

## Neonatal infection: antibiotics for prevention and treatment

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

*NICE guideline <number>*

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

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*Draft for Consultation*

*These evidence reviews were developed  
by NICE Guideline Updates Team*



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# 1 Intrapartum antibiotic prophylaxis for preventing early-onset neonatal infection

## 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**

<b>Population</b>	Women in labour with perceived risk factors (as defined by the study authors) for early-onset neonatal infection
<b>Interventions</b>	<ul style="list-style-type: none"><li>• Antibiotics (and combinations of antibiotics, including intra and inter-class combinations)</li></ul>
<b>Comparator</b>	<ul style="list-style-type: none"><li>• Head-to-head comparison with any of the interventions (including combinations), including intra and inter-class comparisons</li><li>• Placebo</li><li>• No treatment / usual care</li></ul>
<b>Outcomes</b>	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 1.1.3 Methods and process

2 This evidence review was developed using the methods and process described in  
3 [Developing NICE guidelines: the manual](#). Full methods specific to this review  
4 question are described in the [methods document](#).

5 Declarations of interest were recorded according to [NICE's 2018 conflicts of interest](#)  
6 [policy](#).

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

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

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

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

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

## 21 **1.1.4 Effectiveness evidence**

### 22 **1.1.4.1 Included studies**

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

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

36 See [appendix B](#) for the full literature search strategies and [appendix C](#) for a PRISMA  
37 diagram showing the flow of studies.

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

43 See [Appendix D](#) for evidence tables of included studies.

### 44 **1.1.4.2 Excluded studies**

45 See [Appendix I](#) for excluded studies and reasons for exclusion.



1 **1.1.5 Summary of studies included in the effectiveness evidence**2 **Table 2 Summary of included clinical studies**

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
Adair 1996 (n=120) USA	<ul style="list-style-type: none"> <li>Duration of follow-up not reported</li> </ul>	<ul style="list-style-type: none"> <li>Women with meconium stained amniotic fluid</li> </ul>	Ampicillin/ Sulbactam <i>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</i>	IV saline Given intravenously, starting at the time of diagnosis of meconium stained amniotic fluid and repeated every 6 hours until delivery	<ul style="list-style-type: none"> <li>Neonatal</li> <li>Maternal infection: amniotic infection; endometritis</li> </ul>
Edwards 2002 (n=352) USA	<ul style="list-style-type: none"> <li>RCT</li> <li>Duration of follow-up not reported</li> </ul>	<ul style="list-style-type: none"> <li>Spontaneous or induced labour</li> <li>Gestational age of 36 weeks or more</li> <li>Culture proven carriers of group B streptococci</li> </ul>	Penicillin <i>5 MU of penicillin G intravenously followed by 2.5 MU every 4 hours until delivery</i>	Ampicillin <i>2 g intravenously followed by 1g every 4 hours until delivery</i>	<ul style="list-style-type: none"> <li>Suspected neonatal infection</li> <li>Neonatal mortality</li> <li>Neonatal hospital length of stay</li> <li>Maternal infection: endometritis</li> </ul>
Gibbs 1988 (n=48) USA	<ul style="list-style-type: none"> <li>RCT</li> <li>4 weeks follow-up</li> </ul>	<ul style="list-style-type: none"> <li>Women with intra-amniotic infection</li> </ul>	Intrapartum antibiotics <i>2 g ampicillin given intravenously every 6 hours plus 1.5 mg/kg gentamicin given intravenously every 8 hours</i>	Postpartum antibiotics <i>2 g ampicillin given intravenously every 6 hours plus 1.5 mg/kg gentamicin given intravenously every 8 hours</i>	<ul style="list-style-type: none"> <li>Culture confirmed neonatal infection</li> <li>Neonatal length of stay</li> </ul>
Lyell 2010 (n=126) USA	<ul style="list-style-type: none"> <li>RCT</li> <li>Follow-up first 48 hours of life</li> </ul>	<ul style="list-style-type: none"> <li>Women with chorioamnionitis</li> <li>Gestational age 34-42 weeks</li> <li>Maternal age 18 years or over</li> </ul>	Daily gentamicin <i>5 mg/kg gentamicin delivered intravenously, followed by a normal saline placebo after 8 and 16 hours</i>	8 hourly gentamicin <i>Loading dose of 2 mg/kg IV, followed by 1.5 mg/kg after 8 and 16 hours</i>	<ul style="list-style-type: none"> <li>Neonatal infection</li> <li>Maternal infection: endometritis</li> </ul>
Maberry 1991 (n=133) USA	<ul style="list-style-type: none"> <li>RCT</li> <li>Duration of follow-up not reported</li> </ul>	<ul style="list-style-type: none"> <li>Intra-amniotic infection</li> <li>Gestational age &gt;24 weeks</li> </ul>	Dual therapy <i>Ampicillin and gentamicin. No information about doses or timing</i>	Triple therapy <i>Ampicillin, gentamicin and clindamycin.</i>	<ul style="list-style-type: none"> <li>Culture confirmed neonatal infection</li> </ul>

Study	Study type and follow-up time	Population	Intervention	Comparator	Outcomes
				No information about doses or timing	<ul style="list-style-type: none"> <li>Antibiotic suspected neonatal infection</li> <li>Neonatal mortality</li> </ul>
Mattoras 1991 (n=121) Spain	<ul style="list-style-type: none"> <li>RCT</li> <li>Duration of follow-up not reported</li> </ul>	<ul style="list-style-type: none"> <li>Women with GBS colonisation</li> </ul>	Ampicillin 500 mg of ampicillin intravenously/6 h during delivery	No treatment No ampicillin was given. Other aspects of care were the same	<ul style="list-style-type: none"> <li>Neonatal infection</li> </ul>
Morales 1986 (n=263) USA	<ul style="list-style-type: none"> <li>RCT</li> <li>Duration of follow-up not reported</li> </ul>	<ul style="list-style-type: none"> <li>Women with GBS colonisation</li> </ul>	Ampicillin 1 g ampicillin intravenously every 6 hours until delivery	Control No information about whether this arm was no treatment or placebo	<ul style="list-style-type: none"> <li>Culture confirmed neonatal infection</li> </ul>
Nadisauskine 1996 (n=102) USA	<ul style="list-style-type: none"> <li>RCT</li> <li>Duration of follow-up not reported</li> </ul>	<ul style="list-style-type: none"> <li>Women in early active phase of preterm labour Cervical dilation <math>\geq 4</math> cm</li> <li>Gestational age &lt;37 weeks</li> <li>Fetus alive</li> </ul>	Ampicillin 5 g ampicillin IV infusion. Two doses, 4 hours apart	Placebo IV infusion. Two doses, 4 hours apart	<ul style="list-style-type: none"> <li>Neonatal infection</li> <li>Neonatal mortality</li> <li>Maternal infection: chorioamnionitis, puerperal uterine infection</li> </ul>
Tuppurainen 1989 (n=199) Finland	<ul style="list-style-type: none"> <li>RCT</li> <li>Duration of follow-up not reported</li> </ul>	<ul style="list-style-type: none"> <li>Women with group B streptococcus colonisation</li> <li>No allergy to penicillin</li> <li>Did not undergo elective term caesarean section without labour or rupture of fetal membranes</li> </ul>	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	<ul style="list-style-type: none"> <li>Culture confirmed neonatal infection</li> </ul>

1 See [appendix D](#) for full evidence tables.

## 2 1.1.6 Summary of the effectiveness evidence

### 3 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)					

Comparison	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect*
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
<b>Maternal GBS colonisation: Penicillin versus ampicillin</b>					
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
<b>Maternal GBS colonisation: Penicillins versus placebo</b>					
Culture-confirmed neonatal infection	3	587	RR 0.16 (0.03, 0.87)	Low	Favours penicillins
<b>Chorioamnionitis: Ampicillin and gentamicin versus no treatment</b>					
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
<b>Chorioamnionitis: Ampicillin and gentamicin (dual therapy) versus ampicillin, gentamicin and clindamycin (triple therapy)</b>					
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
<b>Chorioamnionitis: Gentamicin (daily) versus gentamicin (8 hourly)</b>					
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
<b>Preterm labour: Ampicillin versus placebo</b>					
Neonatal mortality (within 7 days from birth)	1 (Nadisauskine 1996)	102	RR 0.88 (0.39, 1.96)	Low	Could not differentiate
Maternal infection (chorioamnionitis)	1 (Nadisauskine 1996)	102	RR 0.28 (0.13, 0.62)	Low	Favours ampicillin
Maternal infection (puerperal uterine infection)	1 (Nadisauskine 1996)	102	RR 0.41 (0.20, 0.81)	Very low	Favours ampicillin

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

3 See [appendix F](#) for full GRADE tables.

#### 4 **1.1.7 Economic evidence**

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

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

#### 15 **1.1.8 Economic model**

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

#### 19 **1.1.9 The committee's discussion and interpretation of the evidence**

##### 20 **1.1.9.1. The outcomes that matter most**

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

##### 31 **1.1.9.2 The quality of the evidence**

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

37 The evidence examined the effects of intrapartum antibiotics on four maternal risk  
38 factors (meconium stained amniotic fluid, maternal GBS colonisation, maternal  
39 chorioamnionitis and preterm labour). The studies for each risk factor compared  
40 different combinations of either antibiotics, placebo or no treatment, meaning that  
41 most of the analysis was based on results from individual studies rather than pooled  
42 meta-analyses. The committee had some concerns about how closely the evidence

1 could be applied to current NHS practice as antibiotic resistance has changed  
2 considerably during the time since each of the studies were conducted.

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

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

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

50 Only one study investigated the effects of intrapartum antibiotics for women in  
51 preterm labour. The criteria used to diagnose labour in this study ( $\geq 4$  cm dilation) is  
52 different to how labour is now diagnosed and so the quality of outcomes were

1 downgraded for partial applicability to the review. Although there was limited  
2 evidence, preterm labour was identified as one of the risk factors for neonatal  
3 infection in the risk factors section of this guideline. This, in addition to clinical  
4 experience, meant that the committee felt it was important to include women in  
5 preterm labour in the recommendations for intrapartum antibiotics. The committee  
6 decided that the size of the effects for reducing maternal infection were enough to  
7 make this an strong recommendation to 'use' antibiotics, rather than a  
8 recommendation that antibiotics should be considered. The committee also noted  
9 that this recommendation is consistent with current recommendations from the Royal  
10 College of Obstetricians and Gynaecologists on [Group B Streptococcal Disease,](#)  
11 [Early-onset \(Green top Guideline No.36\).](#)

### 12 **1.1.9.3 Imprecision and clinical importance of effects**

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

21 Issues with imprecision were particularly apparent when considering the number of  
22 babies born to women with chorioamnionitis who developed neonatal infection.  
23 Although the effect estimate indicated that intrapartum antibiotics reduced the  
24 number of babies who developed infection, the confidence intervals indicated a high  
25 degree of uncertainty over this effect. As a result, recommendations were made  
26 based on clinical consensus, and the evidence for chorioamnionitis as a risk factor  
27 for early-onset infection as well as extrapolation from the data for women with GBS  
28 colonisation.

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

### 36 **1.1.9.4 Benefits and harms**

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

49



1 A potential harm associated with intrapartum antibiotics is the development of  
2 antibiotic resistance. To avoid this, it is important that antibiotics are not over-  
3 prescribed or inappropriate ones used. However, the committee did not expect these  
4 recommendations to result in a considerable increase in the number of women or  
5 babies receiving antibiotics. The committee thought that the main impact of the  
6 recommendation on the choice of antibiotics for women with chorioamnionitis would  
7 be to reduce variations in practice in the choice of antibiotic for these women. The  
8 committee highlighted that sometimes a broad-spectrum antibiotic was used to treat  
9 maternal infection, with additional benzylpenicillin prescribed to prevent neonatal  
10 infection. The committee decided to recommend a combination of benzylpenicillin  
11 and gentamicin to both treat maternal infection and prevent neonatal infection.  
12 Gentamicin was given to women in all three of the chorioamnionitis studies, and the  
13 committee considered this an appropriate choice because it is effective against gram  
14 negative bacteria which often cause chorioamnionitis. This recommendation should  
15 improve antibiotic stewardship by reducing prescriptions of broad-spectrum  
16 antibiotics; the committee were aware that women were sometimes prescribed a  
17 broad-spectrum antibiotic to treat chorioamnionitis as well as benzylpenicillin to  
18 prevent neonatal infection. Providing clear recommendations on a combination of  
19 narrow spectrum antibiotics that are effective against bacteria causing  
20 chorioamnionitis as well as those responsible for earlier onset neonatal infection is  
21 expected to result in more efficient use of antibiotics. In addition, the NICE antibiotic  
22 stewardship guideline ([NG63](#)) is available to help make clinicians aware of the issues  
23 associated with antibiotic resistance.

24 An additional issue with the prescribing of antibiotics is nephrotoxicity associated with  
25 the use of gentamicin and the potential for allergic reactions to penicillin. To reduce  
26 the risk of negative effects from allergic reactions the committee included advice on  
27 alternative antibiotics that should be given to women who have an allergy to  
28 penicillin, based on their knowledge and experience. The committee amended the  
29 2012 recommendation on antibiotic alternatives for women who are allergic to  
30 penicillin. They changed the recommended antibiotic from clindamycin because there  
31 is evidence of resistance to GBS emerging in clindamycin, meaning that this  
32 antibiotic should no longer be used routinely. Based on their knowledge and  
33 experience, the committee recommended a cephalosporin with activity against group  
34 B streptococcus as an alternative for women with a penicillin allergy that was not  
35 severe, and vancomycin or an alternative antibiotic with activity against group B  
36 streptococcus in the case of severe penicillin allergy. Cephalosporins were not  
37 recommended in the case of severe penicillin allergy because of an increased  
38 chance of a severe allergic reaction to cephalosporins. The new recommendations  
39 on intrapartum antibiotics in women with penicillin allergy are consistent with those  
40 recommended in the Royal College of Obstetricians and Gynaecologists guideline on  
41 prevention of group B streptococcal infection in neonates.

42

#### 43 **1.1.9.5 Cost effectiveness and resource use**

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

**1 1.1.9.6 Other factors the committee took into account**

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

13 The committee highlighted that many women in the UK are unaware of their GBS  
14 status as screening does not routinely take place in the NHS. This could be a source  
15 of inequality because women with lower socioeconomic status might be less likely to  
16 access private GBS testing. However, the committee agreed that recommendations  
17 for GBS are important for those who are aware of their current status, or those who  
18 had GBS in a previous pregnancy. Although there was no direct evidence on the  
19 impact of GBS in previous pregnancies, the committee highlighted that it is widely  
20 recognised as a factor that can greatly increase the risk of GBS in future  
21 pregnancies. It was therefore agreed that this was an important addition to the  
22 existing recommendations. The committee specified that these women should be  
23 offered antibiotics unless they were confirmed to be GBS negative by a culture  
24 collected between 35 and 37 weeks' gestation in the current pregnancy. The criteria  
25 for a test in late pregnancy was added because GBS status can change before this  
26 time, so only a culture taken between 35 and 37 weeks could accurately rule out  
27 GBS colonisation before delivery.

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



1 **1.1.10 Recommendations supported by this evidence review**

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

5 **1.1.11 References – included studies**

6 **1.1.11.1 Effectiveness**

Adair CD, Ernest JM, Sanchez-Ramos L et al. (1996) Meconium-stained amniotic fluid-associated infectious morbidity: a randomized, double-blind trial of ampicillin-sulbactam prophylaxis. *Obstetrics and gynecology* 88(2): 216-220

Edwards RK, Clark P, Siström CL et al. (2002) Intrapartum antibiotic prophylaxis 1: relative effects of recommended antibiotics on gram-negative pathogens. *Obstetrics and gynecology* 100(3): 534-539

Gibbs RS, Dinsmoor MJ, Newton ER et al. (1988) A randomized trial of intrapartum versus immediate postpartum treatment of women with intra-amniotic infection. *Obstetrics and gynecology* 72(6): 823-828

Lyell DJ, Pullen K, Fuh K et al. (2010) Daily compared with 8-hour gentamicin for the treatment of intrapartum chorioamnionitis: a randomized controlled trial. *Obstetrics and gynecology* 115(2 Pt 1): 344-349

Maberry MC, Gilstrap LC, Bawdon R et al. (1991) Anaerobic coverage for intra-amniotic infection: maternal and perinatal impact. *American journal of perinatology* 8(5): 338-341

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

Morales WJ; Lim DV; Walsh AF (1986) 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* 155(5): 979-983

Nadisauskiene R and Bergström S (1996) Impact of intrapartum intravenous ampicillin on pregnancy outcome in women with preterm labor: a randomised, placebo-controlled study. *Gynecologic and obstetric investigation* 41(2): 85-88

Tuppurainen N and Hallman M (1989) Prevention of neonatal group B streptococcal disease: intrapartum detection and chemoprophylaxis of heavily colonized parturients. *Obstetrics and gynecology* 73(4): 583-587

7

# 1 Appendices

## 2 Appendix A – Review protocols

3 **Review protocol for** What is the clinical and cost effectiveness of intrapartum antibiotic prophylaxis for preventing early-onset  
 4 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: <ul style="list-style-type: none"> <li>• effectiveness of prophylaxis</li> <li>• which class or classes of antibiotics to use</li> </ul>
4.	Searches	Searches will include all of the antibiotic classes and individual antibiotic drugs listed under interventions

		<p>Searches will not distinguish between bactericidal and bacteriostatic agents</p> <p>The following databases will be searched:</p> <ul style="list-style-type: none"><li>• Cochrane Central Register of Controlled Trials (CENTRAL)</li><li>• Cochrane Database of Systematic Reviews (CDSR)</li><li>• Embase</li><li>• MEDLINE (including 'in process' and 'E-pub ahead of print')</li><li>• Database of Abstracts of Reviews of Effect (DARE)</li></ul> <p>Searches will be restricted by:</p> <ul style="list-style-type: none"><li>• English language</li><li>• Human studies</li><li>• Conference abstracts</li></ul> <p>Other searches:</p> <p>None</p>
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		<p>A date limit corresponding to the search date for the previous guideline will be used (01 September 2011).</p> <p>The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.</p> <p>The full search strategies for MEDLINE database will be published in the final review.</p> <p>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.</p>
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

		<p>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.</p>
6.	Population	<p>Inclusion:</p> <p>Women in labour with perceived risk factors (as defined by the study authors) for early-onset neonatal infection, including:</p> <ul style="list-style-type: none"> <li>• Suspected maternal intrapartum infection, including suspected chorioamnionitis</li> <li>• Pyrexia</li> <li>• Pre-term prelabour rupture of membranes</li> <li>• Previous baby with group B streptococcus (GBS)</li> <li>• Previous carrier of group B streptococcus (i.e. in a previous pregnancy)</li> <li>• Discovery of maternal GBS carriage through bacteriological investigation during pregnancy (for example, a urine infection or a swab taken to investigate a vaginal discharge)</li> <li>• Pre-term labour</li> </ul>

		<p>Exclusion:</p> <ul style="list-style-type: none"> <li>• Women with pre-labour rupture of membranes at term (covered in the NICE intrapartum care guideline)</li> </ul>
7.	Intervention/Exposure/Test	<ul style="list-style-type: none"> <li>• Antibiotics (and combinations of antibiotics, including intra and inter-class combinations) including: benzylpenicillin, amoxicillin, ampicillin, co-amoxiclav (Augmentin<sup>®</sup>), teicoplanin, clindamycin, azithromycin, cephalosporins, erythromycin, metronidazole and vancomycin</li> </ul>
8.	Comparator/Reference standard/Confounding factors	<ul style="list-style-type: none"> <li>• Head-to-head comparison with any of the interventions (including combinations) listed above (including intra and inter-class comparisons)</li> <li>• Placebo</li> <li>• No treatment / usual care</li> </ul>
9.	Types of study to be included	<ul style="list-style-type: none"> <li>• Randomised controlled trials (RCTs)</li> <li>• Systematic reviews of RCTs</li> </ul>
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:

		<ul style="list-style-type: none"> <li>• Culture-proven infection from sample taken within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection</li> <li>• 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)</li> <li>• Mortality (at different time points – peri-natal mortality (stillborn or within 7 days from birth) or greater than 7 days from birth)</li> <li>• health-related quality of life, measured using a validated tool (during the neonatal period and at the last time point reported in the study)</li> <li>• hospital length of stay</li> <li>• neurodevelopmental outcomes (measured using a validated tool at the latest time point reported in the study)</li> </ul> <p>Maternal/family outcomes:</p> <ul style="list-style-type: none"> <li>• 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)</li> <li>• Maternal adverse events (during the intrapartum period and at the latest timepoint reported in study):</li> </ul>
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		<ul style="list-style-type: none"> <li>○ serious adverse events</li> <li>○ allergic reaction to antibiotics</li> <li>● Maternal sepsis (during the intrapartum period and within 6 weeks of birth)</li> </ul>
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)	<p>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.</p> <p>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.</p> <p>This review will make use of the priority screening functionality within the EPPI-reviewer software.</p>



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	<p>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).</p> <p>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:</p> <ul style="list-style-type: none"> <li>• Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis.</li> <li>• The presence of significant statistical heterogeneity in the meta-analysis, defined as <math>I^2 \geq 50\%</math>.</li> <li>• Meta-analyses will be performed in Cochrane Review Manager V5.3</li> </ul>

17.	Analysis of sub-groups	<ul style="list-style-type: none"> <li>Antibiotics will be grouped by class for the purpose of the analysis If substantial heterogeneity is encountered (<math>I^2 &gt; 50\%</math>), this will be investigated by analysing antibiotics separately, rather than by class</li> </ul> <p><b>Stratifications</b></p> <ul style="list-style-type: none"> <li>Analysis will be stratified by the population groups specified in item 6.</li> <li>Analysis will be stratified by dose as follows: below range recommended in the SPC, within range recommended in SPC, above range recommended in SPC</li> </ul> <p><b>Subgroups</b></p> <ul style="list-style-type: none"> <li>Timing of antibiotic administration relative to the start of labour</li> </ul>
18.	Type and method of review	<ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Intervention</li> <li><input type="checkbox"/> Diagnostic</li> <li><input type="checkbox"/> Prognostic</li> <li><input type="checkbox"/> Qualitative</li> <li><input type="checkbox"/> Epidemiologic</li> <li><input type="checkbox"/> Service Delivery</li> <li><input type="checkbox"/> Other (please specify)</li> </ul>

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	<b>Review stage</b>	<b>Started</b>	<b>Completed</b>
		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	<p><b>5a. Named contact</b> Guideline Updates Team</p> <p><b>5b Named contact e-mail</b> Nlupdate@nice.org.uk</p> <p><b>5e Organisational affiliation of the review</b> National Institute for Health and Care Excellence (NICE)</p>		
25.	Review team members	<p>From the Guideline Updates Team:</p> <ul style="list-style-type: none"> <li>• Dr Kathryn Hopkins</li> <li>• Dr Clare Dadswell</li> <li>• Mr Gabriel Rogers</li> <li>• Dr Stacey-Chang Douglass</li> <li>• Mr Wesley Hubbard</li> </ul>		
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	<p>NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:</p> <ul style="list-style-type: none"> <li>• notifying registered stakeholders of publication</li> <li>• publicising the guideline through NICE's newsletter and alerts</li> </ul>

		<ul style="list-style-type: none"> <li>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.</li> </ul>
32.	Keywords	Intrapartum antibiotics, early onset neonatal infection
33.	Details of existing review of same topic by same authors	None
34.	Current review status	<input checked="" type="checkbox"/> Ongoing <input type="checkbox"/> Completed but not published <input type="checkbox"/> Completed and published <input type="checkbox"/> Completed, published and being updated <input type="checkbox"/> Discontinued
35..	Additional information	None
36.	Details of final publication	<a href="#">The guideline with supporting evidence reviews will be published on the NICE website.</a>

1

2

## 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 baumannii\* 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 amoxidant\* 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 cephalixin\* 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 secuopen\* 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 tobalex\* 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 ampiclo\* 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 cephiroxime\* 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 cephalixin\* or ceporex\* or keflex\* or kiflone\* or biocef\* or cefanex\* or kefler\* 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 secuopen\* 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-Myticin\*).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 amoxidant\* 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 cephalixin\* or ceporex\* or keflex\* or kiflone\* or biocef\* or cefanex\* or kefler\* or keftab\* or zartan\*):ti,ab,kw
- #84 (cefactor\* 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-Myticin\*):ti,ab,kw
- #111 (amikacin\* or amikin\* or arikayce\*):ti,ab,kw
- #112 (tobram?cin\* or bramitob\* or nebcin\* or Tobi or tobalex\* or tobavisc\* 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 ((prematu\*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 amoxidant\* 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 cephalixin\* 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 raniclор\*)
- 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 secuopen\* 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 tobalex\* or tobavisc\* or vantobra\*)
- 113 MeSH DESCRIPTOR Carbapenems EXPLODE ALL TREES
- 114 (carbapenem\*)
- 115 (meropenem\* or meronem\* or merrem\* or vabomere\*)

- 116 (bleomycin\* 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**

<b>Database: Medline (Ovid)</b>	
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)

<b>Database: MiP (Ovid)</b>	
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)

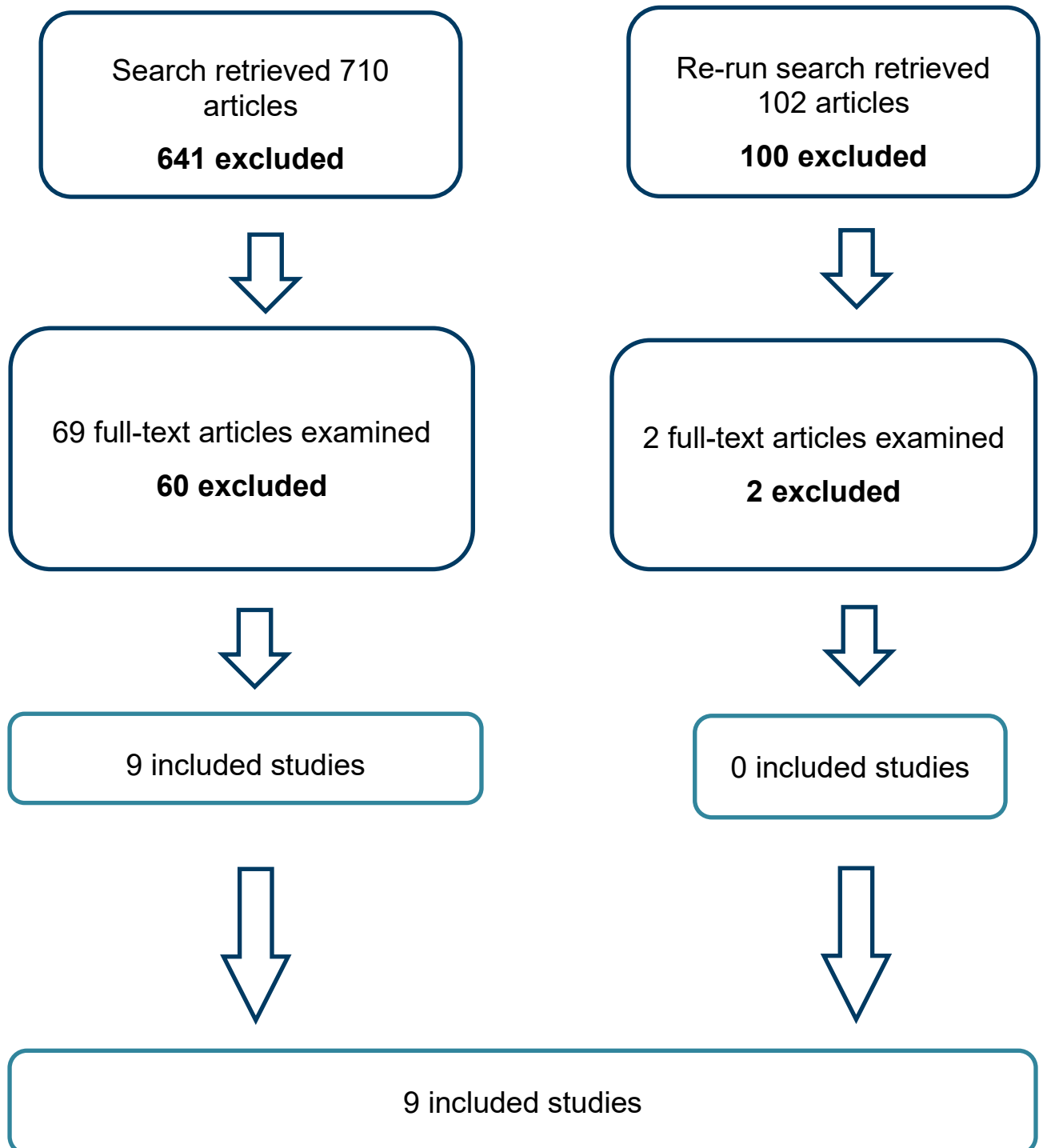
- 58 exp Pharmacoeconomics/ (202216)
- 59 Monte Carlo Method/ (40279)
- 60 Decision Tree/ (13001)
- 61 econom\$.tw. (368838)
- 62 cba.tw. (12788)
- 63 cea.tw. (34786)
- 64 cua.tw. (1498)
- 65 markov\$.tw. (30389)
- 66 (monte adj carlo).tw. (48341)
- 67 (decision adj3 (tree\$ or analys\$)).tw. (23602)
- 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 baumann* 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

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

<b>Methods</b>	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.
<b>Duration of labour / Time from treatment to delivery</b>	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
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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 <i>(Unclear whether an appropriate analysis was used to estimate the effect of assignment to intervention)</i>
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; Siström 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

<b>Study dates</b>	2000-2001
<b>Duration of follow-up</b>	Not explicitly reported - likely to be until discharge from hospital.
<b>Sources of funding</b>	Supported in part by a grant from the Children's Miracle Network
<b>Inclusion criteria</b>	Spontaneous or induced labour Gestational age of 36 weeks or more Culture proven carriers of group B streptococci
<b>Exclusion criteria</b>	Allergy to study medication Antibiotic use in previous 7 days Intrauterine death Planned cesarean delivery Multifetal gestation
<b>Outcome measures</b>	Neonatal antibiotics for suspected bloodstream infection Mortality (timepoint not specified) Length of hospital stay Neonatal Endometritis
<b>Methods</b>	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 <i>(but study powered for antibiotic resistance outcomes)</i>
	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 ( <i>Neonatal length of stay, neonatal mortality</i> )  No information ( <i>No definition for diagnosis of chorioamnionitis, endometritis or neonatal suspected infection</i> )
	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 ( <i>Neonatal length of stay, neonatal mortality</i> )  Some concerns ( <i>No definition for diagnosis of chorioamnionitis, endometritis or neonatal suspected infection</i> )
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 ( <i>Neonatal mortality, neonatal length of stay</i> )  No information ( <i>No definition for diagnosis of chorioamnionitis, endometritis or neonatal suspected infection</i> )

	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 ( <i>Neonatal suspected infection - no definition for diagnosis and limited information about analysis methods</i> )  Some concerns ( <i>Neonatal mortality, neonatal length of stay - limited information about analysis methods</i> )
	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

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



<b>Study dates</b>	May 1987 - November 1987
<b>Duration of follow-up</b>	Four weeks
<b>Sources of funding</b>	None reported
<b>Inclusion criteria</b>	Intra-amniotic infection
<b>Exclusion criteria</b>	<34 weeks gestation Cervical dilation <4 cm at time of diagnosis
<b>Outcome measures</b>	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)
<b>Methods</b>	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)
<b>Postpartum antibiotics (N = 19)</b>	
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 <i>(Differences in the interventions mean caregivers will have been aware of the assigned treatment but antibiotics were the same between arms, only timing differed)</i>
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**

<b>Study type</b>	Randomised controlled trial (RCT)
<b>Sample size</b>	126
<b>Interventions</b>	Gentamicin Daily versus 8-hourly
<b>Study location</b>	USA
<b>Study setting</b>	Labor and Delivery unit at Lucile Packard Children's Hospital at Stanford University Medical Center
<b>Study dates</b>	June 2004 - October 2006
<b>Duration of follow-up</b>	First 48 hours of life
<b>Sources of funding</b>	Department of Obstetrics and Gynecology, Stanford University Medical Center, Stanford, California
<b>Inclusion criteria</b>	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
<b>Exclusion criteria</b>	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
<b>Outcome measures</b>	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
<b>Methods</b>	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)
<b>8 hourly gentamicin (N = 63)</b>	
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 <i>(Endometritis, histological chorioamnionitis, neonatal LOS)</i>
		No information <i>(Neonatal sepsis)</i>
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no <i>(Endometritis, histological chorioamnionitis, neonatal LOS)</i>
		No information <i>(Neonatal sepsis)</i>
	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 <i>(Endometritis, histological chorioamnionitis, neonatal LOS)</i>  Some concerns <i>(Neonatal sepsis - no definition of the outcome)</i>
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 <i>(Endometritis, histological chorioamnionitis, neonatal LOS)</i>  No information <i>(Neonatal sepsis)</i>
	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 <i>(Endometritis, histological chorioamnionitis, neonatal LOS)</i>  No information <i>(Neonatal sepsis)</i>
	Risk-of-bias judgement for selection of the reported result	Low <i>(Endometritis, histological chorioamnionitis, neonatal LOS)</i>  Some concerns <i>(Neonatal sepsis)</i>
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Partially applicable

Section	Question	Answer
		<i>(Women with temperatures of 38°C and above would not be left untreated in clinical practice as they were in the placebo arm)</i>

## 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

<b>Study type</b>	Randomised controlled trial (RCT)
<b>Sample size</b>	133
<b>Interventions</b>	Ampicillin/gentamicin Dual therapy  Ampicillin/gentamicin/clindamycin Triple therapy
<b>Study location</b>	USA
<b>Study setting</b>	Parkland Memorial Hospital
<b>Study dates</b>	December 1987 - January 1989
<b>Duration of follow-up</b>	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
<b>Sources of funding</b>	None reported

<b>Inclusion criteria</b>	Intra-amniotic infection Gestational age >24 weeks
<b>Exclusion criteria</b>	Allergy to study medication Penicillin allergy Mother received antibiotics after delivery Mother was on antibiotics at time of admission
<b>Outcome measures</b>	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
<b>Methods</b>	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 amniotic fluid.  The majority of infants born to mothers with intra-amniotic 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
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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
<b>Triple therapy (N = 64)</b>	
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 <i>(Limited information about methods of analysis)</i>
	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 <i>(Limited information about methods of analysis)</i>
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 <i>(Limited information about methods of analysis)</i>
	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 <i>(Limited information about methods of analysis)</i>
Overall bias and Directness	Risk of bias judgement	High <i>(Limited information about analysis methods and no information about the doses used for dual and triple therapy)</i>
	Overall Directness	Partially applicable

Section	Question	Answer
		<i>(Women with temperatures of 38°C and above would not be left untreated in clinical practice as they were in the placebo arm)</i>

### 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

<b>Study type</b>	Randomised controlled trial (RCT)
<b>Sample size</b>	121
<b>Study location</b>	Spain
<b>Study setting</b>	Single centre, hospital setting
<b>Study dates</b>	Not reported
<b>Duration of follow-up</b>	Not reported.
<b>Sources of funding</b>	Not reported.
<b>Inclusion criteria</b>	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.
<b>Outcome measures</b>	Culture confirmed neonatal infection Group B sepsis only

<b>Methods</b>	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.
<b>Loss to follow-up</b>	Not reported.
<b>Mean maternal age (SD)</b>	Not reported. Reported to be similar across groups.
<b>Mean gestational age (SD)</b>	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
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#### 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 <i>(States that patients were randomly divided into two groups but no further information)</i>
	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 <i>(States that characteristics were similar between the two groups but limited information reported)</i>
	Risk of bias judgement for the randomisation process	High <i>(No information about randomisation or allocation concealment and limited information about baseline characteristics)</i>
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 <i>(Limited information about whether patients or people giving interventions were aware of allocations. Limited information about methods of analysis)</i>

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 <i>(Limited information about analysis methods)</i>
	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 <i>(Limited information about analysis methods)</i>
Overall bias and Directness	Risk of bias judgement	High <i>(No information about randomisation or allocation concealment and limited information about baseline characteristics or analysis methods.)</i>

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

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

	Diagnosed on the basis of positive results of body fluid cultures
<b>Methods</b>	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**

<b>Ampicillin (N = 135)</b>	
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
<b>Control (N = 128)</b>	
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 <i>(Limited information about baseline characteristics)</i>
	Risk of bias judgement for the randomisation process	Some concerns <i>(Limited information about baseline characteristics and no information about allocation concealment)</i>
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 <i>(Limited information about analysis methods)</i>
	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 <i>(Limited information about analysis methods and whether patients or people delivering the intervention were aware of the treatment allocated)</i>
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 <i>(Limited information about analysis methods)</i>
	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 <i>(Limited information about methods of analysis)</i>
Overall bias and Directness	Risk of bias judgement	High <i>(Limited information about allocation concealment, baseline characteristics and analysis methods)</i>
	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

<b>Study type</b>	Randomised controlled trial (RCT)
<b>Sample size</b>	102
<b>Interventions</b>	Ampicillin
<b>Study location</b>	USA
<b>Study setting</b>	Department of Obstetrics and Gynaecology, Kaunas Medical Academy
<b>Study dates</b>	Not reported
<b>Duration of follow-up</b>	Not reported
<b>Sources of funding</b>	None reported
<b>Inclusion criteria</b>	Gestational age <37 weeks Early active phase of preterm labour with cervical dilation $\geq 4$ cm Fetus alive
<b>Exclusion criteria</b>	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



	<p>Membranes ruptured &gt;72 hours</p> <p>Maternal temperature &gt;37.5°C</p> <p>Medical condition necessitating delivery</p>
<b>Outcome measures</b>	<p>Culture confirmed neonatal infection Absence of neonatal infection. Not included in review – no definition of neonatal infection)</p> <p>Mortality Neonatal survival first week</p> <p>Adverse events: Serious adverse events (maternal) Chorioamnionitis (absence of histological chorioamnionitis), Puerperal uterine infection (absence of puerperal uterine infection )</p>
<b>Methods</b>	<p>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)</p> <p>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.</p>

### 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)
<b>Placebo (N = 58)</b>	
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 <i>(Limited information about randomisation and allocation concealment)</i>
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 <i>(Limited information about analysis methods)</i>
	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 <i>(Limited information about analysis methods)</i>
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 <i>(Chorioamnionitis, neonatal death)</i>

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 ( <i>Chorioamnionitis</i> )  No information ( <i>Uterine infection, neonatal infection</i> )
	Risk-of-bias judgement for selection of the reported result	Low ( <i>Chorioamnionitis</i> )  Some concerns ( <i>Uterine infection</i> )
Overall bias and Directness	Risk of bias judgement	High ( <i>Uterine infection - limited information about randomisation, allocation concealment and analysis methods. No information about diagnosis of infection</i> )  Some concerns ( <i>Chorioamnionitis, neonatal mortality - limited information about randomisation, allocation concealment and analysis methods</i> )
	Overall Directness	Some concerns  <i>Criteria to diagnose labour different to that used in current clinical practice</i>

## 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

<b>Study type</b>	Randomised controlled trial (RCT)
<b>Sample size</b>	199
<b>Interventions</b>	Penicillin
<b>Study location</b>	Finland
<b>Study setting</b>	Department of Obstetrics and Gynecology, University Central Hospital, Helsinki
<b>Study dates</b>	December 1983 - January 1986
<b>Duration of follow-up</b>	Not reported but blood cultures were taken within 2 hours of birth
<b>Sources of funding</b>	None reported
<b>Inclusion criteria</b>	Maternal group B streptococcus colonisation No allergy to penicillin Did not undergo elective term cesarean section without labour or rupture of fetal membranes
<b>Outcome measures</b>	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
<b>Methods</b>	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
<b>Mean gestational age (SD)</b>	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 <i>(No information about baseline differences)</i>
	Risk of bias judgement for the randomisation process	Some concerns <i>(No information about baseline values)</i>
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 <i>(Participants and experimenters not blinded to interventions)</i>
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

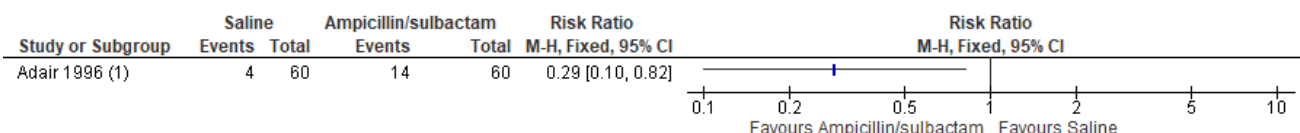


Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware 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 <i>(Outcome assessors not blinded to group assignment but outcome is objective)</i>
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 <i>(Limited information about analysis methods)</i>
	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 <i>(Limited information about baseline values and analysis methods)</i>
	Overall Directness	Directly applicable

## Appendix E – Forest plots

### Meconium stained amniotic fluid: ampicillin and sulbactam vs saline

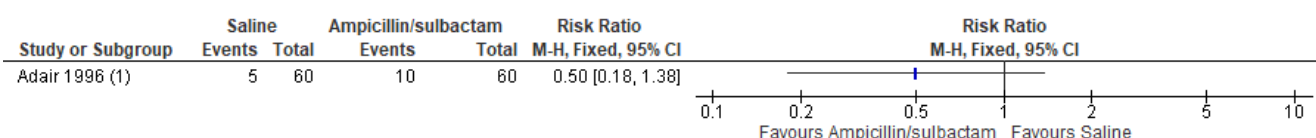
#### Maternal infection (intra-amniotic infection)



**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)

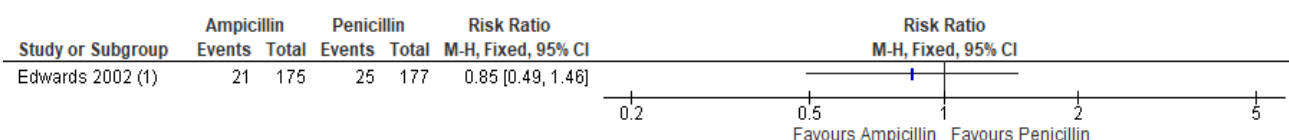


**Footnotes**

(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

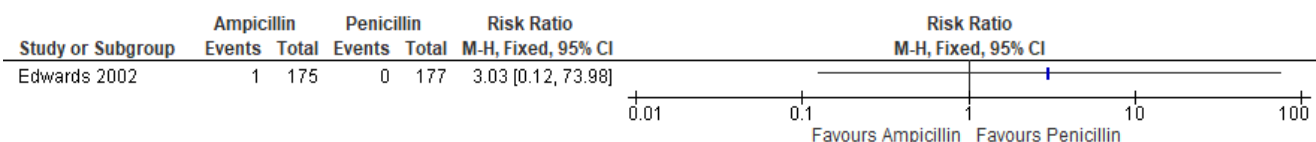
#### Antibiotics for suspected neonatal infection



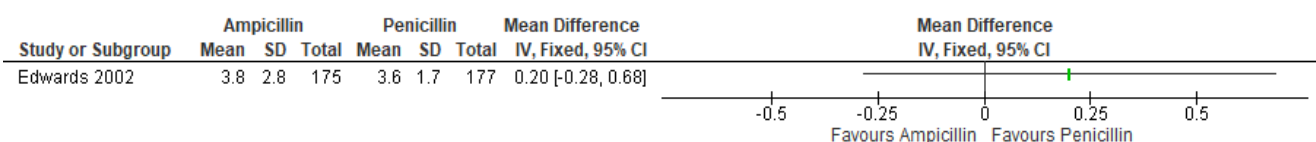
**Footnotes**

(1) Antibiotics for suspected infection

#### Neonatal mortality (timepoint not specified)



#### Neonatal hospital length of stay (days)



## Maternal GBS colonisation: penicillins vs placebo

### Neonatal infection

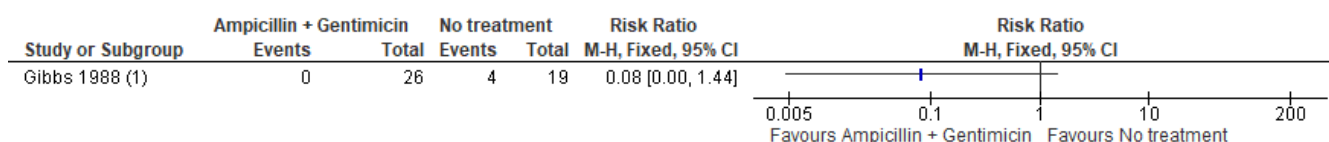


#### Footnotes

- (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

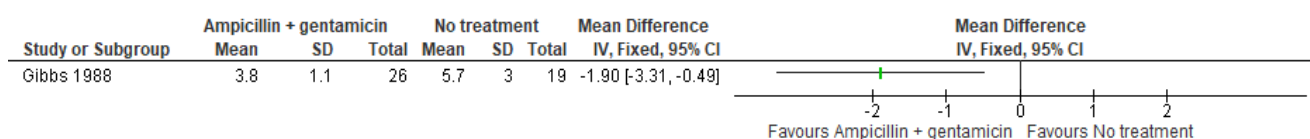
### Neonatal infection



#### Footnotes

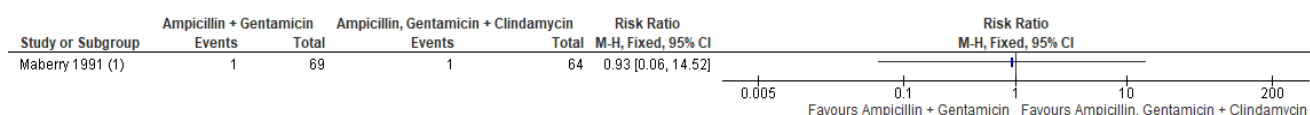
- (1) Culture confirmed neonatal sepsis

## Neonatal hospital length of stay (days)



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

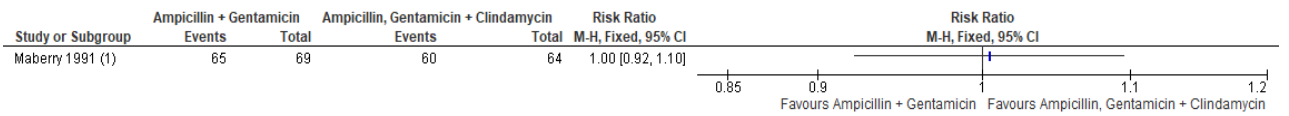
### Culture confirmed neonatal infection



#### Footnotes

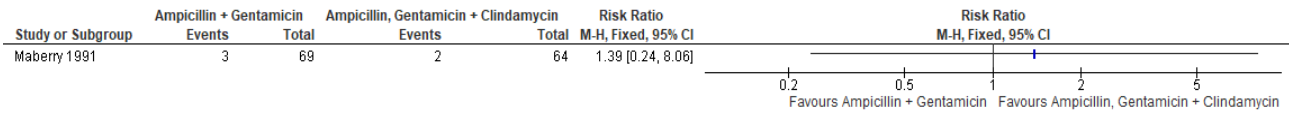
- (1) Culture confirmed sepsis

### Antibiotics for suspected neonatal infection



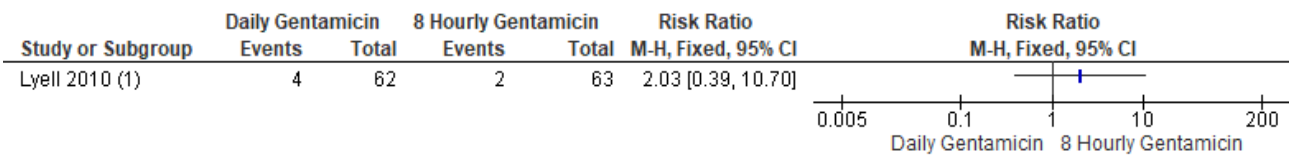
Footnotes  
 (1) Antibiotic treated

### Neonatal mortality (timepoint not specified)



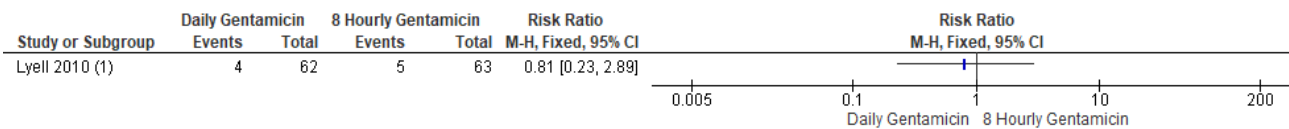
### Chorioamnionitis: gentamicin (daily) vs gentamicin (8 hourly)

#### Neonatal infection



Footnotes  
 (1) Culture confirmed neonatal sepsis

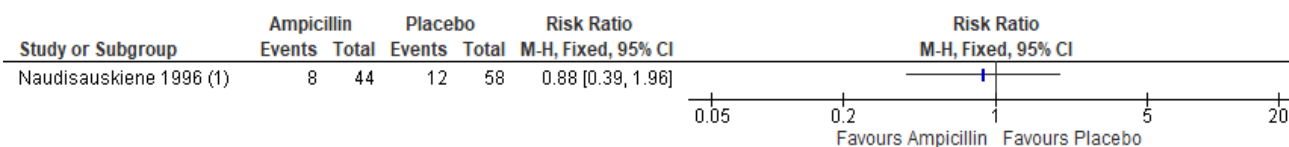
#### Maternal infection (endometritis)



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

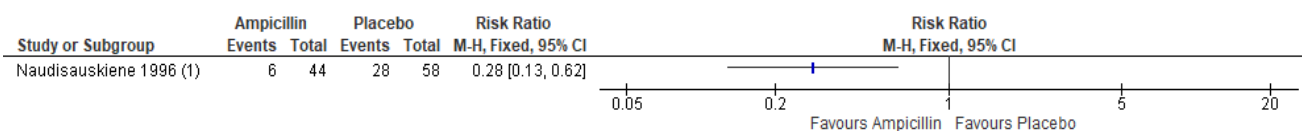
### Preterm labour: ampicillin vs placebo

#### Neonatal mortality (within 7 days from birth)



Footnotes  
 (1) Neonatal survival first week

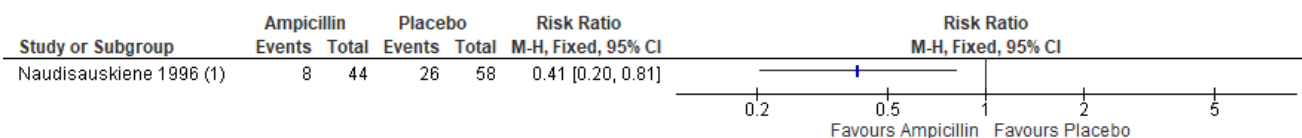
### Maternal infection (chorioamnionitis)



Footnotes

(1) Absence of histological chorioamnionitis

### Maternal infection (puerperal uterine infection)



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
<b>Maternal infection (intra-amniotic infection) (RR &lt;1 favours ampicillin/sulbactam)</b>									
1 (Adair 1996)	Parallel RCT	120	RR 0.29 (0.10, 0.82)	23 per 100	7 per 100 (2, 19)	Serious <sup>1</sup>	N/A <sup>2</sup>	Serious <sup>3</sup>	Low
<b>Maternal infection (endometritis) (RR &lt;1 favours ampicillin/sulbactam)</b>									
1 (Adair 1996)	Parallel RCT	120	RR 0.50 (0.18, 1.38)	17 per 100	8 per 100 (3, 23)	Serious <sup>1</sup>	N/A <sup>2</sup>	Serious <sup>3</sup>	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
<b>Antibiotics for suspected neonatal infection (RR &lt;1 favours ampicillin)</b>									
1 (Edwards 2002)	Parallel RCT	352	RR 0.85 (0.49, 1.46)	14 per 100	12 per 100 (7, 21)	Very serious <sup>1</sup>	N/A <sup>3</sup>	Not serious	Low
<b>Neonatal mortality (timepoint not specified) (RR &lt;1 favours ampicillin)</b>									
1 (Edwards 2002)	Parallel RCT	352	RR 3.03 (0.12, 73.98)	0 per 100	1 per 100 (0, 21)	Serious <sup>2</sup>	N/A <sup>3</sup>	Not serious	Moderate
<b>Neonatal hospital length of stay (days) (MD &lt;0 favours ampicillin)</b>									
1 (Edwards 2002)	Parallel RCT	352	MD 0.20 (-0.28, 0.68)	-	-	Serious <sup>2</sup>	N/A <sup>3</sup>	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
<b>Culture-confirmed neonatal infection (RR &lt;1 favours penicillin)</b>									
3	Parallel RCTs	587	RR 0.16 (0.03, 0.87)	7 per 100	1 per 100 (0, 3)	Very serious <sup>1</sup>	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
<b>Culture-confirmed neonatal infection (RR &lt;1 favours ampicillin and gentamicin)</b>									
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 <sup>1</sup>	Not serious	High
<b>Neonatal hospital length of stay (days) (MD &lt;0 favours ampicillin and gentamicin)</b>									
1 (Gibbs 1988)	Parallel RCT	45	MD -1.90 (-3.31, -0.49)	-	-	Not serious	N/A <sup>1</sup>	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
<b>Culture-confirmed neonatal infection (RR &lt;1 favours ampicillin and gentamicin)</b>									
1 (Maberry 1991)	Parallel RCT	133	RR 0.93 (0.06, 14.52)	2 per 100	1 per 100 (0, 23)	Very serious <sup>1</sup>	N/A <sup>2</sup>	Serious <sup>3</sup>	Very low
<b>Antibiotics for suspected neonatal infection (RR &lt;1 favours ampicillin and gentamicin)</b>									
1 (Maberry 1991)	Parallel RCT	133	RR 1.00 (0.92, 1.10)	94 per 100	94 per 100 (86, 103)	Very serious <sup>1</sup>	N/A <sup>2</sup>	Serious <sup>3</sup>	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
<b>Neonatal mortality (timepoint unspecified) (RR &lt;1 favours ampicillin and gentamicin)</b>									
1 (Maberry 1991)	Parallel RCT	133	RR 1.39 (0.24, 8.06)	3 per 100	4 per 100 (1, 25)	Very serious <sup>1</sup>	N/A <sup>2</sup>	Serious <sup>3</sup>	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
<b>Neonatal infection (RR &lt;1 favours daily gentamicin)</b>									
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 <sup>1</sup>	Serious <sup>2</sup>	Moderate
<b>Maternal infection (endometritis) (RR &lt;1 favours daily gentamicin)</b>									
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 <sup>1</sup>	Serious <sup>2</sup>	Moderate

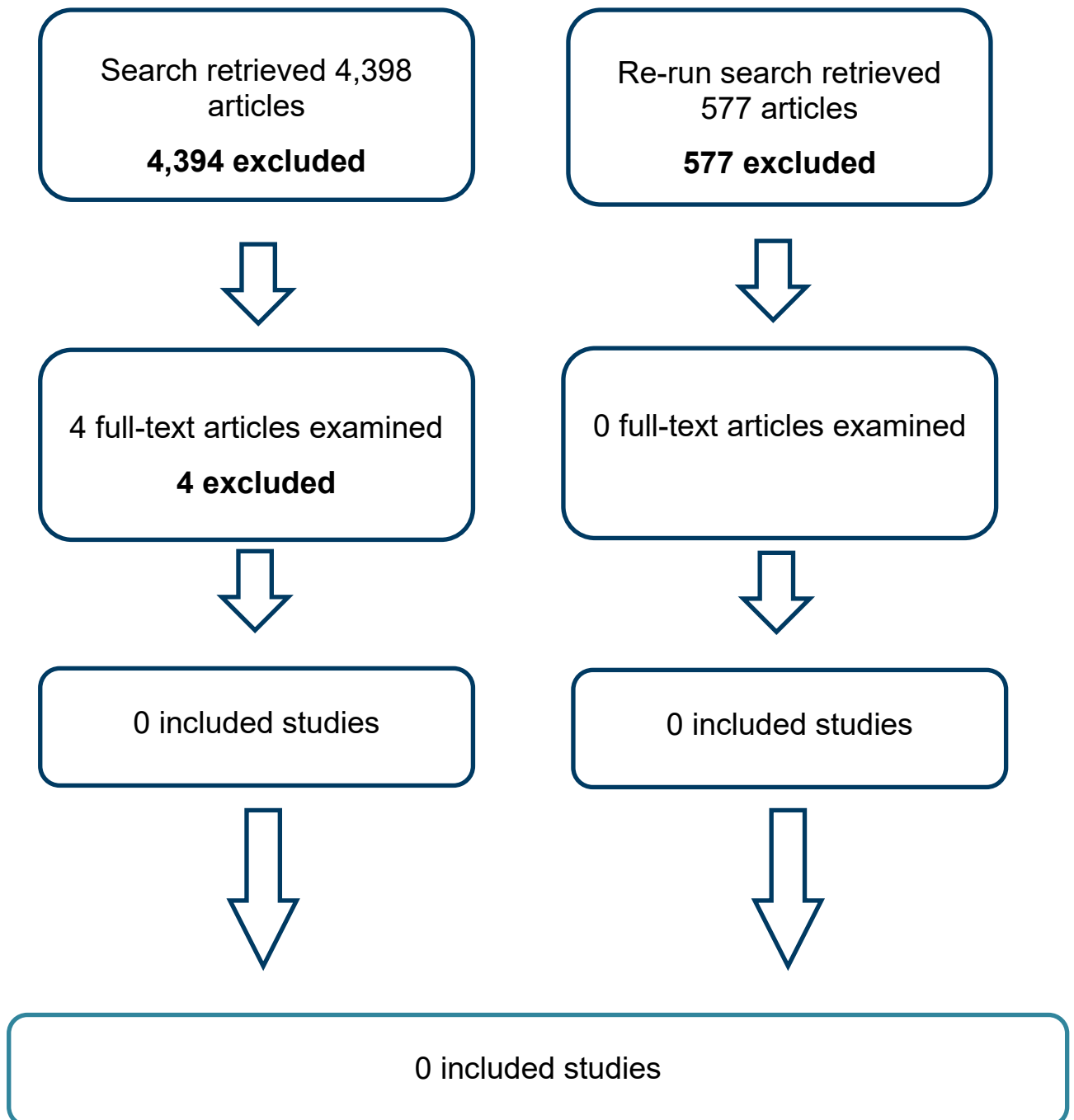
1. Single study. Inconsistency not applicable
2. Single study which is partially applicable. Downgraded 1 level

**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
<b>Neonatal mortality (RR &lt;1 favours ampicillin) (within 7 days from birth)</b>									
1 (Nadisauskiene 1996)	Parallel RCT	102	RR 0.88 (0.39, 1.96)	21 per 100	18 per 100 (8, 41)	Serious <sup>2</sup>	N/A <sup>3</sup>	Serious <sup>4</sup>	Low
<b>Maternal infection (chorioamnionitis) (RR &lt;1 favours ampicillin)</b>									
1 (Nadisauskiene 1996)	Parallel RCT	102	RR 0.28 (0.13, 0.62)	48 per 100	14 per 100 (6, 30)	Serious <sup>2</sup>	N/A <sup>3</sup>	Serious <sup>4</sup>	Low
<b>Maternal infection (puerperal uterine infection) (RR &lt;1 favours ampicillin)</b>									
1 (Nadisauskiene 1996)	Parallel RCT	102	RR 0.41 (0.20, 0.81)	45 per 100	18 per 100 (9, 36)	Very serious <sup>1</sup>	N/A <sup>3</sup>	Serious <sup>4</sup>	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 <i>[Secondary analysis of a randomised trial, but comparison was not randomised]</i>
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 <i>[Compares prophylactic antibiotics given before labour with placebo, rather than intrapartum antibiotics]</i>
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 <i>[Population includes women with prolonged rupture of membranes at term which is excluded from the review protocol. Results for subpopulations not reported.]</i>
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 <i>[3 RCTs reported, all identified in the search]</i>
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 <i>[Concerns localised infection (conjunctivitis)]</i>
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 <i>[Systematic review of women not yet in labour]</i>
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 <i>[Population is women who are not in labour with pre-term rupture of membranes. Does not concern intrapartum antibiotics.]</i>
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 <i>[Although the population was women in preterm labour, women with cervical dilatation &gt;5cm were excluded and more than half of women delivered &gt;28 days after treatment.]</i>
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 <i>[Population is women with pre-term rupture of membranes who are not in labour (no uterine contractions). ]</i>
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 <i>[Systematic review of women with PPRM, not necessarily in labour]</i>
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 <i>[Systematic review of antibiotics to inhibit preterm labour]</i>
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 <i>[Population was 'pre-partum' women]</i>
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 <i>[Prophylactic antibiotics given to the baby after birth]</i>
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 <i>[Population was women with preterm rupture of membranes who were not in labour (at labour onset, all women received the same intrapartum antibiotic treatment)]</i>
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 <i>[Population was healthy women in the 3rd trimester of pregnancy]</i>
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 <i>[Compares different doses of ampicillin]</i>
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 <i>[Population was not women in labour (concerned antibiotics for Preterm, prelabour</i>



Study	Reason for exclusion
the ORACLE I trial. Lancet (London, England) 372(9646): 1310-1318	<i>rupture of membranes). About half of women had not delivered 7 days following study entry.]</i>
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 <i>[The population was confirmed or suspected preterm labour- but vast majority had cervical dilation&lt;2cm and majority (90%) had not delivered after 48h.]</i>
Kenyon Sara, Bouvain 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 <i>[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.]</i>
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 <i>[The population was confirmed or suspected preterm labour- but vast majority had cervical dilation&lt;2cm and majority (90%) had not delivered after 48h.]</i>
Kenyon, Sara; Bouvain, Michel; Neilson, James P (2013) Antibiotics for preterm rupture of membranes. The Cochrane database of systematic reviews: cd001058	- Systematic review checked for relevant studies <i>[All studies either included in the search or not relevant to the review question]</i>
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 <i>[Population was women with P-PROM who were not in labour.]</i>
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 <i>[Population was women with P-PROM who were not necessarily in labour.]</i>
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 <i>[Population was women with P-PROM who were not in active labour. Mean latency was 6/18]</i>

Study	Reason for exclusion
and without sulbactam. <i>Obstetrics and gynecology</i> 86(3): 392-395	<i>days for ampicillin and ampicillin-sulbactam groups, respectively.]</i>
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. <i>Frontiers in microbiology</i> 8: 374	- Systematic review checked for relevant studies <i>[All RCTs identified in the search, previous guideline or not relevant to the review question]</i>
Lockwood CJ, Costigan K, Ghidini A et al. (1993) Double-blind; placebo-controlled trial of piperacillin prophylaxis in preterm membrane rupture. <i>American journal of obstetrics and gynecology</i> 169(4): 970-976	- Population does not match review protocol <i>[Population was women with P-PROM who were not necessarily in labour. Only 50% delivered within 48hrs.]</i>
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. <i>American journal of obstetrics and gynecology</i> 176(5): 1030-1038	- Population does not match review protocol <i>[Population was women with P-PROM not in labour (defined as absence of uterine contractions)]</i>
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. <i>Archives of gynecology and obstetrics</i> 261(4): 173-181	- Review article but not a systematic review <i>[Does not describe search strategy or inclusion criteria]</i>
McCaul JF, Perry KG, Moore JL et al. (1992) Adjunctive antibiotic treatment of women with preterm rupture of membranes or preterm labor. <i>International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics</i> 38(1): 19-24	- Population does not match review protocol <i>[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.]</i>
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. <i>American journal of obstetrics and gynecology</i> 154(1): 98-103	- Population does not match review protocol <i>[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.]</i>
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. <i>American journal of obstetrics and gynecology</i> 165(3): 632-640	- Population does not match review protocol <i>[Population was women with P-PROM who were not in labour.]</i>

Study	Reason for exclusion
<p>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</p>	<p>- Population does not match review protocol</p> <p><i>[Although inclusion criteria was women with preterm labour, the mean treatment to delivery interval &gt;20 days. Treatment was 7 days of oral antibiotics.]</i></p>
<p>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</p>	<p>- Population does not match review protocol</p> <p><i>[Population was women with P-PROM not in established labour]</i></p>
<p>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</p>	<p>- Population does not match review protocol</p> <p><i>[Population was women with P-PROM not in established labour]</i></p>
<p>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</p>	<p>- Population does not match review protocol</p> <p><i>[Population was women with P-PROM who were not necessarily in labour.]</i></p>
<p>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</p>	<p>- Population does not match review protocol</p> <p><i>[Population was women with pre-labour rupture of membranes and mean gestational age was 39 weeks (term)]</i></p>
<p>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</p>	<p>- Population does not match review protocol</p> <p><i>[Women in preterm labour but average duration from treatment to delivery was &gt;7 and &gt;5 weeks in each arm]</i></p>
<p>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</p>	<p>- Population does not match review protocol</p> <p><i>[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]</i></p>
<p>Ohlsson Arne, Shah Vibhuti S (2014) Intrapartum antibiotics for known maternal</p>	<p>- Systematic review checked for relevant studies</p>

Study	Reason for exclusion
Group B streptococcal colonization. Cochrane Database of Systematic Reviews: Reviews issue6	<i>[4 studies all identified in the search]</i>
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 <i>[Population was all women rather than those with perceived risk factors for neonatal infection]</i>
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 <i>[Population was women with P-PROM who were not necessarily in labour.]</i>
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 <i>[Results reported in Oluwanlana 201]</i>
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 <i>[Women in preterm labour but latency to delivery was mean 30 days]</i>
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 <i>[All studies either identified in the search or do not meet the inclusion criteria of this review]</i>

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 <i>[Population was women with P-PROM who were not necessarily in labour (active labour was excluded).]</i>
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 <i>[Systematic review for women who are not in labour]</i>
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 <i>[Included studies were identified in the search]</i>
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 <i>[Women in preterm labour but median latency period was 47.5 days in the treatment arm and 27.0 days for the placebo arm]</i>
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 <i>[Reports searching of databases but no predefined protocol or inclusion criteria]</i>
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 <i>[Only cohort studies included]</i>

**Economic studies**

Study	Reason for exclusion
<p>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.</p>	<p>- Study does not contain a relevant comparison <i>[Focuses on different screening strategies for unspecified intrapartum antibiotics; no specific regimens compared]</i></p>
<p>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.</p>	<p>- Study does not contain a relevant comparison <i>[Focuses on different delivery methods for intrapartum antibiotics; no comparison of different agents]</i></p>
<p>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.</p>	<p>- Study does not contain a relevant comparison and the primary results were not presented as cost per QALYs gained</p>
<p>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.</p>	<p>- Study does not contain a relevant comparison <i>[Compares universal intrapartum antibiotics with screening for maternal GBS]</i></p>



## 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	<p>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.</p> <p>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</p>
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	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

<b>PICO</b>	<p><b>Population:</b></p> <ul style="list-style-type: none"> <li>• Women in labour with meconium stained amniotic fluid</li> </ul> <p><b>Interventions:</b></p> <ul style="list-style-type: none"> <li>• 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</li> </ul> <p><b>Comparator:</b></p> <ul style="list-style-type: none"> <li>• Head-to-head comparison with any of the interventions (including combinations) listed above (including intra and inter-class comparisons)</li> <li>• Placebo</li> <li>• No treatment / usual care</li> </ul> <p><b>Outcomes:</b></p> <p>Neonatal outcomes:</p> <ul style="list-style-type: none"> <li>• Culture-proven infection from sample taken within 72 hours of birth where available or within the study-defined period for early-onset neonatal infection</li> </ul>
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	<ul style="list-style-type: none"> <li>• 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)</li> <li>• Mortality (at different time points – peri-natal mortality (stillborn or within 7 days from birth) or greater than 7 days from birth)</li> <li>• health-related quality of life, measured using a validated tool (during the neonatal period and at the last time point reported in the study)</li> <li>• hospital length of stay</li> <li>• neurodevelopmental outcomes (measured using a validated tool at the latest time point reported in the study)</li> </ul> <p>Maternal/family outcomes:</p> <ul style="list-style-type: none"> <li>• 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)</li> <li>• Maternal adverse events (during the intrapartum period and at the latest timepoint reported in study): <ul style="list-style-type: none"> <li>○ serious adverse events</li> <li>○ allergic reaction to antibiotics</li> </ul> </li> <li>• Maternal sepsis (during the intrapartum period and within 6 weeks of birth)</li> </ul>
<b>Current evidence base</b>	1 RCT
<b>Study design</b>	Randomised controlled trials
<b>Other comments</b>	Study should be adequately powered and based on clinical practice in the UK