses. In future updates, if possible, we will adjust for clustering in the analyses. The largest trial, Kenyon 2001a, reported only one neonatal outcome in a multiple pregnancy (the worst outcome) where more than one outcome was found. The other three trials that enrolled women with a multiple pregnancy reported outcomes for each infant and were incorporated as such into the meta-analysis.

Cross-over trials

We excluded cross-over trials.

Cluster-randomised trials

We did not identify any cluster-randomised trials for inclusion in this review, but we may include trials of this type in future updates. If we do, we plan to include cluster-randomised trials in the analyses along with individually-randomised trials. Their sample sizes will be adjusted using the methods described in the *Ccohrane Handbook* (Higgins 2011) using an estimate of the intracluster

correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.
We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we noted levels of attrition in the 'Risk of bias' table. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

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

Assessment of reporting biases

If 10 or more studies had contributed data to meta-analysis for any particular outcome, we investigated reporting biases (such as publication bias) using funnel plots. We have assessed possible asymmetry visually. If asymmetry was suggested by a visual assessment, we planned to perform exploratory analyses to investigate it. In this version of the review insufficient data were available to allow us to carry out this planned analysis.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If clinical heterogeneity was evident sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful.
The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. Where random-effects analyses were used, the results are presented as the average treatment effect with its 95% confidence interval, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analyses. We considered whether an overall summary was meaningful, and if so, used random-effects analysis to produce it. We assessed subgroup differences by interaction tests available within RevMan (RevMan 2012).

A priori subgroup analyses

The following subgroup analyses were planned.

- Macrolide antibiotics alone compared with no antibiotic.
- Beta-lactam antibiotics alone compared with no antibiotic.
- Macrolide and beta-lactam antibiotics compared with no antibiotic.
- Antibiotics active against anaerobic bacteria compared with no antibiotic.
- Antibiotics compared with no antibiotics commenced between 28 to 36 completed weeks' gestation versus less than 28 completed weeks.

Two additional subgroup analyses were included in this updated of the review as follows.

- Any macrolide antibiotics (including macrolide antibiotics used as a single agent or in combination with other types of antibiotics) versus no macrolide antibiotics (including use of any non-macrolide antibiotics or no antibiotics).
- Any beta-lactam antibiotics (including beta-lactam antibiotics used as a single agent or in combination with other types of antibiotics) versus no beta-lactam antibiotics (including use of any non-beta-lactam antibiotics or no antibiotics).

For subgroup analyses the following subset of outcome measures were included.
For the infant/child.

- Death or major long-term infant neurosensory impairment at time of follow-up.
- Neurosensory impairment long-term: any, and moderate and severe, cerebral palsy.
- Interval between randomisation and birth.

- Birth prior to 37 weeks' gestation.
- Perinatal mortality.
- Stillbirth.
- Neonatal death.
- Infant death.
- Birth within 48 hours of randomisation.
- Intraventricular haemorrhage.
- Necrotising enterocolitis.

For the woman.

- Serious adverse outcome related to antibiotic treatment (respiratory arrest, cardiac arrest, death).
- Maternal adverse drug reaction.
- Maternal infection - chorioamnionitis/amnionitis.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates (greater than 20%), or both, with poor-quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result.

RESULTS

Description of studies

See Characteristics of included studies; and Characteristics of excluded studies.

Results of the search

The previous review update included 11 trials: Cox 1996; Gordon 1995; Kenyon 2001a; McGregor 1991; Newton 1989; Newton 1991; Norman 1994; Oyarzun 1998; Romero 1993; Svare 1997; Watts 1994. A further seven trials were identified and excluded for the reasons described in the table of excluded studies (McCaul 1992; McGregor 1986; McGregor 1988; Morales 1988; Nadisauskiene 1996; Saez-Llorens 1995; Winkler 1988).

In this update, 13 potentially eligible studies were reviewed for inclusion. Three new studies were included: Keuchkerian 2005; Rajaei 2006; Reimer 1999) and 10 were excluded: Gurbuz 2004; Hensen 1987; Jones 2011; Lauterbach 2012.; Naef 1994; Ogasawara 1996; Oszukowski 2000; Ovalle 2006; Ozden 2000; Purwar 1997. In addition, one study Kenyon 2008a reported longer outcomes of Kenyon 2001a.

The review now includes a total of 14 trials randomising 7837 women.

Included studies

Study population

All included studies used similar definitions of preterm labour, which included the presence of uterine contractions and cervical dilatation. As there is no accurate clinical test for the diagnosis of preterm labour this diagnosis relies on a clinical decision which is non-specific; the majority of women in the included studies went on to deliver at term. All studies excluded women with symptoms or signs suggestive of overt clinical infection of the mother or fetus. Gestational ages were similar in all trials with a mean gestational age at entry of 30 to 32 weeks. Two trials Oyarzun 1998 and Kenyon 2001a recruited participants between 34 and 36 weeks' gestation. Reimer 1999 did not report on a specific gestational age at recruitment. Multiple pregnancies were included in four of the 14 trials (Cox 1996; Gordon 1995; Kenyon 2001a; Newton 1991). It was unclear whether Reimer 1999 included multiple pregnancies.

Antibiotic regimens

The studies included a variety of antibiotics and a range of dosing schedules. Antibiotics were administered intravenously in nine of the trials. In three trials, they were administered orally only (Kenyon 2001a; Oyarzun 1998; Rajaei 2006) and four trials used a combination of intravenous infusion followed by oral mediation (Keuchkerian 2005; Newton 1989; Norman 1994; Romero 1993); the remainder using intravenous infusion alone. Ten trials used a combination of antibiotics: Kenyon 2001a used a 2 x 2 factorial design to compare the effects of amoxicillin/clavulanic acid and/or erythromycin with placebo; Newton 1989 (ampicillin and erythromycin), Newton 1991 (ampicillin and sulbactam), Romero 1993 and Oyarzun 1998 (ampicillin/amoxycillin and erythromycin), Norman 1994 and Svare 1997 (ampicillin and metronidazole), Cox 1996 (ampicillin and sulbactam or clavulanic acid), Watts 1994 (mezlocillin and erythromycin); Keuchkerian 2005 used amoxicillin and sulbactam. Four studies used single agent therapy: McGregor 1991 (clindamycin); Gordon 1995 (ceftizoxime); Rajaei 2006 (erythromycin); and Reimer 1999 (mezlocillin). The duration of antibiotic treatment differed: eight trials used a five- to seven-day course (Cox 1996; Keuchkerian 2005; McGregor 1991; Newton 1989; Newton 1991; Norman 1994; Oyarzun 1998; Svare 1997. Romero 1993 used an eight-day course; and Kenyon 2001a, Watts 1994 and Rajaei 2006 10 days. Two studies used a shorter course of three days: Reimer 1999 and Gordon 1995 (initially commenced the trial using a five-day course).

Other management strategies

In 13 of the 14 studies, the antibiotics were used with a policy for tocolysis as standard management. In Kenyon 2001a, 56% of participants received tocolysis. A variety of tocolytic agents were used

in the trials including betamimetics, indomethacin, magnesium sulphate and nifedipine. Antenatal corticosteroid administration to stimulate fetal maturation was reported as part of the clinical protocol in 12 of the included studies. The frequency of steroid usage varied between trials from approximately 30% (Gordon 1995; Newton 1991) to greater than 90% (Keuchkerian 2005; Norman 1994; Oyarzun 1998; Rajaei 2006; Romero 1993; Svare 1997). In Kenyon 2001a, over 80% of participants received antenatal corticosteroids.

Seven studies reported vaginal cultures for Group B Streptococcus (GBS) as part of the study protocol. Four of these trials (McGregor 1991; Newton 1991; Oyarzun 1998; Romero 1993) reported intrapartum antibiotic administration for women with a positive GBS culture, in addition to the study medication. Gordon 1995 withdrew women who had a positive GBS culture from the study and administered intrapartum antibiotics. One study Kenyon 2001a did not collect data on GBS status

Outcome measures

Outcome measures were not always clearly or consistently defined or reported across the trials, with the exception of Kenyon 2001a who reported precise definitions for all outcome measures. The definition of neonatal sepsis was inconsistent across the included studies and there were large differences in the rates of neonatal infection reported. Svare 1997 reported a rate of neonatal sepsis of 22% in controls, whereas the overall rate for controls in all trials was 8.5%. Kenyon 2001a reported on proven sepsis only (blood culture positive), with a rate in the placebo arm of 2%. Kenyon 2001a reported the outcome of major cerebral abnormality (any intraparenchymal cerebral bleed, hydrocephalus, any parenchymal cysts (porencephalic or cystic leukomalacia) (personal communication) on ultrasound prior to hospital discharge. This outcome has been included in the review. Additional neonatal outcomes were included from Keuchkerian 2005 and Rajaei 2006 in this update.

Long-term outcome data, up to seven years of age, were available for one study (Kenyon 2001a) reported in Kenyon 2008a. The follow-up included infants from the initial study who were born to mothers enrolled in the UK, representing 50% of all infants enrolled and 71% of all UK infants. The primary outcome was defined as the presence of any level of functional impairment and secondary outcomes included a range of medical and behavioural outcomes. Educational attainment at seven years was assessed for children attending school in England using results from National Curriculum tests at Key Stage 1. The following outcomes from this follow-up study have been included in the review: infant death (deaths of liveborn infants to 12 months of age); functional impairment (any i.e. severe, moderate or mild combined; and moderate and severe combined) and cerebral palsy (CP) measured using proxy information provided by parents through a postal questionnaire (or by telephone in a small number) using validated tools. Clinical assessment was not feasible due to the numbers of children involved. Functional impairment was obtained using the Health Utilities Index (HUI) Saigal 1994 from which the Multi-Attribute Health Status (MAHS) was derived. The proportion of missing data (of those eligible for follow-up) for these included outcomes are as follows: infant death (to 12 months of age (Nil); at seven years of age, any functional impairment and moderate or severe functional impairment and cerebral palsy (71%). The investigators assessed the characteristics of the responders to the questionnaires and found that they were "broadly similar to the total population enrolled" in the ORACLE II trial (Kenyon 2001a).

Excluded studies

In total, 16 studies were excluded from this review (Gurbuz 2004; Hensen 1987; Lauterbach 2012; McCaul 1992; McGregor 1986; McGregor 1988; Morales 1988; Nadisauskiene 1996; Naef 1994; Ogasawara 1996; Oszukowski 2000; Ovalle 2006; Ozden 2000; Purwar 1997; Saez-Llorens 1995; Winkler 1988).

Five studies were excluded as women with rupture of the membranes were randomised (Nadisauskiene 1996; Naef 1994; Ogasawara 1996; Purwar 1997; Winkler 1988) and are covered by another Cochrane review (Kenyon 2010). One study enrolled women who were not in labour (McGregor 1988) and in another, the intervention was not an antibiotic (Lauterbach 2012). Three studies were excluded as they used a quasi-randomised method of treatment allocation (Ovalle 2006; Ozden 2000; Saez-Llorens 1995) and six studies were excluded as additional information to enable assessment of quality and eligibility were not able to be obtained from the authors (Gurbuz 2004; Hensen 1987; McCaul 1992; McGregor 1986; Morales 1988; Oszukowski 2000). A further study (Jones 2011), reported a methodological study using data from the ORACLE follow-up study (Kenyon 2008a).

Refer to table Characteristics of excluded studies for further details.

Risk of bias in included studies

Overall the quality of the included trials was good. Refer to Characteristics of included studies for further details. for further details and to Figure 1 ; Figure 2 , for a summary of 'Risk of bias' assessments.

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

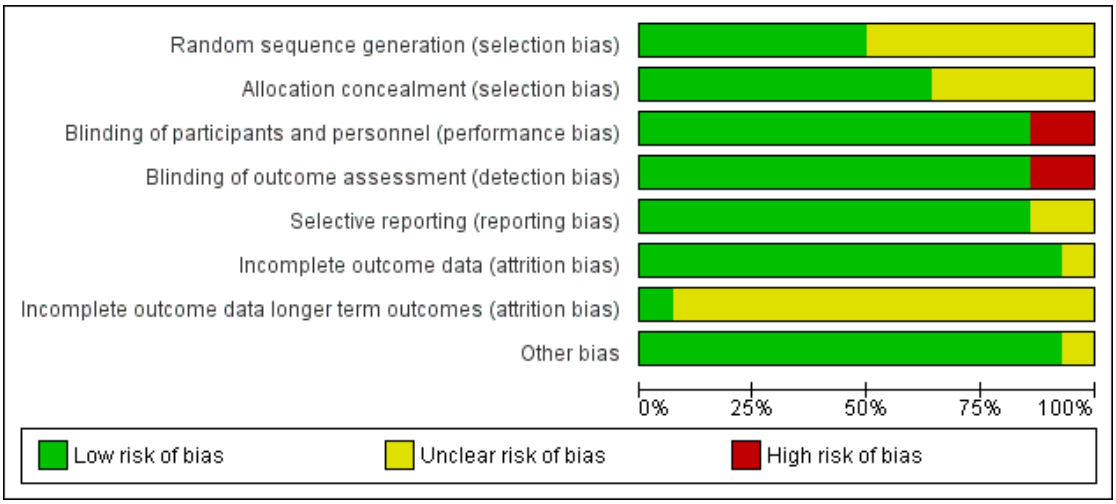
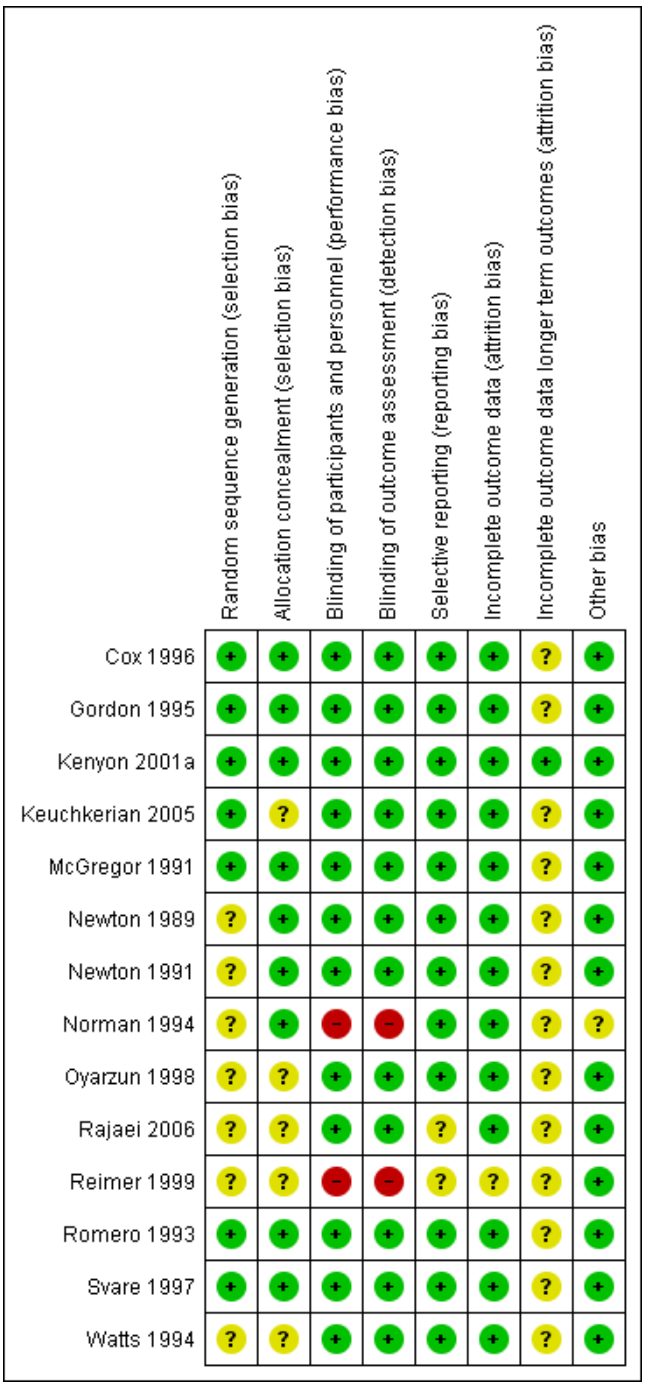


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

In seven trials, the method of sequence generation was unclear (Newton 1989; Newton 1991; Norman 1994; Oyarzun 1998; Rajaei 2006; Reimer 1999; Watts 1994). The remaining seven trials were assessed as having a low risk of bias with respect to sequence generation (Cox 1996; Gordon 1995; Kenyon 2001a; Keuchkerian 2005; McGregor 1991; Romero 1993; Svare 1997).

Allocation concealment

In five trials, the method of allocation concealment was unclear (Keuchkerian 2005; Oyarzun 1998; Rajaei 2006; Reimer 1999; Watts 1994). The nine remaining trials were assessed as having a low risk of bias with respect to allocation concealment.

Blinding

Twelve of the 14 included trials were placebo-controlled, with blinding of caregivers and participants (Cox 1996; Gordon 1995; Kenyon 2001a; Keuchkerian 2005; McGregor 1991; Newton 1989; Newton 1991; Oyarzun 1998; Rajaei 2006; Romero 1993; Svare 1997; Watts 1994. Blinding of outcome assessment was assessed as low risk of bias in these 12 trials.
Two trials were assessed as high risk of bias for both blinding of caregivers and participants and outcome assessment as a placebo was not used (Norman 1994 and Reimer 1999).

Incomplete outcome data

Thirteen studies were assessed as being at low risk of bias for attrition bias with three studies reporting no losses to follow-up (Gordon 1995; Keuchkerian 2005; Watts 1994) and 10 studies reporting less than 20% loss to follow-up (Cox 1996; Kenyon 2001a; McGregor 1991; Newton 1989; Newton 1991; Norman 1994; Oyarzun 1998; Rajaei 2006; Romero 1993; Svare 1997). In one trial (Reimer 1999), it was unclear whether attrition bias was present. Long-term follow-up of infants (to seven years of age) was included for one trial (Kenyon 2001a). This trial was assessed as having a low risk of bias for these outcomes as 71% of all eligible infants were included in the analysis and comparison with outcomes in the general population showed similar event rates (cerebral palsy).

Selective reporting

Twelve studies were assessed as being at low risk of bias for selective reporting (Cox 1996; Gordon 1995; Kenyon 2001a; Keuchkerian 2005; McGregor 1991; Newton 1989; Newton 1991; Norman 1994; Oyarzun 1998; Romero 1993; Svare 1997; Watts 1994) as all expected outcomes were reported.
In two studies, the risk of bias was unclear (Rajaei 2006; Reimer 1999). Reimer 1999 did not report neonatal outcomes however all prespecified outcome measures were reported.

Other potential sources of bias

Thirteen studies were assessed as being at low risk of bias for other potential sources of bias based on baseline characteristics being similar between groups and no other bias apparent (Cox 1996; Gordon 1995; Kenyon 2001a; Keuchkerian 2005; McGregor 1991; Newton 1989; Newton 1991; Oyarzun 1998; Rajaei 2006; Reimer 1999; Romero 1993; Svare 1997; Watts 1994). One trial (Norman 1994) (which showed positive pregnancy prolongation outcomes) was stopped early following an interim analysis and was assessed as being unclear risk of bias.

Effects of interventions

The meta-analysis includes outcomes from 14 included trials randomising 7837 women.

Comparison 1: Any antibiotics versus no antibiotics

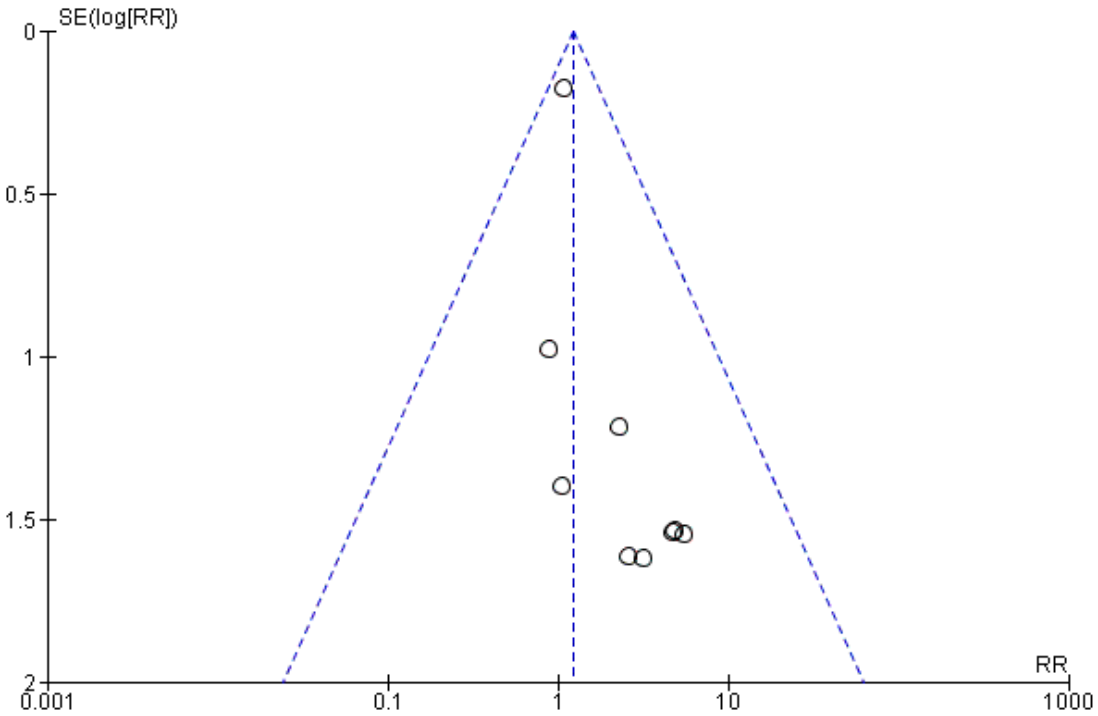
Primary outcome measures

For the infant/child

Perinatal and infant mortality

No statistically significant difference was demonstrated in perinatal mortality (risk ratio (RR) 1.22, 95% confidence interval (CI) 0.88 to 1.69; 10 studies with 7304 women) Analysis 1.1 or stillbirth (RR 0.73, 95% CI 0.43 to 1.26; eight studies, 7080 infants) Analysis 1.2. However, an increase in neonatal deaths was shown for infants of women receiving any prophylactic antibiotics when compared with placebo (RR 1.57, 95% CI 1.03 to 2.40; number needed to treat to harm (NNTH) 149, 95% CI 2500 to 61; nine studies; 7248 infants) Analysis 1.3.
A funnel plot for the analysis of perinatal mortality (Figure 3), including the 10 studies, was reasonably symmetrical therefore not suggestive of important reporting bias or small-study effect.

Figure 3. Funnel plot of comparison: 1 Any antibiotics versus no antibiotics, outcome: 1.1 Perinatal mortality.



Long-term outcomes

Long-term outcomes for the infant/child were available from UK infants enrolled in the large ORACLE II trial Kenyon 2001a. When compared to no antibiotics (placebo), no difference was shown in infant deaths (RR 1.06, 95% CI 0.68 to 1.67; 4654 infants) Analysis 1.4, any functional impairment (RR 1.10, 95% CI 0.99 to 1.23) Analysis 1.5, or moderate to severe impairment (RR1.07, 95% CI 0.89 to 1.28; 3052 infants) Analysis 1.6 at seven years of age.

A marginally non-statistically significant increase in cerebral palsy (CP) at seven years of age was shown (RR 1.82, 95% CI 0.99 to 3.34; 3173 infants) Analysis 1.7.

For the woman

No data were available for other prespecified primary outcomes for the woman, of serious adverse outcome related to antibiotic treatment (respiratory arrest, cardiac arrest, death) or adverse drug reaction requiring cessation of treatment.

Secondary outcome measures

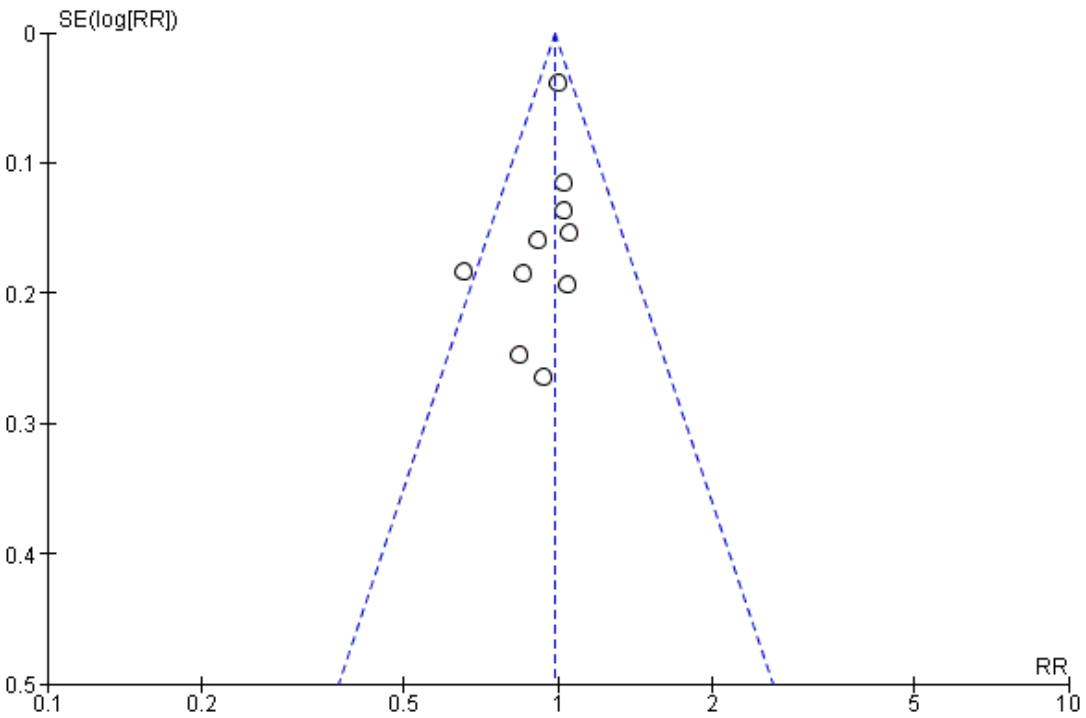
For the infant

Pregnancy prolongation

No difference was shown in birth prior to 36 or 37 weeks' gestation (RR 0.98, 95% CI 0.92 to 1.05; 10 studies, 7387 women) Analysis 1.12. None of the included trials reported the prespecified outcomes of birth prior to 28 or 34 weeks' gestation.

A funnel plot for the analysis of preterm birth (less than 36 or less than 37 weeks) (Figure 4) was symmetrical and therefore not suggestive of important bias or small-study effect.

Figure 4. Funnel plot of comparison: 1 Any antibiotics versus no antibiotics, outcome: 1.12 Preterm birth (< 36 or < 37 weeks).



The Interval between randomisation and birth (days) was longer for women receiving antibiotics (average mean difference (MD) 5.59 days, 95% CI 0.31 to 10.87; random-effects, Tau^2 = 25.22, I^2 = 64%) Analysis 1.11. However, no significant difference was shown in the outcome of birth within 48 hours (RR 1.04, 95% CI 0.89 to 1.23), or seven days from randomisation (RR 0.98, 95% CI 0.87 to 1.10) Analysis 1.10, or for gestational age at birth (average MD 0.53 days, 95% CI 0.00 to 1.06; random-effects, Tau^2 = 0.27, I^2 = 40%) Analysis 1.13.

Upon exploration of the possible reasons for the heterogeneity for the outcomes of Interval from randomisation to birth and gestational age at birth, by examining clinical features of the trials (including population characteristics such as gestation at enrolment, diagnosis of preterm labour and other aspects of routine management of preterm labour, and antibiotic administration regimens), we considered an overall summary was clinically meaningful using a random-effects analysis.

Other neonatal outcomes

No significant difference was shown in the following neonatal outcomes.

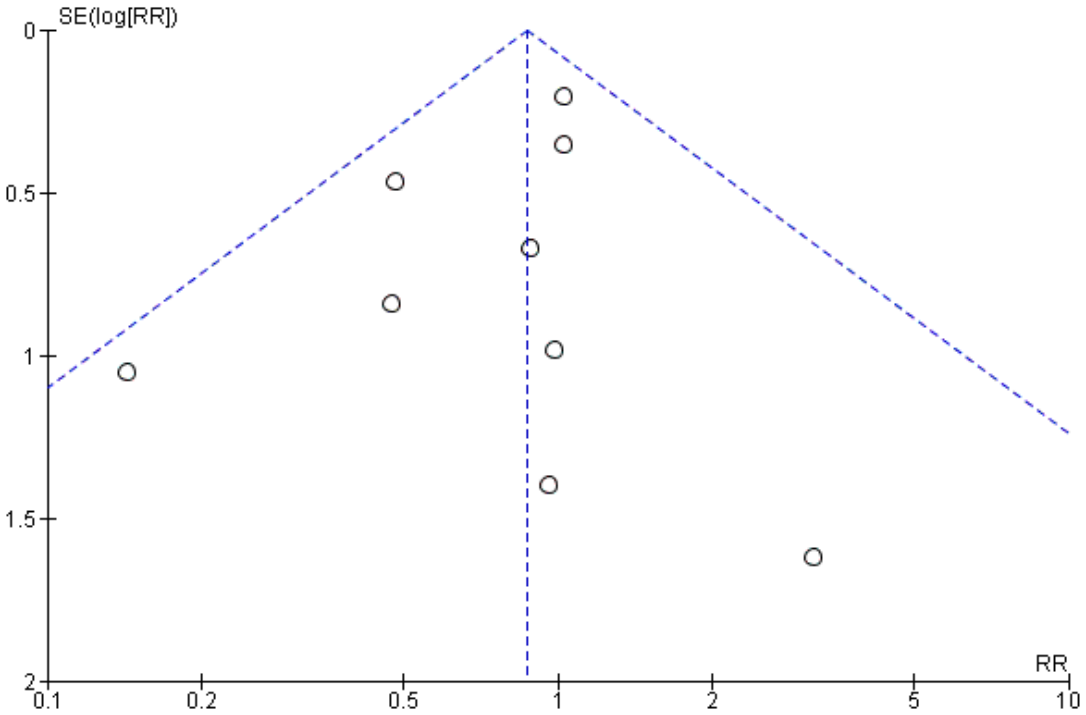
- Birthweight (average MD 58.38, 95% CI -26.24 to 143.00; random-effects, Tau^2 = 8895.21, I^2 = 49%; 12 trials, 7531 infants) Analysis 1.14.
- Birthweight less than 2500 g (average RR 0.97, 95% CI 0.81 to 1.15; random-effects, Tau^2 = 0.02, I^2 = 45%; five trials, 6682 infants) Analysis 1.15.
- Admission to neonatal intensive care or special care (average RR 0.82, 95% CI 0.62 to 1.10, random-effects Tau^2 =0.06, I^2 = 69%; five trials, 6875 infants) Analysis 1.16.

After close inspection of the characteristics of the studies in the analyses (as defined above) for the above outcomes (birthweight less than 2500 g; birthweight; and admission to neonatal Intensive care), we decided that average treatment effect across trials was clinically meaningful and therefore proceeded with random-effects meta analysis (where required) to combine these outcome data.

- Mechanical ventilation (RR 1.02, 95% CI 0.84 to 1.24; one trial, 6241 infants) Analysis 1.17.
- Respiratory distress syndrome (RR 0.99, 95% CI 0.84 to 1.16; nine trials, 7200 infants) Analysis 1.18.
- Neonatal positive blood culture (RR 1.01, 95% CI 0.69 to 1.49; three trials, 6526 infants) Analysis 1.19.
- Neonatal sepsis (RR 0.86, 95% CI 0.64 to 1.16; 10 trials, 7386 infants) Analysis 1.20.

A funnel plot for the analysis of neonatal sepsis was reasonably symmetrical and therefore not suggestive of the presence of important reporting bias or small-study effect. Figure 5.

Figure 5. Funnel plot of comparison: 1 Any antibiotics versus no antibiotics, outcome: 1.20 Neonatal sepsis.



- Intraventricular haemorrhage (RR 0.76, 95% CI 0.48 to 1.19; five trials, 6813 infants) Analysis 1.21.
- Necrotising enterocolitis (RR 1.06, 95% CI 0.64 to 1.73; six trials, 6880 infants) Analysis 1.22.
- Major cerebral abnormality (RR 1.00, 95% CI 0.66 to 1.51; one trial, 6241 infants) Analysis 1.23.
- Chronic lung disease (RR 1.17, 95% CI 0.78 to 1.76; one trial, 6241 infants) Analysis 1.24.

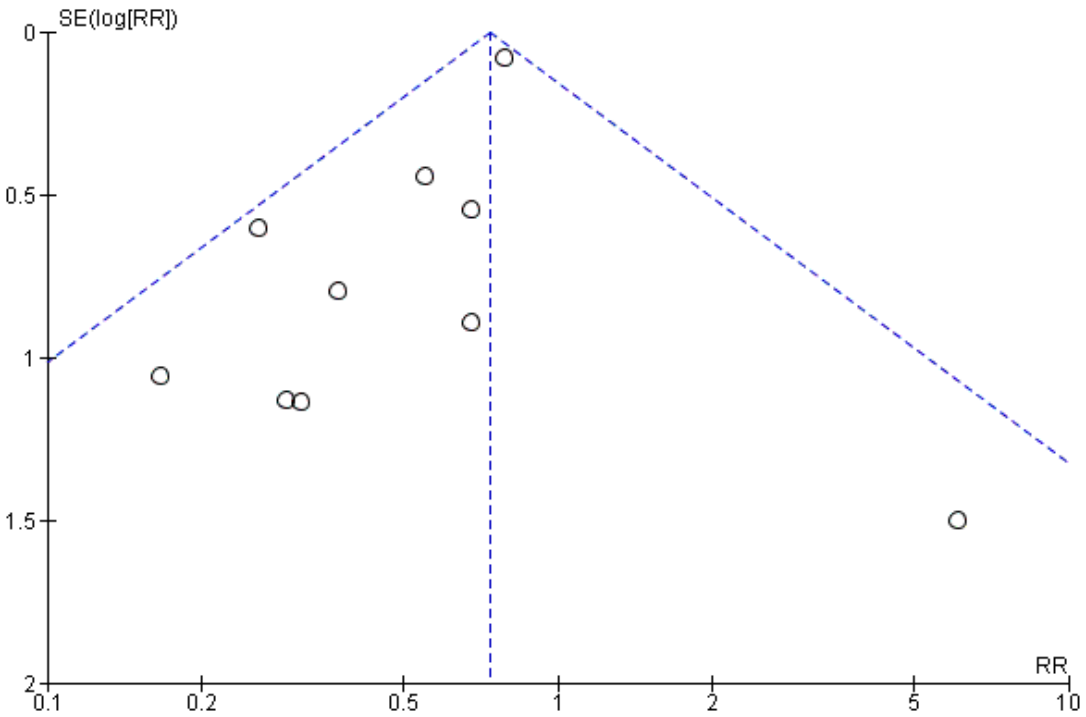
Data were not available for the following prespecified secondary outcomes: cerebral cystic lesions (periventricular leukomalacia, porencephalic cysts) (although Kenyon 2001a reported any major cerebral abnormality on ultrasound prior to discharge, which was included); intraventricular haemorrhage (grades three and four); Apgar score of less than seven at five minutes; retinopathy of prematurity (all stages); retinopathy of prematurity (stages III and IV).

A funnel plot for the analysis of preterm birth (less than 36 or less than 37 weeks) (Figure 4 was symmetrical and therefore not suggestive of the presence of important bias or small-study effect.

For the woman

Meta-analysis of 10 studies including 7371 women showed a statistically significant reduction in maternal infection (chorioamnionitis/endometritis) for women receiving antibiotics (RR 0.74, 95% CI 0.63 to 0.86) giving a number needed to treat to benefit (NNTB) of 34, 95% CI 24 to 63) Analysis 1.9. A funnel plot for this analysis (Figure 6), including the 10 studies was asymmetrical. This suggests that there may be some important biases or small-study effects in the set of studies in this analysis and so these results should be viewed with caution.

Figure 6. Funnel plot of comparison: 1 Any antibiotics versus no antibiotics, outcome: 1.9 Maternal infection.



Maternal adverse drug reaction requiring cessation of treatment was increased in the group of women receiving antibiotics but this did not reach statistical significance (RR 1.32, 95% CI 0.92, 1.89; five studies, 626 women) Analysis 1.8.

Health service utilisation

None of the included studies reported on the prespecified outcome of length of hospital stay for women or infants.

Subgroup analyses

Subgroup analyses were undertaken as follows: *Antibiotic versus no antibiotics subgrouped by type of antibiotic*; and *Any macrolide versus no macrolide antibiotics; and Any beta-lactam versus no beta-lactam antibiotics.* Due to insufficient data, the planned subgroup analysis relating to different gestational age groups at commencement of antibiotics was not able to be undertaken.

Comparison 2: Antibiotic versus no antibiotics subgrouped by type of antibiotic

Exploration of differential effects of single and combination antibiotic therapy compared with no antibiotics was undertaken using the following subgroups.

- Treatment with macrolide antibiotics alone compared with no antibiotic.
- Treatment with beta-lactam antibiotics alone compared with no antibiotic.
- Treatment with macrolide and beta-lactam antibiotics compared with no antibiotic.
- Treatment with antibiotics active against anaerobic bacteria compared with no antibiotic.

Primary outcome measures

For the infant/child

No differences were shown for perinatal mortality, stillbirth, neonatal or infant death.

An increase in CP for the subgroup of children exposed to macrolide (erythromycin) and beta-lactam antibiotics combined compared with no antibiotics was shown (RR 2.83, 95% CI 1.02 to 7.88), giving the NNTH of 35 (95% CI 333 to 9). Cerebral palsy was not statistically significantly increased for beta-lactam alone (RR 1.22, 95% CI 0.41 to 3.63), or for macrolide alone (RR 1.42, 95% CI 0.48 to 4.15). The results were not statistically significantly across subgroups (Chi^2 = 1.41, df = 2 (P = 0.49), I^2

= 0%), Analysis 2.7.

No difference was shown in the measures of functional impairment at seven years of age (test for subgroup differences: Chi² = 0.46, df = 2 (P = 0.80), I² = 0%). A small trend toward an increase in any functional impairment was shown in the subgroups of infants exposed to macrolide and macrolide and beta-lactam antibiotics (RR 1.13, 95% CI 0.94 to 1.35) Analysis 2.5.

For the woman

No data were available for other prespecified primary outcomes for the woman, of serious adverse outcome related to antibiotic treatment (respiratory arrest, cardiac arrest, death) or adverse drug reaction requiring cessation of treatment.

Secondary outcome measures

For the infant/child

Pregnancy prolongation

In the subgroup analysis of antibiotics active against anaerobes, including three studies (McGregor 1991; Norman 1994; Svare 1997) with 293 women, a statistically significant increase in the Interval between randomisation and birth (three studies with 293 women) (MD 10.50 days, 95% CI 4.95 to 16.06) was shown, which was not present in the other subgroups, (test for subgroup differences: Chi² = 13.41, df = 3 (P = 0.004), I² = 77.6%) Analysis 2.11.

No statistically significant differences were evident in short-term infant outcomes across these subgroups

For the woman

No statistically significant differences were evident across the subgroups for the two outcomes for women included in this review of maternal infection or adverse drug reaction requiring cessation of treatment.

Comparison 3: Any macrolide versus no macrolide antibiotics

Primary outcome measures

For the infant/child

The use of any macrolide (erythromycin and erythromycin and co-amoxiclav combined) compared with no macrolide antibiotics (co-amoxiclav or placebo) was associated with an increase in neonatal death (RR 1.52, 95% CI 1.05 to 2.19, NNTH 139, 95% CI 1429 to 61; three trials, 6684 infants) Analysis 3.3.

Data from the UK children in the ORACLE II study showed an increase in any functional impairment (RR 1.11, 95% CI 1.01 to 1.20, NNTH 24, 95% CI 263 to 13) Analysis 3.5 at seven years of age (3052 children) and CP (RR 1.90, 95% CI 1.20 to 3.01, NNTH 64, 95% CI 286 to 29; 3173 children) Analysis 3.7. No difference was shown in moderate/severe functional impairment at seven years of age (RR 1.08, 95% CI 0.93, 1.26; 3052 children) Analysis 3.6.

No difference was shown in:

- Perinatal mortality (RR 1.20, 95% CI 0.89 to 1.60;four trials, 6740 infants) Analysis 3.1.
- Stillbirth (RR 0.70, 95% CI 0.41 to 1.20; two trials, 6518 infants) Analysis 3.2.
- Infant death (RR 1.47, 95% CI 0.99 to 2.18; one trial, 4583 infants) Analysis 3.4.

For the woman

No data were available for other prespecified primary outcomes for the woman, of serious adverse outcome related to antibiotic treatment (respiratory arrest, cardiac arrest, death) or adverse drug reaction requiring cessation of treatment.

Secondary outcome measures

For the infant/child

Pregnancy prolongation

No difference was shown in any other outcomes included in this analysis as follows.

- Birth within 48 hours of randomisation (RR 1.08, 95% CI 0.94 to 1.25; three trials, 6691 infants) Analysis 3.10.
- Interval between randomisation and birth (MD 1.07, 95% CI -3.58, 5.72; random-effects: Tau² = 8.45; I² = 33%; three trials, 6386 infants) Analysis 3.11 Heterogeneity: Tau² = 8.45; Chi² = 3.60, df = 2 (P = 0.17); I² = 44%.
- Birth prior to 36 or 37 weeks' gestation (RR 1.01, 95% CI 0.95 to 1.07; four trials, 6784 infants) Analysis 3.12.

Other neonatal outcomes

No difference was shown in any other outcomes included in this analysis as follows.

- Respiratory distress syndrome (RR 1.04, 95% CI 0.90 to 1.21; four trials, 6740 infants) Analysis 3.13.
- Intraventricular haemorrhage (RR 0.96, 95% CI 0.62 to 1.49; two trials, 6516 infants) .Analysis 3.14.
- Necrotising enterocolitis (RR 1.16, 95% CI 0.74 to 1.80; two trials, 6516 infants) Analysis 3.15.

For the woman

Adverse drug reaction requiring cessation of treatment was increased for women receiving any macrolide antibiotics (erythromycin), however this finding was not statistically significant (RR 1.49, 95% CI 0.93 to 2.40; two trials, 331 women) Analysis 3.8 .

No difference was shown for the outcome of maternal infection (average RR 0.66, 95% CI 0.41 to 1.07; random-effects: Tau² = 0.18, I² = 57%; four trials, 6745 women) Analysis 3.9.

Comparison 4: Any beta-lactam versus no beta-lactam

Primary outcome measures

For the infant/child

The use of any beta-lactam antibiotics (including beta-lactam antibiotics alone or in combination with erythromycin) versus no beta-lactam antibiotics (including erythromycin alone or no antibiotics) was associated with an increase in neonatal death (RR 1.51, 95% CI 1.06 to 2.15, NNTH 143, 95% CI 1250 to 63; seven trials, 7053 infants) Analysis 4.3. Data from UK children in the ORACLE II study showed an increase in CP (RR 1.67, 95% CI 1.06 to 2.61, NNTH 79, 95% CI 909 to 33; one trial, 3173 children) Analysis 4.7.

No difference was shown for the following outcomes.

- Perinatal mortality (RR 1.12, 95% CI 0.84 to 1.48; eight trials, 7109 infants) Analysis 4.1,
- Stillbirth (RR 1.10, 95% CI 0.76 to 1.58; six trials, 6887 infants) Analysis 4.2,
- Infant death (RR 0.94, 95% CI 1.64 to 1.38; one trial, 4654 infants) Analysis 4.4.
- Any functional impairment (RR 1.02, 95% CI 0.93 to 1.11) Analysis 4.5 or moderate/severe functional impairment (RR 1.03, 95% CI 0.88 to 1.20) at seven years of age, (one trial, 3052 children) Analysis 4.6

For the woman

No data were available for other prespecified primary outcomes for the woman, of serious adverse outcome related to antibiotic treatment (respiratory arrest, cardiac arrest, death) or adverse drug reaction requiring cessation of treatment.

Secondary outcome measures

For the infant/child

Pregnancy prolongation

No difference was shown in any other outcomes included in this analysis as follows.

- Birth within 48 hours of randomisation (RR 1.02, 95% CI 0.89 to 1.18; four trials, 6800 infants) Analysis 4.10.
- Interval between randomisation and birth (average MD 3.92, 95% CI -5.08, 12.92; random-effects: $Tau^2 = 44.55$; $I^2 = 72\%$; three trials, 6386 infants) Analysis 4.11.
- Birth prior to 36 or 37 weeks' gestation (RR 0.98, 95% CI 0.92 to 1.04; eight trials, 7185 infants) Analysis 4.12.

Other neonatal outcomes

No difference was shown in any other outcomes included in this analysis as follows.

- Respiratory distress syndrome (RR 1.02, 95% CI 0.88 to 1.19; eight trials, 7108 infants) Analysis 4.13.
- Intraventricular haemorrhage (RR 0.86, 95% CI 0.56 to 1.31; four trials, 6721 infants) Analysis 4.14.
- Necrotising enterocolitis (RR 0.72, 95% CI 0.27 to 1.92; five trials, 6788 infants) Analysis 4.15.

For the woman

Maternal adverse drug reaction requiring cessation of treatment was increased for women receiving any beta-lactam antibiotics compared to no beta-lactam antibiotics (RR 1.61, 95% CI 1.02 to 2.54; NNTH 17, 95% CI 526 to 7; four trials, 523 women) Analysis 4.8. A reduction was shown in maternal infection (RR 0.80, 95% CI 0.69 to 0.92; NNTB 47, 95% CI 31 to 119; eight trials, 7182 women) Analysis 4.9.

DISCUSSION

The trials in this review overall were of reasonably sound methodology, the populations studied were homogeneous, and the results were generally consistent across the trials. The pooled analyses of the 14 trials included in this review were dominated by the results of the ORACLE II trial Kenyon 2001a. This trial differed from the majority of the trials in that (i) it was one of only three trials in which the antibiotics were used orally rather than intravenously, and (ii) it was one of only two trials which recruited women after 34 weeks' gestation. For these two reasons, it is possible therefore that Kenyon 2001a participants may have been less likely to demonstrate a beneficial effect from antibiotics (such as meaningful prolongation of pregnancy), but for almost all short-term outcomes, the results of Kenyon 2001a are consistent with those of the other trials combined.

While the interval between randomisation and birth was longer for women allocated to any prophylactic antibiotics versus no antibiotics, no benefit was shown in other measures of pregnancy prolongation or clinically important short-term outcomes for the infant. Consistent with these findings, no benefit was shown in subgroup analyses by type of antibiotic versus placebo or any erythromycin versus no erythromycin or any beta-lactam antibiotics versus no beta-lactams. The review identified some evidence of harm in short- and long-term infant/child outcomes associated with antibiotic exposure.

An increase in neonatal deaths was shown comparing any antibiotic with placebo and also when comparing any macrolide to no macrolide (erythromycin) and any co-amoxiclav with no co-amoxiclav. The number need to treat to harm (NNTH) statistic indicates that on average 149, 139, and 143 infants respectively exposed to antibiotics would result in one additional neonatal death (although confidence intervals (CIs) were wide, ranging from 61 to 2500 across these comparisons). Follow-up data at seven years of age from the UK children whose mothers joined the ORACLE II trial (Kenyon 2001a) showed the prescription of any macrolide antibiotic (erythromycin) was associated with an increase in functional impairment; the NNTH statistic showed that (on average) 34 infants (95% CI 24 to 63) being exposed to antibiotics would result in one additional child with functional impairment. The risk of cerebral palsy (CP) was also increased by exposure to either any erythromycin versus none, or any co-amoxiclav (beta-lactum)

versus none, and also when used in combination versus placebo, although the overall risk was low. The average number exposed to antibiotics to cause one additional case of CP was 64, 79 and 35 respectively with wide 95% CIs ranging from 9 to 909 across these comparisons.

The subgroup analysis of antibiotics active against anaerobic bacteria including three studies [McGregor 1991 (using clindamycin); Norman 1994 and Svare 1997 (both using a combination of ampicillin and metronidazole)], showed a statistically significant increase in the number of days from enrolment into the trial to birth of 11 days on average (95% CI 5 to 16). Anaerobic bacteria and the anaerobes of bacterial vaginosis (especially the Bacteroides species) have been associated with preterm labour, and it may be that antibiotics with anti-anaerobic activity are more effective in delaying birth. It should be noted, however, that this delay was not shown to confer benefit in terms of clinically important neonatal or longer-term outcomes.

The long-term outcome data in this review came from the well-conducted ORACLE II trial (The ORACLE Children Study - OCS) Kenyon 2008b. The results were derived from infants born to mothers enrolled in the UK representing 71% of the total UK study population. The authors have presented detailed analyses in support of the generalisability of the findings to the UK population Marlow 2012. The rate of CP among the placebo group was low (1.6%) as many of the babies went on to be born at term. However, comparing the rate of CP among the study group with that reported from a Child CP register in the UK, the prevalence of CP was shown to be higher among children in the ORACLE Children Study Marlow 2012. The investigators reported a standardised morbidity ratio in the OCS children (spontaneous preterm labour with intact membranes) of 3.12 (95% CI 2.47-3.87) Marlow 2012. While not included in this review, no differences were reported in the OCS on educational attainment at seven years across the ORACLE II study groups.

The outcome of CP and functional impairment was largely determined by parental questionnaire and, while not as robust as clinical assessment, the primary outcome, and some of the secondary outcomes, were obtained using a validated tools Saigal 1994 . While chance cannot be ruled out completely, it would not be wise to dismiss this finding of increase CP out of hand.

The causal pathway for these findings is unclear. The pathways leading to human parturition are many and incompletely understood. Subclinical infection and inflammation are likely to play a role in a proportion of spontaneous preterm births, but the proportions may be lower than anticipated (evidence suggests subclinical infection rates of 13% to 22% in women with intact membranes Romero 2006). It could be that, if an episode of preterm labour is infective in origin, maternal defences facilitated by the antibiotics may work to suppress labour but not the associated intrauterine and fetal inflammation. This continuing environment could lead to fetal brain injury. A significant proportion of women (and/or their babies) presenting in spontaneous preterm labour may not have underlying infection and therefore will not benefit from treatment with antibiotics and may even be harmed.

The lack of benefit from the antibiotics may be as a consequence of insufficient transplacental transfer of commonly used antibiotics (Heikkinen 2000) and consideration of novel routes of administration may be required (Keelan 2011). Unfortunately, the diagnosis of subclinical infection remains elusive although advances are being made (Cobo 2009; Kayem 2009; Romero 2010). The subgroup of women with possible subclinical infection were not identified within the trials in this review.

Despite prolongation of pregnancy and reductions in maternal infection, the absence of benefit for any clinically important short-term neonatal outcomes and findings of an increase in neonatal death, functional impairment and CP in children at seven years old supports not giving antibiotics to women in preterm labour with intact membranes in the absence of signs of infection. Further research is required to develop sensitive markers of subclinical infection for women in preterm labour with intact membranes, as this is a group that might benefit from future novel interventions including new modalities of antibiotic therapy. Results from this review stress the importance of future trials of interventions to prevent preterm birth must include assessment of important longer-term child outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review do not support the routine use of prophylactic antibiotics for women in preterm labour with intact membranes without signs of infection.

Implications for research

Further research is required to develop sensitive markers of subclinical infection for women in preterm labour with intact membranes, as this is a group that might benefit from future novel interventions including new modalities of antibiotic therapy. Results from this review stress the importance of future trials of interventions to prevent preterm birth must include assessment of important longer-term child outcomes.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Cox 1996

Methods	Single-centre prospective placebo-controlled randomised clinical trial. Dallas, Texas US
Participants	86 women 24-34 weeks' gestation (mean 30 weeks), in preterm labour (cervical change with contractions). Multiple births were included. Exclusions: ruptured membranes, fetal or maternal complications necessitating delivery Multiple births were included.
Interventions	IV ampicillin 2 g with sulbactam 1 g every 6 h x 8 doses, followed by ampicillin - clavulanate 250 mg every 8 h x 5 days or placebo
Outcomes	Primary outcome: delivery > 36 weeks. Other outcomes - maternal: preterm delivery, days of prolongation (in time categories, not mean days), adverse drug reaction. Neonatal: BW, neonatal morbidity and mortality.
Notes	Pre-trial sample size estimation, 39 required in each arm. 86 were randomised, 8 post-randomisation exclusions. Neither tocolysis nor maternal corticosteroid steroids were used. Additional information on trial methods was received from author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers table.
Allocation concealment (selection bias)	Low risk	"Consecutive, numbered, sealed envelopes". Did not state whether opaque however, assignment was by pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled using identical administration regimen in the 2 study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% drop-out rate (total of 6 women) - due to delivery before study commenced or delivered elsewhere. No further information

Cox 1996 (*Continued*)

Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

Gordon 1995

Methods	Single-centre prospective placebo-controlled randomised clinical trial. Ohio State University Centre, US
Participants	117 women 24-35 weeks' gestation in preterm labour receiving tocolysis. Exclusions: ruptured membranes, higher order multiple pregnancies, advanced cervical dilatation, suspected fetal compromise, recent use of antibiotics, recent positive GBS vaginal culture, evidence of maternal infection
Interventions	IV ceftizoxime 2 g every 8 h for 5 days (initially), later reduced to 3 days because of patients' refusal
Outcomes	Primary outcome: delivery > 35 weeks. Other outcomes - Maternal: infection, interval to delivery (mean days), preterm delivery. Neonatal: GA, BW, sepsis or infection.
Notes	Pre-trial sample size estimation indicated that 64 participants were required in each arm Findings are compared with other study findings in commentary. Toclolytics given to all women

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule. Stratification by twin pregnancy
Allocation concealment (selection bias)	Low risk	By the pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind placebo controlled trial" using identical administration regimen in the two study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported

Gordon 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

Kenyon 2001a

Methods	Multicentre placebo-controlled randomised clinical trial across 161 centres (2 x 2 factorial design)
Participants	6295 women at less than 37 weeks' gestation. (GA at entry was approximately 31 weeks) . with intact membranes and thought to be in preterm labour and clinical uncertainty as to whether to use antibiotics. Exclusions: women already receiving antibiotics, or when there was a perceived requirement for antibiotics; when immediate delivery was desirable or imminent; fetus not premature enough to cause concern; contraindications such as allergy, jaundice, use of theophylline, cabamazepine, digoxin, disopyramide, ternefadine, or astemizole (all of which are contra-indicated with erythromycin)
Interventions	4 study groups as follows (all oral administration): n = 6241. 1. 325 mg co-amoxiclav plus 250 mg erythromycin; n = 1551. 2. 325 mg co-amoxiclav plus erythromycin placebo; n = 1534. 3. 250 mg erythromycin plus co-amoxiclav placebo; n = 1600. 4. co-amoxiclav placebo plus erythromycin placebo. n = 1556. All study medication was given orally every 6 h for 10 days or until delivery, whichever occurred earlier
Outcomes	Primary outcome: Composite neonatal outcome of neonatal death or major adverse outcome - i.e. chronic lung disease or major cerebral abnormality on ultrasound before hospital discharge. Secondary outcomes: delivery within 48 h and within 7 days, mode of delivery, number of days in hospital, maternal antibiotic prescription after delivery and before discharge, GA at delivery, BW < 2500 g or < 1500 g, admission to NICU or special care baby unit, neonatal mechanical ventilation, RDS, treatment with surfactant, neonatal sepsis, NEC Long-term follow-up on a subset of enrolled infants at 7 years of age as follows: Functional impairment was assessed using the Mark III Multi-Attribute Health Status classification system. Primary outcome was defined as any level of functional impairment (severe, moderate or mild). Other outcomes included death, behaviour (using the Strengths and Difficulties questionnaire) prespecified questions on respiratory symptoms, hospital admissions, convulsions, other prespecified medical conditions and demographic data. Educational attainment was evaluated for the subset of children in England using data from National Cirriculum Tests at 7 years of age (Key Stage 1)

Kenyon 2001a (*Continued*)

Notes	Pre-trial sample size estimation based on primary outcome measure. Additional data received and included on perinatal mortality, cerebral abnormalities, pregnancy prolongation. Tocolytics given in just over half of women enrolled and maternal corticosteroids in the majority

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomly generated blocks of 4.
Allocation concealment (selection bias)	Low risk	Sequentially numbered boxes of identical appearance dispensed centrally
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial using identical administration regimen in the 2 study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 women (<1%) were lost to follow-up - fairly consistent across the groups
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Low risk	Long-term follow-up at 7 years of age was undertaken for the infants of women enrolled in the UK only; 71% of all children eligible for follow-up (representing 50% of the total trial population) were included in this assessment
Other bias	Low risk	None apparent.

Keuchkerian 2005

Methods	Single-centre placebo-controlled randomised clinical trial. Montevideo, Uruguay
Participants	96 women 24 to 34 weeks' gestation, singleton pregnancy, intact amniotic membranes, no cerclage, diagnosis of threatened preterm labour, cervical dilatation of < 4 cm Exclusions: haemorrhage, congenital anomalies, polyhydramnios, clinical urinary infection, fetal growth retardation, maternal pathologies such as diabetes/hypertension/pre-eclampsia, allergies to amoxicillin

Keuchkerian 2005 (*Continued*)

Interventions	Amoxicillin 1000 mg sulbactam 500 mg IV every 8 h during first 48 h, then amoxicillin 250 mg sulbactam 250 mg every 8 h for 5 days Control: placebo IV fluid, then tablets that look exactly the same as intervention
Outcomes	Primary outcomes: delivery prior to 37 weeks, delivery prior to 32 weeks, delivery within 7 days Other outcomes: neonatal/fetal - Apgar score < 7 at 1 min, RDS, Intraventricular haemorrhage all grades, fetal deaths, neonatal deaths, neonatal sepsis, gestation at birth, BW
Notes	Prior sample size estimation indicated that 40 participants were required in each arm Tocolysis and maternal corticosteroids were included as part of the study protocol Multiple pregnancy excluded. Laboratory sponsored. All data analysed before knowing if belonged to treatment or control group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"a simple randomisation was generated by computer" . " The Laboratory that manufactured the manufactured amoxicillin-sulbactam, randomised both the antibiotic and the placebo"
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes were used. Consecutive or opaque not mentioned however they were prepared by the laboratory
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial using identical administration regimens in the 2 study groups. "All study personnel and participants were blinded to treatment assignment for the duration of the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

McGregor 1991

Methods	Single-centre placebo-controlled randomised clinical trial. Denver, Colorado, Canada
Participants	117 women < 35 weeks' gestation (mean 30.5 weeks) in preterm labour receiving tocolysis. Exclusions: ruptured membranes, multiple pregnancy, suspected fetal compromise, maternal infection and other maternal medical conditions
Interventions	IV clindamycin 900 mg every 8 h x 9 doses or identical placebo. IV therapy was followed by oral clindamycin 300 mg every 6 h x 4 days or identical placebo
Outcomes	Primary outcome: delivery > 36 weeks. Other outcomes - Maternal: mean days of prolongation, infection, pre labour PROM, adverse drug reaction Neonatal: GA at delivery, BW, sepsis, perinatal mortality, length of level 2 and 3 nursery care
Notes	Pre-trial sample size estimation indicated that 57 participants were required in each arm. Additional information on the 14 exclusions (5 antibiotic group, 9 placebo) was received. Tocolysis was included as part of the study protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated random numbers list. "
Allocation concealment (selection bias)	Low risk	By pharmacist.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial using identical administration regimens in the 2 study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12% (14 women) post-randomisation exclusions. 2 women withdrew consent, 1 woman delivered for fetal distress, 3 women developed chorioamnionitis, 1 women for undiagnosed twins, 6 women were excluded for unknown reasons, 1 woman due to a pharmacy error. All exclusions mentioned
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.

McGregor 1991 (*Continued*)

Other bias	Low risk	None apparent.

Newton 1989

Methods	Single-centre placebo-controlled randomised clinical trial. San Antonio, Texas, US
Participants	103 women 24-35 weeks' gestation (mean 31 weeks), in preterm labour, receiving tocolysis. Exclusions: ruptured membranes, multiple gestation, suspected fetal compromise and maternal medical conditions
Interventions	IV ampicillin 2 g every 6 h x 12 doses, plus oral erythromycin (333 mg every 8 h x 7 days) or identical placebos
Outcomes	Primary outcome: mean GA at delivery, mean BW. Other outcomes - Maternal: delivery > 36 weeks' gestation, mean days of prolongation, recurrent preterm labour
Notes	Pre-trial sample size estimation indicated that 50 participants were required in each arm. 8 post-randomisation exclusions. Tocolysis was included as part of the study protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States "assigned randomly in a 1:1 ratio" but does not state how the random sequence was generated
Allocation concealment (selection bias)	Low risk	By pharmacist.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial using identical administration regimens in the 2 study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	8% (8 women) post-randomisation exclusions. Only 1 lost to follow-up. 3 women had additional antibiotics, 2 women delivered prior to study commencement, 1 woman withdrew consent, 1 woman to allergic reaction, 1 woman lost to follow-up

Newton 1989 (*Continued*)

Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

Newton 1991

Methods	Single-centre placebo-controlled randomised clinical trial. San Antonio, Texas, US
Participants	91 women 24-33 weeks' gestation (mean 30 weeks) in preterm labour receiving tocolysis. Exclusions: ruptured membranes, suspected fetal compromise, maternal medical conditions or clinical evidence of maternal infection Multiple births were included.
Interventions	IV ampicillin 2 g/sulbactam 1 g every 6 h x 12 doses plus oral indomethacin (50 mg load, then 25 mg every 6 h x 7 doses) or corresponding placebos
Outcomes	Primary outcomes: mean BW and GA at delivery. Other outcomes - Maternal: infection, adverse drug reaction. Neonatal: neonatal morbidity and mortality, BW < 2500 g, delivery > 35 weeks' gestation
Notes	Pre-trial sample size estimation indicated that 49 participants were required in each arm. 5 post-randomisation exclusions. "The enrolment was halted early (91 enrolled vs 98 projected patients) for administrative reasons." Toclolytics was part of the study protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States "assigned randomly in a 1:1 ratio" but does not state how the random sequence was generated
Allocation concealment (selection bias)	Low risk	By pharmacist.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial using identical administration regimens in the 2 study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.

Newton 1991 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	6% (5 women) post-randomisation exclusions. 1 woman delivered pre-study commencement, 1 woman was given additional antibiotics, 3 women were lost to follow-up
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

Norman 1994

Methods	Multicentre placebo-controlled randomised clinical trial across 3 centres in South Africa
Participants	82 women 26-34 weeks' gestation (mean 31 weeks) in preterm labour receiving tocolysis. Exclusions: ruptured membranes, antepartum haemorrhage, infection, maternal medical conditions, multiple pregnancy
Interventions	IV ampicillin 1 g every 6 h x 4 doses followed by oral amoxicillin 500 mg every 8 h x 5 days, plus metronidazole 1 gm stat then 400 mg orally every 8 h for 5 days
Outcomes	Primary outcome: perinatal mortality. Other outcomes: Maternal: puerperal infection, median days of prolongation, adverse drug reaction. Neonatal: mean GA at delivery, mean BW, neonatal hospital stay, major neonatal morbidity
Notes	Multicentre trial - 3 centres. Pre-trial sample size estimation indicated that 220 participants were required in each group. Study was stopped after 82 women were randomised because of poor recruitment rates. 4 post-randomisation exclusion. Toclolytics was part of the study protocol: Indomethacin 100 mg rectally twice daily for 48 h with concomitant hexoprenaline. Additional information received on methods and data for outcome of prolongation of pregnancy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randmisation, based on group sequential system, was centrally controlled by the MRC Perinatal Mortality Research Unit Capetown."
Allocation concealment (selection bias)	Low risk	Stated "opaque, sealed, numbered randomisation envelopes".

Norman 1994 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Use of placebo was not reported. stated "control group received no antibiotics"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not reported and no use of placebo.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% (4 women) post-randomisation exclusion. 2 women due to protocol violation and 1 woman due to twin pregnancy and 1 woman due to intrauterine death (congenital syphilis)
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Unclear risk	Following a "initial analysis', the study was stopped early due to difficulty in enrolling sufficient numbers of women

Oyarzun 1998

Methods	Single-centre placebo-controlled randomised clinical trial. Chile
Participants	196 women thought to be in labour between 22 and 36 weeks' gestation, singleton pregnancy, with intact membranes, and cervical dilatation < 5 cm
Interventions	Oral amoxicillin 250 mg every 8 h and erythromycin 500 mg orally every 6 h for 7 days, or corresponding placebo
Outcomes	Primary outcomes: RDS, prolongation of pregnancy (median days). Other outcomes: frequency of preterm delivery < 37 weeks and < 34 weeks and perinatal mortality, neonatal sepsis and other morbidity indices
Notes	Pre-trial sample size estimation indicated that for a 30% reduction in RDS ~ 260 participants were required in each group. 23 post-randomisation exclusions. Study medications supplied by Laboratorio Chile. Tocolysis and maternal corticosteroids were included as part of the study protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Oyarzun 1998 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	States 'simple randomisation using tables'.
Allocation concealment (selection bias)	Unclear risk	Details not provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial using identical administration regimens in the 2 study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12% (23 women) post-randomisation exclusions. 13 women were lost to follow-up and 10 women did not complete treatment
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

Rajaei 2006

Methods	Single-centre placebo-controlled randomised clinical trial. Iran
Participants	80 women, with idiopathic preterm labour, between 26-34 weeks - cervical dilatation greater than 1 cm and less than 5 cm, cervical effacement of equal or more than 80%, 4 uterine contractions in 20 minutes, or 8 in 60 minutes with progressive cervical change unresponsive to hydration and sedation Exclusions: 1. presence of a recognised cause of preterm labour or obstetric complication, such as placenta praevia, multiple gestation, abruptio placenta, cervical cerclage, known uterine or fetal anomaly, pregnancy-induced hypertension, premature rupture of membranes, intrauterine fetal death or fetal growth retardation. 2. known or suspected infection such chorioamnionitis, urinary tract infection, pneumonia. 3. fetal indication for delivery 4. clinically significant maternal cardiac, respiratory, liver, renal or immunologic disease 5. use of antibiotics within 2 weeks of commencement of study
Interventions	400 mg erythromycin or an identical-appearing placebo tablet every 6 h for 10 days
Outcomes	Primary: interval to delivery, prolonging pregnancy. Other outcomes: GA at delivery, mean BW, neonatal admission to NICU
Notes	Tocolysis and maternal corticosteroids were included as part of the study protocol

Rajaei 2006 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention of sequence generation. stated "assigned randomly"
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes - whether opaque or sequentially numbered not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial using identical administration regimens in the 2 study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Unclear risk	Pre-specified trial outcome measures were not detailed. Neonatal outcomes were not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	94 enrolled - 14 patients excluded from analysis (15%) (9 due to pregnancy complications fetal distress, pre-eclampsia, vaginal bleeding, chorioamnionitis); 3 received wrong doses of treatment, 5 had were lost to follow-up and 3 stopped medication
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

Reimer 1999

Methods	Single-centre randomised trial. Germany.
Participants	129 women in preterm labour and with intact membranes.
Interventions	Immediate treatment with mezlocillin 2 g IV every 8 h for 3 days
Outcomes	Primary: incidence of preterm birth and chorioamnionitis. Other outcomes: incidence of bacterial vaginosis, use of corticosteroids and tocolytics

Reimer 1999 (*Continued*)

Notes	No mention of multiple pregnancy or GA at recruitment. No neonatal outcomes reported. Tocolysis and maternal corticosteroids were included as part of the study protocol. Authors contacted for additional data and information on study methods

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random numbers generation not described. Stated "prospective randomized trial"
Allocation concealment (selection bias)	Unclear risk	Stated "those assigned to no antibiotic treatment".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Use of placebo was not reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not reported and no use of placebo.
Selective reporting (reporting bias)	Unclear risk	Neonatal outcomes were not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if there were any lost to follow-up.
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

Romero 1993

Methods	Multicentre placebo-controlled randomised clinical trial across 4 centres in the US
Participants	277 women 24-34 weeks' gestation (mean 30.5 weeks) in preterm labour receiving tocolysis. Exclusions: ruptured membranes, multiple pregnancy, suspected fetal compromise, suspected imminent delivery, suspected maternal infection, recent antibiotic use
Interventions	IV ampicillin 1 g every 4 h concomitant IV erythromycin 250 mg every 6 h both for 48 h followed by oral amoxicillin 250 mg every 8 h and erythromycin 333 mg every 8 h for 5 days

Outcomes	Primary outcomes: days prolongation of pregnancy, frequency of preterm delivery. Secondary: perinatal mortality and morbidity. Other outcomes - Maternal: adverse drug reaction, infection, Neonatal: BW, NICU stay
Notes	Multicentre trial - 6 centres. Pre-trial sample size estimation indicated that 350 participants were required for each group. Interim analysis revealed much lower baseline rate of the neonatal morbidity index than was predicted (14% vs 40%). Trial was halted after 277 enrolments. 2 post-randomisation exclusions. Additional information on trial methods were received. Tocolysis and maternal corticosteroids were included as part of the study protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Randomly assigned at an independent centre using computerised randomisation process with stratification by study centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial using identical administration regimens in the 2 study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 2% (4 women) post-randomisation exclusions. 1 woman delivered pre-study commencement, 1 woman diagnosed with a urinary tract infection, 2 women were lost to follow-up
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

Svare 1997

Methods	Multicentre placebo-controlled randomised clinical trial across 6 centres in Denmark
Participants	112 women thought to be in labour between 26 and 34 weeks, singleton pregnancy, cervical dilatation < 4 cm. Exclusion criteria - suspected chorioamnionitis, severe pre-eclampsia
Interventions	IV ampicillin 2 g every 6 h for 24 h, followed by pivampicillin 500 mg orally for 7 days, plus IV metronidazole 500 mg every 8 h for 24 h, followed by metronidazole 400 mg orally every 8 h for 7 days, or identical placebo
Outcomes	Primary outcomes: difference in median days of prolongation of pregnancy of 8 days, difference in mean BW of 200 g. Other outcomes: clinical chorioamnionitis, preterm birth < 37 weeks, Apgar scores, admissions to NICU, days on ventilation, neonatal sepsis
Notes	Multicentre trial - 6 centres. Pre-trial sample size estimation indicated that 200 participants were required. The study was stopped just over half-way because of poor recruitment (110 recruited). 2 post-randomisation exclusions. Also presented were results for eligible women not included, who were of higher GA, raising a concern about generalisability Study medications supplied by LEO Pharmaceutical Products, Copenhagen, Denmark. Additional data and information received from the author. Tocolysis and maternal corticosteroids were included as part of the study protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated numbers stratified by centre.
Allocation concealment (selection bias)	Low risk	Block randomisation by pharmaceutical company using consecutively numbered identical packages
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial using identical administration regimens in the 2 study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated "those assessing the outcomes were blinded to the allocation"
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 2 % (2 women) post-randomisation exclusions. 1 woman had a twin pregnancy and 1 woman did not receive any treatment and allocation code could not be found

Svare 1997 (*Continued*)

Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

Watts 1994

Methods	Single-centre randomised trial. Washington, Seattle, US.
Participants	56 women < 34 weeks' gestation (mean 31 weeks) in preterm labour receiving tocolysis. Exclusions: ruptured membranes, multiple pregnancy, antibiotics within 7 days, cervical dilatation > 4 cm, ruptured membranes, maternal infection, maternal medical conditions
Interventions	IV mezlocillin 3 g IV every 6 h for 5 days and oral erythromycin 333 mg every 8 h for 10 days
Outcomes	Primary: latency, and BW. Secondary: mean BW, mean GA, maternal infection, prolongation of pregnancy > 7 days, maternal adverse drug reaction, neonatal antibiotic therapy, RDS, hospital stay, Apgar scores, perinatal mortality
Notes	No pre-trial power calculations. Additional information and data for the outcome of prolongation of pregnancy were received Partly sponsored by Miles Pharmaceutical Co., Inc. Amniocentesis for lung maturity where possible. women. Tocolysis was were included as part of the study protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not mentioned.
Allocation concealment (selection bias)	Unclear risk	Stated "Randomly assigned in a blinded fashion".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial using identical administration regimens in the 2 study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear, but probably low risk. Placebo-controlled trial.
Selective reporting (reporting bias)	Low risk	All expected outcome results reported.

Watts 1994 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.
Incomplete outcome data longer term outcomes (attrition bias) All outcomes	Unclear risk	Not applicable.
Other bias	Low risk	None apparent.

BW: birthweight
GA: gestational age
GBS: Group B Streptococcus
h: hour(s)
IV: intravenously
NEC: necrotising enterocolitis
NICU: neonatal intensive care unit
PROM: premature rupture of membranes
RDS: respiratory distress syndrome
stat: immediately
vs: versus

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

Study	Reason for exclusion
Gurbuz 2004	Additional information on methods and outcomes to assess eligibility was requested from the authors and had not been forthcoming at the time of the review
Hensen 1987	Personal communication on a planned trial. Unable to locate publication or author
Lauterbach 2012	The intervention in this trial was not an antibiotic.
McCaul 1992	The authors had not provided information on the 47% post-randomisation exclusions at the time of the review
McGregor 1986	The authors had not provided information on the 36% post-randomisation exclusions at the time of the review
McGregor 1988	Women were not in labour.
Morales 1988	The authors had not provided information on the 27% post-randomisation exclusions at the time of the review
Nadisauskiene 1996	Included women with ruptured membranes.
Naef 1994	Included women with ruptured membranes.

(*Continued*)

Ogasawara 1996	Included women with rupture membranes.
Oszukowski 2000	Abstract only with insufficient information on methods and outcomes to enable assessment. Authors were contacted with no response
Ovalle 2006	Quasi-random method of treatment allocation was used.
Ozden 2000	Quasi-random method of treatment allocation was used.
Purwar 1997	Abstract only. Included women with ruptured membranes.
Saez-Llorens 1995	Quasi-random method of treatment allocation was used.
Winkler 1988	Included women with ruptured membranes.

DATA AND ANALYSES

Comparison 1. Any antibiotics versus no antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	10	7304	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.88, 1.69]
2 Stillbirth	8	7080	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.43, 1.26]
3 Neonatal death	9	7248	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.03, 2.40]
4 Infant death	1	4654	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.68, 1.67]
5 Any functional impairment at 7 years of age.	1	3052	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.99, 1.23]
6 Moderate/severe functional impairment at 7 years of age.	1	3052	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.89, 1.28]
7 Cerebral palsy at 7 years	1	3173	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.99, 3.34]
8 Maternal adverse drug reaction requiring cessation of treatment	5	626	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.92, 1.89]
9 Maternal infection	10	7371	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.63, 0.86]
10 Delay in birth (subgrouped by interval)	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Birth within 48 hours	4	6800	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.89, 1.23]
10.2 Birth within 7 days	8	7053	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.87, 1.10]
11 Interval between randomisation and birth (days)	6	2499	Mean Difference (IV, Random, 95% CI)	5.59 [0.31, 10.87]
12 Preterm birth (< 36 or < 37 weeks)	10	7387	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.05]
13 Gestational age at birth	10	986	Mean Difference (IV, Random, 95% CI)	0.53 [0.00, 1.06]
14 Birthweight	12	7531	Mean Difference (IV, Random, 95% CI)	58.38 [-26.24, 143.00]
15 Birthweight < 2500 g	5	6628	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.81, 1.15]
16 Admission to neonatal intensive or special care nursery	5	6875	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.62, 1.10]
17 Neonatal mechanical ventilation	1	6241	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.84, 1.24]
18 Respiratory distress syndrome	9	7200	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.84, 1.16]
19 Neonatal positive blood culture	3	6526	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.69, 1.49]
20 Neonatal sepsis	10	7386	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.64, 1.16]
21 Intraventricular haemorrhage	5	6813	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.48, 1.19]
22 Necrotising enterocolitis	6	6880	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.64, 1.73]
23 Major cerebral abnormality	1	6241	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.66, 1.51]
24 Chronic neonatal lung disease	1	6241	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.78, 1.76]

Comparison 2. Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Beta-lactam antibiotics alone vs no antibiotics	4	2323	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.64, 2.01]
1.2 Macrolide antibiotics alone vs no antibiotics	2	2222	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.64, 2.11]
1.3 Macrolide and beta-lactam antibiotics vs no antibiotics	4	2569	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.79, 2.43]
1.4 Antibiotics active against anaerobic bacteria vs no antibiotics	3	294	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.36, 7.39]
2 Stillbirth	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Beta-lactam antibiotics alone vs no antibiotics	4	2323	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.39, 2.14]
2.2 Macrolide antibiotics alone vs no antibiotics	2	2222	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.20, 1.48]
2.3 Macrolide and beta-lactam antibiotics vs no antibiotics	2	2347	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.28, 1.90]
2.4 Antibiotics active against anaerobic bacteria vs no bacteria	3	294	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Neonatal death	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Beta-lactam antibiotics alone vs no antibiotics	4	2323	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.61, 2.86]
3.2 Macrolide antibiotics alone vs no antibiotics	2	2222	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.77, 3.64]
3.3 Macrolide and beta-lactam antibiotics vs no antibiotics	3	2513	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.88, 3.82]
3.4 Antibiotics active against anaerobic bacteria vs no antibiotics	3	294	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [0.36, 7.39]
4 Infant death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Beta-lactam antibiotics alone vs no antibiotics	1	1515	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.31, 1.65]
4.2 Macrolide antibiotics alone vs no antibiotics	1	1586	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.53, 2.49]
4.3 Macrolide and beta-lactam antibiotics vs no antibiotics	1	1553	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.61, 2.81]
4.4 Antibiotics active against anaerobic bacteria vs no antibiotics	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Any functional impairment at 7 years of age.	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Beta-lactam antibiotics alone vs no antibiotics	1	1008	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.87, 1.25]

5.2 Macrolide antibiotics alone vs no antibiotics	1	1030	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.94, 1.35]
5.3 Macrolide and beta-lactam antibiotics vs no antibiotics	1	1014	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.94, 1.35]
5.4 Antibiotics active against anaerobic bacteria vs no antibiotics	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Moderate/severe functional impairment at 7 years of age.	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Beta-lactam antibiotics alone vs no antibiotics	1	1008	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.75, 1.41]
6.2 Macrolide antibiotics alone vs no antibiotics	1	1030	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.79, 1.48]
6.3 Macrolide and beta-lactam antibiotics vs no antibiotics	1	1014	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.82, 1.53]
6.4 Antibiotics active against anaerobic bacteria vs no antibiotics	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Cerebral palsy at 7 years of age	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Beta-lactam antibiotics alone vs no antibiotics	1	1049	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.41, 3.63]
7.2 Macrolide antibiotics alone vs no antibiotics	1	1073	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.48, 4.15]
7.3 Macrolide and beta-lactam antibiotics vs no antibiotics	1	1052	Risk Ratio (M-H, Random, 95% CI)	2.83 [1.02, 7.88]
7.4 Antibiotics active against anaerobic bacteria vs no antibiotics	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Maternal adverse drug reaction requiring cessation of treatment	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Beta-lactam antibiotics alone vs no antibiotics	1	82	Risk Ratio (M-H, Fixed, 95% CI)	3.15 [0.13, 75.05]
8.2 Macrolide antibiotics alone vs no antibiotics	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.49, 1.59]
8.3 Macrolide and beta-lactam antibiotics vs no antibiotics	2	331	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.93, 2.40]
8.4 Antibiotics active against anaerobic bacteria vs no antibiotics	2	213	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.59, 1.83]
9 Maternal infection	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Beta-lactam antibiotics alone vs no antibiotics	4	2385	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.56, 0.97]
9.2 Macrolide antibiotics alone vs no antibiotics	2	2222	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.62, 1.08]
9.3 Macrolide and beta-lactam antibiotics vs no antibiotics	4	2563	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.64, 0.98]
9.4 Antibiotics active against anaerobic bacteria vs no antibiotics	3	294	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.11, 3.92]
10 Birth within 48 hours of randomisation	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

10.1 Beta-lactam antibiotics alone vs no antibiotics	1	2053	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.75, 1.36]
10.2 Macrolide antibiotics alone vs no antibiotics	1	2119	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.78, 1.42]
10.3 Macrolide and beta-lactam antibiotics vs no antibiotics	3	2520	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.86, 1.45]
10.4 Antibiotics active against anaerobic bacteria vs no antibiotics	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.19, 1.57]
11 Interval between randomisation and birth (days)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 Beta-lactam antibiotics alone vs no antibiotics	1	2053	Mean Difference (IV, Random, 95% CI)	-0.09 [-2.96, 2.78]
11.2 Macrolide antibiotics alone vs no antibiotics	3	2302	Mean Difference (IV, Random, 95% CI)	4.26 [-2.88, 11.41]
11.3 Macrolide and beta-lactam antibiotics vs no antibiotics	3	2221	Mean Difference (IV, Random, 95% CI)	-0.27 [-2.95, 2.41]
11.4 Antibiotics active against anaerobic bacteria vs no antibiotics	3	293	Mean Difference (IV, Random, 95% CI)	10.50 [4.95, 16.06]
12 Preterm birth (< 36 or < 37 weeks' gestation)	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Beta-lactam antibiotics alone vs no antibiotics	5	2430	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.10]
12.2 Macrolide antibiotics alone vs no antibiotics	2	2235	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.91, 1.15]
12.3 Macrolide and beta-lactam antibiotics vs no antibiotics	4	2613	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.89, 1.10]
12.4 Antibiotics active against anaerobic bacteria vs no antibiotics	2	226	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.53, 1.30]
13 Respiratory distress syndrome	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Beta-lactam antibiotics alone vs no antibiotics	3	3278	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.75, 1.16]
13.2 Macrolide antibiotics alone vs no antibiotics	1	3156	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.18]
13.3 Macrolide and beta-lactam antibiotics vs no antibiotics	2	3382	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.29]
13.4 Antibiotics active against anaerobic bacteria vs no antibiotics	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.10, 3.37]
14 Necrotising enterocolitis	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Beta-lactam antibiotics alone vs no antibiotics	3	2227	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.52, 3.32]
14.2 Macrolide antibiotics alone vs no antibiotics	1	2119	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.44, 3.86]

14.3 Macrolide and beta-lactam antibiotics vs no antibiotics	2	2345	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.60, 3.11]
14.4 Antibiotics active against anaerobic bacteria vs no antibiotics	2	190	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 1.01]
15 Intraventricular haemorrhage	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Beta-lactam antibiotics alone vs no antibiotics	3	2241	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.38, 1.87]
15.2 Macrolide antibiotics alone vs no antibiotics	1	2119	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.35, 1.99]
15.3 Macrolide and beta-lactam antibiotics vs no antibiotics	2	2345	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.43, 2.19]
15.4 Antibiotics active against anaerobic bacteria vs no antibiotics	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.46]

Comparison 3. Any macrolide versus no macrolide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	4	6740	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.60]
2 Stillbirth	2	6518	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.41, 1.20]
3 Neonatal death	3	6684	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.05, 2.19]
4 Infant death	1	4583	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.99, 2.18]
5 Any functional impairment at 7 years of age.	1	3052	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.01, 1.20]
6 Moderate/severe functional impairment at 7 years of age.	1	3052	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.26]
7 Cerebral palsy at 7 years	1	3173	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.20, 3.01]
8 Maternal adverse drug reaction requiring cessation of treatment	2	331	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.93, 2.40]
9 Maternal infection	4	6745	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.41, 1.07]
10 Birth within 48 hours of randomisation	3	6691	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.94, 1.25]
11 Interval between randomisation and birth (days)	3	6386	Mean Difference (IV, Random, 95% CI)	1.07 [-3.58, 5.72]
12 Preterm birth (< 36 or < 37 weeks)	4	6784	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
13 Respiratory distress syndrome	4	6740	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.21]
14 Intraventricular haemorrhage	2	6516	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.62, 1.49]
15 Necrotising enterocolitis	2	6516	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.74, 1.80]

Comparison 4. Any beta-lactam versus no beta-lactam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal mortality	8	7109	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.84, 1.48]
2 Stillbirth	6	6887	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.76, 1.58]
3 Neonatal death	7	7053	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.06, 2.15]
4 Infant death	1	4654	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.64, 1.38]
5 Any functional impairment at 7 years of age.	1	3052	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.11]
6 Moderate/severe functional impairment at 7 years of age.	1	3052	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.88, 1.20]
7 Cerebral palsy at 7 years	1	3173	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.06, 2.61]
8 Maternal adverse drug reaction requiring cessation of treatment	4	523	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.02, 2.54]
9 Maternal infection	8	7182	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.69, 0.92]
10 Birth within 48 hours of randomisation	4	6800	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.89, 1.18]
11 Interval between randomisation and birth (days)	3	6386	Mean Difference (IV, Random, 95% CI)	3.92 [-5.08, 12.92]
12 Preterm birth (< 36 or < 37 weeks)	8	7185	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.04]
13 Respiratory distress syndrome	8	7108	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.88, 1.19]
14 Intraventricular haemorrhage	4	6721	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.56, 1.31]
15 Necrotising enterocolitis	5	6788	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.27, 1.92]

Analysis 1.1. Comparison 1 Any antibiotics versus no antibiotics, Outcome 1 Perinatal mortality.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 1 Perinatal mortality

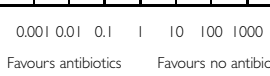
Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	1/40	0/42		0.7 %	3.15 [0.13, 75.05]
Kenyon 2001a	128/4685	39/1556		89.9 %	1.09 [0.77, 1.55]
Keuchkerian 2005	1/47	1/49		1.5 %	1.04 [0.07, 16.19]
McGregor 1991	2/53	0/50		0.8 %	4.72 [0.23, 96.01]
Newton 1991	2/47	0/45		0.8 %	4.79 [0.24, 97.14]
Norman 1994	2/43	2/38		3.3 %	0.88 [0.13, 5.97]
Oyarzun 1998	2/78	1/90		1.4 %	2.31 [0.21, 24.97]
Romero 1993	2/131	0/144		0.7 %	5.49 [0.27, 113.36]
Svare 1997	0/59	0/51			Not estimable
Watts 1994	1/30	0/26		0.8 %	2.61 [0.11, 61.51]
Total (95% CI)	**5213**	**2091**		**100.0 %**	**1.22 [0.88, 1.69]**

Total events: 141 (Antibiotics), 43 (No antibiotics)

Heterogeneity: Chi^2 = 3.87, df = 8 (P = 0.87); I^2 =0.0%

Test for overall effect: Z = 1.18 (P = 0.24)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Any antibiotics versus no antibiotics, Outcome 2 Stillbirth.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 2 Stillbirth

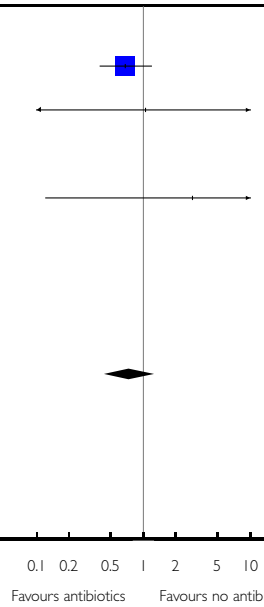
Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	0/40	0/42			Not estimable
Kenyon 2001a	37/4685	18/1556		94.8 %	0.68 [0.39, 1.20]
Keuchkerian 2005	1/47	1/49		3.4 %	1.04 [0.07, 16.19]
McGregor 1991	0/53	0/50			Not estimable
Newton 1991	1/47	0/45		1.8 %	2.88 [0.12, 68.79]
Norman 1994	0/43	0/38			Not estimable
Romero 1993	0/131	0/144			Not estimable
Svare 1997	0/59	0/51			Not estimable
Total (95% CI)	**5105**	**1975**		**100.0 %**	**0.73 [0.43, 1.26]**

Total events: 39 (Antibiotics), 19 (No antibiotics)

Heterogeneity: $Chi^2 = 0.84$, df = 2 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 1.13 (P = 0.26)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Any antibiotics versus no antibiotics, Outcome 3 Neonatal death.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 3 Neonatal death

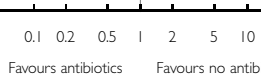
Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	1/40	0/42		1.3 %	3.15 [0.13, 75.05]
Kenyon 2001a	91/4685	21/1556		86.2 %	1.44 [0.90, 2.31]
Keuchkerian 2005	0/47	0/49			Not estimable
McGregor 1991	2/53	0/50		1.4 %	4.72 [0.23, 96.01]
Newton 1991	1/47	0/45		1.4 %	2.88 [0.12, 68.79]
Norman 1994	2/43	2/38		5.8 %	0.88 [0.13, 5.97]
Oyarzun 1998	2/78	1/90		2.5 %	2.31 [0.21, 24.97]
Romero 1993	2/131	0/144		1.3 %	5.49 [0.27, 113.36]
Svare 1997	0/59	0/51			Not estimable
Total (95% CI)	**5183**	**2065**		**100.0 %**	**1.57 [1.03, 2.40]**

Total events: 101 (Antibiotics), 24 (No antibiotics)

Heterogeneity: $Chi^2 = 2.07$, df = 6 (P = 0.91); $I^2 = 0.0\%$

Test for overall effect: Z = 2.08 (P = 0.038)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Any antibiotics versus no antibiotics, Outcome 4 Infant death.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 4 Infant death

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	78/3508	24/1146		100.0 %	1.06 [0.68, 1.67]
Total (95% CI)	**3508**	**1146**		**100.0 %**	**1.06 [0.68, 1.67]**

Total events: 78 (Antibiotics), 24 (No antibiotics)
Heterogeneity: not applicable
Test for overall effect: Z = 0.26 (P = 0.80)
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Any antibiotics versus no antibiotics, Outcome 5 Any functional impairment at 7 years of age..

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 5 Any functional impairment at 7 years of age.

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	957/2317	275/735		100.0 %	1.10 [0.99, 1.23]
Total (95% CI)	**2317**	**735**		**100.0 %**	**1.10 [0.99, 1.23]**

Total events: 957 (Antibiotics), 275 (No antibiotics)
Heterogeneity: not applicable
Test for overall effect: Z = 1.84 (P = 0.066)
Test for subgroup differences: Not applicable

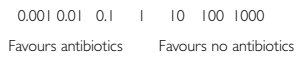
Analysis 1.6. Comparison 1 Any antibiotics versus no antibiotics, Outcome 6 Moderate/severe functional impairment at 7 years of age..

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 6 Moderate/severe functional impairment at 7 years of age.

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	417/2317	124/735		100.0 %	1.07 [0.89, 1.28]
Total (95% CI)	**2317**	**735**		**100.0 %**	**1.07 [0.89, 1.28]**
Total events: 417 (Antibiotics), 124 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
Test for subgroup differences: Not applicable					



Analysis 1.7. Comparison 1 Any antibiotics versus no antibiotics, Outcome 7 Cerebral palsy at 7 years.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 7 Cerebral palsy at 7 years

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	68/2403	12/770		100.0 %	1.82 [0.99, 3.34]
Total (95% CI)	**2403**	**770**		**100.0 %**	**1.82 [0.99, 3.34]**
Total events: 68 (Antibiotics), 12 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.92 (P = 0.055)					
Test for subgroup differences: Not applicable					

Analysis 1.8. Comparison 1 Any antibiotics versus no antibiotics, Outcome 8 Maternal adverse drug reaction requiring cessation of treatment.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 8 Maternal adverse drug reaction requiring cessation of treatment

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	1/40	0/42		1.2 %	3.15 [0.13, 75.05]
McGregor 1991	15/53	16/50		39.8 %	0.88 [0.49, 1.59]
Romero 1993	27/131	20/144		46.1 %	1.48 [0.88, 2.52]
Svare 1997	4/59	1/51		2.6 %	3.46 [0.40, 29.95]
Watts 1994	7/30	4/26		10.4 %	1.52 [0.50, 4.60]
Total (95% CI)	**313**	**313**		**100.0 %**	**1.32 [0.92, 1.89]**

Total events: 54 (Antibiotics), 41 (No antibiotics)

Heterogeneity: $Chi^2 = 3.08$, df = 4 (P = 0.55); $I^2 = 0.0\%$

Test for overall effect: Z = 1.51 (P = 0.13)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Any antibiotics versus no antibiotics, Outcome 9 Maternal infection.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 9 Maternal infection

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gordon 1995	2/58	3/59		0.9 %	0.68 [0.12, 3.91]
Kenyon 2001a	433/4685	183/1556		83.8 %	0.79 [0.67, 0.92]
McGregor 1991	1/53	3/50		0.9 %	0.31 [0.03, 2.92]
Newton 1991	1/43	6/43		1.8 %	0.17 [0.02, 1.33]
Norman 1994	1/43	3/38		1.0 %	0.29 [0.03, 2.71]
Oyarzun 1998	5/83	8/90		2.3 %	0.68 [0.23, 1.99]
Reimer 1999	2/61	6/68		1.7 %	0.37 [0.08, 1.77]
Romero 1993	7/131	14/144		4.1 %	0.55 [0.23, 1.32]
Svare 1997	3/59	0/51		0.2 %	6.07 [0.32, 114.74]
Watts 1994	3/30	10/26		3.3 %	0.26 [0.08, 0.84]
Total (95% CI)	**5246**	**2125**		**100.0 %**	**0.74 [0.63, 0.86]**

Total events: 458 (Antibiotics), 236 (No antibiotics)

Heterogeneity: Chi^2 = 9.96, df = 9 (P = 0.35); I^2 =10%

Test for overall effect: Z = 3.91 (P = 0.000090)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Any antibiotics versus no antibiotics, Outcome 10 Delay in birth (subgrouped by interval).

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 10 Delay in birth (subgrouped by interval)

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Birth within 48 hours					
Kenyon 2001a	478/4685	152/1556		88.2 %	1.04 [0.88, 1.24]
Oyarzun 1998	12/83	13/90		4.8 %	1.00 [0.48, 2.07]
Romero 1993	14/133	10/144		3.7 %	1.52 [0.70, 3.30]
Svare 1997	5/58	8/51		3.3 %	0.55 [0.19, 1.57]
Subtotal (95% CI)	**4959**	**1841**		**100.0 %**	**1.04 [0.89, 1.23]**
Total events: 509 (Antibiotics), 183 (No antibiotics)					
Heterogeneity: Chi^2 = 2.33, df = 3 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.51 (P = 0.61)					
2 Birth within 7 days					
Cox 1996	13/39	14/39		3.0 %	0.93 [0.50, 1.71]
Gordon 1995	6/58	9/59		1.9 %	0.68 [0.26, 1.78]
Kenyon 2001a	724/4685	237/1556		76.9 %	1.01 [0.89, 1.16]
Keuchkerian 2005	4/47	5/49		1.1 %	0.83 [0.24, 2.92]
Norman 1994	16/43	23/38		5.3 %	0.61 [0.39, 0.98]
Romero 1993	29/131	24/144		4.9 %	1.33 [0.82, 2.16]
Svare 1997	12/58	17/51		3.9 %	0.62 [0.33, 1.17]
Watts 1994	13/30	13/26		3.0 %	0.87 [0.49, 1.52]
Subtotal (95% CI)	**5091**	**1962**		**100.0 %**	**0.98 [0.87, 1.10]**
Total events: 817 (Antibiotics), 342 (No antibiotics)					
Heterogeneity: Chi^2 = 8.41, df = 7 (P = 0.30); I^2 =17%					
Test for overall effect: Z = 0.37 (P = 0.71)					

Analysis 1.11. Comparison 1 Any antibiotics versus no antibiotics, Outcome 11 Interval between randomisation and birth (days).

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

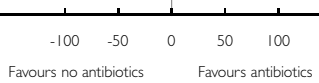
Outcome: 11 Interval between randomisation and birth (days)

Study or subgroup	Antibiotcs N	Mean(SD)	No antibiotics N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kenyon 2001a	1551	43.86 (29.29)	519	44.08 (28.91)		26.5 %	-0.22 [-3.10, 2.66]
McGregor 1991	53	35.3 (24.1)	50	25.4 (20)		16.4 %	9.90 [1.37, 18.43]
Norman 1994	43	23.5 (24.2)	38	16 (22)		14.1 %	7.50 [-2.56, 17.56]
Rajaei 2006	38	33.33 (18.36)	42	26.88 (13.9)		18.8 %	6.45 [-0.74, 13.64]
Svare 1997	58	43.9 (30.7)	51	29.1 (26)		13.3 %	14.80 [4.15, 25.45]
Watts 1994	30	21.4 (22)	26	23.3 (25.3)		11.0 %	-1.90 [-14.41, 10.61]
Total (95% CI)	**1773**		**726**			**100.0 %**	**5.59 [0.31, 10.87]**

Heterogeneity: $Tau^2 = 25.22$; $Chi^2 = 14.01$, df = 5 (P = 0.02); $I^2 = 64\%$

Test for overall effect: Z = 2.07 (P = 0.038)

Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1 Any antibiotics versus no antibiotics, Outcome 12 Preterm birth (< 36 or < 37 weeks).

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 12 Preterm birth (< 36 or < 37 weeks)

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	23/39	22/39		1.9 %	1.05 [0.71, 1.53]
Gordon 1995	35/58	34/59		2.9 %	1.05 [0.77, 1.42]
Kenyon 2001a	1687/4685	559/1556		73.1 %	1.00 [0.93, 1.08]
Keuchkerian 2005	17/47	19/49		1.6 %	0.93 [0.56, 1.57]
McGregor 1991	38/58	37/58		3.2 %	1.03 [0.78, 1.34]
Newton 1989	18/48	21/47		1.8 %	0.84 [0.52, 1.36]
Newton 1991	23/43	27/43		2.4 %	0.85 [0.59, 1.22]
Oyarzun 1998	38/83	45/90		3.8 %	0.92 [0.67, 1.25]
Romero 1993	69/131	74/144		6.1 %	1.02 [0.82, 1.29]
Svare 1997	25/59	33/51		3.1 %	0.65 [0.46, 0.94]
Total (95% CI)	**5251**	**2136**		**100.0 %**	**0.98 [0.92, 1.05]**

Total events: 1973 (Antibiotics), 871 (No antibiotics)

Heterogeneity: $Chi^2 = 6.89$, df = 9 (P = 0.65); $I^2 = 0.0\%$

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable

Analysis 1.13. Comparison 1 Any antibiotics versus no antibiotics, Outcome 13 Gestational age at birth.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

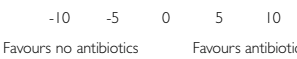
Outcome: 13 Gestational age at birth

Study or subgroup	Antibiotics N	Mean(SD)	No antibiotics N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Cox 1996	39	34.2 (4.43)	39	34.1 (3.88)		6.2 %	0.10 [-1.75, 1.95]
Gordon 1995	58	36 (2.9)	59	35.9 (2.9)		12.8 %	0.10 [-0.95, 1.15]
Keuchkerian 2005	47	37.41 (2.73)	49	37.18 (3.19)		11.3 %	0.23 [-0.96, 1.42]
McGregor 1991	53	35.4 (3.2)	50	34.9 (3.3)		10.5 %	0.50 [-0.76, 1.76]
Newton 1989	48	36.8 (2.9)	47	36.8 (2.8)		11.7 %	0.0 [-1.15, 1.15]
Norman 1994	43	34.3 (3.3)	38	33.1 (3.8)		7.9 %	1.20 [-0.36, 2.76]
Oyarzun 1998	80	31.8 (3.6)	90	32.03 (2.27)		14.6 %	-0.23 [-1.15, 0.69]
Rajaei 2006	38	36.11 (2.32)	42	34.36 (2.33)		13.2 %	1.75 [0.73, 2.77]
Svare 1997	59	36.2 (4.3)	51	34.1 (4.4)		7.4 %	2.10 [0.47, 3.73]
Watts 1994	30	33.1 (4.8)	26	33.5 (4.1)		4.3 %	-0.40 [-2.73, 1.93]
Total (95% CI)	**495**		**491**			**100.0 %**	**0.53 [0.00, 1.06]**

Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 14.91$, df = 9 (P = 0.09); $I^2 = 40\%$

Test for overall effect: Z = 1.98 (P = 0.048)

Test for subgroup differences: Not applicable

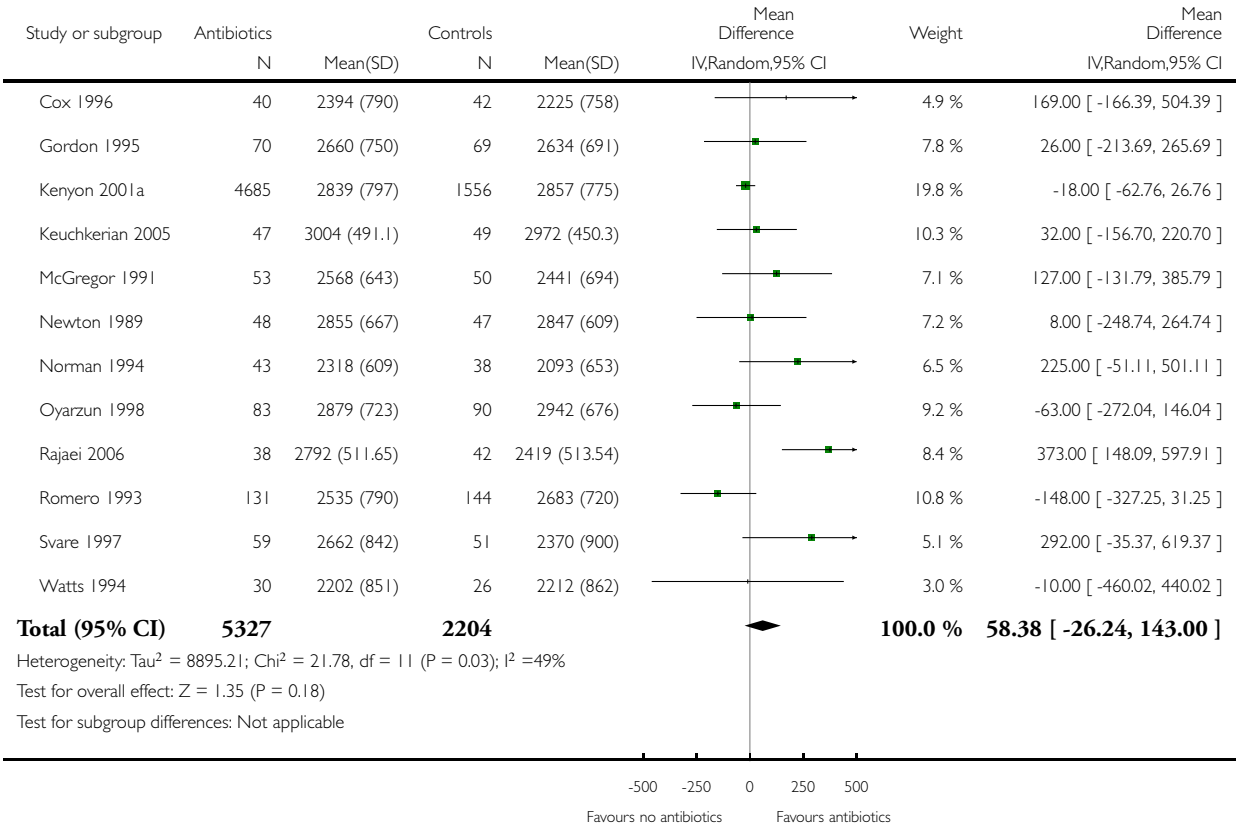


Analysis 1.14. Comparison 1 Any antibiotics versus no antibiotics, Outcome 14 Birthweight.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 14 Birthweight



Analysis 1.15. Comparison 1 Any antibiotics versus no antibiotics, Outcome 15 Birthweight < 2500 g.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 15 Birthweight < 2500 g

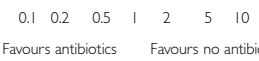
Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Cox 1996	21/40	26/42		14.8 %	0.85 [0.58, 1.24]
Kenyon 2001a	1342/4685	419/1556		41.2 %	1.06 [0.97, 1.17]
McGregor 1991	21/53	26/50		12.6 %	0.76 [0.50, 1.17]
Newton 1991	31/45	26/47		18.2 %	1.25 [0.90, 1.72]
Svare 1997	23/59	27/51		13.2 %	0.74 [0.49, 1.11]
Total (95% CI)	**4882**	**1746**		**100.0 %**	**0.97 [0.81, 1.15]**

Total events: 1438 (Antibiotics), 524 (No antibiotics)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.29$, df = 4 (P = 0.12); $I^2 = 45\%$

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1 Any antibiotics versus no antibiotics, Outcome 16 Admission to neonatal intensive or special care nursery.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 16 Admission to neonatal intensive or special care nursery

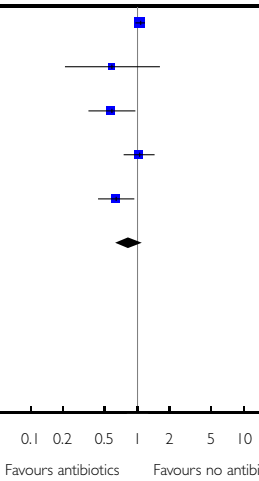
Study or subgroup	Any antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Kenyon 2001a	1216/4685	380/1556		32.7 %	1.06 [0.96, 1.17]
Oyarzun 1998	5/78	10/90		6.3 %	0.58 [0.21, 1.62]
Rajaei 2006	13/38	25/42		16.5 %	0.57 [0.35, 0.95]
Romero 1993	44/133	46/144		23.1 %	1.04 [0.74, 1.45]
Svare 1997	23/58	32/51		21.3 %	0.63 [0.43, 0.93]
Total (95% CI)	**4992**	**1883**		**100.0 %**	**0.82 [0.62, 1.10]**

Total events: 1301 (Any antibiotic), 493 (No antibiotic)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 12.76$, df = 4 (P = 0.01); $I^2 = 69\%$

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

Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1 Any antibiotics versus no antibiotics, Outcome 17 Neonatal mechanical ventilation.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 17 Neonatal mechanical ventilation

Study or subgroup	Any antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	371/4685	121/1556		100.0 %	1.02 [0.84, 1.24]
Total (95% CI)	**4685**	**1556**		**100.0 %**	**1.02 [0.84, 1.24]**
Total events: 371 (Any antibiotic), 121 (No antibiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.86)					
Test for subgroup differences: Not applicable					

Analysis 1.18. Comparison 1 Any antibiotics versus no antibiotics, Outcome 18 Respiratory distress syndrome.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 18 Respiratory distress syndrome

Study or subgroup	Any antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	8/40	8/42		2.9 %	1.05 [0.44, 2.53]
Kenyon 2001a	399/4685	138/1556		77.8 %	0.96 [0.80, 1.16]
Keuchkerian 2005	3/47	3/49		1.1 %	1.04 [0.22, 4.91]
Newton 1991	12/47	13/45		5.0 %	0.88 [0.45, 1.73]
Norman 1994	3/43	6/38		2.4 %	0.44 [0.12, 1.65]
Oyarzun 1998	9/78	7/90		2.4 %	1.48 [0.58, 3.80]
Romero 1993	14/131	11/144		3.9 %	1.40 [0.66, 2.97]
Svare 1997	2/58	3/51		1.2 %	0.59 [0.10, 3.37]
Watts 1994	13/30	8/26		3.2 %	1.41 [0.69, 2.86]
Total (95% CI)	**5159**	**2041**		**100.0 %**	**0.99 [0.84, 1.16]**

Total events: 463 (Any antibiotic), 197 (No antibiotic)

Heterogeneity: $Chi^2 = 4.50$, df = 8 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 0.15 (P = 0.88)

Test for subgroup differences: Not applicable

Analysis 1.19. Comparison 1 Any antibiotics versus no antibiotics, Outcome 19 Neonatal positive blood culture.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 19 Neonatal positive blood culture

Study or subgroup	Any antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gordon 1995	2/58	2/59		3.9 %	1.02 [0.15, 6.98]
Kenyon 2001a	96/4685	31/1556		92.4 %	1.03 [0.69, 1.54]
Oyarzun 1998	1/78	2/90		3.7 %	0.58 [0.05, 6.24]
Total (95% CI)	**4821**	**1705**		**100.0 %**	**1.01 [0.69, 1.49]**

Total events: 99 (Any antibiotic), 35 (No antibiotic)

Heterogeneity: $Chi^2 = 0.22$, df = 2 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 0.06 (P = 0.95)

Test for subgroup differences: Not applicable

Analysis 1.20. Comparison 1 Any antibiotics versus no antibiotics, Outcome 20 Neonatal sepsis.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 20 Neonatal sepsis

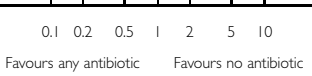
Study or subgroup	Any antibiotic n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	1/40	0/42		0.5 %	3.15 [0.13, 75.05]
Gordon 1995	2/70	2/69		2.2 %	0.99 [0.14, 6.80]
Kenyon 2001a	96/4685	31/1556		50.7 %	1.03 [0.69, 1.54]
Keuchkerian 2005	0/47	0/49			Not estimable
McGregor 1991	2/53	4/50		4.5 %	0.47 [0.09, 2.46]
Newton 1991	1/47	1/45		1.1 %	0.96 [0.06, 14.85]
Norman 1994	4/43	4/38		4.6 %	0.88 [0.24, 3.29]
Oyarzun 1998	1/78	8/90		8.1 %	0.14 [0.02, 1.13]
Romero 1993	14/131	15/144		15.6 %	1.03 [0.52, 2.04]
Svare 1997	6/58	11/51		12.7 %	0.48 [0.19, 1.20]
Total (95% CI)	**5252**	**2134**		**100.0 %**	**0.86 [0.64, 1.16]**

Total events: 127 (Any antibiotic), 76 (No antibiotics)

Heterogeneity: $Chi^2 = 6.62$, df = 8 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1 Any antibiotics versus no antibiotics, Outcome 21 Intraventricular haemorrhage.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 21 Intraventricular haemorrhage

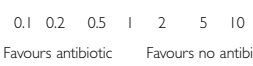
Study or subgroup	Any antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	55/4685	22/1556		79.9 %	0.83 [0.51, 1.36]
Keuchkerian 2005	0/47	0/49			Not estimable
Newton 1991	2/47	2/45		4.9 %	0.96 [0.14, 6.51]
Romero 1993	1/131	1/144		2.3 %	1.10 [0.07, 17.40]
Svare 1997	1/58	5/51		12.9 %	0.18 [0.02, 1.46]
Total (95% CI)	**4968**	**1845**		**100.0 %**	**0.76 [0.48, 1.19]**

Total events: 59 (Any antibiotic), 30 (No antibiotic)

Heterogeneity: $Chi^2 = 2.09$, df = 3 (P = 0.55); $I^2 = 0.0\%$

Test for overall effect: Z = 1.20 (P = 0.23)

Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1 Any antibiotics versus no antibiotics, Outcome 22 Necrotising enterocolitis.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 22 Necrotising enterocolitis

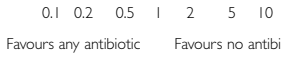
Study or subgroup	Any antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	0/40	1/42		4.5 %	0.35 [0.01, 8.34]
Kenyon 2001a	58/4685	12/1556		55.1 %	1.61 [0.86, 2.98]
Newton 1991	1/47	1/45		3.1 %	0.96 [0.06, 14.85]
Norman 1994	0/43	5/38		17.8 %	0.08 [0.00, 1.41]
Romero 1993	3/131	5/144		14.6 %	0.66 [0.16, 2.71]
Svare 1997	0/58	1/51		4.9 %	0.29 [0.01, 7.06]
Total (95% CI)	**5004**	**1876**		**100.0 %**	**1.06 [0.64, 1.73]**

Total events: 62 (Any antibiotic), 25 (No antibiotic)

Heterogeneity: $Chi^2 = 6.38$, df = 5 (P = 0.27); $I^2 = 22\%$

Test for overall effect: Z = 0.21 (P = 0.83)

Test for subgroup differences: Not applicable



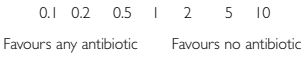
Analysis 1.23. Comparison 1 Any antibiotics versus no antibiotics, Outcome 23 Major cerebral abnormality.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 23 Major cerebral abnormality

Study or subgroup	Any antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	87/4685	29/1556		100.0 %	1.00 [0.66, 1.51]
Total (95% CI)	**4685**	**1556**		**100.0 %**	**1.00 [0.66, 1.51]**
Total events: 87 (Any antibiotics), 29 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.02 (P = 0.99)					
Test for subgroup differences: Not applicable					



Analysis 1.24. Comparison 1 Any antibiotics versus no antibiotics, Outcome 24 Chronic neonatal lung disease.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 1 Any antibiotics versus no antibiotics

Outcome: 24 Chronic neonatal lung disease

Study or subgroup	Any antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	102/4685	29/1556		100.0 %	1.17 [0.78, 1.76]
Total (95% CI)	**4685**	**1556**		**100.0 %**	**1.17 [0.78, 1.76]**
Total events: 102 (Any antibiotic), 29 (No antibiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.75 (P = 0.46)					
Test for subgroup differences: Not applicable					

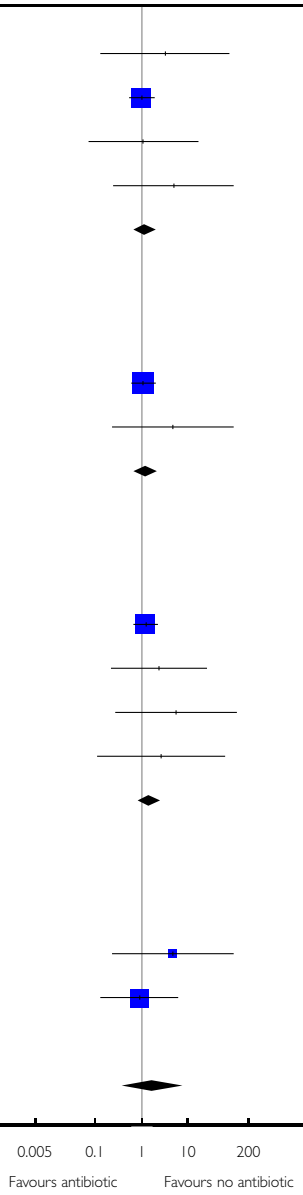
Analysis 2.1. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 1 Perinatal mortality.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 1 Perinatal mortality

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Beta-lactam antibiotics alone vs no antibiotics					
Cox 1996	1/40	0/42		2.3 %	3.15 [0.13, 75.05]
Kenyon 2001a	38/1534	13/519		90.8 %	0.99 [0.53, 1.84]
Keuchkerian 2005	1/47	1/49		4.6 %	1.04 [0.07, 16.19]
Newton 1991	2/47	0/45		2.4 %	4.79 [0.24, 97.14]
Subtotal (95% CI)	**1668**	**655**		**100.0 %**	**1.13 [0.64, 2.01]**
Total events: 42 (Antibiotics), 14 (No antibiotics)					
Heterogeneity: Chi^2 = 1.47, df = 3 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.42 (P = 0.67)					
2 Macrolide antibiotics alone vs no antibiotics					
Kenyon 2001a	43/1600	13/519		97.4 %	1.07 [0.58, 1.98]
McGregor 1991	2/53	0/50		2.6 %	4.72 [0.23, 96.01]
Subtotal (95% CI)	**1653**	**569**		**100.0 %**	**1.17 [0.64, 2.11]**
Total events: 45 (Antibiotics), 13 (No antibiotics)					
Heterogeneity: Chi^2 = 0.90, df = 1 (P = 0.34); I^2 =0.0%					
Test for overall effect: Z = 0.51 (P = 0.61)					
3 Macrolide and beta-lactam antibiotics vs no antibiotics					
Kenyon 2001a	47/1551	13/519		90.9 %	1.21 [0.66, 2.22]
Oyarzun 1998	2/78	1/90		4.3 %	2.31 [0.21, 24.97]
Romero 1993	2/131	0/144		2.2 %	5.49 [0.27, 113.36]
Watts 1994	1/30	0/26		2.5 %	2.61 [0.11, 61.51]
Subtotal (95% CI)	**1790**	**779**		**100.0 %**	**1.39 [0.79, 2.43]**
Total events: 52 (Antibiotics), 14 (No antibiotics)					
Heterogeneity: Chi^2 = 1.32, df = 3 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 1.15 (P = 0.25)					
4 Antibiotics active against anaerobic bacteria vs no antibiotics					
McGregor 1991	2/53	0/50		19.5 %	4.72 [0.23, 96.01]
Norman 1994	2/43	2/38		80.5 %	0.88 [0.13, 5.97]
Svare 1997	0/59	0/51			Not estimable
Subtotal (95% CI)	**155**	**139**		**100.0 %**	**1.63 [0.36, 7.39]**



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Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 4 (Antibiotics), 2 (No antibiotics)					
Heterogeneity: Chi^2 = 0.87, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.52)					
Test for subgroup differences: Chi^2 = 0.42, df = 3 (P = 0.94), I^2 =0.0%					

Analysis 2.2. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 2 Stillbirth.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 2 Stillbirth

Study or subgroup	Antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Beta-lactam antibiotics alone vs no antibiotics					
Cox 1996	0/40	0/42			Not estimable
Kenyon 2001a	14/1534	6/519		85.8 %	0.79 [0.30, 2.04]
Keuchkerian 2005	1/47	1/49		9.4 %	1.04 [0.07, 16.19]
Newton 1991	1/47	0/45		4.9 %	2.88 [0.12, 68.79]
Subtotal (95% CI)	**1668**	**655**		**100.0 %**	**0.91 [0.39, 2.14]**
Total events: 16 (Antibiotic), 7 (No antibiotic)					
Heterogeneity: Chi^2 = 0.60, df = 2 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 0.20 (P = 0.84)					
2 Macrolide antibiotics alone vs no antibiotics					
Kenyon 2001a	10/1600	6/519		100.0 %	0.54 [0.20, 1.48]
McGregor 1991	0/53	0/50			Not estimable
Subtotal (95% CI)	**1653**	**569**		**100.0 %**	**0.54 [0.20, 1.48]**
Total events: 10 (Antibiotic), 6 (No antibiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.20 (P = 0.23)					

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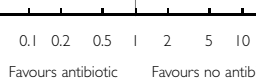
Study or subgroup	Antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 Macrolide and beta-lactam antibiotics vs no antibiotics					
Kenyon 2001a	13/1551	6/519		100.0 %	0.73 [0.28, 1.90]
Romero 1993	0/133	0/144			Not estimable
Subtotal (95% CI)	**1684**	**663**		**100.0 %**	**0.73 [0.28, 1.90]**
Total events: 13 (Antibiotic), 6 (No antibiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.51)					
4 Antibiotics active against anaerobic bacteria vs no bacteria					
McGregor 1991	0/53	0/50			Not estimable
Norman 1994	0/43	0/38			Not estimable
Svare 1997	0/59	0/51			Not estimable
Subtotal (95% CI)	**155**	**139**			**Not estimable**
Total events: 0 (Antibiotic), 0 (No antibiotic)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.61, df = 2 (P = 0.74), I^2 =0.0%					

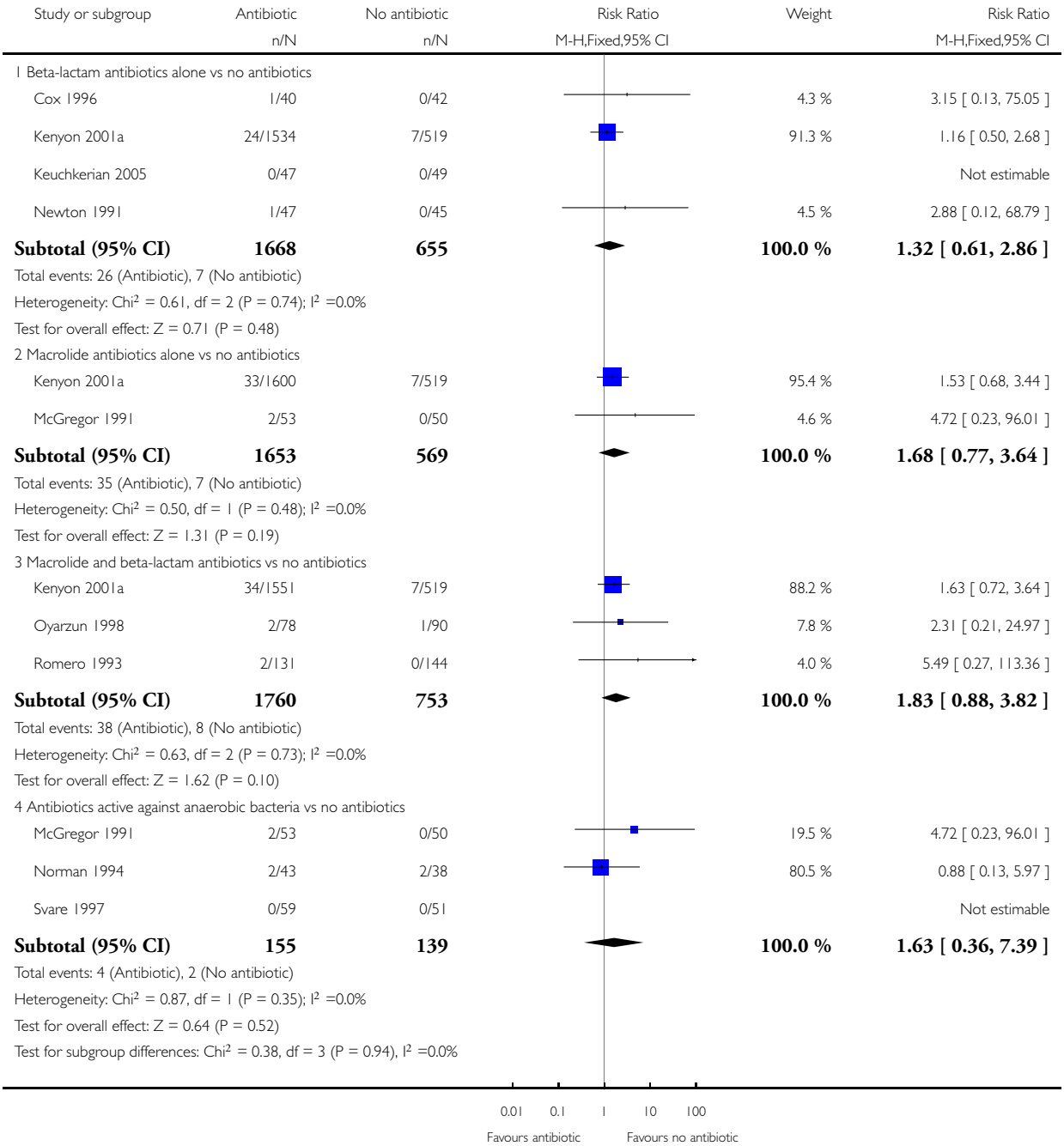


Analysis 2.3. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 3 Neonatal death.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 3 Neonatal death



Analysis 2.4. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 4 Infant death.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 4 Infant death

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Beta-lactam antibiotics alone vs no antibiotics					
Kenyon 2001a	17/1133	8/382		100.0 %	0.72 [0.31, 1.65]
Subtotal (95% CI)	**1133**	**382**		**100.0 %**	**0.72 [0.31, 1.65]**
Total events: 17 (Antibiotics), 8 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
2 Macrolide antibiotics alone vs no antibiotics					
Kenyon 2001a	29/1204	8/382		100.0 %	1.15 [0.53, 2.49]
Subtotal (95% CI)	**1204**	**382**		**100.0 %**	**1.15 [0.53, 2.49]**
Total events: 29 (Antibiotics), 8 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.35 (P = 0.72)					
3 Macrolide and beta-lactam antibiotics vs no antibiotics					
Kenyon 2001a	32/1171	8/382		100.0 %	1.30 [0.61, 2.81]
Subtotal (95% CI)	**1171**	**382**		**100.0 %**	**1.30 [0.61, 2.81]**
Total events: 32 (Antibiotics), 8 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
4 Antibiotics active against anaerobic bacteria vs no antibiotics					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antibiotics), 0 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi² = 1.17, df = 2 (P = 0.56), I² =0.0%					

Analysis 2.5. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 5 Any functional impairment at 7 years of age..

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 5 Any functional impairment at 7 years of age.

Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Beta-lactam antibiotics alone vs no antibiotics					
Kenyon 2001a	299/763	92/245		100.0 %	1.04 [0.87, 1.25]
Subtotal (95% CI)	**763**	**245**		**100.0 %**	**1.04 [0.87, 1.25]**
Total events: 299 (Antibiotics), 92 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.45 (P = 0.65)					
2 Macrolide antibiotics alone vs no antibiotics					
Kenyon 2001a	333/785	92/245		100.0 %	1.13 [0.94, 1.35]
Subtotal (95% CI)	**785**	**245**		**100.0 %**	**1.13 [0.94, 1.35]**
Total events: 333 (Antibiotics), 92 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					
3 Macrolide and beta-lactam antibiotics vs no antibiotics					
Kenyon 2001a	325/769	92/245		100.0 %	1.13 [0.94, 1.35]
Subtotal (95% CI)	**769**	**245**		**100.0 %**	**1.13 [0.94, 1.35]**
Total events: 325 (Antibiotics), 92 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
4 Antibiotics active against anaerobic bacteria vs no antibiotics					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antibiotics), 0 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.46, df = 2 (P = 0.80), I^2 =0.0%					

Analysis 2.6. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 6 Moderate/severe functional impairment at 7 years of age..

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 6 Moderate/severe functional impairment at 7 years of age.

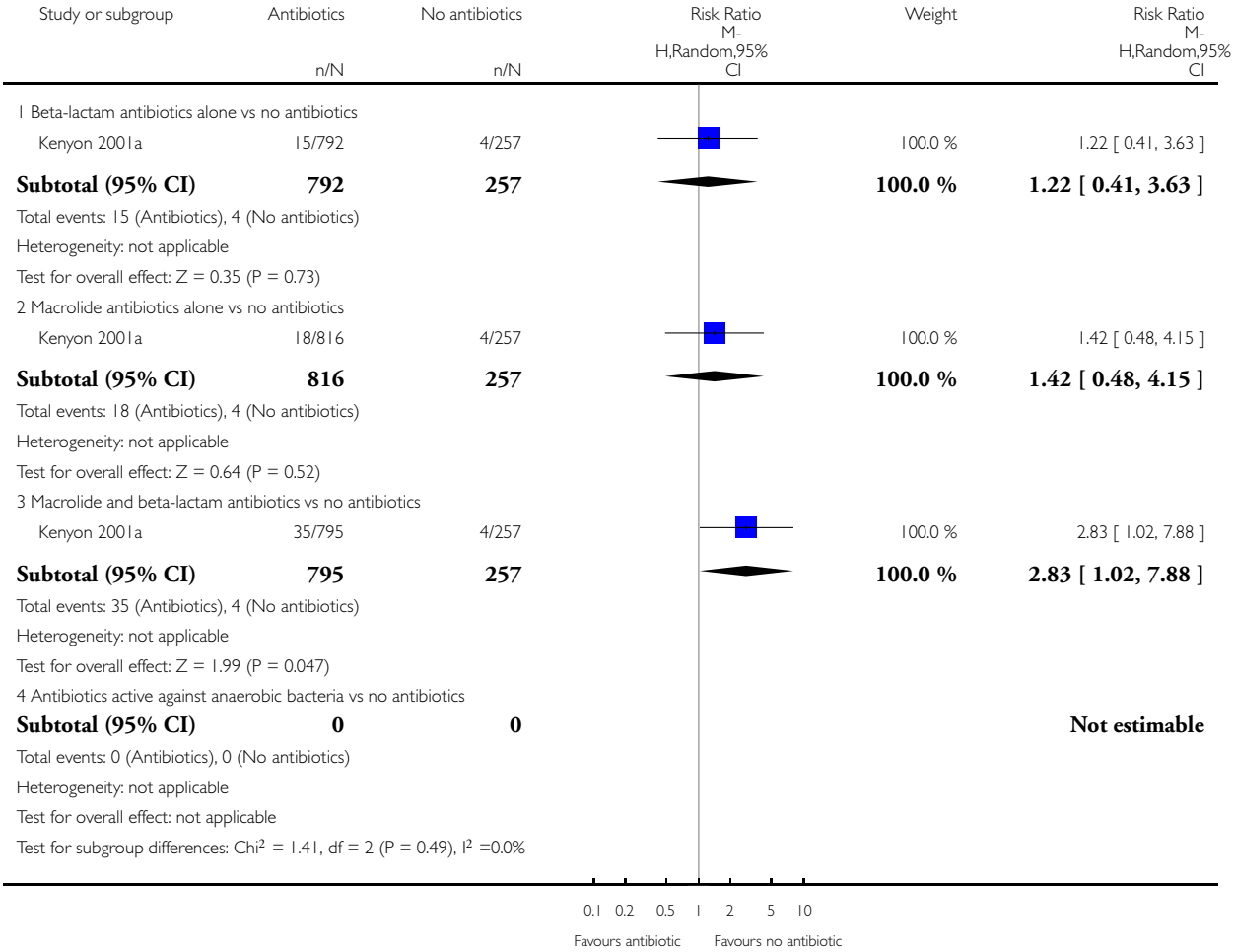
Study or subgroup	Antibiotics n/N	No antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Beta-lactam antibiotics alone vs no antibiotics					
Kenyon 2001a	131/763	41/245		100.0 %	1.03 [0.75, 1.41]
Subtotal (95% CI)	**763**	**245**		**100.0 %**	**1.03 [0.75, 1.41]**
Total events: 131 (Antibiotics), 41 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.16 (P = 0.88)					
2 Macrolide antibiotics alone vs no antibiotics					
Kenyon 2001a	142/785	41/245		100.0 %	1.08 [0.79, 1.48]
Subtotal (95% CI)	**785**	**245**		**100.0 %**	**1.08 [0.79, 1.48]**
Total events: 142 (Antibiotics), 41 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					
3 Macrolide and beta-lactam antibiotics vs no antibiotics					
Kenyon 2001a	144/769	41/245		100.0 %	1.12 [0.82, 1.53]
Subtotal (95% CI)	**769**	**245**		**100.0 %**	**1.12 [0.82, 1.53]**
Total events: 144 (Antibiotics), 41 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.49)					
4 Antibiotics active against anaerobic bacteria vs no antibiotics					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Antibiotics), 0 (No antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.14, df = 2 (P = 0.93), I^2 =0.0%					

Analysis 2.7. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 7 Cerebral palsy at 7 years of age.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 7 Cerebral palsy at 7 years of age

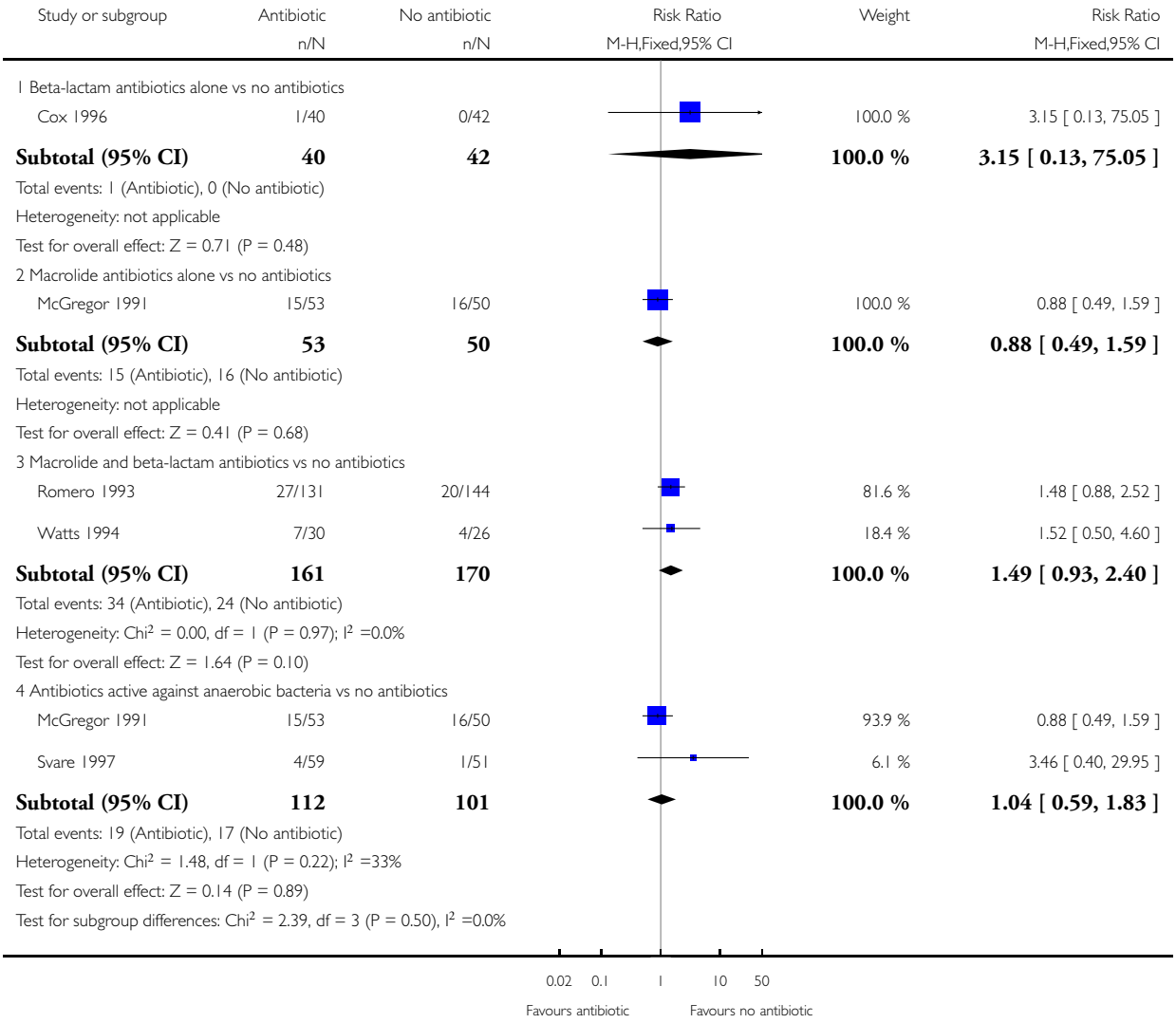


Analysis 2.8. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 8 Maternal adverse drug reaction requiring cessation of treatment.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 8 Maternal adverse drug reaction requiring cessation of treatment

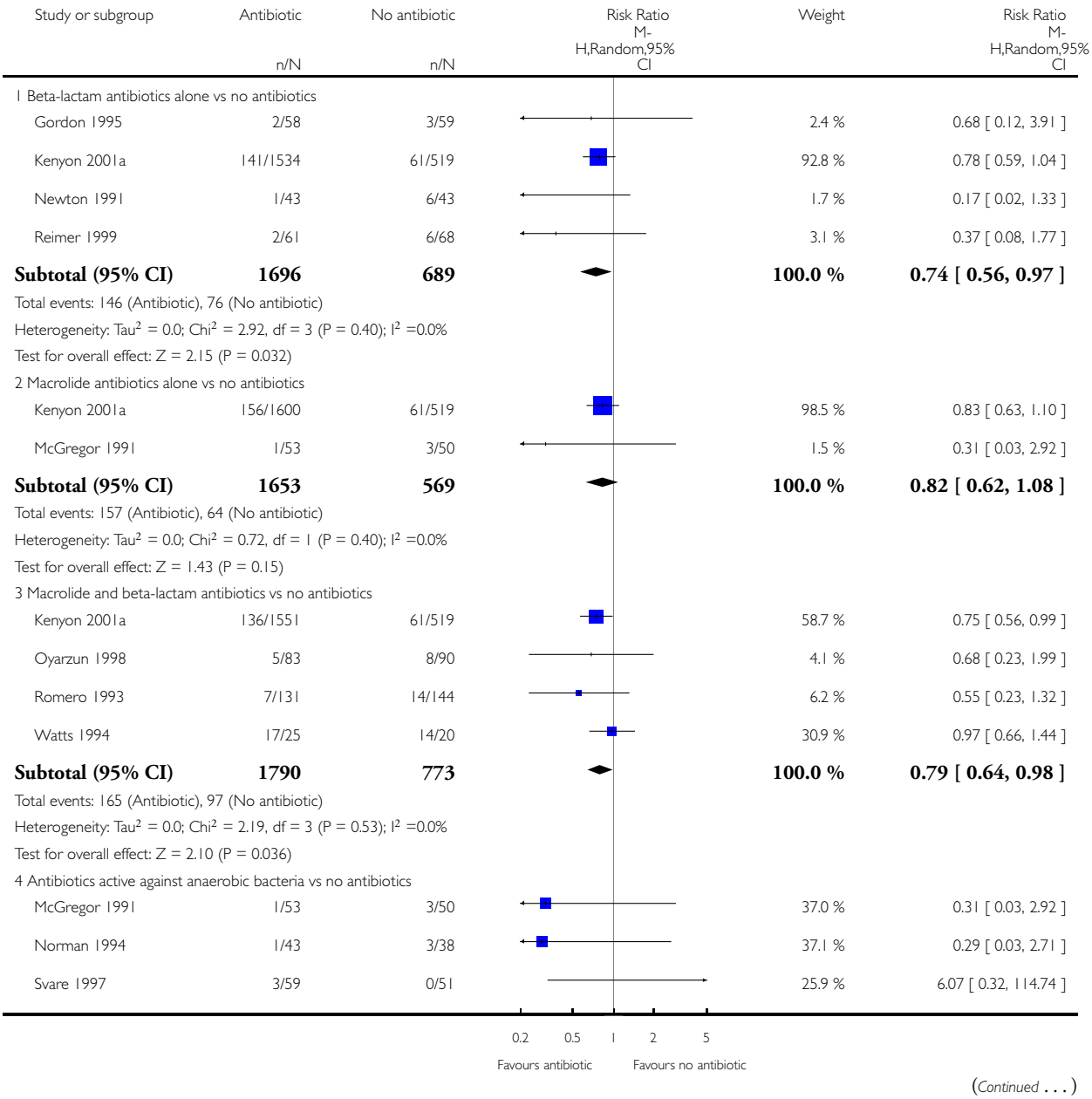


Analysis 2.9. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 9 Maternal infection.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 9 Maternal infection



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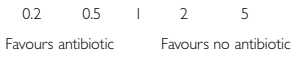
Study or subgroup	Antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**155**	**139**		**100.0 %**	**0.66 [0.11, 3.92]**
Total events: 5 (Antibiotic), 6 (No antibiotic)					
Heterogeneity: Tau^2 = 0.94; Chi^2 = 3.22, df = 2 (P = 0.20); I^2 =38%					
Test for overall effect: Z = 0.46 (P = 0.65)					
Test for subgroup differences: Chi^2 = 0.29, df = 3 (P = 0.96), I^2 =0.0%					



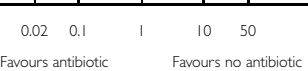
Analysis 2.10. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 10 Birth within 48 hours of randomisation.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 10 Birth within 48 hours of randomisation

Study or subgroup	Antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Beta-lactam antibiotics alone vs no antibiotics					
Kenyon 2001a	152/1534	51/519		100.0 %	1.01 [0.75, 1.36]
Subtotal (95% CI)	**1534**	**519**		**100.0 %**	**1.01 [0.75, 1.36]**
Total events: 152 (Antibiotic), 51 (No antibiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
2 Macrolide antibiotics alone vs no antibiotics					
Kenyon 2001a	166/1600	51/519		100.0 %	1.06 [0.78, 1.42]
Subtotal (95% CI)	**1600**	**519**		**100.0 %**	**1.06 [0.78, 1.42]**
Total events: 166 (Antibiotic), 51 (No antibiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
3 Macrolide and beta-lactam antibiotics vs no antibiotics					
Kenyon 2001a	166/1551	51/519		77.6 %	1.09 [0.81, 1.47]
Oyarzun 1998	12/83	13/90		12.7 %	1.00 [0.48, 2.07]



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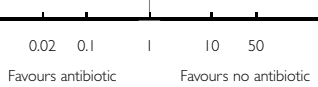
Study or subgroup	Antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Romero 1993	14/133	10/144		9.7 %	1.52 [0.70, 3.30]
Subtotal (95% CI)	**1767**	**753**		**100.0 %**	**1.12 [0.86, 1.45]**
Total events: 192 (Antibiotic), 74 (No antibiotic)					
Heterogeneity: Chi^2 = 0.71, df = 2 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 0.85 (P = 0.39)					
4 Antibiotics active against anaerobic bacteria vs no antibiotics					
Svare 1997	5/58	8/51		100.0 %	0.55 [0.19, 1.57]
Subtotal (95% CI)	**58**	**51**		**100.0 %**	**0.55 [0.19, 1.57]**
Total events: 5 (Antibiotic), 8 (No antibiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					
Test for subgroup differences: Chi^2 = 1.76, df = 3 (P = 0.62), I^2 =0.0%					

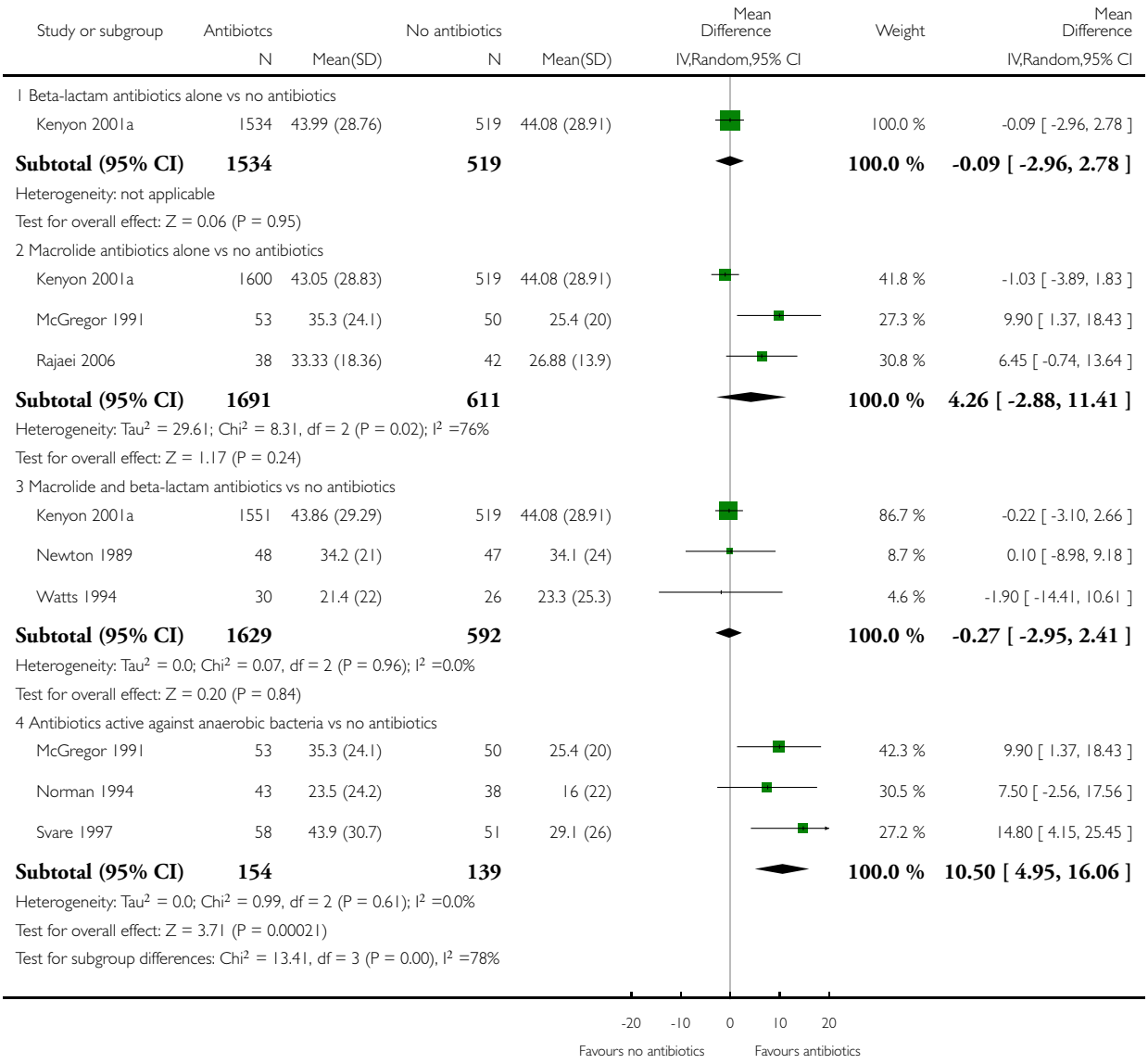


Analysis 2.11. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 11 Interval between randomisation and birth (days).

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 11 Interval between randomisation and birth (days)



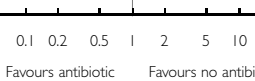
Analysis 2.12. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 12 Preterm birth (< 36 or < 37 weeks' gestation).

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 12 Preterm birth (< 36 or < 37 weeks' gestation)

Study or subgroup	Antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Beta-lactam antibiotics alone vs no antibiotics					
Cox 1996	23/39	22/39		8.1 %	1.05 [0.71, 1.53]
Gordon 1995	35/58	34/59		12.8 %	1.05 [0.77, 1.42]
Kenyon 2001a	545/1534	186/519		65.8 %	0.99 [0.87, 1.13]
Keuchkerian 2005	17/47	19/49		4.4 %	0.93 [0.56, 1.57]
Newton 1991	23/43	27/43		9.0 %	0.85 [0.59, 1.22]
Subtotal (95% CI)	**1721**	**709**		**100.0 %**	**0.99 [0.89, 1.10]**
Total events: 643 (Antibiotic), 288 (No antibiotic)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.92$, df = 4 (P = 0.92); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.25 (P = 0.81)					
2 Macrolide antibiotics alone vs no antibiotics					
Kenyon 2001a	584/1600	186/519		80.6 %	1.02 [0.89, 1.16]
McGregor 1991	38/58	37/58		19.4 %	1.03 [0.78, 1.34]
Subtotal (95% CI)	**1658**	**577**		**100.0 %**	**1.02 [0.91, 1.15]**
Total events: 622 (Antibiotic), 223 (No antibiotic)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.96); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.33 (P = 0.74)					
3 Macrolide and beta-lactam antibiotics vs no antibiotics					
Kenyon 2001a	558/1551	186/519		62.5 %	1.00 [0.88, 1.15]
Newton 1989	18/48	21/47		4.7 %	0.84 [0.52, 1.36]
Oyarzun 1998	38/83	45/90		11.3 %	0.92 [0.67, 1.25]
Romero 1993	69/131	74/144		21.4 %	1.02 [0.82, 1.29]
Subtotal (95% CI)	**1813**	**800**		**100.0 %**	**0.99 [0.89, 1.10]**
Total events: 683 (Antibiotic), 326 (No antibiotic)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.82$, df = 3 (P = 0.85); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.20 (P = 0.84)					
4 Antibiotics active against anaerobic bacteria vs no antibiotics					
McGregor 1991	38/58	37/58		53.6 %	1.03 [0.78, 1.34]
Svare 1997	25/59	33/51		46.4 %	0.65 [0.46, 0.94]



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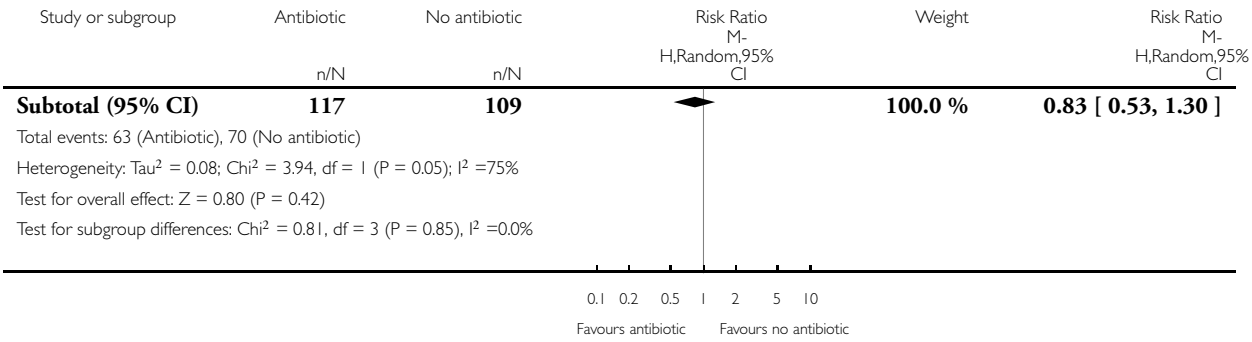
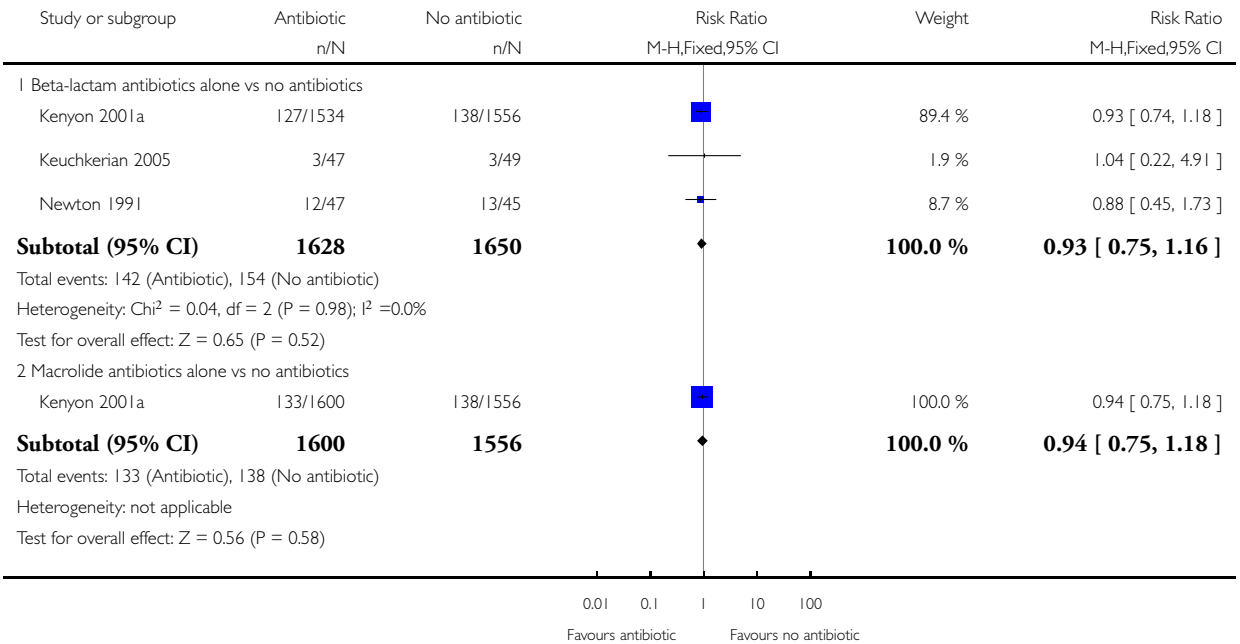


Analysis 2.13. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 13 Respiratory distress syndrome.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 13 Respiratory distress syndrome



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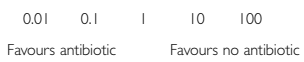
Study or subgroup	Antibiotic n/N	No antibiotic n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 Macrolide and beta-lactam antibiotics vs no antibiotics					
Kenyon 2001a	139/1551	138/1556		92.9 %	1.01 [0.81, 1.27]
Romero 1993	14/131	11/144		7.1 %	1.40 [0.66, 2.97]
Subtotal (95% CI)	**1682**	**1700**		**100.0 %**	**1.04 [0.84, 1.29]**
Total events: 153 (Antibiotic), 149 (No antibiotic)					
Heterogeneity: Chi^2 = 0.66, df = 1 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 0.34 (P = 0.73)					
4 Antibiotics active against anaerobic bacteria vs no antibiotics					
Svare 1997	2/58	3/51		100.0 %	0.59 [0.10, 3.37]
Subtotal (95% CI)	**58**	**51**		**100.0 %**	**0.59 [0.10, 3.37]**
Total events: 2 (Antibiotic), 3 (No antibiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
Test for subgroup differences: Chi^2 = 0.92, df = 3 (P = 0.82), I^2 =0.0%					

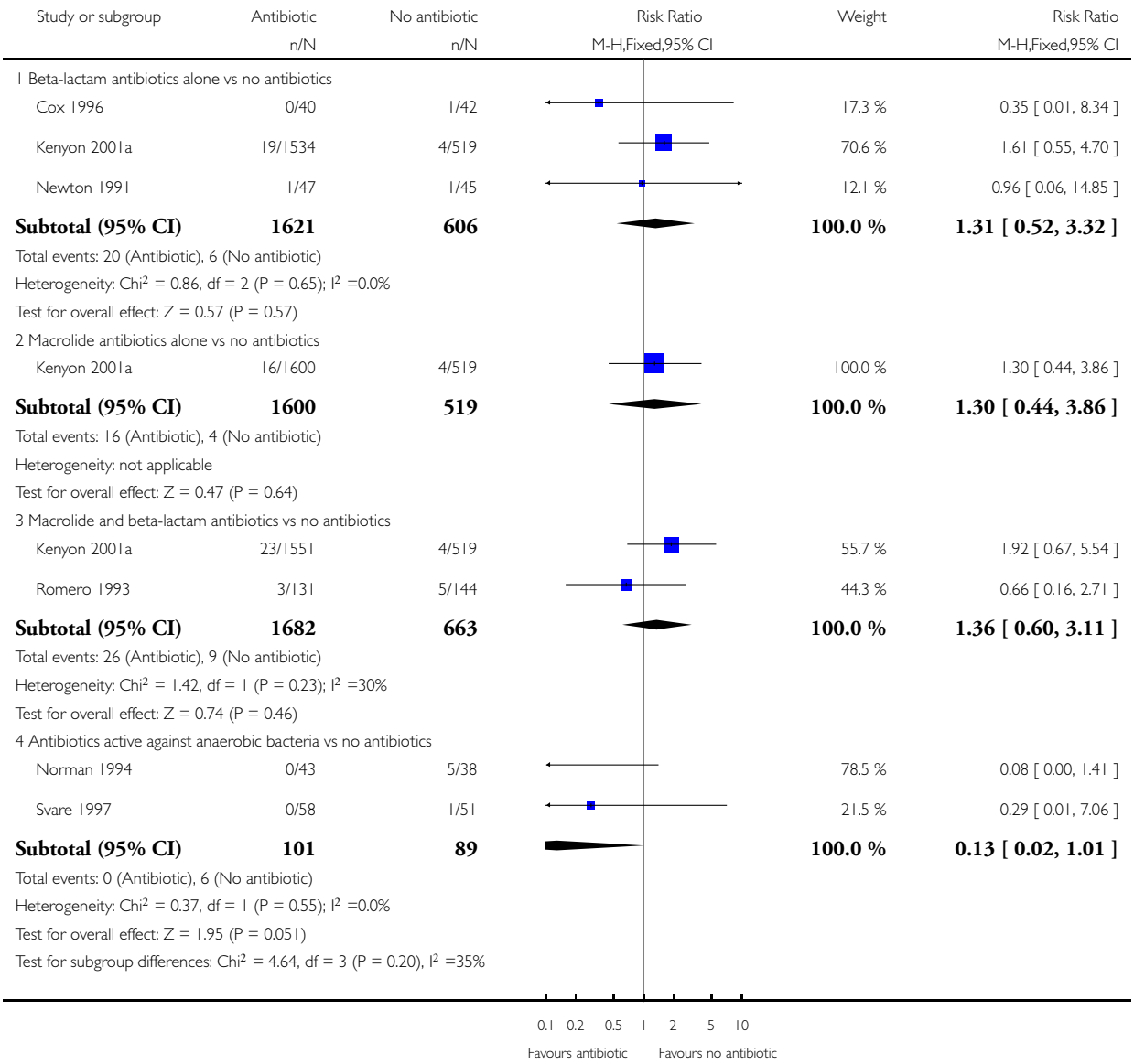


Analysis 2.14. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 14 Necrotising enterocolitis.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 14 Necrotising enterocolitis

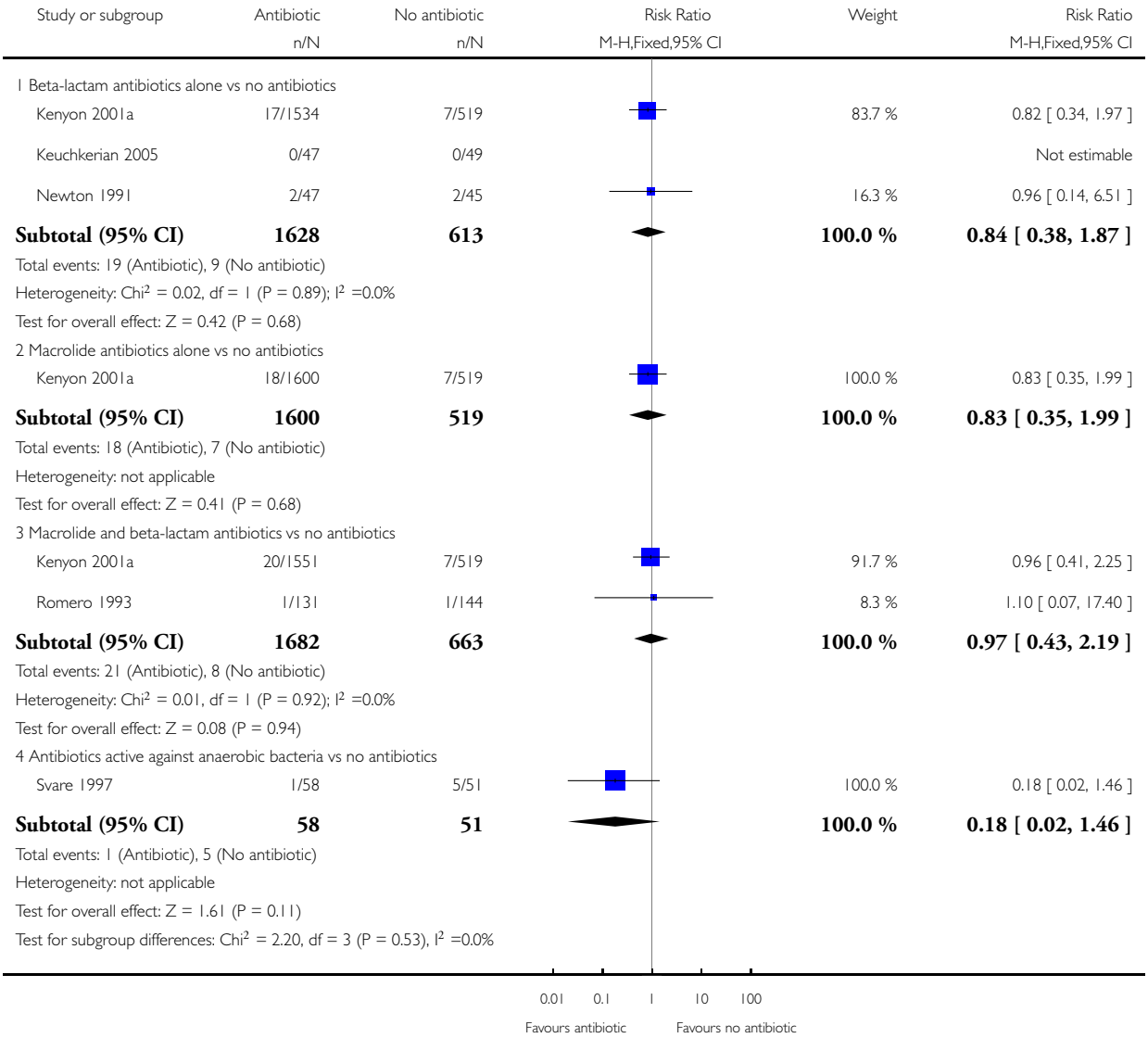


Analysis 2.15. Comparison 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic), Outcome 15 Intraventricular haemorrhage.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 2 Antibiotics versus no antibiotics (subgrouped by type of antibiotic)

Outcome: 15 Intraventricular haemorrhage



Analysis 3.1. Comparison 3 Any macrolide versus no macrolide, Outcome 1 Perinatal mortality.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 1 Perinatal mortality

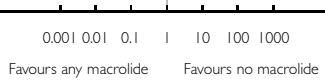
Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	90/3151	77/3090		97.6 %	1.15 [0.85, 1.55]
Oyarzun 1998	2/78	1/90		1.2 %	2.31 [0.21, 24.97]
Romero 1993	2/131	0/144		0.6 %	5.49 [0.27, 113.36]
Watts 1994	1/30	0/26		0.7 %	2.61 [0.11, 61.51]
Total (95% CI)	**3390**	**3350**		**100.0 %**	**1.20 [0.89, 1.60]**

Total events: 95 (Any macrolide), 78 (No macrolide)

Heterogeneity: Chi^2 = 1.58, df = 3 (P = 0.66); I^2 =0.0%

Test for overall effect: Z = 1.19 (P = 0.23)

Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3 Any macrolide versus no macrolide, Outcome 2 Stillbirth.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 2 Stillbirth

Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	23/3151	32/3090		100.0 %	0.70 [0.41, 1.20]
Romero 1993	0/133	0/144			Not estimable
Total (95% CI)	**3284**	**3234**		**100.0 %**	**0.70 [0.41, 1.20]**

Total events: 23 (Any macrolide), 32 (No macrolide)

Heterogeneity: not applicable

Test for overall effect: Z = 1.29 (P = 0.20)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Any macrolide versus no macrolide, Outcome 3 Neonatal death.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 3 Neonatal death

Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	67/3151	45/3090		97.0 %	1.46 [1.00, 2.12]
Oyarzun 1998	2/78	1/90		2.0 %	2.31 [0.21, 24.97]
Romero 1993	2/131	0/144		1.0 %	5.49 [0.27, 113.36]
Total (95% CI)	**3360**	**3324**		**100.0 %**	**1.52 [1.05, 2.19]**

Total events: 71 (Any macrolide), 46 (No macrolide)

Heterogeneity: Chi^2 = 0.85, df = 2 (P = 0.65); I^2 =0.0%

Test for overall effect: Z = 2.24 (P = 0.025)

Test for subgroup differences: Not applicable

Analysis 3.4. Comparison 3 Any macrolide versus no macrolide, Outcome 4 Infant death.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 4 Infant death

Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	61/2304	41/2279		100.0 %	1.47 [0.99, 2.18]
Total (95% CI)	**2304**	**2279**		**100.0 %**	**1.47 [0.99, 2.18]**
Total events: 61 (Any macrolide), 41 (No macrolide)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.93 (P = 0.053)					
Test for subgroup differences: Not applicable					

Analysis 3.5. Comparison 3 Any macrolide versus no macrolide, Outcome 5 Any functional impairment at 7 years of age..

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 5 Any functional impairment at 7 years of age.

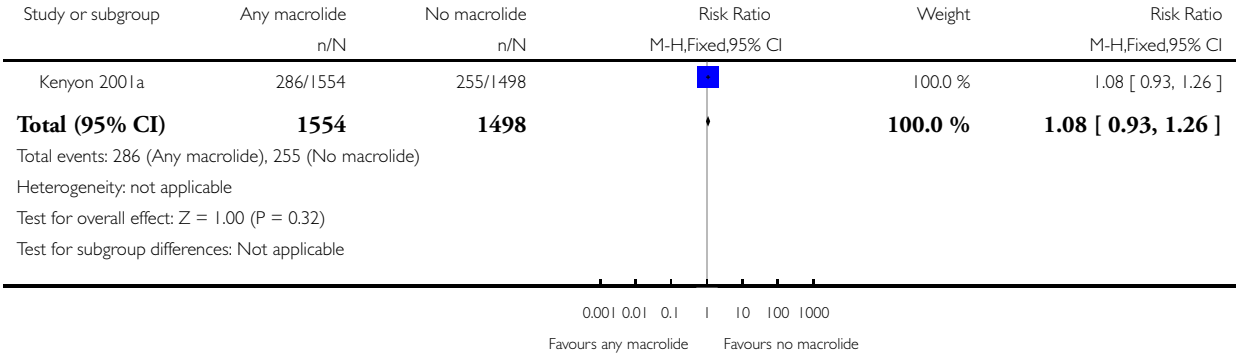
Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	658/1554	574/1498		100.0 %	1.11 [1.01, 1.20]
Total (95% CI)	**1554**	**1498**		**100.0 %**	**1.11 [1.01, 1.20]**
Total events: 658 (Any macrolide), 574 (No macrolide)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.26 (P = 0.024)					
Test for subgroup differences: Not applicable					

Analysis 3.6. Comparison 3 Any macrolide versus no macrolide, Outcome 6 Moderate/severe functional impairment at 7 years of age..

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 6 Moderate/severe functional impairment at 7 years of age.

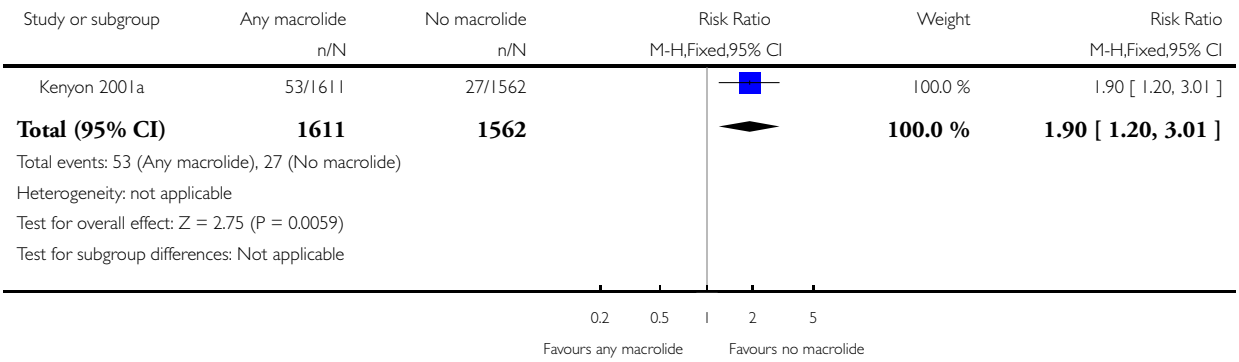


Analysis 3.7. Comparison 3 Any macrolide versus no macrolide, Outcome 7 Cerebral palsy at 7 years.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 7 Cerebral palsy at 7 years



Analysis 3.8. Comparison 3 Any macrolide versus no macrolide, Outcome 8 Maternal adverse drug reaction requiring cessation of treatment.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 8 Maternal adverse drug reaction requiring cessation of treatment

Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Romero 1993	27/131	20/144		81.6 %	1.48 [0.88, 2.52]
Watts 1994	7/30	4/26		18.4 %	1.52 [0.50, 4.60]
Total (95% CI)	**161**	**170**		**100.0 %**	**1.49 [0.93, 2.40]**

Total events: 34 (Any macrolide), 24 (No macrolide)
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable

Analysis 3.9. Comparison 3 Any macrolide versus no macrolide, Outcome 9 Maternal infection.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 9 Maternal infection

Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Kenyon 2001a	292/3151	324/3090		53.1 %	0.88 [0.76, 1.03]
Oyarzun 1998	5/83	8/90		14.6 %	0.68 [0.23, 1.99]
Romero 1993	7/131	14/144		19.5 %	0.55 [0.23, 1.32]
Watts 1994	3/30	10/26		12.8 %	0.26 [0.08, 0.84]
Total (95% CI)	**3395**	**3350**		**100.0 %**	**0.66 [0.41, 1.07]**

Total events: 307 (Any macrolide), 356 (No macrolide)
Heterogeneity: Tau^2 = 0.11; Chi^2 = 5.26, df = 3 (P = 0.15); I^2 =43%
Test for overall effect: Z = 1.68 (P = 0.093)
Test for subgroup differences: Not applicable

Analysis 3.10. Comparison 3 Any macrolide versus no macrolide, Outcome 10 Birth within 48 hours of randomisation.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 10 Birth within 48 hours of randomisation

Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	332/3151	304/3090		93.3 %	1.07 [0.92, 1.24]
Oyarzun 1998	12/83	13/90		3.8 %	1.00 [0.48, 2.07]
Romero 1993	14/133	10/144		2.9 %	1.52 [0.70, 3.30]
Total (95% CI)	**3367**	**3324**		**100.0 %**	**1.08 [0.94, 1.25]**

Total events: 358 (Any macrolide), 327 (No macrolide)

Heterogeneity: $Chi^2 = 0.79$, df = 2 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 1.08 (P = 0.28)

Test for subgroup differences: Not applicable

Analysis 3.11. Comparison 3 Any macrolide versus no macrolide, Outcome 11 Interval between randomisation and birth (days).

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 11 Interval between randomisation and birth (days)

Study or subgroup	Any macrolide N	Mean(SD)	No macrolide N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kenyon 2001a	3151	43.45 (29.06)	3099	44.04 (28.03)		62.8 %	-0.59 [-2.01, 0.83]
Rajaei 2006	38	33.33 (18.36)	42	26.88 (13.9)		25.7 %	6.45 [-0.74, 13.64]
Watts 1994	30	21.4 (22)	26	23.3 (25.3)		11.5 %	-1.90 [-14.41, 10.61]
Total (95% CI)	**3219**		**3167**			**100.0 %**	**1.07 [-3.58, 5.72]**

Heterogeneity: $Tau^2 = 8.45$; $Chi^2 = 3.60$, df = 2 (P = 0.17); $I^2 = 44\%$

Test for overall effect: Z = 0.45 (P = 0.65)

Test for subgroup differences: Not applicable

Analysis 3.12. Comparison 3 Any macrolide versus no macrolide, Outcome 12 Preterm birth (< 36 or < 37 weeks).

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 12 Preterm birth (< 36 or < 37 weeks)

Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	1142/3151	1104/3090		89.2 %	1.01 [0.95, 1.08]
Newton 1989	18/48	21/47		1.7 %	0.84 [0.52, 1.36]
Oyarzun 1998	38/83	45/90		3.5 %	0.92 [0.67, 1.25]
Romero 1993	69/131	74/144		5.6 %	1.02 [0.82, 1.29]
Total (95% CI)	**3413**	**3371**		**100.0 %**	**1.01 [0.95, 1.07]**

Total events: 1267 (Any macrolide), 1244 (No macrolide)

Heterogeneity: $Chi^2 = 0.97$, df = 3 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 0.27 (P = 0.79)

Test for subgroup differences: Not applicable

Analysis 3.13. Comparison 3 Any macrolide versus no macrolide, Outcome 13 Respiratory distress syndrome.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 13 Respiratory distress syndrome

Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	272/3151	265/3090		91.3 %	1.01 [0.86, 1.18]
Oyarzun 1998	9/78	7/90		2.2 %	1.48 [0.58, 3.80]
Romero 1993	14/131	11/144		3.6 %	1.40 [0.66, 2.97]
Watts 1994	13/30	8/26		2.9 %	1.41 [0.69, 2.86]
Total (95% CI)	**3390**	**3350**		**100.0 %**	**1.04 [0.90, 1.21]**

Total events: 308 (Any macrolide), 291 (No macrolide)

Heterogeneity: $Chi^2 = 2.00$, df = 3 (P = 0.57); $I^2 = 0.0\%$

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable

Analysis 3.14. Comparison 3 Any macrolide versus no macrolide, Outcome 14 Intraventricular haemorrhage.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 14 Intraventricular haemorrhage

Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	38/3151	39/3090		97.6 %	0.96 [0.61, 1.49]
Romero 1993	1/131	1/144		2.4 %	1.10 [0.07, 17.40]
Total (95% CI)	**3282**	**3234**		**100.0 %**	**0.96 [0.62, 1.49]**

Total events: 39 (Any macrolide), 40 (No macrolide)

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%

Test for overall effect: Z = 0.19 (P = 0.85)

Test for subgroup differences: Not applicable

Analysis 3.15. Comparison 3 Any macrolide versus no macrolide, Outcome 15 Necrotising enterocolitis.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 3 Any macrolide versus no macrolide

Outcome: 15 Necrotising enterocolitis

Study or subgroup	Any macrolide n/N	No macrolide n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	39/3151	31/3090		86.8 %	1.23 [0.77, 1.97]
Romero 1993	3/131	5/144		13.2 %	0.66 [0.16, 2.71]
Total (95% CI)	**3282**	**3234**		**100.0 %**	**1.16 [0.74, 1.80]**

Total events: 42 (Any macrolide), 36 (No macrolide)

Heterogeneity: Chi^2 = 0.68, df = 1 (P = 0.41); I^2 =0.0%

Test for overall effect: Z = 0.65 (P = 0.52)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 1 Perinatal mortality.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 1 Perinatal mortality

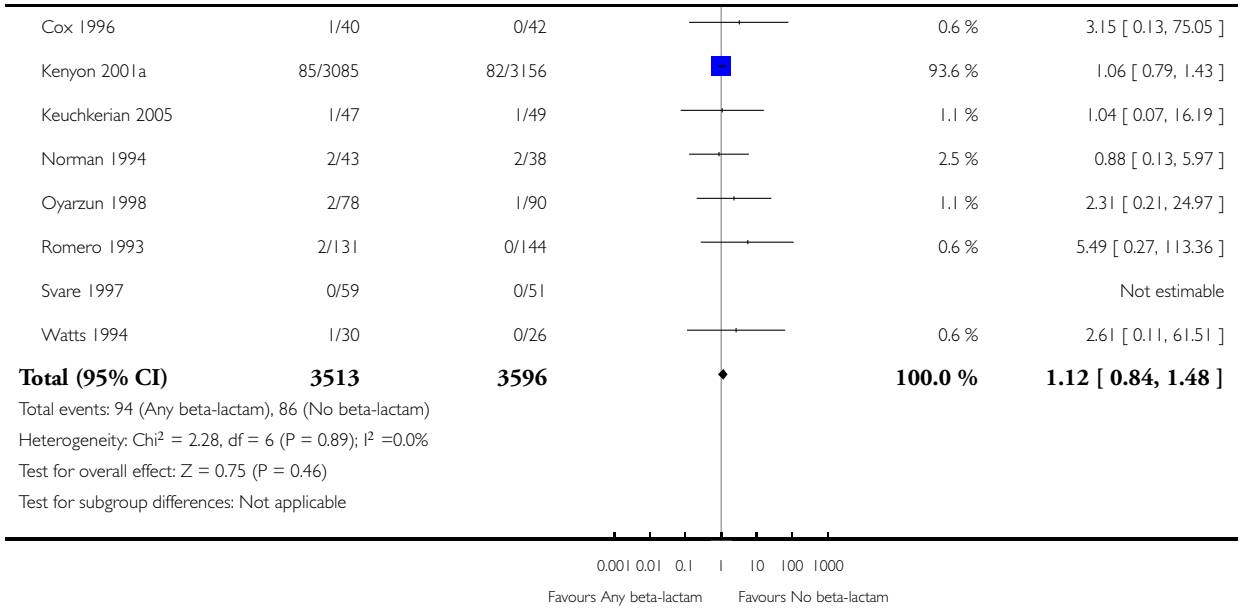
Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	1/40	0/42		0.6 %	3.15 [0.13, 75.05]
Kenyon 2001a	85/3085	82/3156		93.6 %	1.06 [0.79, 1.43]
Keuchkerian 2005	1/47	1/49		1.1 %	1.04 [0.07, 16.19]
Norman 1994	2/43	2/38		2.5 %	0.88 [0.13, 5.97]
Oyarzun 1998	2/78	1/90		1.1 %	2.31 [0.21, 24.97]
Romero 1993	2/131	0/144		0.6 %	5.49 [0.27, 113.36]
Svare 1997	0/59	0/51			Not estimable
Watts 1994	1/30	0/26		0.6 %	2.61 [0.11, 61.51]
Total (95% CI)	**3513**	**3596**		**100.0 %**	**1.12 [0.84, 1.48]**

Total events: 94 (Any beta-lactam), 86 (No beta-lactam)

Heterogeneity: $Chi^2 = 2.28$, df = 6 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 0.75 (P = 0.46)

Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 2 Stillbirth.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 2 Stillbirth

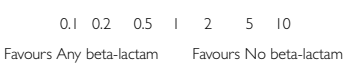
Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	0/40	0/42			Not estimable
Kenyon 2001a	58/3085	54/3156		98.2 %	1.10 [0.76, 1.59]
Keuchkerian 2005	1/47	1/49		1.8 %	1.04 [0.07, 16.19]
Norman 1994	0/43	0/38			Not estimable
Romero 1993	0/133	0/144			Not estimable
Svare 1997	0/59	0/51			Not estimable
Total (95% CI)	**3407**	**3480**		**100.0 %**	**1.10 [0.76, 1.58]**

Total events: 59 (Any beta-lactam), 55 (No beta-lactam)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 3 Neonatal death.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 3 Neonatal death

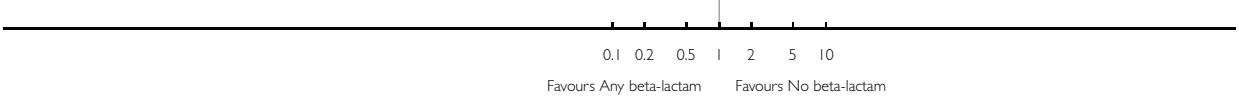
Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	1/40	0/42		1.0 %	3.15 [0.13, 75.05]
Kenyon 2001a	67/3151	45/3090		91.9 %	1.46 [1.00, 2.12]
Keuchkerian 2005	0/47	0/49			Not estimable
Norman 1994	2/43	2/38		4.3 %	0.88 [0.13, 5.97]
Oyarzun 1998	2/78	1/90		1.9 %	2.31 [0.21, 24.97]
Romero 1993	2/131	0/144		1.0 %	5.49 [0.27, 113.36]
Svare 1997	0/59	0/51			Not estimable
Total (95% CI)	**3549**	**3504**		**100.0 %**	**1.51 [1.06, 2.15]**

Total events: 74 (Any beta-lactam), 48 (No beta-lactam)

Heterogeneity: $Chi^2 = 1.36$, df = 4 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 2.26 (P = 0.024)

Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 4 Infant death.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 4 Infant death

Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	49/2304	53/2350		100.0 %	0.94 [0.64, 1.38]
Total (95% CI)	**2304**	**2350**		**100.0 %**	**0.94 [0.64, 1.38]**
Total events: 49 (Any beta-lactam), 53 (No beta-lactam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
Test for subgroup differences: Not applicable					

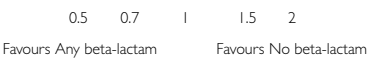
Analysis 4.5. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 5 Any functional impairment at 7 years of age..

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 5 Any functional impairment at 7 years of age.

Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	624/1532	608/1520		100.0 %	1.02 [0.93, 1.11]
Total (95% CI)	**1532**	**1520**		**100.0 %**	**1.02 [0.93, 1.11]**
Total events: 624 (Any beta-lactam), 608 (No beta-lactam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.41 (P = 0.68)					
Test for subgroup differences: Not applicable					



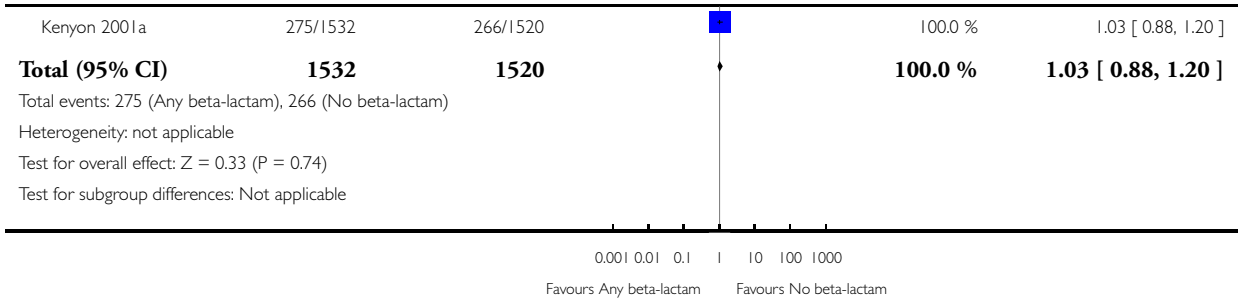
Analysis 4.6. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 6 Moderate/severe functional impairment at 7 years of age..

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 6 Moderate/severe functional impairment at 7 years of age.

Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	275/1532	266/1520		100.0 %	1.03 [0.88, 1.20]
Total (95% CI)	**1532**	**1520**		**100.0 %**	**1.03 [0.88, 1.20]**
Total events: 275 (Any beta-lactam), 266 (No beta-lactam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
Test for subgroup differences: Not applicable					



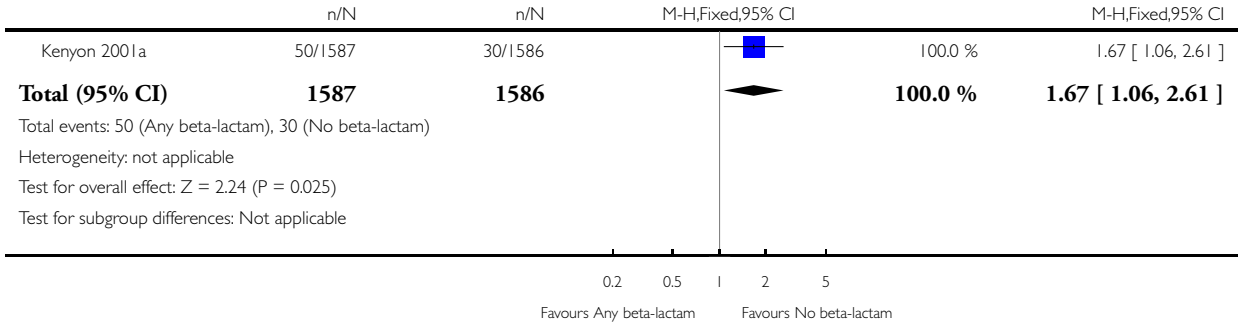
Analysis 4.7. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 7 Cerebral palsy at 7 years.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 7 Cerebral palsy at 7 years

Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	50/1587	30/1586		100.0 %	1.67 [1.06, 2.61]
Total (95% CI)	**1587**	**1586**		**100.0 %**	**1.67 [1.06, 2.61]**
Total events: 50 (Any beta-lactam), 30 (No beta-lactam)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.24 (P = 0.025)					
Test for subgroup differences: Not applicable					



Analysis 4.8. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 8 Maternal adverse drug reaction requiring cessation of treatment.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 8 Maternal adverse drug reaction requiring cessation of treatment

Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	1/40	0/42		2.0 %	3.15 [0.13, 75.05]
Romero 1993	27/131	20/144		76.5 %	1.48 [0.88, 2.52]
Svare 1997	4/59	1/51		4.3 %	3.46 [0.40, 29.95]
Watts 1994	7/30	4/26		17.2 %	1.52 [0.50, 4.60]
Total (95% CI)	**260**	**263**		**100.0 %**	**1.61 [1.02, 2.54]**
Total events: 39 (Any beta-lactam), 25 (No beta-lactam)					
Heterogeneity: Chi^2 = 0.75, df = 3 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 2.02 (P = 0.043)					
Test for subgroup differences: Not applicable					

Analysis 4.9. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 9 Maternal infection.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 9 Maternal infection

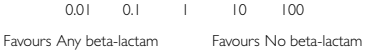
Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gordon 1995	2/58	3/59		0.8 %	0.68 [0.12, 3.91]
Kenyon 2001a	277/3085	339/3156		88.4 %	0.84 [0.72, 0.97]
Norman 1994	1/43	3/38		0.8 %	0.29 [0.03, 2.71]
Oyarzun 1998	5/83	8/90		2.0 %	0.68 [0.23, 1.99]
Reimer 1999	2/61	6/68		1.5 %	0.37 [0.08, 1.77]
Romero 1993	7/131	14/144		3.5 %	0.55 [0.23, 1.32]
Svare 1997	3/59	0/51		0.1 %	6.07 [0.32, 114.74]
Watts 1994	3/30	10/26		2.8 %	0.26 [0.08, 0.84]
Total (95% CI)	**3550**	**3632**		**100.0 %**	**0.80 [0.69, 0.92]**

Total events: 300 (Any beta-lactam), 383 (No beta-lactam)

Heterogeneity: Chi^2 = 8.18, df = 7 (P = 0.32); I^2 =14%

Test for overall effect: Z = 3.03 (P = 0.0025)

Test for subgroup differences: Not applicable



Analysis 4.10. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 10 Birth within 48 hours of randomisation.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 10 Birth within 48 hours of randomisation

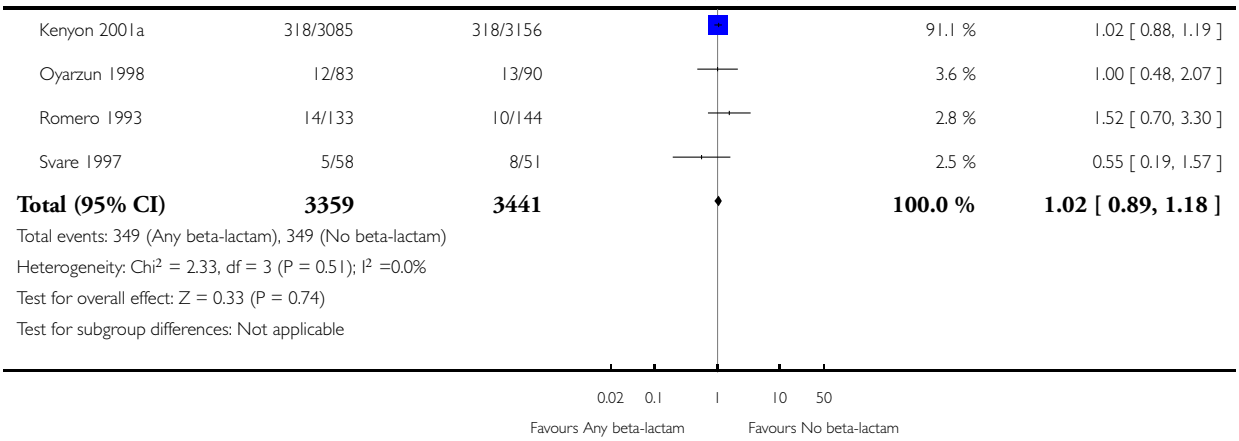
Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	318/3085	318/3156		91.1 %	1.02 [0.88, 1.19]
Oyarzun 1998	12/83	13/90		3.6 %	1.00 [0.48, 2.07]
Romero 1993	14/133	10/144		2.8 %	1.52 [0.70, 3.30]
Svare 1997	5/58	8/51		2.5 %	0.55 [0.19, 1.57]
Total (95% CI)	**3359**	**3441**		**100.0 %**	**1.02 [0.89, 1.18]**

Total events: 349 (Any beta-lactam), 349 (No beta-lactam)

Heterogeneity: $Chi^2 = 2.33$, df = 3 (P = 0.51); $I^2 = 0.0\%$

Test for overall effect: Z = 0.33 (P = 0.74)

Test for subgroup differences: Not applicable



Analysis 4.11. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 11 Interval between randomisation and birth (days).

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 11 Interval between randomisation and birth (days)

Study or subgroup	Any beta-lactam N	Mean(SD)	No beta-lactam N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kenyon 2001a	3065	43.93 (29.02)	3156	43.56 (28.87)		46.8 %	0.37 [-1.07, 1.81]
Svare 1997	58	43.9 (30.7)	51	29.1 (26)		28.5 %	14.80 [4.15, 25.45]
Watts 1994	30	21.4 (22)	26	23.3 (25.3)		24.7 %	-1.90 [-14.41, 10.61]
Total (95% CI)	**3153**		**3233**			**100.0 %**	**3.92 [-5.08, 12.92]**

Heterogeneity: $Tau^2 = 44.55$; $Chi^2 = 7.09$, df = 2 (P = 0.03); $I^2 = 72\%$

Test for overall effect: Z = 0.85 (P = 0.39)

Test for subgroup differences: Not applicable

Analysis 4.12. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 12 Preterm birth (< 36 or < 37 weeks).

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 12 Preterm birth (< 36 or < 37 weeks)

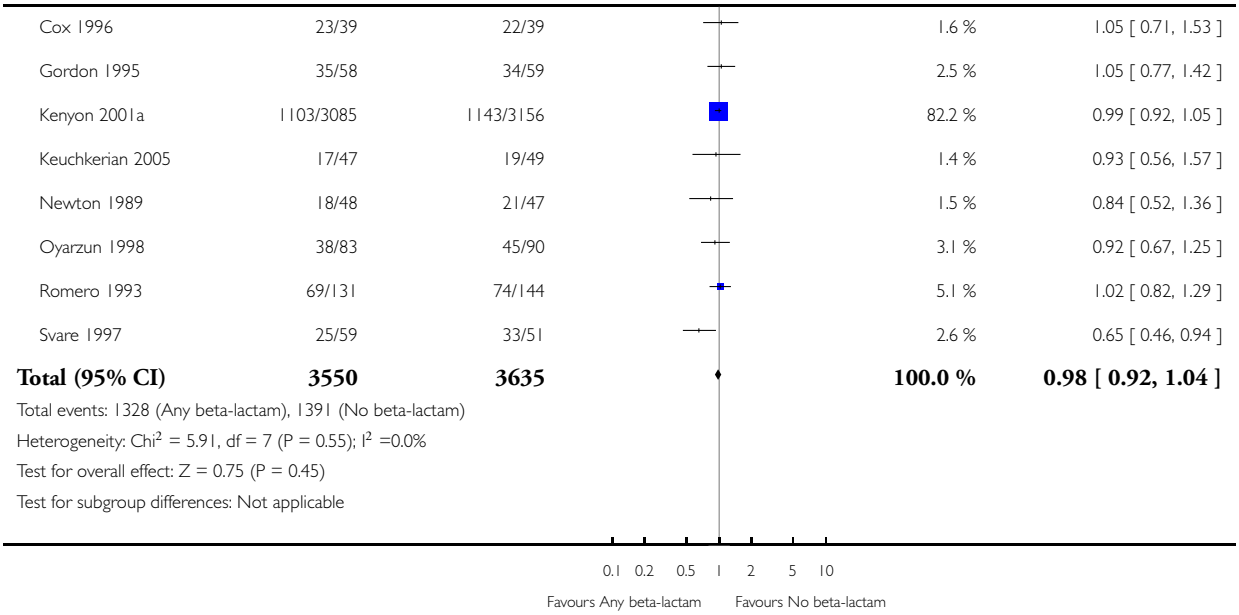
Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	23/39	22/39		1.6 %	1.05 [0.71, 1.53]
Gordon 1995	35/58	34/59		2.5 %	1.05 [0.77, 1.42]
Kenyon 2001a	1103/3085	1143/3156		82.2 %	0.99 [0.92, 1.05]
Keuchkerian 2005	17/47	19/49		1.4 %	0.93 [0.56, 1.57]
Newton 1989	18/48	21/47		1.5 %	0.84 [0.52, 1.36]
Oyarzun 1998	38/83	45/90		3.1 %	0.92 [0.67, 1.25]
Romero 1993	69/131	74/144		5.1 %	1.02 [0.82, 1.29]
Svare 1997	25/59	33/51		2.6 %	0.65 [0.46, 0.94]
Total (95% CI)	**3550**	**3635**		**100.0 %**	**0.98 [0.92, 1.04]**

Total events: 1328 (Any beta-lactam), 1391 (No beta-lactam)

Heterogeneity: Chi^2 = 5.91, df = 7 (P = 0.55); I^2 =0.0%

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable



Analysis 4.13. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 13 Respiratory distress syndrome.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 13 Respiratory distress syndrome

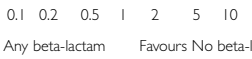
Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cox 1996	8/40	8/42		2.5 %	1.05 [0.44, 2.53]
Kenyon 2001a	266/3085	271/3156		85.4 %	1.00 [0.85, 1.18]
Keuchkerian 2005	3/47	3/49		0.9 %	1.04 [0.22, 4.91]
Norman 1994	3/43	6/38		2.0 %	0.44 [0.12, 1.65]
Oyarzun 1998	9/78	7/90		2.1 %	1.48 [0.58, 3.80]
Romero 1993	14/131	11/144		3.3 %	1.40 [0.66, 2.97]
Svare 1997	2/58	3/51		1.0 %	0.59 [0.10, 3.37]
Watts 1994	13/30	8/26		2.7 %	1.41 [0.69, 2.86]
Total (95% CI)	**3512**	**3596**		**100.0 %**	**1.02 [0.88, 1.19]**

Total events: 318 (Any beta-lactam), 317 (No beta-lactam)

Heterogeneity: Chi^2 = 4.06, df = 7 (P = 0.77); I^2 =0.0%

Test for overall effect: Z = 0.32 (P = 0.75)

Test for subgroup differences: Not applicable



Analysis 4.14. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 14 Intraventricular haemorrhage.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 14 Intraventricular haemorrhage

Study or subgroup	Any beta-lactam n/N	No beta-lactam n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kenyon 2001a	37/3085	40/3156		86.3 %	0.95 [0.61, 1.48]
Keuchkerian 2005	0/47	0/49			Not estimable
Romero 1993	1/131	1/144		2.1 %	1.10 [0.07, 17.40]
Svare 1997	1/58	5/51		11.6 %	0.18 [0.02, 1.46]
Total (95% CI)	**3321**	**3400**		**100.0 %**	**0.86 [0.56, 1.31]**

Total events: 39 (Any beta-lactam), 46 (No beta-lactam)

Heterogeneity: $Chi^2 = 2.37$, $df = 2$ ($P = 0.31$); $I^2 = 16\%$

Test for overall effect: $Z = 0.70$ ($P = 0.48$)

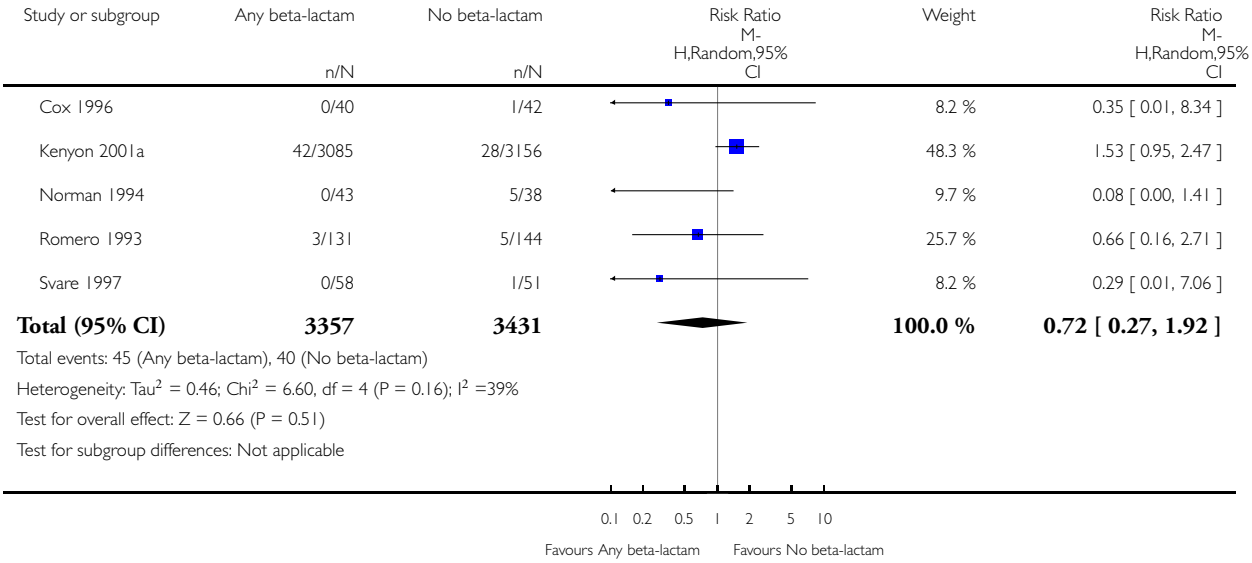
Test for subgroup differences: Not applicable

Analysis 4.15. Comparison 4 Any beta-lactam versus no beta-lactam, Outcome 15 Necrotising enterocolitis.

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 4 Any beta-lactam versus no beta-lactam

Outcome: 15 Necrotising enterocolitis



APPENDICES

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

The standard methods of The Cochrane Collaboration were used as described in the Cochrane Reviewers' Handbook (Clarke 2001). Trials under consideration were evaluated for appropriateness for inclusion and methodological quality without consideration of their results. The review authors independently applied the inclusion criteria to all potentially eligible trials and, for all included trials, independently evaluated methodological quality and extracted data. Differences in interpretation were resolved by discussion.

Methods used for assessing trial quality:

Six major sources of potential bias and methods of avoidance of these biases were considered when assessing trial quality as follows.

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding (performance bias and detection bias)
4. Incomplete outcome data (attrition bias)
5. Selective reporting (reporting bias)
6. Other bias

The quality assessment rating for bias was:

1. low risk
2. unclear risk
3. high risk

Data collection and analysis:

Trial data were extracted by the two review authors independently. Missing or incomplete data were sought in all cases from the trial authors and included in the results where possible. Additional information was sought from investigators of the included study (Reimer 1999) and additional information from 2 trials (Kenyon 2008a; Gurbuz 2004). For further details, see table of 'Characteristics of included studies' and 'Characteristics of excluded studies'.

Analyses were conducted using a fixed-effect model. However, in the overall analysis two outcomes were noted to have statistically significant heterogeneity: 'Admission to neonatal intensive care' and, 'Interval from randomisation to delivery (days)'. On visual inspection of the graph and subsequent sensitivity analyses, it appeared that the source of heterogeneity was the trials which used antibiotics active against anaerobic organisms. Based on the results of sensitivity analyses by type of antibiotic (excluding trial using antibiotics active against anaerobic antibiotics and also by random-effects versus fixed-effect models), it was decided the outcome of 'Interval from randomisation to delivery (days)' would not be combined in an overall analysis as this summary statistic would be potentially misleading. However, the outcome of 'Admission to neonatal intensive care' was included using a random-effects model as the results for this outcome were similar to that of the sensitivity analysis by type of antibiotic used.

Subgroup analyses were performed by type of antibiotic used as follows:

- treatment with macrolide antibiotics alone;
- treatment with beta-lactam antibiotics alone;
- treatment with macrolide and beta-lactam antibiotics;
- treatment with antibiotics active against anaerobic bacteria.

To avoid unit of analysis problems, data from the Kenyon 2001a (which employed a factorial design - three antibiotic arms and one placebo) were included in these subgroup analyses following an adjustment to the placebo group. In these subgroup analyses, each of the antibiotic arms from this trial were compared to the same placebo group (three comparisons). Therefore, the numerator and denominator for all reported outcomes in the placebo arm were divided by three for categorical data and for outcomes reported on a continuous scale dividing the denominators only by three. A sensitivity analysis comparing the results of the unadjusted with the adjusted analyses demonstrated only minimal differences for all reported outcomes.

Results are presented using relative risk (RR) for categorical data and weighted mean difference (WMD) for variables measured on a continuous scale and include 95 per cent confidence intervals (CI). Results are also expressed using number needed to treat (NNT) where appropriate.

Appendix 2. Electronic Search Methods

The Cochrane Pregnancy and Childbirth Group will conduct a further search on submission of the update. The Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

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

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

In addition, a search including the electronic databases: MEDLINE (1965 to Mar 2012), using text terms: antibiotic*, preterm, prematur*, labour, labor, infection, amnionitis, chorioamnionitis. A manual search of the references of all retrieved articles will be performed.

No language restrictions will be applied.

WHAT'S NEW

Last assessed as up-to-date: 3 October 2013.

Date	Event	Description
3 October 2013	New citation required and conclusions have changed	Conclusions changed, as described.
3 October 2013	New search has been performed	This update includes an additional three studies (Keuchkerian 2005; Rajaei 2006; Reimer 1999) including 305 women giving a total of 14 studies and 7837 women now included in this review In this update, an increase in neonatal deaths was shown for infants of women allocated to receive any prophylactic antibiotics. Follow-up data at seven years of age from the UK children whose mothers joined ORACLE II trial (Kenyon 2001a) showed the prescription of a macrolide antibiotic (erythromycin) was associated with an increase in functional impairment. The risk of cerebral palsy was also increased with the use of antibiotics An increase in maternal adverse drug reaction was shown in women receiving any macrolide (erythromycin alone or in combination with beta-lactams) antibiotics The conclusions of the review are changed. This evidence supports not giving antibiotics to women in preterm labour with intact membranes in the absence of signs of infection

HISTORY

Protocol first published: Issue 2, 1997

Review first published: Issue 1, 1998

Date	Event	Description
30 April 2010	Amended	Search updated. Twelve reports added to Studies awaiting classification
21 August 2008	Amended	Converted to new review format.
20 August 2002	New search has been performed	New search conducted.
20 August 2002	New citation required and conclusions have changed	This review updates the King 2002. In this update, the title has been changed to 'Prophylactic antibiotics for inhibiting preterm labour with intact mem-

(*Continued*)

		branes' to clarify the focus of the review. Also in this update, changes have been made to the descriptions of some outcomes measures and subgroup analyses as follows: Several additional important neonatal outcomes have been included. Subgroup analyses by type of antibiotics have been modified to enhance clinical relevance as follows: 1. 'Single antibiotic therapy versus no antibiotics' - description changed to 'Macrolide antibiotics versus no antibiotics'. 2. 'Combination antibiotics therapy versus no antibiotics' - description changed to 'Macrolide and beta-lactam antibiotics versus no antibiotics'. These changes are indicated by * in the review. This update includes the addition of data from the Kenyon 2001a trial. The earlier version of this review contained data for the outcomes of 1187 women. With the inclusion of the Kenyon 2001a trial, this review now contains outcomes for 7428 women. The earlier version indicated some maternal and neonatal benefits (less maternal and neonatal infection, some prolongation of pregnancy) and a concern about increased perinatal mortality. With the inclusion of data from Kenyon 2001a in this update, these 'benefits' (with the exception of reduced maternal infection) are no longer apparent, but there is a concern about a trend towards increased neonatal mortality

CONTRIBUTIONS OF AUTHORS

Vicki Flenady compiled the review in consultation with co-authors. Glenda Halwey worked with Vicki Flenady to assess studies for inclusion and extract data. Owen Stock extracted information on the new studies for this update, assisted in interpretation of the results and editing the review. Nadia Badawi assisted with interpretation of the results. Sara Kenyon provided information on study characteristics of the ORACLE trial and follow-up study, assisted in interpretation of the findings and editing the review. All authors commented on drafts of the review and approved the final version before submission.

DECLARATIONS OF INTEREST

Sara Kenyon led the ORACLE trial and was the CI for the ORACLE Children's Study.

SOURCES OF SUPPORT

Internal sources

- Department of Perinatal Medicine, Royal Women's Hospital, Melbourne, Victoria, Australia.
- Mater Medical Research Institute, Sth Brisbane, Queensland, Australia.

External sources

- Commonwealth Department of Health and Ageing, Canberra, Australian Capital Territory, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update October 2013, primary and secondary outcomes have been defined. Additional outcomes measures are included as primary outcomes. These are: serious maternal adverse outcome related to antibiotic treatment (respiratory arrest, cardiac arrest, death) and a composite measure of death (fetal, neonatal, or later death up to the time of follow-up) or major long-term infant neurosensory impairment. Further, the list of outcomes measures included in subgroup analyses are now restricted to those which are considered to be most clinically important. Two additional comparisons were included: Any macrolide antibiotics versus No macrolide antibiotics; and Any beta-lactam antibiotics versus No beta-lactam antibiotics. We also removed the exclusion criterion according to attrition rates.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [adverse effects; therapeutic use]; Antibiotic Prophylaxis [adverse effects; *methods]; Macrolides [adverse effects; therapeutic use]; Obstetric Labor, Premature [*prevention & control]; Perinatal Mortality; Pregnancy Complications, Infectious [drug therapy]; Randomized Controlled Trials as Topic; beta-Lactams [adverse effects; therapeutic use]

MeSH check words

Female; Humans; Pregnancy