National Institute for Health and Care Excellence

Final

Neonatal infection: antibiotics for prevention and treatment

[B] Evidence review for intrapartum antibiotic prophylaxis for reducing early-onset neonatal infection

NICE guideline NG195

Evidence reviews underpinning recommendations 1.2.1-1.2.8 and research recommendations in the NICE guideline

April 2021

Final

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1.1 Review question

What is the clinical and cost effectiveness of intrapartum antibiotic prophylaxis for preventing early-onset neonatal infection?

1.1.1 Introduction

Neonatal infection is a significant cause of mortality and morbidity in newborn babies. It can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. Early-onset neonatal infection is less common than late-onset neonatal infection, but it is often more severe. It is present in 1 of every 1,000 newborn babies and responsible for 9 of every 1,000 neonatal admissions. Group B streptococcus (GBS) and *Escherichia coli* are the most common organisms identified. Overall mortality is reported to be about 10% but is even higher in preterm babies. Up to 7% of babies who survive GBS infection have a consequent physical disability or neurophysiological disorder.

Intrapartum antibiotics are often given to the mother during labour if the baby is believed to be at risk of early-onset neonatal infection. Factors such as chorioamnionitis, maternal colonisation with group B streptococcus or pre-term labour are thought to be potential risk factors for the baby developing neonatal infection. If these, or other risk factors, are present then giving antibiotics to the mother during labour may help to reduce the risk of the baby developing early-onset infection.

The aim of this review is to establish the clinical and cost-effectiveness of intrapartum antibiotic prophylaxis for preventing early-onset neonatal infection, including which classes of antibiotics should be used. See appendix A for full details of the review protocol.

1.1.2 Summary of the protocol

Table 1 PICO table

Population	Women in labour with perceived risk factors (as defined by the study authors) for early-onset neonatal infection
Interventions	• Antibiotics (and combinations of antibiotics, including intra and inter-class combinations)
Comparator	• Head-to-head comparison with any of the interventions (including combinations), including intra and inter-class comparisons • Placebo • No treatment / usual care
Outcomes	Neonatal outcomes:

- Culture-proven infection from sample taken within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection
- Antibiotics for suspected bloodstream infection (Antibiotics for suspected bloodstream infection was chosen as a surrogate outcome for infection, as not all infection will be culture proven)
- Mortality (at two time points – peri-natal mortality (stillborn or within 7 days from birth) or greater than 7 days from birth)
- health-related quality of life, measured using a validated tool (during the neonatal period and at the last time point reported in the study)
- length of hospital stay
- neurodevelopmental outcomes (measured using a validated tool at the latest time point reported in the study)

Maternal/family outcomes:

- psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory) (during the intrapartum period and at the latest timepoint reported in study)
- Maternal adverse events (during the intrapartum period and at the latest timepoint reported in study):
- serious adverse events
    - allergic reaction to antibiotics
    - Maternal sepsis (during the intrapartum period and within 6 weeks of birth)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Full methods specific to this review question are described in the methods document.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Randomised controlled trials (RCTs) and systematic reviews of RCTs were considered as a source for primary studies. The review protocol specified that, where possible, subgroup analyses would be conducted for different classes of antibiotics but if substantial heterogeneity was found then different types of antibiotics would be analysed separately. However, the studies included in the review reported on a range of risk factors and combinations of antibiotics for the intervention and control arms. This variation in both populations and interventions meant that most outcomes had to be presented as individual study results rather than using pooled meta-analysis.

The 2012 version of the guideline also reviewed evidence on the effectiveness of intrapartum antibiotics but used a very broad definition of 'intrapartum' to determine whether studies were included in the review. Studies on women with suspected or threatened preterm labour or preterm rupture of membranes were included even when the population was not women in established labour and the mean latency between randomisation and birth was several weeks or more. The committee noted that antibiotics given in pregnancy when birth is not imminent are given for a different purpose and have a different balance of benefit and harms than intrapartum antibiotics. They are usually given at a lower dose and mode of administration (oral rather than intravenous). Subsequent to the publication of the 2012 version of this

guideline, the effectiveness of antibiotics in pregnancy for women with prelabour preterm rupture of membranes has been reviewed in the NICE guideline on preterm birth. For this review, only studies where the majority of women were in labour at the time of initiation of randomised treatment were included. As a result, many studies that were included in the previous guideline were excluded from this review as they reported long periods of time between antibiotics being given and delivery of the baby. These studies are listed in the excluded studies table (Appendix I) together with the reasons for exclusion.

Maternal sepsis was one of the outcomes listed in the protocol, but no evidence was found. Instead, the committee decided that all outcomes relating to maternal infection should be included in the review but downgraded for indirectness in the GRADE assessment of that outcome. Evidence found in the research for maternal infection included chorioamnionitis, puerperal uterine infection and endometritis.

This review did not use the GRADE imprecision parameter as part of the quality assessment of outcome measures. Where the interpretation of the effect is stated in the quality assessment table (Table 3), an outcome was reported as 'could not differentiate between trial arms' when the confidence intervals crossed the line of no effect. The imprecision associated with a particular outcome and more detailed discussions of the effects are described in the committee's discussion of the evidence.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search was carried out to identify RCTs and systematic reviews published since the date of the previous search. The search returned a total of 672 results. These were added to the 38 studies that were included in the previous version of the guideline. Of these, 69 were identified as potential includes, with full text articles ordered and reviewed against the inclusion criteria. Nine RCTs met the inclusion criteria and were included within the review. All included studies were papers that were part of the previous guideline update. No new studies were identified that met the inclusion criteria.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 102 results of which 2 were identified as possible included studies. After full text review, 0 met the inclusion criteria. In total there were therefore 9 studies (all RCTs) which met the inclusion criteria for this review.

See appendix B for the full literature search strategies and appendix C for a PRISMA diagram showing the flow of studies.

The previous review excluded studies if they were not conducted in the EU, USA, Canada, Australia or New Zealand. The committee did not think this restriction was necessary and so the excluded studies list from the previous update was checked to ensure that no studies excluded based on location met the inclusion criteria for this review. No additional studies were found that met our inclusion criteria.

See Appendix D for evidence tables of included studies.

1.1.4.2 Excluded studies

See Appendix I for excluded studies and reasons for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of included clinical studies

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
Adair 1996 (n=120) USA	• Duration of follow-up not reported	• Women with meconium stained amniotic fluid	Ampicillin/ Sulbactam *3.0 g of pre-prepared ampicillin/sulbactam intravenously, starting at the time of diagnosis of meconium stained amniotic fluid and repeated every 6 hours until delivery*	IV saline Given intravenously, starting at the time of diagnosis of meconium stained amniotic fluid and repeated every 6 hours until delivery	• Neonatal sepsis • Maternal infection: intra amniotic infection; endometritis
Edwards 2002 (n=352) USA	• RCT • Duration of follow-up not reported	• Spontaneous or induced labour • Gestational age of 36 weeks or more • Culture proven carriers of group B streptococci	Penicillin *5 MU of penicillin G intravenously followed by 2.5 MU every 4 hours until delivery*	Ampicillin *2 g intravenously followed by 1g every 4 hours until delivery*	• Suspected neonatal infection • Neonatal mortality • Neonatal hospital length of stay • Maternal infection: endometritis
Gibbs 1988 (n=48) USA	• RCT • 4 weeks follow-up	• Women with intra-amniotic infection	Intrapartum antibiotics *2 g ampicillin given intravenously every 6 hours plus 1.5 mg/kg gentamicin given intravenously every 8 hours*	Postpartum antibiotics *2 g ampicillin given intravenously every 6 hours plus 1.5 mg/kg gentamicin given intravenously every 8 hours*	• Culture confirmed neonatal infection • Neonatal length of stay
Lyell 2010 (n=126) USA	• RCT • Follow-up first 48 hours of life	• Women with chorioamnionitis • Gestational age 34-42 weeks	Daily gentamicin *5 mg/kg gentamicin delivered intravenously, followed by a*	8 hourly gentamicin *Loading dose of 2 mg/kg IV, followed by 1.5 mg/kg after 8 and 16 hours*	• Neonatal infection • Maternal infection: endometritis

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		• Maternal age 18 years or over	*normal saline placebo after 8 and 16 hours*		
Maberry 1991 (n=133) USA	• RCT • Duration of follow-up not reported	• Intra-amniotic infection • Gestational age >24 weeks	Dual therapy *Ampicillin and gentamicin. No information about doses or timing*	Triple therapy *Ampicillin, gentamicin and clindamycin. No information about doses or timing*	• Culture confirmed neonatal infection • Antibiotics for suspected neonatal infection • Neonatal mortality
Mattoras 1991 (n=121) Spain	• RCT • Duration of follow-up not reported	• Women with GBS colonisation	Ampicillin *500 mg of ampicillin intravenously/6 h during delivery*	No treatment *No ampicillin was given. Other aspects of care were the same*	• Neonatal infection
Morales 1986 (n=263) USA	• RCT • Duration of follow-up not reported	• Women with GBS colonisation	Ampicillin *1 g ampicillin intravenously every 6 hours until delivery*	Control *No information about whether this arm was no treatment or placebo*	• Culture confirmed neonatal infection
Nadisauskine 1996 (n=102) USA	• RCT • Duration of follow-up not reported	• Women in early active phase of preterm labour *Cervical dilation ≥4 cm* • Gestational age <37 weeks • Fetus alive	Ampicillin *5 g ampicillin IV infusion. Two doses, 4 hours apart*	Placebo *IV infusion. Two doses, 4 hours apart*	• Neonatal infection • Neonatal mortality • Maternal infection: chorioamnionitis; puerperal uterine infection
Tuppurainen 1989 (n=199) Finland	• RCT • Duration of follow-up not reported	• Women with group B streptococcus colonisation	Penicillin *5 million units of Penicillin G given intravenously every 6 hours during labour*	Control *No information about whether control was no treatment or placebo*	• Culture confirmed neonatal infection

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
		• No allergy to penicillin • Did not undergo elective term caesarean section without labour or rupture of fetal membranes			

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3 Quality assessment of clinical studies included in the evidence review

Comparison	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect*
Meconium stained amniotic fluid: Ampicillin/sulbactam versus saline (placebo)					
Maternal infection (Intra-amniotic infection)	1 (Adair 1996)	120	RR 0.29 (0.10, 0.82)	Low	Favours ampicillin/ sulbactam
Maternal infection (endometritis)	1 (Adair 1996)	120	RR 0.50 (0.18, 1.38)	Low	Could not differentiate
Maternal GBS colonisation: Penicillin versus ampicillin					
Antibiotics for suspected neonatal infection	1 (Edwards 2002)	352	RR 0.85 (0.49, 1.46)	Low	Could not differentiate
Neonatal mortality (timepoint not specified)	1 (Edwards 2002)	352	RR 3.03 (0.12, 73.98)	Moderate	Could not differentiate
Neonatal hospital length of stay (days)	1 (Edwards 2002)	352	MD 0.20 (-0.28, 0.68)	Moderate	Could not differentiate
Maternal GBS colonisation: Penicillins versus placebo					
Culture-confirmed neonatal infection	3	587	RR 0.16 (0.03, 0.87)	Low	Favours penicillins
Chorioamnionitis: Ampicillin and gentamicin versus no treatment					
Culture-confirmed neonatal infection	1 (Gibbs 1988)	45	RR 0.08 (0.00, 1.44)	High	Could not differentiate
Neonatal hospital length of stay (days)	1 (Gibbs 1988)	45	MD -1.90 (-3.31, -0.49)	High	Favours ampicillin and gentamicin
Chorioamnionitis: Ampicillin and gentamicin (dual therapy) versus ampicillin, gentamicin and clindamycin (triple therapy)					

Comparison	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect*
Culture-confirmed neonatal infection	1 (Maberry 1991)	133	RR 0.93 (0.06, 14.52)	Very low	Could not differentiate
Antibiotics for suspected neonatal infection	1 (Maberry 1991)	133	RR 1.00 (0.92, 1.10)	Very low	Could not differentiate
Neonatal mortality (timing unspecified)	1 (Maberry 1991)	133	RR 1.39 (0.24, 8.06)	Very low	Could not differentiate
Chorioamnionitis: Gentamicin (daily) versus gentamicin (8 hourly)					
Neonatal infection	1 (Lyell 2010)	125	RR 2.03 (0.39, 10.70)	Moderate	Could not differentiate
Maternal infection (endometritis)	1 (Lyell 2010)	125	RR 0.81 (0.23, 2.98)	Moderate	Could not differentiate
Preterm labour: Ampicillin versus placebo					
Neonatal mortality (within 7 days from birth)	1 (Nadisauskiene 1996)	102	RR 0.88 (0.39, 1.96)	Low	Could not differentiate
Maternal infection (chorioamnionitis)	1 (Nadisauskiene 1996)	102	RR 0.28 (0.13, 0.62)	Low	Favours ampicillin
Maternal infection (puerperal uterine infection)	1 (Nadisauskiene 1996)	102	RR 0.41 (0.20, 0.81)	Very low	Favours ampicillin

*Based on the direction of effect and whether confidence intervals cross the line of no effect.

See appendix F for full GRADE tables.

1.1.7 Economic evidence

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 4,398 studies. Based on title and abstract screening, 4,394 of the studies could confidently be excluded for this question. 4 studies were excluded following the full-text review.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 577 results. Based on title and abstract screening, all the studies could confidently be excluded for this question. Thus, the review for this question does not include any study from the existing literature.

1.1.8 Economic model

No economic modelling was undertaken for this review because of a lack of economic evidence and because the committee agreed that other topics were higher priorities for economic evaluation.

1.1.9 The committee's discussion and interpretation of the evidence

1.1.9.1. The outcomes that matter most

The committee were particularly interested in the effects of intrapartum antibiotics on the number of babies who either developed early-onset neonatal infection or who were given antibiotics for suspected infection. Neonatal infections are extremely serious and can result in death and long-term disability and so the committee focused on these outcomes. Although the focus of this guideline is neonatal infection, the committee were also interested in the effects of intrapartum antibiotics on maternal infection. No studies reported the maternal sepsis outcome that was stated in the protocol, but the committee agreed to consider other maternal infection outcomes, particularly those relating to chorioamnionitis and endometritis which they agreed could be used as indirect measures relating to maternal sepsis.

1.1.9.2 The quality of the evidence

Evidence ranged from low- to high-risk of bias and the neonatal outcomes were directly applicable to the review. The quality of outcomes for maternal infection were downgraded as they did not fully match the protocol definition of maternal sepsis. However, the committee decided that these were still important indicators of maternal outcomes and should be included within the review.

The evidence examined the effects of intrapartum antibiotics on four maternal risk factors (meconium stained amniotic fluid, maternal GBS colonisation, maternal chorioamnionitis and preterm labour). The studies for each risk factor compared different combinations of either antibiotics, placebo or no treatment, meaning that most of the analysis was based on results from individual studies rather than pooled meta-analyses. The committee had some concerns about how closely the evidence could be applied to current NHS practice as antibiotic resistance has changed considerably during the time since each of the studies were conducted.

One study examined the use of intrapartum antibiotics for women with meconium-stained amniotic fluid. This study used an antibiotic combination of ampicillin and sulbactam which is not licensed for use in the UK. Although the committee did not think these results were sufficient to be able to make a practice recommendation, it agreed that they should be used to develop a research recommendation on the effectiveness of intrapartum antibiotics for women with meconium stained amniotic fluid (Appendix K).

Four studies examined the effectiveness of intrapartum antibiotics for mothers who are colonised with GBS. Three compared the use of penicillin or ampicillin against placebo or no treatment and one compared the effectiveness of penicillin against ampicillin. The committee discussed the differences between the criteria used for diagnosing labour in the studies and those used in current UK practice. The differences in diagnostic criteria mean that many of the women in the studies received intrapartum antibiotics earlier than they would have in practice. However, the committee decided these results were still applicable to the review as women received the necessary antibiotics, even if earlier than necessary. These studies were therefore not downgraded for applicability. GBS colonisation was identified as one of the risk factors for neonatal infection in the risk factors section of this guideline, and so the committee decided that this should be a strong recommendation to 'use' antibiotics, rather than a recommendation that antibiotics should be considered. GBS in a previous pregnancy was also identified as a risk factor for neonatal infection, and so the committee extended the recommendation from the 2012 version of this guideline to state that women who had GBS in a

previous pregnancy, and have not had a negative test in the current pregnancy, should also be offered intrapartum antibiotics.

The effectiveness of intrapartum antibiotics given to mothers with chorioamnionitis was investigated by 3 studies. Again, the committee discussed the changes in antibiotic resistance since these studies were published, and how the antibiotics that were given to women may no longer be the most effective choice. The committee also highlighted differences between how chorioamnionitis was diagnosed in the studies and in clinical practice. One of the main issues in the criteria used for diagnosis in the studies was a minimum temperature of approximately 38°C. The committee discussed how women with similar temperatures in clinical practice would be given antibiotics and would not be left untreated as they were in the placebo or no treatment arms of these trials. The quality of the outcomes from these studies were therefore downgraded for being partially applicable to the review. There was also limited evidence to determine the effects of intrapartum antibiotics, with two of the studies comparing different antibiotic regimens, and only one study comparing intrapartum antibiotics against no treatment. This study reported neonatal, but no maternal, outcomes. However, the committee decided that recommendations for women with chorioamnionitis were important because this was identified as a risk factor for early-onset neonatal infection in the risk factors section of this guideline. Chorioamnionitis would be treated with antibiotics in practice to prevent harm to the mother, and the committee wanted to make recommendations on choice of antibiotics that would also reduce the risk of neonatal infection in the baby. The committee therefore used this information, in addition to their clinical experience, when deciding that intrapartum antibiotics should be offered to this group of women.

Only one study investigated the effects of intrapartum antibiotics for women in preterm labour. The criteria used to diagnose labour in this study (≥4 cm dilation) is different to how labour is now diagnosed and so the quality of outcomes were downgraded for partial applicability to the review. Although there was limited evidence, preterm labour was identified as one of the risk factors for neonatal infection in the risk factors section of this guideline. This, in addition to clinical experience, meant that the committee felt it was important to include women in preterm labour in the recommendations for intrapartum antibiotics. The committee decided that the size of the effects for reducing maternal infection were enough to make this an strong recommendation to ‘use’ antibiotics, rather than a recommendation that antibiotics should be considered. The committee also noted that this recommendation is consistent with current recommendations from the Royal College of Obstetricians and Gynaecologists on Group B Streptococcal Disease, Early-onset (Green top Guideline No.36).

1.1.9.3 Imprecision and clinical importance of effects

No published minimally important differences were found, and none were prespecified by the committee. The committee discussed the effect sizes and confidence intervals from each of the outcomes, and whether this influenced its interpretation of the results. Most of the outcomes were based on the results of a single study and the committee were aware that this was likely to result in wider confidence intervals, and therefore less certainty over the effects of intrapartum antibiotics. The low prevalence of early-onset neonatal infection was an additional issue which potentially increased the imprecision of the results.

Issues with imprecision were particularly apparent when considering the number of babies born to women with chorioamnionitis who developed neonatal infection. Although the effect estimate indicated that intrapartum antibiotics reduced the number of babies who developed infection, the confidence intervals indicated a high

degree of uncertainty over this effect. As a result, recommendations were made based on clinical consensus, and the evidence for chorioamnionitis as a risk factor for early-onset infection as well as extrapolation from the data for women with GBS colonisation.

Meta-analysis could be performed for one outcome (neonatal infection for babies born to mothers with GBS colonisation). From 3 studies with wide confidence intervals, the meta-analysis produced a pooled result that had a more precise estimate of the effect of intrapartum antibiotics. The committee were more confident in this effect than those that were reported from single studies, and so this evidence was used as a basis for the recommendation to use intrapartum antibiotics in this group of women.

1.1.9.4 Benefits and harms

The benefits of intrapartum antibiotics can include both treating infection in the mother and reducing the risk of early-onset infection in the baby. This can reduce the potential short- and long-term harms related to infection as well as reducing associated healthcare costs. Earlier treatment of maternal infection, or preventing a baby developing neonatal infection, will also result in a shorter length of stay in hospital following the birth. These benefits were demonstrated in the evidence, with fewer babies developing neonatal infection when intrapartum antibiotics were given to women who were colonised with GBS. When antibiotics were given to women in preterm labour, fewer of the mothers developed infection and intrapartum antibiotics given to women with chorioamnionitis resulted in shorter neonatal length of stay. For this reason, the committee decided to recommend that intrapartum antibiotics are used for women with clinical chorioamnionitis.

A potential harm associated with intrapartum antibiotics is the development of antibiotic resistance. To avoid this, it is important that antibiotics are not over-prescribed or inappropriate ones used. However, the committee did not expect these recommendations to result in a considerable increase in the number of women or babies receiving antibiotics. The committee thought that the main impact of the recommendation on the choice of antibiotics for women with chorioamnionitis would be to reduce variations in practice in the choice of antibiotic for these women. The committee highlighted that sometimes a broad-spectrum antibiotic was used to treat maternal infection, with additional benzylpenicillin prescribed to prevent neonatal infection. The committee decided to recommend a combination of benzylpenicillin, gentamicin and metronidazole to both treat maternal infection and prevent neonatal infection. Gentamicin was given to women in all three of the chorioamnionitis studies, and the committee considered this an appropriate choice because it is effective against gram negative bacteria which often cause chorioamnionitis. Metronidazole was included because this will cover any anaerobic organisms that may be causing infection. This recommendation should improve antibiotic stewardship by reducing prescriptions of broad-spectrum antibiotics; the committee were aware that women were sometimes prescribed a broad-spectrum antibiotic to treat chorioamnionitis as well as benzylpenicillin to prevent neonatal infection. Providing clear recommendations on a combination of narrow spectrum antibiotics that are effective against bacteria causing chorioamnionitis as well as those responsible for earlier onset neonatal infection is expected to result in more efficient use of antibiotics. In addition, the NICE antibiotic stewardship guideline (NG63) is available to help make clinicians aware of the issues associated with antibiotic resistance.

An additional issue with the prescribing of antibiotics is nephrotoxicity associated with the use of gentamicin and the potential for allergic reactions to penicillin. To reduce the risk of negative effects from allergic reactions the committee included advice on alternative antibiotics that should be given to women who have an allergy to penicillin, based on their knowledge and experience. The committee amended the 2012 recommendation on antibiotic alternatives for women who are allergic to penicillin. They changed the recommended antibiotic from clindamycin because there is evidence of resistance to GBS emerging in clindamycin, meaning that this antibiotic should no longer be used routinely. Based on their knowledge and experience, the committee recommended a cephalosporin with activity against group B streptococcus as an alternative for women with a penicillin allergy that was not severe, and vancomycin or an alternative antibiotic with activity against group B streptococcus in the case of severe penicillin allergy. Cephalosporins were not recommended in the case of severe penicillin allergy because of an increased chance of a severe allergic reaction to cephalosporins. The new recommendations on intrapartum antibiotics in women with penicillin allergy are consistent with those recommended in the Royal College of Obstetricians and Gynaecologists guideline on prevention of group B streptococcal infection in neonates.

For women who have had a GBS test, the committee did not think it was necessary to distinguish between a positive result from the NHS or a private clinic. Although some tests may have higher false positive rates, all women with positive tests should be treated as if they have GBS so that no mothers who have babies who are at higher risk of infection are missed. Discussions with women who have tested positive for GBS should be the same irrespective of where the test result came from. The committee were more concerned about a woman not receiving treatment because of a false negative test result, and so they decided to specify that a negative test should be from enrichment culture or PCR on rectovaginal swab samples.

1.1.9.5 Cost effectiveness and resource use

As there was no economic evidence, the committee discussed the cost effectiveness of intrapartum antibiotics based on their clinical experience. The committee noted many of the recommendations remain the same as in the 2012 guideline, and where new recommendations are made, these changes reflect common practice in many units. As such, the committee did not believe these recommendations would have a significant resource impact. However, as the cost of antibiotics are minimal relative to the significant costs associated with infection, the committee agreed that these recommendations are likely to result in cost savings at the population level.

1.1.9.6 Other factors the committee took into account

The committee discussed how meconium stained amniotic fluid is not widely considered as a reason to give women intrapartum antibiotics. Despite this, one study suggested that antibiotics may be effective for this group. However, given the age of the study and the use of antibiotics that are not licensed in the UK, the committee agreed that there was not currently enough evidence for them to confidently recommend this as a reason to give intrapartum antibiotics. It also discussed the difficulties in defining meconium stained amniotic fluid, which can vary depending on factors such as health and whether a woman has had an epidural. Given these uncertainties, the committee decided to make a research recommendation so that more evidence will be available for this group of women in future guideline updates (Appendix K).

The committee highlighted that many women in the UK are unaware of their GBS status as screening does not routinely take place in the NHS. This could be a source of inequality because women with lower socioeconomic status might be less likely to access private GBS testing. However, the committee agreed that recommendations for GBS are important for those who are aware of their current status, or those who had GBS in a previous pregnancy. Although there was no direct evidence on the impact of GBS in previous pregnancies, the committee highlighted that it is widely recognised as a factor that can greatly increase the risk of GBS in future pregnancies. It was therefore agreed that this was an important addition to the existing recommendations. The committee specified that these women should be offered antibiotics unless they were confirmed to be GBS negative by a culture collected between 35 and 37 weeks' gestation, or 3-5 weeks before the anticipated delivery date in the current pregnancy. The criteria for a test in late pregnancy was added because GBS status can change before this time. Cultures taken between 35 and 37 weeks where a baby is delivered at term, or 3-5 weeks before the expected delivery date when a baby will be delivered earlier, such as when expecting twins,is the most accurate way to rule out GBS colonisation before delivery. Although these results do not guarantee a woman's GBS status at the time of birth, a result for a test taken during these time periods is the most accurate indication.

A recommendation retained from the previous guideline was guidance on the timing of intrapartum antibiotics. This recommends that women are given the first dose of antibiotics as soon as possible and that treatment is continued until birth. The committee decided to add that the woman needs to be in labour before being given antibiotics to avoid unnecessary exposure to antibiotics for a prolonged period. This should ensure that women who have been prescribed intrapartum antibiotics are given them at the most appropriate time, rather than as soon as they are admitted to hospital if this is before the beginning of labour (for example for women admitted for induction of labour).

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.1-1.2.8 and the research recommendation on intrapartum antibiotics for women with meconium stained fluid (Appendix K).

1.1.11 References – included studies

1.1.11.1 Effectiveness

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Appendices

Appendix A – Review protocols

Review protocol for What is the clinical and cost effectiveness of intrapartum antibiotic prophylaxis for preventing early-onset neonatal infection?

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Intrapartum antibiotics to prevent early onset neonatal infection
2.	Review question	What is the clinical and cost effectiveness of intrapartum antibiotic prophylaxis for preventing early-onset neonatal infection?
3.	Objective	To evaluate the clinical and cost effectiveness of intrapartum antibiotic prophylaxis in the prevention of early-onset neonatal infection Considerations to include: • effectiveness of prophylaxis • which class or classes of antibiotics to use
4.	Searches	Searches will include all of the antibiotic classes and individual antibiotic drugs listed under interventions

		Searches will not distinguish between bactericidal and bacteriostatic agents The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE (including 'in process' and 'E-pub ahead of print') • Database of Abstracts of Reviews of Effect (DARE) Searches will be restricted by: • English language • Human studies • Conference abstracts Other searches: None

		A date limit corresponding to the search date for the previous guideline will be used (01 September 2011). The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review. This question formed part of the previous guideline (38 RCTs). The previous guideline restricted the review by geographical area. The current committee are unwilling to make this restriction for reviews of interventions. This was because the committee believed that while pathogens, risk factors and health care systems differ by geographic region, the relative effectiveness of interventions is likely to be less affected, and useful information may be obtained from all geographical regions. We will use the included studies from the previous review as a source of studies from this review and use a date limit corresponding to the search date from the previous guideline. We will also examine the list of excluded studies and also consider any studies excluded on the basis of geographical location for inclusion in addition.
5.	Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in neonates. It may be early-onset (within 72 hours of birth) or late-onset (more

		than 72 hours after birth). Neonatal infection can lead to life-threatening sepsis, which accounts for 10% of all neonatal deaths. To reduce mortality from early-onset neonatal infection, the current NICE guideline recommends antibiotic prophylaxis during labour to be based on multiple risk factors, clinical indicators and red flags collectively.
6.	Population	Inclusion: Women in labour with perceived risk factors (as defined by the study authors) for early-onset neonatal infection, including: • Suspected maternal intrapartum infection, including suspected chorioamnionitis • Pyrexia • Pre-term prelabour rupture of membranes • Previous baby with group B streptococcus (GBS) • Previous carrier of group B streptococcus (i.e. in a previous pregnancy) • Discovery of maternal GBS carriage through bacteriological investigation during pregnancy (for example, a urine infection or a swab taken to investigate a vaginal discharge) • Pre-term labour

		Exclusion: • Women with pre-labour rupture of membranes at term (covered in the NICE intrapartum care guideline)
7.	Intervention/Exposure/Test	• Antibiotics (and combinations of antibiotics, including intra and inter-class combinations) including: benzylpenicillin, amoxicillin, ampicillin, co-amoxiclav (Augmentin®), teicoplanin, clindamycin, azithromycin, cephalosporins, erythromycin, metronidazole and vancomycin
8.	Comparator/Reference standard/Confounding factors	• Head-to-head comparison with any of the interventions (including combinations) listed above (including intra and inter-class comparisons) • Placebo • No treatment / usual care
9.	Types of study to be included	• Randomised controlled trials (RCTs) • Systematic reviews of RCTs
10.	Other exclusion criteria	Non-English language studies
11.	Context	NICE guideline CG149 Neonatal infection will be updated by this question.
12.	Primary outcomes (critical outcomes)	Neonatal outcomes:

		• Culture-proven infection from sample taken within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection • Antibiotics for suspected bloodstream infection (Antibiotics for suspected bloodstream infection was chosen as a surrogate outcome for infection, as not all infection will be culture proven) • Mortality (at different time points – peri-natal mortality (stillborn or within 7 days from birth) or greater than 7 days from birth) • health-related quality of life, measured using a validated tool (during the neonatal period and at the last time point reported in the study) • hospital length of stay • neurodevelopmental outcomes (measured using a validated tool at the latest time point reported in the study) Maternal/family outcomes: • psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory) (during the intrapartum period and at the latest timepoint reported in study) • Maternal adverse events (during the intrapartum period and at the latest timepoint reported in study):

		○ serious adverse events ○ allergic reaction to antibiotics • Maternal sepsis (during the intrapartum period and within 6 weeks of birth)
13.	Secondary outcomes (important outcomes)	Not applicable. The committee did not wish to distinguish between critical and important outcomes as they considered all of the specified outcomes important for decision making.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data will be extracted from the included studies into a standardised form for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and comparator used ; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias. Study investigators may be contacted for missing data where time and resources allow. This review will make use of the priority screening functionality within the EPPI-reviewer software.

15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane RoB 2.0 checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. • Meta-analyses will be performed in Cochrane Review Manager V5.3

17.	Analysis of sub-groups	• Antibiotics will be grouped by class for the purpose of the analysis If substantial heterogeneity is encountered (I^2>50%), this will be investigated by analysing antibiotics separately, rather than by class **Stratifications** • Analysis will be stratified by the population groups specified in item 6. • Analysis will be stratified by dose as follows: below range recommended in the SPC, within range recommended in SPC, above range recommended in SPC **Subgroups** • Timing of antibiotic administration relative to the start of labour
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	01/01/2019		
22.	Anticipated completion date	12/08/2020		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches		
		Piloting of the study selection process		
		Formal screening of search results against eligibility criteria		
		Data extraction		

		Risk of bias (quality) assessment		
		Data analysis		
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** NIupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	From the Guideline Updates Team: • Dr Kathryn Hopkins • Dr Clare Dadswell • Mr Gabriel Rogers • Dr Stacey-Chang Douglass • Mr Wesley Hubbard		
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must		

		declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Intrapartum antibiotics, early onset neonatal infection
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	The guideline with supporting evidence reviews will be published on the NICE website.

Appendix B – Literature search strategies

Clinical search literature search strategy

The search was conducted on 13th December 2019. The following databases were searched:

Medline, Medline In Process, Medline E-pub Ahead of print, Embase, (all via the Ovid platform), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, (both via the Wiley platform), and the DARE database (via the CRD platform).

As this was an update search. A date limit was applied between February 2011 and December 2019.

Population and Antibiotic Terms

The search terms used to identify information on population and antibiotics are reproduced below for all databases. The population and antibiotic terms were combined as 'And' to identify papers that discussed both.

Medline, Medline in Process & Medline E-pub Ahead of Print

1 exp Infant, Newborn/

2 Term Birth/

3 Infant Care/

4 Perinatal Care/

5 Intensive Care Units, Neonatal/

6 Intensive Care, Neonatal/

7 Infant Health/

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw.

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw.

10 or/1-9

11 exp Bacterial Infections/

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

13 exp Sepsis/

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw.

15 (septic* adj4 shock*).tw.

16 (bacter?emia* or bacill?emia*).tw.

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw.

18 or/11-17

19 exp Streptococcus/

20 exp Staphylococcus/

21 (streptococc* or staphylococc*).tw.

22 (GBS or MRSA or NRCS-A or MSSA).tw.

23 (met?icillin-resistant adj3 aureus).tw.

24 exp Escherichia coli/

25 ((Escheric* or E) adj2 coli).tw.

26 exp Listeria/

27 listeria*.tw.

28 exp Klebsiella/

29 klebsiella*.tw.

30 exp Pseudomonas/

31 (pseudomonas or chryseomonas or flavimonas).tw.

32 Enterobacteriaceae/

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.

34 ((enteric or coliform) adj2 bac*).tw.

35 exp Neisseria/

36 neisseria*.tw.

37 exp Haemophilus influenzae/

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw.

39 exp Serratia/

40 serratia*.tw.

41 exp Cronobacter/

42 (cronobact* or sakazaki* or malonatic*).tw.

43 exp Acinetobacter/

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw.

45 exp Fusobacterium/

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.

47 exp Enterococcus/

48 enterococc*.tw.

49 or/19-48

50 18 or 49

51 10 and 50

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw.

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw.

54 52 or 53

55 51 or 54

56 Antibiotic Prophylaxis/

57 ((antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid* or bacteriostat*) and (prophyla* or premedic* or pre-medic* or prevent*)).tw.

58 56 or 57

59 exp Anti-Bacterial Agents/

60 exp Penicillins/

61 penicillin*.tw.

62 (benzylpenicillin* or crystapen* or bicillin* or triplopen* or pentids* or pfizerpen*).tw.

63 (amox?cillin* or hydroxyamp?cillin* or almodan* or amix* or amopen* or amoram* or amoxident* or amoxidin* or amoxil* or amoxymed* or amrit* or flemoxin* or galenamox* or rimoxallin* or amiclav* or augmentin* or heliclear* or amoxiclav* or biomox* or DisperMox* or larotid* or moxatag* or polymox* or trimox* or wymox* or amoclan* or omeclamox* or prevpac*).tw.

64 (ampicillin* or KS-R1 or aminobenzylpenicillin* or amfipen* or flu-amp* or magnapen* or penbritin* or rimacillin* or vidopen* or ampiclox* or dicapen* or D-Amp* or marcillin* or omnipen* or polycillin* or principen* or totacillin* or unasyn*).tw.

65 Teicoplanin/

66 (teicoplanin* or teichom?cin* or targocid*).tw.

67 Clindamycin/

68 (clindam?cin* or dalacin* or zindaclin* or Duac or refobacin* or treclin* or cleocin* or Clinda-Derm* or ClindaMax* or clindagel* or clindesse* or clindets* or evoclin* or acanya* or benzaclin* or clindacin* or onexton* or PledgaClin* or veltin* or ziana*).tw.

69 (azithrom?cin* or azyter* or clamelle* or zedbac* or zithromax* or AzaSite* or zmax*).tw.

70 exp Cephalosporins/

71 (cephalosporin* or cephalosporanic* or cepham?cin*).tw.

72 (cefamandole* or kefadol* or mandol*).tw.

73 (cefazolin* or kefzol* or ancef* or zolicef*).tw.

74 (cefepim* or renapime* or maxipime*).tw.

75 (cefsulodin* or monaspor*).tw.

76 (ceftibuten* or cedax*).tw.

77 (cefuroxime* or cephuroxime* or aprokam* or ximaract* or zinacef* or zinnat* or ceftin* or kefurox*).tw.

78 (cefotaxim* or cephotaxim* or cefizox*).tw.

79 (cefixime* or suprax*).tw.

80 (ceftizoxime* or cefizox*).tw.

81 (cef?triaxon* or rocephin*).tw.

82 (cephalothin* or cefalotin* or keflin*).tw.

83 (cefalexin* or cephalexin* or ceporex* or keflex* or kiflone* or biocef* or cefanex* or keflet* or keftab* or zartan*).tw.

84 (cefaclor* or bacticlor* or distaclor* or keftid* or ceclor* or raniclor*).tw.

85 (cefadroxil* or cephadroxyl* or baxan* or duricef* or ultracef*).tw.

86 (cefradine* or cephradine* or nicef* or velosef* or anspor*).tw.

87 (ceftazidime* or fortum* or kefadim* or zavicefta* or ceptaz* or fortaz* or tazicef* or tazidime*).tw.

88 (cefoxitin* or mefoxin* or renoxitin*).tw.

89 (ceftaroline* or zinforo* or teflaro*).tw.

90 exp Erythromycin/

91 (erythrom?cin* or arpim?cin* or eryacne* or erycen* or erymax* or erymin* or erythrocin* or erythrolar* or erythromid* or erythroped* or ilosone* or retcin* or rommix* or ronmix* or stiem?cin* or tiloryth* or aknem?cin* or benzam?cin* or isotrexin* or zineryt* or Ak-Mycin* or Akne-Mycin* or Del-Mycin* or E-Base or E-Mycin or emgel* or eram?cin* or Ery-Tab* or Ery-sol* or eryc or erycette* or eryderm* or erygel* or erymax* or eryped* or Erythra-Derm* or ilot?cin* or pediam?cin* or robim?cin* or rom?cin* or staticin or T-Stat or theram?cin* or wyam?cin* or aktipak* or eryzole* or pediazole*).tw.

92 (clarithrom?cin* or clarosip* or febzin* or klaricid* or mycifor* or HeliMet* or heliclear* or biaxin* or omeclamox-pak* or prevpac* or clarie xl* or xetinin xl*).tw.

93 Metronidazole/

94 (metronidazole* or acea* or anabact* or elyzol* or flagyl* or metrogel* or metrolyl* or metrosa* or metrotop* or metrozol* or nidazol* or noritate* or norzol* or rosiced* or rozex* or vaginyl* or zadstat* or zidoval* or zyomet* or entamizole*).tw.

95 Vancomycin/

96 (vancom?cin* or vancocin* or firvanq* or lyphocin* or vancocin* or vancoled*).tw.

97 (azlocillin* or securopen* or azlin*).tw.

98 (mezlocillin* or baypen* or mezlin*).tw.

99 (piperacillin* or pipril* or tazocin* or pipracil* or zosyn*).tw.

100 (pivampicillin* or pondocillin* or miraxid*).tw.

101 (talampicillin* or talpen*).tw.

102 (carbenicillin* or pyopen* or geopen*).tw.

103 (carfecillin* or uticillin*).tw.

104 (flucloxacillin* or floxacillin* or fluorochloroxacillin* or floxapen* or fluclomix* or galfloxin* or ladropen* or stafoxil* or staphlipen* or zoxin*).tw

105 exp Glycopeptides/

106 (glycopeptide* or lipoglycopeptide*).tw.

107 exp Aminoglycosides/

108 aminoglycoside*.tw.

109 (gentamicin* or gentamycin* or gentacycol* or G-Myticin* or GMyticin*).tw.

110 (cidom?cin* or garam?cin* or genticin* or lugacin* or collatamp* or refobacin* or septocoll* or septopal* or vipsogal* or genoptic* or gentacidin* or gentafair* or gentak* or gentasol* or gentrasul* or jenam?cin* or Ocu-Mycin*).tw.

111 (amikacin* or amikin* or arikayce*).tw.

112 (tobram?cin* or bramitob* or nebcin* or Tobi or tobralex* or tobravisc* or vantobra*).tw.

113 exp Carbapenems/

114 carbapenem*.tw.

115 (meropenem* or meronem* or merrem* or vabomere*).tw.

116 (bleom?cin* or Bleo or blenoxane*).tw.

117 or/59-116

118 Pre-Exposure Prophylaxis/

119 Post-Exposure Prophylaxis/

120 Preventive Medicine/

121 Primary Prevention/

122 Secondary Prevention/

123 Tertiary Prevention/

124 (prophyla* or premedic* or pre-medic* or prevent*).tw.

125 or/118-124

126 117 and 125

127 58 or 126

128 55 and 127

129 Animals/ not Humans/

130 128 not 129

131 limit 130 to english language

Embase

1 newborn/

2 term birth/

3 infant care/

4 perinatal care/

5 neonatal intensive care unit/

6 newborn intensive care/

7 child health/

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw.

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw.

10 or/1-9

11 exp bacterial infection/

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw.

13 exp sepsis/

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw.

15 (septic* adj4 shock*).tw.

16 (bacter?emia* or bacill?emia*).tw.

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw.

18 or/11-17

19 exp Streptococcus/

20 exp Staphylococcus/

21 (streptococc* or staphylococc*).tw.

22 (GBS or MRSA or NRCS-A or MSSA).tw.

23 (met?icillin-resistant adj3 aureus).tw.

24 exp Escherichia coli/

25 ((Escheric* or E) adj2 coli).tw.

26 exp Listeria/

27 listeria*.tw.

28 exp Klebsiella/

29 klebsiella*.tw.

30 exp Pseudomonas/

31 (pseudomonas or chryseomonas or flavimonas).tw.

32 Enterobacteriaceae/

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw.

34 ((enteric or coliform) adj2 bac*).tw.

35 exp Neisseria/

36 neisseria*.tw.

37 exp Haemophilus influenzae/

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw.

39 exp Serratia/

40 serratia*.tw.

41 exp cronobacter/

42 (cronobact* or sakazaki* or malonatic*).tw.

43 exp Acinetobacter/

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw.

45 exp Fusobacterium/

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw.

47 exp Enterococcus/

48 enterococc*.tw.

49 or/19-48

50 18 or 49

51 10 and 50

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw.

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw.

54 52 or 53

55 51 or 54

56 antibiotic prophylaxis/

57 ((antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid* or bacteriostat*) and (prophyla* or premedic* or pre-medic* or prevent*)).tw.

58 56 or 57

59 exp antiinfective agent/

60 exp penicillin derivative/

61 penicillin*.tw.

62 (benzylpenicillin* or crystapen* or bicillin* or triplopen* or pentids* or pfizerpen*).tw.

63 (amox?cillin* or hydroxyamp?cillin* or almodan* or amix* or amopen* or amoram* or amoxident* or amoxidin* or amoxil* or amoxymed* or amrit* or flemoxin* or galenamox* or rimoxallin* or amiclav* or augmentin* or heliclear* or amoxiclav* or biomox* or DisperMox* or larotid* or moxatag* or polymox* or trimox* or wymox* or amoclan* or omeclamox* or prevpac*).tw.

64 (ampicillin* or KS-R1 or aminobenzylpenicillin* or amfipen* or flu-amp* or magnapen* or penbritin* or rimacillin* or vidopen* or ampiclox* or dicapen* or D-Amp* or marcillin* or omnipen* or polycillin* or principen* or totacillin* or unasyn*).tw.

65 teicoplanin/

66 (teicoplanin* or teichom?cin* or targocid*).tw.

67 clindamycin/

68 (clindam?cin* or dalacin* or zindaclin* or Duac or refobacin* or treclin* or cleocin* or Clinda-Derm* or ClindaMax* or clindagel* or clindesse* or clindets* or evoclin* or acanya* or benzaclin* or clindacin* or onexton* or PledgaClin* or veltin* or ziana*).tw.

69 azithromycin/

70 (azithrom?cin* or azyter* or clamelle* or zedbac* or zithromax* or AzaSite* or zmax*).tw.

71 exp cephalosporin derivative/

72 (cephalosporin* or cephalosporanic* or cepham?cin*).tw.

73 (cefamandole* or kefadol* or mandol*).tw.

74 (cefazolin* or kefzol* or ancef* or zolicef*).tw.

75 (cefepim* or renapime* or maxipime*).tw.

76 (cefsulodin* or monaspor*).tw.

77 (ceftibuten* or cedax*).tw.

78 (cefuroxime* or cephuroxime* or aprokam* or ximaract* or zinacef* or zinnat* or ceftin* or kefurox*).tw.

79 (cefotaxim* or cephotaxim* or cefizox*).tw.

80 (cefixime* or suprax*).tw.

81 (ceftizoxime* or cefizox*).tw.

82 (cef?triaxon* or rocephin*).tw.

83 (cephalothin* or cefalotin* or keflin*).tw.

84 (cefalexin* or cephalexin* or ceporex* or keflex* or kiflone* or biocef* or cefanex* or keflet* or keftab* or zartan*).tw.

85 (cefaclor* or bacticlor* or distaclor* or keftid* or ceclor* or raniclor*).tw.

86 (cefadroxil* or cephadroxyl* or baxan* or duricef* or ultracef*).tw.

87 (cefradine* or cephradine* or nicef* or velosef* or anspor*).tw. (

88 (ceftazidime* or fortum* or kefadim* or zavicefta* or ceptaz* or fortaz* or tazicef* or tazidime*).tw. (

89 (cefoxitin* or mefoxin* or renoxitin*).tw.

90 (ceftaroline* or zinforo* or teflaro*).tw.

91 erythromycin/

92 (erythrom?cin* or arpim?cin* or eryacne* or erycen* or erymax* or erymin* or erythrocin* or erythrolar* or erythromid* or erythroped* or ilosone* or retcin* or rommix* or ronmix* or stiem?cin* or tiloryth* or aknem?cin* or benzam?cin* or isotrexin* or zineryt* or Ak-Mycin* or Akne-Mycin* or Del-Mycin* or E-Base or E-Mycin or emgel* or eram?cin* or Ery-Tab* or Ery-sol* or eryc or erycette* or eryderm* or erygel* or erymax* or eryped* or Erythra-Derm* or ilot?cin* or pediam?cin* or robim?cin* or rom?cin* or staticin or T-Stat or theram?cin* or wyam?cin* or aktipak* or eryzole* or pediazole*).tw.

93 clarithromycin/

94 (clarithrom?cin* or clarosip* or febzin* or klaricid* or mycifor* or HeliMet* or heliclear* or biaxin* or omeclamox-pak* or prevpac* or clarie xl* or xetinin xl*).tw.

95 metronidazole/

96 (metronidazole* or acea* or anabact* or elyzol* or flagyl* or metrogel* or metrolyl* or metrosa* or metrotop* or metrozol* or nidazol* or noritate* or norzol* or rosiced* or rozex* or vaginyl* or zadstat* or zidoval* or zyomet* or entamizole*).tw.

97 vancomycin/

98 (vancom?cin* or vancocin* or firvanq* or lyphocin* or vancocin* or vancoled*).tw. (38961)

99 (azlocillin* or securopen* or azlin*).tw.

100 (mezlocillin* or baypen* or mezlin*).tw.

101 (piperacillin* or pipril* or tazocin* or pipracil* or zosyn*).tw.

102 (pivampicillin* or pondocillin* or miraxid*).tw.

103 (talampicillin* or talpen*).tw.

104 (carbenicillin* or pyopen* or geopen*).tw.

105 (carfecillin* or uticillin*).tw.

106 (flucloxacillin* or floxacillin* or fluorochloroxacillin* or floxapen* or fluclomix* or galfloxin* or ladropen* or stafoxil* or staphlipen* or zoxin*).tw.

107 exp glycopeptide/

108 (glycopeptide* or lipoglycopeptide*).tw.

109 aminoglycoside/

110 aminoglycoside*.tw.

111 gentamicin/

112 (gentamicin* or gentamycin* or gentacycol* or G-Myticin* or GMyticin*).tw.

113 (cidom?cin* or garam?cin* or genticin* or lugacin* or collatamp* or refobacin* or septocoll* or septopal* or vipsogal* or genoptic* or gentacidin* or gentafair* or gentak* or gentasol* or gentrasul* or jenam?cin* or Ocu-Mycin*).tw.

114 amikacin/

115 (amikacin* or amikin* or arikayce*).tw.

116 tobramycin/

117 (tobram?cin* or bramitob* or nebcin* or Tobi or tobralex* or tobravisc* or vantobra*).tw.

118 carbapenem derivative/

119 carbapenem*.tw.

120 meropenem/

121 (meropenem* or meronem* or merrem* or vabomere*).tw.

122 (bleom?cin* or Bleo or blenoxane*).tw.

123 or/59-122

124 prophylaxis/ or infection prevention/ or post exposure prophylaxis/ or pre-exposure prophylaxis/ or vector control/

125 preventive medicine/

126 primary prevention/

127 secondary prevention/

128 tertiary prevention/

129 (prophyla* or premedic* or pre-medic* or prevent*).tw.

130 or/124-129

131 123 and 130

132 58 or 131

133 55 and 132

134 nonhuman/ not human/

135 133 not 134

136 limit 135 to english language

137 limit 136 to (conference abstract or conference paper or "conference review")

138 136 not 137

Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials

#1 MeSH descriptor: [Infant, Newborn] explode all trees

#2 MeSH descriptor: [Term Birth] this term only

#3 MeSH descriptor: [Infant Care] this term only

#4 MeSH descriptor: [Perinatal Care] this term only

#5 MeSH descriptor: [Intensive Care Units, Neonatal] this term only

#6 MeSH descriptor: [Intensive Care, Neonatal] this term only

#7 MeSH descriptor: [Infant Health] this term only

#8 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*)):ti,ab,kw

#9 ((premature* or pre-mature* or preterm* or pre-term*) near/4 (child* or infant* or baby* or babies* or offspring)):ti,ab,kw

#10 {or #1-#9}

#11 MeSH descriptor: [Bacterial Infections] explode all trees

#12 ((bacter* or strep* or staph* or GNB) near/4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)):ti,ab,kw

#13 MeSH descriptor: [Sepsis] explode all trees

#14 (sepsis or septic?emia* or py?emia* or pyho?emia*):ti,ab,kw

#15 (septic* near/4 shock*):ti,ab,kw

#16 (bacter?emia* or bacill?emia*):ti,ab,kw

#17 ((blood*) near/4 (infect* or contamin* or invas* or invad*)):ti,ab,kw

#18 {or #11-#17}

#19 MeSH descriptor: [Streptococcus] explode all trees

#20 MeSH descriptor: [Staphylococcus] explode all trees

#21 (streptococc* or staphylococc*):ti,ab,kw

#22 (GBS or MRSA or NRCS-A or MSSA):ti,ab,kw

#23 (met?icillin-resistant near/3 aureus):ti,ab,kw

#24 MeSH descriptor: [Escherichia coli] explode all trees

#25 ((Escheric* or E) near/2 (coli)):ti,ab,kw

#26 MeSH descriptor: [Listeria] explode all trees

#27 (listeria*):ti,ab,kw

#28 MeSH descriptor: [Klebsiella] explode all trees

#29 (klebsiella*):ti,ab,kw

#30 MeSH descriptor: [Pseudomonas] explode all trees

#31 (pseudomonas or chryseomonas or flavimonas):ti,ab,kw

#32 MeSH descriptor: [Enterobacteriaceae] explode all trees

#33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia):ti,ab,kw

#34 ((enteric or coliform) near/2 (bac*)):ti,ab,kw

#35 MeSH descriptor: [Neisseria] explode all trees

#36 (neisseria*):ti,ab,kw

#37 MeSH descriptor: [Haemophilus influenzae] explode all trees

#38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) near/2 (influenz* or pfeiffer* or meningitidis)):ti,ab,kw

#39 MeSH descriptor: [Serratia] explode all trees

#40 (serratia*):ti,ab,kw

#41 MeSH descriptor: [Cronobacter] explode all trees

#42 (cronobact* or sakazaki* or malonatic*):ti,ab,kw

#43 MeSH descriptor: [Acinetobacter] explode all trees

#44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*):ti,ab,kw

#45 MeSH descriptor: [Fusobacterium] explode all trees

#46 (fusobact* or sphaerophor* or necrophorum or nucleatum):ti,ab,kw

#47 MeSH descriptor: [Enterococcus] explode all trees

#48 (enterococc*):ti,ab,kw

#49 {or #19-#48}

#50 #18 or #49

#51 #10 and #50

#52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) near/4 (infect*)):ti,ab,kw

#53 ((premature* or pre-mature* or "preterm*" or "pre-term*") near/4 (child* or infant* or baby* or babies* or offspring) near/4 (infect*)):ti,ab,kw

#54 #52 or #53

#55 #51 or #54

#56 MeSH descriptor: [Antibiotic Prophylaxis] this term only

#57 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid* or bacteriostat*) and (prophyla* or premedic* or pre-medic* or prevent*):ti,ab,kw

#58 #56 or #57

#59 MeSH descriptor: [Anti-Bacterial Agents] explode all trees

#60 MeSH descriptor: [Penicillins] explode all trees

#61 (penicillin*):ti,ab,kw

#62 (benzylpenicillin* or crystapen* or bicillin* or triplopen* or pentids* or pfizerpen*):ti,ab,kw

#63 (amox?cillin* or hydroxyamp?cillin* or almodan* or amix* or amopen* or amoram* or amoxident* or amoxidin* or amoxil* or amoxymed* or amrit* or flemoxin* or galenamox* or rimoxallin* or amiclav* or augmentin* or heliclear* or amoxiclav* or biomox* or DisperMox* or larotid* or moxatag* or polymox* or trimox* or wymox* or amoclan* or omeclamox* or prevpac*):ti,ab,kw

#64 (ampicillin* or KS-R1 or aminobenzylpenicillin* or amfipen* or flu-amp* or magnapen* or penbritin* or rimacillin* or vidopen* or ampiclox* or dicapen* or D-Amp* or marcillin* or omnipen* or polycillin* or principen* or totacillin* or unasyn*):ti,ab,kw

#65 MeSH descriptor: [Teicoplanin] this term only

#66 (teicoplanin* or teichom?cin* or targocid*):ti,ab,kw

#67 MeSH descriptor: [Clindamycin] this term only

#68 (clindam?cin* or dalacin* or zindaclin* or Duac or refobacin* or treclin* or cleocin* or Clinda-Derm* or ClindaMax* or clindagel* or clindesse* or clindets* or evoclin* or acanya* or benzaclin* or clindacin* or onexton* or PledgaClin* or veltin* or ziana*):ti,ab,kw

#69 (azithrom?cin* or azyter* or clamelle* or zedbac* or zithromax* or AzaSite* or zmax*):ti,ab,kw

#70 MeSH descriptor: [Cephalosporins] explode all trees

#71 (cephalosporin* or cephalosporanic* or cepham?cin*):ti,ab,kw

#72 (cefamandole* or kefadol* or mandol*):ti,ab,kw

#73 (cefazolin* or kefzol* or ancef* or zolicef*):ti,ab,kw

#74 (cefepim* or renapime* or maxipime*):ti,ab,kw

#75 (cefsulodin* or monaspor*):ti,ab,kw

#76 (ceftibuten* or cedax*):ti,ab,kw

#77 (cefuroxime* or cephuroxime* or aprokam* or ximaract* or zinacef* or zinnat* or ceftin* or kefurox*):ti,ab,kw

#78 (cefotaxim* or cephotaxim* or cefizox*):ti,ab,kw

#79 (cefixime* or suprax*):ti,ab,kw

#80 (ceftizoxime* or cefizox*):ti,ab,kw

#81 (cef?triaxon* or rocephin*):ti,ab,kw

#82 (cephalothin* or cefalotin* or keflin*):ti,ab,kw

#83 (cefalexin* or cephalexin* or ceporex* or keflex* or kiflone* or biocef* or cefanex* or keflet* or keftab* or zartan*):ti,ab,kw

#84 (cefaclor* or bacticlor* or distaclor* or keftid* or ceclor* or raniclor*):ti,ab,kw

#85 (cefadroxil* or cephadroxyl* or baxan* or duricef* or ultracef*):ti,ab,kw

#86 (cefradine* or cephradine* or nicef* or velosef* or anspor*):ti,ab,kw

#87 (ceftazidime* or fortum* or kefadim* or zavicefta* or ceptaz* or fortaz* or tazicef* or tazidime*):ti,ab,kw

#88 (cefoxitin* or mefoxin* or renoxitin*):ti,ab,kw

#89 (ceftaroline* or zinforo* or teflaro*):ti,ab,kw

#90 MeSH descriptor: [Erythromycin] explode all trees

#91 (erythrom?cin* or arpim?cin* or eryacne* or erycen* or erymax* or erymin* or erythrocin* or erythrolar* or erythromid* or erythroped* or ilosone* or retcin* or rommix* or ronmix* or stiem?cin* or tiloryth* or aknem?cin* or benzam?cin* or isotrexin* or zineryt* or Ak-Mycin* or Akne-Mycin* or Del-Mycin* or E-Base or E-Mycin or emgel* or eram?cin* or Ery-Tab* or Ery-sol* or eryc or erycette* or eryderm* or erygel* or erymax* or eryped* or Erythra-Derm* or ilot?cin* or pediam?cin* or robim?cin* or rom?cin* or staticin or T-Stat or theram?cin* or wyam?cin* or aktipak* or eryzole* or pediazole*):ti,ab,kw

#92 (clarithrom?cin* or clarosip* or febzin* or klaricid* or mycifor* or HeliMet* or heliclear* or biaxin* or omeclamox-pak* or prevpac* or clarie xl* or xetinin xl*):ti,ab,kw

#93 MeSH descriptor: [Metronidazole] this term only

#94 (metronidazole* or acea* or anabact* or elyzol* or flagyl* or metrogel* or metrolyl* or metrosa* or metrotop* or metrozol* or nidazol* or noritate* or norzol* or rosiced* or rozex* or vaginyl* or zadstat* or zidoval* or zyomet* or entamizole*):ti,ab,kw

#95 MeSH descriptor: [Vancomycin] this term only

#96 (vancom?cin* or vancocin* or firvanq* or lyphocin* or vancocin* or vancoled*):ti,ab,kw

#97 (azlocillin* or securopen* or azlin*):ti,ab,kw

#98 (mezlocillin* or baypen* or mezlin*):ti,ab,kw

#99 (piperacillin* or pipril* or tazocin* or pipracil* or zosyn*):ti,ab,kw

#100 (pivampicillin* or pondocillin* or miraxid*):ti,ab,kw

#101 (talampicillin* or talpen*):ti,ab,kw

#102 (carbenicillin* or pyopen* or geopen*):ti,ab,kw

#103 (carfecillin* or uticillin*):ti,ab,kw

#104 (flucloxacillin* or floxacillin* or fluorochloroxacillin* or floxapen* or fluclomix* or galfloxin* or ladropen* or stafoxil* or staphlipen* or zoxin*):ti,ab,kw

#105 MeSH descriptor: [Glycopeptides] explode all trees

#106 (glycopeptide* or lipoglycopeptide*):ti,ab,kw

#107 MeSH descriptor: [Aminoglycosides] explode all trees

#108 (aminoglycoside*):ti,ab,kw

#109 (gentamicin* or gentamycin* or gentacycol* or G-Myticin* or GMyticin*):ti,ab,kw

#110 (cidom?cin* or garam?cin* or genticin* or lugacin* or collatamp* or refobacin* or septocoll* or septopal* or vipsogal* or genoptic* or gentacidin* or gentafair* or gentak* or gentasol* or gentrasul* or jenam?cin* or Ocu-Mycin*):ti,ab,kw

#111 (amikacin* or amikin* or arikayce*):ti,ab,kw

#112 (tobram?cin* or bramitob* or nebcin* or Tobi or tobralex* or tobravisc* or vantobra*):ti,ab,kw

#113 MeSH descriptor: [Carbapenems] explode all trees

#114 (carbapenem*):ti,ab,kw

#115 (meropenem* or meronem* or merrem* or vabomere*):ti,ab,kw

#116 (bleom?cin* or Bleo or blenoxane*):ti,ab,kw

#117 {or #59-#116}

#118 MeSH descriptor: [Pre-Exposure Prophylaxis] this term only

#119 MeSH descriptor: [Post-Exposure Prophylaxis] this term only

#120 MeSH descriptor: [Preventive Medicine] this term only

#121 MeSH descriptor: [Primary Prevention] this term only

#122 MeSH descriptor: [Secondary Prevention] this term only

#123 MeSH descriptor: [Tertiary Prevention] this term only

#124 (prophyla* or premedic* or pre-medic* or prevent*):ti,ab,kw

#125 {or #118-#124}

#126 #117 and #125

#127 #58 or #126

DARE

1 MeSH DESCRIPTOR Infant, Newborn EXPLODE ALL TREES

2 MeSH DESCRIPTOR Term Birth

3 MeSH DESCRIPTOR Infant Car

4 MeSH DESCRIPTOR Perinatal Care

5 MeSH DESCRIPTOR Intensive Care Units, Neonatal

6 MeSH DESCRIPTOR Intensive Care, Neonatal

7 MeSH DESCRIPTOR Infant Health

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*)

9 ((premature* or pre-mature* or preterm* or pre-term*) NEAR4 (child* or infant* or baby* or babies* or offspring))

10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)

11 MeSH DESCRIPTOR Bacterial Infections EXPLODE ALL TREES

12 ((bacter* or strep* or staph* or GNB) NEAR4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*))

13 MeSH DESCRIPTOR Sepsis EXPLODE ALL TREES

14 (sepsis or septic?emia* or py?emia* or pyho?emia*)

15 (septic* NEAR4 shock*)

16 (bacter?emia* or bacill?emia*)

17 ((blood*) NEAR4 (infect* or contamin* or invas* or invad*))

18 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)

19 MeSH DESCRIPTOR Streptococcus EXPLODE ALL TREES

20 MeSH DESCRIPTOR Staphylococcus EXPLODE ALL TREES

21 (streptococc* or staphylococc*)

22 (GBS or MRSA or NRCS-A or MSSA)

23 (met?icillin-resistant NEAR3 aureus)

24 MeSH DESCRIPTOR Escherichia coli EXPLODE ALL TREES

25 ((Escheric* or E) NEAR2 (coli))

26 MeSH DESCRIPTOR listeria EXPLODE ALL TREES

27 (listeria*)

28 MeSH DESCRIPTOR Klebsiella EXPLODE ALL TREES

29 (klebsiella*)

30 MeSH DESCRIPTOR Pseudomonas EXPLODE ALL TREES

31 (pseudomonas or chryseomonas or flavimonas)

32 MeSH DESCRIPTOR Enterobacteriaceae EXPLODE ALL TREES

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia)

34 ((enteric or coliform) NEAR2 (bac*))

35 MeSH DESCRIPTOR Neisseria EXPLODE ALL TREES

36 (neisseria*)

37 MeSH DESCRIPTOR Haemophilus influenzae EXPLODE ALL TREES

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) NEAR2 (influenz* or pfeiffer* or meningitidis))

39 MeSH DESCRIPTOR Serratia EXPLODE ALL TREES

40 (serratia*)

41 MeSH DESCRIPTOR Cronobacter EXPLODE ALL TREES

42 (cronobact* or sakazaki* or malonatic*)

43 MeSH DESCRIPTOR Acinetobacter EXPLODE ALL TREES

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*)

45 MeSH DESCRIPTOR Fusobacterium EXPLODE ALL TREES

46 (fusobact* or sphaerophor* or necrophorum or nucleatum)

47 MeSH DESCRIPTOR enterococcus EXPLODE ALL TREES

48 (enterococc*)

49 (#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48)

50 (#18 OR #49)

51 (#10 AND #50)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) NEAR4 (infect*))

53 ((prematur*e or pre-mature* or preterm* or pre-term*) NEAR4 (child* or infant* or baby* or babies* or offspring) NEAR4 (infect*))

54 (#52 OR #53)

55 (#51 OR #54)

56 MeSH DESCRIPTOR Antibiotic Prophylaxis

57 ((antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid* or bacteriostat*) and (prophyla* or premedic* or pre-medic* or prevent*))

58 #56 OR #57

59 MeSH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL TREES

60 MeSH DESCRIPTOR Penicillins EXPLODE ALL TREES

61 (penicillin*)

62 (benzylpenicillin* or crystapen* or bicillin* or triplopen* or pentids* or pfizerpen*)

63 (amox?cillin* or hydroxyamp?cillin* or almodan* or amix* or amopen* or amoram* or amoxident* or amoxidin* or amoxil* or amoxymed* or amrit* or flemoxin* or galenamox* or rimoxallin* or amiclav* or augmentin* or heliclear* or amoxiclav* or biomox* or DisperMox* or larotid* or moxatag* or polymox* or trimox* or wymox* or amoclan* or omeclamox* or prevpac*)

64 (ampicillin* or KS-R1 or aminobenzylpenicillin* or amfipen* or flu-amp* or magnapen* or penbritin* or rimacillin* or vidopen* or ampiclox* or dicapen* or D-Amp* or marcillin* or omnipen* or polycillin* or principen* or totacillin* or unasyn*)

65 MeSH DESCRIPTOR Teicoplanin

66 (teicoplanin* or teichom?cin* or targocid*)

67 MeSH DESCRIPTOR Clindamycin

68 (clindam?cin* or dalacin* or zindaclin* or Duac or refobacin* or treclin* or cleocin* or Clinda-Derm* or ClindaMax* or clindagel* or clindesse* or clindets* or evoclin* or acanya* or benzaclin* or clindacin* or onexton* or PledgaClin* or veltin* or ziana*

69 (azithrom?cin* or azyter* or clamelle* or zedbac* or zithromax* or AzaSite* or zmax*)

70 MeSH DESCRIPTOR Cephalosporins EXPLODE ALL TREES

71 (cephalosporin* or cephalosporanic* or cepham?cin*)

72 (cefamandole* or kefadol* or mandol*)

73 (cefazolin* or kefzol* or ancef* or zolicef*)

74 (cefepim* or renapime* or maxipime*)

75 (cefsulodin* or monaspor*)

76 (ceftibuten* or cedax*)

77 (cefuroxime* or cephuroxime* or aprokam* or ximaract* or zinacef* or zinnat* or ceftin* or kefurox*)

78 (cefotaxim* or cephotaxim* or cefizox*)

79 (cefixime* or suprax*)

80 (ceftizoxime* or cefizox*)

81 (cef?triaxon* or rocephin*)

82 (cephalothin* or cefalotin* or keflin*)

83 (cefalexin* or cephalexin* or ceporex* or keflex* or kiflone* or biocef* or cefanex* or keflet* or keftab* or zartan*)

84 (cefaclor* or bacticlor* or distaclor* or keftid* or ceclor* or raniclor*)

85 (cefadroxil* or cephadroxyl* or baxan* or duricef* or ultracef*)

86 (cefradine* or cephradine* or nicef* or velosef* or anspor*)

87 (ceftazidime* or fortum* or kefadim* or zavicefta* or ceptaz* or fortaz* or tazicef* or tazidime*)

88 (cefoxitin* or mefoxin* or renoxitin*)

89 (ceftaroline* or zinforo* or teflaro*)

90 MeSH DESCRIPTOR Erythromycin EXPLODE ALL TREES

91 (erythrom?cin* or arpim?cin* or eryacne* or erycen* or erymax* or erymin* or erythrocin* or erythrolar* or erythromid* or erythroped* or ilosone* or retcin* or rommix* or ronmix* or stiem?cin* or tiloryth* or aknem?cin* or benzam?cin* or isotrexin* or zineryt* or Ak-Mycin* or Akne-Mycin* or Del-Mycin* or E-Base or E-Mycin or emgel* or eram?cin* or Ery-Tab* or Ery-sol* or eryc or erycette* or eryderm* or erygel* or erymax* or eryped* or Erythra-Derm* or ilot?cin* or pediam?cin* or robim?cin* or rom?cin* or staticin or T-Stat or theram?cin* or wyam?cin* or aktipak* or eryzole* or pediazole*)

92 (clarithrom?cin* or clarosip* or febzin* or klaricid* or mycifor* or HeliMet* or heliclear* or biaxin* or omeclamox-pak* or prevpac* or clarie xl* or xetinin xl*)

93 MeSH DESCRIPTOR Metronidazole

94 (metronidazole* or acea* or anabact* or elyzol* or flagyl* or metrogel* or metrolyl* or metrosa* or metrotop* or metrozol* or nidazol* or noritate* or norzol* or rosiced* or rozex* or vaginyl* or zadstat* or zidoval* or zyomet* or entamizole*)

95 MeSH DESCRIPTOR Vancomycin

96 (vancom?cin* or vancocin* or firvanq* or lyphocin* or vancocin* or vancoled*)

97 (azlocillin* or securopen* or azlin*)

98 (mezlocillin* or baypen* or mezlin*)

99 (piperacillin* or pipril* or tazocin* or pipracil* or zosyn*)

100 (pivampicillin* or pondocillin* or miraxid*)

101 (talampicillin* or talpen*)

102 (carbenicillin* or pyopen* or geopen*)

103 (carfecillin* or uticillin*)

104 (flucloxacillin* or floxacillin* or fluorochloroxacillin* or floxapen* or fluclomix* or galfloxin* or ladropen* or stafoxil* or staphlipen* or zoxin*)

105 MeSH DESCRIPTOR Glycopeptides EXPLODE ALL TREES

106 (glycopeptide* or lipoglycopeptide*)

107 MeSH DESCRIPTOR Aminoglycosides EXPLODE ALL TREES

108 (aminoglycoside*)

109 (gentamicin* or gentamycin* or gentacycol* or G-Myticin* or GMyticin*)

110 (cidom?cin* or garam?cin* or genticin* or lugacin* or collatamp* or refobacin* or septocoll* or septopal* or vipsogal* or genoptic* or gentacidin* or gentafair* or gentak* or gentasol* or gentrasul* or jenam?cin* or Ocu-Mycin*)

111 (amikacin* or amikin* or arikayce*)

112 (tobram?cin* or bramitob* or nebcin* or Tobi or tobralex* or tobravisc* or vantobra*)

113 MeSH DESCRIPTOR Carbapenems EXPLODE ALL TREES

114 (carbapenem*)

115 (meropenem* or meronem* or merrem* or vabomere*)

116 (bleom?cin* or Bleo or blenoxane*)

117 #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116

118 MeSH DESCRIPTOR Pre-Exposure Prophylaxis

119 MeSH DESCRIPTOR Post-Exposure Prophylaxis

120 MeSH DESCRIPTOR Preventive Medicine

121 MeSH DESCRIPTOR Primary Prevention

122 MeSH DESCRIPTOR Secondary Prevention

123 MeSH DESCRIPTOR Tertiary Prevention

124 (prophyla* or premedic* or pre-medic* or prevent*)

125 #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124

126 #117 AND #125

127 #58 OR #126

128 #55 AND #127

129 * IN DARE

130 #128 AND #129

131 * IN DARE FROM 2011 TO 2019

Search Filters

The following search filters were combined as ‘And’ with the population and antibiotic terms for the Medline databases and Embase. Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and DARE are systematic review or randomised controlled trial databases so did not require the addition of a filter.

The Medline versions of the filters are reproduced below. Embase has validated translations of these that were used in the search.

Randomised Controlled Trial

1. randomized controlled trial.pt.

2. randomi?ed.mp.

3. placebo.mp.

4. or/1-3

Systematic Review

1 MEDLINE or pubmed).tw.

2 systematic review.tw.

3 systematic review.pt.

4 meta-analysis.pt.

5 intervention$.ti.

6 or/1-5

Health Economics literature search strategy

Sources searched to identify economic evaluations

- MEDLINE (Ovid)
- MEDLINE in Process (Ovid)
- Medline E-pubs (Ovid)
- Embase (Ovid)
- EconLit (Ovid)

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update in July 2019. Search filters to retrieve economic evaluations and quality of life papers were appended to the population and intervention terms to identify relevant evidence. Searches were not undertaken for qualitative RQs. Searches were re-run in July 2020 where the filters were added to the population terms.

Health economics search strategy

Database: Medline (Ovid)
1 exp Infant, Newborn/ (607120)
2 Term Birth/ (2958)
3 Infant Care/ (9209)
4 Perinatal Care/ (4613)
5 Intensive Care Units, Neonatal/ (14748)
6 Intensive Care, Neonatal/ (5673)
7 Infant Health/ (783)
8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (394580)
9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (50922)
10 or/1-9 (791905)
11 exp Bacterial Infections/ (886598)

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (148920)

13 exp Sepsis/ (123123)

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (100090)

15 (septic* adj4 shock*).tw. (19697)

16 (bacter?emia* or bacill?emia*).tw. (26877)

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (38725)

18 or/11-17 (1097119)

19 exp Streptococcus/ (78627)

20 exp Staphylococcus/ (104852)

21 (streptococc* or staphylococc*).tw. (206696)

22 (GBS or MRSA or NRCS-A or MSSA).tw. (27020)

23 (met?icillin-resistant adj3 aureus).tw. (23563)

24 exp Escherichia coli/ (278943)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (289781)

26 exp Listeria/ (15143)

27 listeria*.tw. (18688)

28 exp Klebsiella/ (19836)

29 klebsiella*.tw. (26962)

30 exp Pseudomonas/ (71592)

31 (pseudomonas or chryseomonas or flavimonas).tw. (85911)

32 Enterobacteriaceae/ (18945)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (30291)

34 ((enteric or coliform) adj2 bac*).tw. (5982)

35 exp Neisseria/ (20482)

36 neisseria*.tw. (18785)

37 exp Haemophilus influenzae/ (13731)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (19500)

39 exp Serratia/ (6599)

40 serratia*.tw. (8439)

41 exp Cronobacter/ (655)

42 (cronobact* or sakazaki* or malonatic*).tw. (958)

43 exp Acinetobacter/ (9822)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (15154)

45 exp Fusobacterium/ (3796)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (5425)

47 exp Enterococcus/ (19718)

48 enterococc*.tw. (26150)

49 or/19-48 (765874)

50 18 or 49 (1614537)

51 10 and 50 (65444)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (16079)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (946)

54 52 or 53 (16770)

55 51 or 54 (74853)

56 Economics/ (27206)

57 exp "Costs and Cost Analysis"/ (237006)

58 Economics, Dental/ (1911)

59 exp Economics, Hospital/ (24558)

60 exp Economics, Medical/ (14206)

61 Economics, Nursing/ (3999)

62 Economics, Pharmaceutical/ (2941)

63 Budgets/ (11315)

64 exp Models, Economic/ (15053)

65 Markov Chains/ (14321)

66 Monte Carlo Method/ (28322)

67 Decision Trees/ (11133)

68 econom$.tw. (238765)

69 cba.tw. (9764)

70 cea.tw. (20532)

71 cua.tw. (999)

72 markov$.tw. (17997)

73 (monte adj carlo).tw. (29925)

74 (decision adj3 (tree$ or analys$)).tw. (13431)

75 (cost or costs or costing$ or costly or costed).tw. (460618)

76 (price$ or pricing$).tw. (33468)

77 budget$.tw. (23716)

78 expenditure$.tw. (49355)

79 (value adj3 (money or monetary)).tw. (2096)

80 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3485)

81 or/56-80 (926379)

82 "Quality of Life"/ (194718)

83 quality of life.tw. (229884)

84 "Value of Life"/ (5706)

85 Quality-Adjusted Life Years/ (12284)

86 quality adjusted life.tw. (10842)

87 (qaly$ or qald$ or qale$ or qtime$).tw. (8901)

88 disability adjusted life.tw. (2741)

89 daly$.tw. (2486)

90 Health Status Indicators/ (23409)

91 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (22454)

92 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1323)

93 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (4902)

94 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (29)

95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (381)

96 (euroqol or euro qol or eq5d or eq 5d).tw. (9001)

97 (qol or hql or hqol or hrqol).tw. (44126)

98 (hye or hyes).tw. (60)
99 health$ year$ equivalent$.tw. (38)
100 utilit$.tw. (171457)
101 (hui or hui1 or hui2 or hui3).tw. (1304)
102 disutili$.tw. (396)
103 rosser.tw. (94)
104 quality of wellbeing.tw. (14)
105 quality of well-being.tw. (381)
106 qwb.tw. (190)
107 willingness to pay.tw. (4500)
108 standard gamble$.tw. (783)
109 time trade off.tw. (1037)
110 time tradeoff.tw. (238)
111 tto.tw. (899)
112 or/82-111 (493012)
113 81 or 112 (1350947)
114 55 and 113 (3480)
115 limit 114 to ed=20190716-20200724 (226)
116 animals/ not humans/ (4686781)
117 115 not 116 (213)
118 limit 117 to english language (208)

Database: MiP (Ovid)
1 exp Infant, Newborn/ (0)
2 Term Birth/ (0)
3 Infant Care/ (0)
4 Perinatal Care/ (0)
5 Intensive Care Units, Neonatal/ (0)
6 Intensive Care, Neonatal/ (0)
7 Infant Health/ (0)

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (32462)

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (4347)

10 or/1-9 (34405)

11 exp Bacterial Infections/ (0)

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (17517)

13 exp Sepsis/ (0)

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (12331)

15 (septic* adj4 shock*).tw. (2749)

16 (bacter?emia* or bacill?emia*).tw. (2792)

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (4519)

18 or/11-17 (35377)

19 exp Streptococcus/ (0)

20 exp Staphylococcus/ (0)

21 (streptococc* or staphylococc*).tw. (22112)

22 (GBS or MRSA or NRCS-A or MSSA).tw. (4384)

23 (met?icillin-resistant adj3 aureus).tw. (3264)

24 exp Escherichia coli/ (0)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (21337)

26 exp Listeria/ (0)

27 listeria*.tw. (2351)

28 exp Klebsiella/ (0)

29 klebsiella*.tw. (4101)

30 exp Pseudomonas/ (0)

31 (pseudomonas or chryseomonas or flavimonas).tw. (10779)

32 Enterobacteriaceae/ (0)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (4282)

34 ((enteric or coliform) adj2 bac*).tw. (585)

35 exp Neisseria/ (0)

36 neisseria*.tw. (1256)

37 exp Haemophilus influenzae/ (0)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (1064)

39 exp Serratia/ (0)

40 serratia*.tw. (829)

41 exp Cronobacter/ (0)

42 (cronobact* or sakazaki* or malonatic*).tw. (168)

43 exp Acinetobacter/ (0)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (2747)

45 exp Fusobacterium/ (0)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (821)

47 exp Enterococcus/ (0)

48 enterococc*.tw. (3589)

49 or/19-48 (59520)

50 18 or 49 (83682)

51 10 and 50 (2543)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (1246)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (81)

54 52 or 53 (1309)

55 51 or 54 (3367)

56 Economics/ (0)

57 exp "Costs and Cost Analysis"/ (0)

58 Economics, Dental/ (0)

59 exp Economics, Hospital/ (0)

60 exp Economics, Medical/ (0)

61 Economics, Nursing/ (0)

62 Economics, Pharmaceutical/ (0)

63 Budgets/ (0)

64 exp Models, Economic/ (0)

65 Markov Chains/ (1)

66 Monte Carlo Method/ (2)

67 Decision Trees/ (0)

68 econom$.tw. (47080)

69 cba.tw. (456)

70 cea.tw. (2004)

71 cua.tw. (198)

72 markov$.tw. (5795)

73 (monte adj carlo).tw. (17215)

74 (decision adj3 (tree$ or analys$)).tw. (2609)

75 (cost or costs or costing$ or costly or costed).tw. (99726)

76 (price$ or pricing$).tw. (6047)

77 budget$.tw. (5074)

78 expenditure$.tw. (6509)

79 (value adj3 (money or monetary)).tw. (364)

80 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (502)

81 or/56-80 (172313)

82 "Quality of Life"/ (0)

83 quality of life.tw. (40043)

84 "Value of Life"/ (0)

85 Quality-Adjusted Life Years/ (0)

86 quality adjusted life.tw. (1728)

87 (qaly$ or qald$ or qale$ or qtime$).tw. (1455)

88 disability adjusted life.tw. (523)

89 daly$.tw. (479)

90 Health Status Indicators/ (0)

91 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (2735)

92 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (779)

93 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (773)

94 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (5)

95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (20)

96 (euroqol or euro qol or eq5d or eq 5d).tw. (1711)

97 (qol or hql or hqol or hrqol).tw. (7636)

98 (hye or hyes).tw. (8)

99 health$ year$ equivalent$.tw. (2)

100 utilit$.tw. (32031)

101 (hui or hui1 or hui2 or hui3).tw. (203)

102 disutili$.tw. (60)

103 rosser.tw. (4)

104 quality of wellbeing.tw. (9)

105 quality of well-being.tw. (29)

106 qwb.tw. (13)

107 willingness to pay.tw. (957)

108 standard gamble$.tw. (62)

109 time trade off.tw. (119)

110 time tradeoff.tw. (11)

111 tto.tw. (145)

112 or/82-111 (74419)

113 81 or 112 (236895)

114 55 and 113 (231)

115 limit 114 to dt=20190716-20200724 (89)

116 animals/ not humans/ (1)

117 115 not 116 (89)

118 limit 117 to english language (89)

Database: Medline E-pubs (Ovid)

1 exp Infant, Newborn/ (0)

2 Term Birth/ (0)

3 Infant Care/ (0)

4 Perinatal Care/ (0)

5 Intensive Care Units, Neonatal/ (0)

6 Intensive Care, Neonatal/ (0)

7 Infant Health/ (0)

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (6371)

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (1421)

10 or/1-9 (6871)

11 exp Bacterial Infections/ (0)

12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (2219)

13 exp Sepsis/ (0)

14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (1706)

15 (septic* adj4 shock*).tw. (361)

16 (bacter?emia* or bacill?emia*).tw. (347)

17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (688)

18 or/11-17 (4700)

19 exp Streptococcus/ (0)

20 exp Staphylococcus/ (0)

21 (streptococc* or staphylococc*).tw. (2264)

22 (GBS or MRSA or NRCS-A or MSSA).tw. (468)

23 (met?icillin-resistant adj3 aureus).tw. (345)

24 exp Escherichia coli/ (0)

25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (2275)

26 exp Listeria/ (0)

27 listeria*.tw. (198)

28 exp Klebsiella/ (0)

29 klebsiella*.tw. (476)

30 exp Pseudomonas/ (0)

31 (pseudomonas or chryseomonas or flavimonas).tw. (1004)

32 Enterobacteriaceae/ (0)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (460)

34 ((enteric or coliform) adj2 bac*).tw. (64)

35 exp Neisseria/ (0)

36 neisseria*.tw. (177)

37 exp Haemophilus influenzae/ (0)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (149)

39 exp Serratia/ (0)

40 serratia*.tw. (72)

41 exp Cronobacter/ (0)

42 (cronobact* or sakazaki* or malonatic*).tw. (14)

43 exp Acinetobacter/ (0)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (290)

45 exp Fusobacterium/ (0)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (112)

47 exp Enterococcus/ (0)

48 enterococc*.tw. (403)

49 or/19-48 (6238)

50 18 or 49 (9619)

51 10 and 50 (455)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (255)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (16)

54 52 or 53 (268)

55 51 or 54 (651)

56 Economics/ (0)

57 exp "Costs and Cost Analysis"/ (0)

58 Economics, Dental/ (0)

59 exp Economics, Hospital/ (0)

60 exp Economics, Medical/ (0)

61 Economics, Nursing/ (0)

62 Economics, Pharmaceutical/ (0)

63 Budgets/ (0)

64 exp Models, Economic/ (0)

65 Markov Chains/ (0)

66 Monte Carlo Method/ (0)

67 Decision Trees/ (0)

68 econom$.tw. (6645)

69 cba.tw. (61)

70 cea.tw. (331)

71 cua.tw. (17)

72 markov$.tw. (718)

73 (monte adj carlo).tw. (1219)

74 (decision adj3 (tree$ or analys$)).tw. (519)

75 (cost or costs or costing$ or costly or costed).tw. (13246)

76 (price$ or pricing$).tw. (954)

77 budget$.tw. (555)

78 expenditure$.tw. (1143)

79 (value adj3 (money or monetary)).tw. (65)

80 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (51)

81 or/56-80 (21922)

82 "Quality of Life"/ (0)

83 quality of life.tw. (7520)

84 "Value of Life"/ (0)

85 Quality-Adjusted Life Years/ (0)

86 quality adjusted life.tw. (388)

87 (qaly$ or qald$ or qale$ or qtime$).tw. (329)

88 disability adjusted life.tw. (101)

89 daly$.tw. (88)

90 Health Status Indicators/ (0)

91 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (479)

92 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (50)

93 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (180)

94 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (1)

95 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (4)

96 (euroqol or euro qol or eq5d or eq 5d).tw. (407)

97 (qol or hql or hqol or hrqol).tw. (1460)

98 (hye or hyes).tw. (1)

99 health$ year$ equivalent$.tw. (0)

100 utilit$.tw. (4989)

101 (hui or hui1 or hui2 or hui3).tw. (18)

102 disutili$.tw. (12)

103 rosser.tw. (0)

104 quality of wellbeing.tw. (0)

105 quality of well-being.tw. (9)

106 qwb.tw. (3)

107 willingness to pay.tw. (184)

108 standard gamble$.tw. (7)

109 time trade off.tw. (20)

110 time tradeoff.tw. (2)

111 tto.tw. (18)

112 or/82-111 (12826)

113 81 or 112 (32909)

114 55 and 113 (55)

115 limit 114 to english language (55)

Database: Embase (Ovid)
1 newborn/ (526097)
2 term birth/ (3569)
3 infant care/ (1049)
4 perinatal care/ (14198)
5 neonatal intensive care unit/ (10192)
6 newborn intensive care/ (26405)
7 child health/ (27137)
8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (536460)
9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (68782)
10 or/1-9 (841089)
11 exp bacterial infection/ (838120)
12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (208658)
13 exp sepsis/ (263922)
14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (168012)
15 (septic* adj4 shock*).tw. (36223)
16 (bacter?emia* or bacill?emia*).tw. (40194)
17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (61015)
18 or/11-17 (1201558)
19 exp Streptococcus/ (128274)
20 exp Staphylococcus/ (209430)
21 (streptococc* or staphylococc*).tw. (262126)
22 (GBS or MRSA or NRCS-A or MSSA).tw. (46092)
23 (met?icillin-resistant adj3 aureus).tw. (34157)
24 exp Escherichia coli/ (361361)
25 (((Escheric* or E) adj2 coli) or ecoli*).tw. (339772)
26 exp Listeria/ (24096)
27 listeria*.tw. (22102)
28 exp Klebsiella/ (59561)

29 klebsiella*.tw. (42289)

30 exp Pseudomonas/ (144052)

31 (pseudomonas or chryseomonas or flavimonas).tw. (118130)

32 Enterobacteriaceae/ (23812)

33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (42447)

34 ((enteric or coliform) adj2 bac*).tw. (7285)

35 exp Neisseria/ (32218)

36 neisseria*.tw. (22936)

37 exp Haemophilus influenzae/ (29007)

38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (24329)

39 exp Serratia/ (14280)

40 serratia*.tw. (10397)

41 exp cronobacter/ (817)

42 (cronobact* or sakazaki* or malonatic*).tw. (1214)

43 exp Acinetobacter/ (27955)

44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (23888)

45 exp Fusobacterium/ (7678)

46 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (7403)

47 exp Enterococcus/ (49841)

48 enterococc*.tw. (37571)

49 or/19-48 (967441)

50 18 or 49 (1894492)

51 10 and 50 (70672)

52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (21945)

53 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (1283)

54 52 or 53 (22885)

55 51 or 54 (83775)

56 exp Health Economics/ (845404)

57 exp "Health Care Cost"/ (290992)

58 exp Pharmacoeconomics/ (202216)

59 Monte Carlo Method/ (40279)

60 Decision Tree/ (13001)

61 econom$.tw. (368838)

62 cba.tw. (12788)

63 cea.tw. (34786)

64 cua.tw. (1498)

65 markov$.tw. (30389)

66 (monte adj carlo).tw. (48341)

67 (decision adj3 (tree$ or analys$)).tw. (23602)

68 (cost or costs or costing$ or costly or costed).tw. (772396)

69 (price$ or pricing$).tw. (57398)

70 budget$.tw. (38616)

71 expenditure$.tw. (74588)

72 (value adj3 (money or monetary)).tw. (3455)

73 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (8625)

74 or/56-73 (1760062)

75 "Quality of Life"/ (469927)

76 Quality Adjusted Life Year/ (26663)

77 Quality of Life Index/ (2774)

78 Short Form 36/ (29036)

79 Health Status/ (127411)

80 quality of life.tw. (439622)

81 quality adjusted life.tw. (19747)

82 (qaly$ or qald$ or qale$ or qtime$).tw. (20178)

83 disability adjusted life.tw. (4103)

84 daly$.tw. (4016)

85 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (41434)

86 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2420)

87 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (9462)

88 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (61)

89 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (455)

90 (euroqol or euro qol or eq5d or eq 5d).tw. (20619)

91 (qol or hql or hqol or hrqol).tw. (97056)

92 (hye or hyes).tw. (135)

93 health$ year$ equivalent$.tw. (41)

94 utilit$.tw. (289831)

95 (hui or hui1 or hui2 or hui3).tw. (2300)

96 disutili$.tw. (924)

97 rosser.tw. (124)

98 quality of wellbeing.tw. (42)

99 quality of well-being.tw. (486)

100 qwb.tw. (253)

101 willingness to pay.tw. (8837)

102 standard gamble$.tw. (1104)

103 time trade off.tw. (1708)

104 time tradeoff.tw. (291)

105 tto.tw. (1683)

106 or/75-105 (989974)

107 74 or 106 (2593254)

108 55 and 107 (5731)

109 limit 108 to dc=20190716-20200724 (558)

110 nonhuman/ not human/ (4649157)

111 109 not 110 (522)

112 limit 111 to english language (510)

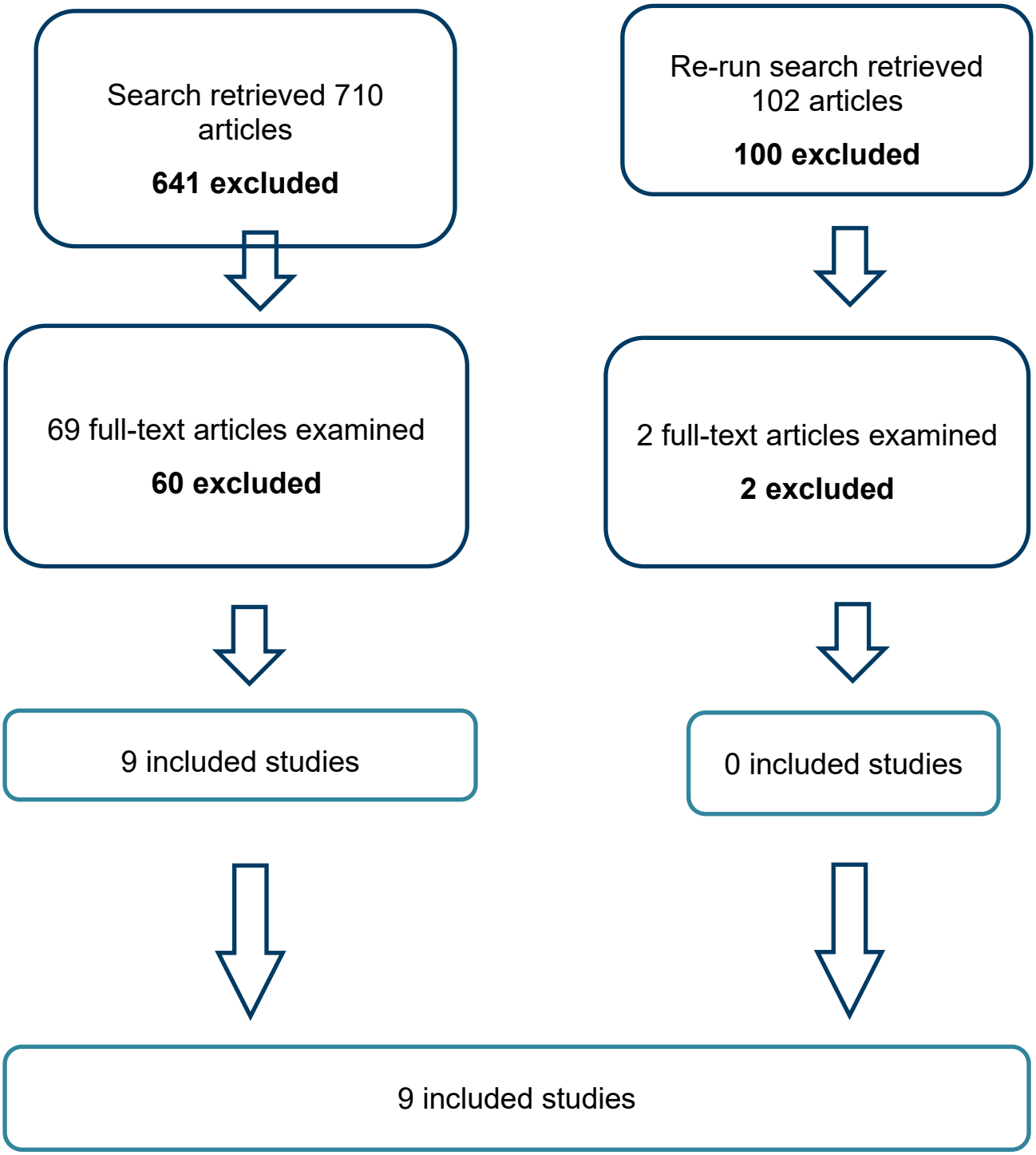
113 limit 112 to (conference abstract or conference paper or "conference review") (113)

114 112 not 113 (397)

Database: Econlit (Ovid)
1 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (732)
2 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (45)
3 1 or 2 (767)
4 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (49)
5 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (17)
6 (septic* adj4 shock*).tw. (1)
7 (bacter?emia* or bacill?emia*).tw. (3)
8 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (17)
9 (streptococc* or staphylococc*).tw. (18)
10 (GBS or MRSA or NRCS-A or MSSA).tw. (40)
11 (met?icillin-resistant adj3 aureus).tw. (8)
12 (((Escheric* or E) adj2 coli) or ecoli*).tw. (47)
13 listeria*.tw. (6)
14 klebsiella*.tw. (0)
15 (pseudomonas or chryseomonas or flavimonas).tw. (6)
16 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (1)
17 ((enteric or coliform) adj2 bac*).tw. (0)
18 neisseria*.tw. (1)
19 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (14)
20 serratia*.tw. (0)
21 (cronobact* or sakazaki* or malonatic*).tw. (1)
22 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (2)
23 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (0)
24 enterococc*.tw. (5)
25 or/4-24 (194)
26 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (11)
27 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (1)

28	26 or 27 (12)
29	25 or 28 (205)
30	3 and 29 (15)
31	limit 30 to yr="2019 -Current" (1)

Appendix C – Effectiveness evidence study selection



Appendix D – Effectiveness evidence

Adair, 1996

Bibliographic Reference	Adair CD; Ernest JM; Sanchez-Ramos L; Burrus DR; Boles ML; Veille JC; Meconium-stained amniotic fluid-associated infectious morbidity: a randomized, double-blind trial of ampicillin-sulbactam prophylaxis.; Obstetrics and gynecology; 1996; vol. 88 (no. 2)

Study details

Sample size	120
Interventions	Ampicillin/sulbactam Placebo
Study location	USA
Study setting	Single centre, hospital setting.
Study dates	1994 to 1995
Duration of follow-up	Not explicitly stated. Likely to be until discharge from neonatal unit.
Sources of funding	Partially funded by Roerig, a division of Pfizer Phramaceuticals.
Inclusion criteria	Meconium stained amniotic fluid
Outcome measures	Neonatal infection Incidence of sepsis. Not included in review – no definition of sepsis diagnosis Maternal adverse events (intra-amniotic infection) Temperature >100.5◦F and the presence of one or more of: fetal and/or maternal tachycardia, uterine tenderness, foul smelling amniotic fluid or leucocytosis Maternal adverse events (endometritis) Postpartum endometritis: temperature >100.5◦F on 2 occasions after delivery with the presence of uterine tenderness, foul-smelling lochia and/or leukocytosis

Methods	During labour if clinical intra-amniotic infection occurred, the managing physician was allowed to choose antibiotic coverage at their discretion. If CS was done cefazolin 2.0 gm was administered at cord clamping. Medical records were reviewed after discharge to obtain outcome data.
Duration of labour / Time from treatment to delivery	Not reported

Study arms

Ampicillin/Sulbactam (N = 60)

3.0 g of pre-prepared ampicillin/sulbactam intravenously, starting at the time of diagnosis of meconium stained amniotic fluid and repeated every 6 hours until delivery

Loss to follow-up	0/60
Mean maternal age (SD)	24.5 years (6.3)
Mean gestational age (SD)	39.8 weeks (1.0)

Placebo (N = 60)

Saline given intravenously, starting at the time of diagnosis of meconium stained amniotic fluid and repeated every 6 hours until delivery

Interventions	Ampicillin/sulbactam Placebo

Loss to follow-up	0/60
Mean maternal age (SD)	25.9 years (6.3)
Mean gestational age (SD)	39.9 weeks (1.2)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably no
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information

Section	Question	Answer
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Probably yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Unclear whether an appropriate analysis was used to estimate the effect of assignment to intervention)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No information
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No information

Section	Question	Answer
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Some concerns *(No pre-specified plans for analysis and limited information about definitions and time points)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Intra-amniotic infection; endometritis: Limited information about analysis)*
	Overall Directness	Directly applicable

Edwards, 2002

Bibliographic Reference Edwards RK; Clark P; Sistrom CL; Duff P; Intrapartum antibiotic prophylaxis 1: relative effects of recommended antibiotics on gram-negative pathogens.; Obstetrics and gynecology; 2002; vol. 100 (no. 3)

Study details

Study type	Randomised controlled trial (RCT)
Sample size	352
Interventions	Ampicillin Penicillin
Study location	USA
Study setting	Single centre, hospital setting

Study dates	2000-2001
Duration of follow-up	Not explicitly reported - likely to be until discharge from hospital.
Sources of funding	Supported in part by a grant from the Children's Miracle Network
Inclusion criteria	Spontaneous or induced labour Gestational age of 36 weeks or more Culture proven carriers of group B streptococci
Exclusion criteria	Allergy to study medication Antibiotic use in previous 7 days Intrauterine death Planned cesarean delivery Multifetal gestation
Outcome measures	Neonatal antibiotics for suspected bloodstream infection Mortality (timepoint not specified) Length of hospital stay Neonatal Endometritis
Methods	Additional antibiotics were administered only if a subject developed chorioamnionitis or required prophylaxis against puerperal endometritis (eg, because of a cesarean delivery or manual placental extraction). Details for obtaining neonatal outcomes are not reported.

Study arms

Penicillin (N = 177)

5 MU of penicillin G intravenously followed by 2.5 MU every 4 hours until delivery

Loss to follow-up	67 did not receive 2 doses of antibiotic or received additional antibiotic. However they were still included in the intention to treat analysis (reported).
Mean maternal age (SD)	23.7 years (5.7)
Mean gestational age (SD)	39.0 weeks (1.4)
Duration of labour / Time from treatment to delivery	Labour duration (mean, SD): 12.7 hours (6.8)

Ampicillin (N = 175)

2 g intravenously followed by 1g every 4 hours until delivery

Loss to follow-up	59 did not receive 2 doses of antibiotic or received additional antibiotic. However they were still included in the intention to treat analysis (reported).
Mean maternal age (SD)	23.5 years (5.7)
Mean gestational age (SD)	39.0 weeks (1.5)
Duration of labour / Time from treatment to delivery	Labour duration (mean, SD): 12.7 hours (5.9)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No information
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No information
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Probably yes *(but study powered for antibiotic resistance outcomes)*
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	Risk-of-bias judgement for missing outcome data	Low

Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes *(Neonatal length of stay, neonatal mortality)* No information *(No definition for diagnosis of chorioamnionitis, endometritis or neonatal suspected infection)*
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No information
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low *(Neonatal length of stay, neonatal mortality)* Some concerns *(No definition for diagnosis of chorioamnionitis, endometritis or neonatal suspected infection)*
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no *(Neonatal mortality, neonatal length of stay)* No information *(No definition for diagnosis of chorioamnionitis, endometritis or neonatal suspected infection)*

	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No information
	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High *(Neonatal suspected infection - no definition for diagnosis and limited information about analysis methods)* Some concerns *(Neonatal mortality, neonatal length of stay - limited information about analysis methods)*
	Overall Directness	Directly applicable

Gibbs, 1988

Bibliographic Reference Gibbs RS; Dinsmoor MJ; Newton ER; Ramamurthy RS; A randomized trial of intrapartum versus immediate postpartum treatment of women with intra-amniotic infection.; Obstetrics and gynecology; 1988; vol. 72 (no. 6)

Study details

Study type	Randomised controlled trial (RCT)
Sample size	48
Interventions	Ampicillin/gentamicin
Study location	USA
Study setting	Department of Obstetrics, Gynecology and Pediatrics, Texas

Study dates	May 1987 - November 1987
Duration of follow-up	Four weeks
Sources of funding	None reported
Inclusion criteria	Intra-amniotic infection
Exclusion criteria	<34 weeks gestation Cervical dilation <4 cm at time of diagnosis
Outcome measures	Culture confirmed neonatal infection Bacteremia or death with a clinical diagnosis of sepsis and positive peripheral cultures Length of hospital stay Neonatal length of stay (days)
Methods	Timing and route of delivery determined by usual practice. Mothers were treated with IV antibiotics until they were afebrile for approximately 48 hours Peripheral blood cultures in the baby were performed after delivery. All babies were given antibiotics (75 mg/kg ampicillin every 12 hours plus 2.5 mg/kg gentamicin every 12 hours) within 2 hours of birth. If blood cultures and x-rays were negative then antibiotics were stopped after 72 hours

Study arms

Intrapartum antibiotics (N = 26) 2 g ampicillin given intravenously every 6 hours plus 1.5 mg/kg gentamicin given intravenously every 8 hours. Therapy was initiated as soon as possible after randomisation during the intrapartum period

Mean maternal age (SD)	23.7 years (7.0)
Mean gestational age (SD)	39.3 weeks (2.2)
Duration of labour / Time from treatment to delivery	Duration of labour (mean, SD): 19.2 hours (19.2)

Postpartum antibiotics (N = 19)

2 g ampicillin given intravenously every 6 hours plus 1.5 mg/kg gentamicin given intravenously every 8 hours. Therapy was begun immediately after cord clamping. Babies from this group were classified as 'no treatment' as antibiotic therapy given to the mother was started after delivery

Mean maternal age (SD)	20.1 years (3.5)
Mean gestational age (SD)	40.1 weeks (2.5)
Duration of labour / Time from treatment to delivery	Duration of labour (mean, SD): 19.7 hours (15.0)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes

Section	Question	Answer
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Differences in the interventions mean caregivers will have been aware of the assigned treatment but antibiotics were the same between arms, only timing differed)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Probably yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable

Lyell, 2010

Bibliographic Reference	Lyell DJ; Pullen K; Fuh K; Zamah AM; Caughey AB; Benitz W; El-Sayed YY; Daily compared with 8-hour gentamicin for the treatment of intrapartum chorioamnionitis: a randomized controlled trial.; Obstetrics and gynecology; 2010; vol. 115 (no. 2 Pt 1)

Study details

Study type	Randomised controlled trial (RCT)
Sample size	126
Interventions	Gentamicin Daily versus 8-hourly
Study location	USA
Study setting	Labor and Delivery unit at Lucile Packard Children's Hospital at Stanford University Medical Center
Study dates	June 2004 - October 2006
Duration of follow-up	First 48 hours of life
Sources of funding	Department of Obstetrics and Gynecology, Stanford University Medical Center, Stanford, California
Inclusion criteria	Chorioamnionitis and in active labour or undergoing induction of labour. Chorioamnionitis was defined clinically by a maternal temperature of 38.0°C or greater, without another source of fever, with fetal tachycardia (greater than 160 beats per minute), and/or maternal tachycardia (110 beats per minute or greater) Gestational age 34-42 weeks Maternal age 18 years or over
Exclusion criteria	Allergy to study medication Allergy to ampicillin, gentamicin, or clindamycin Intrauterine death Preterm premature rupture of membranes if antibiotics to prolong the pregnancy had been administered Maternal renal disease with creatinine >1.0 mg/dl Hearing loss

	HIV Potentially lethal fetal anomalies
Outcome measures	Culture confirmed neonatal infection Neonatal sepsis (complete blood count with differential and a blood culture at admission. CRP levels were followed every 24 hours during the first 32-48 hours of life Adverse events: Serious adverse events (maternal) Endometritis (fever greater than 38°C with uterine tenderness more than 24 hours after delivery); histological chorioamnionitis
Methods	Women undergoing cesarean delivery also received clindamycin 900 mg IV every 8 hours for a total of three doses for additional coverage of anaerobic organisms. Patients received 1 g of acetaminophen if their temperature was persistently greater than 38°C. Placentas were sent to pathology for histologic evaluation for chorioamnionitis. All neonates were, by unit protocol, evaluated for sepsis with a complete blood count with differential and a blood culture at admission, followed C-reactive protein levels every 24 hours during the first 32–48 hours of life. Empiric weight-based ampicillin and gentamicin were administered until C-reactive protein results were available

Study arms

Daily gentamicin (N = 62)

5 mg/kg gentamicin delivered intravenously, followed by a normal saline placebo after 8 and 16 hours. All women also received ampicillin, 2 g IV every 6 hours for 4 doses total

Mean maternal age (SD)	25.5 years (6.1)
Mean gestational age (SD)	39.9 weeks (IQR 39.0 - 40.8)

Duration of labour / Time from treatment to delivery	Duration of gentamicin to delivery (mean, SD): 149 mins (176)

8 hourly gentamicin (N = 63)

Loading dose of 2 mg/kg IV, followed by 1.5 mg/kg after 8 and 16 hours. All women also received ampicillin, 2 g IV every 6 hours for 4 doses total

Mean maternal age (SD)	25.8 years (6.0)
Mean gestational age (SD)	40.1 weeks (IQR 39.6 - 40.7)
Duration of labour / Time from treatment to delivery	Duration of gentamicin to delivery (mean, SD): 167 mins (219)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes *(Endometritis, histological chorioamnionitis, neonatal LOS)* No information *(Neonatal sepsis)*
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no *(Endometritis, histological chorioamnionitis, neonatal LOS)* No information *(Neonatal sepsis)*
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No

Section	Question	Answer
	Risk-of-bias judgement for measurement of the outcome	Low *(Endometritis, histological chorioamnionitis, neonatal LOS)* Some concerns *(Neonatal sepsis - no definition of the outcome)*
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no *(Endometritis, histological chorioamnionitis, neonatal LOS)* No information *(Neonatal sepsis)*
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no *(Endometritis, histological chorioamnionitis, neonatal LOS)* No information *(Neonatal sepsis)*
	Risk-of-bias judgement for selection of the reported result	Low *(Endometritis, histological chorioamnionitis, neonatal LOS)* Some concerns *(Neonatal sepsis)*
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Partially applicable

Section	Question	Answer
		(Women with temperatures of 38◦Cand above would not be left untreated in clinical practice as they were in the placebo arm)

Maberry, 1991

Bibliographic Reference	Maberry MC; Gilstrap LC; Bawdon R; Little BB; Dax J; Anaerobic coverage for intra-amnionic infection: maternal and perinatal impact.; American journal of perinatology; 1991; vol. 8 (no. 5)

Study details

Study type	Randomised controlled trial (RCT)
Sample size	133
Interventions	Ampicillin/gentamicin Dual therapy Ampicillin/gentamicin/clindamycin Triple therapy
Study location	USA
Study setting	Parkland Memorial Hospital
Study dates	December 1987 - January 1989
Duration of follow-up	Not clearly reported but some maternal temperature monitored for 48 hours after delivery and babies given antibiotics for at least first 48 hours of life
Sources of funding	None reported

Inclusion criteria	Intra-amniotic infection Gestational age >24 weeks
Exclusion criteria	Allergy to study medication Penicillin allergy Mother received antibiotics after delivery Mother was on antibiotics at time of admission
Outcome measures	Culture confirmed neonatal infection Positive blood or spinal fluid culture or a positive urine latex test for group B Streptococcus Neonatal antibiotics for suspected bloodstream infection 'Antibiotic treated' Neonatal mortality
Methods	Intra-amniotic infection definition: temperature of 38°C or higher in the presence of labor and ruptured membranes. In addition, one or more of the following were present: maternal tachycardia, fetal tachycardia, uterine tenderness, or foul-smelling amnionic fluid. The majority of infants born to mothers with intra-amnionic infection who were treated with antibiotics intrapartum, received ampicillin and gentamicin for at least 48 hours pending blood culture results.

Study arms

Dual therapy (N = 69)

Ampicillin and gentamicin. No information about doses or timing

Mean maternal age (SD)	Not reported

Mean gestational age (SD)	≤36 weeks: 88% ≥36 weeks: 12%
Duration of labour / Time from treatment to delivery	Duration of rupture of membranes to delivery: Average (no specific information): 16.1 hours

Triple therapy (N = 64)

Ampicillin, gentamicin and clindamycin. No information about doses or timing

Mean maternal age (SD)	Not reported
Mean gestational age (SD)	≤36 weeks: 88% ≥36 weeks: 12%
Duration of labour / Time from treatment to delivery	Duration of rupture of membranes to delivery: Average (no specific information): 18.8 hours

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information

Section	Question	Answer
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No information
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No information
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information *(Limited information about methods of analysis)*
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Probably yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Limited information about methods of analysis)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Probably yes

Section	Question	Answer
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No information
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No information *(Limited information about methods of analysis)*
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No information
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Some concerns *(Limited information about methods of analysis)*
Overall bias and Directness	Risk of bias judgement	High *(Limited information about analysis methods and no information about the doses used for dual and triple therapy)*
	Overall Directness	Partially applicable

Section	Question	Answer
		(Women with temperatures of 38◦Cand above would not be left untreated in clinical practice as they were in the placebo arm)

Mattoras,R., Garcia-Perea,A., Omenaca,F., ez-Enciso,M., Madero,R., Usandizaga, 1991

Bibliographic Reference Mattoras,R., Garcia-Perea,A., Omenaca,F., ez-Enciso,M., Madero,R., Usandizaga J; Intrapartum chemoprophylaxis of early-onset group B streptococcal disease; European Journal of Obstetrics Gynecology and Reproductive Biology; 1991; vol. 40; 57-62

Study details

Study type	Randomised controlled trial (RCT)
Sample size	121
Study location	Spain
Study setting	Single centre, hospital setting
Study dates	Not reported
Duration of follow-up	Not reported.
Sources of funding	Not reported.
Inclusion criteria	Culture proven carriers of group B streptococci Low vaginal and rectal cultures were taken and between 17 and 42 weeks. The mean time between the moment the smear was taken and delivery was 5.74 weeks.
Outcome measures	Culture confirmed neonatal infection Group B sepsis only

Methods	A blood culture in search of group B streptococci was carried out when infection was suspected. In asymptomatic babies, a blood culture was not performed systematically.
Loss to follow-up	Not reported.
Mean maternal age (SD)	Not reported. Reported to be similar across groups.
Mean gestational age (SD)	Not reported. Reported to be similar across groups.

Study arms

Ampicillin (N = 57)

500 mg of ampicillin intravenously/6 h during delivery. The antibiotic was usually administered at the beginning of the first period, but when admission occurred in advanced first period, the antibiotic was administered later. In caesarean section without labour, ampicillin was administered 2 h before surgery. In 46 women a single dose was used, whereas 2 doses were employed in the other 9 women whose labour lasted > 6 h. An identical dose of erythromycin was used for two women who had a history of allergy to penicillin.

Duration of labour / Time from treatment to delivery	Not reported

No treatment (N = 64)

No ampicillin was given. Other aspects of care were the same.

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	No information *(States that patients were randomly divided into two groups but no further information)*
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No information *(States that characteristics were similar between the two groups but limited information reported)*
	Risk of bias judgement for the randomisation process	High *(No information about randomisation or allocation concealment and limited information about baseline characteristics)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No information
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No information
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Limited information about whether patients or people giving interventions were aware of allocations. Limited information about methods of analysis)*

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Probably yes
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No information *(Limited information about analysis methods)*
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Some concerns *(Limited information about analysis methods)*
Overall bias and Directness	Risk of bias judgement	High *(No information about randomisation or allocation concealment and limited information about baseline characteristics or analysis methods.)*

Section	Question	Answer
	Overall Directness	Directly applicable

Morales, 1986

Bibliographic Reference Morales WJ; Lim DV; Walsh AF; Prevention of neonatal group B streptococcal sepsis by the use of a rapid screening test and selective intrapartum chemoprophylaxis.; American journal of obstetrics and gynecology; 1986; vol. 155 (no. 5)

Study details

Study type	Randomised controlled trial (RCT)
Sample size	263
Interventions	Ampicillin
Study location	USA
Study setting	Orange County Health Department maternity clinics
Study dates	May 1984 - October 1985
Duration of follow-up	Not reported
Sources of funding	None reported
Inclusion criteria	Maternal group B streptococcus colonisation
Exclusion criteria	None reported
Outcome measures	Culture confirmed neonatal infection

	Diagnosed on the basis of positive results of body fluid cultures
Methods	All babies underwent cultures for group B streptococci at two sites, the oropharynx and the skin surface, and the cultures were processed by the Orlando Regional Medical Center laboratory. In addition a urine latex-agglutination screen for group B streptococcal infection was performed on each infant. Infants were observed and antibiotic therapy was started only on the basis of clinical signs of infection.

Study arms

Ampicillin (N = 135)

1 g ampicillin intravenously every 6 hours until delivery

Mean maternal age (SD)	Not reported
Mean gestational age (SD)	Not reported
Duration of labour / Time from treatment to delivery	Not reported

Control (N = 128)

No information about whether this arm was no treatment or placebo. Included patients with ampicillin allergy so may be no treatment

Mean maternal age (SD)	Not reported

Mean gestational age (SD)	Not reported
Duration of labour / Time from treatment to delivery	Not reported

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Probably yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No information *(Limited information about baseline characteristics)*
	Risk of bias judgement for the randomisation process	Some concerns *(Limited information about baseline characteristics and no information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No information
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No information

Section	Question	Answer
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information *(Limited information about analysis methods)*
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Probably yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Limited information about analysis methods and whether patients or people delivering the intervention were aware of the treatment allocated)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No information
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no

Section	Question	Answer
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No information *(Limited information about analysis methods)*
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Some concerns *(Limited information about methods of analysis)*
Overall bias and Directness	Risk of bias judgement	High *(Limited information about allocation concealment, baseline characteristics and analysis methods)*
	Overall Directness	Directly applicable

Nadisauskiene, 1996

Bibliographic Reference Nadisauskiene R; Bergström S; Impact of intrapartum intravenous ampicillin on pregnancy outcome in women with preterm labor: a randomised, placebo-controlled study.; Gynecologic and obstetric investigation; 1996; vol. 41 (no. 2)

Study details

Study type	Randomised controlled trial (RCT)
Sample size	102
Interventions	Ampicillin
Study location	USA
Study setting	Department of Obstetrics and Gynaecology, Kaunas Medical Academy
Study dates	Not reported
Duration of follow-up	Not reported
Sources of funding	None reported
Inclusion criteria	Gestational age <37 weeks Early active phase of preterm labour with cervical dilation ≥4 cm Fetus alive
Exclusion criteria	Allergy to study medication Ampicillin allergy Evidence of active infection which required antibiotic therapy Antibiotic use in previous 7 days Multifetal gestation Placenta praevia History of vaginal bleeding during current pregnancy

	Membranes ruptured >72 hours Maternal temperature >37.5°C Medical condition necessitating delivery
Outcome measures	Culture confirmed neonatal infection Absence of neonatal infection. Not included in review – no definition of neonatal infection) Mortality Neonatal survival first week Adverse events: Serious adverse events (maternal) Chorioamnionitis (absence of histological chorioamnionitis), Puerperal uterine infection (absence of puerperal uterine infection)
Methods	Due to the low gestational age among several women enrolled, it was judged clinically necessary to postpone delivery by additional tocolytic treatment in order to achieve pulmonary maturation in 58 women (32: magnesium sulphate, 26: phenoterolhydrobromide) At a cervical dilatation of 7 cm, the neonatologists were alerted to observe the newborns soon after birth in the neonatal ward. Placenta and fetal membranes were harvested and biopsies were taken for subsequent fixation in 5% formaldehyde. Tissue specimens were embedded in paraffin, sectioned and stained with hematoxylin and eosin. At least three sections from each patient were investigated blindly by a pathologist for evidence of inflammation. Histological chorioamnionitis was defined as the presence of polymorphonuclear leukocytes in amnion and chorion.

Study arms

Ampicillin (N = 44)

5 g ampicillin IV infusion. Two doses, 4 hours apart. If delivery proceeded quickly the second dose was given to ensure that the last dose was given at least 1 h before delivery

Mean maternal age (SD)	26 years (6)

Mean gestational age (SD)	28 weeks
Duration of labour / Time from treatment to delivery	Interval from first IV dose to delivery (mean, SD): 14.2 hours (8.0)

Placebo (N = 58)

IV infusion. Two doses, 4 hours apart. If delivery proceeded quickly the second dose was given to ensure that the last dose was given at least 1 h before delivery

Mean maternal age (SD)	25 years (5)
Mean gestational age (SD)	30 weeks
Duration of labour / Time from treatment to delivery	Interval from first IV dose to delivery (mean, SD): 11.0 hours (6.2)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	No information *(States that patients were randomly allocated to an intervention but no further information)*
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information

Section	Question	Answer
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Some concerns *(Limited information about randomisation and allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Probably no
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information *(Limited information about analysis methods)*
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Probably yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Limited information about analysis methods)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No *(Chorioamnionitis, neonatal death)*

Section	Question	Answer
		No information *(No information about diagnosis of uterine infection or neonatal infection)*
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No information
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No *(Chorioamnionitis)* No information *(No information about diagnosis of uterine infection or neonatal infection)*
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No information
	Risk-of-bias judgement for measurement of the outcome	Low *(Chorioamnionitis)* Some concerns *(Uterine infection, neonatal infection)*
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No information *(Limited information about analysis methods)*
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no *(Chorioamnionitis)* No information *(Uterine infection, neonatal infection)*

Section	Question	Answer
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no *(Chorioamnionitis)* No information *(Uterine infection, neonatal infection)*
	Risk-of-bias judgement for selection of the reported result	Low *(Chorioamnionitis)* Some concerns *(Uterine infection)*
Overall bias and Directness	Risk of bias judgement	High *(Uterine infection - limited information about randomisation, allocation concealment and analysis methods. No information about diagnosis of infection)* Some concerns *(Chorioamnionitis, neonatal mortality - limited information about randomisation, allocation concealment and analysis methods)*
	Overall Directness	Some concerns *Criteria to diagnose labour different to that used in current clinical practice*

Tuppurainen, 1989

Bibliographic Reference Tuppurainen N; Hallman M; Prevention of neonatal group B streptococcal disease: intrapartum detection and chemoprophylaxis of heavily colonized parturients.; Obstetrics and gynecology; 1989; vol. 73 (no. 4)

Study details

Study type	Randomised controlled trial (RCT)
Sample size	199
Interventions	Penicillin
Study location	Finland
Study setting	Department of Obstetrics and Gynecology, University Central Hospital, Helsinki
Study dates	December 1983 - January 1986
Duration of follow-up	Not reported but blood cultures were taken within 2 hours of birth
Sources of funding	None reported
Inclusion criteria	Maternal group B streptococcus colonisation No allergy to penicillin Did not undergo elective term cesarean section without labour or rupture of fetal membranes
Outcome measures	Culture confirmed neonatal infection Diagnosed if: 1. severe symptoms, including respiratory distress and signs of shock within 48 hours of birth, 2. positive blood cultures or presence of GBS in superficial cultures and 3. leukopenia or elevated CRP
Methods	Blood samples were taken from babies for bacterial cultures within 2 hours of birth. Other superficial samples (from external ear canal, eye and umbilicus) were taken for cultures within 30 mins of birth. CRP and leukocyte counts were followed for at least 72 hours
Mean gestational age (SD)	Not reported

Study arms

Penicillin (N = 88)

5 million units of Penicillin G given intravenously every 6 hours during labour. If delivery did not take place within 18 hours, penicillin prophylaxis was continued by giving 1,000,000 units penicillin V orally every 8 hours until delivery

Mean maternal age (SD)	Not reported
Mean gestational age (SD)	Not reported
Duration of labour / Time from treatment to delivery	Not reported

Control (N = 111)

No information about whether control was no treatment or placebo

Mean maternal age (SD)	Not reported
Mean gestational age (SD)	Not reported
Duration of labour / Time from treatment to delivery	Not reported

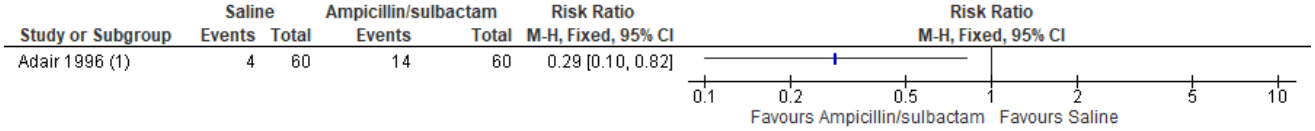
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Probably yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No information *(No information about baseline differences)*
	Risk of bias judgement for the randomisation process	Some concerns *(No information about baseline values)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No information
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Participants and experimenters not blinded to interventions)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low *(Outcome assessors not blinded to group assignment but outcome is objective)*
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No information *(Limited information about analysis methods)*
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(Limited information about baseline values and analysis methods)*
	Overall Directness	Directly applicable

Appendix E – Forest plots

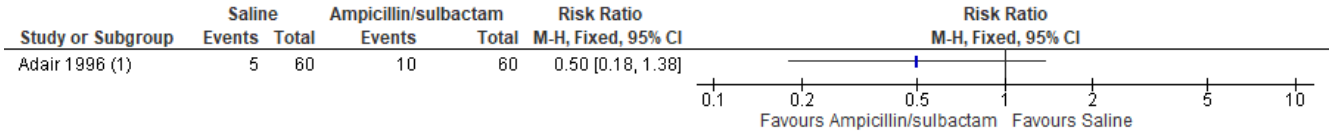
Meconium stained amniotic fluid: ampicillin and sulbactam vs saline

Maternal infection (intra-amniotic infection)



Footnotes
(1) Temperature >100.5 F and the presence of one or more of: fetal and/or maternal tachycardia, uterine tenderness, foul smelling amniotic fluid or leukocytosis

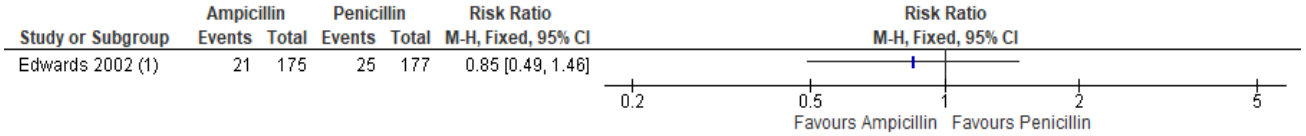
Maternal infection (endometritis)



Footnotes
(1) Postpartum endometritis: temperature >100.5F on 2 occasions after delivery with the presence of uterine tenderness, foul-smelling lochia and/or leukocytosis

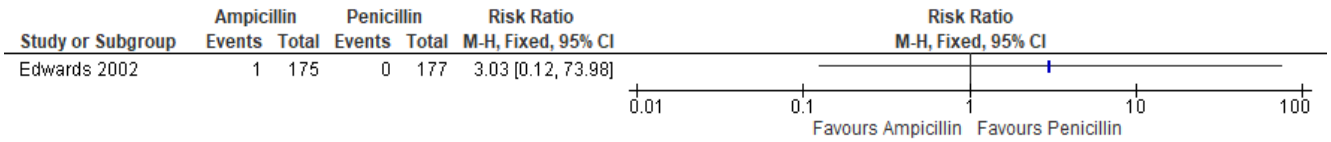
Maternal GBS colonisation: penicillin vs ampicillin

Antibiotics for suspected neonatal infection

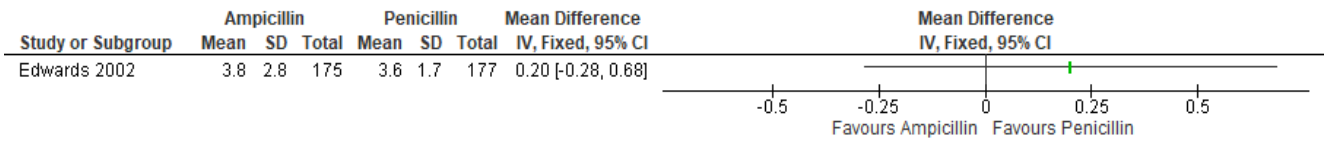


Footnotes
(1) Antibiotics for suspected infection

Neonatal mortality (timepoint not specified)



Neonatal hospital length of stay (days)

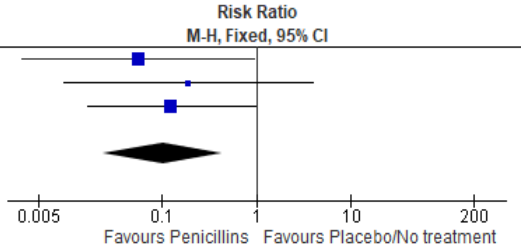


Maternal GBS colonisation: penicillins vs placebo

Neonatal infection

Study or Subgroup	Penicillins Events	Total	Placebo/No treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mattoras 1991 (1)	0	60	9	65	44.4%	0.06 [0.00, 0.96]
Morales 1986 (2)	0	135	2	128	12.5%	0.19 [0.01, 3.91]
Tuppurainen 1989 (3)	1	88	10	111	43.1%	0.13 [0.02, 0.97]
Total (95% CI)		**283**		**304**	**100.0%**	**0.10 [0.02, 0.44]**
Total events	1		21			

Heterogeneity: Chi² = 0.36, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 3.09 (P = 0.002)

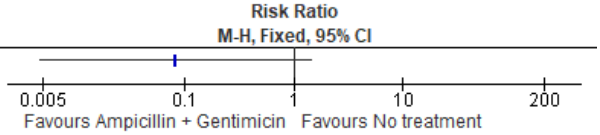


Footnotes
(1) Ampicillin v no treatment. Group B streptococcal sepsis
(2) Ampicillin v control. Culture confirmed group B streptococcal sepsis
(3) Penicillin G v control. Culture confirmed early-onset group B streptococcal disease

Chorioamnionitis: ampicillin and gentamicin vs no treatment

Neonatal infection

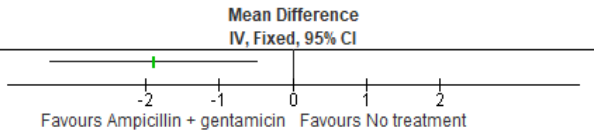
Study or Subgroup	Ampicillin + Gentimicin Events	Total	No treatment Events	Total	Risk Ratio M-H, Fixed, 95% CI
Gibbs 1988 (1)	0	26	4	19	0.08 [0.00, 1.44]



Footnotes
(1) Culture confirmed neonatal sepsis

Neonatal hospital length of stay (days)

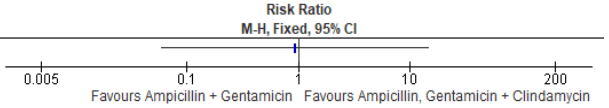
Study or Subgroup	Ampicillin + gentamicin Mean	SD	Total	No treatment Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Gibbs 1988	3.8	1.1	26	5.7	3	19	-1.90 [-3.31, -0.49]



Chorioamnionitis: ampicillin and gentamicin (dual therapy) vs ampicillin, gentamicin and clindamycin (triple therapy)

Culture confirmed neonatal infection

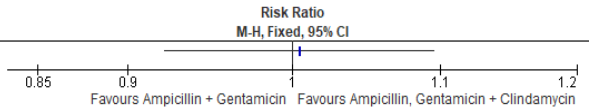
Study or Subgroup	Ampicillin + Gentamicin Events	Total	Ampicillin, Gentamicin + Clindamycin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Maberry 1991 (1)	1	69	1	64	0.93 [0.06, 14.52]



Footnotes
(1) Culture confirmed sepsis

Antibiotics for suspected neonatal infection

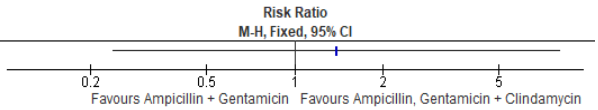
Study or Subgroup	Ampicillin + Gentamicin Events	Total	Ampicillin, Gentamicin + Clindamycin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Maberry 1991 (1)	65	69	60	64	1.00 [0.92, 1.10]



Footnotes
(1) Antibiotic treated

Neonatal mortality (timepoint not specified)

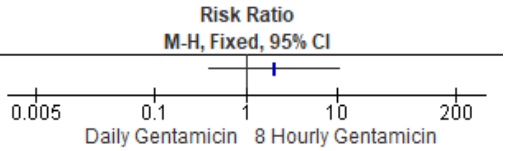
Study or Subgroup	Ampicillin + Gentamicin Events	Total	Ampicillin, Gentamicin + Clindamycin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Maberry 1991	3	69	2	64	1.39 [0.24, 8.06]



Chorioamnionitis: gentamicin (daily) vs gentamicin (8 hourly)

Neonatal infection

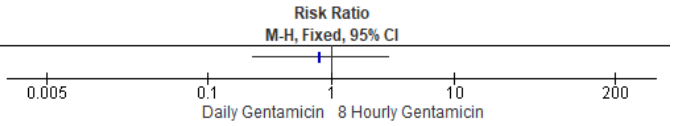
Study or Subgroup	Daily Gentamicin Events	Total	8 Hourly Gentamicin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Lyell 2010 (1)	4	62	2	63	2.03 [0.39, 10.70]



Footnotes
(1) Culture confirmed neonatal sepsis

Maternal infection (endometritis)

Study or Subgroup	Daily Gentamicin Events	Total	8 Hourly Gentamicin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Lyell 2010 (1)	4	62	5	63	0.81 [0.23, 2.89]

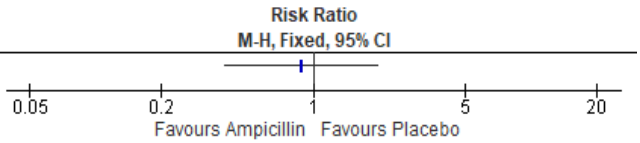


Footnotes
(1) Fever greater than 38°C with uterine tenderness more than 24 hours after delivery

Preterm labour: ampicillin vs placebo

Neonatal mortality (within 7 days from birth)

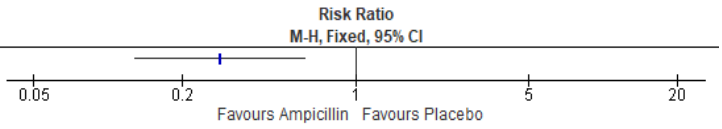
Study or Subgroup	Ampicillin Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Naudisauskiene 1996 (1)	8	44	12	58	0.88 [0.39, 1.96]



Footnotes
(1) Neonatal survival first week

Maternal infection (chorioamnionitis)

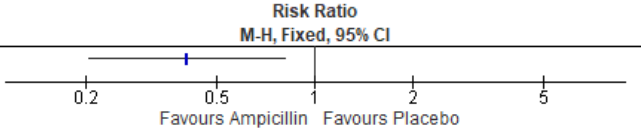
Study or Subgroup	Ampicillin Events	Ampicillin Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Naudisauskiene 1996 (1)	6	44	28	58	0.28 [0.13, 0.62]



Footnotes
(1) Absence of histological chorioamnionitis

Maternal infection (puerperal uterine infection)

Study or Subgroup	Ampicillin Events	Ampicillin Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Naudisauskiene 1996 (1)	8	44	26	58	0.41 [0.20, 0.81]



Footnotes
(1) Absence of puerperal uterine infection

Appendix F – GRADE tables

As part of the NICE pilot project, the quality of outcomes in intervention reviews was based on risk of bias, inconsistency and indirectness. Imprecision was considered by the committee and is covered in the committee's discussion of the evidence (section 1.1.9), but was not used to downgrade outcome quality. Further information can be found in the guideline methods chapter.

Meconium stained amniotic fluid: Ampicillin/sulbactam versus saline (placebo)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Maternal infection (intra-amniotic infection) (RR <1 favours ampicillin/sulbactam)									
1 (Adair 1996)	Parallel RCT	120	RR 0.29 (0.10, 0.82)	23 per 100	7 per 100 (2, 19)	Serious[1]	N/A[2]	Serious[3]	Low
Maternal infection (endometritis) (RR <1 favours ampicillin/sulbactam)									
1 (Adair 1996)	Parallel RCT	120	RR 0.50 (0.18, 1.38)	17 per 100	8 per 100 (3, 23)	Serious[1]	N/A[2]	Serious[3]	Low

1. Single study at moderate risk of bias. Downgraded 1 level
2. Single study. Inconsistency not applicable
3. Single study which is partially applicable. Downgraded 1 level

Maternal GBS colonisation: Penicillin versus ampicillin

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Antibiotics for suspected neonatal infection (RR <1 favours ampicillin)									
1 (Edwards 2002)	Parallel RCT	352	RR 0.85 (0.49, 1.46)	14 per 100	12 per 100 (7, 21)	Very serious[1]	N/A[3]	Not serious	Low
Neonatal mortality (timepoint not specified) (RR <1 favours ampicillin)									
1 (Edwards 2002)	Parallel RCT	352	RR 3.03 (0.12, 73.98)	0 per 100	1 per 100 (0, 21)	Serious[2]	N/A[3]	Not serious	Moderate
Neonatal hospital length of stay (days) (MD <0 favours ampicillin)									
1 (Edwards 2002)	Parallel RCT	352	MD 0.20 (-0.28, 0.68)	-	-	Serious[2]	N/A[3]	Not serious	Moderate

1. Single study at high risk of bias. Downgraded 2 levels
2. Single study at moderate risk of bias. Downgraded 1 level
3. Single study. Inconsistency not applicable

Maternal GBS colonisation: Penicillins versus placebo/no treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Culture-confirmed neonatal infection (RR <1 favours penicillin)									
3	Parallel RCTs	587	RR 0.16 (0.03, 0.87)	7 per 100	1 per 100 (0, 3)	Very serious[1]	Not serious	Not serious	Low

1. >33.3% of weight of studies at high risk of bias. Downgraded 2 levels

Chorioamnionitis: Ampicillin and gentamicin versus no treatment

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Culture-confirmed neonatal infection (RR <1 favours ampicillin and gentamicin)									
1 (Gibbs 1988)	Parallel RCT	45	RR 0.08 (0.00, 1.44)	21 per 100	2 per 100 (0, 30)	Not serious	N/A[1]	Not serious	High
Neonatal hospital length of stay (days) (MD <0 favours ampicillin and gentamicin)									
1 (Gibbs 1988)	Parallel RCT	45	MD -1.90 (-3.31, -0.49)	-	-	Not serious	N/A[1]	Not serious	High

1. Single study. Inconsistency not applicable

Chorioamnionitis: Ampicillin and gentamicin (dual therapy) versus ampicillin, gentamicin and clindamycin (triple therapy)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Culture-confirmed neonatal infection (RR <1 favours ampicillin and gentamicin)									
1 (Maberry 1991)	Parallel RCT	133	RR 0.93 (0.06, 14.52)	2 per 100	1 per 100 (0, 23)	Very serious[1]	N/A[2]	Serious[3]	Very low
Antibiotics for suspected neonatal infection (RR <1 favours ampicillin and gentamicin)									
1 (Maberry 1991)	Parallel RCT	133	RR 1.00 (0.92, 1.10)	94 per 100	94 per 100 (86, 103)	Very serious[1]	N/A[2]	Serious[3]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Neonatal mortality (timepoint unspecified) (RR <1 favours ampicillin and gentamicin)									
1 (Maberry 1991)	Parallel RCT	133	RR 1.39 (0.24, 8.06)	3 per 100	4 per 100 (1, 25)	Very serious[1]	N/A[2]	Serious[3]	Very low

1. Single study at high risk of bias. Downgraded 2 levels
2. Single study. Inconsistency not applicable
3. Single study which is partially applicable. Downgraded 1 level

Chorioamnionitis: Gentamicin (daily) versus gentamicin (8 hourly)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Neonatal infection (RR <1 favours daily gentamicin)									
1 (Lyell 2010)	Parallel RCT	125	RR 2.03 (0.39, 10.70)	3 per 100	6 per 100 (1, 34)	Not serious	N/A[1]	Serious[2]	Moderate
Maternal infection (endometritis) (RR <1 favours daily gentamicin)									
1 (Lyell 2010)	Parallel RCT	125	RR 0.81 (0.23, 2.98)	8 per 100	6 per 100 (2, 23)	Not serious	N/A[1]	Serious[2]	Moderate

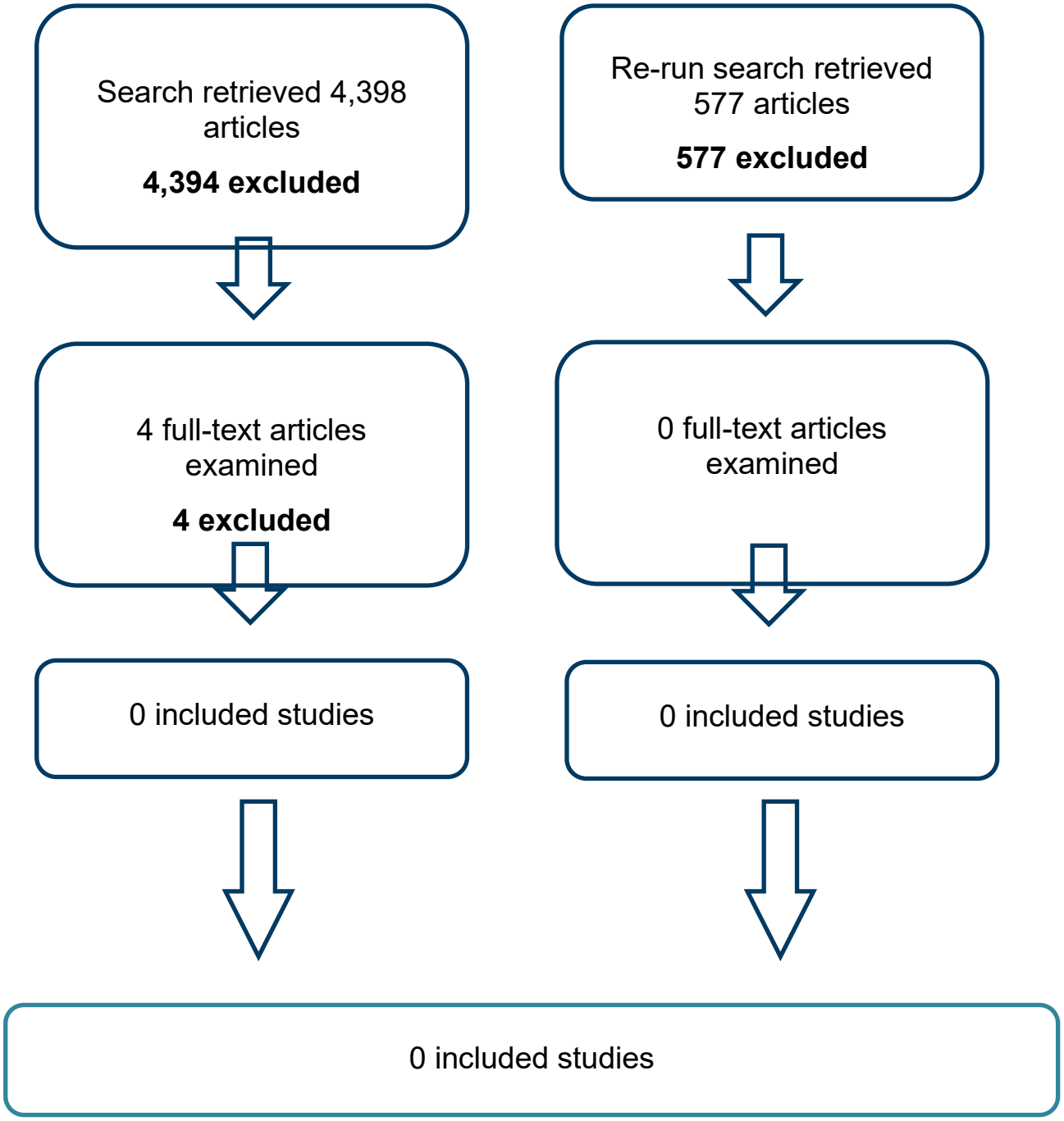
1. Single study. Inconsistency not applicable
2. Single study which is partially applicable. Downgraded 1 level

Preterm labour: Ampicillin versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Neonatal mortality (RR <1 favours ampicillin) (within 7 days from birth)									
1 (Nadisauskiene 1996)	Parallel RCT	102	RR 0.88 (0.39, 1.96)	21 per 100	18 per 100 (8, 41)	Serious[2]	N/A[3]	Serious[4]	Low
Maternal infection (chorioamnionitis) (RR <1 favours ampicillin)									
1 (Nadisauskiene 1996)	Parallel RCT	102	RR 0.28 (0.13, 0.62)	48 per 100	14 per 100 (6, 30)	Serious[2]	N/A[3]	Serious[4]	Low
Maternal infection (puerperal uterine infection) (RR <1 favours ampicillin)									
1 (Nadisauskiene 1996)	Parallel RCT	102	RR 0.41 (0.20, 0.81)	45 per 100	18 per 100 (9, 36)	Very serious[1]	N/A[3]	Serious[4]	Very low

1. Single study at high risk of bias. Downgraded 2 levels
2. Single study at moderate risk of bias. Downgraded 1 level
3. Single study. Inconsistency not applicable
4. Single study which is partially applicable. Downgraded 1 level

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence is available as none of the studies in the economic search results were found to be relevant.

Appendix I – Health economic model

This question was not prioritised for original economic analysis.

Appendix J – Excluded studies

Clinical studies

Study	Reason for exclusion
(2019) The Effect of Non-penicillin Antibiotic Regimens on Neonatal Outcomes in Preterm Premature Rupture of Membranes. AJP reports 9(1): E67-E71	- Not a relevant study design *[Secondary analysis of a randomised trial, but comparison was not randomised]*
Amon E, Lewis SV, Sibai BM et al. (1988) Ampicillin prophylaxis in preterm premature rupture of the membranes: a prospective randomized study. American journal of obstetrics and gynecology 159(3): 539-543	- Study does not contain a relevant intervention *[Compares prophylactic antibiotics given before labour with placebo, rather than intrapartum antibiotics]*
Baird, D. and Campbell, B. (2018) Effectiveness of intrapartum antibiotics for meconium-stained amniotic fluid. American Family Physician 98(9): 570a-570b	- Review article but not a systematic review
Boyer KM and Gotoff SP (1986) Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. The New England journal of medicine 314(26): 1665-1669	- Population does not match review protocol *[Population includes women with prolonged rupture of membranes at term which is excluded from the review protocol. Results for subpopulations not reported.]*
Braye, Kathryn, Ferguson, John, Davis, Deborah et al. (2018) Effectiveness of intrapartum antibiotic prophylaxis for early-onset group B Streptococcal infection: An integrative review. Women and birth : journal of the Australian College of Midwives 31(4): 244-253	- Systematic review checked for relevant studies *[3 RCTs reported, all identified in the search]*
Burr, Sarah E, Camara, Bully, Oluwalana, Claire et al. (2017) Does azithromycin given to women in labour decrease ocular bacterial infection in neonates? A double-blind, randomized trial. BMC infectious diseases 17(1): 799	- Population does not match review protocol *[Concerns localised infection (conjuctivitis)]*
Chaim, W; Maymon, E; Mazor, M (1998) A review of the role of trials of the use of antibiotics in women with preterm labor and intact membranes. Archives of gynecology and obstetrics 261(4): 167-172	- Review article but not a systematic review
Chatzakis, C., Papatheodorou, S., Sarafidis, K. et al. (2019) The effect of prophylactic antibiotics for preterm prelabor rupture of membranes on perinatal outcomes: a network meta-analysis of randomized controlled trials. Ultrasound in	- Duplicate reference

Study	Reason for exclusion
obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology	
Chatzakis, C, Papatheodorou, S, Sarafidis, K et al. (2019) Effect on perinatal outcome of prophylactic antibiotics in preterm prelabor rupture of membranes: network meta-analysis of randomized controlled trials. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology	- Population does not match review protocol *[Systematic review of women not yet in labour]*
Christmas JT, Cox SM, Andrews W et al. (1992) Expectant management of preterm ruptured membranes: effects of antimicrobial therapy. Obstetrics and gynecology 80(5): 759-762	- Population does not match review protocol *[Population is women who are not in labour with pre-term rupture of membranes. Does not concern intrapartum antibiotics.]*
Cox SM, Bohman VR, Sherman ML et al. (1996) Randomized investigation of antimicrobials for the prevention of preterm birth. American journal of obstetrics and gynecology 174(1 Pt 1): 206-210	- Population does not match review protocol *[Although the population was women in preterm labour, women with cervical dilatation >5cm were excluded and more than half of women delivered >28 days after treatment.]*
Dunlop,P.D.M., Crowley,P.A., Lamont,R.F., Hawkins D (1986) Preterm ruptured membranes, no contractions. J Obstet Gynaecol: 92-96	- Population does not match review protocol *[Population is women with pre-term rupture of membranes who are not in labour (no uterine contractions).]*
Egarter, C, Leitich, H, Karas, H et al. (1996) Antibiotic treatment in preterm premature rupture of membranes and neonatal morbidity: a metaanalysis. American journal of obstetrics and gynecology 174(2): 589-597	- Population does not match review protocol *[Systematic review of women with PPROM, not necessarily in labour]*
Flenady, V., Hawley, G., Stock, O.M. et al. (2013) Prophylactic antibiotics for inhibiting preterm labour with intact membranes. Cochrane Database of Systematic Reviews 2013(12): cd000246	- Population does not match review protocol *[Systematic review of antibiotics to inhibit preterm labour]*
Gilbert, RE, Pike, K, Kenyon, SL et al. (2005) The effect of prepartum antibiotics on the type of neonatal bacteraemia: insights from the MRC ORACLE trials. BJOG 112(6): 830-832	- Population does not match review protocol *[Population was 'pre-partum' women]*
Goel, A, Nangia, S, Saili, A et al. (2012) Prophylactic Antibiotics and Sepsis in Neonates Born through Meconium Stained Amniotic Fluid	- Conference abstract

Study	Reason for exclusion
(MSAF) – A Randomized Controlled Trial. Pediatric academic societies annual meeting; 2012 april 28 - may 1; boston ma, united states	
Goel, Ankita, Nangia, Sushma, Saili, Arvind et al. (2015) Role of prophylactic antibiotics in neonates born through meconium-stained amniotic fluid (MSAF)--a randomized controlled trial. European journal of pediatrics 174(2): 237-43	- Population does not match review protocol *[Prophylactic antibiotics given to the baby after birth]*
Grable IA, Garcia PM, Perry D et al. (1996) Group B Streptococcus and preterm premature rupture of membranes: a randomized, double-blind clinical trial of antepartum ampicillin. American journal of obstetrics and gynecology 175(4 Pt 1): 1036-1042	- Population does not match review protocol *[Population was women with preterm rupture of membranes who were not in labour (at labour onset, all women received the same intrapartum antibiotic treatment)]*
Hasperhoven, G F, Al-Nasiry, S, Bekker, V et al. (2020) Universal screening versus risk-based protocols for antibiotic prophylaxis during childbirth to prevent early-onset group B streptococcal disease: a systematic review and meta-analysis. BJOG : an international journal of obstetrics and gynaecology 127(6): 680-691	- Systematic review. Checked for possible includes
Hernández, y Ballinas A; López Farán, JA; Gámez Guevara, C (2011) Comparison of maternal and perinatal outcomes in the conservative treatment preterm premature membrane rupture between the use of erythromycin and clindamycin. Ginecologia y obstetricia de mexico 79(7): 403-410	- Study not reported in English
Johnson JR, Colombo DF, Gardner D et al. (2001) Optimal dosing of penicillin G in the third trimester of pregnancy for prophylaxis against group B Streptococcus. American journal of obstetrics and gynecology 185(4): 850-853	- Population does not match review protocol *[Population was healthy women in the 3rd trimester of pregnancy]*
Kahramanoglu, Ilker, Baktiroglu, Merve, Senol, Taylan et al. (2016) Comparison of two different antibiotic regimens for the prophylaxis of cases with preterm premature rupture of membranes: a randomized clinical trial. Ginekologia polska 87(10): 701-705	- Comparator in study does not match that specified in protocol *[Compares different doses of ampicillin]*
Kenyon S, Pike K, Jones DR et al. (2008) Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of	- Population does not match review protocol *[Population was not women in labour (concerned antibiotics for Preterm, prelabour*

Study	Reason for exclusion
the ORACLE I trial. Lancet (London, England) 372(9646): 1310-1318	*rupture of membranes). About half of women had not delivered 7 days following study entry.]*
Kenyon S, Pike K, Jones DR et al. (2008) Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. Lancet (London, England) 372(9646): 1319-1327	- Population does not match review protocol *[The population was confirmed or suspected preterm labour- but vast majority had cervical dilation<2cm and majority (90%) had not delivered after 48h.]*
Kenyon Sara, Boulvain Michel, Neilson James P (2013) Antibiotics for preterm rupture of membranes. Cochrane Database of Systematic Reviews: Reviews issue12	- Duplicate reference
Kenyon SL, Taylor DJ, Tarnow-Mordi W et al. (2001) Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. ORACLE Collaborative Group. Lancet (London, England) 357(9261): 979-988	- Population does not match review protocol *[Population was not women in labour (concerned antibiotics for Preterm, prelabour rupture of membranes). About half of women had not delivered 7 days following study entry.]*
Kenyon SL, Taylor DJ, Tarnow-Mordi W et al. (2001) Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. ORACLE Collaborative Group. Lancet (London, England) 357(9261): 989-994	- Population does not match review protocol *[The population was confirmed or suspected preterm labour- but vast majority had cervical dilation<2cm and majority (90%) had not delivered after 48h.]*
Kenyon, Sara; Boulvain, Michel; Neilson, James P (2013) Antibiotics for preterm rupture of membranes. The Cochrane database of systematic reviews: cd001058	- Systematic review checked for relevant studies *[All studies either included in the search or not relevant to the review question]*
Kurki T, Hallman M, Zilliacus R et al. (1992) Premature rupture of the membranes: effect of penicillin prophylaxis and long-term outcome of the children. American journal of perinatology 9(1): 11-16	- Population does not match review protocol *[Population was women with P-PROM who were not in labour.]*
Lewis DF, Adair CD, Robichaux AG et al. (2003) Antibiotic therapy in preterm premature rupture of membranes: Are seven days necessary? A preliminary, randomized clinical trial. American journal of obstetrics and gynecology 188(6): 1413	- Population does not match review protocol *[Population was women with P-PROM who were not necessarily in labour.]*
Lewis DF, Fontenot MT, Brooks GG et al. (1995) Latency period after preterm premature rupture of membranes: a comparison of ampicillin with	- Population does not match review protocol *[Population was women with P-PROM who were not in active labour. Mean latency was 6/18*

Study	Reason for exclusion
and without sulbactam. Obstetrics and gynecology 86(3): 392-395	*days for amplicillin and amplicillin-sublactam groups, respectively.]*
Li, Shunming, Huang, Jingya, Chen, Zhiyao et al. (2017) Antibiotic Prevention for Maternal Group B Streptococcal Colonization on Neonatal GBS-Related Adverse Outcomes: A Meta-Analysis. Frontiers in microbiology 8: 374	- Systematic review checked for relevant studies *[All RCTs identified in the search, previous guideline or not relevant to the review question]*
Lockwood CJ, Costigan K, Ghidini A et al. (1993) Double-blind; placebo-controlled trial of piperacillin prophylaxis in preterm membrane rupture. American journal of obstetrics and gynecology 169(4): 970-976	- Population does not match review protocol *[Population was women with P-PROM who were not necessarily in labour. Only 50% delivered within 48hrs.]*
Lovett SM, Weiss JD, Diogo MJ et al. (1997) A prospective, double-blind, randomized, controlled clinical trial of ampicillin-sulbactam for preterm premature rupture of membranes in women receiving antenatal corticosteroid therapy. American journal of obstetrics and gynecology 176(5): 1030-1038	- Population does not match review protocol *[Population was women with P-PROM not in labour (defined as absence of uterine contractions)]*
Maymon, E, Chaim, W, Sheiner, E et al. (1998) A review of randomized clinical trials of antibiotic therapy in preterm premature rupture of the membranes. Archives of gynecology and obstetrics 261(4): 173-181	- Review article but not a systematic review *[Does not describe search strategy or inclusion criteria]*
McCaul JF, Perry KG, Moore JL et al. (1992) Adjunctive antibiotic treatment of women with preterm rupture of membranes or preterm labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 38(1): 19-24	- Population does not match review protocol *[Population was women with P-PROM who were not in labour or women with suspected preterm labour. However the mean latency between treatment and delivery was over 30 days for this group. Oral antibiotics were used.]*
McGregor JA, French JI, Reller LB et al. (1986) Adjunctive erythromycin treatment for idiopathic preterm labor: results of a randomized, double-blinded, placebo-controlled trial. American journal of obstetrics and gynecology 154(1): 98-103	- Population does not match review protocol *[Population was women with pre-term labour. However, mean latency between treatment and delivery was 40/34 days in the treatment and placebo groups respectively. 7 days of oral antibiotics were used.]*
McGregor JA; French JI; Seo K (1991) Antimicrobial therapy in preterm premature rupture of membranes: results of a prospective, double-blind, placebo-controlled trial of erythromycin. American journal of obstetrics and gynecology 165(3): 632-640	- Population does not match review protocol *[Population was women with P-PROM who were not in labour.]*

Study	Reason for exclusion
McGregor JA; French JI; Seo K (1991) Adjunctive clindamycin therapy for preterm labor: results of a double-blind, placebo-controlled trial. American journal of obstetrics and gynecology 165(4 Pt 1): 867-875	- Population does not match review protocol *[Although inclusion criteria was women with preterm labour, the mean treatment to delivery interval>20 days. Treatment was 7 days of oral antibiotics.]*
Mercer BM, Miodovnik M, Thurnau GR et al. (1997) Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. JAMA 278(12): 989-995	- Population does not match review protocol *[Population was women with P-PROM not in established labour]*
Mercer BM, Moretti ML, Prevost RR et al. (1992) Erythromycin therapy in preterm premature rupture of the membranes: a prospective, randomized trial of 220 patients. American journal of obstetrics and gynecology 166(3): 794-802	- Population does not match review protocol *[Population was women with P-PROM not in established labour]*
Morales WJ, Angel JL, O'Brien WF et al. (1989) Use of ampicillin and corticosteroids in premature rupture of membranes: a randomized study. Obstetrics and gynecology 73(5 Pt 1): 721-726	- Population does not match review protocol *[Population was women with P-PROM who were not necessarily in labour.]*
Nabhan, Ashraf F; Elhelaly, Amr; Elkadi, Mohamed (2014) Antibiotic prophylaxis in prelabor spontaneous rupture of fetal membranes at or beyond 36 weeks of pregnancy. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 124(1): 59-62	- Population does not match review protocol *[Population was women with pre-labour rupture of membranes and mean gestational age was 39 weeks (term)]*
Nadisauskiene R; Bergström S; Kilda A (1996) Ampicillin in the treatment of preterm labor: a randomised, placebo-controlled study. Gynecologic and obstetric investigation 41(2): 89-92	- Population does not match review protocol *[Women in preterm labour but average duration from treatment to delivery was >7 and >5 weeks in each arm]*
Newton ER, Shields L, Ridgway LE et al. (1991) Combination antibiotics and indomethacin in idiopathic preterm labor: a randomized double-blind clinical trial. American journal of obstetrics and gynecology 165(6 Pt 1): 1753-1759	- Population does not match review protocol *[Included women in preterm labour but median of 26 days between drug administration and delivery. Some women delivered up to 12 weeks after drug administration]*
Ohlsson Arne, Shah Vibhuti S (2014) Intrapartum antibiotics for known maternal	- Systematic review checked for relevant studies

Study	Reason for exclusion
Group B streptococcal colonization. Cochrane Database of Systematic Reviews: Reviews issue6	*[4 studies all identified in the search]*
Ohlsson, Arne and Shah, Vibhuti S (2013) Intrapartum antibiotics for known maternal Group B streptococcal colonization. The Cochrane database of systematic reviews: cd007467	- More recent systematic review included that covers the same topic
Oluwalana, C., Camara, B., Bottomley, C. et al. (2017) Azithromycin in labor lowers clinical infections in mothers and newborns: A double-blind trial. Pediatrics 139(2): e20162281	- Population does not match review protocol *[Population was all women rather than those with perceived risk factors for neonatal infection]*
Owen J; Groome LJ; Hauth JC (1993) Randomized trial of prophylactic antibiotic therapy after preterm amnion rupture. American journal of obstetrics and gynecology 169(4): 976-981	- Population does not match review protocol *[Population was women with P-PROM who were not necessarily in labour.]*
Pyati, SP, Ramamurthy, RS, Amma, P et al. (1979) Prospective evaluation of penicillin prophylaxis for neonatal group B streptococcal (GBS) infection. Pediatric research 13: 503a	- Conference abstract
Roca, A., Oluwalana, C., Camara, B. et al. (2015) Prevention of bacterial infections in the newborn by pre-delivery administration of azithromycin: Study protocol of a randomized efficacy trial. BMC Pregnancy and Childbirth 15(1): 302	- Study protocol *[Results reported in Oluwanlana 201]*
Romero R, Sibai B, Caritis S et al. (1993) Antibiotic treatment of preterm labor with intact membranes: a multicenter, randomized, double-blinded, placebo-controlled trial. American journal of obstetrics and gynecology 169(4): 764-774	- Population does not match review protocol *[Women in preterm labour but latency to delivery was mean 30 days]*
Schauf, V; Tolpin, M; Ghaey, K (1982) Penicillin prophylaxis against neonatal group B streptococcal infection - is it safe?. Pediatric research 15: 307a	- Conference abstract
Seedat, Farah, Stinton, Chris, Patterson, Jacoby et al. (2017) Adverse events in women and children who have received intrapartum antibiotic prophylaxis treatment: a systematic review. BMC pregnancy and childbirth 17(1): 247	- Systematic review checked for relevant studies *[All studies either identified in the search or do not meet the inclusion criteria of this review]*

Study	Reason for exclusion
Segel SY, Miles AM, Clothier B et al. (2003) Duration of antibiotic therapy after preterm premature rupture of fetal membranes. American journal of obstetrics and gynecology 189(3): 799-802	- Population does not match review protocol *[Population was women with P-PROM who were not necessarily in labour (active labour was excluded).]*
Simcox, R, Sin, WT-A, Seed, PT et al. (2007) Prophylactic antibiotics for the prevention of preterm birth in women at risk: a meta-analysis. Australian & New Zealand journal of obstetrics & gynaecology 47(5): 368-377	- Population does not match review protocol *[Systematic review for women who are not in labour]*
Siriwachirachai Thitiporn, Sangkomkamhang Ussanee S, Lumbiganon Pisake, Laopaiboon Malinee (2014) Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections. Cochrane Database of Systematic Reviews: Reviews issue11	- Duplicate reference
Siriwachirachai, Thitiporn, Sangkomkamhang, Ussanee S, Lumbiganon, Pisake et al. (2014) Antibiotics for meconium-stained amniotic fluid in labour for preventing maternal and neonatal infections. The Cochrane database of systematic reviews: cd007772	- Systematic review checked for relevant studies *[Included studies were identified in the search]*
Svare J, Langhoff-Roos J, Andersen LF et al. (1997) Ampicillin-metronidazole treatment in idiopathic preterm labour: a randomised controlled multicentre trial. British journal of obstetrics and gynaecology 104(8): 892-897	- Population does not match review protocol *[Women in preterm labour but median latency period was 47.5 days in the treatment arm and 27.0 days for the placebo arm]*
Wolf, M.F., Sgayer, I., Miron, D. et al. (2020) A novel extended prophylactic antibiotic regimen in preterm pre-labor rupture of membranes: A randomized trial. International Journal of Infectious Diseases 96: 254-259	- Study does not contain outcomes of interest
Yudin, M.H., van Schalkwyk, J., Eyk, N.V. et al. (2009) Antibiotic Therapy in Preterm Premature Rupture of the Membranes. Journal of Obstetrics and Gynaecology Canada 31(9): 863-867	- Review article but not a systematic review *[Reports searching of databases but no predefined protocol or inclusion criteria]*
Zimmermann, P. and Curtis, N. (2019) Effect of intrapartum antibiotics on the intestinal microbiota of infants: A systematic review. Archives of Disease in Childhood: Fetal and Neonatal Edition	- Systematic review checked for relevant studies *[Only cohort studies included]*

Economic studies

Study	Reason for exclusion
Akker-van Marle, M.E., Rijnders, M.E., Dommelen, P., et al. (2005) Cost-effectiveness of different treatment strategies with intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal disease. BJOG. 2005 Jun;112(6):820-6.	- Study does not contain a relevant comparison *[Focuses on different screening strategies for unspecified intrapartum antibiotics; no specific regimens compared]*
Colbourn,T., Asseburg,C., Bojke,L., et al. (2007) Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses. Health Technology Assessment (Winchester, England), 11, 1-226.	- Study does not contain a relevant comparison *[Focuses on different delivery methods for intrapartum antibiotics; no comparison of different agents]*
Daniels, J., Gray, J., Pattison, H., et al. (2009) Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness. Health Technology Assessment (Winchester, England), 13, 1-154.	- Study does not contain a relevant comparison and the primary results were not presented as cost per QALYs gained
Turrentine, M.A., Ramirez, M.M., Mastrobattista, J.M. (2009) Cost-effectiveness of universal prophylaxis in pregnancy with prior group B streptococci colonization. Infectious Diseases in Obstetrics and Gynecology 2009:934698.	- Study does not contain a relevant comparison *[Compares universal intrapartum antibiotics with screening for maternal GBS]*

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

What is the clinical and cost-effectiveness of intrapartum antibiotics for women with meconium stained amniotic fluid?

K.1.2 Why this is important

One RCT was identified which evaluated the effectiveness of intrapartum antibiotics given to women with meconium stained amniotic fluid. This compared the effects of ampicillin and sulbactam given during labour against placebo. However, this single study was published in 1996, and antibiotic resistance has changed considerably since then. In addition, the combination of antibiotics given to the women are not licensed for use in the UK.

Further research is needed using a robust study design such as a parallel RCT to examine the effectiveness of intrapartum antibiotics for women with meconium stained amniotic fluid. This should focus on antibiotics licensed in the UK and based on practice in the NHS. Research in this area is essential to help determine whether giving intrapartum antibiotics to women with meconium stained amniotic fluid can help to reduce the number of babies who develop early-onset neonatal infection, and whether this can improve maternal outcomes.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Neonatal infection can have serious consequences if left untreated but can be difficult to diagnose. Intrapartum antibiotics can help to reduce the risk of a baby developing early-onset neonatal infection. By identifying the maternal risk factors that can put a baby at greater risk of infection, it is possible to give treatment to the mother during labour and reduce the number of babies who need treatment, or experience the harms associated with infection, after birth. If research establishes that intrapartum antibiotics are effective for women with meconium stained amniotic fluid, then the number of women who are given intrapartum antibiotics may increase in future. This may help to reduce the number of babies who require treatment for early-onset neonatal infection, and reduce the number who experience the various harms associated with infection. Reducing the number of babies who require treatment will also reduce costs to the NHS and reduce hospital length of stay. If the use of intrapartum antibiotics also reduces adverse events in the mother then this will reduce the number of

	women requiring treatment after delivery and any associated costs.
Relevance to NICE guidance	The committee were able to make recommendations on other risk factors that indicate that intrapartum antibiotics should be given to the mother. Current evidence for women with meconium stained amniotic fluid as a risk factor is limited and not based on UK practice. Future research will help to establish whether this is another risk factor that should result in a mother being given intrapartum antibiotic treatment.
Relevance to the NHS	The outcome would determine whether women with meconium stained amniotic fluid would benefit from being given intrapartum antibiotics to reduce the risk of negative health outcomes for both the mother and the baby. If negative health outcomes are reduced then there will also be reductions in the costs of follow-up treatments.
National priorities	Medium
Current evidence base	This review identified 1 study reporting data on maternal outcomes when women with meconium stained amniotic fluid were given intrapartum antibiotics. No evidence was provided for the effects on culture-proven neonatal infection or other neonatal outcomes, and evidence was not based on current UK practice.
Equality considerations	No specific equality concerns are relevant to this research recommendation.

K.1.4 Modified PICO table

PICO	
	Population: • Women in labour with meconium stained amniotic fluid **Interventions:** • Antibiotics (and combinations of antibiotics, including intra and inter-class combinations) including: benzylpenicillin, amoxicillin, ampicillin, co-amoxiclav (Augmentin®), teicoplanin, clindamycin, azithromycin, cephalosporins, erythromycin, metronidazole and vancomycin **Comparator:** • Head-to-head comparison with any of the interventions (including combinations) listed above (including intra and inter-class comparisons) • Placebo • No treatment / usual care **Outcomes:** Neonatal outcomes: • Culture-proven infection from sample taken within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection

	• Antibiotics for suspected bloodstream infection (Antibiotics for suspected bloodstream infection was chosen as a surrogate outcome for infection, as not all infection will be culture proven) • Mortality (at different time points – peri-natal mortality (stillborn or within 7 days from birth) or greater than 7 days from birth) • health-related quality of life, measured using a validated tool (during the neonatal period and at the last time point reported in the study) • hospital length of stay • neurodevelopmental outcomes (measured using a validated tool at the latest time point reported in the study) Maternal/family outcomes: • psychological distress in baby's family as measured using a validated scale (e.g. parental stressor scale NICU; modified Rutter Malaise Inventory) (during the intrapartum period and at the latest timepoint reported in study) • Maternal adverse events (during the intrapartum period and at the latest timepoint reported in study): o serious adverse events o allergic reaction to antibiotics • Maternal sepsis (during the intrapartum period and within 6 weeks of birth)
Current evidence base	1 RCT
Study design	Randomised controlled trials
Other comments	Study should be adequately powered and based on clinical practice in the UK