Intrapartum antibiotics for known maternal Group B streptococcal colonization (Review)

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[Intervention Review]

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Cochrane Database of Systematic Reviews, Issue 3, 2009 (Status in this issue: **New**)

DOI: 10.1002/14651858.CD007467.pub2
This version first published online: 8 July 2009 in Issue 3, 2009.
Last assessed as up-to-date: 29 April 2009. (Help document - Dates and Statuses explained)

This record should be cited as: Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. **Cochrane Database of Systematic Reviews** 2009, Issue 3. Art. No.: CD007467. DOI: 10.1002/14651858.CD007467.pub2.

ABSTRACT

Background

Maternal colonization with group B **streptococcus** (GBS) during pregnancy increases the risk of neonatal infection by vertical transmission. Administration of intrapartum antibiotic prophylaxis (IAP) during labor has been associated with a reduction in early onset GBS disease (EOGBSD). However, treating all colonized women during labor exposes a large number of women and infants to possible adverse effects without benefit.

Objectives

To assess the effect of IAP for maternal GBS colonization on neonatal: 1) all cause mortality and 2) morbidity from proven and probable EOGBSD, late onset GBS disease (LOD), maternal infectious outcomes and allergic reactions to antibiotics.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (April 2009).

Selection criteria

Randomized trials assessing the impact of maternal IAP on neonatal GBS infections were included.

Data collection and analysis

We independently assessed eligibility and quality of the studies.

Main results

Three trials (involving 852 women) evaluating the effects of IAP versus no treatment were included. The risk of bias was high. The use of IAP did not significantly reduce the incidence of all cause mortality, mortality from GBS infection or from infections caused by bacteria other than GBS. The incidence of early GBS infection was reduced with IAP compared to no treatment (risk ratio 0.17, 95% confidence interval (CI) 0.04 to 0.74, three trials, 488 infants; risk difference -0.04, 95% CI -0.07 to -0.01; number needed to treat to

benefit 25, 95% CI 14 to 100, I^2 0%). The incidence of LOD or sepsis from organisms other than GBS and puerperal infection was not significantly different between groups.

One trial (involving 352 women) compared intrapartum ampicillin versus penicillin and reported no significant difference in neonatal or maternal outcomes.

Authors' conclusions

Intrapartum antibiotic prophylaxis appeared to reduce EOGBSD, but this result may well be a result of bias as we found a high risk of bias for one or more key domains in the study methodology and execution. There is lack of evidence from well designed and conducted trials to recommend IAP to reduce neonatal EOGBSD.

Ideally the effectiveness of IAP to reduce neonatal GBS infections should be studied in adequately sized double-blind controlled trials. The opportunity to conduct such trials has likely been lost, as practice guidelines (albeit without good evidence) have been introduced in many jurisdictions.

PLAIN LANGUAGE SUMMARY

Intrapartum antibiotics for known maternal Group B streptococcal colonization

Women, men and children of all ages can be colonized with Group B **streptococcus** (GBS) bacteria without having any symptoms; bacteria are particularly found in the gastrointestinal tract, vagina and urethra. This is the situation in both developed and developing countries. About one in 2000 newborn babies have Group B **streptococcus** bacterial infections, usually evident as respiratory disease, general sepsis, or meningitis within the first week. The baby contracts the infection from the mother during labor. Giving the mother an antibiotic directly into a vein during labor causes bacterial counts to fall rapidly, which suggests possible benefits but pregnant women need to be screened. Many countries have guidelines on screening for GBS in pregnancy and treatment with antibiotics. Some risk factors for an affected baby are preterm and low birthweight; prolonged labor; prolonged rupture of the membranes (more than 12 hours); severe changes in fetal heart rate during the first stage of labor; and gestational diabetes. Very few of the women in labor who are GBS positive give birth to babies who are infected with GBS and antibiotics can have harmful effects such as severe maternal allergic reactions, increase in drug-resistant organisms and exposure of newborn infants to resistant bacteria, and postnatal maternal and neonatal yeast infections.

This review finds that giving antibiotics is not supported by conclusive evidence. The review identified four trials involving 852 GBS positive women. Three trials, which were around 20 years old, compared ampicillin or penicillin to no treatment and found no clear differences in newborn deaths although the occurrence of early GBS infection in the newborn was reduced with antibiotics. The antibiotics ampicillin and penicillin were no different from each other in one trial with 352 GBS positive women. All cases of perinatal GBS infections are unlikely to be prevented even if an effective vaccine is developed.

BACKGROUND

Description of the condition

Historical background

The etiology of neonatal sepsis varies with geographical location and changes over time (Nyhan 1958; Ohlsson 1986). Although, asymptomatic vaginal carriage of Group B haemolytic **streptococci** (GBS) was described in 1935 (Lancefield 1935), the first report of GBS sepsis in a neonate did not appear until 1964 (Eickhoff 1964).

Since the 1970s, GBS is one of the most common causes of neonatal infectious morbidity and mortality in the US (McCracken 1973), Canada (Allardice 1982), UK (Lloyd 1976), other European countries (Bergqvist 1974; Cayeux 1972; Schröder 1979; Vesikari 1989) and Australia (Fliegner 1990).

GBS causes significant maternal and perinatal morbidity (Institute of Medicine 1985), asymptomatic bacteriuria in pregnancy (Hastings 1986) as well as urinary tract and other infections in the adult non-pregnant population (Ho 2006).

In 1990, the Group B Strep Association, an advocacy group, was formed by parents (Group B Strep Association 2008). Broad me-

dia coverage followed and in 1992 the first guidelines for GBS prevention were published in the US (AAP 1992; ACOG 1992).

Maternal colonization with Group B *streptococci* and transmission

The gastrointestinal tract, vagina and urethra serve as reservoirs for GBS. An overview in 1992, reported maternal colonization rates from 19 studies (1980 to 1991) ranging from 1.6% in Israel, to 28% in England. The transmission rate for GBS colonization from mother to infant varied from 35% in England, to 69% in Brazil, with the incidence of early onset GBS disease varying from 0.2 per 1000 livebirths in Israel, to 5.0 per 1000 livebirths in the US (Ohlsson 1992). Stoll (Stoll 1998) reviewed maternal GBS colonization rates in developing countries where the overall colonization rate was 12.7% (34 studies with 7730 women). Among only those studies in which the methods to ascertain colonization was adequate, the colonization rate was 17.8% (675 of 3801 women). The colonization rates were; in the Middle East/North Africa, 22%; Asia/Pacific, 19%; Sub-Saharan Africa, 19%; India/Pakistan, 12%; and the Americas, 14% respectively. The authors concluded that the range of colonization reported from developing countries is similar to that identified in population studies in the United States (Stoll 1998). There is likely an increasing rate of GBS neonatal infections in developing countries (Osrin 2004).

A recent systematic review on the prevalence of maternal GBS colonization in European countries, identified 21 studies published between 1996 and 2006, that reported on 24,093 women (Barcaite 2008). Among the studies, GBS vaginal colonization rates ranged from 6.5% to 36%, with one third of the studies reporting rates of 20% or greater. The carriage rates varied with Eastern Europe 19.7% to 29.3%, Western Europe 11% to 21%, Scandinavia 24.3% to 36%, and Southern Europe 6.5% to 32% (Barcaite 2008).

Early onset GBS neonatal disease (EOD)

Early onset disease (EOD) occurs, by definition, during the first seven days of life, with the vast majority of cases (approximately 90%) present during the first 24 hours of life (Garland 1991; Yagupsky 1991). Neonates with EOD present with respiratory disease (54%), sepsis without focus (27%) and meningitis (15%) (Yagupsky 1991). Risk factors for EOD include: GBS bacteriuria during pregnancy; gestational age less than 37 weeks (Håkansson 2006); previous infant with invasive GBS disease (Schrag 2002); preterm labor/delivery (Dillon 1987; Garland 1991; Yagupsky 1991); birthweight less than 2500 g (Baker 1973; Dillon 1987; Schuchat 1990; Yagupsky 1991); prolonged labor (Dillon 1987); prelabor rupture of the membranes (Dillon 1987; Garland 1991); prolonged membrane rupture (more than 12 hours) (Baker 1973; Garland 1991); black race (Schuchat 1990); teenage mother (Schuchat 1990); previous miscarriage (Schuchat 1990); maternal infection including chorioamnionitis (Dillon 1987); bacteraemia (Dillon 1987); sepsis (Garland 1991); urinary tract infection (Dillon 1987; Wood 1981); maternal fever in labor (Dillon 1987); gestational age more than 42 weeks (Christensen 1983); severe changes in fetal heart rate during the first stage of labor (Christensen 1983) and gestational diabetes (Håkansson 2006).

A number of infants born to GBS negative mothers, but infected with GBS at birth, have been reported (Hamada 2008; Mereghetti 2007). This may be due to false negative tests in the mother or to a change in GBS colonization status between the time the test was performed and the time when the mother gave birth. False negative culture results may be due to inappropriate sampling methods, the choice of media the sample was plated on, or the method of transporting the sample to the laboratory. In a recent study from two tertiary perinatal centres in Canada, antepartum or intrapartum predisposing factors for neonatal GBS infection were recognized in 62% of cases (Hamada 2008). In the same study, all infants born at term survived, but the mortality rate for preterm neonates with early symptomatic disease (and who presented with shock and thrombocytopenia) was 6% (Hamada 2008).

Late onset GBS disease (LOD)

Late onset disease (LOD) occurs beyond seven days of life and can develop up to three months of age (Yagupsky 1991). Risk factors for late onset disease include non-white race and preterm birth (Yagupsky 1991). Neonates with LOD present with sepsis (46%), meningitis (37%), urinary tract infection (7%), osteoarthritis (6%), respiratory disease (4%) and cellulitis (4%) (Yagupsky 1991).

The organism and its detection

Streptococci are Gram-positive cocci that occur in pairs or chains (Lancefield 1933).They are divided into three groups by the type of haemolysis on blood agar plates: -haemolytic, -haemolytic or -haemolytic **streptococci**. GBS is a -haemolytic **streptococcus**. Serologic grouping is based on the polysaccharide capsule in GBS. GBS strains isolated in the 1970s were serotypes I, II, and III; but new serotypes (IV, V, VI, VIII) have since emerged. Recently a proposed IX serotype was isolated (Slotved 2007).

Polymerase chain reaction (PCR) and optical immunoassay are candidates for rapid near patient intrapartum GBS testing to determine whether women in labor are colonized with GBS (Gavino 2007; Honest 2006).

Burden of illness

In the US in the early 1980s, the total number of maternal GBS infections was estimated to be 47,885 and the number of neonatal cases 11,074 (7198 with EOD). The total cost of disease burden was estimated at $726.8 million (US) per year. The incidence of EOD in the UK, in the absence of systematic screening or widespread use of intrapartum antibiotics, was 0.5 per 1000 births

with vaginal carriage rates comparable to those in the US (RCOG 2003). In a population-based cohort in Sweden (1997 to 2001), the incidence of EOD was 0.4 per 1000 live births with the total burden of illness of early onset GBS morbidity approximately three times higher (Håkansson 2006). A considerable number of infants are diagnosed with probable early-onset GBS neonatal sepsis possibly as a result of maternal treatment intrapartum that inhibits growth in blood and cerebrospinal fluid but does not alleviate clinical symptoms, signs, nor death (Carbonell-Estrany 2008).

Preventive measures

Several GBS vaccine candidates have been developed against the nine currently identified GBS serotypes (Johri 2006) and a type III conjugate vaccine has been found to be safe and immunogenic in pregnant women (Johri 2006). Further advances in GBS vaccine development are likely through combining genomics with newer proteomic technologies (Johri 2006). The projected health benefits of maternal GBS vaccination in the era of chemoprophylaxis could be considerable (Sinha 2005).

Chlorhexidine vaginal treatment, with or without neonatal wash, reduced GBS bacterial load but showed no impact on EOD (Stade 2004). A systematic review including non-randomized studies suggests that important reductions in maternal and neonatal sepsis (not restricted to GBS as a cause) in developing countries may be achieved using this method (Goldenberg 2006).

Induction of labor with intravenous (IV) oxytocin may be preferable for GBS positive women with prelabor rupture of membranes at term as infections are reduced (Hannah 1997).

To date, the most commonly used prevention intervention is intrapartum chemoprophylaxis with antibiotics to mothers with known GBS colonization. This review will focus on this aspect of prevention of GBS neonatal disease. To date four approaches have been recommended for the prevention of neonatal GBS infections: a risk based strategy; a screening (vaginal/rectal GBS cultures) based strategy; a combined risk/screening-based strategy and a combined risk/screening-based strategy using the PCR test (Van den Akker 2005). This topic has been previously reviewed (Shah 2001), but deserves to be updated in a separate review using Cochrane guidelines.

Guidelines for prevention of GBS neonatal infections

In 1992, the first guidelines for GBS prevention were published in the US (AAP 1992; ACOG 1992). Since then numerous guidelines with different recommendations have been published by various organizations (AAP 1997; ACOG 1996; CDC 1996; CDC 2002; RCOG 2003; Shah 2001; SOGC 1994; SOGC 1997; SOGC 2004).

Although these current guidelines are based on studies of poor quality (Ohlsson 1994), there seems to be a temporary association between the introduction of guidelines and a decline in the GBS EOD rate (CDC 2005; CDC 2007; Schrag 2002). However, there has been no reduction in LOD GBS disease in infants (CDC 2007). Mortality has decreased. The same literature has been interpreted differently by different professional organizations. All cases of EOD cannot be prevented.

Description of the intervention

In 1976, chemoprophylaxis was first proposed for reducing maternal GBS colonization in labor to reduce neonatal disease (Ablow 1976). Non-randomized studies showed that intravenous ampicillin given during labor to GBS positive women could significantly reduce neonatal GBS colonization, and a non-significant reduction in GBS neonatal invasive disease was reported (Allardice 1982; Yow 1979). Currently in the US, penicillin is the drug of choice for intrapartum prophylaxis given every four hours intravenously until the baby is born (CDC 2002).

Adverse effects

Severe allergic reaction to antibiotics has been reported among mothers giving birth (Berthier 2007; Jao 2006). The incidence of postnatal maternal and neonatal yeast infections may increase with the use of intrapartum antibiotics (Dinsmoor 2005). There is a growing concern about antibiotic resistance to erythromycin (3.8% to 21.2%) and clindamycin (2.7% to 20%) (Barcaite 2008). Intrapartum antibiotic prophylaxis may increase exposure of neonates to ampicillin resistant **Enterobacteriaceae** (Edwards 2002).

How the intervention might work

Vaginal GBS colony counts fall rapidly after intrapartum penicillin-G administration which may, to some degree, explain the possible effectiveness of chemoprophylaxis (McNanley 2007).

Why it is important to do this review

It is important to know if intrapartum antibiotics do more good than harm in trying to reduce mortality and morbidity from neonatal GBS infections. Most women colonized with GBS are asymptomatic, so screening is necessary if these women are to be identified. However, of the women in labor who are GBS positive, very few will give birth to babies who are infected with GBS. Hence, giving IV antibiotics to all women in labor who are GBS positive will put a large number of women and babies at risk of adverse effects unnecessarily. These adverse effects include potentially fatal anaphylaxis, increase in drug-resistant organisms and the medicalization of labor and the neonatal period (RCOG 2003).

A critical review of randomized controlled trials of intrapartum chemoprophylaxis of perinatal GBS infections identified numerous methodological flaws (Ohlsson 1994). Whether we are using

the optimal strategy for GBS management in pregnancy has been questioned (Yodin 2006). A Cochrane review adopting high-quality methodology is, therefore, justified.

OBJECTIVES

Primary objective

- To assess the effect of intrapartum antibiotics for maternal Group B haemolytic streptococci (GBS) colonization on mortality from any cause, from GBS infection and from organisms other than GBS.

Secondary objectives

- To assess the effect of intrapartum antibiotics for maternal GBS colonization on neonatal morbidity from early onset neonatal GBS infection (as defined under outcomes below).
- To assess the effect of intrapartum antibiotics for maternal GBS colonization on probable early (postnatal age less than seven days) neonatal GBS infection.
- To assess the effect of intrapartum antibiotics for maternal GBS colonization on late onset GBS sepsis (sepsis due to GBS in an infant at least seven days old).
- To assess the effect of intrapartum antibiotics for maternal GBS colonization on long-term child development (motor and cognitive).
- To assess the effect of intrapartum antibiotics for maternal GBS colonization on maternal outcomes including; chorioamnionitis, sepsis, urinary tract infection, hospital stay and allergic reactions to antibiotics.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized trials assessing the impact of intrapartum antibiotics on neonatal GBS colonization and infections.

Types of participants

Mothers known to be colonized with GBS in the vaginal/intestinal tract and/or the urinary tract at any time during the pregnancy and at < 35 weeks and ≥ 35 weeks' gestation. Mothers giving birth vaginally or by caesarean section were included.

Types of interventions

Intervention

Intrapartum administration of antibiotics to mothers known to be GBS positive (by culture or rapid detection test) from a vaginal or rectal swab (or both) or from urine.

Comparison

Placebo or no treatment to mothers known to be GBS positive (by culture or rapid detection test) from a vaginal or rectal swab (or both) or from urine. In a deviation from our protocol we decided to include studies that compared the effectiveness of one antibiotic versus another.

Types of outcome measures

Primary outcomes

Neonatal

All cause mortality
Mortality from early (postnatal age less than seven days) onset culture positive neonatal GBS infection including one or more of the following conditions.
a) Sepsis - defined as symptoms and signs of sepsis and a bacterial culture positive for GBS (obtained in a sterile manner from normally sterile body fluids such as blood, cerebrospinal fluid or urine, or culture from internal organs at autopsy).
b) Pneumonia in the neonate (postnatal age less than seven days) - defined as symptoms and signs and radiographic findings consistent with pneumonia and positive culture for GBS (obtained from tracheal aspirate or by culture of lung tissue at autopsy).
Mortality from infections (as per a and b above) caused by bacteria other than GBS.

Secondary outcomes

Neonatal

Early (postnatal age less than seven days) GBS infection in a neonate - defined as symptoms and signs of sepsis or pneumonia in a neonate born to a GBS positive mother, and positive GBS bacterial cultures (from normally sterile body fluids obtained from the neonate).
Probable early (postnatal age less than seven days) GBS infection in a neonate - defined as symptoms and signs of sepsis or pneumonia

in a neonate born to a GBS positive mother, and bacterial cultures from normally sterile body fluids obtained from the neonate that were negative for GBS.
Late onset GBS sepsis - sepsis due to GBS in an infant at least seven days old.
Neonatal sepsis, meningitis, urinary tract infection or pneumonia due to bacterial organisms other than GBS, to drug resistant bacteria and to fungi.
Initial hospital stay.
Long-term follow-up assessments of infants, at an age of 12 months or later, using a validated assessment tool for motor or cognitive functions (or both).

Maternal

1. Chorioamnionitis defined as a temperature of more than 38^0C on two occasions in labor with uterine tenderness or chorioamnionitis diagnosed on placental histopathology.
2. Sepsis in the peri/postpartum period.
3. Urinary tract infection with any bacteria in the peri/postpartum period.
4. Hospital stay
5. Allergic reactions to antibiotics.
6. Puerperal infection defined according to clinical criteria - uterine tenderness, uterine subinvolution and fever in the absence of any other known cause of infection in the postpartum period. We included this outcome in deviation from our protocol as it was reported in one study.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Coordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (April 2009).
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

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

Data collection and analysis

Both review authors assessed the validity of each study using the criteria outlined in the **Cochrane Handbook for Systematic Reviews of Interventions** (Higgins 2008). The review authors were not blinded to authors, institution or journal of publication for articles considered for inclusion.
All abstracts and published full reports identified as potentially relevant by the literature search were assessed by both review authors for inclusion in the review. Each review author independently extracted data using a pre-designed data extraction form, and then compared results and resolved differences. Arne Ohlsson (AO) entered data into RevMan (RevMan 2008) and Vibhuti Shah (VS) cross checked the printouts against her own data extraction forms. Differences were resolved by consensus.
In future updates of this review, where studies are identified as abstracts, the primary authors will be contacted to ascertain whether a full publication is available, if the full paper was not identified in an electronic database. Information from the primary author will be sought if the published article does not provide adequate information for the review.

Selection of studies

All potential studies identified from the search strategy were assessed for eligibility for inclusion independently by the two review authors (AO and VS). We resolved any disagreement through discussion or consulted a third person as an arbitrator.

Data extraction and management

We designed a form to extract data. For eligible studies, we extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we would have consulted a third person. Data were entered into Review Manager software (RevMan 2008) and checked for accuracy.
When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

We independently assessed the risk of bias for each study using the criteria outlined in the **Cochrane Handbook for Systematic Reviews**

of Interventions (Higgins 2008). Any disagreement was resolved by discussion or by involving a third assessor as an arbitrator.

(1) Sequence generation (checking for possible selection bias)

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

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

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

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

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

(3) Blinding (checking for possible performance bias)

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

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

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

(5) Selective reporting bias

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

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

(6) Other sources of bias

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

- yes;
- no;
- unclear.

(7) Overall risk of bias

We make explicit judgements about whether studies were at high risk of bias, according to the criteria given in the Handbook (Higgins 2008). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - see 'Sensitivity analysis'.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as summary risk ratio (RR) with 95% confidence intervals (CI). When appropriate we present risk difference (RD) with 95% CI. If the RD was found to be statistically significant we calculated the number needed to treat to benefit (NNTB) and in the case of a harmful effects (if they had been identified) we would have calculated the number needed to treat to harm (NNTH).

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. Standardized mean difference will be used in future updates of this review to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomized trials

No cluster-randomized trials were identified.

Crossover trials

Crossover trials were not considered appropriate for this review topic.

Dealing with missing data

For included studies, levels of attrition was noted. The impact of including studies with high levels of missing data in the overall assessment of treatment effect was explored by using sensitivity analyses.

For all outcomes analyses were carried out, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomized to each group in the analyses. The denominator for each outcome in each trial is the number randomized minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis (Higgins 2003). If we identified substantial (moderate or high) heterogeneity we explored it by prespecified sensitivity analyses. We used the adjectives of low (25%), moderate (50%) and high (75%) assigned to values for I^2 by Higgins (Higgins 2003).

Assessment of reporting biases

Where we suspected reporting bias (see 'Selective reporting bias' above), we attempted to contact study authors asking them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, the impact of including such studies in the overall assessment of results was explored by a sensitivity analysis.

Data synthesis

We carried out statistical analyses using the Review Manager software (RevMan 2008). We used the fixed-effect inverse variance meta-analysis for combining data where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Where there was clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials we used the random-effects meta-analysis.

If substantial heterogeneity was identified in a fixed-effect meta-analysis this was noted and the analysis repeated using a random-effects method, as a sensitivity analysis.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses when possible based on:

1. timing of bacterial cultures in the mother at < 35 weeks' post menstrual age verses bacterial cultures in the mother > 35 weeks' gestation or more.
2. GBS colonization ascertained by bacterial culture (from the vagina or the rectum, or both) versus GBS colonization ascertained by a rapid screening test.

We planned to perform subgroup analyses only for the primary outcomes (infant mortality from any cause, infant mortality from GBS infection and infant mortality from infections other than GBS). As only one study reported on these outcomes (Boyer 1986) subgroup analyses were not possible based on the two criteria listed above.

We did not conduct subgroup analyses based on heterogeneity, as for many outcomes there was only one study included and for those outcomes with more than one study there was no important heterogeneity (i.e. I^2 values were less than 25 %).

Sensitivity analysis

As we have noted discrepancies between numbers enrolled in trials as reported in abstracts and full text reports of the same trial (Ohlsson 1999), sensitivity analyses were to be performed excluding abstracts. As no abstracts were included we did not conduct these planned sensitivity analyses.

No additional sensitivity analyses were planned a priori.

RESULTS

Description of studies

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

The search conducted in December 2008 resulted in 24 references to 13 studies (several studies were reported on at different stages during the study period and/or different aspects of the study was reported on in different publications). Of the13 studies, nine were excluded as they studied the effect of chlorhexidine vaginal wash (n = 2) (Dykes 1987; Facchinetti 2002); were not true randomized controlled trials (n = 2) (Morales 1986; Sáez-Llorens 1995); did

not report on outcomes of interest for this review (three) (Belady 1996; Easmon 1983; Gibbs 1996) or treatment with antibiotics started outside of the intrapartum period (two) (Merenstein 1980; Pinette 2005). For further details see 'Characteristics of excluded studies'. An updated search in April 2009 found no new trials.

Only four studies qualified for the inclusion in this review. Two studies (Boyer 1986; Matorras 1990) compared ampicillin to no treatment for GBS intrapartum prophylaxis and one study compared penicillin to no treatment (Tuppurainen 1989). None of these three studies used a placebo treatment in the control group. One study compared the effects of ampicillin versus penicillin G (Edwards 2002). For further details please see 'Characteristics of included studies'.

Risk of bias in included studies

Overall the quality of these four studies was poor and the risk of bias high as defined by Higgins 2008; there was plausible bias that seriously weakens confidence in the results; there was high risk of bias for one or more key domains; and the proportion of information from all studies was at high risk of bias sufficient to affect the interpretation of the results.

No study reported on a pre-set sample size. No placebo was used in the three studies comparing one antibiotic versus no treatment (Boyer 1986; Matorras 1990; Tuppurainen 1989). Consequently, patients, care providers and researchers in these three studies were not blinded to group assignment. The total number of women enrolled in these three studies was 500 (239 in the treatment group and 261 in the control group). These three studies were published more than 19 years ago. Two studies reported on results after different numbers of women had been enrolled (Boyer 1986; Tuppurainen 1989). In one study the authors clearly waited for an additional neonatal outcome in the control group (Gotoff 1984) and when this outcome occurred they published their final report (Boyer 1986). In addition, they changed their level of significance from a two-tailed to an one-tailed statistical test and thus reached statistical significance from a previous report of the same ongoing study. In the Boyer 1986 study women who developed intrapartum fever were excluded as were their offspring from the analyses, which is remarkable in a study that attempted to prevent infections. In 11% of the women randomized the maternal and neonatal outcomes were not reported. In the study by Tuppurainen (Tuppurainen 1989) there was imbalance in allocation of participants to the two groups; 44% of the participants were allocated to the intervention group and 56% to the control group. This represents a large deviation from the expected ratio of 50:50 possibly due to mothers dropping out of the intervention group but not the control group.

We used judgement in assessing the neonatal and maternal outcomes as definitions of outcomes were often not clear. In the only included study that compared ampicillin to penicillin for GBS prophylaxis (Edwards 2002) the authors did not state in which group the only neonatal infection occurred and they do not provide a definition for their outcomes of suspected infection and chorioamnionitis.

Effects of interventions

Four trials involving 852 women were included. Three trials (n = 500) compared ampicillin or penicillin to no treatment (Boyer 1986; Matorras 1990; Tuppurainen 1989) and one trial enrolling 352 women compared ampicillin with penicillin for GBS positive women. Group B streptococcus carriage was ascertained by vaginal/rectal cultures in three studies (Boyer 1986; Edwards 2002; Matorras 1990). The cultures were performed at variable postmenstrual ages. In one study a rapid latex agglutination test was performed at the time of the mother giving birth (Tuppurainen 1989).

(1) Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Primary outcomes for the infant

Only one study reported on the three primary outcomes (Boyer 1986).

- There was no statistically significant effect of intrapartum antibiotics compared to no treatment on neonatal mortality from all causes (risk ratio (RR) 0.19, 95% confidence interval (CI) 0.01 to 3.82, one trial, 164 infants, test for heterogeneity not applicable) (see Analysis 1.1).
- There was no statistically significant effect of intrapartum antibiotics compared to no treatment on neonatal mortality from GBS infection (RR 0.31, 95% CI 0.01 to 7.50, one trial, 164 infants, test for heterogeneity not applicable) (see Analysis 1.2).
- There was no statistically significant effect of intrapartum antibiotics compared to no treatment on neonatal mortality from infections caused by bacteria other than GBS (RR 0.31, 95% CI 0.01 to 7.50, one trial, 164 infants, test for heterogeneity not applicable) (see Analysis 1.3).

Secondary outcomes for the infant

One or more studies reported on most of the pre-determined secondary outcomes. The number of infants included varied from 289 to 488.

- There was a statistically significant reduction in the incidence of early (postnatal age less than seven days) GBS infection in neonates following intrapartum antibiotics compared to no treatment (RR 0.17, 95% CI 0.04 to

0.74, three trials, 488 infants, I^2 0%; risk difference (RD) -0.04, 95% CI -0.07 to -0.01, I^2 0%; number needed to treat to benefit (NNTB) 25, 95% CI 14 to 100, I^2 0%) (see Analysis 1.4).

- There was a statistically significant reduction in the incidence of probable early (postnatal age less than seven days) GBS infection in a neonate following intrapartum antibiotics compared to no treatment (RR 0.17, 95% CI 0.03 to 0.91, two trials, 324 infants, I^2 0%; RD -0.05, 95% CI -0.09 to -0.01; NNTB 20, 95% CI 11 to 100, I^2 0%) (see Analysis 1.5).
- There was no statistically significant reduction in the incidence of late onset (seven days old or more) GBS infection in a neonate following intrapartum antibiotics compared to no treatment (RR 0.36, 95% CI 0.01 to 8.69, two trials, 289 infants, test for heterogeneity not applicable) (see Analysis 1.6).
- There was no statistically significant difference in the incidence of neonatal sepsis, meningitis, urinary tract infection or pneumonia due to bacterial organisms other than GBS following intrapartum antibiotics compared to no treatment (RR 1.00, 95% CI 0.15 to 6.79, two trials, 289 infants, I^2 4%) (see Analysis 1.7).
- No other predetermined neonatal outcomes of interest were reported.

Secondary outcomes for the mother.

- There was no statistically significant effect on maternal sepsis in the peri/postpartum period (RR 0.31, 95% CI 0.01 to 7.49, one study, 160 women, test for heterogeneity not applicable) (see Analysis 1.8).
- There was no statistically significant effect on puerperal infection (RR 0.16, 95% CI 0.01 to 3.03, one study, 121 women, test for heterogeneity not applicable) (see Analysis 1.9).
- No other predetermined maternal outcomes of interest were reported.

As there was only one study that reported on our primary outcome, we did not perform subgroup analyses based on heterogeneity. As no abstracts were included we did not perform any analyses excluding abstracts. The authors did not provide sufficient information for us to do separate analyses based on timing of antenatal test to detect GBS or timing of the administration of antibiotics to the mother.

(2) Intrapartum ampicillin versus penicillin for GBS positive women

One study qualified for inclusion (Edwards 2002) enrolling 352 participants. Most of the outcomes reported lacked a definition. We contacted the first author but were unable to obtain information from him.

Primary outcomes for the infant

- There was no statistically significant effect on neonatal mortality from all causes comparing intrapartum administration of ampicillin with penicillin (RR 3.03, 95% CI 0.12 to 73.98, one study 352 infants, test for heterogeneity not applicable). The one death was caused by a lethal congential heart condition and not due to an infection (see Analysis 2.1).

Secondary outcomes for the infant

- There was no statistically significant effect on suspected neonatal infection (definition not provided by the authors) comparing intrapartum administration of ampicillin with penicillin (RR 0.85, 95% CI 0.49 to 1.46, one study 352 infants) (see Analysis 2.2).
- There was no statistically significant difference in the length of initial hospital stay for neonates comparing intrapartum administration of ampicillin with penicillin (mean difference (MD) 0.20 days , 95% CI -0.28 to 0.68) (see Analysis 2.3).

Secondary outcomes for the mother

- There were no allergic reactions reported in either the ampicillin nor the penicillin group (see Analysis 2.4).
- There was no statistically significant effect on chorioamnionitis (definition not provided) comparing intrapartum administration of ampicillin with penicillin (RR 0.91, 95% CI 0.38 to 2.19, one study, 352 women, test for heterogeneity not applicable) (see Analysis 2.5).
- There was no statistically significant effect on endometritis (definition not provided) comparing intrapartum administration of ampicillin with penicillin (RR 3.03, 95% CI 0.32 to 28.89, one study, 352 women, test for heterogeneity not applicable) (see Analysis 2.6).

DISCUSSION

It is remarkable that in North America the commonly implemented practice of intrapartum antibiotic prophylaxis to GBS colonized women has been so poorly studied. Only three randomized controlled trials conducted more than 20 years ago in three different countries and enrolling a total of 500 women have been published. We identified serious concerns of bias in these trials affecting our ability to draw conclusions from this systematic review. Concerns include no preset sample sizes, the lack of a placebo in the control groups, women and care-providers not blinded to group assignment, reporting on outcomes while the trials were ongoing, and exclusion of women who developed signs of infections

in labor. As these trials were conducted and published prior to the CONSORT guidelines the description of important aspects of study design, execution and the reporting of data are missing (Begg 1996).

The attack rate for neonatal GBS sepsis has been reported as 0.5 per 1000 live births in the UK in the absence of systematic screening or widespread use of antibiotics (RCOG 2003). It is therefore not possible to draw meaningful conclusions from studies that today have only included a total of 500 women, even when appreciating the fact that some of these women were at a higher risk for neonatal GBS infections than the pregnant population at large.

Acknowledging our serious concerns about bias in the three included trials, we did combine the studies and found a statistically significant reduction in early GBS neonatal infection. A similar statistically significant point estimate was obtained for RR for probable early GBS infection. Intrapartum antibiotic prophylaxis appeared to reduce EOGBSD, but this result may well be a result of bias as we found a high risk of bias for one or more key domains in the study methodology and execution. It should be noted that the attack rate in the control groups were 4.7% (47/1000 infants) and 5.7 % (57/1000 infants) respectively for these two outcomes, which seems exceedingly high. In one of our previous reviews on the topic conducted 15 years ago we decided not to combine the results of the same studies that are included in this current review, as we raised similar serious concerns about bias (Ohlsson 1994). The conclusion remains the same "**Intrapartum chemoprophylaxis to reduce perinatal GBS infections are not supported by conclusive evidence from well designed and conducted randomized controlled trials**" (Ohlsson 1994). All cases of perinatal GBS infections cannot be prevented.

AUTHORS' CONCLUSIONS

Implications for practice

In the three studies investigating the effects of intrapartum antibiotics versus no treatment for Group B haemolytic **streptococci** (GBS) colonized women we identified high risks of bias for one or more key domains in the study methodology and execution. The information from all studies was at high risk of bias sufficient to affect the interpretation of the results. Based on this review we conclude that there is no valid information from these three small, old and biased trials to inform clinical practice.

Information on whether intrapartum ampicillin is preferable to penicillin for GBS colonized women is lacking.

Implications for research

Ideally the effectiveness of intrapartum antibiotics to GBS colonized women to reduce neonatal GBS infections should be studied in adequately sized double blind controlled trials. The opportunities to conduct such trials have likely been lost as practice guidelines have been introduced in many jurisdictions. It should be noted that the guidelines have changed many times, indicating that they are not based on clear evidence informing best clinical practice. Even if an effective vaccine to prevent GBS infections will be developed in the future, a need for intrapartum prophylaxis (if proven effective) is still likely to be present as all women will not be immunized and the vaccine may not be effective in women giving birth preterm.

ACKNOWLEDGEMENTS

We acknowledge with appreciation the support from Mrs G Gyte in completing this review.

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* **Indicates the major publication for the study**

CHARACTERISTICS OF STUDIES

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

Boyer 1986

Methods	Randomized controlled trial. I Blinding of randomisation - no. II Blinding of intervention - no. III Complete follow up - no. IV Blinding of outcome measurement - no.
Participants	180 women with vaginal, rectal or both specimens positive for group B **streptococcus** (in the majority of women the interval between the time of cultures and parturition was > 10 weeks) and at the time of giving birth had the following risk factors (selective intrapartum prophylaxis**)**: preterm labor (< 37 weeks of gestation) or prolonged rupture of membranes (> 12 hours). If women in the control group developed intrapartum fever (temperature > 37.5ºC) they were excluded from the study group and were treated with ampicillin. Exclusion criteria: penicillin allergy or need for other antimicrobial agents. Study period: prior to May 1982 (first report in abstract form by Boyer 1982). Study period: May 1979 to September 1981 (second report Boyer 1983). Study period: May 1979 to September 1984 (final report Boyer 1986). Multi center study, USA (Private obstetrician's clinics, a health maintenance organization and the obstetric clinics of Micheal Reese Hospital and Medical Center).
Interventions	Women in the treatment group (n = 94): received 2 g of ampicillin intravenously followed by 1 g every 4 hours until giving birth. Women in the control group (n = 86) received no ampicillin. If the mother had received ampicillin, the infant was treated with four doses of intramuscular ampicillin (50 mg/kg) every 12 hours. Infants born to untreated women received antibiotics only if symptoms of sepsis were observed. In all symptomatic infants (presence of respiratory distress, asphyxia, or signs of infection at birth regardless of maternal treatment) cerebrospinal fluid examination was performed and treatment with ampicillin and kanamycin commenced until the results of blood and surface cultures were available.
Outcomes	**Primary outcomes** **Neonatal** All cause mortality Mortality from early (postnatal age less than 7 days) onset culture positive neonatal GBS infection including one or more of the following conditions. a) Sepsis - defined as symptoms and signs of sepsis and a bacterial culture positive for GBS (obtained in a sterile manner from normally sterile body fluids such as blood, cerebrospinal fluid or urine, or culture from internal organs at autopsy).

Boyer 1986 (**Continued**)

	b) Pneumonia in the neonate (postnatal age less than 7 days) - defined as symptoms and signs and radiographic findings consistent with pneumonia and positive culture for GBS (obtained from tracheal aspirate or by culture of lung tissue at autopsy). Mortality from infections (as per a and b above) caused by bacteria other than GBS. **Secondary outcomes** **Neonatal** Early (postnatal age less than 7 days) GBS infection in a neonate - defined as symptoms and signs of sepsis or pneumonia in a neonate born to a GBS positive mother, and positive GBS bacterial cultures (from normally sterile body fluids obtained from the neonate). Late onset GBS sepsis - sepsis due to GBS in an infant at least 7 days old. Neonatal sepsis due to bacterial organisms other than GBS. **Maternal** Sepsis in the peri/postpartum period.
Notes	Determined the incidence of group B **streptococcus** bacteraemia in infants born to 1648 women with prenatal colonization who did not participate in the randomized study. Antibiotics were administered to 232 of these women and blood culture obtained from mother or their infant if sepsis was suspected.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Participants were assigned to ampicillin or control groups (with an allocation ratio of 1:1) on the basis of sequential selection of sealed opaque envelopes containing assignments generated from a table of random numbers.
Allocation concealment?	No	Sequential selection of opaque envelopes. Although there was adequate sequence generation it would very soon become obvious to which group the next mother would be assigned as the allocation ratio was 1:1. Although the allocation ratio was 1:1 there is an imbalance in the numbers of women allocated to the 2 groups: 94 in the ampicillin group and 86 in the control group. After excluding 20 women (13 women who developed intrapartum fever and 7 for whom there were randomisation errors or incomplete data, 83 women (85 infants) remained in the ampicillin group and 77 (79 infants) in the control group.
Blinding? All outcomes	No	"**Neither the patient nor the obstetricians were blinded to the assignment to study groups**". We have interpreted the information as that the sequence generation was adequate but from then on the study was open to patients and care givers.

Boyer 1986 (**Continued**)

Incomplete outcome data addressed? All outcomes	Yes	13 women were excluded as they developed intrapartum fever (7 in the ampicillin group and 6 in the control group) and 7 in whom there were randomization errors or incomplete data (4 in the ampicillin group and 3 in the control group).
Free of selective reporting?	No	Concerns addressed in the cells above and below.
Free of other bias?	No	The results of this ongoing study has been reported on three occasions. In the first report (Boyer 1982) there were 71 infants in the ampicillin group and there were 128 infants in the control group (the number of mothers randomized was not reported). Blood cultures were positive in 4 heavily colonized infants whose mothers were not treated with ampicillin; no blood cultures were positive among infants whose mothers were treated (P = .17). In the second report (Boyer 1983) 80 women were randomized; 43 received ampicillin chemoprophylaxis and 37 did not. One infant in the control group had GBS bacteraemia. Between the second (Boyer 1983) and third (final, Boyer 1986) publication Gotoff in a letter to the editor (Gotoff 1984) wrote "**In order to show efficacy in preventing GBS disease, we need an additional case in our control group**". It seems clear that the researchers were aware of study results throughout the study and stopped recruitment when statistical significance (1-tailed) had been achieved. Between the second (Boyer 1983) and the third publication (Boyer 1986) the authors changed their test of significance for comparisons of colonization, bacteraemia, and the rate of postpartum febrile morbidity from a 2-tailed to a 1-tailed test. It is remarkable that in a study of perinatal infections 13 women were excluded as they developed intrapartum fever (7 in the ampicillin group and 6 in the control group).

Edwards 2002

Methods	Randomized controlled trial. I Blinding of randomisation - yes. II Blinding of intervention - can't tell. III Complete follow up - yes. IV Blinding of outcome measurement - can't tell.
Participants	Women who were at a gestational age of 36 weeks or more, were in spontaneous or induced labor and were culture-proven carriers of group B **streptococci**. Cultures for GBS were obtained at the time of admission for spontaneous or induced labor. Exclusion criteria included planned cesarean section, antibiotics taken within the preceding 7 days, a history of allergy to penicillins, multifetal gestation, or antepartum fetal death.

Edwards 2002 (**Continued**)

	Study period 26 February 2000 to 22 May 2001.
Interventions	175 women received ampicillin (2 g of ampicillin IV followed by 1 g every 4 hours until giving birth) and 177 received penicillin (5 million units of penicillin G IV, followed by 2.5 million units every 4 hours until giving birth).
Outcomes	All cause mortality. Suspected infection (the authors do not provide a definition). Initial hospital stay (neonatal). Chorioamnionitis (definition not provided). Endometritis (definition not provided). Allergic reactions to antibiotics (maternal).
Notes	We contacted (5 January 2009) the primary author to provide us with information in which treatment group the early-onset neonatal infection occurred and what their definition of suspected infection was. As of 7 May 2009, we have not received an answer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A random number-generating software program was used to assign participants to groups.
Allocation concealment?	Yes	Participants were randomized, by selection of the next opaque envelope containing an order sheet, to receive intrapartum antibiotic prophylaxis with ampicillin or penicillin.
Blinding? All outcomes	Unclear	It is not stated whether the women and the care-givers were aware of what antibiotic was administered.
Incomplete outcome data addressed? All outcomes	Yes	Outcomes reported for all women randomized.
Free of selective reporting?	Unclear	The authors report on an intent-to-treat analysis and a per-protocol analysis
Free of other bias?	Yes	The study appears to be free of other sources of bias.

Matorras 1990

Methods	Randomized controlled trial. I Blinding of randomisation - no. II Blinding of intervention - no. III Complete follow up - yes. IV Blinding of outcome measurement - no.
Participants	121 women with group B **streptococcal** colonization (vaginal and/or rectal swabs). The gestational age at which cultures were obtained ranged from 17 and 42 weeks (mean 32.98 weeks; standard deviation +/- 5.03 weeks). Study period: not reported. Single centre study, Spain.
Interventions	Women in the treatment group (n = 57) received 500 mg of ampicillin IV every 6 hours until delivery. If induction of labor, antibiotics were administered at the beginning of induction, and if caesarean section without labor, 2 hours prior to surgery. Patients allergic to penicillin received erythromycin. In the control group (n = 64) no ampicillin prophylaxis or placebo was administered.
Outcomes	Information on the different parameters analysed were obtained retrospectively from clinical histories. Early (postnatal age less than 7 days) GBS infection in a neonate - defined as symptoms and signs of sepsis or pneumonia in a neonate born to a GBS positive mother, and positive GBS bacterial cultures (from normally sterile body fluids obtained from the neonate) (Matorras 1991). Probable early (postnatal age less than 7 days) GBS infection in a neonate - defined as symptoms and signs of sepsis or pneumonia in a neonate born to a GBS positive mother, and bacterial cultures from normally sterile body fluids obtained from the neonate that were negative for GBS (Matorras 1991). Late onset GBS sepsis - sepsis due to GBS in an infant at least 7 days old. Neonatal sepsis due to bacterial organisms other than GBS (Matorras 1991). Late onset sepsis (Matorras 1991). Puerperal infection: defined according to clinical criteria- uterine tenderness, uterine subinvolution and fever in the absence of any other known cause of infection.
Notes	In order to assess the impact of GBS maternal colonization for infective puerperal morbidity, the non-carrier patients were compared with the GBS carrier patients who did not receive prophylaxis.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	It is stated that "....women were randomly divided" into 2 groups.

Matorras 1990 (Continued)

Allocation concealment?	Unclear	Insufficient information to permit judgement of "yes" or "no".
Blinding? All outcomes	No	The control group received no intervention (no placebo).
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Insufficient information to permit judgement of "yes" or "no".
Free of other bias?	Unclear	The study appears to be free of other sources of bias. The results of the randomized part of this study which formed the part of a larger cohort study has been reported on at least 3 occasions. The number of randomized women was the same in all three reports (n = 121). The rate of puerperal infection was reported in Matorras 1990. In an abstract (Omenaca 1987) the rate of neonatal sepsis caused by GBS was reported as 3 % (2/57) in babies whose mothers received prophylaxis and 13.8% (9/64) in infants of untreated mothers. In the final report (Matorras 1991) the authors report that there was no case of GBS sepsis in the prophylaxis group compared to three cases in the control group. Clinically infected newborns represented 3.3% in the prophylaxis group vs 13.8% in the control group.

Tuppurainen 1989

Methods	Randomized controlled trial. I Blinding of randomisation - no. II Blinding of intervention - no. III Complete follow up - yes. IV Blinding of outcome measurement - no.
Participants	Women with a positive group B **streptococcus** latex test before giving birth (in labor), no history of penicillin allergy and no elective term caesarean section without labor or rupture of fetal membranes were eligible. In woman with a positive streptolatex test admitted for induction of labor but who did not give birth and returned home, the test was repeated if 3 or more days had passed since the first test. Study period: December 1983 and January 1986 except for a 6 month period in 1984 to 85. Single center, Finland.

Tuppurainen 1989 (**Continued**)

Interventions	Women in the treatment group (n = 88) received 5 million units penicillin G IV every 6 hours during labor. If labor lasted more than 18 hours, 1 million units penicillin V administered orally every 8 hours until parturition (penicillin was chosen as no resistant strains of group B **streptococcus** had been detected in the institution where the study was conducted). In the control group (n = 111) women received no prophylaxis or placebo. Newborns born to group B **streptococcus** positive women were evaluated as follows. 1. Blood culture was obtained within 2 hours of birth. 2. Pharyngeal aspirate and other superficial samples for culture from the external ear canal, eye, and umbilicus were taken within 30 minutes of birth. 3. Urine sample for streptolatex text was collected. Cerebrospinal fluid examined was performed if the infant had symptoms and/or signs of sepsis or of meningeal involvement.
Outcomes	Early (postnatal age less than 7 days) GBS infection in a neonate - defined as symptoms and signs of sepsis or pneumonia in a neonate born to a GBS positive mother, and positive GBS bacterial cultures (from normally sterile body fluids obtained from the neonate). Probable early (postnatal age less than 7 days) GBS infection in a neonate - defined as symptoms and signs of sepsis or pneumonia in a neonate born to a GBS positive mother, and bacterial cultures from normally sterile body fluids obtained from the neonate that were negative for GBS.
Notes	No mention of severity of illness in the newborn or details provided regarding duration of hospitalisation and antibiotic administration. No mention of benefits/adverse reactions to the mother.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information about sequence generation process to permit judgement of "yes" or "no".
Allocation concealment?	No	Participants were assigned to the penicillin or control group based on sequential selection of sealed envelopes containing the treatment instructions. However, the authors state "**There was no blinding in the assignment to study groups**". There was imbalance in allocation of participants to the two groups; 44% of the participants were allocated to the intervention group and 56% to the control group.
Blinding? All outcomes	No	No blinding as the control group received no intervention (no placebo was used).

Incomplete outcome data addressed? All outcomes	Yes	No missing outcome data.
Free of selective reporting?	Yes	The authors reported outcomes for women with positive streptolatex test who were randomized (199) and those who were not randomized (157 women who gave birth before the test results were available and 21 women with a history of penicillin allergy. Outcomes for 8565 women who were streptolatex negative were reported. These women gave birth to six neonates with early-onset GBS disease.
Free of other bias?	No	Results of the study were first reported in abstract form in 1986 (Tuppurainen 1986) when 94 patients had been randomized, 36 received intrapartum penicillin and 58 did not. Seven of the 58 (12%) neonates whose mother did not receive penicillin developed early onset GBS disease. One neonate whose mother received penicillin had intrauterine pneumonia probably due to GBS. It appears that results of the study were known on an ongoing basis.

GBS: Group B haemolytic **streptococci**
IV: intravenous
vs: versus

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

Belady 1996	Randomized controlled trial comparing ampicillin versus penicillin for group B **streptococcus** prophylaxis. No placebo or untreated control group was included. Reports only on colonization rates. In a separate abstract from the same study (Davies 1998) the authors do not report on maternal infections as per randomized groups.
Dykes 1987	This study reported on the effects of chlorhexidine for prevention of neonatal colonization with group B **streptococci**. This intervention is the topic of another Cochrane review.
Easmon 1983	This randomized controlled study reports only on maternal and neonatal colonization, which were not considered important outcomes in our review.
Facchinetti 2002	The objective of this randomized controlled trial was to study the efficacy of intrapartum vaginal flushing with chlorhexidine compared with ampicillin in preventing group B **streptococcus** transmission to neonates. This is the topic of a separate Cochrane review.

(**Continued**)

Gibbs 1996	This randomized controlled study reported on the effect of 2% clindamycin cream administered intravaginally during labor to group B **streptococcal**-colonized pregnant women. Outcomes included only maternal and neonatal colonization, which were not considered important outcomes for this review.
Merenstein 1980	In this study treatment with antibiotics started at 38 weeks postmenstrual age not intrapartum.
Morales 1986	In this study the control group included randomly selected patients and those with a history of ampicillin allergy.
Pinette 2005	In this study pregnant women positive for GBS at 35 to 37 weeks' postmenstrual age were randomized to receive intramuscular benzathine penicillin G suspension versus no treatment. Intrapartum all the women received prophylaxis according to CDC guidelines.
Sáez-Llorens 1995	This study was an open, non-randomized trial.

DATA AND ANALYSES

Comparison 1. Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality from all causes	1	164	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.82]
2 Neonatal mortality from early onset GBS infection	1	164	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.50]
3 Neonatal mortality from infections caused by bacteria other than GBS	1	164	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.50]
4 Early (postnatal age less than 7 days) GBS infection in a neonate	3	488	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.04, 0.74]
5 Probable early (postnatal age less than 7 days) GBS infection in a neonate	2	324	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.03, 0.91]
6 Late onset (7 days old or more) GBS infection in a neonate	2	289	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.69]
7 Neonatal sepsis due to bacterial organisms other than GBS	2	289	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.15, 6.79]
8 Maternal sepsis in the peri/ postpartum period	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.49]
9 Puerperal infection (definition not provided)	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 3.03]

Comparison 2. Intrapartum ampicillin versus penicillin for GBS positive women

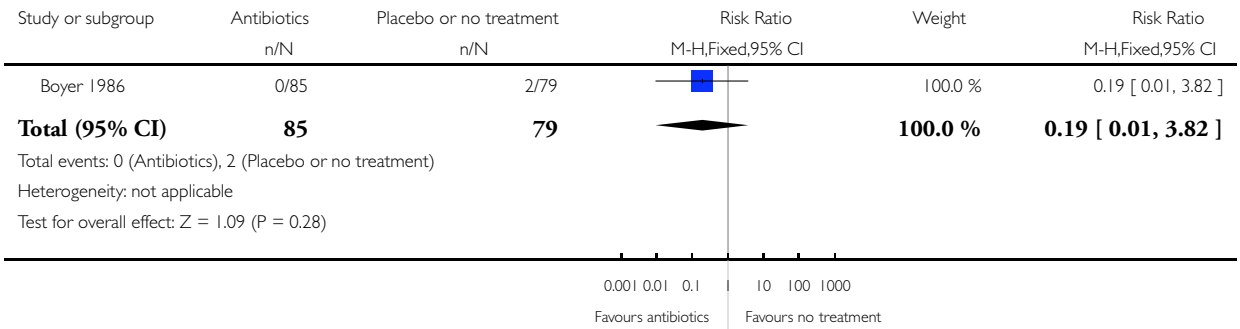
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal mortality from all causes	1	352	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.12, 73.98]
2 Suspected neonatal infection (definition not provided)	1	352	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.49, 1.46]
3 Initial hospital stay (days) for neonates	1	352	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.28, 0.68]
4 Maternal allergic reactions to antibiotics	1	352	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Chorioamnionitis (definition not provided)	1	352	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.38, 2.19]
6 Endometritis (definition not provided)	1	352	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.32, 28.89]

Analysis 1.1. Comparison 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women, Outcome 1 Neonatal mortality from all causes.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Outcome: 1 Neonatal mortality from all causes

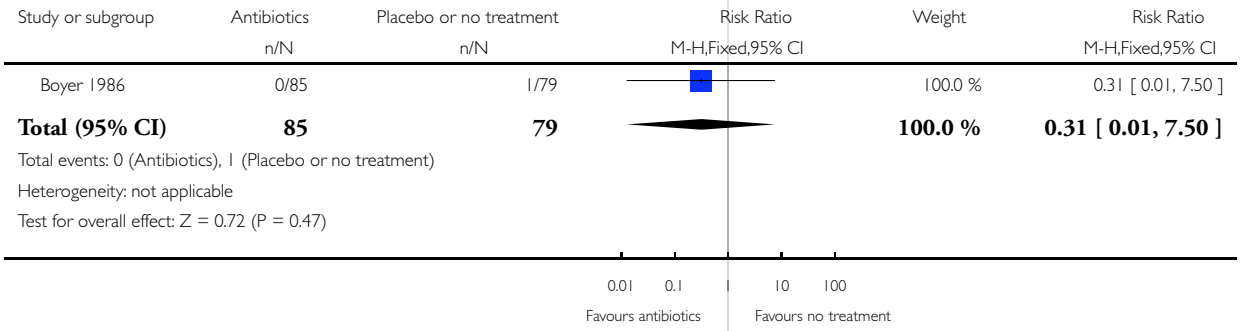


Analysis 1.2. Comparison 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women, Outcome 2 Neonatal mortality from early onset GBS infection.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Outcome: 2 Neonatal mortality from early onset GBS infection



Analysis 1.3. Comparison 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women, Outcome 3 Neonatal mortality from infections caused by bacteria other than GBS.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Outcome: 3 Neonatal mortality from infections caused by bacteria other than GBS

Study or subgroup	Antibiotics n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Boyer 1986	0/85	1/79		100.0 %	0.31 [0.01, 7.50]
Total (95% CI)	**85**	**79**		**100.0 %**	**0.31 [0.01, 7.50]**
Total events: 0 (Antibiotics), 1 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					

Analysis 1.4. Comparison 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women, Outcome 4 Early (postnatal age less than 7 days) GBS infection in a neonate.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Outcome: 4 Early (postnatal age less than 7 days) GBS infection in a neonate

Study or subgroup	Antibiotics n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Boyer 1986	0/85	4/79		37.5 %	0.10 [0.01, 1.89]
Matorras 1990	0/60	3/65		27.0 %	0.15 [0.01, 2.93]
Tuppurainen 1989	1/88	5/111		35.5 %	0.25 [0.03, 2.12]
Total (95% CI)	**233**	**255**		**100.0 %**	**0.17 [0.04, 0.74]**
Total events: 1 (Antibiotics), 12 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 0.25, df = 2 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 2.37 (P = 0.018)					

Analysis 1.5. Comparison 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women, Outcome 5 Probable early (postnatal age less than 7 days) GBS infection in a neonate.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Outcome: 5 Probable early (postnatal age less than 7 days) GBS infection in a neonate

Study or subgroup	Antibiotics n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Matorras 1990	1/60	5/65		49.6 %	0.22 [0.03, 1.80]
Tuppurainen 1989	0/88	5/111		50.4 %	0.11 [0.01, 2.04]
Total (95% CI)	**148**	**176**		**100.0 %**	**0.17 [0.03, 0.91]**

Total events: 1 (Antibiotics), 10 (Placebo or no treatment)

Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² =0.0%

Test for overall effect: Z = 2.07 (P = 0.039)

Analysis 1.6. Comparison 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women, Outcome 6 Late onset (7 days old or more) GBS infection in a neonate.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Outcome: 6 Late onset (7 days old or more) GBS infection in a neonate

Study or subgroup	Antibiotics n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Boyer 1986	0/85	0/79		0.0 [0.0, 0.0]
Matorras 1990	0/60	1/65		0.36 [0.01, 8.69]
Total (95% CI)	**145**	**144**		**0.36 [0.01, 8.69]**

Total events: 0 (Antibiotics), 1 (Placebo or no treatment)

Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%

Test for overall effect: Z = 0.63 (P = 0.53)

Analysis 1.7. Comparison 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women, Outcome 7 Neonatal sepsis due to bacterial organisms other than GBS.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Outcome: 7 Neonatal sepsis due to bacterial organisms other than GBS

Study or subgroup	Antibiotics n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Boyer 1986	0/85	1/79		76.4 %	0.31 [0.01, 7.50]
Matorras 1990	1/60	0/65		23.6 %	3.25 [0.13, 78.18]
Total (95% CI)	**145**	**144**		**100.0 %**	**1.00 [0.15, 6.79]**

Total events: 1 (Antibiotics), 1 (Placebo or no treatment)

Heterogeneity: Chi^2 = 1.04, df = 1 (P = 0.31); I^2 =4%

Test for overall effect: Z = 0.00 (P = 1.0)

Analysis 1.8. Comparison 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women, Outcome 8 Maternal sepsis in the peri/postpartum period.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Outcome: 8 Maternal sepsis in the peri/postpartum period

Study or subgroup	Antibiotics n/N	Placebo or no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Boyer 1986	0/83	1/77		100.0 %	0.31 [0.01, 7.49]
Total (95% CI)	**83**	**77**		**100.0 %**	**0.31 [0.01, 7.49]**

Total events: 0 (Antibiotics), 1 (Placebo or no treatment)

Heterogeneity: not applicable

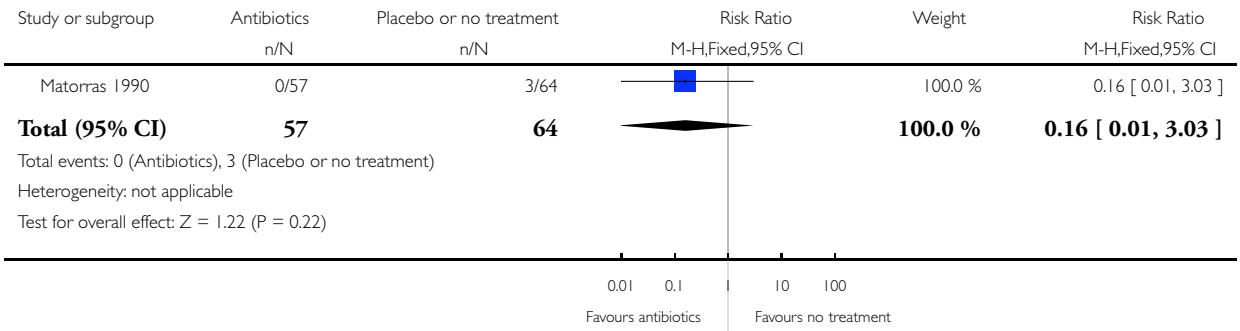
Test for overall effect: Z = 0.72 (P = 0.47)

Analysis 1.9. Comparison 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women, Outcome 9 Puerperal infection (definition not provided).

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 1 Intrapartum antibiotics versus placebo or no treatment for GBS positive women

Outcome: 9 Puerperal infection (definition not provided)

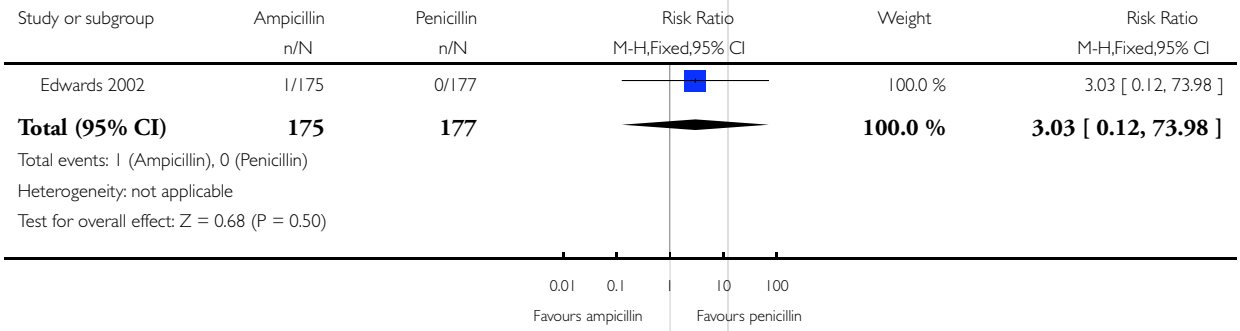


Analysis 2.1. Comparison 2 Intrapartum ampicillin versus penicillin for GBS positive women, Outcome 1 Neonatal mortality from all causes.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 2 Intrapartum ampicillin versus penicillin for GBS positive women

Outcome: 1 Neonatal mortality from all causes



Analysis 2.2. Comparison 2 Intrapartum ampicillin versus penicillin for GBS positive women, Outcome 2 Suspected neonatal infection (definition not provided).

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 2 Intrapartum ampicillin versus penicillin for GBS positive women

Outcome: 2 Suspected neonatal infection (definition not provided)

Study or subgroup	Ampicillin n/N	Penicillin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Edwards 2002	21/175	25/177		100.0 %	0.85 [0.49, 1.46]
Total (95% CI)	**175**	**177**		**100.0 %**	**0.85 [0.49, 1.46]**
Total events: 21 (Ampicillin), 25 (Penicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.56)					

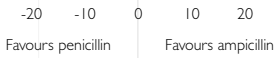
Analysis 2.3. Comparison 2 Intrapartum ampicillin versus penicillin for GBS positive women, Outcome 3 Initial hospital stay (days) for neonates.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 2 Intrapartum ampicillin versus penicillin for GBS positive women

Outcome: 3 Initial hospital stay (days) for neonates

Study or subgroup	Ampicillin N	Mean(SD)	Penicillin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Edwards 2002	175	3.8 (2.8)	177	3.6 (1.7)		100.0 %	0.20 [-0.28, 0.68]
Total (95% CI)	**175**		**177**			**100.0 %**	**0.20 [-0.28, 0.68]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.81 (P = 0.42)							



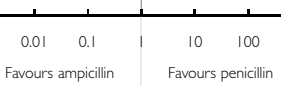
Analysis 2.4. Comparison 2 Intrapartum ampicillin versus penicillin for GBS positive women, Outcome 4 Maternal allergic reactions to antibiotics.

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 2 Intrapartum ampicillin versus penicillin for GBS positive women

Outcome: 4 Maternal allergic reactions to antibiotics

Study or subgroup	Ampicillin n/N	Penicillin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Edwards 2002	0/175	0/177		0.0 [0.0, 0.0]
Total (95% CI)	**175**	**177**		**0.0 [0.0, 0.0]**
Total events: 0 (Ampicillin), 0 (Penicillin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



Analysis 2.5. Comparison 2 Intrapartum ampicillin versus penicillin for GBS positive women, Outcome 5 Chorioamnionitis (definition not provided).

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 2 Intrapartum ampicillin versus penicillin for GBS positive women

Outcome: 5 Chorioamnionitis (definition not provided)

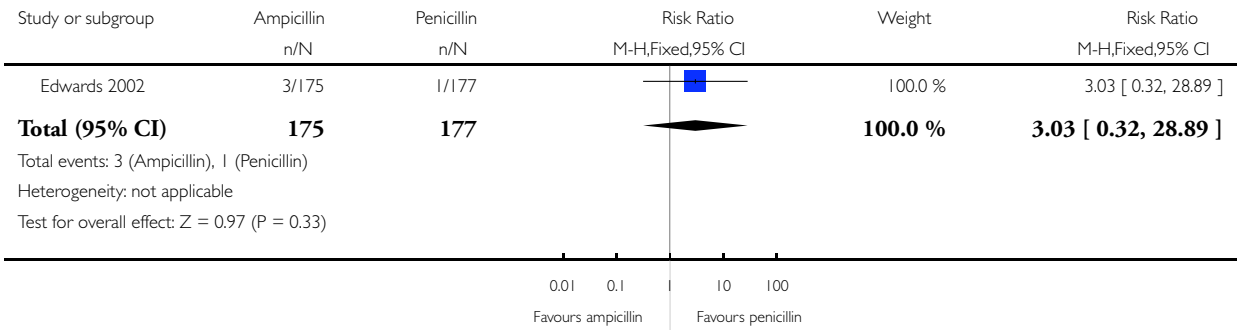
Study or subgroup	Ampicillin n/N	Penicillin n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Edwards 2002	9/175	10/177		100.0 %	0.91 [0.38, 2.19]
Total (95% CI)	**175**	**177**		**100.0 %**	**0.91 [0.38, 2.19]**
Total events: 9 (Ampicillin), 10 (Penicillin)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.21 (P = 0.83)					

Analysis 2.6. Comparison 2 Intrapartum ampicillin versus penicillin for GBS positive women, Outcome 6 Endometritis (definition not provided).

Review: Intrapartum antibiotics for known maternal Group B streptococcal colonization

Comparison: 2 Intrapartum ampicillin versus penicillin for GBS positive women

Outcome: 6 Endometritis (definition not provided)



HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 3, 2009

CONTRIBUTIONS OF AUTHORS

Both review authors contributed to the protocol and the review. Arne Ohlsson wrote the text and Vibhuti Shah made important contributions to the protocol and edited the text. Both review authors contributed to all steps of the full review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Paediatrics, Mount Sinai Hospital, Canada.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In a deviation from our protocol we included studies that compared one antibiotic versus another for GBS prophylaxis. We considered this inclusion to be important to ascertain whether one antibiotic would be preferable to another and to be able to estimate the expected attack rate of GBS infection in infants exposed to any antibiotic. We included the outcome of puerperal infection as it was reported in one study. We included the outcome of chorioamnionitis from one study although the authors did not provide a definition. From the same study we included endometritis (no definition) as an outcome in spite of the fact that this was not one of our pre-determined outcomes.