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

King J, Flenady V

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

http://www.thecochranelibrary.com

TABLE OF CONTENTS

ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 2
OBJECTIVES . . . 2
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW . . . 2
SEARCH METHODS FOR IDENTIFICATION OF STUDIES . . . 3
METHODS OF THE REVIEW . . . 3
DESCRIPTION OF STUDIES . . . 4
METHODOLOGICAL QUALITY . . . 4
RESULTS . . . 5
DISCUSSION . . . 5
AUTHORS' CONCLUSIONS . . . 6
POTENTIAL CONFLICT OF INTEREST . . . 6
ACKNOWLEDGEMENTS . . . 6
SOURCES OF SUPPORT . . . 6
REFERENCES . . . 6
TABLES . . . 8
Characteristics of included studies . . . 8
Characteristics of excluded studies . . . 13
ANALYSES . . . 13
Comparison 01. Any antibiotics versus no antibiotics . . . 13
Comparison 02. Antibiotic therapy (subgrouped by type of antibiotic) . . . 14
INDEX TERMS . . . 14
COVER SHEET . . . 15
GRAPHS AND OTHER TABLES . . . 16
Analysis 01.01. Comparison 01 Any antibiotics versus no antibiotics, Outcome 01 Preterm birth (<36 or <37 weeks) 16
Analysis 01.02. Comparison 01 Any antibiotics versus no antibiotics, Outcome 02 Delay in delivery (subgrouped by interval) . . . 17
Analysis 01.03. Comparison 01 Any antibiotics versus no antibiotics, Outcome 03 No antenatal corticosteroids . . . 18
Analysis 01.04. Comparison 01 Any antibiotics versus no antibiotics, Outcome 04 Maternal adverse drug reaction . . . 18
Analysis 01.05. Comparison 01 Any antibiotics versus no antibiotics, Outcome 05 Maternal infection . . . 19
Analysis 01.06. Comparison 01 Any antibiotics versus no antibiotics, Outcome 06 Perinatal mortality . . . 20
Analysis 01.07. Comparison 01 Any antibiotics versus no antibiotics, Outcome 07 Fetal death . . . 21
Analysis 01.08. Comparison 01 Any antibiotics versus no antibiotics, Outcome 08 Neonatal death . . . 21
Analysis 01.09. Comparison 01 Any antibiotics versus no antibiotics, Outcome 09 Birthweight <2500g . . . 22
Analysis 01.10. Comparison 01 Any antibiotics versus no antibiotics, Outcome 10 Birthweight . . . 22
Analysis 01.11. Comparison 01 Any antibiotics versus no antibiotics, Outcome 11 Gestational age at birth . . . 23
Analysis 01.12. Comparison 01 Any antibiotics versus no antibiotics, Outcome 12 Admission to neonatal intensive or special care nursery . . . 23
Analysis 01.13. Comparison 01 Any antibiotics versus no antibiotics, Outcome 13 Respiratory distress syndrome . . . 24
Analysis 01.14. Comparison 01 Any antibiotics versus no antibiotics, Outcome 14 Neonatal mechanical ventilation . . . 24
Analysis 01.15. Comparison 01 Any antibiotics versus no antibiotics, Outcome 15 Chronic neonatal lung disease . . . 25
Analysis 01.16. Comparison 01 Any antibiotics versus no antibiotics, Outcome 16 Neonatal sepsis . . . 25
Analysis 01.17. Comparison 01 Any antibiotics versus no antibiotics, Outcome 17 Neonatal positive blood culture . . . 26
Analysis 01.18. Comparison 01 Any antibiotics versus no antibiotics, Outcome 18 Necrotising enterocolitis . . . 26
Analysis 01.19. Comparison 01 Any antibiotics versus no antibiotics, Outcome 19 Intraventricular haemorrhage . . . 27
Analysis 01.20. Comparison 01 Any antibiotics versus no antibiotics, Outcome 20 Major cerebral abnormality . . . 27
Analysis 02.01. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 01 Preterm birth (<36 or <37 weeks' gestation) . . . 28
Analysis 02.02. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 02 Interval between randomisation and delivery (days) . . . 29

Analysis 02.03. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 03 Delivery within 48 hours 30
Analysis 02.04. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 04 Delivery within 7 days 31
Analysis 02.05. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 05 No antenatal corticosteroids 32
Analysis 02.06. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 06 Maternal adverse drug reaction 33
Analysis 02.07. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 07 Maternal infection 34
Analysis 02.08. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 08 Perinatal mortality 35
Analysis 02.09. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 09 Fetal death . . 36
Analysis 02.10. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 10 Neonatal death . 37
Analysis 02.11. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 11 Birthweight <2500g 38
Analysis 02.12. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 12 Birthweight . . 39
Analysis 02.13. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 13 Gestational age at birth 40
Analysis 02.14. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 14 Admission to neonatal intensive or special care nursery 41
Analysis 02.15. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 15 Respiratory distress syndrome 42
Analysis 02.16. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 16 Neonatal mechanical ventilation 43
Analysis 02.17. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 17 Chronic neonatal lung disease 44
Analysis 02.18. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 18 Neonatal sepsis . 45
Analysis 02.19. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 19 Neonatal positive blood culture 46
Analysis 02.20. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 20 Necrotising enterocolitis 47
Analysis 02.21. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 21 Intraventricular haemorrhage 48
Analysis 02.22. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 22 Major cerebral abnormality 49

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

King J, Flenady V

This record should be cited as:
King J, Flenady V. Prophylactic antibiotics for inhibiting preterm labour with intact membranes. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD000246. DOI: 10.1002/14651858.CD000246.

This version first published online: 21 October 2002 in Issue 4, 2002.
Date of most recent substantive amendment: 21 August 2002

ABSTRACT

Background
The contribution of subclinical genital tract infection to the aetiology of preterm birth is gaining increasing recognition, but the role of prophylactic antibiotic treatment in the management of preterm labour is uncertain. 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, 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 strategy
We searched the Cochrane Pregnancy and Childbirth Group's specialised register of controlled trials (May 2002), the Cochrane Controlled Trials Register (The Cochrane Library, Issue 1, 2002), MEDLINE (1965 to May 2002). Other sources included contacting recognised experts and cross referencing relevant material.

Selection criteria
Randomised trials which 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
Standard methods of the Cochrane Collaboration and the Cochrane Pregnancy and Childbirth Group were used. Evaluation of methodological quality and trial data extraction were undertaken independently by the authors. Results are presented using relative risk for categorical data and weighted mean difference for continuous data.

Main results
This review has been updated (2002) to include data from the 'ORACLE II 2001' trial (six times larger than the previous 10 trials combined), which now dominates the results of this review. Meta-analysis of the 11 included trials (7428 women enrolled) shows a reduction in maternal infection with the use of prophylactic antibiotics (relative risk 0.74, 95% confidence interval 0.64 to 0.87) but fails to demonstrate a benefit or harm for any of the prespecified neonatal outcomes.

Authors' conclusions
This review fails to demonstrate a clear overall benefit from prophylactic antibiotic treatment for preterm labour with intact membranes on neonatal outcomes and raises concerns about increased neonatal mortality for those who received antibiotics. This treatment cannot therefore be currently recommended for routine practice. Further research may be justified (when sensitive markers for subclinical infection become available) in order to determine if there is a subgroup of women who could experience benefit from antibiotic treatment for preterm labour prior to membrane rupture, and to identify which antibiotic or combination of antibiotics is most effective.

PLAIN LANGUAGE SUMMARY

No clear benefit for the use of antibiotics for women going into labour too early with the membranes still intact

Premature babies can have a range of complications which often require admission to a neonatal intensive care unit. Some of these complications are so severe that they result in disability or death in the early weeks, and sometimes disability later on in life. Infection without any symptoms (low grade infection) in the cervix and uterus may trigger labour contractions resulting in labour starting too soon and the birth of a premature baby. In theory, antibiotics could stop this infection and prevent the baby being born too early. The review of trials found no overall benefit for antibiotics given to the mother in this situation.

BACKGROUND

Preterm birth is a major contributor to the burden of perinatal mortality and morbidity. Little progress has been made over the last two decades in reducing the incidence of preterm birth despite a wide range of therapeutic interventions (Moutquin 1996). The contribution of subclinical genital tract infection to the aetiology of preterm birth is gaining increasing recognition but the role of antibiotic treatment in the management of preterm labour is uncertain. As rupture of the membranes has a major impact on the progression of preterm labour, it is considered important to assess the potential benefit of commencing prophylactic antibiotic therapy (usually given as an adjunct to tocolysis) prior to membrane rupture.

It has also been hypothesised that the type of antibiotic may be important. Those 'macrolide' antibiotics (such as clindamycin and erythromycin) which shut down bacterial virulence have theoretical advantages over the beta-lactam antibiotics (penicillins, cephalosporins), which by destroying bacteria release endotoxins which may worsen the outcomes for infants born preterm (McGregor 1997). Furthermore, the anaerobic organisms responsible for bacterial vaginosis (especially Bacteroides) have been implicated in the aetiology of preterm labour, and those antibiotics active against anaerobic organisms (clindamycin, metronidazole) may be more effective as an adjunct to tocolysis, if such organisms are present (Hauth 1995).

OBJECTIVES

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

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All published and unpublished randomised trials which 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).

Types of participants

Women thought to be in preterm labour with intact membranes between 20 and 36 completed weeks of gestation.

Types of intervention

Any antibiotics, administered intravenously or orally in the management of preterm labour with intact membranes.

Types of outcome measures

Maternal outcomes:
interval between randomisation and delivery;
delivery prior to 37 completed weeks;
delivery prior to 34 completed weeks;
delivery prior to 28 completed weeks;
chorioamnionitis/amnionitis;
postpartum pyrexia;
adverse drug reaction;
length of hospital stay.

Baby outcomes:
fetal death;
neonatal death;
perinatal mortality;
Apgar score of less than seven at five minutes;
neonatal sepsis;
admission to neonatal intensive care*;
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;

length of hospital stay.

A priori sub-group analyses:

treatment commenced prior to 24 completed weeks;
treatment commenced between 25 and 33 completed weeks;
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.

*Outcomes and subgroup analyses modified or added in this update.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

This review has drawn on the search strategy developed for the Pregnancy and Childbirth Group as a whole. The full list of journals and conference proceedings as well as the search strategies for the electronic databases, which are searched by the Group on behalf of its reviewers, are described in detail in the 'Search strategies for the identification of studies section' within the editorial information about the Cochrane Pregnancy and Childbirth Group. Briefly, the Group searches on a regular basis MEDLINE, the Cochrane Controlled Trials Register and reviews the Contents tables of a further 38 relevant journals received via ZETOC, an electronic current awareness service.

Relevant trials, which are identified through the Group's search strategy, are entered into the Group's Specialised Register of Controlled Trials. Please see Review Group's details for more detailed information. Date of last search: May 2002

In addition, the reviewers conducted a systematic literature search which included electronic databases: the Cochrane Controlled Trials Register (The Cochrane Library, Issue 1, 2002), MEDLINE (1965 to May 2002), using text terms: antibiotic*, preterm, prematur*, labour, labor, infection, amnionitis, chorioamnionitis. A manual search of the references of all retrieved articles was also performed. Other sources included contacting recognised experts and cross referencing relevant material.

METHODS OF THE 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 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:
Four major sources of potential bias and methods of avoidance of these biases were considered when assessing trial quality as follows:
(1) Selection bias - blinding of randomisation.
(2) Performance bias - blinding of intervention.
(3) Attrition bias - complete follow up.
(4) Detection bias - blinding of outcome assessment.
The quality assessment rating for the blinding of randomisation was given a rating of:
A - adequate;
B - unclear;
C - inadequate; or
D - not used.
Other aspects of trial quality (blinding of intervention, completeness of follow up, blinding of outcome assessment) were given a rating of : yes, cannot tell, no.

Data collection and analysis:
Trial data were extracted by the two reviewers independently. Missing or incomplete data were sought in all cases from the authors and included in the results where possible. Additional information was sought from investigators of all included studies and additional information was provided for seven trials (McGregor 1991; Romero 1993; Watts 1994; Norman 1994; Cox 1996; Svare 1997; ORACLE II 2001). For further details, see table of 'Characteristics of included studies'.

Analyses were conducted using a fixed effects 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 versus fixed effects 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 ORACLE II 2001(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.

DESCRIPTION OF STUDIES

This review includes the following eleven trials: Newton 1989; Newton 1991; McGregor 1991; Romero 1993; Norman 1994; Watts 1994; Gordon 1995; Cox 1996; Svare 1997; Oyarzun 1998, ORACLE II 2001. 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; Winkler 1988; Saez-Llorens 1995). A further four trials are awaiting assessment pending information on methods and outcomes from the authors (Hensen 1987; Naef 1994; Ogasawara 1999; Oszukowski 2000).

All included studies used similar definitions of preterm labour which included the presence of uterine contractions and cervical dilatation. All studies excluded women with symptoms or signs suggestive of clinical infection. Gestational ages were similar in all trials with a mean gestational age at entry of 30 to 32 weeks. Two trials Oyarzun 1998 and ORACLE II 2001 recruited participants between 34 and 36 weeks' gestation. Multiple pregnancies were included in four of the eleven trials (Newton 1991; Gordon 1995; Cox 1996; ORACLE II 2001).

In nine studies, the antibiotics were used as an adjunct to tocolysis. Cox 1996 did not use tocolysis. In ORACLE II 2001, 56.4 per cent of participants received tocolysis. A variety of tocolytic agents were used in the trials including betamimetics, indomethacin, magnesium sulphate and nifedipine. Steroid administration to stimulate fetal maturation was reported as part of the clinical protocol in 10 of the included studies. The frequency of steroid usage varied between trials from approximately 30 per cent (Newton 1991; Gordon 1995) to greater than 90 per cent (Romero 1993; Norman 1994; Svare 1997; Oyarzun 1998). Cox 1996 did not use corticosteroids. In ORACLE II 2001, over 80 per cent of participants received corticosteroids.

Seven studies included vaginal cultures for Group B Strep (GBS) as part of the study protocol. Four of these trials (Newton 1991; McGregor 1991; Romero 1993; Oyarzun 1998) reported intrapartum antibiotic administration to GBS culture positive women in addition to the study medication. Gordon 1995 withdrew GBS culture positive women from the study and administered intrapartum antibiotics. The ORACLE II 2001 report did not describe the protocol for women with positive GBS cultures, nor did the report include any separate data for this group (however, 11.8 per cent of women in the placebo group received antibiotics outside of the study protocol).

The studies included a variety of antibiotics and a range of dosing schedules. Antibiotics were administered intravenously in nine of the trials. In two trials, they were administered orally (Oyarzun 1998; ORACLE II 2001). ORACLE II 2001 used a 2 x 2 factorial design to compare the effects of ampicillin/clavulonate and/or erythromycin with placebo. A further nine trials used a combination of antibiotics: Newton 1989 (ampicillin and erythromycin), Newton 1991 (ampicillin and sulbactam), Romero 1993, Oyarzun 1998 (ampicillin/amoxycillin and erythromycin), Norman 1994 and Svare 1997 (ampicillin and metronidazole), Cox 1996 (ampicillin and sulbactam or clavulonic acid), Watts 1994 (mezlocillin and erythromycin). A further two trials used single agent therapy: McGregor 1991(clindamycin), Gordon 1995 (ceftizoxime).

Outcome variables were not always clearly or consistently defined or reported across the trials. The definition of neonatal sepsis was not consistent across the trials and there were large differences in the rates of neonatal infection between the trials. Svare 1997 reported a rate of neonatal sepsis of 22 per cent in controls whereas the overall rate for controls in all trials was 8.5 per cent. ORACLE II 2001 reported on proven sepsis only (blood culture positive), with a rate in the placebo arm of two per cent. ORACLE II 2001 employed precise definitions of all outcome variables. ORACLE II 2001 reported the outcome of major cerebral abnormality defined as either haemorrhage or hydrocephalus or cysts (personal communication) on ultrasound prior to hospital discharge. This outcome has been included in the review. ORACLE II 2001 reported only one neonatal outcome in a multiple pregnancy (the worst outcome) where more than one outcome was found. The other three trials which enrolled women with a multiple pregnancy reported outcomes for each infant and were incorporated as such into the meta-analysis. For further details see table of 'Characteristics of included studies'.

METHODOLOGICAL QUALITY

The overall quality of the included studies was good. All of the trials used formal randomisation procedures (confirmation from authors was obtained when necessary). Allocation concealment was adequate in all of the included trials. Ten of the 11 included trials used a double blind placebo control methodology, the exception

being Norman 1994. All trials except Norman 1994 confirmed blinded assessment of outcomes.

Nine trials reported post randomisation exclusions, however, the rates of exclusion of women after randomisation were reasonably low (range one per cent to 12 per cent). Information on post randomisation exclusions was sought in all cases; however, no additional data for these exclusions could be included in the analysis. Pre-trial power calculations were documented in 10 of the 11 included studies, with the exception of Watts 1994. Five of the 10 trials which reported pre-trial sample size estimations were halted prematurely because of low recruitment rates or lower baseline outcome rates than had been predicted.

RESULTS

The meta-analysis includes outcomes for 11 included trials (7428 women enrolled).

Overall analysis:
Maternal infection (chorioamnionitis/endometritis) was significantly reduced in the group who received antibiotics (nine studies, 7242 participants; (relative risk (RR) 0.74; 95% confidence interval (CI) 0.64 to 0.87). The number need to treat is 33 (95% CI 20,100).

No statistically significant differences were demonstrated in any of the other maternal outcomes including mean gestational age at delivery and frequency of preterm birth. No statistically significant benefit from antibiotic administration was demonstrated in any of the prespecified neonatal outcomes including perinatal mortality (RR 1.22, 95% CI 0.88 to 1.70) where a trend towards a reduction in fetal deaths (RR 0.72, 95% CI 0.42 to 1.25) was outweighed by a stronger trend towards an increase in neonatal deaths in the antibiotic group (RR 1.52, 95% CI 0.99 to 2.34). None of the trials reported on the prespecified outcomes of birth prior to 28 or prior to 34 weeks' gestation, and data on these outcomes were not able to be obtained from the authors.

Subgroup analyses by type of antibiotics:
Four subgroup analyses were performed, in order to explore possible differences in the effects of single and combination antibiotic therapy of three categories of antibiotics (macrolide antibiotics, beta-lactam antibiotics, a combination of beta-lactam and macrolide antibiotics and antibiotics active against anaerobes). In these subgroup analyses, no clear differential effects could be detected on any of the outcomes reported. However, the subgroup analysis of antibiotics active against anaerobes which included three trials (McGregor 1991; Norman 1994; Svare 1997) and a total of 294 women, showed a statistically significant increase in the interval from randomisation to delivery (two trials) (WMD 10.5 days, 95% CI 4.95 to 16.06), a reduction in the number of women giving birth within seven days of enrolment (two trials) (RR 0.62, 95% CI 0.42 to 0.90), and fewer admissions to neonatal intensive care unit (one trial) (RR 0.63, 95% CI 0.43 to 0.93).

DISCUSSION

The trials overall were of sound methodology, the populations studied were reasonably homogeneous, and the results were generally consistent across the trials. The pooled analyses of the eleven trials included in this review were dominated by the results of ORACLE II 2001 which was six times larger than the previous ten trials combined. This trial differed from the majority of the trials in that (i) it was one of only two 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 ORACLE II 2001 participants may have been less likely to demonstrate a beneficial effect from antibiotics (such as meaningful prolongation of pregnancy), but for almost all outcomes, the results of ORACLE II 2001 are consistent with those of the other trials combined.

The absence of a beneficial impact on any of the prespecified neonatal outcomes should enable clinicians to confidently withhold the routine prescribing of antibiotics to women in preterm labour with intact membranes, as an adjunct to tocolysis.

Although there is increasing awareness that subclinical infection plays a role in the aetiology of preterm labour, it is certainly not the only pathway leading to preterm labour. For this reason it is not possible that all women (and/or their babies) in preterm labour with intact membranes could benefit from antibiotic treatment. Clearly only those women in preterm labour who have subclinical intrauterine infection as the cause of their contractions could experience benefit from treatment with antibiotics, but there are no means of identifying this subgroup within the trials in this review. There may have been some participants within these trials who experienced benefit and others who experienced either no benefit or actual harm. This may explain the overall lack of benefit demonstrated in this review. A further explanation for these findings could be that by the time preterm labour has become established as a result of intrauterine infection, even though the membranes are still intact, the process has advanced too far for the treatment to be effective in terms of reduction of perinatal morbidity and mortality. In these circumstances, where intrauterine infection is the triggering stimulus for preterm labour it is highly likely that the mother will experience benefit from antibiotic treatment, although less benefit (or even harm) might accrue for the fetus/neonate. The findings in this review, of a (non statistically significant) trend towards a reduction in fetal deaths, in the antibiotic group, outweighed by a stronger trend towards an increase in neonatal deaths, might also be biologically plausible and deserve further consideration. The finding of a reduction in maternal infection in women receiving prophylactic antibiotics, needs to be seen in the light of an incidence in the control group of 11.2%.

Given that maternal infection is clinically relatively easy to diagnose and treat, this would argue against prophylactic antibiotics to prevent it, as 88.9% of women would be receiving antibiotics unnecessarily.

The trials of McGregor 1991 (using clindamycin), Norman 1994 and Svare 1997 (both using a combination of ampicillin and metronidazole) were the only trials which showed a statistically significant increase in the number of days from enrolment into the trial to delivery and the numbers of women giving birth less than seven days from enrolment. Both clindamycin and metronidazole have activity against 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 delivery. It should be noted, however, that this delay has not yet been shown in these trials to confer a significant reduction in neonatal sepsis or overall morbidity indices. No differences in outcomes associated with the use of bacteriostatic as compared with bactericidal antibiotics or single therapy compared to combination therapy were revealed by the sub-group analyses. This is consistent with the overall findings of the review which failed to demonstrate any clear benefit.

AUTHORS' CONCLUSIONS

Implications for practice

Prophylactic antibiotics cannot be recommended in the routine management of women in preterm labour with intact membranes.

Implications for research

Further research is required to develop sensitive serological and/or bacteriological or markers of subclinical infection for women in preterm labour with intact membranes, as this is a group which might benefit from early antibiotic treatment, which will need to be addressed by clinical trials. Other research agenda should include the type of antibiotic/s, especially addressing the trend identified in this review of improved outcomes with antibiotics active against anaerobes. Any further clinical trials addressing problems surrounding preterm birth should incorporate explicit a priori definitions of relevant unequivocal clinical endpoints to enable clear interpretation and to facilitate pooling of results.

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

We would like to thank Staffan Bergstrom, Susan Cox, Janice French, Sara Kenyon, John Morrison, Karin Norman, Roberto Romero, Jens Svare and Elizabeth Thom and Heather Watts for assistance in providing unpublished data from their clinical trials and for clarifications of other queries.

SOURCES OF SUPPORT

External sources of support

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

Internal sources of support

- Department of Perinatal Medicine, Royal Women's Hospital, Melbourne, Victoria AUSTRALIA
- Centre for Clinical Studies-Women's and Children's Health, Mater Hospital, Sth Brisbane, Queensland AUSTRALIA

REFERENCES

References to studies included in this review

Cox 1996 *{published data only}*

Cox SM, Boham V, Sherman ML, Leveno KJ. Single-center randomized placebo controlled trial of antimicrobials for prevention of preterm birth [abstract]. *American Journal of Obstetrics and Gynecology* 1994;**170**:388.

Cox SM, Bohman VR, Sherman L, Leveno KJ. Randomized investigation of antimicrobials for the prevention of preterm birth. *American Journal of Obstetrics and Gynecology* 1996;**174**(1):206–10.

Gordon 1995 *{published data only}*

Gordon M, Samuels P, Shubert P, Johnson F, Gebauer C, Iams J. A randomized, prospective study of adjunctive ceftizoxime in preterm labor. *American Journal of Obstetrics and Gynecology* 1995;**172**(5): 1546–52.

Gordon M, Shubert PJ, Samuels P, Johnson F, Gebauer C, Iams JD. A randomized prospective study of adjunctive ceftizoxime in preterm labor [abstract]. *American Journal of Obstetrics and Gynecology* 1994; **170**:389.

McGregor 1991 *{published data only}*

* McGregor JA, French JI, Seo K. Adjunctive clindamycin therapy for preterm labor: results of a double-blind, placebo-controlled trial. *American Journal of Obstetrics and Gynecology* 1991;**165**(4):867–75.

McGregor JA, French JI, Seo K. Adjunctive clindamycin therapy for preterm labor: results of a double-blinded randomized, placebo-

controlled trial. *American Journal of Obstetrics and Gynecology* 1991; **164**(1 Pt 2):259.

Newton 1989 *{published data only}*
Newton ER, Dinsmoor MJ, Gibbs RS. A randomized, blinded, placebo-controlled trial of antibiotics in idiopathic preterm labor. *Obstetrics and Gynecology* 1989;**74**(4):562–6.

Newton 1991 *{published data only}*
Newton ER, Shields L, Ridgway LE, Berkus MD, Elliott BD. Combination antibiotics and indomethacin in idiopathic preterm labor: a randomized double-blind clinical trial. *American Journal of Obstetrics and Gynecology* 1991;**165**(6):1753–9.

Norman 1994 *{published and unpublished data}*
Norman K, Pattinson R, de Sousa, de Jong P. PRAM: a preterm labour management randomised controlled trial investigating antibiotic intervention on a multicentre basis. Proceedings of 26th British Congress of Obstetrics and Gynaecology; 1992; Manchester, UK, 1992:3.

* Norman K, Pattinson RC, de Souza J, de Jong P, Moller G, Kirsten G. Ampicillin and metronidazole treatment in preterm labour: a multicentre, randomised controlled trial. *British Journal of Obstetrics and Gynaecology* 1994;**101**:404–8.

Norman K, Pattinson RC, Kirsten G, De Sousa J, De Jong P, Moller G. PRAM: a preliminary report. Proceedings of 10th Conference on Priorities in Perinatal Care in South Africa; 1994 Mar 12-15; Eastern Transvaal, South Africa, 1991 33–8.

ORACLE II 2001 *{published and unpublished data}*
Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. *Lancet* 2001;**357**:991–6.

Oyarzun 1998 *{published data only}*
Oyarzun E, Gomez R, Rioseco A, Gonzalez P, Gutierrez P, Donoso E, et al. Antibiotic treatment in preterm labor and intact membranes: a randomized, double-blinded, placebo-controlled trial. *Journal of Maternal Fetal Medicine* 1998;**7**:105–10.

Romero 1993 *{published data only}*
Romero R, Sibai B, Caritis S, Paul R, Depp R, Klebanoff M, et al. Antibiotic treatment of preterm labour with intact membranes: a multicenter, randomized, double blind, placebo-controlled trial. *American Journal of Obstetrics and Gynecology* 1993;**168**(1 Pt 2):288.

* Romero R, Sibai B, Caritis S, Paul R, Depp R, Rosen M, et al. Antibiotic treatment of preterm labor with intact membranes: a multicenter, randomized, double-blinded, placebo-controlled trial. *American Journal of Obstetrics and Gynecology* 1993;**169**(4):764–74.

Svare 1997 *{published and unpublished data}*
Svare J, Langhoff-Roos J, Andersen L, Kryger-Baggesen N, Borch-Christensen H, Heisterberg L, et al. Ampicillin-metronidazole treatment in threatening preterm delivery. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(167):1.

* Svare J, Langhoff -Roos J, Andersen LF, Kryger-Baggesen N, Borch-Christensen H, Heisterberg L, et al. Ampicillin-metronidazole treatment in idiopathic preterm labour: a randomised controlled multicentre trial. *British Journal of Obstetrics and Gynaecology* 1997;**104**: 892–7.

Svare J, Langhoff-Ross J, Anderson LF, Baggesen NK, Borch-Christensen H, Heisterberg L, et al. Antibiotic treatment in preterm labor or preterm premature rupture of the membranes - a randomised controlled double-blind trial [abstract]. *Acta Obstetrica et Gynecologica Scandinavica Supplement* 1996;**75**:36.

Watts 1994 *{published and unpublished data}*
Watts DH, Krohn MA, Hillier SL, Eschenbach DA. Randomized trial of antibiotics in addition to tocolytic therapy to treat preterm labor. *Infectious Diseases in Obstetrics and Gynecology* 1994;**1**:220–7.

References to studies excluded from this review

McCaul 1992
McCaul JF, Perry KG, Martin RW, Morrison C. Treatment of idiopathic preterm rupture of membranes or labor with adjunctive ampicillin. *American Journal of Obstetrics and Gynecology* 1991;**164**:376.

* McCaul JF, Perry KG, Moore JL, Martin RW, Bucovaz ET, Morrison JC. Adjunctive antibiotic treatment of women with preterm rupture of membranes or preterm labor. *International Journal of Gynecology and Obstetrics* 1992;**38**:19–24.

Morrison JC. Antibiotic treatment for patients in preterm labor 20-34 weeks with intact membranes. Personal communication December 14 1993.

McGregor 1986
McGregor JA, French JI, Reller LB, Todd JK, Makowski EL. Adjunctive erythromycin treatment for idiopathic preterm labour: results of a randomized, double-blind, placebo-controlled trial. *American Journal of Obstetrics and Gynecology* 1986;**154**:98–103.

McGregor 1988
McGregor JA, French JI, Richter R, Vuchetich M, Bachus V, Franco-Buff A, et al. Prospective, double-blinded, randomized, controlled trial of short-course erythromycin (E) base in women at high risk of preterm birth. Proceedings of the Society for Gynecologic Investigation, 1988.

Morales 1988
Morales W, Angel JL, O'Brien WF, Knuppel RA, Finazzo M. A randomized study of antibiotic therapy in idiopathic preterm labor. *Obstetrics and Gynecology* 1988;**72**(6):829–33.

Nadisauskiene 1996
Nadisauskiene R, Bergstrom S. Impact of intrapartum intravenous ampicillin on pregnancy outcome in women with preterm labor: a randomised placebo-controlled study. *Gynecologic and Obstetric Investigation* 1996;**41**:85–8.

* Nadisauskiene R, Bergstrom S, Kilda A. Ampicillin in the treatment of preterm labor: a randomised, placebo-controlled study. *Gynecologic and Obstetric Investigation* 1996;**41**:89–92.

Nadisauskiene R, Kilda A. Ampicillin in the treatment of preterm labour. *International Journal of Gynecology and Obstetrics* 1994;**46**: 232.

Nadisauskiene R, Vaitkiene D. The impact of ampicillin in the treatment of preterm labour [abstract]. Proceedings of 14th European Congress of Perinatal Medicine; 1994; Helsinki, Finland, 1994 416.

Saez-Llorens 1995
Saez-Llorens X, Ah-Chu M, Castano E, Cortes L, Torres A, Suarez M, et al. Intrapartum prophylaxis with ceftriaxone decreases rates of

bacterial colonization and early-onset infection in newborns. *Clinical Infectious Diseases* 1995;**21**:876–80.

Winkler 1988

Winkler M, Baumann L, Ruckhaberle K, Schiller E. Erythromicin therapy for subclinical uterine infections in threatened preterm delivery - a preliminary report. *Journal of Perinatal Medicine* 1988;**16: 253**:256.

References to studies awaiting assessment

Hensen 1987

Hensen B. A randomized prospective study of antibiotic therapy for the treatment and prevention of premature labor. Personal communication 1987.

Naef 1994

Naef RW, Magann EF, Allbert JR, Roberts WE, Martin RW, Morrison JC. Prospective comparison of empiric antibiotic therapy in patients with idiopathic preterm labor. *American Journal of Obstetrics and Gynecology* 1994;**170**:376.

Ogasawara 1999

Ogasawara KK, Goodwin TM. Efficacy of azithromycin in reducing lower genital ureaplasma urealyticum colonization in women at risk for preterm delivery. *Journal of Maternal Fetal Medicine* 1999;**8**:12–6.

* Ogasawara KK, Goodwin TM. The efficacy of treating ureaplasma urealyticum in patients with preterm labor or preterm rupture of membranes. *American Journal of Obstetrics and Gynecology* 1996;**174**: 401.

Oszukowski 2000

Oszukowski P, Pieta A, Nowak M. The influence of antibiotics in preterm labor on the inherited infection rate in newborns [abstract]. XVI FIGO World Congress of Obstetrics and Gynecology; 2000 Sept 3-8; Washington DC, USA, 2000, Book 3 70.

Additional references

Clarke 2001

Clarke M, Oxman AD, editors. Cochrane Reviewers' Handbook 4.1.4 [updated October 2001]. In: Review Manager (RevMan) [Computer program]. Version 4.1. Oxford, England: The Cochrane Collaboration, 2001.

Hauth 1995

Hauth JC, Goldenberg RL, Andrews WW, DuBard MB, Copper RL. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *New England Journal of Medicine* 1995;**333**:1732–6.

McGregor 1997

McGregor J, French J. Evidence-based prevention of preterm birth and rupture of membranes: infection and inflammation. *JSOGC* 1997:835–51.

Moutquin 1996

Moutquin J, Valerie M, Oliver I. Preterm Birth Prevention: Effectiveness of Current Strategies. *JSOGC* 1996:571–86.

References to other published versions of this review

Crowley 1995

Crowley P. Antibiotics in preterm labour with intact membranes. [revised 05 May 1994] In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) Pregnancy and Childbirth Module. In: The Cochrane Database of Systematic Reviews [database on disk and CDROM]. The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

King 1998

King J, Flenady V. Antibiotics for preterm labour with intact membranes (Cochrane review). *The Cochrane Library* 1998, Issue 1.

** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Cox 1996
Methods	Blinding of randomisation: Yes - randomly assigned by pharmacist using a computer generated random numbers table and consecutive sealed envelopes. Blinding of intervention: Yes - placebo controlled. Complete follow up: No - 9% post randomisation exclusions. Blinding of outcome measure: Yes.
Participants	86 women 24-34 weeks gestation (mean 30 weeks), in preterm labour (cervical change with contractions). Exclusions: ruptured membranes, fetal or maternal complications necessitating delivery.
Interventions	IV ampicillin 2g with sulbactam 1g every 6 hours x 8 doses, followed by ampicillin - clavulanate 250mg every 8 hours 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.

Characteristics of included studies (*Continued*)

	Neonatal: birthweight, 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 steroids were used. Additional information on trial methods was received from author.
Allocation concealment	A – Adequate

Study	**Gordon 1995**
Methods	Blinding of randomisation: Yes - randomly assigned by pharmacist using computer generated list of random numbers. Stratification for twin pregnancy. Blinding of intervention: Yes - placebo controlled. Complete follow up: Yes. Blinding of outcome measure: Yes.
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 2g every 8 hours 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, adverse drug reaction. Neonatal: sepsis.
Notes	Pre-trial sample size estimation indicated that 64 participants were required in each arm.
Allocation concealment	A – Adequate

Study	**McGregor 1991**
Methods	Blinding of randomisation: Yes - randomly assigned by pharmacist from a computer generated list of random numbers. Blinding of intervention: Yes - placebo controlled. Complete follow up: No - 12% post-randomisation exclusions. Blinding of outcome measure: Yes.
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 900mg every 8 hours x 9 doses or identical placebo. IV therapy was followed by oral clindamycin 300mg every 6 hours x 4 days or identical placebo.
Outcomes	Primary outcome: delivery >36 weeks. Other outcomes - Maternal: mean days of prolongation, infection, prelabour PROM, adverse drug reaction Neonatal: gestational age at delivery, birthweight, 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.
Allocation concealment	A – Adequate

Study	**Newton 1989**
Methods	Blinding of randomisation: Yes - randomly assigned by the pharmacy. Blinding of intervention: Yes - placebo controlled. Complete follow up: No - 8% post randomisation exclusions. Blinding of outcome measure: Yes.
Participants	103 women 24-35 weeks gestation (mean 31 weeks), in preterm labour, receiving tocolysis.

Characteristics of included studies (*Continued*)

	Exclusions: ruptured membranes, multiple gestation, suspected fetal compromise and maternal medical conditions.
Interventions	IV ampicillin 2g every 6 hours x 12 doses, plus oral erythromycin (333mg every 8 hours x 7 days) or identical placebos.
Outcomes	Primary outcome: mean gestational age at delivery, mean birthweight. 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.
Allocation concealment	A – Adequate

Study	**Newton 1991**
Methods	Blinding of randomisation: Yes - randomly assigned by the pharmacist. Blinding of intervention: Yes - placebo controlled. Complete follow up: No - 5% post randomisation exclusions. Blinding of outcome measure: Yes.
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.
Interventions	IV ampicillin 2g/sulbactam 1g every 6 hours x 12 doses plus oral indomethacin (50mg load, then 25mg every 6 hours x 7 doses) or corresponding placebos.
Outcomes	Primary outcomes: mean birthweight and gestational age at delivery. Other outcomes - Maternal: infection, adverse drug reaction. Neonatal: neonatal morbidity and mortality, birthweight <2500g, 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."
Allocation concealment	A – Adequate

Study	**Norman 1994**
Methods	Multicentre trial - 3 centres. Blinding of randomisation: Yes - randomly assigned using opaque sealed envelopes. Blinding of intervention: No. Complete follow up: No - one post randomisation exclusion. Blinding of outcome measure: No.
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 1g every 6 hours x 4 doses followed by oral amoxicillin 500mg every 8 hours x 5 days, plus metronidazole 1gm stat then 400mg orally every 8 hours for 5 days, or corresponding placebos.
Outcomes	Primary outcome: perinatal mortality. Other outcomes: Maternal: puerperal infection, median days of prolongation, adverse drug reaction. Neonatal: mean gestational age at delivery, mean birthweight, neonatal hospital stay, major neonatal morbidity.
Notes	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. 1 post randomisation exclusion. Indomethacin 100mg rectally twice daily for 48 hours with concomitant hexoprenaline. Additional information received on methods and data for outcome of prolongation of pregnancy.
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**ORACLE II 2001**
Methods	Multicentre trial - 161 centres (2 x 2 factorial design). Blinding of randomisation: Yes - pre numbered treatment packs dispensed centrally. Blinding of intervention: Yes - placebo controlled. Complete follow up: No - <1% post randomisation exclusions. Blinding of outcome measure: Yes.
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	Four study groups as follows (all oral administration): 1. 325 mg co-amoxiclav plus 250mg erythromycin; 2. 325 mg co-amoxiclav plus erythromycin placebo; 3. 250mg erythromycin plus co-amoxiclav placebo; 4. co-amoxiclav placebo plus erythromycin placebo. All study medication was given orally every six hours for 10 days or until delivery, whichever occurred earlier.
Outcomes	Primary outcome: Composite neonatal outcome of neonatal death or major adverse outcome - ie chronic lung disease or major cerebral abnormality on ultrasound before hospital discharge. Secondary outcomes: delivery within 48hrs and within 7 days, mode of delivery, number of days in hospital, maternal antibiotic prescription after delivery and before discharge, GA at delivery, BW <2500g or <1500g, admission to NICU or special care baby unit, neonatal mechanical ventilation, RDS, treatment with surfactant, neonatal sepsis, NEC.
Notes	Pre-trial sample size estimation based on primary outcome measure. Additional data received and included on perinatal mortality, cerebral abnormalities, pregnancy prolongation. 40 post randomisation exclusions.
Allocation concealment	A – Adequate

Study	**Oyarzun 1998**
Methods	Blinding of randomisation: Can't tell. Blinding of intervention: Yes - placebo controlled. Complete follow up: No - 12% post randomisation exclusions. Blinding of outcome measure: Yes.
Participants	196 women thought to be in labour between 22 and 36 weeks gestation, singleton pregnancy, with intact membranes, and cervical dilatation <5cm.
Interventions	Oral amoxicillin 250mg every 8h and erythromycin 500 mg orally every 6h 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 postrandomisation exclusions. Study medications supplied by Laboratorio Chile.
Allocation concealment	B – Unclear

Study	**Romero 1993**
Methods	Multicentre trial - 6 centres.

Characteristics of included studies (*Continued*)

	Blinding of randomisation: Yes - randomly assigned at an independent centre using computerised randomisation process with stratification by study centre. Blinding of intervention: Yes placebo controlled. Complete follow up: No - < 1% post randomisation exclusions. Blinding of outcome measure: Yes.
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 1gm every 4 hours concomitant IV erythromycin 250mg every 6 hours both for 48 hours followed by oral amoxicillin 250mgs every 8 hours and erythromycin 333mg every 8 hours for 5 days.
Outcomes	Primary outcomes - Maternal: median days prolongation of pregnancy, frequency of preterm delivery. Neonatal: perinatal mortality and morbidity. Other outcomes - Maternal: adverse drug reaction, infection, Neonatal: birthweight, NICU stay.
Notes	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 postrandomisation exclusions. Additional information on trial methods were received.
Allocation concealment	A – Adequate

Study	**Svare 1997**
Methods	Blinding of randomisation: Yes - Block randomisation by pharmaceutical company supplying the medications, in packages of 10, computer generated numbers. Study medicine delivered in consecutively numbered identical packages. Blinding of intervention: Yes. Placebo controlled. Complete follow up: No - <2 % postrandomisation exclusions. Blinding of outcome measure: Yes.
Participants	112 women thought to be in labour between 26 and 34 weeks, singleton pregnancy, cervical dilatation <4cm. Exclusion criteria - suspected chorioamnionitis, severe pre-eclampsia.
Interventions	IV ampicillin 2g every 6h for 24h, followed by pivampicin 500mg orally for 7 days, plus IV metronidazole 500mg every 8h for 24h, followed by metronidazole 400mg orally every 8h for 7 days, or identical placebo.
Outcomes	Primary outcomes: difference in median days of prolongation of pregnancy of 8 days, difference in mean birthweight of 200g. Other outcomes: clinical chorioamnionitis, preterm birth <37 weeks, Apgar scores, admissions to NICU, days on ventilation, neonatal sepsis.
Notes	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 gestational age, raising a concern about generalisability. Study medications supplied by LEO Pharmaceutical Products, Copenhagen, Denmark. Additional data and information received from the author.
Allocation concealment	A – Adequate

Study	**Watts 1994**
Methods	Blinding of randomisation: Yes - randomly assigned by pharmacist using a computerised blocked randomisation table. Blinding of intervention: Yes placebo controlled. Complete follow up: Yes. Blinding of outcome measure: Yes.
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 >4cm, ruptured membranes, maternal infection, maternal medical conditions.
Interventions	IV mezlocillin 3g IV every 6 hours for 5 days and oral erythromycin 333mg every 8 hours for 10 days.
Outcomes	Maternal: mean birthweight, mean gestational age, maternal infection, prolongation of pregnancy >7 days, adverse drug reaction. Neonatal: antibiotic therapy, RDS, hospital stay, Apgar scores, perinatal mortality.
Notes	No pre-trial power calculations. Study supported in part by a grant from Miles Pharmaceutical Co, Inc. Additional information and data for the outcome of prolongation of pregnancy were received.
Allocation concealment	A – Adequate

BW = birth weight
GA = gestational age
GBS = Group B Streptococcus
h = hour(s)
IV = intravenously
NEC = necrotising enterocolitis
NICU = neonatal intensive care unit
RDS = respiratory distress syndrome
stat = immediately
vs = versus

Characteristics of excluded studies

Study	Reason for exclusion
McCaul 1992	Information on the 47% post randomisation exclusions has not been received.
McGregor 1986	The authors have not been able to provide information on the 36% post randomisation exclusions.
McGregor 1988	Women were not in labour.
Morales 1988	27% post randomisation exclusions. No further information has been received.
Nadisauskiene 1996	Included women with ruptured membranes. Author has been contacted for information on the outcomes of the women with intact membranes. Response not received at the time of submission of this review.
Saez-Llorens 1995	Quasi-random method of treatment allocation was used
Winkler 1988	Included women with ruptured membranes. Despite communication with the author the reviewers were unable to determine outcomes for the population with intact membranes.

ANALYSES

Comparison 01. Any antibiotics versus no antibiotics

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Preterm birth (<36 or <37 weeks)	9	7291	Relative Risk (Fixed) 95% CI	0.99 [0.92, 1.05]
02 Delay in delivery (subgrouped by interval)			Relative Risk (Fixed) 95% CI	Subtotals only
03 No antenatal corticosteroids	4	6745	Relative Risk (Fixed) 95% CI	1.11 [0.99, 1.24]
04 Maternal adverse drug reaction	5	626	Relative Risk (Fixed) 95% CI	1.32 [0.92, 1.89]
05 Maternal infection	9	7242	Relative Risk (Fixed) 95% CI	0.74 [0.64, 0.87]
06 Perinatal mortality	9	7208	Relative Risk (Fixed) 95% CI	1.22 [0.88, 1.70]
07 Fetal death	7	6986	Relative Risk (Fixed) 95% CI	0.72 [0.42, 1.25]
08 Neonatal death	7	6877	Relative Risk (Fixed) 95% CI	1.52 [0.99, 2.34]

09 Birthweight <2500g	5	6628	Relative Risk (Fixed) 95% CI	1.04 [0.95, 1.13]
10 Birthweight	10	7355	Weighted Mean Difference (Fixed) 95% CI	-8.53 [-48.15, 31.10]
11 Gestational age at birth	8	810	Weighted Mean Difference (Fixed) 95% CI	0.29 [-0.17, 0.75]
12 Admission to neonatal intensive or special care nursery	4	6795	Relative Risk (Fixed) 95% CI	1.03 [0.94, 1.13]
13 Respiratory distress syndrome	8	7104	Relative Risk (Fixed) 95% CI	0.99 [0.84, 1.16]
14 Neonatal mechanical ventilation	1	6241	Relative Risk (Fixed) 95% CI	1.02 [0.84, 1.24]
15 Chronic neonatal lung disease	1	6241	Relative Risk (Fixed) 95% CI	1.17 [0.78, 1.76]
16 Neonatal sepsis	9	7290	Relative Risk (Fixed) 95% CI	0.86 [0.64, 1.16]
17 Neonatal positive blood culture	3	6526	Relative Risk (Fixed) 95% CI	1.01 [0.69, 1.49]
18 Necrotising enterocolitis	6	6880	Relative Risk (Fixed) 95% CI	1.06 [0.64, 1.73]
19 Intraventricular haemorrhage	4	6717	Relative Risk (Fixed) 95% CI	0.76 [0.48, 1.19]
20 Major cerebral abnormality	1	6241	Relative Risk (Fixed) 95% CI	1.00 [0.66, 1.51]

Comparison 02. Antibiotic therapy (subgrouped by type of antibiotic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Preterm birth (<36 or <37 weeks' gestation)			Relative Risk (Fixed) 95% CI	Subtotals only
02 Interval between randomisation and delivery (days)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
03 Delivery within 48 hours			Relative Risk (Fixed) 95% CI	Subtotals only
04 Delivery within 7 days			Relative Risk (Fixed) 95% CI	Subtotals only
05 No antenatal corticosteroids			Relative Risk (Fixed) 95% CI	Subtotals only
06 Maternal adverse drug reaction			Relative Risk (Fixed) 95% CI	Subtotals only
07 Maternal infection			Relative Risk (Fixed) 95% CI	Subtotals only
08 Perinatal mortality			Relative Risk (Fixed) 95% CI	Subtotals only
09 Fetal death			Relative Risk (Fixed) 95% CI	Subtotals only
10 Neonatal death			Relative Risk (Fixed) 95% CI	Subtotals only
11 Birthweight <2500g			Relative Risk (Fixed) 95% CI	Subtotals only
12 Birthweight			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
13 Gestational age at birth			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
14 Admission to neonatal intensive or special care nursery			Relative Risk (Fixed) 95% CI	Subtotals only
15 Respiratory distress syndrome			Relative Risk (Fixed) 95% CI	Subtotals only
16 Neonatal mechanical ventilation			Relative Risk (Fixed) 95% CI	Subtotals only
17 Chronic neonatal lung disease			Relative Risk (Fixed) 95% CI	Subtotals only
18 Neonatal sepsis			Relative Risk (Fixed) 95% CI	Subtotals only
19 Neonatal positive blood culture			Relative Risk (Fixed) 95% CI	Subtotals only
20 Necrotising enterocolitis			Relative Risk (Fixed) 95% CI	Subtotals only
21 Intraventricular haemorrhage			Relative Risk (Fixed) 95% CI	Subtotals only
22 Major cerebral abnormality			Relative Risk (Fixed) 95% CI	Subtotals only

INDEX TERMS

Medical Subject Headings (MeSH)

Antibiotic Prophylaxis [*methods]; Obstetric Labor, Premature [*drug therapy]; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Prophylactic antibiotics for inhibiting preterm labour with intact membranes
Authors	King J, Flenady V
Contribution of author(s)	James King and Vicki Flenady worked as equal partners in the production of this review.
Issue protocol first published	1997/2
Review first published	1998/1
Date of most recent amendment	22 May 2006
Date of most recent SUBSTANTIVE amendment	21 August 2002
What's New	This review updates the existing review 'Antibiotics for preterm labour with intact membranes' which was first published in the Cochrane Library Issue 1, 1998. In this update, the title has been changed to 'Prophylactic antibiotics for inhibiting preterm labour with intact membranes' 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 ORACLE II 2001 trial. The earlier version of this review contained data for the outcomes of 1187 women. With the inclusion of the ORACLE II 2001 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 ORACLE II 2001 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.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 May 2002
Date authors' conclusions section amended	Information not supplied by author
Contact address	A/Prof James F King Consultant in Perinatal Epidemiology Department of Perinatal Medicine

Royal Women's Hospital
Carlton
Victoria
3053
AUSTRALIA
E-mail: james.king@rwh.org.au
Tel: +61 3 93442607
Fax: +61 3 93471761

DOI 10.1002/14651858.CD000246

Cochrane Library number CD000246

Editorial group Cochrane Pregnancy and Childbirth Group

Editorial group code HM-PREG

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Any antibiotics versus no antibiotics, Outcome 01 Preterm birth (<36 or <37 weeks)

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

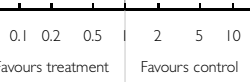
Outcome: 01 Preterm birth (<36 or <37 weeks)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1996	23/39	22/39		1.9	1.05 [0.71, 1.53]
Gordon 1995	35/58	34/59		3.0	1.05 [0.77, 1.42]
McGregor 1991	38/58	37/58		3.3	1.03 [0.78, 1.34]
Newton 1989	18/48	21/47		1.9	0.84 [0.52, 1.36]
Newton 1991	23/43	27/43		2.4	0.85 [0.59, 1.22]
ORACLE II 2001	1687/4685	559/1556		74.3	1.00 [0.93, 1.08]
Oyarzun 1998	38/83	45/90		3.8	0.92 [0.67, 1.25]
Romero 1993	69/131	74/144		6.2	1.02 [0.82, 1.29]
Svare 1997	25/59	33/51		3.1	0.65 [0.46, 0.94]
Total (95% CI)	5204	2087		100.0	0.99 [0.92, 1.05]

Total events: 1956 (Treatment), 852 (Control)

Test for heterogeneity chi-square=6.85 df=8 p=0.55 I^2 =0.0%

Test for overall effect z=0.44 p=0.7



Analysis 01.02. Comparison 01 Any antibiotics versus no antibiotics, Outcome 02 Delay in delivery (subgrouped by interval)

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 02 Delay in delivery (subgrouped by interval)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Delivery within 48 hrs					
ORACLE II 2001	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 (Treatment), 183 (Control)					
Test for heterogeneity chi-square=2.33 df=3 p=0.51 I^2 =0.0%					
Test for overall effect z=0.51 p=0.6					
02 Delivery within 7 days					
Cox 1996	13/39	14/39		3.1	0.93 [0.50, 1.71]
Gordon 1995	6/58	9/59		1.9	0.68 [0.26, 1.78]
Norman 1994	16/43	23/38		5.3	0.61 [0.39, 0.98]
ORACLE II 2001	724/4685	237/1556		77.7	1.01 [0.89, 1.16]
Romero 1993	29/131	24/144		5.0	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)	5044	1913		100.0	0.98 [0.87, 1.10]
Total events: 813 (Treatment), 337 (Control)					
Test for heterogeneity chi-square=8.36 df=6 p=0.21 I^2 =28.2%					
Test for overall effect z=0.34 p=0.7					

Analysis 01.03. Comparison 01 Any antibiotics versus no antibiotics, Outcome 03 No antenatal corticosteroids

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 03 No antenatal corticosteroids

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gordon 1995	37/58	39/59		8.3	0.97 [0.74, 1.26]
ORACLE II 2001	940/4685	279/1556		90.2	1.12 [0.99, 1.26]
Romero 1993	7/133	7/144		1.4	1.08 [0.39, 3.00]
× Svare 1997	0/59	0/51		0.0	Not estimable
Total (95% CI)	4935	1810		100.0	1.11 [0.99, 1.24]
Total events: 984 (Treatment), 325 (Control)					
Test for heterogeneity chi-square=1.04 df=2 p=0.59 I^2 =0.0%					
Test for overall effect z=1.75 p=0.08					

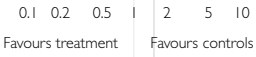
Analysis 01.04. Comparison 01 Any antibiotics versus no antibiotics, Outcome 04 Maternal adverse drug reaction

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 04 Maternal adverse drug reaction

Study	n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (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 (), 41 (Control)					
Test for heterogeneity chi-square=3.08 df=4 p=0.55 I^2 =0.0%					
Test for overall effect z=1.51 p=0.1					



Analysis 01.05. Comparison 01 Any antibiotics versus no antibiotics, Outcome 05 Maternal infection

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

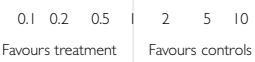
Outcome: 05 Maternal infection

Study		Control	Relative Risk (Fixed)	Weight	Relative Risk (Fixed)
	n/N	n/N	95% CI	(%)	95% CI
Gordon 1995	2/58	3/59		0.9	0.68 [0.12, 3.91]
McGregor 1991	1/53	3/50		1.0	0.31 [0.03, 2.92]
Newton 1991	1/43	6/43		1.9	0.17 [0.02, 1.33]
Norman 1994	1/43	3/38		1.0	0.29 [0.03, 2.71]
ORACLE II 2001	433/4685	183/1556		85.3	0.79 [0.67, 0.92]
Oyarzun 1998	5/83	8/90		2.4	0.68 [0.23, 1.99]
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)	5185	2057		100.0	0.74 [0.64, 0.87]

Total events: 456 (), 230 (Control)

Test for heterogeneity chi-square=9.19 df=8 p=0.33 I^2 =13.0%

Test for overall effect z=3.78 p=0.0002



Analysis 01.06. Comparison 01 Any antibiotics versus no antibiotics, Outcome 06 Perinatal mortality

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

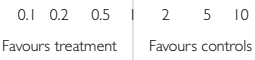
Outcome: 06 Perinatal mortality

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1996	1/40	0/42		0.8	3.15 [0.13, 75.05]
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]
ORACLE II 2001	128/4685	39/1556		91.3	1.09 [0.77, 1.55]
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		0.0	Not estimable
Watts 1994	1/30	0/26		0.8	2.61 [0.11, 61.51]
Total (95% CI)	5166	2042		100.0	1.22 [0.88, 1.70]

Total events: 140 (), 42 (Control)

Test for heterogeneity chi-square=3.86 df=7 p=0.80 I^2 =0.0%

Test for overall effect z=1.19 p=0.2



Analysis 01.07. Comparison 01 Any antibiotics versus no antibiotics, Outcome 07 Fetal death

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 07 Fetal death

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Cox 1996	0/40	0/42		0.0	Not estimable
× McGregor 1991	0/53	0/50		0.0	Not estimable
Newton 1991	1/47	0/45		1.9	2.88 [0.12, 68.79]
× Norman 1994	0/43	0/38		0.0	Not estimable
ORACLE II 2001	37/4685	18/1556		98.1	0.68 [0.39, 1.20]
× Romero 1993	0/133	0/144		0.0	Not estimable
× Svare 1997	0/59	0/51		0.0	Not estimable
Total (95% CI)	5060	1926		100.0	0.72 [0.42, 1.25]

Total events: 38 (Treatment), 18 (Control)

Test for heterogeneity chi-square=0.77 df=1 p=0.38 I^2 =0.0%

Test for overall effect z=1.16 p=0.2

Analysis 01.08. Comparison 01 Any antibiotics versus no antibiotics, Outcome 08 Neonatal death

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 08 Neonatal death

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1996	1/40	0/42		1.4	3.15 [0.13, 75.05]
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		5.9	0.88 [0.13, 5.97]
ORACLE II 2001	91/4685	21/1556		87.4	1.44 [0.90, 2.31]
Oyarzun 1998	2/78	1/90		2.6	2.31 [0.21, 24.97]
× Svare 1997	0/59	0/51		0.0	Not estimable
Total (95% CI)	5005	1872		100.0	1.52 [0.99, 2.34]

Total events: 99 (Treatment), 24 (Control)

Test for heterogeneity chi-square=1.38 df=5 p=0.93 I^2 =0.0%

Test for overall effect z=1.90 p=0.06

Analysis 01.09. Comparison 01 Any antibiotics versus no antibiotics, Outcome 09 Birthweight <2500g

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 09 Birthweight <2500g

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1996	21/40	26/42		3.4	0.85 [0.58, 1.24]
McGregor 1991	21/53	26/50		3.6	0.76 [0.50, 1.17]
Newton 1991	31/45	26/47		3.5	1.25 [0.90, 1.72]
ORACLE II 2001	1342/4685	419/1556		85.5	1.06 [0.97, 1.17]
Svare 1997	23/59	27/51		3.9	0.74 [0.49, 1.11]
Total (95% CI)	4882	1746		100.0	1.04 [0.95, 1.13]

Total events: 1438 (Treatment), 524 (Control)

Test for heterogeneity chi-square=7.29 df=4 p=0.12 I^2 =45.1%

Test for overall effect z=0.88 p=0.4

Analysis 01.10. Comparison 01 Any antibiotics versus no antibiotics, Outcome 10 Birthweight

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 10 Birthweight

Study	Controls N	Controls Mean(SD)	N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Cox 1996	40	2394.00 (790.00)	42	2225.00 (758.00)		1.4	169.00 [-166.39, 504.39]
Gordon 1995	70	2660.00 (750.00)	69	2634.00 (691.00)		2.7	26.00 [-213.69, 265.69]
McGregor 1991	53	2568.00 (643.00)	50	2441.00 (694.00)		2.3	127.00 [-131.79, 385.79]
Newton 1989	48	2855.00 (667.00)	47	2847.00 (609.00)		2.4	8.00 [-248.74, 264.74]
Norman 1994	43	2318.00 (609.00)	38	2093.00 (653.00)		2.1	225.00 [-51.11, 501.11]
ORACLE II 2001	4685	2839.00 (797.00)	1556	2857.00 (775.00)		78.4	-18.00 [-62.76, 26.76]
Oyarzun 1998	83	2879.00 (723.00)	90	2942.00 (676.00)		3.6	-63.00 [-272.04, 146.04]
Romero 1993	131	2535.00 (790.00)	144	2683.00 (720.00)		4.9	-148.00 [-327.25, 31.25]
Svare 1997	59	2662.00 (842.00)	51	2370.00 (900.00)		1.5	292.00 [-35.37, 619.37]
Watts 1994	30	2202.00 (851.00)	26	2212.00 (862.00)		0.8	-10.00 [-460.02, 440.02]
Total (95% CI)	5242		2113			100.0	-8.53 [-48.15, 31.10]

Test for heterogeneity chi-square=10.97 df=9 p=0.28 I^2 =18.0%

Test for overall effect z=0.42 p=0.7

Analysis 01.11. Comparison 01 Any antibiotics versus no antibiotics, Outcome 11 Gestational age at birth

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

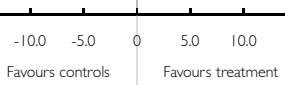
Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 11 Gestational age at birth

Study	Controls N	Controls Mean(SD)	Controls N	Controls Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Cox 1996	39	34.20 (4.43)	39	34.10 (3.88)		6.2	0.10 [-1.75, 1.95]
Gordon 1995	58	36.00 (2.90)	59	35.90 (2.90)		19.1	0.10 [-0.95, 1.15]
McGregor 1991	53	35.40 (3.20)	50	34.90 (3.30)		13.3	0.50 [-0.76, 1.76]
Newton 1989	48	36.80 (2.90)	47	36.80 (2.80)		16.0	0.00 [-1.15, 1.15]
Norman 1994	43	34.30 (3.30)	38	33.10 (3.80)		8.7	1.20 [-0.36, 2.76]
Oyarzun 1998	80	31.80 (3.60)	90	32.03 (2.27)		25.0	-0.23 [-1.15, 0.69]
Svare 1997	59	36.20 (4.30)	51	34.10 (4.40)		7.9	2.10 [0.47, 3.73]
Watts 1994	30	33.10 (4.80)	26	33.50 (4.10)		3.9	-0.40 [-2.73, 1.93]
Total (95% CI)	410		400			100.0	0.29 [-0.17, 0.75]

Test for heterogeneity chi-square=8.12 df=7 p=0.32 I^2 =13.8%

Test for overall effect z=1.23 p=0.2



Analysis 01.12. Comparison 01 Any antibiotics versus no antibiotics, Outcome 12 Admission to neonatal intensive or special care nursery

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

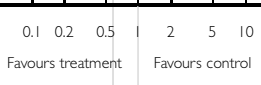
Outcome: 12 Admission to neonatal intensive or special care nursery

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
ORACLE II 2001	1216/4685	380/1556		86.7	1.06 [0.96, 1.17]
Oyarzun 1998	5/78	10/90		1.4	0.58 [0.21, 1.62]
Romero 1993	44/133	46/144		6.7	1.04 [0.74, 1.45]
Svare 1997	23/58	32/51		5.2	0.63 [0.43, 0.93]
Total (95% CI)	4954	1841		100.0	1.03 [0.94, 1.13]

Total events: 1288 (Treatment), 468 (Control)

Test for heterogeneity chi-square=7.90 df=3 p=0.05 I^2 =62.0%

Test for overall effect z=0.66 p=0.5



Analysis 01.13. Comparison 01 Any antibiotics versus no antibiotics, Outcome 13 Respiratory distress syndrome

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 13 Respiratory distress syndrome

Study		Control	Relative Risk (Fixed)	Weight	Relative Risk (Fixed)
	n/N	n/N	95% CI	(%)	95% CI
Cox 1996	8/40	8/42		3.0	1.05 [0.44, 2.53]
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]
ORACLE II 2001	399/4685	138/1556		78.7	0.96 [0.80, 1.16]
Oyarzun 1998	9/78	7/90		2.5	1.48 [0.58, 3.80]
Romero 1993	14/131	11/144		4.0	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		3.3	1.41 [0.69, 2.86]
Total (95% CI)	5112	1992		100.0	0.99 [0.84, 1.16]

Total events: 460 (), 194 (Control)

Test for heterogeneity chi-square=4.50 df=7 p=0.72 I^2 =0.0%

Test for overall effect z=0.16 p=0.9

Analysis 01.14. Comparison 01 Any antibiotics versus no antibiotics, Outcome 14 Neonatal mechanical ventilation

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

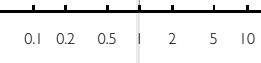
Outcome: 14 Neonatal mechanical ventilation

Study	Treatment	Control	Relative Risk (Fixed)	Weight	Relative Risk (Fixed)
	n/N	n/N	95% CI	(%)	95% CI
ORACLE II 2001	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 (Treatment), 121 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=0.18 p=0.9

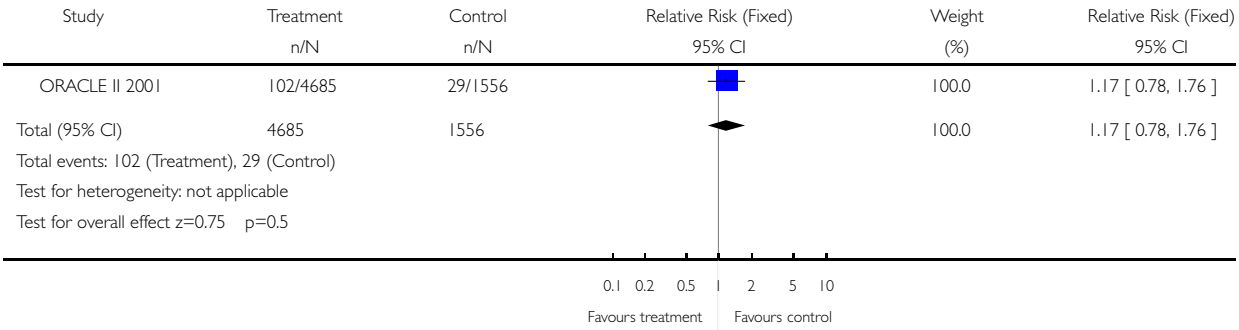


Analysis 01.15. Comparison 01 Any antibiotics versus no antibiotics, Outcome 15 Chronic neonatal lung disease

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 15 Chronic neonatal lung disease

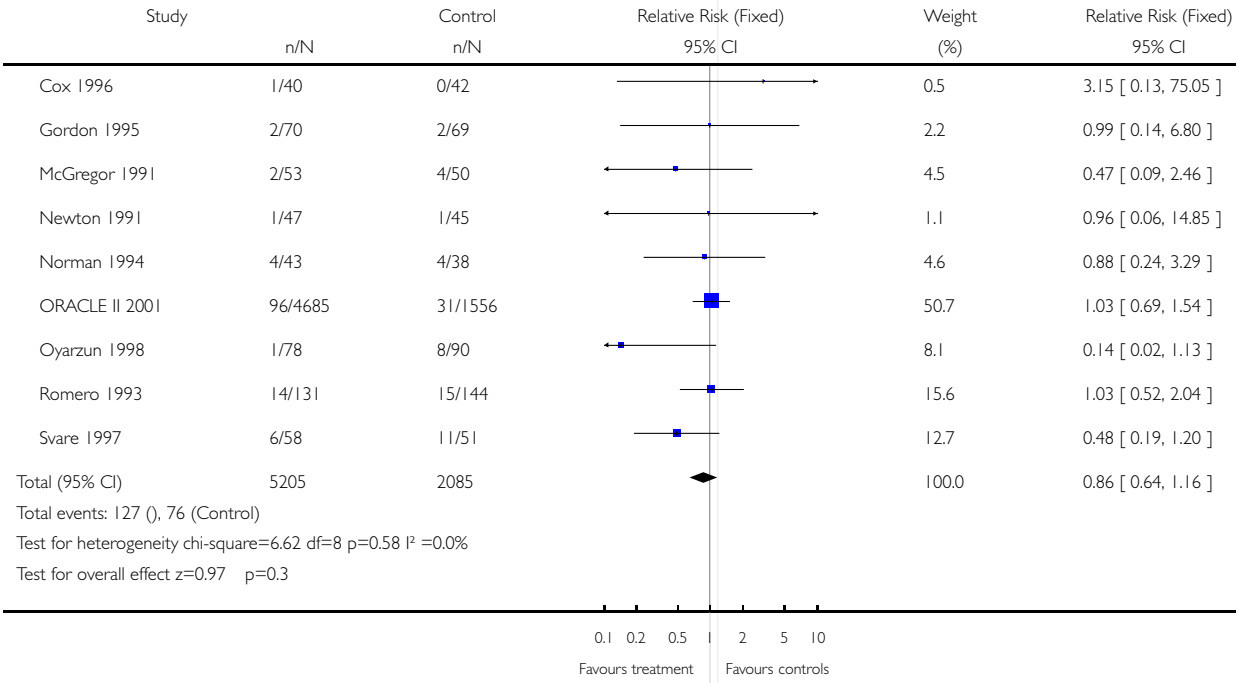


Analysis 01.16. Comparison 01 Any antibiotics versus no antibiotics, Outcome 16 Neonatal sepsis

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 16 Neonatal sepsis



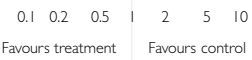
Analysis 01.17. Comparison 01 Any antibiotics versus no antibiotics, Outcome 17 Neonatal positive blood culture

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 17 Neonatal positive blood culture

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Gordon 1995	2/58	2/59		3.9	1.02 [0.15, 6.98]
ORACLE II 2001	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 (Treatment), 35 (Control)					
Test for heterogeneity chi-square=0.22 df=2 p=0.90 I^2 =0.0%					
Test for overall effect z=0.06 p=1					



Analysis 01.18. Comparison 01 Any antibiotics versus no antibiotics, Outcome 18 Necrotising enterocolitis

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 18 Necrotising enterocolitis

Study	n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Cox 1996	0/40	1/42		4.5	0.35 [0.01, 8.34]
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]
ORACLE II 2001	58/4685	12/1556		55.1	1.61 [0.86, 2.98]
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 (), 25 (Control)					
Test for heterogeneity chi-square=6.38 df=5 p=0.27 I^2 =21.7%					
Test for overall effect z=0.21 p=0.8					

Analysis 01.19. Comparison 01 Any antibiotics versus no antibiotics, Outcome 19 Intraventricular haemorrhage

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 19 Intraventricular haemorrhage

Study		Control	Relative Risk (Fixed)	Weight	Relative Risk (Fixed)
	n/N	n/N	95% CI	(%)	95% CI
Newton 1991	2/47	2/45		4.9	0.96 [0.14, 6.51]
ORACLE II 2001	55/4685	22/1556		79.9	0.83 [0.51, 1.36]
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)	4921	1796		100.0	0.76 [0.48, 1.19]
Total events: 59 (), 30 (Control)					
Test for heterogeneity chi-square=2.09 df=3 p=0.55 I^2 =0.0%					
Test for overall effect z=1.20 p=0.2					

Analysis 01.20. Comparison 01 Any antibiotics versus no antibiotics, Outcome 20 Major cerebral abnormality

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 01 Any antibiotics versus no antibiotics

Outcome: 20 Major cerebral abnormality

Study	Treatment	Control	Relative Risk (Fixed)	Weight	Relative Risk (Fixed)
	n/N	n/N	95% CI	(%)	95% CI
ORACLE II 2001	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 (Treatment), 29 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.02 p=1					

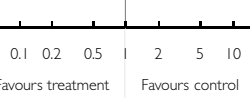
Analysis 02.01. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 01 Preterm birth (<36 or <37 weeks' gestation)

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 01 Preterm birth (<36 or <37 weeks' gestation)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Betalactam antibiotics alone vs no antibiotics					
Cox 1996	23/39	22/39		6.1	1.05 [0.71, 1.53]
Gordon 1995	35/58	34/59		9.3	1.05 [0.77, 1.42]
Newton 1991	23/43	27/43		7.5	0.85 [0.59, 1.22]
ORACLE II 2001	545/1534	186/519		77.1	0.99 [0.87, 1.13]
Subtotal (95% CI)	1674	660		100.0	0.99 [0.88, 1.11]
Total events: 626 (Treatment), 269 (Control)					
Test for heterogeneity chi-square=0.88 df=3 p=0.83 I^2 =0.0%					
Test for overall effect z=0.19 p=0.9					
02 Macrolide antibiotics alone vs no antibiotics					
McGregor 1991	38/58	37/58		11.6	1.03 [0.78, 1.34]
ORACLE II 2001	584/1600	186/519		88.4	1.02 [0.89, 1.16]
Subtotal (95% CI)	1658	577		100.0	1.02 [0.90, 1.15]
Total events: 622 (Treatment), 223 (Control)					
Test for heterogeneity chi-square=0.00 df=1 p=0.96 I^2 =0.0%					
Test for overall effect z=0.31 p=0.8					
03 Macrolide and betalactam antibiotics vs no antibiotics					
Newton 1989	18/48	21/47		5.1	0.84 [0.52, 1.36]
ORACLE II 2001	558/1551	186/519		67.4	1.00 [0.88, 1.15]
Oyarzun 1998	38/83	45/90		10.4	0.92 [0.67, 1.25]
Romero 1993	69/131	74/144		17.0	1.02 [0.82, 1.29]
Subtotal (95% CI)	1813	800		100.0	0.99 [0.89, 1.10]
Total events: 683 (Treatment), 326 (Control)					
Test for heterogeneity chi-square=0.82 df=3 p=0.85 I^2 =0.0%					
Test for overall effect z=0.19 p=0.8					
04 Antibiotics active against anaerobic bacteria vs no antibiotics					
McGregor 1991	38/58	37/58		51.1	1.03 [0.78, 1.34]
Svare 1997	25/59	33/51		48.9	0.65 [0.46, 0.94]
Subtotal (95% CI)	117	109		100.0	0.85 [0.68, 1.05]
Total events: 63 (Treatment), 70 (Control)					
Test for heterogeneity chi-square=3.94 df=1 p=0.05 I^2 =74.6%					
Test for overall effect z=1.52 p=0.1					

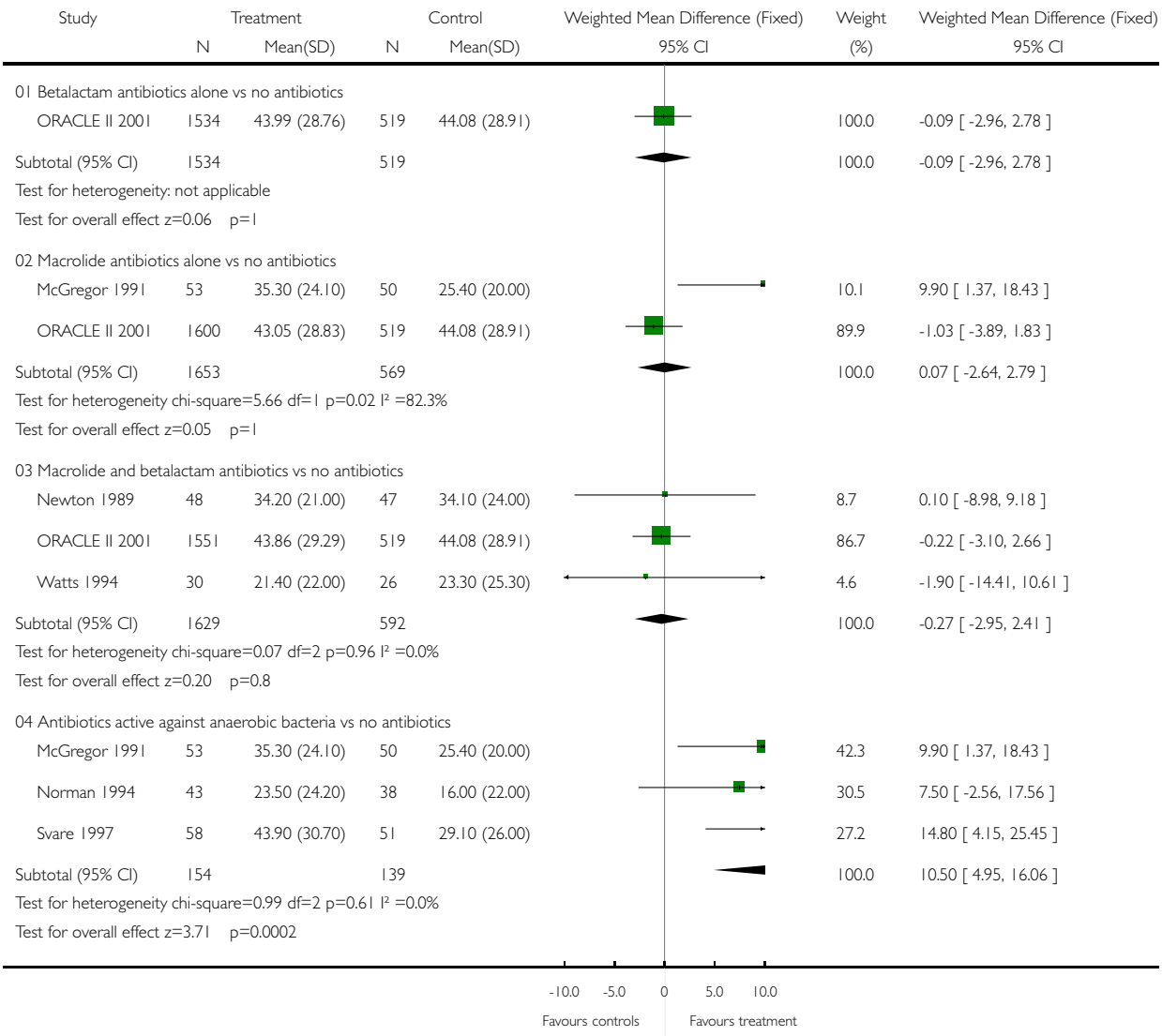


Analysis 02.02. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 02 Interval between randomisation and delivery (days)

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 02 Interval between randomisation and delivery (days)



Analysis 02.03. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 03 Delivery within 48 hours

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 03 Delivery within 48 hours

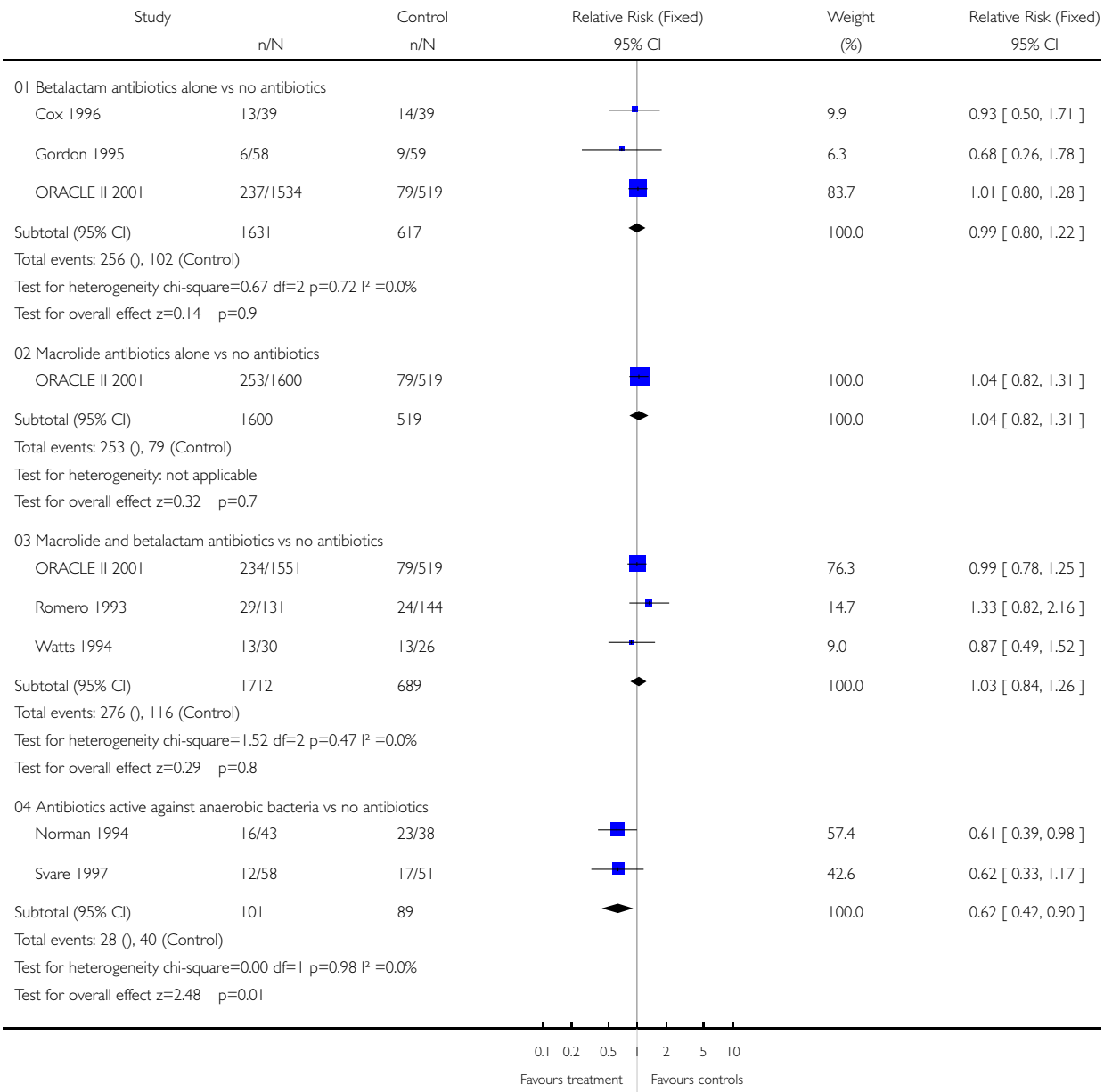
Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Betalactam antibiotics alone vs no antibiotics					
ORACLE II 2001	152/1534	51/519		100.0	1.01 [0.75, 1.36]
Subtotal (95% CI)	1534	519		100.0	1.01 [0.75, 1.36]
Total events: 152 (Treatment), 51 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.05 p=1					
02 Macrolide antibiotics alone vs no antibiotics					
ORACLE II 2001	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 (Treatment), 51 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.36 p=0.7					
03 Macrolide and betalactam antibiotics vs no antibiotics					
ORACLE II 2001	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]
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 (Treatment), 74 (Control)					
Test for heterogeneity chi-square=0.71 df=2 p=0.70 I^2 =0.0%					
Test for overall effect z=0.85 p=0.4					
04 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 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.12 p=0.3					

Analysis 02.04. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 04 Delivery within 7 days

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 04 Delivery within 7 days

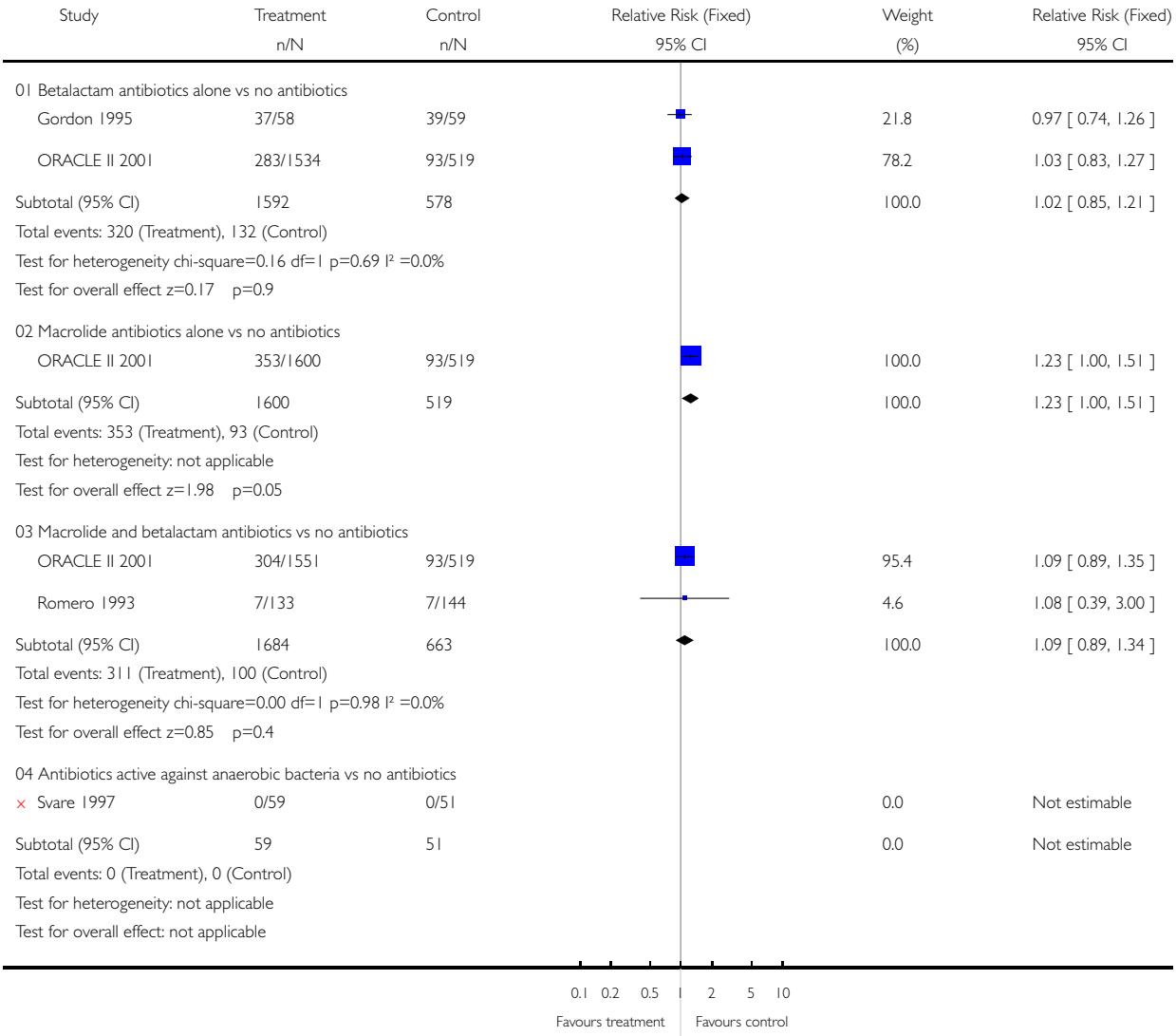


Analysis 02.05. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 05 No antenatal corticosteroids

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 05 No antenatal corticosteroids

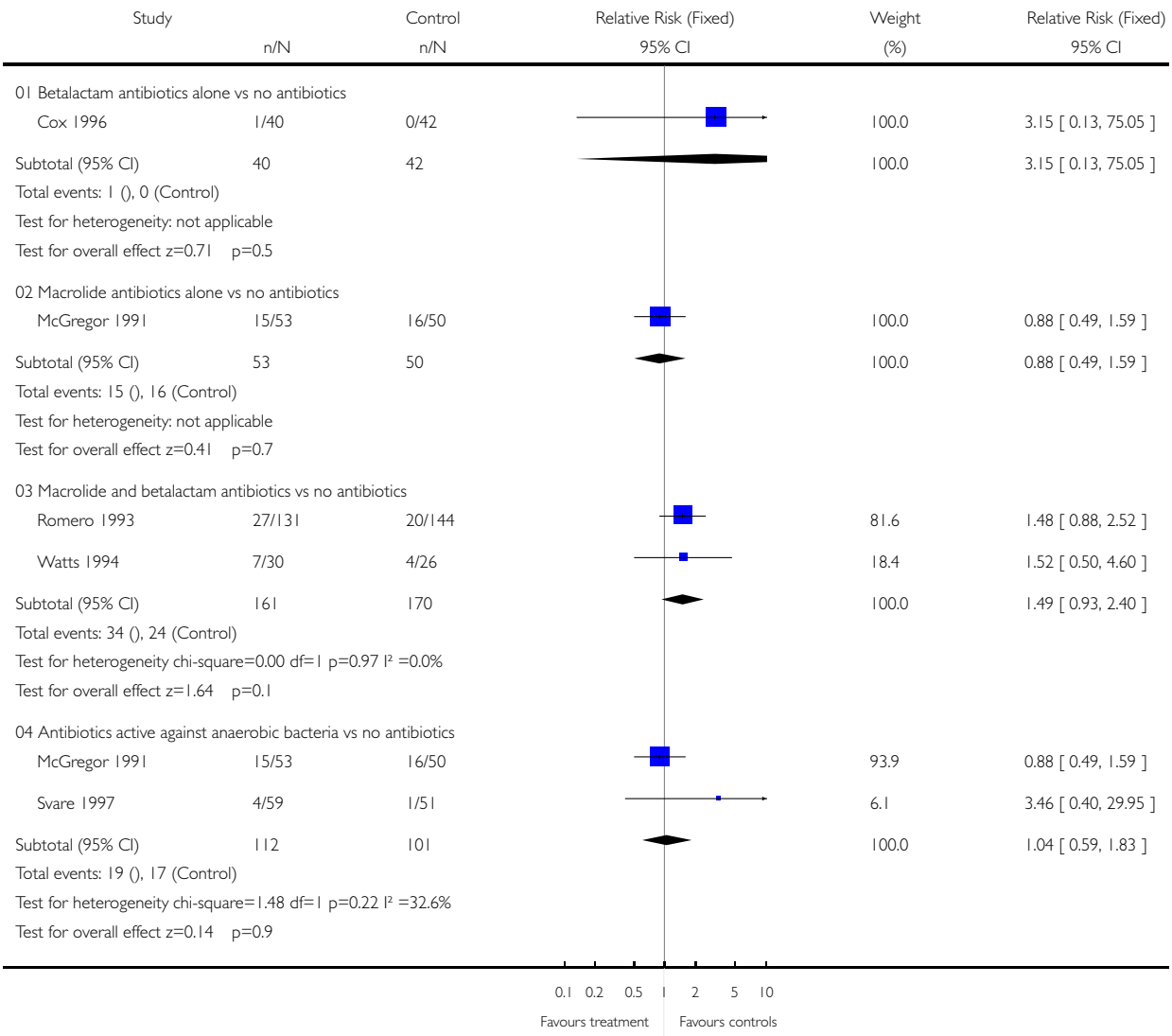


Analysis 02.06. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 06 Maternal adverse drug reaction

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 06 Maternal adverse drug reaction

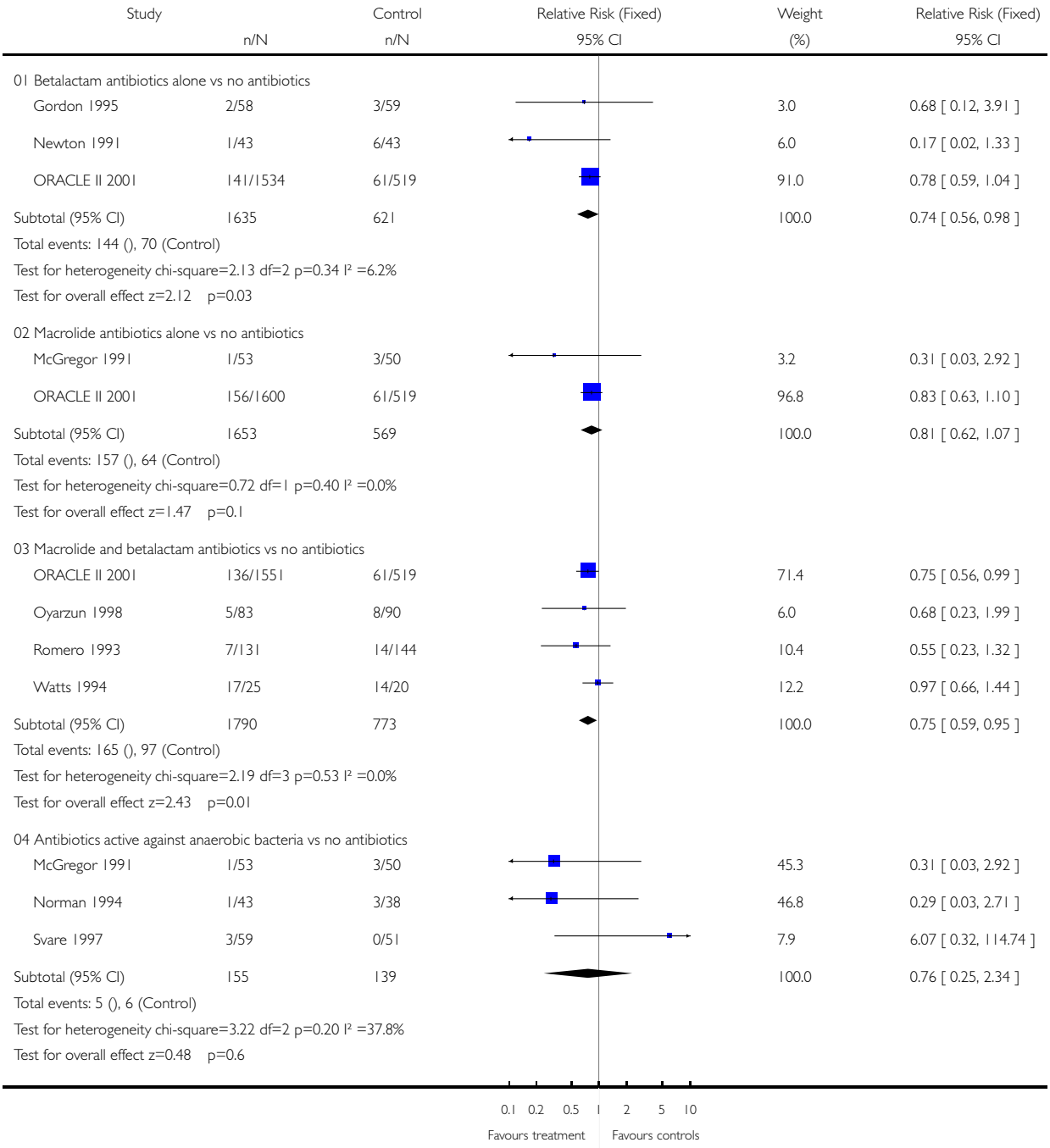


Analysis 02.07. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 07 Maternal infection

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 07 Maternal infection

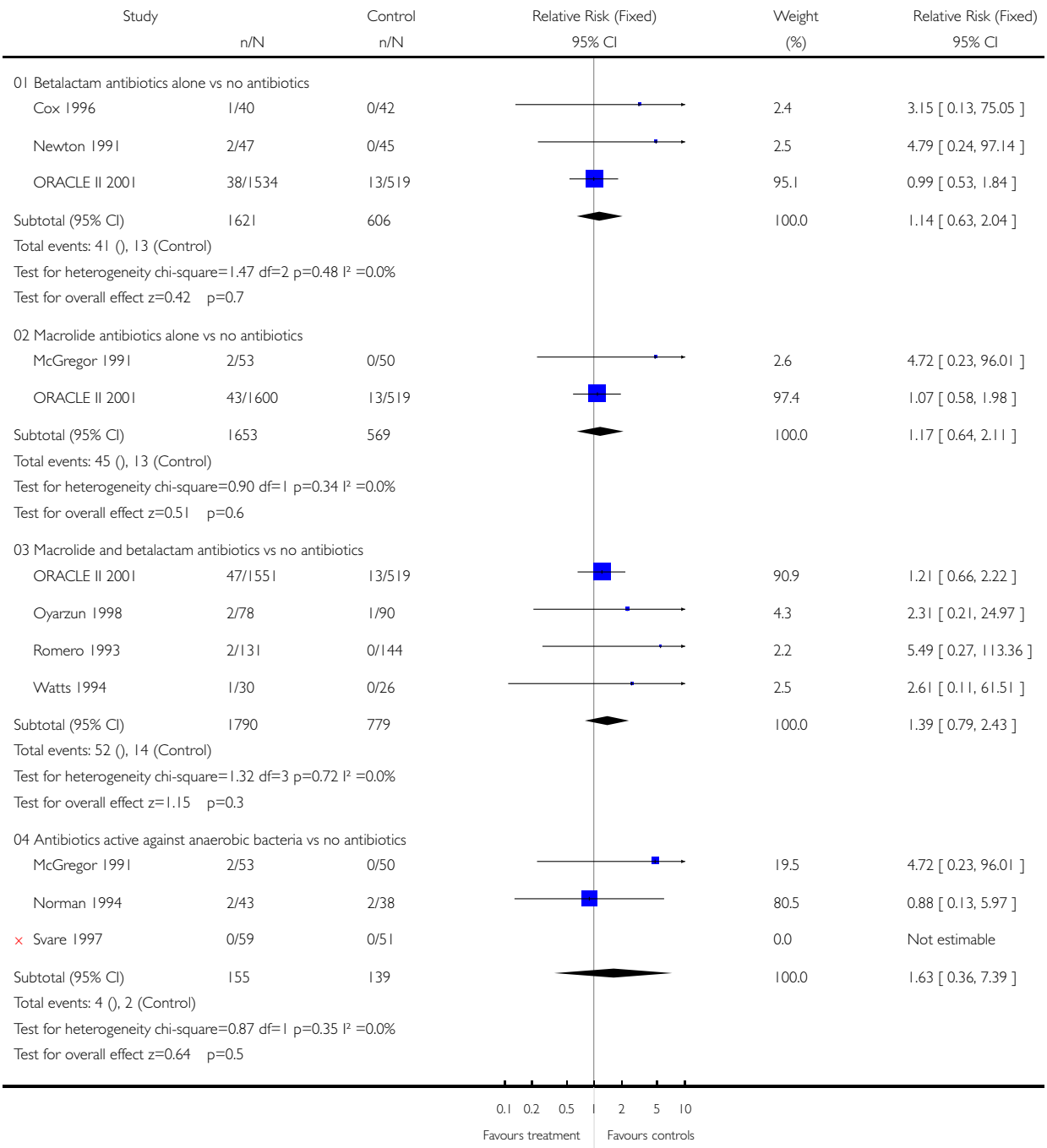


Analysis 02.08. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 08 Perinatal mortality

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 08 Perinatal mortality



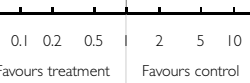
Analysis 02.09. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 09 Fetal death

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 09 Fetal death

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Betalactam antibiotics alone vs no antibiotics					
× Cox 1996	0/40	0/42		0.0	Not estimable
Newton 1991	1/47	0/45		5.4	2.88 [0.12, 68.79]
ORACLE II 2001	14/1534	6/519		94.6	0.79 [0.30, 2.04]
Subtotal (95% CI)	1621	606		100.0	0.90 [0.37, 2.21]
Total events: 15 (Treatment), 6 (Control)					
Test for heterogeneity chi-square=0.59 df=1 p=0.44 I^2 =0.0%					
Test for overall effect z=0.23 p=0.8					
02 Macrolide antibiotics alone vs no antibiotics					
× McGregor 1991	0/53	0/50		0.0	Not estimable
ORACLE II 2001	10/1600	6/519		100.0	0.54 [0.20, 1.48]
Subtotal (95% CI)	1653	569		100.0	0.54 [0.20, 1.48]
Total events: 10 (Treatment), 6 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.20 p=0.2					
03 Macrolide and betalactam antibiotics vs no antibiotics					
ORACLE II 2001	13/1551	6/519		100.0	0.73 [0.28, 1.90]
× Romero 1993	0/133	0/144		0.0	Not estimable
Subtotal (95% CI)	1684	663		100.0	0.73 [0.28, 1.90]
Total events: 13 (Treatment), 6 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.65 p=0.5					
04 Antibiotics active against anaerobic bacteria vs no antibiotics					
× McGregor 1991	0/53	0/50		0.0	Not estimable
× Norman 1994	0/43	0/38		0.0	Not estimable
× Svare 1997	0/59	0/51		0.0	Not estimable
Subtotal (95% CI)	155	139		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

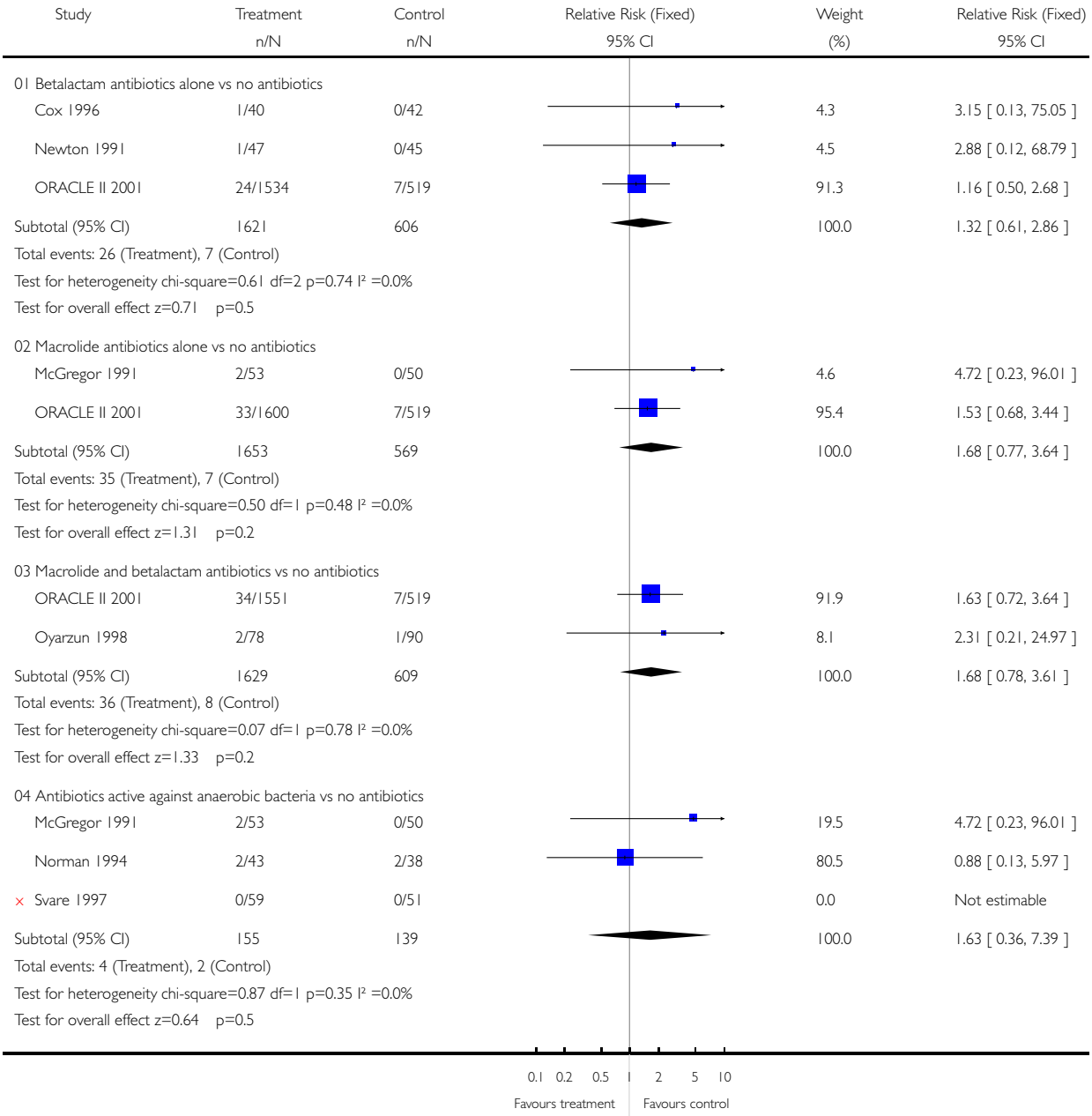


Analysis 02.10. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 10 Neonatal death

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 10 Neonatal death

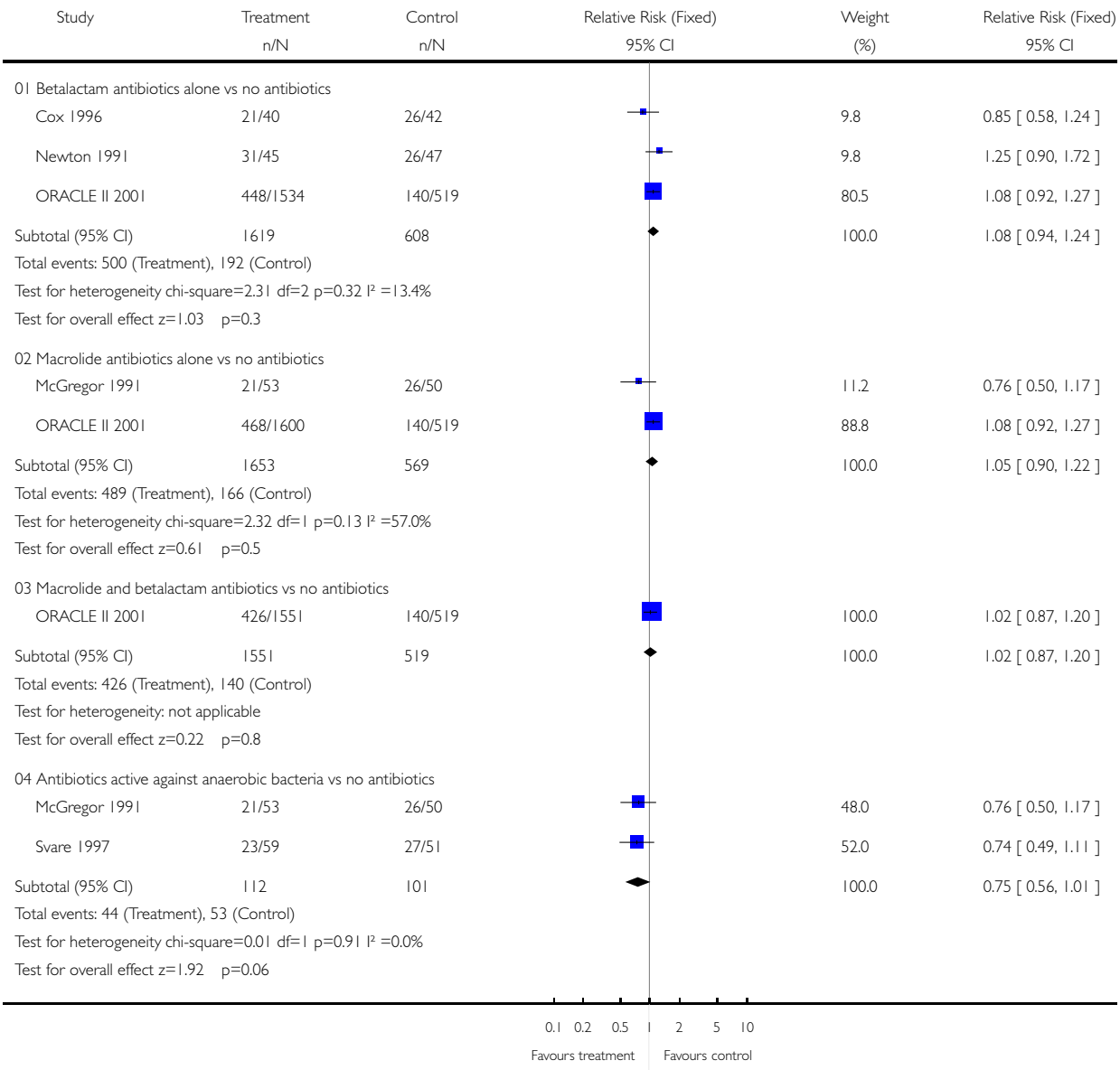


Analysis 02.11. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 11 Birthweight <2500g

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 11 Birthweight <2500g



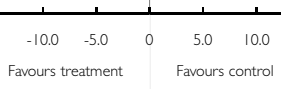
Analysis 02.12. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 12 Birthweight

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 12 Birthweight

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 Betalactam antibiotics alone vs no antibiotics							
Cox 1996	40	2394.00 (790.00)	42	2225.00 (758.00)		4.7	169.00 [-166.39, 504.39]
Gordon 1995	70	2660.00 (750.00)	69	2634.00 (691.00)		9.1	26.00 [-213.69, 265.69]
ORACLE II 2001	1534	2842.00 (810.00)	519	2857.00 (775.00)		86.2	-15.00 [-93.03, 63.03]
Subtotal (95% CI)	1644		630			100.0	-2.67 [-75.12, 69.78]
Test for heterogeneity chi-square=1.16 df=2 p=0.56 I² =0.0%							
Test for overall effect z=0.07 p=0.9							
02 Macrolide antibiotics alone vs no antibiotics							
McGregor 1991	53	2568.00 (643.00)	50	2441.00 (694.00)		8.1	127.00 [-131.79, 385.79]
ORACLE II 2001	1600	2823.00 (788.00)	519	2857.00 (775.00)		91.9	-34.00 [-111.05, 43.05]
Subtotal (95% CI)	1653		569			100.0	-20.89 [-94.74, 52.95]
Test for heterogeneity chi-square=1.37 df=1 p=0.24 I² =26.8%							
Test for overall effect z=0.55 p=0.6							
03 Macrolide and betalactam antibiotics vs no antibiotics							
Newton 1989	48	2855.00 (667.00)	47	2847.00 (609.00)		6.3	8.00 [-248.74, 264.74]
ORACLE II 2001	1551	2851.00 (794.00)	519	2857.00 (775.00)		69.2	-6.00 [-83.51, 71.51]
Oyarzun 1998	83	2879.00 (723.00)	90	2942.00 (676.00)		9.5	-63.00 [-272.04, 146.04]
Romero 1993	131	2535.00 (790.00)	144	2683.00 (720.00)		12.9	-148.00 [-327.25, 31.25]
Watts 1994	30	2202.00 (851.00)	26	2212.00 (862.00)		2.1	-10.00 [-460.02, 440.02]
Subtotal (95% CI)	1843		826			100.0	-28.99 [-93.46, 35.48]
Test for heterogeneity chi-square=2.22 df=4 p=0.70 I² =0.0%							
Test for overall effect z=0.88 p=0.4							
04 Antibiotics active against anaerobic bacteria vs no antibiotics							
McGregor 1991	53	2568.00 (643.00)	50	2441.00 (694.00)		39.9	127.00 [-131.79, 385.79]
Norman 1994	43	2318.00 (609.00)	38	2093.00 (653.00)		35.1	225.00 [-51.11, 501.11]
Svare 1997	59	2662.00 (842.00)	51	2370.00 (900.00)		25.0	292.00 [-35.37, 619.37]
Subtotal (95% CI)	155		139			100.0	202.58 [39.01, 366.14]
Test for heterogeneity chi-square=0.64 df=2 p=0.73 I² =0.0%							
Test for overall effect z=2.43 p=0.02							

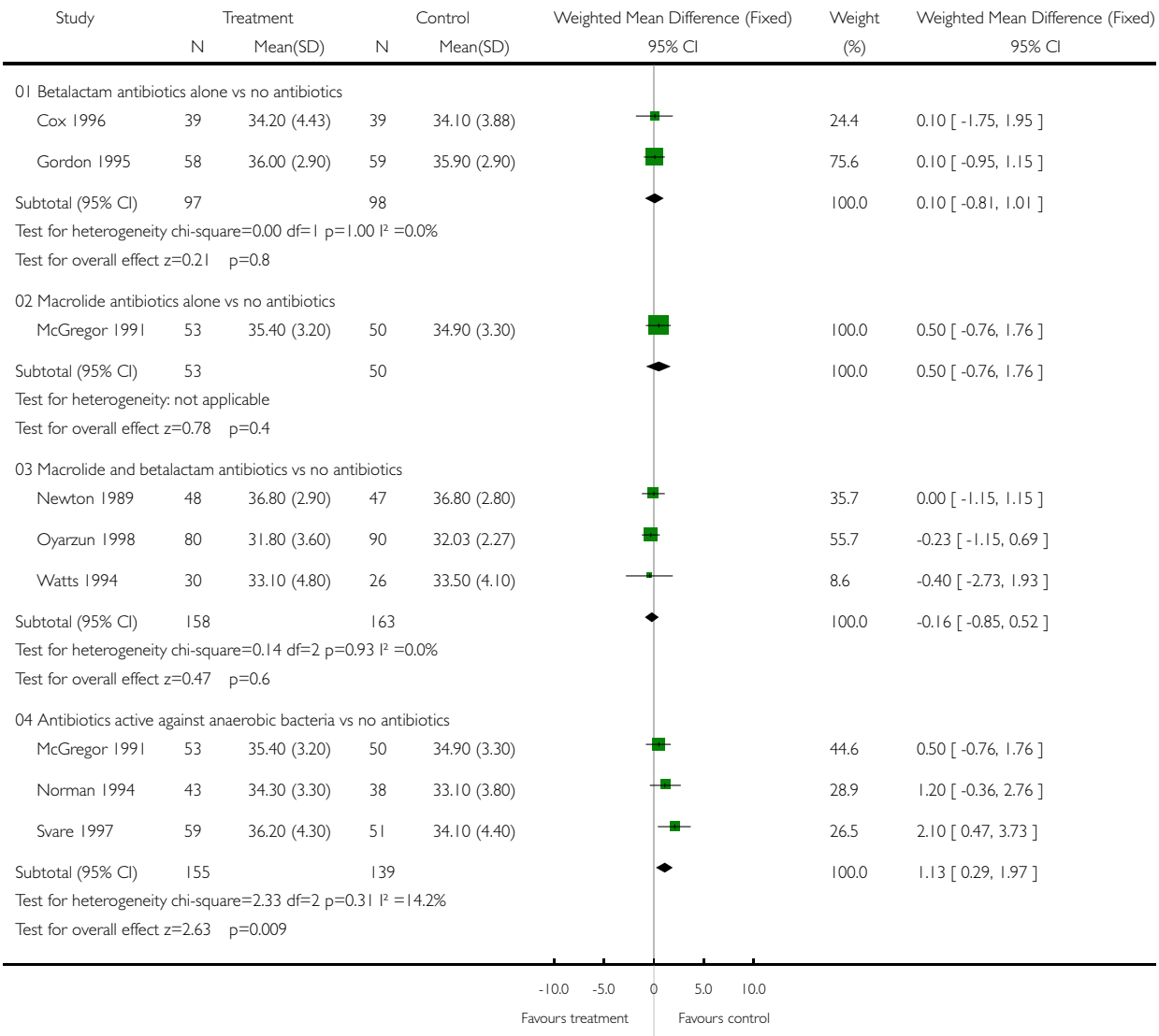


Analysis 02.13. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 13 Gestational age at birth

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 13 Gestational age at birth



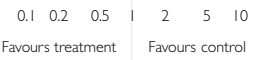
Analysis 02.14. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 14 Admission to neonatal intensive or special care nursery

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 14 Admission to neonatal intensive or special care nursery

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Betalactam antibiotics alone vs no antibiotics					
ORACLE II 2001	403/1534	127/519		100.0	1.07 [0.90, 1.28]
Subtotal (95% CI)	1534	519		100.0	1.07 [0.90, 1.28]
Total events: 403 (Treatment), 127 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.81 p=0.4					
02 Macrolide antibiotics alone vs no antibiotics					
ORACLE II 2001	424/1600	127/519		100.0	1.08 [0.91, 1.29]
Subtotal (95% CI)	1600	519		100.0	1.08 [0.91, 1.29]
Total events: 424 (Treatment), 127 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.91 p=0.4					
03 Macrolide and betalactam antibiotics vs no antibiotics					
ORACLE II 2001	389/1551	127/519		78.1	1.02 [0.86, 1.22]
Oyarzun 1998	5/78	10/90		3.8	0.58 [0.21, 1.62]
Romero 1993	44/133	46/144		18.1	1.04 [0.74, 1.45]
Subtotal (95% CI)	1762	753		100.0	1.01 [0.87, 1.18]
Total events: 438 (Treatment), 183 (Control)					
Test for heterogeneity chi-square=1.18 df=2 p=0.55 I^2 =0.0%					
Test for overall effect z=0.12 p=0.9					
04 Antibiotics active against anaerobic bacteria vs no antibiotics					
Svare 1997	23/58	32/51		100.0	0.63 [0.43, 0.93]
Subtotal (95% CI)	58	51		100.0	0.63 [0.43, 0.93]
Total events: 23 (Treatment), 32 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.36 p=0.02					

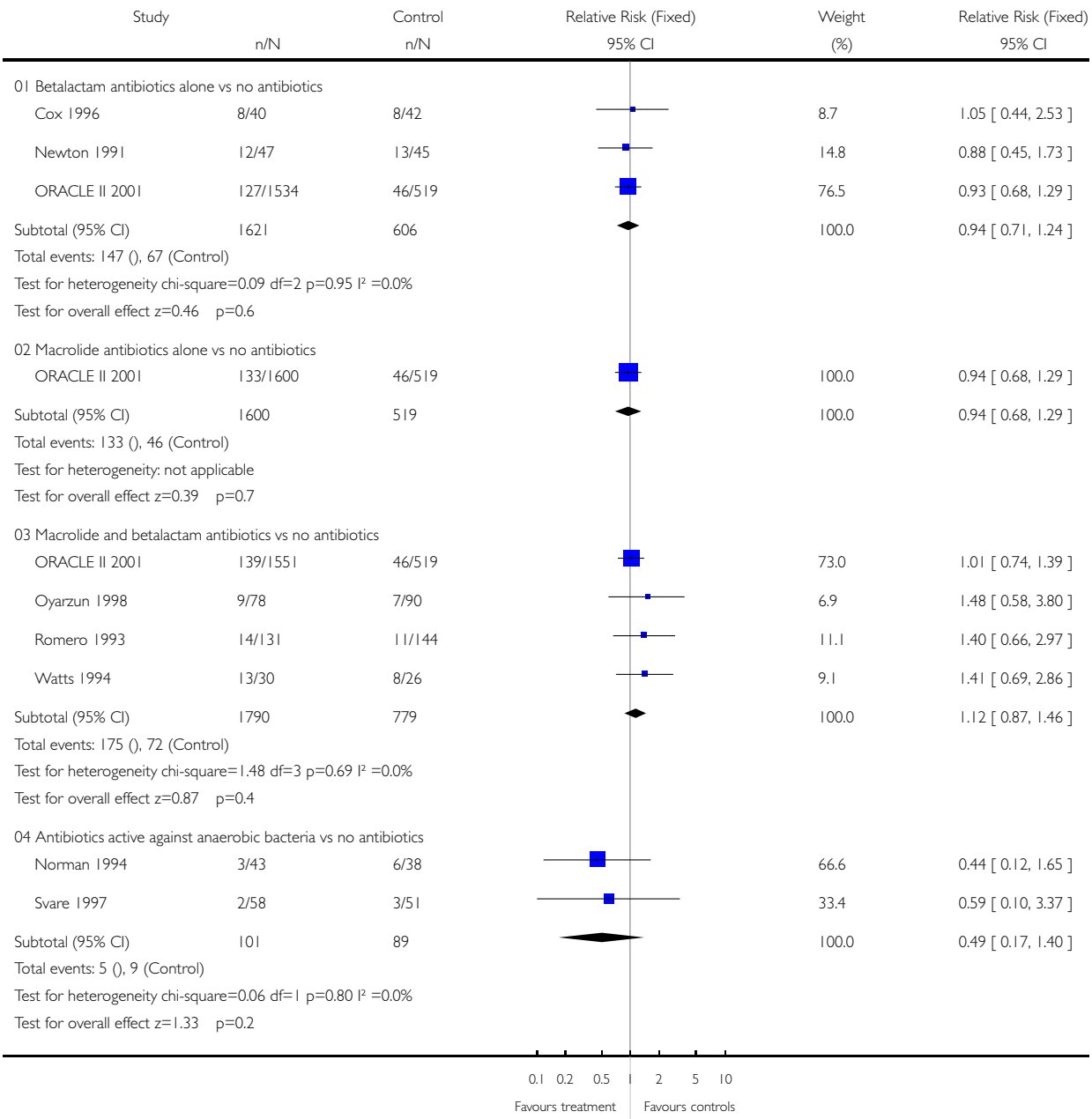


Analysis 02.15. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 15 Respiratory distress syndrome

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 15 Respiratory distress syndrome

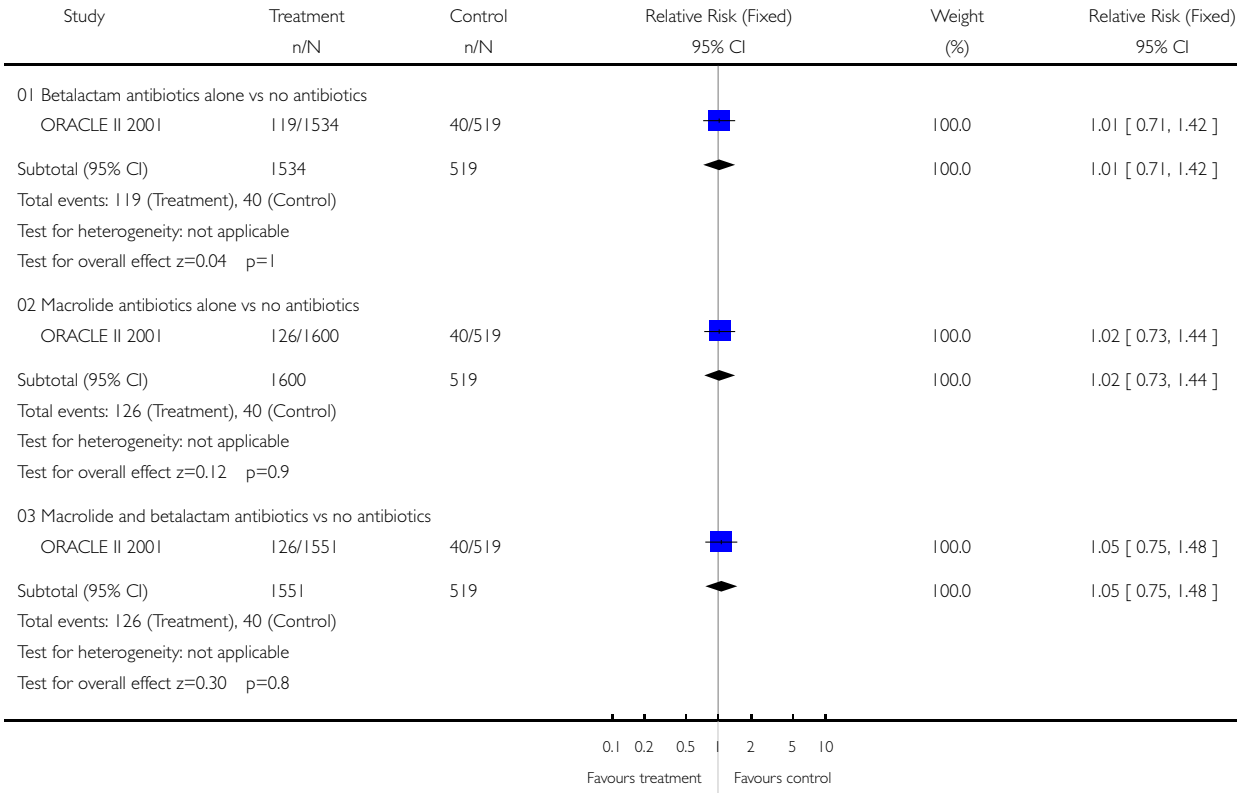


Analysis 02.16. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 16 Neonatal mechanical ventilation

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 16 Neonatal mechanical ventilation

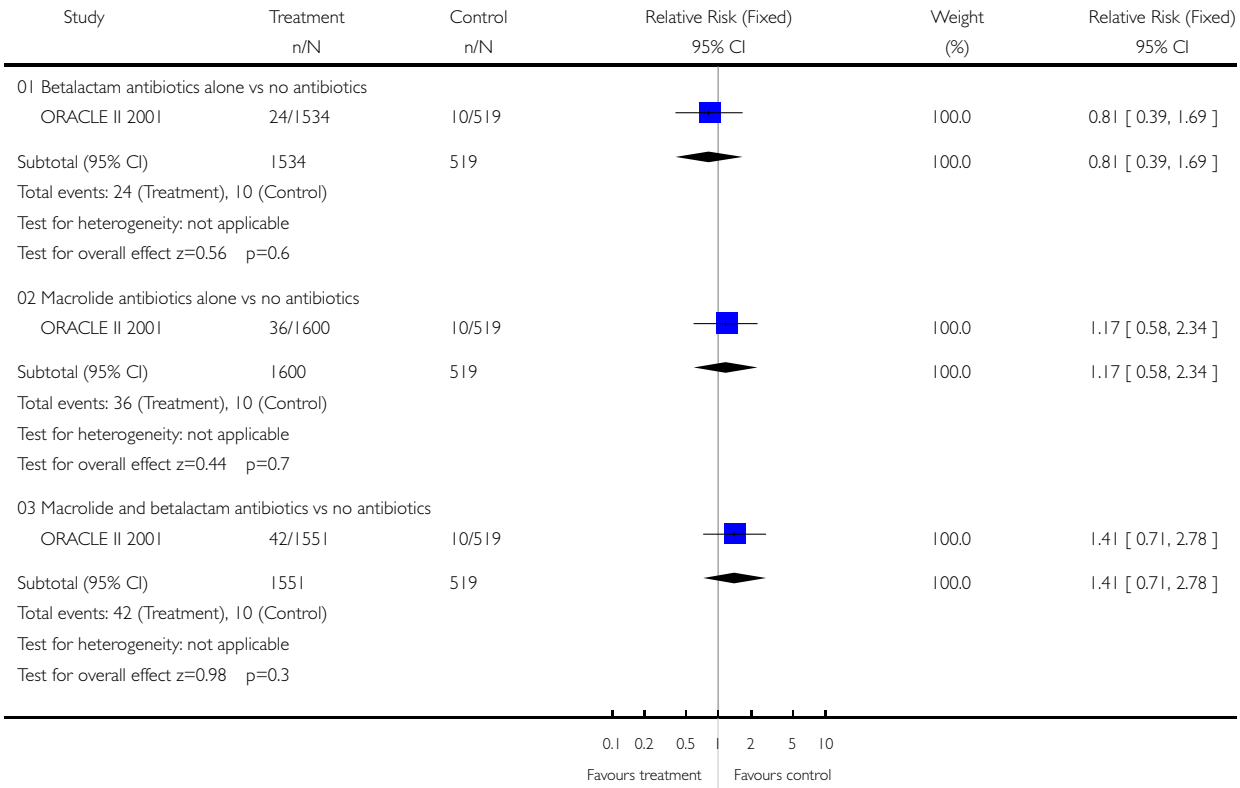


Analysis 02.17. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 17 Chronic neonatal lung disease

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 17 Chronic neonatal lung disease

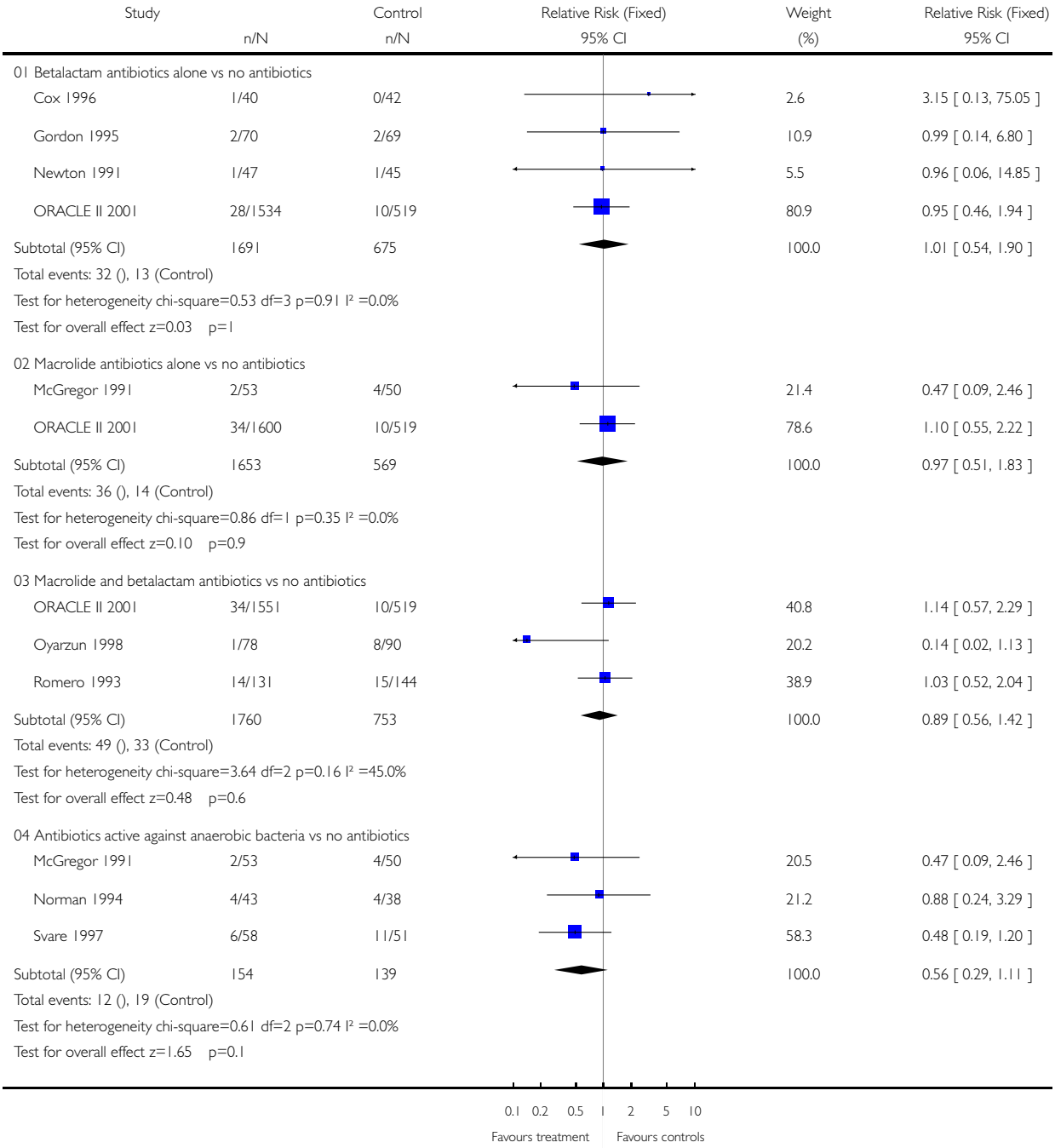


Analysis 02.18. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 18 Neonatal sepsis

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 18 Neonatal sepsis



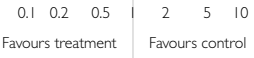
Analysis 02.19. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 19 Neonatal positive blood culture

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 19 Neonatal positive blood culture

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Betalactam antibiotics alone vs no antibiotics					
Gordon 1995	2/58	2/59		11.7	1.02 [0.15, 6.98]
ORACLE II 2001	28/1534	10/519		88.3	0.95 [0.46, 1.94]
Subtotal (95% CI)	1592	578		100.0	0.96 [0.49, 1.87]
Total events: 30 (Treatment), 12 (Control)					
Test for heterogeneity chi-square=0.00 df=1 p=0.95 I^2 =0.0%					
Test for overall effect z=0.13 p=0.9					
02 Macrolide antibiotics alone vs no antibiotics					
ORACLE II 2001	34/1600	10/519		100.0	1.10 [0.55, 2.22]
Subtotal (95% CI)	1600	519		100.0	1.10 [0.55, 2.22]
Total events: 34 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.27 p=0.8					
03 Macrolide and betalactam antibiotics vs no antibiotics					
ORACLE II 2001	34/1551	10/519		89.0	1.14 [0.57, 2.29]
Oyarzun 1998	1/78	2/90		11.0	0.58 [0.05, 6.24]
Subtotal (95% CI)	1629	609		100.0	1.08 [0.55, 2.10]
Total events: 35 (Treatment), 12 (Control)					
Test for heterogeneity chi-square=0.29 df=1 p=0.59 I^2 =0.0%					
Test for overall effect z=0.21 p=0.8					

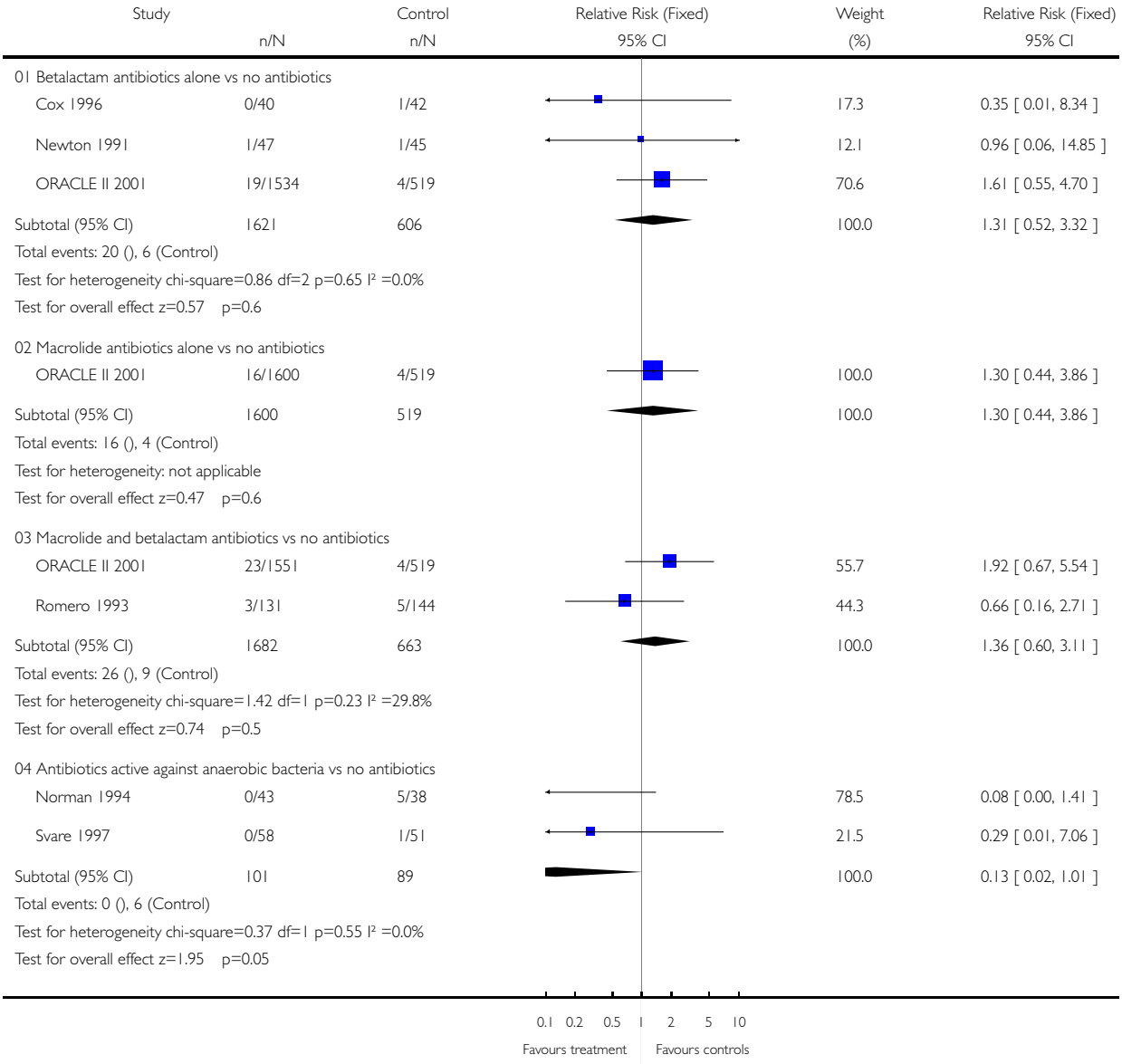


Analysis 02.20. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 20 Necrotising enterocolitis

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 20 Necrotising enterocolitis

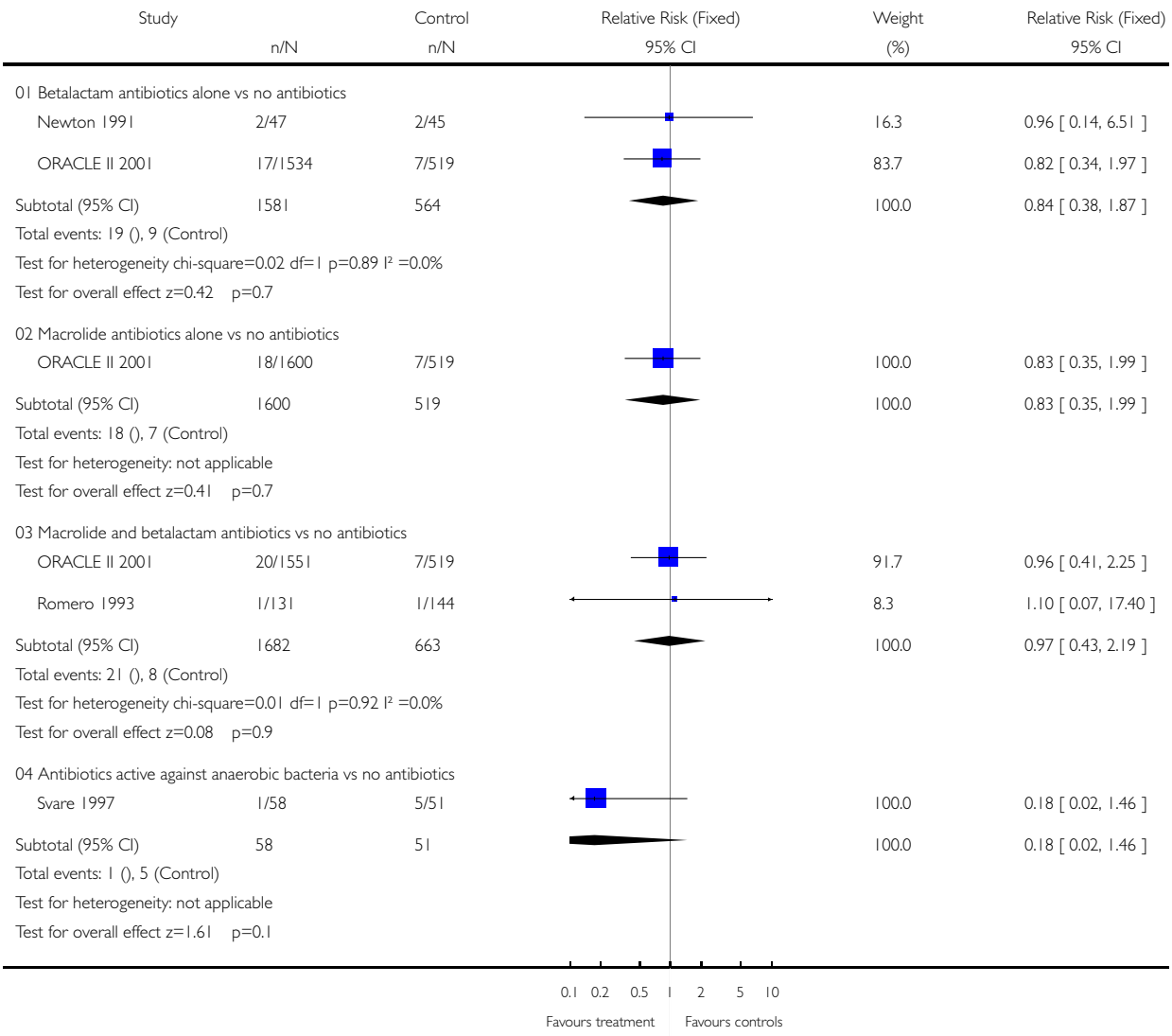


Analysis 02.21. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 21 Intraventricular haemorrhage

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 21 Intraventricular haemorrhage



Analysis 02.22. Comparison 02 Antibiotic therapy (subgrouped by type of antibiotic), Outcome 22 Major cerebral abnormality

Review: Prophylactic antibiotics for inhibiting preterm labour with intact membranes

Comparison: 02 Antibiotic therapy (subgrouped by type of antibiotic)

Outcome: 22 Major cerebral abnormality

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Betalactam antibiotics alone vs no antibiotics					
ORACLE II 2001	27/1534	10/519		100.0	0.91 [0.45, 1.87]
Subtotal (95% CI)	1534	519		100.0	0.91 [0.45, 1.87]
Total events: 27 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.25 p=0.8					
02 Macrolide antibiotics alone vs no antibiotics					
ORACLE II 2001	26/1600	10/519		100.0	0.84 [0.41, 1.74]
Subtotal (95% CI)	1600	519		100.0	0.84 [0.41, 1.74]
Total events: 26 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.46 p=0.6					
03 Macrolide and betalactam antibiotics vs no antibiotics					
ORACLE II 2001	34/1551	10/519		100.0	1.14 [0.57, 2.29]
Subtotal (95% CI)	1551	519		100.0	1.14 [0.57, 2.29]
Total events: 34 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.36 p=0.7