

Antibiotics and preterm birth

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Abstract: The risk of preterm labour in the presence of maternal infection is 30% to 50%. Antibiotics may induce a significant 12-20% reduction in neonatal infections following preterm rupture of the membranes and may prolong pregnancy significantly.

Methods: Aiming to evaluate the effectiveness of using antibiotics at any time during pregnancy to prevent preterm birth, Cochrane Library, MEDLINE, BIOSIS, EMBase, and CINAHL was searched and no language restrictions was applied. Reviews and RCT's assessing the use of antibiotics during pregnancy with outcome data on preterm labour and birth were selected.

Results: more than forty randomised controlled trials published between 1966 and the present day were included. They showed mild decrease in the incidence of preterm birth before 37 weeks with the use of antibiotics. Added to that, an average 34% less maternal infective morbidity with the use of antibiotics compared to placebo or no treatment for all antibiotic groups, all indications, and all gestational ages.

More than fifteen reviews published between 1993 and the present day were included, showing an average 30% decrease in the incidence of neonatal morbidity, 45% less maternal infective morbidity and an average 17% increase in the maternal adverse effects with the use of antibiotics compared to placebo or no treatment for all indications and all gestational ages.

In both trials and reviews, there is a noticeable increase in preterm births with the use of Metronidazole compared to placebo or no treatment

Conclusions: The result of this umbrella review does not support the use of antibiotics during pregnancy except when there is a clear evidence of infection with extreme caution, regular follow-ups and monitoring of the patient. In addition to, not supporting the use of metronidazole during pregnancy.

Keywords: Preterm labour, maternal infection, Umbrella review, Metronidazole, Antibiotics, Pregnancy, Neonatal morbidity.

I. Background

Preterm labour is a clinical syndrome characterized by regular uterine contractions, cervical ripening with progressive changes, and / or membrane rupture occurring after the gestational age of viability (20 weeks, 500 grams weight) and before 37 completed weeks (259 days) of pregnancy [1-4]. Preterm birth is one of the most important problems in medicine today with an alarming frequency and economic impact [5]. With an incidence in most developed countries of 5-10% prematurity has major neonatal implications and is the single most common cause of perinatal death with an overall neonatal mortality rate of 41/1000 live births [4]. In spite of the advances in obstetric care, the rate of prematurity has not decreased over the past 40 years. In fact, most studies in the industrialized countries states that preterm labour and delivery has increased slightly. Neonatal mortality rates have declined in recent years largely because of improved neonatal intensive care and better access to these services [3, 6]. With appropriate medical care, neonatal survival dramatically improves as gestational age progress, with over 50% of neonates surviving at 25 weeks gestation, and over 90% surviving by 28-29 weeks gestation. However, these premature infants are often left with long term neurological impairment [4, 6].

Short term morbidities associated with preterm delivery include respiratory distress syndrome, intraventricular haemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and patent ductus arteriosus. Long term morbidities include cerebral palsy, mental retardation, and retinopathy of prematurity [1, 6]. The risk for these morbidities is directly related to the gestational age and birth weight. For example, cerebral palsy, defined as non-progressive motor dysfunction with origin around the time of birth, complicates around 2/1000 of all live births. The relative risk for a preterm infant to develop cerebral palsy is 40 times that for term infants. Approximately 8-10% of surviving newborns weighing less than 1000 grams at birth will develop cerebral palsy. These infants also have substantial higher rates of mental retardation and visual disabilities, as well as neurobehavioral dysfunction and poor school performance [6]. Economically preterm birth account for 57% of the initial care of the USA neonates or nearly \$6 billion annually [5]. The lifetime costs per preterm birth have been estimated at £511,614 [7].

Preterm labour has 3 obstetrical antecedents:

- (1) Spontaneous preterm labour which accounts for 50% of cases.
- (2) Spontaneous membrane ruptures which almost always result in delivery within 1 week and account for 30% of cases.
- (3) Indicated preterm birth which is the decision of the obstetrician to induce labor or perform a caesarean section because of fetal or maternal indication, and this accounts for 20% of cases [5, 6, 8]. Infection has emerged during the last 20 years as an important and frequent mechanism of disease in preterm labour. Indeed, it is the only pathological process for which a firm causal link with prematurity has been established and for which a defined molecular pathophysiology is known. Moreover, fetal infection has been implicated in the genesis of fetal and neonatal injury leading to cerebral palsy and chronic lung disease [9, 10]. The following evidence implicates infection as the cause of almost 40-50% of preterm birth:
 - (1) Histological chorioamnionitis is consistently increased in cases of preterm birth.
 - (2) Clinical infection is increased in the infant and the mother after preterm birth.
 - (3) Several genital tract isolates are associated with preterm birth.
 - (4) 10-15% of amniotic fluid cultures from preterm labour patients are positive for microorganisms.
 - (5) Infection cause cytokines and prostaglandin production
 - (6) Bacteria and bacterial products induce preterm birth in animal models [11].

The infection may be either generalized or more commonly a local urogenital tract infection. Generalized infections (for example; pneumonia, pyelonephritis, malaria, typhoid fever, periodontal disease, etc.) has been associated with preterm labour and delivery. Yet, many of these conditions are rare in developed countries. Thus, the risk attributable to systemic maternal infection for prematurity is considered to be low [9, 12]. It has been estimated that at least 40% of all preterm births occur to mothers with intrauterine infection. Moreover, the lower the gestational age at delivery the greater the frequency of intrauterine infection (Figure 1) [2, 9].

Figure 1
Microorganisms isolated from the amniotic cavity
of patients with preterm labour

Family	Microorganisms
Genital Mycoplasma	Ureaplasma urealyticum Mycoplasma hominis
Aerobes	Group B streptococci Enterococci
Viridans streptococci	Gardnerella vaginalis Hemophilus influenza Pseudomonas species Lactobacilli Coliforms Corynebacterium Moraxella Staphylococci Acinetobacter wolffi Bacillus cereus Capnocytophaga species Diphtheroids Enterobacter cloacae
Anaerobes	Fusobacterium species Veillonella parvula Peptostreptococcus species Propionibacterium species Peptococcus species Bacteroides species Neisseria species
Yeasts	Candida species

Microorganisms may gain access to the amniotic cavity and the fetus through the following pathways:

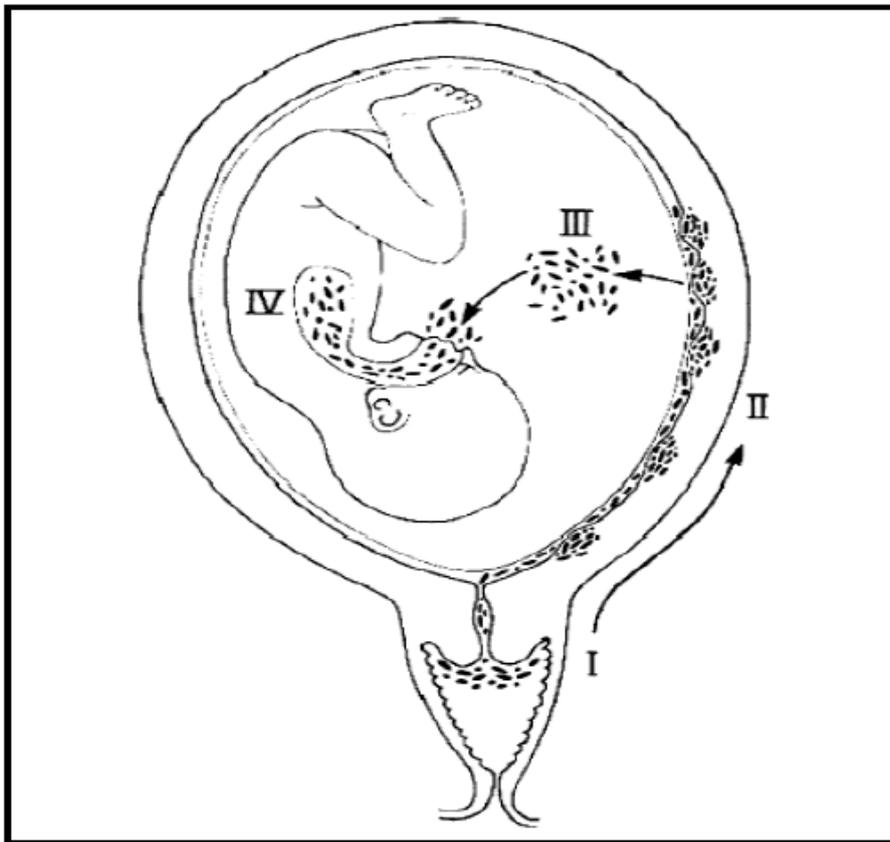
- (1) Ascending from the vagina and the cervix.
- (2) Haematogenous dissemination through the placenta.
- (3) Retrograde seeding from the peritoneal cavity through the fallopian tubes.
- (4) Accidental introduction at the time of invasive procedures, such as amniocentesis, percutaneous fetal blood sampling, chorionic villous sampling or shunting [2, 7, 9].

The most common pathway of intrauterine infection is the ascending route. Evidence in support of this includes:

- (1) Histological chorioamnionitis is more common and severe at the site of membrane rupture than in other locations, such as the placental chorionic plate or the umbilical cord.
- (2) In virtually all cases of congenital pneumonia chorioamnionitis is present.
- (3) Bacteria identified in cases of congenital infections are similar to those found in the lower genital tract.
- (4) In twin gestations, histological chorioamnionitis is more common in the firstborn twin and has not been demonstrated only in the second twin, as the membranes of the first twin are generally opposed to the cervix, this is taken as evidence in favour of an ascending infection[2, 9].

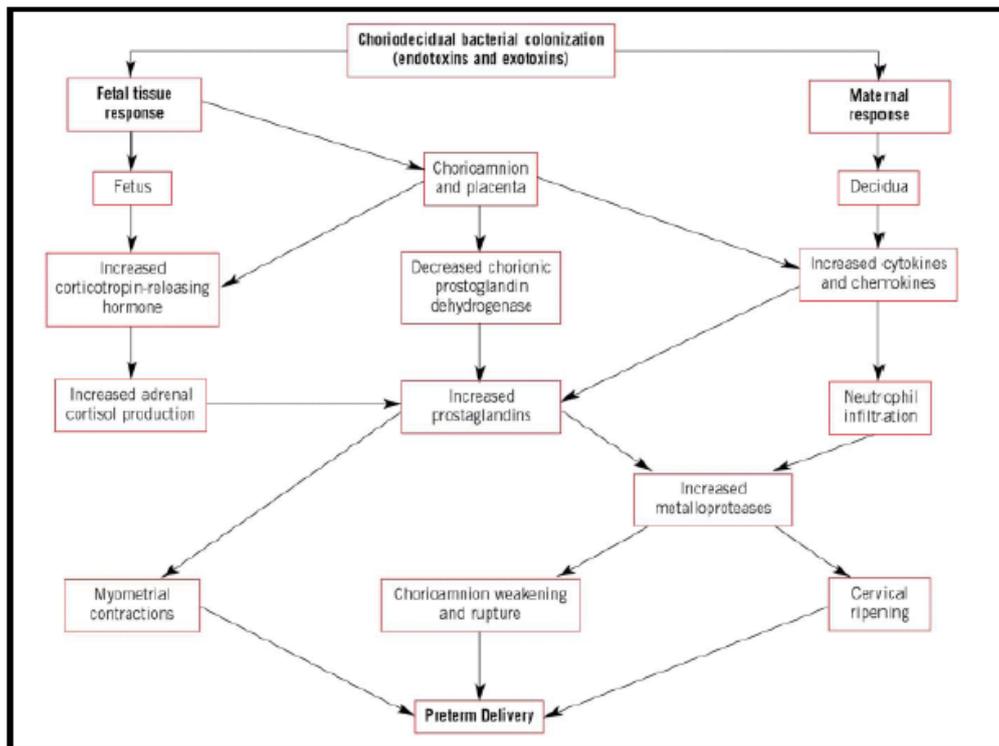
Ascending intrauterine infection is considered to have four stages (Figure 2).

Figure 2
Stages of ascending infection
 Adapted from Romero 1988 with permission



Stage I consists of a change in the vaginal/cervical microbial flora or the presence of pathologic organisms in the cervix, bacterial vaginosis may be an early manifestation of this initial stage. Once microorganisms gain access to the intrauterine cavity, they reside in the decidua (stage II). A localized inflammatory reaction leads to deciduitis. Microorganisms may then reside in the chorion and amnion. The infection may invade the fetal vessels (choriovasculitis) or proceed through the amnion (amnionitis) into the amniotic cavity, leading to microbial invasion of the amniotic cavity or an intra-amniotic infection (stage III). Rupture of the membranes is not a prerequisite for intraamniotic infection, as microorganisms are capable of crossing intact membranes. Once in the amniotic cavity, the bacteria may gain access to the fetus through various ports of entry (stage IV). Seeding from any of these sites to the fetal circulation may result in fetal bacteraemia and sepsis[2, 9, 13]. Stage IV is the most advanced and serious stage with overall mortality rate ranges between 25% and 90%[2, 9]. The mean rate of positive amniotic fluid cultures for microorganisms in patients with preterm labour and intact membranes is 12.8%, and those in patients with preterm premature rupture of membranes is 32.4%[9]. Microorganisms produce different bioactive substances helping them to induce preterm labour and the pathway can be summarized as follows (Figure 3).

Figure 3
Potential pathway for bacteria to initiate preterm labour
Adapted from Goldenberg 2000 with permission



The presence of sialidases facilitates bacterial attachment and break down of mucin while mucinases assist microbial ascent into the decidua (uterine tissue). Metalloproteolytic enzymes and other microbial bioactive substances act directly on cervical collagen and amnionchorion leading to premature cervical ripening and weakening the fetal membranes with subsequent preterm premature rupture of the membranes. Microorganisms stimulate the maternal monocytes and macrophages resulting in the production of phospholipase A2 which is an enzyme that liberate arachidonic acid from the phospholipids of the membranes leading to the synthesis of prostaglandins E2 and F2 α by the placental membranes. Similarly, protease toxins activate the deciduas and fetal membranes to produce Cytokines such as Tumour Necrosis Factor (TNF), Interleukin (IL1a, IL1b, IL6, IL8), and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF). In response to the activation of local inflammatory reaction Prostaglandins synthesis and release are stimulated leading to stimulate uterine contractions. Moreover, in infected foetuses, there is an increase in both fetal hypothalamic and placental production of corticotrophin releasing hormone leading to increase in fetal corticotrophin secretion, which in turn increases fetal adrenal cortisol production leading to increased production of prostaglandins. Also, when the fetus is infected, there is a high increase in the production of cytokines and marked decrease in the delivery time[6, 9, 13-15].

In pregnancy, the genital tract flora is more abundant with an increase in the number of aerobes and a decrease in the number of anaerobes. As pregnancy advances, the genital tract flora becomes progressively more benign, until at term, the upper vaginal flora is composed mainly of organisms of low virulence which threaten no significant hazard to the fetus[16]. Bacterial vaginosis is a polymicrobial condition caused by the increased prevalence of anaerobes including Gardnerella vaginalis, Bacteroides spp., and Mobiluncus and Mycoplasma hominis. There is an associated reduction in hydrogen peroxide producing Lactobacilli and a dramatic increase in the anaerobe to aerobe ratio.

The criteria used to diagnose bacterial vaginosis are:

- a. Vaginal PH >4.5.
- b. Grey homogenous vaginal discharge.
- c. Presence of clue cells in a wet mount preparation of vaginal fluid.
- d. Positive amine test in which a fishy odour is released after the addition of 10% potassium hydroxide (KOH) to the vaginal fluid[1, 3, 4, 10, 17, 18].

The current recommendation by the centre for disease control and prevention (CDC) {Atlanta, GA, USA} and the UK drug and therapeutics bulletin is to screen and treat bacterial vaginosis in high risk pregnancies [19].

Asymptomatic bacteriuria, defined as more than 100,000 colonies of a single bacterial species per ml of urine, cultured from midstream sample, is present in 2-7% of pregnant women. The most commonly isolated bacteria are *Escherichia coli*. Pregnancy does not increase the incidence of asymptomatic bacteriuria; however, pyelonephritis develops in 20-40% of pregnant women with untreated asymptomatic bacteriuria and if not treated will cause preterm labour[1, 20]. The centers for disease control and prevention (CDC) recommends that pregnant women with bacteriuria be treated at the time of diagnosis[1].

Because infection is clearly associated with preterm births, it has been logical to ask whether antibiotics can prevent prematurity. Antibiotics may induce a significant 12-20% reduction in neonatal infections following preterm rupture of the membranes and also may prolong pregnancy significantly [10, 12]. Moreover antibiotics may be used prophylactically for those women at high risk of preterm birth, or may be given as adjuvant therapy with tocolytics for those women who are in preterm labour[10].

II. Methods and Materials

1. Objectives

To evaluate the effectiveness of using antibiotics at any time during pregnancy to prevent preterm birth.

2. Criteria for considering studies for this review

2.1 Types of studies

All reviews assessing the use of antibiotics during pregnancy with outcome data on preterm labour and birth. In addition, all randomised clinical trials assessing the use of antibiotics during pregnancy with outcome data on preterm labour and birth.

2.2 Types of participants

Pregnant women.

2.3 Types of interventions

Antibiotics versus placebo, no treatment, or any other intervention to prevent preterm labour and birth.

2.4 Types of outcome measures

Main;

1. Preterm birth before 34 weeks.

2. Neonatal morbidity (includes; intraventricular haemorrhage, neonatal sepsis, pneumonia, ophthalmia neonatorum, and necrotizing enterocolitis).

Other outcomes of interest;

1. Preterm birth before 28 weeks.

2. Preterm birth before 37 weeks.

3. Maternal infective morbidity (includes; any infection diagnosed by fever, blood culture, urine culture, high vaginal swab, or any other method of diagnosis and classified by author as infective morbidity).

4. Maternal adverse effects (includes; palpitation, flushes, nausea, vomiting, diarrhoea, abdominal pain, rashes, headache, and dizziness).

3. Search strategy for identification of studies

The following databases was searched the Cochrane Library, MEDLINE, BIOSIS, EMBase, and CINAHL. Reviews and Randomised clinical trials identified through the searching activities and fit to the criteria for selecting studies mentioned above included. No language restrictions was applied.

4. Methods of the umbrella review

4.1 Methods for the reviews

Selection of reviews:

For inclusion all potential reviews identified as a result of the search strategy was studied.

Data extraction and management:

We designed a form to extract data from the reviews. Two review authors extracted the data using the agreed form. We resolved discrepancies through discussion.

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

Measures of treatment effect:

We carried out a statistical analysis using fixed effect meta-analysis for combining data in the absence of heterogeneity if reviews are sufficiently similar. Heterogeneity was found and explored by sensitivity analysis followed by random effect meta-analysis.

Assessment of methodological quality of included reviews:

Methods used in each review and its quality was described.

Validity and quality of each study was assessed using the following criteria;

(1) Quality assessment:

We designed a form to assess the quality of the reviews based on the QUOROM reviews quality checklist, with score of 1 point for each yes and 0 score for each no (with the exception of restriction of search where no scores and yes scores 0) the maximum score is 27. We assigned each review using the following criteria;

(A) Excellent quality: score of 24 or more (out of 27 points).

(B) Good quality: score of 20 to 23.

(C) Fair quality: score of 16 to 19.

(D) Poor quality: score of 15 or less.

(2) Presence of studies assessment: (as stated in the inclusion and exclusion criteria of the review e.g. randomised controlled trials, observational studies).

We assessed the presence of studies in each review using the following criteria:

(1) There are studies included in the review.

(2) There are no studies included in the review.

Assessment of heterogeneity:

Tests of heterogeneity was applied between reviews, using the I^2 statistic.

When high levels of heterogeneity among the reviews identified, (exceeding 50%); a random-effects meta-analysis was used as an overall summary.

Sensitivity analysis was carried out to explore the effect of reviews quality. This involved analysis based on an A, B, C, or D rating of the quality assessment and 1, or 2 in the presence of studies assessment. Reviews of poor quality (those rating D) or with no studies included (those rating 2) were excluded in the analysis, in order to assess for any substantive difference to the overall result.

4.2 Methods for the randomised clinical trials

Selection of studies

All potential studies we identify as a result of the search strategy was assessed for inclusion.

Data extraction and management

A form was designed to extract data.

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

Assessment of methodological quality of included studies

Methods used for generation of the randomisation sequence was described for each trial.

Validity of each study was assessed using the following criteria;

(1) Selection bias (randomisation and allocation concealment)

We assigned a quality score for each trial, using the following criteria:

(A) Adequate concealment of allocation: such as telephone randomisation, consecutively numbered sealed opaque envelopes;

(B) Unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;

(C) Inadequate concealment of allocation: such as open list of random number tables, use of case record numbers, dates of birth or days of the week.

(D) Randomisation not used.

(2) Attrition bias (loss of participants, e.g. withdrawals, dropouts, protocol deviations)

We assessed completeness to follow up using the following criteria:

(A) less than 5% loss of participants;

(B) 5% to 9.9% of loss of participants;

(C) 10% to 19.9% loss of participants;

(D) More than 20% loss of participants.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We assessed blinding using the following criteria:

(1) blinding of participants (yes/no/unclear);

(2) blinding of caregiver (yes/no/unclear);

(3) blinding of outcome assessment (yes/no/unclear).

Measures of treatment effect

Fixed-effect meta-analysis was used for combining data in the absence of significant heterogeneity if trials are sufficiently similar. Heterogeneity was found this was explored by sensitivity analysis followed by random effect meta-analysis.

Unit of analysis issues

Cluster-randomised trials was planned to be included in the analyses along with individually randomised trials. Their sample sizes were to be adjusted using the methods described in Gates 2005 using an estimate of the intraclass correlation coefficient (ICC) derived from the trial (if possible), or from another source. If ICC's from other sources are used, this was to be reported and sensitivity analyses conducted to investigate the effect of variation in the ICC. If we identify both cluster randomised trials and individually randomised trials, we plan to synthesise the relevant information. We consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

Dealing with missing data

Data on all participants with available data were analysed in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomised, and there is sufficient information in the trial report, we attempted to restore them to the correct group.

Assessment of heterogeneity

Tests of heterogeneity was applied between trials, using the I^2 statistic. We identified high levels of heterogeneity among the trials, (exceeding 50%); a random-effects meta-analysis was used as an overall summary.

Sensitivity analysis was carried out to explore the effect of trial quality. This involved analysis based on an A, B, C, or D rating of selection bias and attrition bias. Studies of poor quality were excluded in the analysis (those rating D) in order to assess for any substantive difference to the overall result.

Subgroup analyses

The following subgroup analyses was carried out;

- According to the indication for the use of the antibiotics;
 - Dental indications.
 - Genital infections including sexually transmitted diseases.
 - Urinary tract infections.
 - Other indications.
- According to the antibiotic group;
 - Penicillins and Cephalosporins.
 - Macrolide antibiotics.
 - Metronidazole.
 - Other antibiotics.
 - Combination of two or more of the groups mentioned above.
- According to the stage of pregnancy
 - Less than 16 weeks.
 - 16 weeks or more.
 - Mixed or not stated.

III. Results

56 Randomised controlled trials published between 1966 and the present day were considered for this umbrella review, 45 were included and 11 excluded due to being a subgroup analysis of one of the included trials, not using antibiotics in the trial, or not being a proper intention to treat analysis with the loss of more than 20% of the participants. For detailed characteristics of excluded trials see (Figure 4) 33 reviews published between 1993 and the present day were considered for this umbrella review, 18 were included and 14 excluded due to poor quality, synthesis of opinion based on different data and not on meta-analysis of studies, using outcomes not included in this umbrella review, or not including any studies. For detailed characteristics of excluded reviews see (Figure 4). One review is ongoing. For detailed characteristics of this ongoing review see (Figure 4).

1. Methodological quality of included studies

26 of the included trials were multicenter trials. Only one randomised trial used antibiotic control to compare the use of 3 antibiotics versus 2 antibiotics [Maberry 1991]. For detailed description of the included trials see (Figure 4).

4 of the included reviews were not Cochran reviews [Egarter 1996;Guise 2001;Leitich 2003;Turrentine 1995]. For detailed description of the included reviews see Figure 4.

Figure 4
Characteristics of excluded randomised controlled trials

Study	Reason for exclusion
Goldenberg 2001	This is a subgroup analysis of Carey 2000.
Gordon 1995	This is not a proper intention to treat analysis as 47% of the participants are lost to follow up, protocol violations, and withdrawals.
Jacobson 2001	This is not a proper intention to treat analysis as 30% of the participants are lost to follow up, protocol violations, and withdrawals.
Kigozi 2003	This is a subgroup analysis of Gray 2001.
Lopez 2002	There is no use of antibiotics in this trial, just periodontal treatment.
McCaul 1992	This is not a proper intention to treat analysis as 34% of the participants are lost to follow up, protocol violations, and withdrawals.
McGregor 1986	This is not a proper intention to treat analysis as 71% of the participants are lost to follow up, protocol violations, and withdrawals.
Paul 1998	This is not a proper intention to treat analysis as 26% of the participants are lost to follow up, protocol violations, and withdrawals.
Rosenstein 2000	This is a subgroup analysis of a cohort study.
Wing 1999	This is not a proper randomised controlled clinical trial, the same antibiotics used for the in patient group and the out patient group with no control group.

Table 1
Characteristics of excluded reviews

Review	Reason for exclusion
Carey 2001	Poor quality literature review.
Gibbs 1997	Poor quality literature review and synthesis of opinion based on different data and not on meta-analysis of studies.
Kirschbaum 1993	Poor quality review.
Klein 2004	Poor quality review.
Lamont 2003	Poor quality literature review and synthesis of opinion based on different data and not on meta-analysis of studies.
Lamont 2005	Poor quality literature review and synthesis of opinion based on different data and not on meta-analysis of studies.
Lewis 1995	Poor quality review.
Mertz 2001	Poor quality literature review and synthesis of opinion based on different observations and not on meta-analysis of studies.
Orton 2005	Excellent quality review, 6 randomised controlled trials included, with outcomes not included in this umbrella review (anaemia, abortion, neonatal jaundice, and treatment failure).
Peyron 1999	Good quality review, no included studies.
Tebes 2003	Poor quality literature review and synthesis of opinion based on different observations and not on meta-analysis of studies and with no differentiation between reviews and trials.
Thorp 2002	Faire quality review, 13 randomised controlled trials included, with outcomes not included in this umbrella review (days gained from entry to delivery and birth weight).
Walker 2001	Good quality review, no included studies.
Young 2001	Good quality review, 10 randomised controlled trials included, with one outcome not included in this umbrella review (persistent candidiasis).

2.Results of included randomised controlled trials meta-analysis:

There is an average 9% decrease in the incidence of preterm birth before 37 weeks with the use of antibiotics compared to placebo or no treatment for all antibiotic groups, all indications, and all gestational ages {Risk Ratio (RR) 0.93, 95% Confidence Interval (95%CI) 0.89, 0.98, and Probability (P) 0.003 for all antibiotics versus placebo or no treatment, RR 0.90, 95%CI 0.84, 0.97, P 0.006 for all indications versus placebo or no treatment, RR 0.90, 95%CI 0.84, 0.97, P 0.005 for all gestational ages versus placebo or no treatment}.

There is an average 34% less maternal infective morbidity with the use of antibiotics compared to placebo or no treatment for all antibiotic groups, all indications, and all gestational ages {RR 0.67, 95%CI 0.50, 0.90, P 0.009 for all antibiotics versus placebo or no treatment and all indications versus placebo or no treatment, RR 0.64, 95%CI 0.49, 0.85, P 0.002 for all gestational ages versus placebo or no treatment}.

For the rest of the outcomes in the subgroups analysis the results are not statistically significant.

Although not statistically significant, (Figure 5), there is a noticeable increase in preterm births with the use of Metronidazole compared to placebo or no treatment {RR 1.19, 95%CI 0.88, 1.61, P 0.26 before 37 weeks, RR 1.17, 95%CI 0.90, 1.51, P 0.24 before 34 weeks, RR 2.61, 95%CI 0.71, 9.62, P 0.15 before 28 weeks}.

Figure 5
Results of randomised controlled trials random effect meta-analysis

Comparison	RR	95% CI	P
All antibiotics versus placebo or no treatment			
Preterm birth before 34 weeks	1.03	1.00, 1.06	0.07
Neonatal morbidity	0.90	0.77, 1.05	0.18
Preterm birth before 28 weeks	0.96	0.83, 1.12	0.63
Preterm birth before 37 weeks	0.93	0.89, 0.98	0.003
Maternal infective morbidity	0.67	0.50, 0.90	0.009
Maternal adverse effects	1.24	0.96, 1.61	0.10
All antibiotics versus antibiotics control			
Preterm birth before 34 weeks	*	*	*
Neonatal morbidity	1.39	0.24, 8.06	0.71
Preterm birth before 28 weeks	*	*	*
Preterm birth before 37 weeks	0.93	0.37, 2.33	0.87
Maternal infective morbidity	1.86	0.67, 5.14	0.23
Maternal adverse effects	*	*	*
All indications versus placebo or no treatment			
Preterm birth before 34 weeks	1.03	0.99, 1.07	0.18
Neonatal morbidity	0.84	0.69, 1.04	0.10
Preterm birth before 28 weeks	1.02	0.80, 1.30	0.88
Preterm birth before 37 weeks	0.90	0.84, 0.97	0.006
Maternal infective morbidity	0.67	0.50, 0.90	0.009
Maternal adverse effects	1.24	0.96, 1.61	0.10
All indications versus antibiotic control			
Preterm birth before 34 weeks	*	*	*
Neonatal morbidity	1.39	0.24, 8.06	0.71
Preterm birth before 28 weeks	*	*	*
Preterm birth before 37 weeks	0.93	0.37, 2.33	0.87
Maternal infective morbidity	1.86	0.67, 5.14	0.23
Maternal adverse effects	*	*	*
All gestational ages versus placebo or no treatment			
Preterm birth before 34 weeks	1.03	0.99, 1.07	0.17
Neonatal morbidity	0.84	0.69, 1.04	0.10
Preterm birth before 28 weeks	1.02	0.80, 1.30	0.88
Preterm birth before 37 weeks	0.90	0.84, 0.97	0.005
Maternal infective morbidity	0.64	0.49, 0.85	0.002
Maternal adverse effects	1.17	0.85, 1.63	0.34
All gestational ages versus antibiotic control			
Preterm birth before 34 weeks	*	*	*
Neonatal morbidity	1.39	0.24, 8.06	0.71
Preterm birth before 28 weeks	*	*	*
Preterm birth before 37 weeks	0.93	0.37, 2.33	0.87
Maternal infective morbidity	1.86	0.67, 5.14	0.23
Maternal adverse effects	*	*	*

3.Results of included reviews meta-analysis:

There is an average 30% decrease in the incidence of neonatal morbidity with the use of antibiotics compared to placebo or no treatment for all antibiotic groups, all indications, and all gestational ages {RR 0.77, 95%CI 0.59, 1.00 for all antibiotics versus placebo or no treatment, RR 0.69, 95%CI 0.53, 0.89 for all indications versus placebo or no treatment, RR 0.64, 95%CI 0.51, 0.81 for all gestational ages versus placebo or no treatment}.

There is an average 45% less maternal infective morbidity with the use of antibiotics compared to placebo or no treatment for all antibiotic groups, all indications, and all gestational ages {RR 0.59, 95%CI 0.47, 0.70 for all antibiotics versus placebo or no treatment, RR 0.53, 95%CI 0.40, 0.70 for all indications versus placebo or no treatment, RR 0.53, 95%CI 0.40, 0.70 for all gestational ages versus placebo or no treatment}.

There is an average 17% increase in the maternal adverse effects with the use of antibiotics compared to placebo or no treatment for all indications, and all gestational ages {RR 1.17, 95%CI 1.00, 1.37 for all indications versus placebo or no treatment and all gestational ages versus placebo or no treatment}. In the case of all antibiotics versus placebo or no treatment, maternal adverse effects increased with antibiotics to 16% but did not reach statistical significance {RR 1.16, 95%CI 1.00, 1.35, P 0.06}.

For the rest of the outcomes in the subgroups analysis the results are not statistically significant.

Although not statistically significant, (Figure 6), there is a noticeable increase in preterm births with the use of Metronidazole compared to placebo or no treatment {RR 1.02, 95%CI 0.89, 1.17, P 0.81 before 37 weeks, RR 1.07, 95%CI 0.79, 1.45, P 0.66 before 34 weeks, no studies compared metronidazole to placebo or no treatment before 28 weeks}.

Figure 6
Results of reviews random effect meta-analysis

Comparison	RR	95% CI	P
All antibiotics versus placebo or no treatment			
Preterm birth before 34 weeks	1.07	0.79, 1.45	0.66
Neonatal morbidity	0.77	0.59, 1.00	0.05
Preterm birth before 28 weeks	*	*	*
Preterm birth before 37 weeks	0.95	0.89, 1.02	0.15
Maternal infective morbidity	0.59	0.47, 0.74	<0.00001
Maternal adverse effects	1.16	1.00, 1.35	0.06
All antibiotics versus antibiotics control			
Preterm birth before 34 weeks	*	*	*
Neonatal morbidity	0.88	0.50, 1.53	0.64
Preterm birth before 28 weeks	*	*	*
Preterm birth before 37 weeks	1.00	0.98, 1.02	1.00
Maternal infective morbidity	1.00	0.89, 1.12	0.98
Maternal adverse effects	0.57	0.14, 2.40	0.45
All indications versus placebo or no treatment			
Preterm birth before 34 weeks	1.07	0.79, 1.45	0.66
Neonatal morbidity	0.69	0.53, 0.89	0.005
Preterm birth before 28 weeks	*	*	*
Preterm birth before 37 weeks	0.95	0.88, 1.04	0.27
Maternal infective morbidity	0.53	0.40, 0.70	<0.00001
Maternal adverse effects	1.17	1.00, 1.37	0.04
All indications versus antibiotic control			
Preterm birth before 34 weeks	*	*	*
Neonatal morbidity	0.62	0.29, 1.35	0.23
Preterm birth before 28 weeks	*	*	*
Preterm birth before 37 weeks	0.99	0.96, 1.03	0.73

Maternal infective morbidity	1.01	0.68, 1.51	0.97
Maternal adverse effects	0.27	0.16, 0.46	<0.00001
All gestational ages versus placebo or no treatment			
Preterm birth before 34 weeks	1.07	0.79, 1.45	0.66
Neonatal morbidity	0.64	0.51, 0.81	0.0003
Preterm birth before 28 weeks	*	*	*
Preterm birth before 37 weeks	0.95	0.88, 1.04	0.27
Maternal infective morbidity	0.53	0.40, 0.70	<0.00001
Maternal adverse effects	1.17	1.00, 1.37	0.04
All gestational ages versus antibiotic control			
Preterm birth before 34 weeks	*	*	*
Neonatal morbidity	0.62	0.29, 1.35	0.23
Preterm birth before 28 weeks	*	*	*
Preterm birth before 37 weeks	0.99	0.96, 1.03	0.73
Maternal infective morbidity	1.01	0.68, 1.51	0.97
Maternal adverse effects	0.27	0.16, 0.46	<0.00001

IV. Discussion

By comparing the above results, we can see that regardless of the antibiotic group, indication, and gestational age there is 39% decrease in the maternal infective morbidity with the use of antibiotics during pregnancy compared to placebo or no treatment, which is accompanied by 17% increase in the maternal adverse effects, Figure 7 and 8.

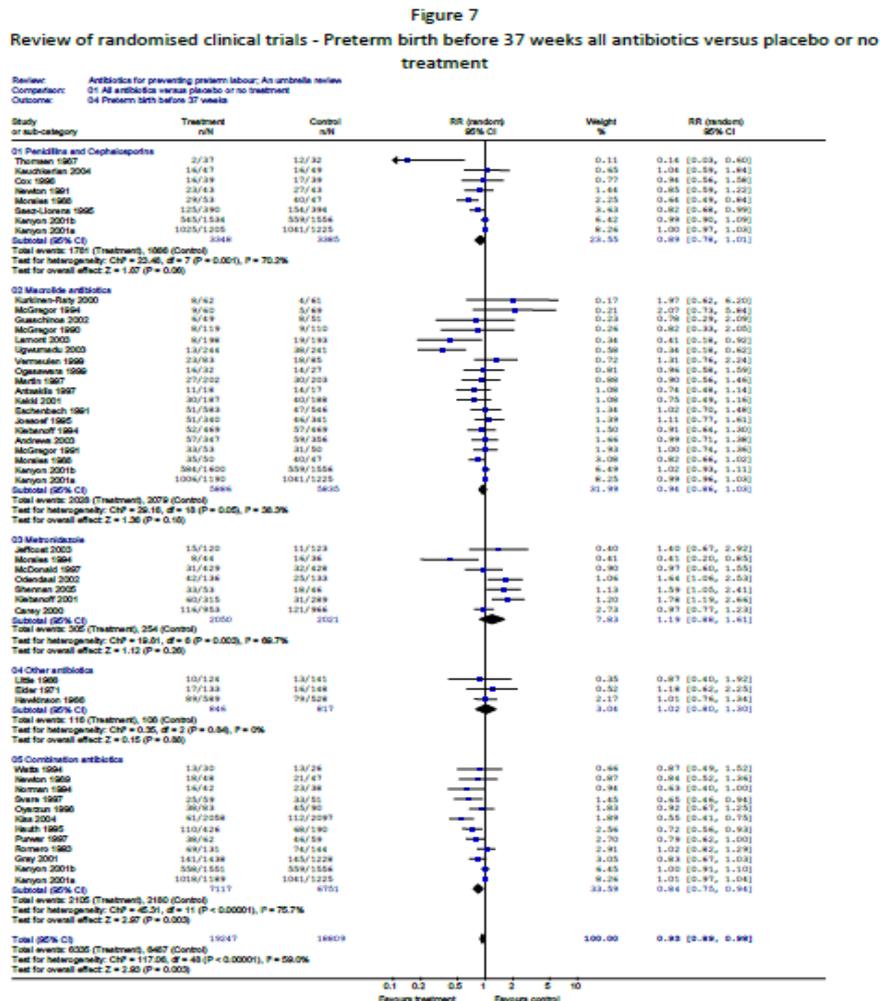
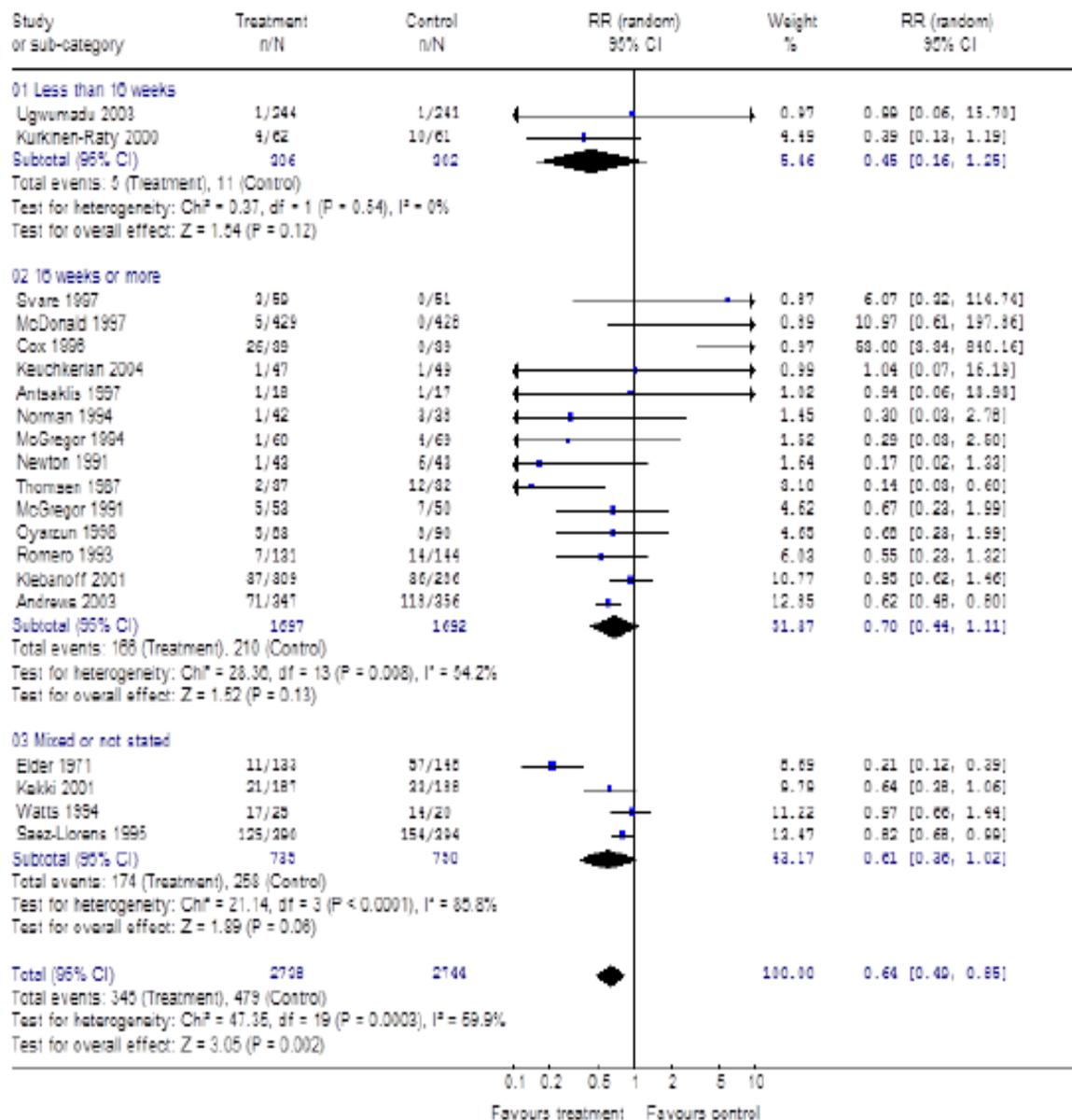


Figure 8

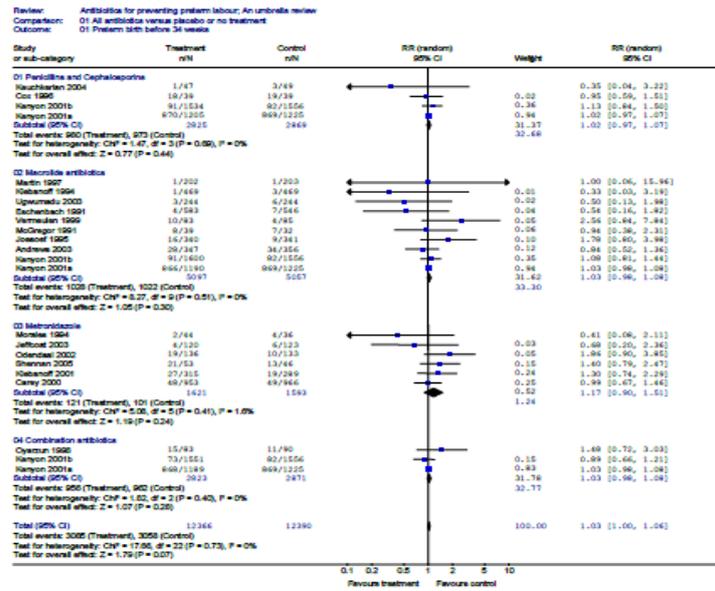
Review of randomised clinical trials - Maternal infective morbidity all gestational ages versus placebo or no treatment

Review: Antibiotics for preventing preterm labour; An umbrella review
 Comparison: 05 All gestational ages versus placebo or no treatment
 Outcome: 05 Maternal infective morbidity



Again regardless of the antibiotic group, indication, and gestational age there is 9% decrease in the incidence of preterm birth before 37 weeks with the use of antibiotics compared to placebo or no treatment, but there is no significant effect for antibiotics use to prevent preterm birth before 34 weeks which is more important clinically Figure 9.

Figure 9
Review of randomised clinical trials - Preterm birth before 34 weeks all antibiotics versus placebo or no treatment



There is 30% decrease in the incidence of neonatal morbidity with the use of antibiotics compared to placebo or no treatment regardless of the antibiotic group, indication, and gestational age. This Decrease in neonatal morbidity is noticed in infants up to the age of 6 weeks, but recent study [Kenyon 2008b] followed up the long-term effects on children after exposure to antibiotics that were given to their mothers when they were in spontaneous preterm labour with intact membranes and without overt signs of clinical infection, in this follow up study they found that the prescription of antibiotics for these women was associated with an increase in functional impairment among their children at 7 years of age and The risk of cerebralpalsy was increased. There is a positive association between using metronidazole and increase the incidence of preterm labour this results supports the previous findings by other researchers [Carey 2000, Kigozi 2003, Klebanoff 2001, Shennan 2005, Simcox 2007] Figure 10 and 11.

Figure 10
Review of randomised clinical trials - Preterm birth before 28 weeks all antibiotics versus placebo or no treatment

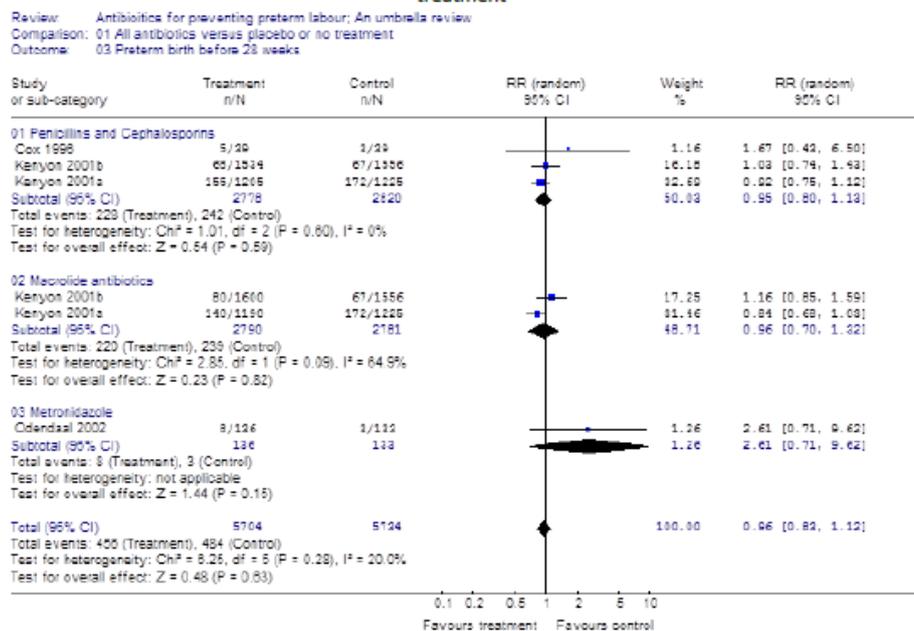
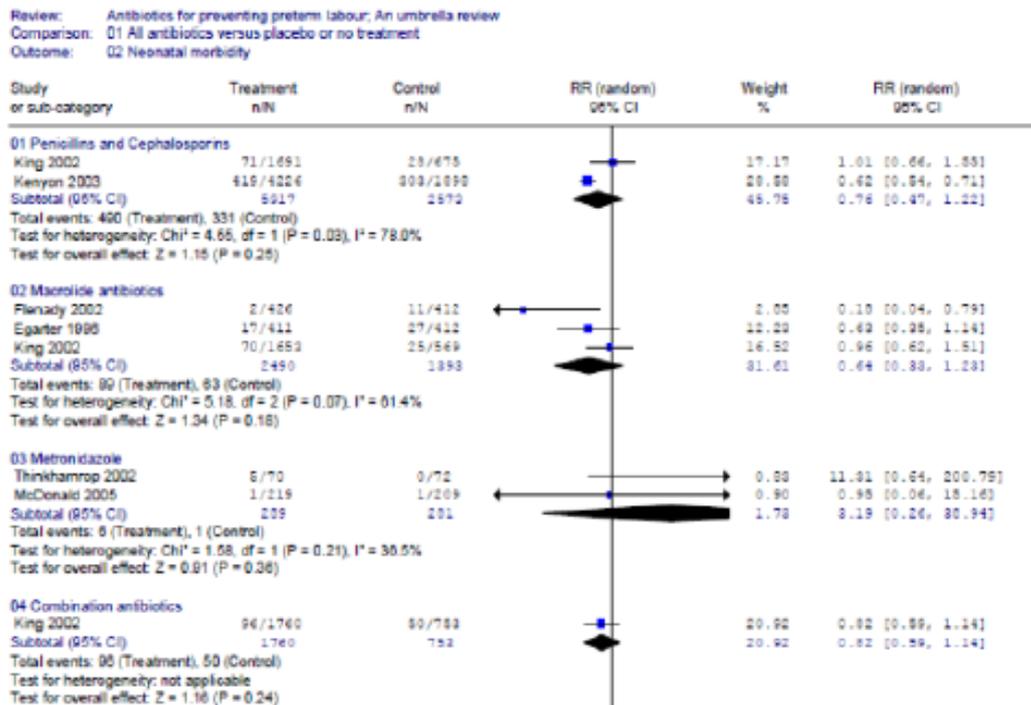


Figure 11

Review of reviews – Neonatal morbidity all antibiotics versus placebo or no treatment



V. Conclusion

The results of this umbrella review prove that the use of antibiotics during pregnancy have no effect in preventing preterm labour before 34 weeks, but also may increase the risk of preterm labour specially metronidazole, and this is accompanied by an increase in the maternal adverse effects including palpitation, flushes, nausea, vomiting, diarrhoea, abdominal pain, rashes, headache, and dizziness.

Implications for practice

The result of this umbrella review does not support the use of antibiotics during pregnancy except when there is a clear evidence of infection with extreme caution, regular follow ups and monitoring of the patient. We do not support the use of metronidazole during pregnancy.

Implications for research

There is a real need for a randomised controlled trial designed to test antibiotics versus antibiotics, the trials should be appropriately sized and Outcomes should include preterm labour and birth at clinically significant gestational ages, neonatal and maternal infective morbidity and adverse effects.

Effects of metronidazole on pregnancy needs further investigation.

Long term effects of antibiotics on infants and children needs further investigation.

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