National Institute for Health and Care Excellence

Final

Neonatal infection: antibiotics for prevention and treatment

[H] Evidence review for antibiotics for treating late-onset neonatal infection

NICE guideline NG195

Evidence reviews underpinning recommendations 1.10.1-1.11.7 in the NICE guideline

April 2021

Final

These evidence reviews were developed by NICE Guideline Updates Team

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1.1 Review question

What is the optimal antibiotic treatment regimen for suspected late-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. Late-onset neonatal infection (infection that occurs more than 72 hours after birth), is present in 7 of every 1000 newborn babies and is responsible for 61 of every 1000 neonatal admissions. Coagulase-negative staphylococci, Enterobacteriaceae and Staphylococcus aureus are the most common organisms identified.

Antibiotics are given to the baby if it is suspected that they have late-onset neonatal infection. There are a range of different antibiotics, and combinations of antibiotics that can be given to a baby to help treat late-onset neonatal infection. Establishing which treatment is the most effective will help to reduce the harms associated with late-onset infection. The aim of this review is to establish the clinical and cost-effectiveness of antibiotics for treating late-onset neonatal infection, including which classes of antibiotics should be used.

1.1.2 Summary of the protocol

Table 1 PICO table

Population	Babies with suspected late-onset neonatal bacterial infection (from 72 hours to 28 days after birth or based on study definition of late-onset neonatal infection)
Interventions	Antibiotics (and combinations of antibiotics, including intra and inter-class combinations)
Comparator	• Head-to-head comparison with any of the interventions (including combinations). Inter-class comparisons will only be included if antibiotics are analysed separately, rather than by class • Comparisons of different treatment durations • Placebo • No treatment / usual care
Outcomes	Neonatal outcomes: • Culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies) • Relapse (during the neonatal period at the latest time point reported in the study) • Mortality (during the neonatal period at the latest time point reported in the study) • Hospital length of stay • Duration to culture negative • Adverse drug reactions specifically related to antibiotics • Neurodevelopmental outcomes (measured using a validated tool at the latest time point reported in the study) • Antimicrobial resistance (culture proven)

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)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A. For details of full methods used in this review, see the methods document.

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

Randomised controlled trials (RCTs) and systematic reviews of RCTs were considered for inclusion. RCT evidence was available for all outcomes except antibiotic resistance, and so observational studies were considered for this outcome, as specified in the review protocol. Priority screening was used for this the review. In total, 2949 studies (60% of the database) were screened before the stopping criteria was met. For further information on priority screening and the stopping criteria see the methods document.

The review protocol specified that subgroup analyses would be conducted for different classes of antibiotics unless substantial heterogeneity. If heterogeneity was evident then different types of antibiotics would be analysed separately. However, the studies included in the review reported on a range of antibiotics for the intervention and control arms. This variation in both populations and interventions meant that all outcomes had to be presented as individual study results rather than using pooled meta-analysis. No data were found to perform subgroup analyses for term versus preterm babies, presence of a central catheter or babies with a history of previous surgery.

One of the outcomes in the protocol was adverse drug reactions specifically related to antibiotics. The committee advised that the two main adverse reactions it was interested in were hearing impairment and adverse events affecting the kidneys.

Where observational studies were included for antibiotic resistance outcomes, only those that used a comparative observational design were included. Studies that used a non-comparative design were excluded from the review because the review protocol specified a comparative design.

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

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A combined search for this review and the review on antifungals for late-onset neonatal infection (see Evidence Review I – Antifungals) returned a total of 4,896 results. Of these, 118 were identified as potential includes for either review question, with full text articles ordered and reviewed against the inclusion criteria. Ten studies met the inclusion criteria for this review, 8 RCTs and 2 observational studies.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 347 results of which 8 were identified as possible included studies. After full text review, 2 met the inclusion criteria. In total there were therefore 12 studies which met the inclusion criteria for this review, 9 parallel RCTs and 3 observational studies.

1.1.4.2 Excluded studies

See appendix J for excluded studies and reasons for exclusion.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of included clinical studies

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
Randomised controlled trials					
Abdel-Hady 2011 (n=30) Egypt	Until discharge	• Infants at risk or with clinical features and laboratory criteria of sepsis • Gestational age ≥36 weeks • Body weight ≥2500 g	Amikacin once per day *Once daily dose - 15 mg/kg*	Amikacin twice per day *Twice daily dose – 7.5 mg/kg per dose*	• Duration to culture negative
English 2004 (n=312) Kenya	4 days	• Age *Less than 3 months (until January 2001) then less than 2 months (from February 2001)*	Once daily gentamicin *Initial dose of 8 mg/kg followed by single dose per day based on weight and age*	Multi-dose gentamicin *Dose based on weight and age, given 2-3 times per day*	• Neonatal mortality
Gwee 2019 (n=111) Australia	The duration of treatment	• *Age* *0-90 days* • Anticipated that vancomycin therapy would be administered for >48 hours	Intermittent vancomycin infusion *Dose recommended by BNFc*	Continuous vancomycin infusion *After a loading dose of 15 mg/kg infused over 1 hour*	• Duration to culture negative *Mean time to clearance of bacteraemia*
Kosalaraksa 2004 (n=64) Thailand	7 days or duration of treatment	• Age *0-7 days old* • Body weight *≥2000 g* • APGAR score	Once daily gentamicin *5 mg/kg every 24 hours*	Twice daily gentamicin *2.5 mg/kg every 12 hours*	• Responders *clinical response: improvement within 72 hours of treatment*

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
		>6 at 5 minutes • Suspected sepsis			
Lutsar 2020 (n=272) 6 European countries	28 days	• Age *Between 72 hours and 90 days* • Clinical or culture proven late-onset sepsis	• Meropenem *given via 30-minute intravenous infusion at a dose of 20 mg/kg every 8 hours*	• Standard of care *Ampicillin and gentamicin or cefotaxime and gentamicin administered according to the BNFc*	• Mortality • Relapse • Adverse events
Molyneux 2017 (n=348) Malawi	1 and 6 months after hospital discharge	• Age *≤2 months* • Clinical suspicion of severe sepsis, pneumonia or meningitis	Benzylpenicillin and gentamicin *8 hourly IV benzylpenicillin 50,000 iu/kg (100,000 iu for meningitis). Daily gentamicin 6 mg/kg IV (smaller doses for low birth weight infants and very premature babies). Given for 5-14 days*	Ceftriaxone *Ceftriaxone IV 50 -100 mg/kg od (depending on age). Given for 5-14 days*	• Mortality • Adverse drug reactions related to antibiotics *Hearing loss*
Ramasamy 2014 (n=90) India	Within 2 weeks of discharge	• Age *3 - 28 days* • Suspected sepsis • Babies admitted to hospital	Cloxacillin and amikacin *No information on dose*	Cefotaxime and gentamicin *No information on dose*	• Neonatal mortality
Shabaan 2017 (n=102) Egypt	48 hours then weekly (end point is unclear)	• Age *<28 days of life* • Confirmed sepsis • Gram negative bacteria sensitive to meropenem	Meropenem infusion *Intravenous open-label meropenem at a dose of 20 mg/kg/dose every 8 hours over 4 hours (40 mg/kg/dose every 8 hours for meningitis and pseudomonas infection)*	Conventional meropenem *Intravenous open-label meropenem at a dose of 20 mg/kg/dose administered over 30 minutes every 8 hours (40 mg/kg/dose every 8 hours for meningitis and pseudomonas infection)*	• Mortality • Culture negative 7 days after starting therapy • Adverse drug reactions related to antibiotics *Acute kidney injury*

Study	Follow-up time	Population	Intervention	Comparator	Outcomes
Taheri 2011 (n=135) Iran	48 hours	• Suspected sepsis • Term neonates	Ampicillin and ceftizoxime *Doses based on age*	Ampicillin and amikacin *Doses based on age*	• Responders *non-responder: looking ill, worsening in general condition or persistence of initial symptoms and signs along with abnormal laboratory findings after 48 hours*
Observational studies					
De Champs 1994 (n=636) France	Not reported	• Age *Less than 28 days* • Baby received antibiotic therapy while in the hospital	Gentamicin and ampicillin *Intramuscular gentamicin 5 mg/kg/day in addition to IV ampicillin 200 mg/kg/day*	Amikacin *Intramuscular amikacin 15 mg/kg/day*	• Antibiotic resistance (no specific timepoint)
Demirel 2015 (n=77) Turkey	Until 48th hour of treatment	• Gestational age <34 weeks • Babies given vancomycin for suspected or well-established late-onset sepsis	Intermittent vancomycin infusion *Vancomycin HCl DBL injectable vial 500 mg, diluted with 5% dextrose to obtain a final concentration of 5 mg/dl. Total dose was calculated from the Neofax manual*	Continuous vancomycin infusion *Loading dose of 10 mg/kg followed by a total daily dose infused over 24 hours. Total daily dose was calculated from the Neofax manual*	• Antibiotic resistance (beginning of treatment and 48th hour of treatment)
Patel 2020 (n=101) USA	Not reported	• Received at least 24 hours of cefotaxime or ceftazidime within pre-specified time frames in the NICU	Cefotaxime *No information about doses or timing*	Ceftazidime *No information about doses or timing*	• Antibiotic resistance (no specific timepoint)

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3 Quality assessment of outcomes in the evidence review

Comparison	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Amikacin: Once versus twice daily dose					
Duration to culture negative (days)	1 (Abdel-Hady 2011)	30	MD -0.70 (-3.29, 1.89)	Very low	Could not differentiate
Gentamicin: Once versus twice daily dose					
Responders (clinical response: improvement within 72 hours of treatment)	1 (Kosalaraksa 2004)	51	RR 0.93 (0.82, 1.06)	Very low	Could not differentiate
Gentamicin: Once daily versus multi dose					
Neonatal mortality (timepoint not specified)	1 (English 2004)	297	RR 1.07 (0.59, 1.92)	Moderate	Could not differentiate
Meropenem: Conventional dose versus infusion					
Culture negative 7 days after starting therapy	1 (Shabaan 2017)	102	RR 1.45 (1.10, 1.90)	Low	Favours infusion
Neonatal mortality (timepoint not specified)	1 (Shabaan 2017)	102	RR 2.29 (1.03, 5.08)	Low	Favours infusion
Adverse drug reactions (acute kidney injury)	1 (Shabaan 2017)	102	RR 4.00 (1.20, 13.34)	Low	Favours infusion
Meropenem: Meropenem versus standard of care (ampicillin-gentamicin or cefotaxime-gentamicin)					
Neonatal mortality at 28 days	1 (Lutsar 2020)	271	RR 1.42 (0.56, 3.62)	Moderate	Could not differentiate
Relapse by 28 days	1 (Lutsar 2020)	75	RR 1.13 (0.41, 3.12)	Moderate	Could not differentiate
Adverse drug reactions (hearing impairment) at 28 days	1 (Lutsar 2020)	131	RR 0.52 (0.25, 1.05)	Moderate	Could not differentiate
Vancomycin: Continuous versus intermittent infusion					
Time to culture negative	1 (Gwee 2019)	111	MD -9.20 (-14.14, -4.26)	Low	Favours continuous
Methicillin-resistant staphylococcus infections (beginning of treatment)	1 (Demirel 2015)	77	RR 0.66 (0.29, 1.50)	Very low	Could not differentiate
Methicillin-resistant staphylococcus infections (48th hour of treatment)	1 (Demirel 2015)	77	RR 0.57 (0.05, 6.02)	Very low	Could not differentiate
Cefotaxime versus ceftazidime					
Antibiotic resistance ((multidrug resistant organism after initial antibiotic course – no specific timepoint)	1 (Patel 2020)	101	RR 5.22 (0.28, 98.49)	Low	Could not differentiate
Ampicillin-amikacin versus ampicillin-ceftizoxime					

Comparison	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Responders (non-responder: looking ill, worsening in general condition or persistence of initial symptoms and signs along with abnormal laboratory findings after 48 hours)	1 (Taheri 2011)	135	RR 1.03 (0.89, 1.19)	Very low	Could not differentiate
Benzylpenicillin-gentamicin versus ceftriaxone					
Neonatal mortality (inpatients)	1 (Molyneux 2017)	331	RR 1.00 (0.54, 1.84)	Low	Could not differentiate
Neonatal mortality (6 months follow-up)	1 (Molyneux 2017)	331	RR 0.83 (0.50, 1.39)	Low	Could not differentiate
Adverse drug reactions (hearing loss)	1 (Molyneux 2017)	331	RR 1.69 (0.60, 4.79)	Low	Could not differentiate
Cloxacillin-amikacin versus cefotaxime-gentamicin					
Neonatal mortality (before hospital discharge)	1 (Ramasamy 2014)	90	RR 0.38 (0.11, 1.27)	Low	Could not differentiate
Gentamicin-ampicillin versus amikacin					
Gentamicin-resistance (no specific timepoint)					
Escheria coli bacteria	1 (De Champs 1994)	224	RR 0.29 (0.04, 2.40)	Very low	Could not differentiate
Enterobacter clocae bacteria	1 (De Champs 1994)	74	RR 2.74 (1.45, 5.19)	Very low	Favours amikacin
Pseudomonas aeruginosa bacteria	1 (De Champs 1994)	59	RR 0.87 (0.53, 1.40)	Very low	Could not differentiate
Other aerobic Gram-negative bacilli	1 (De Champs 1994)	44	RR 0.05 (0.00, 0.71)	Very low	Favours gentamicin-ampicillin
Staphylococcus aureas bacteria	1 (De Champs 1994)	90	RR 1.09 (0.72, 1.64)	Very low	Could not differentiate
Coagulase-negative staphylococci bacteria	1 (De Champs 1994)	135	RR 1.01 (0.80, 1.28)	Very low	Could not differentiate
All bacteria	1 (De Champs 1994)	626	RR 1.19 (0.98, 1.44)	Very low	Could not differentiate
Amikacin-resistance (no specific timepoint)					
Escheria coli bacteria	1 (De Champs 1994)	224	RR 0.20 (0.01, 3.58)	Very low	Could not differentiate
Enterobacter clocae bacteria	1 (De Champs 1994)	74	RR 2.45 (0.12, 49.15)	Very low	Could not differentiate

Comparison	No. studies	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Pseudomonas aeruginosa bacteria	1 (De Champs 1994)	59	RR 4.22 (1.22, 14.64)	Very low	Favours amikacin
Other aerobic Gram-negative bacilli	1 (De Champs 1994)	44	RR 0.05 (0.00, 0.78)	Very low	Favours gentamicin-ampicillin
Staphylococcus aureas bacteria	1 (De Champs 1994)	90	RR 2.52 (0.11, 60.25)	Very low	Could not differentiate
Coagulase-negative staphylococci bacteria	1 (De Champs 1994)	135	RR 0.78 (0.14, 4.55)	Very low	Could not differentiate
All bacteria	1 (De Champs 1994)	626	RR 0.50 (0.26, 0.97)	Very low	Favours gentamicin-ampicillin
Ceftazidime-resistance (no specific timepoint)					
Escheria coli bacteria	1 (De Champs 1994)	224	RR 0.20 (0.01, 3.58)	Very low	Could not differentiate
Enterobacter clocae bacteria	1 (De Champs 1994)	74	RR 39.71 (2.54, 619.56)	Very low	Favours amikacin
E. aerogenes bacteria	1 (De Champs 1994)	26	RR 1.44 (0.60, 3.49)	Very low	Could not differentiate
Pseudomonas aeruginosa bacteria	1 (De Champs 1994)	59	RR 5.43 (0.60, 48.97)	Very low	Could not differentiate
Other aerobic Gram-negative bacilli	1 (De Champs 1994)	44	RR 0.36 (0.05, 2.69)	Very low	Could not differentiate
Staphylococcus aureas bacteria	1 (De Champs 1994)	90	RR 1.09 (0.72, 1.64)	Very low	Could not differentiate
Coagulase-negative staphylococci bacteria	1 (De Champs 1994)	135	RR 0.44 (0.29, 0.67)	Very low	Favours gentamicin-ampicillin
All bacteria	1 (De Champs 1994)	626	RR 1.22 (0.95, 1.56)	Very low	Could not differentiate

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 4,398 studies. Based on title and abstract screening, 4,385 of the studies could confidently be excluded for this question. 13 studies were excluded following the full-text review.

The search was re-run in July 2020 to identify any studies which had been published since the date of the original search. This returned a total of 577 results. Based on title and

abstract screening, all the studies could confidently be excluded for this question. Thus, the review for this question does not include any study from the existing literature.

1.1.7.2 Excluded studies

See appendix J for excluded economic studies.

1.1.8 Economic model

Although this question was originally prioritised for original economic analysis, the evidence identified in the clinical review did not readily lend itself to a decision-model – that is, the identified trials compare a limited range of regimens in heterogeneous circumstances. Therefore, the committee agreed that it would not be appropriate to force the evidence together as if it constituted a comprehensive network of approaches which apply to a homogeneous group of babies. Accordingly, the committee agreed that no meaningful economic modelling could be performed.

1.1.9 The committee's discussion and interpretation of the evidence

1.1.9.1. The outcomes that matter most

The committee agreed that all the outcomes specified in the protocol were important to consider when treating suspected late-onset infection. Antibiotic resistance was highlighted as one of the key outcomes because this can be a concern when treating babies for neonatal infection, where treatment is typically started before blood test results are available. Although no RCTs reported data on antibiotic resistance, three observational studies reported this outcome for vancomycin, cefotaxime, ceftazidime, gentamicin and amikacin. Neonatal infection can have serious short- and long-term consequences for the health of a baby and so duration to a negative culture is also important. Longer duration of infection can result in increased length of stay which can affect outcomes for both the baby and the baby's family, as well as increased costs for the NHS. Only two studies reported duration to culture negative, with information for this outcome provided for amikacin and vancomycin.

1.1.9.2 The quality of the evidence

Evidence ranged from very low- to moderate-quality, with most of the outcomes either very low- or low-quality. Many of the studies were downgraded for risk of bias due to limited information about the analysis methods. No two studies compared the same combination of antibiotics, and outcomes were therefore based on individual, relatively small, study results rather than pooled meta-analyses. As a result, comparisons for many of the outcomes had wide confidence intervals, reducing the committee's confidence in the effects. The committee also stated that one of the antibiotics used (ceftizoxime) is not licensed in the UK and therefore no recommendations could be based on that evidence.

The committee highlighted that none of the evidence was based in the UK. The bacteria that cause late-onset neonatal infection vary according to geographical region, and so the quality of outcomes from all studies were downgraded due to partial applicability of the data. The most effective choice of antibiotic may therefore be different to those that would be most effective for use in the NHS. However, this is not expected to have affected the recommendations as the most appropriate antibiotics can vary between neonatal units and the choice of antibiotics should therefore be based on local prescribing policy. This is reflected in the choice of antibiotics recommendation.

When considering the evidence for antibiotic resistance, the committee noted that one of the three studies to report this outcome was from Turkey, which may have a different resistance

pattern to the UK, and was therefore downgraded for partial applicability to the review. Another study was published in 1994, since when antibiotic resistance is likely to have changed. The third study did not report the doses of antibiotics given to babies and so this was downgraded for risk of bias.

Many of the studies in the review included babies who were born at term. While this is an important population to consider, the committee highlighted that late-onset infection is most common in pre-term babies. These studies were not downgraded for applicability as the populations was still in scope for the review. However, as the evidence provided limited information on pre-term babies, the committee decided to make recommendations for this group based on its clinical experience and current standards of best practice.

1.1.9.3 Imprecision and clinical importance of effects

There was considerable imprecision in some of the effect estimates. Much of this may have arisen from the lack of evidence, with only one study comparing each combination of antibiotics. As a result, even where the effect estimate favoured one treatment over another, confidence intervals often crossed the line of no effect. This, in addition to the low quality of evidence due to risk of bias and applicability issues, reduced the committee's confidence in some of the potential effects of different antibiotics. Given this high level of imprecision, the committee decided to make the recommendations based on a combination of the evidence and their clinical experience. As the committee decided to make broad, rather than specific, guidance for choice of antibiotics, the uncertainty in the results is not expected to have greatly impacted on the final recommendations.

1.1.9.4 Benefits and harms

The committee noted that the bacteria responsible for late-onset infection and antibiotic resistance vary according to geographical region, meaning that there is no single optimal treatment option. The committee therefore recommended that local antibiotic susceptibility and resistance data should be taken into account when choosing which antibiotics to use.

The evidence considered by the committee was sparse and in general did not favour one antibiotic over another. One study compared the use of meropenem to standard of care. Other studies made comparisons between different doses, or dosing strategies of the same antibiotic, including amikacin, gentamicin and meropenem. Some studies examined the effectiveness of different combinations of antibiotics (see Table 3 for a summary of the evidence). While most of the evidence did not favour a particular antibiotic, there was some evidence to suggest that an infusion of meropenem is more effective than a conventional dose, and that a continuous dose of vancomycin will result in a shorter time to culture negative than an intermittent infusion of vancomycin, However, these results were from single studies with small sample sizes and low quality evidence. Given the limited, low quality, evidence base the committee decided that a research recommendation would be useful to help inform decisions in future updates of this guideline (Appendix K). If research can identify a particular antibiotic, or combination of antibiotics, that is the most effective for treating late-onset infection, then future updates of this guideline can provide more specific recommendations to clinicians. This may help to reduce the length of time that babies are exposed to antibiotics as well as reducing the serious consequences of infection.

The committee agreed to cross refer to existing NICE guidance on antibiotic treatment for community acquired late-onset infection (from the NICE sepsis guideline – NG51) as none of the evidence reviewed contradicted the recommendation on choice of antibiotic made in that guideline, and the committee agreed that it reflected current practice. The recommendation in the sepsis guideline states that babies should be given either ceftriaxone or cefotaxime, depending on corrected gestational age. Only one study in this review investigated the use of ceftriaxone, and two reported outcomes for cefotaxime, one in combination with gentamicin.

All studies were low quality but the results did not highlight any concerns over the effectiveness or safety of giving either antibiotic to neonates.

The committee noted that recommendations from the sepsis guideline may not apply to babies who acquire late-onset neonatal infection while being treated on the neonatal unit, as the bacteria responsible for these infections are likely to differ. For this group, the committee made broad, rather than specific, recommendations on the choice of antibiotics. The evidence reviewed by the committee did not favour broader spectrum antibiotics over combinations of narrower spectrum antibiotics. For instance, there was no clear difference in neonatal mortality or adverse drug reactions when the effects of benzylpenicillin-gentamicin was compared to ceftriaxone or when meropenem was compared to either ampicillin-gentamicin or cefotaxime-gentamicin.. The committee were also aware that using broad-spectrum antibiotics in neonates is associated with altered gut flora, increased risk of invasive fungal infection and the development of antibiotic resistance, and so a combination of narrow spectrum antibiotics was recommended as first-line treatment. This recommendation is designed to provide broad guidance on antibiotic use but may not result in a substantial change in practice from what clinicians are currently doing based on local guidance. The recommendation that first-line treatment is based on the use of narrow-spectrum antibiotics may help to reduce the development of resistance to broad-spectrum antibiotics.

The committee was in agreement that the recommendations should not define specific antibiotic regimens as the evidence did not clearly favour one antibiotic over another, and the most effective regimen may vary between neonatal units, depending on local antibiotic susceptibility and resistance data. However, it was highlighted that there may be situations where examples of an acceptable antibiotic regimen may be helpful. Flucloxacillin plus gentamicin was therefore given as an example of a narrow-spectrum antibiotic combination that could be used, alongside an example of a broad-spectrum antibiotic. An example of an additional antibiotic that should be included if necrotising enterocolitis is suspected was also added to the recommendations. This was thought to be important as many babies in a neonatal unit may have necrotising enterocolitis, which can lead to neonatal infection, The committee also chose to highlight that the selected antibiotics should be effective against both Gram-negative and Gram-positive bacteria, as late-onset infection can be caused by a number of different bacteria and this is important information to take into account when choosing which antibiotic to use. As the recommendations could lead to the use of gentamicin, the committee thought it was important to signpost clinicians to the recommendations on therapeutic drug monitoring, as these include important considerations for the safety and effectiveness of treatment.

The evidence for this review used a range of dosing strategies and treatment durations and so recommendations on the duration of treatment and discharge were based on the existing recommendations for babies with suspected early-onset infection from the 2012 version of this guideline. The committee agreed that similar recommendations were applicable to both groups of babies and reflect current practice. Although the recommendations were broadly the same as those for babies with early-onset infection, the duration of initial treatment was recommended to be 48 hours for babies with late-onset rather than 36 hours. This was thought to reflect the different bacteria that cause late-onset infection, which grow more slowly and have a lower load in the bloodstream than those that cause early-onset infection. This means that it can take longer for a blood culture to become positive for late-onset infection and so treatment needs to continue for longer until a negative blood culture result can be confirmed. To help with treatment decisions, the 2012 version of the guideline recommended that healthcare professionals with experience in neonatal infection should be available to provide microbiological or paediatric infection disease advice. The committee decided that this recommendation is also important when making decisions about antibiotic treatment for late-onset infection.

The committee also decided to add that antibiotic treatment could continue beyond 7 days if longer treatment is needed because of the site of the infection, such as when there is intra-abdominal co-pathology, necrotising enterocolitis, osteomyelitis or infection of a central venous catheter. There was no evidence for the specific situations where longer treatment would be required, but the committee based their decisions on their knowledge and experience. An additional recommendation was added which explains when treatment duration could be shorter than 7 days. Providing guidance on this should reduce the number of babies who receive antibiotic treatment for longer than necessary, thereby improving antibiotic stewardship. These recommendations will give clinicians confidence about the most appropriate course of treatment when a baby is suspected of having late-onset infection.

1.1.9.5 Cost effectiveness and resource use

As no original economic modelling was performed, the committee discussed the cost-effectiveness of antibiotic treatment of late-onset infections based on their clinical experience. The committee agreed that antibiotics are inexpensive, whereas the costs associated with infection, including but not limited to death and lifelong morbidity, are potentially very high. The committee therefore agreed that any antibiotic regimen that minimises the incidence of infections is bound to be cost saving at the population level, supporting strong recommendations in favour of the use of antibiotics for suspected infection.

The committee also noted that, while the evidence for this question concentrates on premature babies in neonatal critical care, there is also a group of neonates who are born at term and later acquire an infection in the community. Committee members noted that outpatient antibiotic treatment of these babies is possible, and has become more common, in part because it is less resource-intensive (at least in the short-term). However, the committee had seen no evidence about the effectiveness or costs of this approach, so it did not make any explicit recommendations about it.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.10.1-1.11.7 and the research recommendation on antibiotics for suspected late-onset neonatal infection.

1.1.11 References – included studies

1.1.11.1 Effectiveness

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Appendices

Appendix A – Review protocols

Review protocol for what is the optimal antibiotic treatment regimen for suspected late-onset neonatal infection?

ID	Field	Content
0.	PROSPERO registration number	CRD42020169422
1.	Review title	Antibiotics for treating late-onset neonatal infection
2.	Review question	7.1 What is the optimal antibiotic treatment regimen for suspected late-onset neonatal infection?
3.	Objective	To identify an effective and safe antibiotic choice and regimen for the treatment of suspected late-onset neonatal infection
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE (including 'in process' and 'E-pub ahead of print') • Database of Abstracts of Reviews of Effect (DARE)

		Searches will be restricted by: • English language • Human studies • Conference abstracts Other searches: None The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review. No date restrictions have been applied for this question.
5.	Condition or domain being studied	Neonatal infection is a significant cause of mortality and morbidity in newborn babies. Late-onset neonatal infection occurs more than 72 hours after birth and can lead to life-threatening sepsis. Late-onset neonatal infection is present in 7 of every 1000 newborn babies and responsible for 61 of every 1000 neonatal admissions. Coagulase-negative staphylococci, Enterobacteriaceae and *Staphylococcus aureus* are the most common organisms identified. Prompt antibiotic treatment for neonatal infection can save lives.

6.	Population	Inclusion: • Babies with suspected late-onset neonatal bacterial infection (from 72 hours to 28 days after birth or based on study definition of late-onset neonatal infection) Exclusion: • Babies with suspected or confirmed non-bacterial infections. • Babies with suspected or confirmed syphilis. • Babies with localised infections. • Babies with suspected or confirmed bacterial infection resulting from therapeutic interventions such as surgery. Babies with a history of surgery which was not the cause of the infection will not be excluded.
7.	Intervention/Exposure/Test	Antibiotics (and combinations of antibiotics, including intra and inter-class combinations) used to treat suspected early-onset neonatal bacterial infection, including: • penicillins (for example, benzylpenicillin, amoxicillin, ampicillin and flucloxacillin) • cephalosporins (for example, cefuroxime, cefotaxime and ceftazidime) • carbapenems (for example, meropenem)

		• glycopeptides (for example, vancomycin) • aminoglycosides (for example, gentamicin, amikacin and tobramycin)
8.	Comparator/Reference standard/Confounding factors	• Head-to-head comparison with any of the interventions (including combinations) listed above. Inter-class comparisons will only be included if antibiotics are analysed separately, rather than by class because of substantial heterogeneity in the class-level model (see section on 'analysis of subgroups'). • Comparisons of different treatment durations • Placebo • No treatment/ usual care
9.	Types of study to be included	• Randomised controlled trials (RCTs) • Systematic reviews of RCTs • Observational studies (for antibiotic resistance outcome only, if insufficient RCT evidence is available for this outcome such that, in the committee's view, observational evidence could reasonably be expected to provide more robust information to inform decision making).
10.	Other exclusion criteria	• Non-English language studies • Conference abstracts, theses, dissertations

11.	Context	Most babies are treated on neonatal units or neonatal intensive care units. Babies admitted from home are usually treated on paediatric units or paediatric intensive care units.
12.	Primary outcomes (critical outcomes)	Neonatal outcomes • culture-proven infection from sample taken between 72 hours (where available) and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies). Where 72 hours is not stated, outcomes for late-onset neonatal infection will be taken from the study-defined period for late-onset neonatal infection • Relapse (during the neonatal period at the latest time point reported in the study) • Mortality (during the neonatal period at the latest time point reported in the study) • Length of hospital stay • Duration to culture negative • Adverse drug reactions specifically related to antibiotics • Neurodevelopmental outcomes (measured using a validated tool at the latest time point reported in the study) • Antimicrobial resistance (culture-proven) 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 neonatal period and at the latest timepoint reported in study)
13.	Secondary outcomes (important outcomes)	Not applicable. The committee did not wish to distinguish between critical and important outcomes as they considered all of the specified outcomes important for decision making.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. Data will be extracted from the included studies 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 control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.

		This review will make use of the priority screening functionality within the EPPI-reviewer software. A stopping rule will be used to terminate screening if the following criteria are met: - At least 50% of the database has been screened - 500 records have been screened with no further included studies Reference lists of systematic reviews will also be checked for potential includes
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the Cochrane RoB v2.0 checklist as described in Developing NICE guidelines: the manual. The ROBIS checklist will be used to assess systematic reviews. Cochrane ROBINS-I will be used to assess observational studies for antibiotic resistance data.
16.	Strategy for data synthesis	Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are

		presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3
17.	Analysis of sub-groups	• Antibiotics will be grouped by class for the purpose of the analysis If substantial heterogeneity is encountered ($I^2>50\%$), this will be investigated by analysing antibiotics separately, rather than by class. • When data are available for different doses, doses will be grouped together in the analysis as follows: below the BNF recommended dose, at the BNF recommended dose, above the recommended dose. **Subgroups (to be investigated irrespective of presence of statistical heterogeneity)** • term babies and preterm babies • current presence of central catheter • babies with history of previous surgery (in particular abdominal or cardiac surgery, the type of surgery will be noted in studies

		included in the evidence review and further subgrouping discussed with committee members)		
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	01/01/2020		
22.	Anticipated completion date	12/08/2020		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**

		Preliminary searches		
		Piloting of the study selection process		
		Formal screening of search results against eligibility criteria		
		Data extraction		
		Risk of bias (quality) assessment		
		Data analysis		
24.	Named contact	**5a. Named contact** Guideline Updates Team **5b Named contact e-mail** NIupdate@nice.org.uk **5e Organisational affiliation of the review**		

		National Institute for Health and Care Excellence (NICE)
25.	Review team members	From the Guideline Updates Team: • Dr Kathryn Hopkins • Dr Clare Dadswell • Mr Fadi Chehadah • Mr Gabriel Rogers • Mr Wesley Hubbard
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team 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: https://www.nice.org.uk/guidance/indevelopment/gid-ng10111

29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Late onset neonatal infection, antibiotic treatment regimen
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published

		☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Clinical search literature search strategy

The search was conducted on 14th January 2020. 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, (via the Wiley platform), and the DARE database (via the CRD platform).

Population and intervention terms

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) or ecoli*).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 exp Anti-Bacterial Agents/
57 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid* or bacteriostat*).tw.
58 exp Penicillins/
59 penicillin*.tw.
60 (benzylpenicillin* or crystapen* or bicillin* or triplopen* or pentids* or pfizerpen*).tw.
61 (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.
62 (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.
63 Teicoplanin/
64 (teicoplanin* or teichom?cin* or targocid*).tw.
65 Clindamycin/
66 (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.
67 (azithrom?cin* or azyter* or clamelle* or zedbac* or zithromax* or AzaSite* or zmax*).tw.
68 exp Cephalosporins/
69 (cephalosporin* or cephalosporanic* or cepham?cin*).tw.
70 (cefamandole* or kefadol* or mandol*).tw.
71 (cefazolin* or kefzol* or ancef* or zolicef*).tw.

72 (cefepim* or renapime* or maxipime*).tw.
73 (cefsulodin* or monaspor*).tw.
74 (ceftibuten* or cedax*).tw.
75 (cefuroxime* or cephuroxime* or aprokam* or ximaract* or zinacef* or zinnat* or ceftin* or kefurox*).tw.
76 (cefotaxim* or cephotaxim* or cefizox*).tw.
77 (cefixime* or suprax*).tw.
78 (ceftizoxime* or cefizox*).tw.
79 (cef?triaxon* or rocephin*).tw.
80 (cephalothin* or cefalotin* or keflin*).tw.
81 (cefalexin* or cephalexin* or ceporex* or keflex* or kiflone* or biocef* or cefanex* or keflet* or keftab* or zartan*).tw.
82 (cefaclor* or bacticlor* or distaclor* or keftid* or ceclor* or raniclor*).tw.
83 (cefadroxil* or cephadroxyl* or baxan* or duricef* or ultracef*).tw.
84 (cefradine* or cephradine* or nicef* or velosef* or anspor*).tw.
85 (ceftazidime* or fortum* or kefadim* or zavicefta* or ceptaz* or fortaz* or tazicef* or tazidime*).tw.
86 (cefoxitin* or mefoxin* or renoxitin*).tw.
87 (ceftaroline* or zinforo* or teflaro*).tw.
88 exp Erythromycin/
89 (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.
90 (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.
91 Metronidazole/
92 (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.
93 Vancomycin/
94 (vancom?cin* or vancocin* or firvanq* or lyphocin* or vancocin* or vancoled*).tw.
95 (azlocillin* or securopen* or azlin*).tw.
96 (mezlocillin* or baypen* or mezlin*).tw.
97 (piperacillin* or pipril* or tazocin* or pipracil* or zosyn*).tw.
98 (pivampicillin* or pondocillin* or miraxid*).tw.
99 (talampicillin* or talpen*).tw.
100 (carbenicillin* or pyopen* or geopen*).tw.
101 (carfecillin* or uticillin*).tw.
102 (flucloxacillin* or floxacillin* or fluorochloroxacillin* or floxapen* or fluclomix* or galfloxin* or ladropen* or stafoxil* or staphlipen* or zoxin*).tw.
103 exp Glycopeptides/
104 (glycopeptide* or lipoglycopeptide*).tw.
105 (bleom?cin* or Bleo or blenoxane*).tw.
106 exp Aminoglycosides/
107 aminoglycoside*.tw.
108 (gentamicin* or gentamycin* or gentacycol* or G-Myticin* or GMyticin*).tw.

109 (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.
110 (amikacin* or amikin* or arikayce*).tw.
111 (tobram?cin* or bramitob* or nebcin* or Tobi or tobralex* or tobravisc* or vantobra*).tw.
112 exp Carbapenems/
113 (carbapenem* or thienam?cin*).tw.
114 (meropenem* or meronem* or merrem* or vabomere* or penem*).tw.
115 (doripenem* or doribax* or finibax*).tw.
116 (ertapenem* or invanz*).tw.
117 (imipenem* or primaxin* or recarbrio*).tw.
118 or/56-117
119 55 and 118
120 Animals/ not Humans/
121 119 not 120
122 limit 121 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) or ecoli*).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 exp antiinfective agent/
57 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid* or bacteriostat*).tw.
58 exp penicillin derivative/
59 penicillin*.tw.
60 (benzylpenicillin* or crystapen* or bicillin* or triplopen* or pentids* or pfizerpen*).tw.
61 (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.
62 (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.
63 teicoplanin/
64 (teicoplanin* or teichom?cin* or targocid*).tw.
65 clindamycin/
66 (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.
67 azithromycin/
68 (azithrom?cin* or azyter* or clamelle* or zedbac* or zithromax* or AzaSite* or zmax*).tw.

69 exp cephalosporin derivative/
70 (cephalosporin* or cephalosporanic* or cepham?cin*).tw.
71 (cefamandole* or kefadol* or mandol*).tw.
72 (cefazolin* or kefzol* or ancef* or zolicef*).tw.
73 (cefepim* or renapime* or maxipime*).tw.
74 (cefsulodin* or monaspor*).tw.
75 (ceftibuten* or cedax*).tw.
76 (cefuroxime* or cephuroxime* or aprokam* or ximaract* or zinacef* or zinnat* or ceftin* or kefurox*).tw.
77 (cefotaxim* or cephotaxim* or cefizox*).tw.
78 (cefixime* or suprax*).tw.
79 (ceftizoxime* or cefizox*).tw.
80 (cef?triaxon* or rocephin*).tw.
81 (cephalothin* or cefalotin* or keflin*).tw.
82 (cefalexin* or cephalexin* or ceporex* or keflex* or kiflone* or biocef* or cefanex* or keflet* or keftab* or zartan*).tw.
83 (cefaclor* or bacticlor* or distaclor* or keftid* or ceclor* or raniclor*).tw.
84 (cefadroxil* or cephadroxyl* or baxan* or duricef* or ultracef*).tw.
85 (cefradine* or cephradine* or nicef* or velosef* or anspor*).tw.
86 (ceftazidime* or fortum* or kefadim* or zavicefta* or ceptaz* or fortaz* or tazicef* or tazidime*).tw.
87 (cefoxitin* or mefoxin* or renoxitin*).tw.
88 (ceftaroline* or zinforo* or teflaro*).tw.
89 erythromycin/
90 (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.
91 clarithromycin/
92 (clarithrom?cin* or clarosip* or febzin* or klaricid* or mycifor* or HeliMet* or heliclear* or biaxin* or omeclamox-pak* or prevpac* or clarie xl* or xetinin xl*).tw.
93 metronidazole/
94 (metronidazole* or acea* or anabact* or elyzol* or flagyl* or metrogel* or metrolyl* or metrosa* or metrotop* or metrozol* or nidazol* or noritate* or norzol* or rosiced* or rozex* or vaginyl* or zadstat* or zidoval* or zyomet* or entamizole*).tw.
95 vancomycin/
96 (vancom?cin* or vancocin* or firvanq* or lyphocin* or vancocin* or vancoled*).tw.
97 (azlocillin* or securopen* or azlin*).tw.
98 (mezlocillin* or baypen* or mezlin*).tw.
99 (piperacillin* or pipril* or tazocin* or pipracil* or zosyn*).tw.
100 (pivampicillin* or pondocillin* or miraxid*).tw.
101 (talampicillin* or talpen*).tw.
102 (carbenicillin* or pyopen* or geopen*).tw.
103 (carfecillin* or uticillin*).tw.
104 (flucloxacillin* or floxacillin* or fluorochloroxacillin* or floxapen* or fluclomix* or galfloxin* or ladropen* or stafoxil* or staphlipen* or zoxin*).tw.
105 exp glycopeptide/
106 (glycopeptide* or lipoglycopeptide*).tw.

107 (bleom?cin* or Bleo or blenoxane*).tw.
108 aminoglycoside/
109 aminoglycoside*.tw.
110 gentamicin/
111 (gentamicin* or gentamycin* or gentacycol* or G-Myticin* or GMyticin*).tw.
112 (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.
113 amikacin/
114 (amikacin* or amikin* or arikayce*).tw.
115 tobramycin/
116 (tobram?cin* or bramitob* or nebcin* or Tobi or tobralex* or tobravisc* or vantobra*).tw.
117 carbapenem derivative/
118 (carbapenem* or thienam?cin*).tw.
119 meropenem/
120 (meropenem* or meronem* or merrem* or vabomere* or penem*).tw.
121 doripenem/
122 (doripenem* or doribax* or finibax*).tw.
123 ertapenem/
124 (ertapenem* or invanz*).tw.
125 imipenem/
126 (imipenem* or primaxin* or recarbrio*).tw.
127 or/56-126
128 55 and 127
129 nonhuman/ not human/
130 128 not 129
131 limit 130 to english language
132 limit 131 to (conference abstract or conference paper or "conference review")
133 131 not 132

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)) or (ecoli*))):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 trees20
#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: [Anti-Bacterial Agents] explode all trees
#57 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid* or bacteriostat*):ti,ab,kw
#58 MeSH descriptor: [Penicillins] explode all trees
#59 (penicillin*):ti,ab,kw
#60 (benzylpenicillin* or crystapen* or bicillin* or triplopen* or pentids* or pfizerpen*):ti,ab,kw

#61 (amox?cillin* or hydroxyamp?cillin* or almodan* or amix* or amopen* or amoram* or amoxident* or amoxidin* or amoxil* or amoxymed* or amrit* or flemoxin* or galenamox* or rimoxallin* or amiclav* or augmentin* or heliclear* or amoxiclav* or biomox* or DisperMox* or larotid* or moxatag* or polymox* or trimox* or wymox* or amoclan* or omeclamox* or prevpac*):ti,ab,kw
#62 (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
#63 MeSH descriptor: [Teicoplanin] this term only
#64 (teicoplanin* or teichom?cin* or targocid*):ti,ab,kw
#65 MeSH descriptor: [Clindamycin] this term only
#66 (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
#67 (azithrom?cin* or azyter* or clamelle* or zedbac* or zithromax* or AzaSite* or zmax*):ti,ab,kw
#68 MeSH descriptor: [Cephalosporins] explode all trees
#69 (cephalosporin* or cephalosporanic* or cepham?cin*):ti,ab,kw
#70 (cefamandole* or kefadol* or mandol*):ti,ab,kw
#71 (cefazolin* or kefzol* or ancef* or zolicef*):ti,ab,kw
#72 (cefepim* or renapime* or maxipime*):ti,ab,kw
#73 (cefsulodin* or monaspor*):ti,ab,kw
#74 (ceftibuten* or cedax*):ti,ab,kw
#75 (cefuroxime* or cephuroxime* or aprokam* or ximaract* or zinacef* or zinnat* or ceftin* or kefurox*):ti,ab,kw
#76 (cefotaxim* or cephotaxim* or cefizox*):ti,ab,kw
#77 (cefixime* or suprax*):ti,ab,kw
#78 (ceftizoxime* or cefizox*):ti,ab,kw
#79 (cef?triaxon* or rocephin*):ti,ab,kw
#80 (cephalothin* or cefalotin* or keflin*):ti,ab,kw
#81 (cefalexin* or cephalexin* or ceporex* or keflex* or kiflone* or biocef* or cefanex* or keflet* or keftab* or zartan*):ti,ab,kw
#82 (cefaclor* or bacticlor* or distaclor* or keftid* or ceclor* or raniclor*):ti,ab,kw
#83 (cefadroxil* or cephadroxyl* or baxan* or duricef* or ultracef*):ti,ab,kw
#84 (cefradine* or cephradine* or nicef* or velosef* or anspor*):ti,ab,kw
#85 (ceftazidime* or fortum* or kefadim* or zavicefta* or ceptaz* or fortaz* or tazicef* or tazidime*):ti,ab,kw
#86 (cefoxitin* or mefoxin* or renoxitin*):ti,ab,kw
#87 (ceftaroline* or zinforo* or teflaro*):ti,ab,kw
#88 MeSH descriptor: [Erythromycin] explode all trees
#89 (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
#90 (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
#91 MeSH descriptor: [Metronidazole] this term only

#92 (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
#93 MeSH descriptor: [Vancomycin] this term only
#94 (vancom?cin* or vancocin* or firvanq* or lyphocin* or vancocin* or vancoled*):ti,ab,kw

#95 (azlocillin* or securopen* or azlin*):ti,ab,kw
#96 (mezlocillin* or baypen* or mezlin*):ti,ab,kw
#97 (piperacillin* or pipril* or tazocin* or pipracil* or zosyn*):ti,ab,kw
#98 (pivampicillin* or pondocillin* or miraxid*):ti,ab,kw
#99 (talampicillin* or talpen*):ti,ab,kw
#100 (carbenicillin* or pyopen* or geopen*):ti,ab,kw
#101 (carfecillin* or uticillin*):ti,ab,kw
#102 (flucloxacillin* or floxacillin* or fluorochloroxacillin* or floxapen* or fluclomix* or galfloxin* or ladropen* or stafoxil* or staphlipen* or zoxin*):ti,ab,kw
#103 MeSH descriptor: [Glycopeptides] explode all trees
#104 (glycopeptide* or lipoglycopeptide*):ti,ab,kw
#105 (bleom?cin* or Bleo or blenoxane*):ti,ab,kw
#106 MeSH descriptor: [Aminoglycosides] explode all trees
#107 (aminoglycoside*):ti,ab,kw
#108 (gentamicin* or gentamycin* or gentacycol* or G-Myticin* or GMyticin*):ti,ab,kw
#109 (cidom?cin* or garam?cin* or genticin* or lugacin* or collatamp* or refobacin* or septocoll* or septopal* or vipsogal* or genoptic* or gentacidin* or gentafair* or gentak* or gentasol* or gentrasul* or jenam?cin* or Ocu-Mycin*):ti,ab,kw
#110 (amikacin* or amikin* or arikayce*):ti,ab,kw
#111 (tobram?cin* or bramitob* or nebcin* or Tobi or tobralex* or tobravisc* or vantobra*):ti,ab,kw
#112 MeSH descriptor: [Carbapenems] explode all trees
#113 (carbapenem* or thienam?cin*):ti,ab,kw
#114 (meropenem* or meronem* or merrem* or vabomere* or penem*):ti,ab,kw
#115 (doripenem* or doribax* or finibax*):ti,ab,kw
#116 (ertapenem* or invanz*):ti,ab,kw
#117 (imipenem* or primaxin* or recarbrio*):ti,ab,kw
#118 {or #56-#117}
#119 #55 and #118
#120 (conference):pt
#121 (clinicaltrials or trialsearch):so
#122 #120 or #121
#123 #119 not #122

DARE

1 MeSH DESCRIPTOR Infant, Newborn EXPLODE ALL TREES
2 MeSH DESCRIPTOR Term Birth
3 MeSH DESCRIPTOR Infant Care
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) OR (ecoli*)))
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
33 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia)
34 ((enteric or coliform) NEAR2 (bac*))
35 MeSH DESCRIPTOR Neisseria EXPLODE ALL TREES
36 (neisseria*)
37 MeSH DESCRIPTOR Haemophilus influenzae EXPLODE ALL TREES
38 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) NEAR2 (influenz* or pfeiffer* or meningitidis))
39 MeSH DESCRIPTOR Serratia EXPLODE ALL TREES
40 (serratia*)
41 MeSH DESCRIPTOR Cronobacter EXPLODE ALL TREES
42 (cronobact* or sakazaki* or malonatic*)
43 MeSH DESCRIPTOR Acinetobacter EXPLODE ALL TREES
44 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*)
45 MeSH DESCRIPTOR Fusobacterium EXPLODE ALL TREES
46 (fusobact* or sphaerophor* or necrophorum or nucleatum)
47 MeSH DESCRIPTOR Enterococcus EXPLODE ALL TREES
48 (enterococc*)
49 (#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48)
50 #18 OR #49
51 #10 AND #50
52 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) NEAR4 (infect*))

53 ((prematur*e or pre-mature* or preterm* or pre-term*) NEAR4 (child* or infant* or baby* or babies* or offspring) NEAR4 (infect*))
54 #52 OR #53
55 #51 OR #54
56 MeSH DESCRIPTOR Anti-Bacterial Agents EXPLODE ALL TREES
57 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid* or bacteriostat*)
58 MeSH DESCRIPTOR Penicillins EXPLODE ALL TREES
59 (penicillin*)
60 (benzylpenicillin* or crystapen* or bicillin* or triplopen* or pentids* or pfizerpen*)
61 (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*)
62 (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*)
63 MeSH DESCRIPTOR Teicoplanin
64 (teicoplanin* or teichom?cin* or targocid*)
65 MeSH DESCRIPTOR Clindamycin
66 (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*)
67 (azithrom?cin* or azyter* or clamelle* or zedbac* or zithromax* or AzaSite* or zmax*)
68 MeSH DESCRIPTOR Cephalosporins
69 (cephalosporin* or cephalosporanic* or cepham?cin*)
70 (cefamandole* or kefadol* or mandol*)
71 (cefazolin* or kefzol* or ancef* or zolicef*)
72 (cefepim* or renapime* or maxipime*)
73 (cefsulodin* or monaspor*)
74 (ceftibuten* or cedax*)
75 (cefuroxime* or cephuroxime* or aprokam* or ximaract* or zinacef* or zinnat* or ceftin* or kefurox*)
76 (cefotaxim* or cephotaxim* or cefizox*)
77 (cefixime* or suprax*)
78 (ceftizoxime* or cefizox*)
79 (cef?triaxon* or rocephin*)
80 (cephalothin* or cefalotin* or keflin*)
81 (cefalexin* or cephalexin* or ceporex* or keflex* or kiflone* or biocef* or cefanex* or keflet* or keftab* or zartan*)
82 (cefaclor* or bacticlor* or distaclor* or keftid* or ceclor* or raniclor*)
83 (cefadroxil* or cephadroxyl* or baxan* or duricef* or ultracef*)
84 (cefradine* or cephradine* or nicef* or velosef* or anspor*)
85 (ceftazidime* or fortum* or kefadim* or zavicefta* or ceptaz* or fortaz* or tazicef* or tazidime*)
86 (cefoxitin* or mefoxin* or renoxitin*)
87 (ceftaroline* or zinforo* or teflaro*)
88 MeSH DESCRIPTOR Erythromycin EXPLODE ALL TREES
89 (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*)
90 (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*)
91 MeSH DESCRIPTOR Metronidazole
92 (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*)
93 MeSH DESCRIPTOR Vancomycin
94 (vancom?cin* or vancocin* or firvanq* or lyphocin* or vancocin* or vancoled*)
95 (azlocillin* or securopen* or azlin*)
96 (mezlocillin* or baypen* or mezlin*)
97 (piperacillin* or pipril* or tazocin* or pipracil* or zosyn*)
98 (pivampicillin* or pondocillin* or miraxid*)
99 (talampicillin* or talpen*)
100 (carbenicillin* or pyopen* or geopen*)
101 (carfecillin* or uticillin*)
102 (flucloxacillin* or floxacillin* or fluorochloroxacillin* or floxapen* or fluclomix* or galfloxin* or ladropen* or stafoxil* or staphlipen* or zoxin*)
103 MeSH DESCRIPTOR Glycopeptides EXPLODE ALL TREES
104 (glycopeptide* or lipoglycopeptide*)
105 (bleom?cin* or Bleo or blenoxane*)
106 MeSH DESCRIPTOR Aminoglycosides EXPLODE ALL TREES
107 (aminoglycoside*)
108 (gentamicin* or gentamycin* or gentacycol* or G-Myticin* or GMyticin*)
109 (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*)
110 (amikacin* or amikin* or arikayce*)
111 (tobram?cin* or bramitob* or nebcin* or Tobi or tobralex* or tobravisc* or vantobra*)
112 MeSH DESCRIPTOR Carbapenems EXPLODE ALL TREES
113 (carbapenem* or thienam?cin*)
114 (meropenem* or meronem* or merrem* or vabomere* or penem*)
115 (doripenem* or doribax* or finibax*)
116 (ertapenem* or invanz*)
117 (imipenem* or primaxin* or recarbrio*)
118 #56 OR #57 OR #58 OR #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 OR #117
119 #55 AND #118
120 * IN DARE
121 #119 AND #120

Search Filters

The following search filters were combined as 'And' with the population and intervention 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

Observational Studies

1 Observational Studies as Topic/
2 Observational Study/
3 Epidemiologic Studies/
4 exp Case-Control Studies/
5 exp Cohort Studies/
6 Cross-Sectional Studies/
7 Controlled Before-After Studies/
8 Historically Controlled Study/
9 Interrupted Time Series Analysis/
10 Comparative Study.pt.
11 case control$.tw.
12 case series.tw.
13 (cohort adj (study or studies)).tw.
14 cohort analy$.tw.
15 (follow up adj (study or studies)).tw.
16 (observational adj (study or studies)).tw.
17 longitudinal.tw.
18 prospective.tw.
19 retrospective.tw.
20 cross sectional.tw.
21 or/1-20

Antibiotic resistance terms.

The following terms were used for all databases and combined as 'AND' with the observational studies filter.

1 Drug Resistance, Microbial/
2 exp Drug Resistance, Bacterial/
3 Drug Resistance, Multiple/
4 (AR or AMR or ABR or MDR or MBR).tw.
5 (resist* or tolera* or nonsuscept* or non-suscept*).tw.
6 R Factors/
7 (r adj2 (factor* or plasmid*)).tw.
8 Superinfection/
9 (superbug* or super bug* or superinfect* or super infect* or superinvas* or super invas*).tw.
10 ((inappropriat* or irrational* or imprudent* or unnecessar* or incorrect* or irrespons* or misus* or improper* or error* or mistake* or indiscriminat* or suboptim* or sub-optim* or bad or badly or inefficient* or uncontrol* or overus* or excess* or vary* or varia* or poor*) adj4 (antibacter* or anti-bacter* or antibiotic* or anti-biotic* or antimycobact* or anti-mycobact* or bacteriocid* or bacteriostat*) adj4 (prescr* or adminis* or dispens* or "use" or usag* or utili* or provi* or distribut* or therap* or treatment* or expos* or consum*)).tw.

11 or/1-10

Health Economics literature search strategy

Sources searched to identify economic evaluations

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

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

Health economics search strategy

Database: Medline (Ovid)
1 exp Infant, Newborn/ (607120)
2 Term Birth/ (2958)
3 Infant Care/ (9209)
4 Perinatal Care/ (4613)

5 Intensive Care Units, Neonatal/ (14748)

6 Intensive Care, Neonatal/ (5673)

7 Infant Health/ (783)

8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (394580)

9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (50922)

10 or/1-9 (791905)

11 exp Bacterial Infections/ (886598)

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

13 exp Sepsis/ (123123)

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

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

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

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

18 or/11-17 (1097119)

19 exp Streptococcus/ (78627)

20 exp Staphylococcus/ (104852)

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

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

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

24 exp Escherichia coli/ (278943)

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

26 exp Listeria/ (15143)

27 listeria*.tw. (18688)

28 exp Klebsiella/ (19836)

29 klebsiella*.tw. (26962)

30 exp Pseudomonas/ (71592)

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

32 Enterobacteriaceae/ (18945)

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

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

35 exp Neisseria/ (20482)

36 neisseria*.tw. (18785)

37 exp Haemophilus influenzae/ (13731)

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

39 exp Serratia/ (6599)

40 serratia*.tw. (8439)

41 exp Cronobacter/ (655)

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

43 exp Acinetobacter/ (9822)

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

45 exp Fusobacterium/ (3796)

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

47 exp Enterococcus/ (19718)

48 enterococc*.tw. (26150)

49 or/19-48 (765874)

50 18 or 49 (1614537)

51 10 and 50 (65444)

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

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

54 52 or 53 (16770)

55 51 or 54 (74853)

56 Economics/ (27206)

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

58 Economics, Dental/ (1911)

59 exp Economics, Hospital/ (24558)

60 exp Economics, Medical/ (14206)

61 Economics, Nursing/ (3999)

62 Economics, Pharmaceutical/ (2941)

63 Budgets/ (11315)

64 exp Models, Economic/ (15053)

65 Markov Chains/ (14321)

66 Monte Carlo Method/ (28322)

67 Decision Trees/ (11133)

68 econom$.tw. (238765)

69 cba.tw. (9764)

70 cea.tw. (20532)

71 cua.tw. (999)

72 markov$.tw. (17997)

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

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

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

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

77 budget$.tw. (23716)

78 expenditure$.tw. (49355)

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

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

81 or/56-80 (926379)

82 "Quality of Life"/ (194718)

83 quality of life.tw. (229884)

84 "Value of Life"/ (5706)

85 Quality-Adjusted Life Years/ (12284)

86 quality adjusted life.tw. (10842)

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

88 disability adjusted life.tw. (2741)

89 daly$.tw. (2486)

90 Health Status Indicators/ (23409)

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

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

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

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

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

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

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

98 (hye or hyes).tw. (60)

99 health$ year$ equivalent$.tw. (38)

100 utilit$.tw. (171457)

101 (hui or hui1 or hui2 or hui3).tw. (1304)

102 disutili$.tw. (396)

103 rosser.tw. (94)

104 quality of wellbeing.tw. (14)

105 quality of well-being.tw. (381)

106 qwb.tw. (190)

107 willingness to pay.tw. (4500)

108 standard gamble$.tw. (783)

109 time trade off.tw. (1037)

110 time tradeoff.tw. (238)

111 tto.tw. (899)

112 or/82-111 (493012)

113 81 or 112 (1350947)

114 55 and 113 (3480)
115 limit 114 to ed=20190716-20200724 (226)
116 animals/ not humans/ (4686781)
117 115 not 116 (213)
118 limit 117 to english language (208)

Database: MiP (Ovid)
1 exp Infant, Newborn/ (0)
2 Term Birth/ (0)
3 Infant Care/ (0)
4 Perinatal Care/ (0)
5 Intensive Care Units, Neonatal/ (0)
6 Intensive Care, Neonatal/ (0)
7 Infant Health/ (0)
8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (32462)
9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (4347)
10 or/1-9 (34405)
11 exp Bacterial Infections/ (0)
12 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (17517)
13 exp Sepsis/ (0)
14 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (12331)
15 (septic* adj4 shock*).tw. (2749)
16 (bacter?emia* or bacill?emia*).tw. (2792)
17 (blood* adj4 (infect* or contamin* or invas* or invad*)).tw. (4519)
18 or/11-17 (35377)
19 exp Streptococcus/ (0)
20 exp Staphylococcus/ (0)

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

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

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

24 exp Escherichia coli/ (0)

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

26 exp Listeria/ (0)

27 listeria*.tw. (2351)

28 exp Klebsiella/ (0)

29 klebsiella*.tw. (4101)

30 exp Pseudomonas/ (0)

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

32 Enterobacteriaceae/ (0)

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

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

35 exp Neisseria/ (0)

36 neisseria*.tw. (1256)

37 exp Haemophilus influenzae/ (0)

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

39 exp Serratia/ (0)

40 serratia*.tw. (829)

41 exp Cronobacter/ (0)

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

43 exp Acinetobacter/ (0)

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

45 exp Fusobacterium/ (0)

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

47 exp Enterococcus/ (0)

48 enterococc*.tw. (3589)

49 or/19-48 (59520)

50 18 or 49 (83682)

51 10 and 50 (2543)

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

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

54 52 or 53 (1309)

55 51 or 54 (3367)

56 Economics/ (0)

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

58 Economics, Dental/ (0)

59 exp Economics, Hospital/ (0)

60 exp Economics, Medical/ (0)

61 Economics, Nursing/ (0)

62 Economics, Pharmaceutical/ (0)

63 Budgets/ (0)

64 exp Models, Economic/ (0)

65 Markov Chains/ (1)

66 Monte Carlo Method/ (2)

67 Decision Trees/ (0)

68 econom$.tw. (47080)

69 cba.tw. (456)

70 cea.tw. (2004)

71 cua.tw. (198)

72 markov$.tw. (5795)

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

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

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

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

77 budget$.tw. (5074)

78 expenditure$.tw. (6509)

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

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

81 or/56-80 (172313)

82 "Quality of Life"/ (0)

83 quality of life.tw. (40043)

84 "Value of Life"/ (0)

85 Quality-Adjusted Life Years/ (0)

86 quality adjusted life.tw. (1728)

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

88 disability adjusted life.tw. (523)

89 daly$.tw. (479)

90 Health Status Indicators/ (0)

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

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

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

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

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

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

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

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

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

100 utilit$.tw. (32031)

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

102 disutili$.tw. (60)
103 rosser.tw. (4)
104 quality of wellbeing.tw. (9)
105 quality of well-being.tw. (29)
106 qwb.tw. (13)
107 willingness to pay.tw. (957)
108 standard gamble$.tw. (62)
109 time trade off.tw. (119)
110 time tradeoff.tw. (11)
111 tto.tw. (145)
112 or/82-111 (74419)
113 81 or 112 (236895)
114 55 and 113 (231)
115 limit 114 to dt=20190716-20200724 (89)
116 animals/ not humans/ (1)
117 115 not 116 (89)
118 limit 117 to english language (89)

Database: Medline E-pubs (Ovid)
1 exp Infant, Newborn/ (0)
2 Term Birth/ (0)
3 Infant Care/ (0)
4 Perinatal Care/ (0)
5 Intensive Care Units, Neonatal/ (0)
6 Intensive Care, Neonatal/ (0)
7 Infant Health/ (0)
8 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (6371)
9 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (1421)

10 or/1-9 (6871)

11 exp Bacterial Infections/ (0)

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

13 exp Sepsis/ (0)

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

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

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

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

18 or/11-17 (4700)

19 exp Streptococcus/ (0)

20 exp Staphylococcus/ (0)

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

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

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

24 exp Escherichia coli/ (0)

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

26 exp Listeria/ (0)

27 listeria*.tw. (198)

28 exp Klebsiella/ (0)

29 klebsiella*.tw. (476)

30 exp Pseudomonas/ (0)

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

32 Enterobacteriaceae/ (0)

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

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

35 exp Neisseria/ (0)

36 neisseria*.tw. (177)

37 exp Haemophilus influenzae/ (0)

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

39 exp Serratia/ (0)

40 serratia*.tw. (72)

41 exp Cronobacter/ (0)

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

43 exp Acinetobacter/ (0)

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

45 exp Fusobacterium/ (0)

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

47 exp Enterococcus/ (0)

48 enterococc*.tw. (403)

49 or/19-48 (6238)

50 18 or 49 (9619)

51 10 and 50 (455)

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

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

54 52 or 53 (268)

55 51 or 54 (651)

56 Economics/ (0)

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

58 Economics, Dental/ (0)

59 exp Economics, Hospital/ (0)

60 exp Economics, Medical/ (0)

61 Economics, Nursing/ (0)

62 Economics, Pharmaceutical/ (0)

63 Budgets/ (0)

64 exp Models, Economic/ (0)

65 Markov Chains/ (0)

66 Monte Carlo Method/ (0)

67 Decision Trees/ (0)

68 econom$.tw. (6645)

69 cba.tw. (61)

70 cea.tw. (331)

71 cua.tw. (17)

72 markov$.tw. (718)

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

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

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

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

77 budget$.tw. (555)

78 expenditure$.tw. (1143)

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

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

81 or/56-80 (21922)

82 "Quality of Life"/ (0)

83 quality of life.tw. (7520)

84 "Value of Life"/ (0)

85 Quality-Adjusted Life Years/ (0)

86 quality adjusted life.tw. (388)

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

88 disability adjusted life.tw. (101)

89 daly$.tw. (88)

90 Health Status Indicators/ (0)

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

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

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

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

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

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

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

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

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

100 utilit$.tw. (4989)

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

102 disutili$.tw. (12)

103 rosser.tw. (0)

104 quality of wellbeing.tw. (0)

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

106 qwb.tw. (3)

107 willingness to pay.tw. (184)

108 standard gamble$.tw. (7)

109 time trade off.tw. (20)

110 time tradeoff.tw. (2)

111 tto.tw. (18)

112 or/82-111 (12826)

113 81 or 112 (32909)

114 55 and 113 (55)

115 limit 114 to english language (55)

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

27 listeria*.tw. (22102)

28 exp Klebsiella/ (59561)

29 klebsiella*.tw. (42289)

30 exp Pseudomonas/ (144052)

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

32 Enterobacteriaceae/ (23812)

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

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

35 exp Neisseria/ (32218)

36 neisseria*.tw. (22936)

37 exp Haemophilus influenzae/ (29007)

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

39 exp Serratia/ (14280)

40 serratia*.tw. (10397)

41 exp cronobacter/ (817)

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

43 exp Acinetobacter/ (27955)

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

45 exp Fusobacterium/ (7678)

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

47 exp Enterococcus/ (49841)

48 enterococc*.tw. (37571)

49 or/19-48 (967441)

50 18 or 49 (1894492)

51 10 and 50 (70672)

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

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

54 52 or 53 (22885)

55 51 or 54 (83775)

56 exp Health Economics/ (845404)

57 exp "Health Care Cost"/ (290992)

58 exp Pharmacoeconomics/ (202216)

59 Monte Carlo Method/ (40279)

60 Decision Tree/ (13001)

61 econom$.tw. (368838)

62 cba.tw. (12788)

63 cea.tw. (34786)

64 cua.tw. (1498)

65 markov$.tw. (30389)

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

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

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

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

70 budget$.tw. (38616)

71 expenditure$.tw. (74588)

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

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

74 or/56-73 (1760062)

75 "Quality of Life"/ (469927)

76 Quality Adjusted Life Year/ (26663)

77 Quality of Life Index/ (2774)

78 Short Form 36/ (29036)

79 Health Status/ (127411)

80 quality of life.tw. (439622)

81 quality adjusted life.tw. (19747)

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

83 disability adjusted life.tw. (4103)

84 daly$.tw. (4016)

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

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

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

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

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

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

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

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

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

94 utilit$.tw. (289831)

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

96 disutili$.tw. (924)

97 rosser.tw. (124)

98 quality of wellbeing.tw. (42)

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

100 qwb.tw. (253)

101 willingness to pay.tw. (8837)

102 standard gamble$.tw. (1104)

103 time trade off.tw. (1708)

104 time tradeoff.tw. (291)

105 tto.tw. (1683)

106 or/75-105 (989974)

107 74 or 106 (2593254)

108 55 and 107 (5731)

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

110 nonhuman/ not human/ (4649157)

111 109 not 110 (522)

112 limit 111 to english language (510)

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

114 112 not 113 (397)

Database: Econlit (Ovid)

1 (newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*).tw. (732)

2 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring)).tw. (45)

3 1 or 2 (767)

4 ((bacter* or strep* or staph* or GNB) adj4 (infect* or diseas* or contaminat* or mening* or pneumon* or nosocomial*)).tw. (49)

5 (sepsis or septic?emia* or py?emia* or pyho?emia*).tw. (17)

6 (septic* adj4 shock*).tw. (1)

7 (bacter?emia* or bacill?emia*).tw. (3)

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

9 (streptococc* or staphylococc*).tw. (18)

10 (GBS or MRSA or NRCS-A or MSSA).tw. (40)

11 (met?icillin-resistant adj3 aureus).tw. (8)

12 (((Escheric* or E) adj2 coli) or ecoli*).tw. (47)

13 listeria*.tw. (6)

14 klebsiella*.tw. (0)

15 (pseudomonas or chryseomonas or flavimonas).tw. (6)

16 (enterobact* or sodalis or paracolobactrum or ewingella or leclercia).tw. (1)

17 ((enteric or coliform) adj2 bac*).tw. (0)

18 neisseria*.tw. (1)

19 ((h?emophil* or H or bacter* or bacill* or mycobacter* or coccobac*) adj2 (influenz* or pfeiffer* or meningitidis)).tw. (14)

20 serratia*.tw. (0)

21 (cronobact* or sakazaki* or malonatic*).tw. (1)

22 (acinetobact* or herellea* or mima or baumanni* or genomosp* or calcoacetic*).tw. (2)

23 (fusobact* or sphaerophor* or necrophorum or nucleatum).tw. (0)

24 enterococc*.tw. (5)

25 or/4-24 (194)

26 ((newborn* or new born* or neonat* or neo-nat* or perinat* or peri-nat*) adj4 infect*).tw. (11)

27 ((premature* or pre-mature* or preterm* or pre-term*) adj4 (child* or infant* or baby* or babies* or offspring) adj4 infect*).tw. (1)

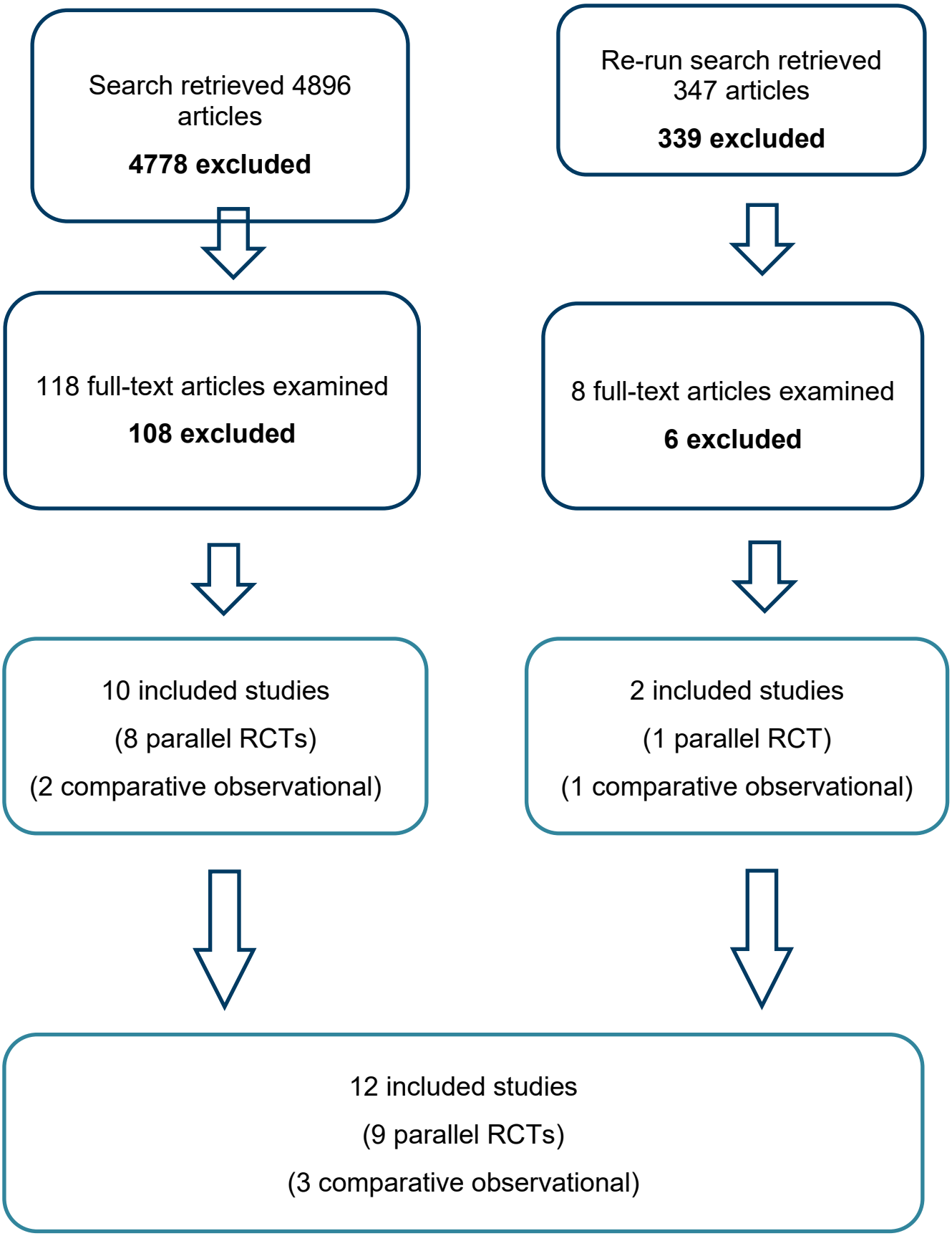
28 26 or 27 (12)

29 25 or 28 (205)

30 3 and 29 (15)

31 limit 30 to yr="2019 -Current" (1)

Appendix C – Effectiveness evidence study selection



Appendix D – Effectiveness evidence

Randomised controlled trials

Abdel-Hady, 2011

Bibliographic Reference	Abdel-Hady, E; El Hamamsy, M; Hedaya, M; Awad, H; The efficacy and toxicity of two dosing-regimens of amikacin in neonates with sepsis.; Journal of clinical pharmacy and therapeutics; 2011; vol. 36 (no. 1); 45-52

Study details

Study type	Randomised controlled trial (RCT)
Study location	Egypt
Study setting	Neonatal Intensive Care Unit of Gynecology, Ain-Shams University Hospital
Study dates	March 2007 - January 2008
Duration of follow-up	Every 48 hours until discharge
Sources of funding	None reported
Inclusion criteria	Infants at risk or with clinical features and laboratory criteria of sepsis Gestational age ≥36 weeks Body weight ≥2500 g
Exclusion criteria	Infants with history of cardiopulmonary arrest (either at birth or during hospitalization) Congenital malformations with known involvement of ear or genito-urinary tract

	Administration of other nephrotoxic drugs e.g. furosemide, vancomycin Presence of neuromuscular disorder Major congenital abnormalities
Sample size	30
Interventions	Once daily Amikacin (1 dose 15 mg/kg) Twice daily Amikacin (2 doses 7.5 mg/kg)
Outcome measures	Duration to culture negative

Study arms

Amikacin 15mg/kg (N = 15)

15 mg/kg once per day

Split between study groups	15
Loss to follow-up	0
Condition specific characteristics	Gestational age (weeks) Mean (SD): 37.8 (1.6) Culture confirmed infection (n) 3 (20%)

Amikacin 7.5 mg/kg (N = 15)

Amikacin 7.5 mg/kg twice per day (total dose 15 mg/kg/day)

Condition specific characteristics	Gestational age (weeks) Mean (SD): 38.1 (1.4) Culture confirmed infection (n) 2 (13.3%)

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	No *(Allocated in order of birth date)*
	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
	Risk of bias judgement for the randomisation process	High *(Randomisation based on birthweight so not truly randomised. No information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No information

Section	Question	Answer
	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
	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?	No *(Clinical outcomes, not subjective measures)*
	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 information

Section	Question	Answer
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low *(Unclear whether assessor was aware of assigned intervention but outcomes were clinical, objective measures)*
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
	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	High *(Participants assigned to an intervention based on birth date so not truly randomised. No information on allocation concealment)*
	Overall Directness	Partially applicable *(Not based in the UK so bacteria that cause infection may differ. Includes babies with early- and late-onset infection. Results not reported separately)*

English, 2004

Bibliographic Reference	English, M; Mohammed, S; Ross, A; Ndirangu, S; Kokwaro, G; Shann, F; Marsh, K; A randomised, controlled trial of once daily and multi-dose daily gentamicin in young Kenyan infants.; Archives of disease in childhood; 2004; vol. 89 (no. 7); 665-9

Study details

Study type	Randomised controlled trial (RCT)
Study location	Kenya
Study setting	Kilifi District Hospital
Study dates	August 2000 - April 2001
Duration of follow-up	4 days (96 hour blood sample)
Sources of funding	Wellcome Trust (UK)
Inclusion criteria	Age Less than 3 months (until January 2001) then less than 2 months (from February 2001)
Exclusion criteria	Major congenital abnormalities Weight <1 kg Tetanus Gentamicin had been given previously Anuria History of anuria for 24 hours

	Admission creatinine was outside a defined acceptable range
Sample size	312
Interventions	Once daily gentamicin Twice daily gentamicin
Outcome measures	Mortality (time point not specified)

Study arms

Once daily gentamicin (N = 155)

All babies received initial dose of 8 mg/kg before continuing with dosing adjusted for weight and age: Babies aged 7 days and under: Weight <2 kg = 2 mg/kg/day; Weight >2 kg = 4 mg/kg/day Babies greater than 7 days: Weight <2 kg: 4 mg/kg/day; Weight >2 kg: 6 mg/kg/day

Split between study groups	155
Loss to follow-up	11
Condition specific characteristics	Age (days) Median (IQR): 8 (4-30)

Multi-dose gentamicin (N = 142)

Babies aged 7 days and under: 2.5 mg/kg twice per day Babies greater than 7 days: Weight <2 kg: 2.5 mg/kg twice per day; Weight >2 kg: 2.5 mg/kg three times per day

Condition specific characteristics	Age (days) Median (IQR): 13 (4-32)

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
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

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?	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?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	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?	No
	Risk-of-bias judgement for measurement of the outcome	Low *(Assessors were aware of the assigned intervention but outcomes were objective measures)*

Section	Question	Answer
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
	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	Partially applicable *(Includes babies with early- and late-onset infection. Results not reported separately. Not based in the UK so bacteria that cause infection may differ. Gentamicin dose for some was above recommended in the UK)*

Gwee, 2019

Bibliographic Reference	Gwee, A.; Cranswick, N.; McMullan, B.; Perkins, E.; Bolisetty, S.; Gardiner, K.; Daley, A.; Ward, M.; Chiletti, R.; Donath, S.; Hunt, R.; Curtis, N.; Continuous versus intermittent vancomycin infusions in infants: A randomized controlled trial; Pediatrics; 2019; vol. 143 (no. 2); e20182179

Study details

Study type	Randomised controlled trial (RCT)
Study location	Australia
Study setting	NICU and PICU at RCH Melbourne and the NICU at The Royal Hospital for Women in Sydney
Study dates	September 2014 - December 2017
Duration of follow-up	Duration of vancomycin therapy
Sources of funding	Murdoch Children's Research Institute
Inclusion criteria	Age 0-90 days Anticipated that vancomycin therapy would be administered for >48 hours
Exclusion criteria	Gestational age Corrected GA <25 weeks Known glycopeptide allergy Renal impairment Receiving extracorporeal membrane oxygenation Vancomycin administration within previous 72 hours
Sample size	111
Interventions	Intermittent vancomycin infusion Continuous vancomycin infusion

Outcome measures	Duration to culture negative Mean time to clearance of bacteraemia

Study arms

Intermittent vancomycin infusion (N = 54)

Dose recommended by BNFc

Loss to follow-up	0
% Female	47%
Condition specific characteristics	Gestational age (weeks) 34.4 (5.2) Age (days) 23 (21) Birth weight (g) 2294 (1033) Culture-confirmed infection (n) 12 (26%)

Continuous vancomycin infusion (N = 57)

After a loading dose of 15 mg/kg infused over 1 hour

Loss to follow-up	3
% Female	52.8%
Condition specific characteristics	Gestational age (weeks) 34.0 (4.4) Age (days) 23 (19) Birth weight (g) 2248 (1036) Number with culture-confirmed fungal infection 11 (24%)

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	2.1. Were participants aware of their assigned intervention during the trial?	No

Section	Question	Answer
interventions (effect of assignment to intervention)		
	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
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 information *(Limited information about the outcome)*
	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

Section	Question	Answer
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no *(Objective outcome)*
	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Limited information about the outcome)*
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis?	Probably yes *(Limited 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/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Some concerns *(Limited information about analysis methods)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Limited information about outcome and analysis methods)*
	Overall Directness	Partially applicable *(Not based in the UK so bacteria that cause infection may differ. Includes babies with early- and late-onset infection. Results not reported separately)*

Kosalaraksa, 2004

Bibliographic Reference	Kosalaraksa, Pope; Janthep, Pakamas; Jirapradittha, Junya; Taksaphan, Sukanya; Kiatchoosakun, Pakaphan; Once versus twice daily dose of gentamicin therapy in Thai neonates.; Journal of the Medical Association of Thailand = Chotmaihet thangphaet; 2004; vol. 87 (no. 4); 372-6

Study details

Study type	Randomised controlled trial (RCT)
Study location	Thailand
Study setting	Neonatal Care Unit at Srinagarind Hospital, Khon Kaen University, Northeast Thailand
Study dates	May 2000 - August 2001
Duration of follow-up	7 days or until end of treatment
Sources of funding	Faculty of Medicine, Khon Kaen University
Inclusion criteria	Age 0-7 days old Body weight ≥2000 g APGAR score >6 at 5 minutes Suspected sepsis Diagnosis not defined
Exclusion criteria	History of perinatal asphyxia

	History of shock History of cardiopulmonary arrest History of seizure or neuromuscular disorder History of anomalies of the kidney or ear
Sample size	64
Interventions	Once daily gentamicin Twice daily gentamicin
Outcome measures	Responders (clinical response: improvement within 72 hours of treatment)

Study arms

Once daily gentamicin (N = 33)

5 mg/kg every 24 hours

Split between study groups	33
Condition specific characteristics	Gestational age (weeks) Mean (SD): 38.4 (1.8) Birth weight (g) Mean (SD): 3044 (475)

Twice daily gentamicin (N = 31)

2.5 mg/kg every 12 hours

Split between study groups	31
Condition specific characteristics	Gestational age (weeks) Mean (SD): 38.6 (2.1) Birth weight (g) Mean (SD): 3036 (497)

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?	Probably 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

Section	Question	Answer
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Probably 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?	No information
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Probably yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Limited information about analysis methods)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably 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 ?	No information *(Measure of 'signs of improvement' is unclear)*
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes

Section	Question	Answer
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably yes
	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	Some concerns *(Definition of the outcome is not entirely clear and outcome assessors were probably aware of the assigned intervention)*
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 or whether outcome assessors were blinded to assignment)*
	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 information
	Risk-of-bias judgement for selection of the reported result	Some concerns *(Limited information about analysis methods or whether outcome assessors were blinded to assignment)*
Overall bias and Directness	Risk of bias judgement	High *(Limited information about definition of the outcome, analysis methods or whether outcome assessors were blinded to assignment)*

Section	Question	Answer
	Overall Directness	Partially applicable *(Not based in the UK so bacteria that cause infection may differ. Study includes early- and late onset infection (up to 7 days for late-onset). Results not reported separately)*

Lutsar, 2020

Bibliographic Reference Lutsar, Irja; Chazallon, Corine; Trafojer, Ursula; de Cabre, Vincent Meiffredy; Auriti, Cinzia; Bertaina, Chiara; Calo Carducci, Francesca Ippolita; Canpolat, Fuat Emre; Esposito, Susanna; Fournier, Isabelle; Hallik, Maarja; Heath, Paul T; Ilmoja, Mari-Liis; Iosifidis, Elias; Kuznetsova, Jelena; Meyer, Laurence; Metsvaht, Tuuli; Mitsiakos, George; Pana, Zoi Dorothea; Mosca, Fabio; Pugni, Lorenza; Roilides, Emmanuel; Rossi, Paolo; Sarafidis, Kosmas; Sanchez, Laura; Sharland, Michael; Usonis, Vytautas; Warris, Adilia; Aboulker, Jean-Pierre; Giaquinto, Carlo; NeoMero, Consortium; Meropenem vs standard of care for treatment of neonatal late onset sepsis (NeoMero1): A randomised controlled trial.; PloS one; 2020; vol. 15 (no. 3); e0229380

Study details

Study type	Randomised controlled trial (RCT)
Study location	Estonia, Greece, Italy, Lithuania, Spain and Turkey
Study setting	18 NICUs
Study dates	September 2012 - November 2014
Duration of follow-up	28 days
Sources of funding	European Commission

Inclusion criteria	Age Between 72 hours and 90 days Clinical or culture proven late-onset sepsis Culture confirmed LOS: presence of at least one positive culture from a normally sterile site together with at least one abnormal clinical or laboratory parameter within the 24 hours prior to randomisation Clincal sepsis: Postmenstrual age <44 weeks and the presence of at least two clinical and two laboratory parameters within the 24 hours prior to randomisation (criteria defined by the European Medicines Agency Expert Meeting on Neonatal and Paediatric Sepsis)
Exclusion criteria	Administration of any systemic antibiotics for more than 24 hours within the 7 days prior to randomisation Late-onset sepsis caused by microorganisms suspected or known to be resistant to study antibiotics Severe congenital malformations if the baby was not expected to survive for more than three months Renal failure and/or requirement of hemofiltration or peritoneal dialysis Known intolerance of study medication
Sample size	272
Interventions	Meropenem Standard of care Ampicillin and gentamicin or cefotaxime and gentamicin
Outcome measures	Mortality Median 2 days after end of antibiotics and at day 28 Relapse By day 28. Clinical relapses were defined as recurrence of LOS together with initiation of a new course of antibiotic treatment, and microbiological relapse as an isolation of a phenotypically similar organism from a normally sterile site in a patient with signs of infection. Adverse events Hearing impairment

Study arms

Meropenem (N = 136)

Meropenem given via 30-minute intravenous infusion at a dose of 20 mg/kg every 8 hours (every 12 hours for babies with gestational age <32 weeks and postnatal age <2 weeks)

Split between study groups	78
Loss to follow-up	13
% Female	47%
Condition specific characteristics	Median gestational age (IQR) 31.6 weeks (26.4-37.3) Median postnatal age (IQR) 16 days (8-30) Median birth weight (IQR) 1540 g (840-2830)

Standard of care (N = 136)

Ampicillin and gentamicin or cefotaxime and gentamicin administered according to the British National Formulary for Children

Split between study groups	136
Loss to follow-up	7
% Female	47%

Condition specific characteristics	Median gestational age (IQR) 30.6 weeks (27.0-36.3) Median postnatal age (IQR) 16 days (8-30) Median birth weight (IQR) 1340 g (850-2530)

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?	Probably 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
	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

Section	Question	Answer
	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?	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 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 *(Objective outcomes)*
	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 ?	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

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	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Partially applicable (*Not based in the UK so bacteria that cause infection may differ*)

Molyneux, 2017

Bibliographic Reference Molyneux, Elizabeth M; Dube, Queen; Banda, Francis M; Chiume, Msandeni; Singini, Isaac; Mallewa, Macpherson; Schwalbe, Edward C; Heyderman, Robert S; The Treatment of Possible Severe Infection in Infants: An Open Randomized Safety Trial of Parenteral Benzylpenicillin and Gentamicin Versus Ceftriaxone in Infants <60 days of Age in Malawi.; The Pediatric infectious disease journal; 2017; vol. 36 (no. 12); e328-e333

Study details

Study type	Randomised controlled trial (RCT)
Study location	Malawi
Study setting	Pediatric department of the Queen Elizabeth Central Hospital
Study dates	March 2010 - February 2013
Duration of follow-up	1 and 6 months after hospital discharge

Sources of funding	The Wellcome Trust
Inclusion criteria	Age ≤2 months Clinical suspicion of severe sepsis, pneumonia or meningitis
Exclusion criteria	Jaundice Clinical severe jaundice (yellow discoloration of the skin extending to the lower limbs) Known hypersensitivity to antibiotics Hospitalised for >72 hours
Sample size	348
Interventions	Penicillin-gentamicin Ceftriaxone
Condition specific characteristics	Culture confirmed infection (n) Positive CSF culture: 42 (14.3%). Positive cultures for GBS: 6 (14.6%) Positive blood culture: 105 (30.1%). Positive cultures for GBS: 15 (14.3%)
Outcome measures	Mortality (inpatients and 6 -month follow up) Adverse drug reactions related to antibiotics Hearing loss

Study arms

Benzylpenicillin and gentamicin (N = 161)

8 hourly IV benzylpenicillin 50,000 iu/kg (100,000 iu 8 hourly IV for bacterial meningitis) and daily gentamicin 6 mg/kg IV (standard smaller doses for low birth weight infants and very premature babies) for 5-14 days

Split between study groups	161
Loss to follow-up	3
% Female	48%
Condition specific characteristics	Birth weight (g) Median (IQR): 3100 (1900-4200)

Ceftriaxone (N = 170)

Ceftriaxone IV 50 -100 mg/kg od (depending on age) for 5-14 days

Split between study groups	170
Loss to follow-up	1
% Female	49%
Condition specific characteristics	Birth weight (g) Median (IQR): 3200 (1900-4500)

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
	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?	No information
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Limited information about analysis)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes

Section	Question	Answer
	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
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	No information *(Limited information about analysis methods)*
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(Limited information about analysis methods)*
	Overall Directness	Partially applicable *(Not based in the UK so bacteria that cause infection may differ. Includes babies with early-*

Section	Question	Answer
		and late-onset infection. Results not reported separately)

Ramasamy, 2014

Bibliographic Reference	Ramasamy, Suresh; Biswal, Niranjan; Bethou, Adhisivam; Mathai, Betsy; Comparison of two empiric antibiotic regimen in late onset neonatal sepsis--a randomized controlled trial.; Journal of tropical pediatrics; 2014; vol. 60 (no. 1); 83-6

Study details

Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Extramural nursery of the Paediatrics Department, JIPMER, Pondicherry
Study dates	Not reported
Duration of follow-up	Before discharge and within 2 weeks of discharge
Sources of funding	None reported
Inclusion criteria	Age 3 - 28 days

	Suspected sepsis Evidence of late-onset sepsis (at least one clinical parameter and 2 positive septic screen test Babies admitted to hospital
Exclusion criteria	Major congenital abnormalities Weight Very low birth weight (<1500 g) Gestational age Extreme prematurity (<28 weeks) Congenital heart disease Severe asphyxia 5 minute APGAR <5 Received antibiotics before admission
Sample size	90
Interventions	Cloxicillin-Amikacin Cefotaxime-gentamicin
Outcome measures	Mortality (before hospital discharge) Rehospitalisation

Study arms

Cloxacillin and amikacin (N = 40)

No information on dosage

Split between study groups	40
% Female	35%
Condition specific characteristics	Gestational age (weeks) Preterm: 23%; Term: 77% Birth weight (g) <2500 g: 35%; >2500 g: 65%

Cefotaxime and Gentamicin (N = 50)

No information on dosage

Split between study groups	50
% Female	40%
Condition specific characteristics	Gestational age (weeks) Preterm: 12%; Term: 86%; Postterm: 2% Birth weight (g) <2500 g: 30%; >2500 g: 70%

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
	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
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Probably yes
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Limited information about analysis methods)*

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?	No
	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
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Some concerns *(Limited information about analysis methods)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(Limited information about analysis methods)*
	Overall Directness	Partially directly applicable

Section	Question	Answer
		(Not based in the UK so bacteria that cause infection may differ. No information about dose)

Shabaan, 2017

Bibliographic Reference	Shabaan, Abd Elazeez; Nour, Islam; Elsayed Eldegla, Heba; Nasef, Nehad; Shouman, Basma; Abdel-Hady, Hesham; Conventional Versus Prolonged Infusion of Meropenem in Neonates With Gram-negative Late-onset Sepsis: A Randomized Controlled Trial.; The Pediatric infectious disease journal; 2017; vol. 36 (no. 4); 358-363

Study details

Study type	Randomised controlled trial (RCT)
Study location	Egypt
Study setting	NICU of Mansoura University Children's Hospital, Mansoura
Study dates	August 2013 - June 2015
Duration of follow-up	48 hours then weekly
Sources of funding	None
Inclusion criteria	Age <28 days of life Confirmed sepsis

	Sepsis after 72 hours of age (positive blood, cerebrospinal fluid, urine and/or synovial fluid cultures) Gram negative bacteria sensitive to meropenem
Exclusion criteria	Major congenital abnormalities Gestational age Small for gestational age Renal impairment Renal failure (serum creatinine >1.5 mg/dl, urine output <0.5 ml/kg/hour Gram positive late onset sepsis Chromosomal anomalies Inborn errors of metabolism Clinical or laboratory evidence of a congenital infection
Sample size	102
Interventions	Meropenem Infusion vs conventional
Outcome measures	Culture negative 7 days after starting therapy Mortality (timepoint not specified) Adverse drug reactions related to antibiotics Acute kidney injury

Study arms

Meropenem infusion (N = 51)

Administered every 8 hours over 4 hours. Intravenous open-label meropenem at a dose of 20 mg/kg/dose every 8 hours (40 mg/kg/dose every 8 hours for meningitis and pseudomonas infection)

Split between study groups	51
% Female	51%
Condition specific characteristics	Gestational age (weeks) Mean (SD): 34.3 (3.5) Age (days) 8 (6-13) Birth weight (g) Mean (SD): 2153 (797)

Conventional meropenem (N = 51)

Administered every 8 hours over 30 minutes. Intravenous open-label meropenem at a dose of 20 mg/kg/dose every 8 hours (40 mg/kg/dose every 8 hours for meningitis and pseudomonas infection)

Split between study groups	51
% Female	41%
Condition specific characteristics	Gestational age (weeks) Mean (SD): 33.5 (3.8) Age (days) Median (IQR): 6 (5-15)

	Birth weight (g) Mean (SD): 1893 (629)

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?	Probably no *(Mostly similar but higher % of babies were preterm in conventional group)*
	Risk of bias judgement for the randomisation process	Some concerns *(Higher % of babies were preterm in conventional group)*
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?	Yes

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?	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
	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 ?	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

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	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(More babies in conventional group were preterm which may indicate issues with randomisation)*
	Overall Directness	Partially applicable(*Not based in the UK so bacteria that cause infection may differ).*

Taheri, 2011

Bibliographic Reference Taheri, Peymaneh Alizadeh; Eslamieh, Hossein; Salamati, Peyman; Is ceftizoxime an appropriate surrogate for amikacin in neonatal sepsis treatment? A randomized clinical trial.; Acta medica Iranica; 2011; vol. 49 (no. 8); 499-503

Study details

Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Bahrami Hospital
Study dates	March 2008 - March 2010
Duration of follow-up	48 hours

Sources of funding	None reported
Inclusion criteria	Suspected sepsis Positive for any of: (1) temperature instability i.e. axillary temperature >38.5 or <36; (2) respiratory distress i.e. mean respiratory rate >60 or hypoxia with PaCO2 <60 mmHg or signs of acute respiratory distress syndrome; (3) poor feeding; (4) poor perfusion i.e. renal output <0.5 cc/kg/hr or metabolic acidosis with pH<7.2 or increased capillary refill >3s; (5) cardiovascular instability i.e. heart rate >160 or decreased blood pressure more than 2 standard deviation below normal for age; (6) decreased neonates movement associated with central cyanosis or any other symptoms or signs suggesting neonatal sepsis Term neonates
Exclusion criteria	None reported
Sample size	135
Condition specific characteristics	Late-onset sepsis (%) 54%
Interventions	Amikacin-ampicillin Ampicillin-ceftizoxime
Outcome measures	Responders (non-responder: looking ill, worsening in general condition or persistence of initial symptoms and signs along with abnormal laboratory findings after 48 hours)

Study arms

Ampicillin and ceftizoxime (N = 70) Ampicillin 50 mg/kg/dose TDS (age <1 week); 50 mg/kg/dose TDS (age >1 week). Ceftizoxime 50 mg/kg/dose BID (age <1 week); 50 mg/kg/dose TDS (age >1 week)

Split between study groups	70
Condition specific characteristics	Age (days) Mean: 9.4 Culture confirmed infection (n) 13 (19%)

Ampicillin and amikacin (N = 65)

Ampicillin 50 mg/kg/dose TDS (age <1 week); 50 mg/kg/dose TDS (age >1 week). Amikacin 10 mg/kg/dose BID (age <1 week); 10 mg/kg/dose TDS (age >1 week)

Condition specific characteristics	Age (days) Mean: 9.34 Culture confirmed infection (n) 11 (17%)

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 randomised but no further information)*
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No

Section	Question	Answer
	Risk of bias judgement for the randomisation process	Some concerns *(Limited information about randomisation. No information about allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
	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 information
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information
	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 *(No information about analysis methods or whether people giving the interventions were aware of the assigned intervention)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Probably 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 *(Culture positive infection. Unsure - responders (not culture confirmed))*
	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 *(Culture confirmed. Some concerns for responders)*
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/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Some concerns *(Limited information about analysis methods)*
Overall bias and Directness	Risk of bias judgement	High *(No information about randomisation, allocation concealment or blinding. Limited information about analysis methods)*
	Overall Directness	Partially applicable *(Not based in the UK so bacteria that cause infection may differ. Includes babies with early- and*

Section	Question	Answer
		late-onset infection. Results not reported separately)

Observational studies

de Champs, 1994

Bibliographic Reference	de Champs, C; Franchineau, P; Gourgand, J M; Loriette, Y; Gaulme, J; Sirot, J; Clinical and bacteriological survey after change in aminoglycoside treatment to control an epidemic of Enterobacter cloacae.; The Journal of hospital infection; 1994; vol. 28 (no. 3); 219-29

Study details

Study type	Retrospective cohort study
Study location	France
Study setting	Neonatal and paediatric intensive care unit
Study dates	January 1989 - July 1989 and August 1989 - July 1990
Duration of follow-up	Bacterial samples taken according to the occurrence of infection signs

Sources of funding	Direction de la Recherche et des Etudes Doctorales
Inclusion criteria	Age Less than 28 days Baby received antibiotic therapy while in the hospital
Exclusion criteria	None reported
Sample size	636
Interventions	Gentamicin-ampicillin Amikacin
Outcome measures	Antibiotic resistance (no specific timepoint)

Study arms

Gentamicin + Ampicillin (N = 238)

Intramuscular gentamicin 5 mg/kg/day in addition to IV ampicillin 200 mg/kg/day

Split between study groups	238
Condition specific characteristics	Age (days) <1: 66.8%; 1-2: 14.3%; >2: 18.9% Birth weight (g) Mean (SD): 2600 (800)

Amikacin (N = 398)

Intramuscular amikacin 15 mg/kg/day

Split between study groups	398
Condition specific characteristics	Age (days) <1: 70.9%; 1-2: 15.1%; >2: 14.1% Birth weight (g) Mean (SD): 2500 (700)

Risk of bias

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably yes
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Probably no
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No

Section	Question	Answer
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
	Risk of bias judgement for confounding	Serious *(Neonates in each group were from different points in time. Limited information about analysis methods)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information

Section	Question	Answer
	4.3. Were important co-interventions balanced across intervention groups?	No information
	4.4. Was the intervention implemented successfully for most participants?	No *(Greater proportion not given antibiotics in the amikacin group)*
	4.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
	Risk of bias judgement for deviations from intended interventions	Moderate *(Greater proportion not given antibiotics in the amikacin group)*
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No *(Many excluded because charts were not available)*
	5.2 Were participants excluded due to missing data on intervention status?	Yes
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Yes
	Risk of bias judgement for missing data	Serious *(High proportion of patients excluded because of missing chart data)*
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no
	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably no

Section	Question	Answer
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(High proportion of patients excluded because of missing chart data. Higher proportion excluded from amikacin group and participants for each group were recruited at two different time points)*
	Directness	Partially Applicable *(Not based in the UK so bacteria that cause infection may differ. Includes babies with early- and late-onset infection. Results not reported separately)*

Demirel, 2015

Bibliographic Reference	Demirel, B; Imamoglu, E; Gursoy, T; Demirel, U; Topcuoglu, S; Karatekin, G; Ovali, F; Comparison of intermittent versus continuous vancomycin infusion for the treatment of late-onset sepsis in preterm infants.; Journal of neonatal-perinatal medicine; 2015; vol. 8 (no. 2); 149-55

Study details

Study type	Retrospective cohort study
Study location	Turkey
Study setting	Neonatal Intensive Care Unit (NICU) of Zeynep Kamil Maternity and Children's Hospital, Istanbul
Study dates	Not reported
Duration of follow-up	48th hour of treatment
Sources of funding	None reported
Inclusion criteria	Gestational age <34 weeks Babies given vancomycin for suspected or well-established late-onset sepsis
Exclusion criteria	Major congenital abnormalities Known hypersensitivity to antibiotics History of anaphylactic reaction to vancomycin Renal or multi-organ failure Previously received vancomycin
Sample size	77

Interventions	Intermittent vancomycin infusion Continuous vancomycin infusion
Outcome measures	Antibiotic resistance (beginning of treatment and 48th hour of treatment)

Study arms

Intermittent vancomycin infusion (N = 41)

Vancomycin HCl DBL injectable vial 500 mg, diluted with 5% dextrose to obtain a final concentration of 5 mg/dl as recommended in the Neofax manual. Total dose was calculated from the Neofax manual

Split between study groups	41
Loss to follow-up	0
% Female	32%
Condition specific characteristics	Gestational age (weeks) Mean (SD): 29.3 (2.9) Birth weight (g) Mean (SD): 1269 (230)

Continuous vancomycin infusion (N = 36)

Vancomycin HCl DBL injectable vial 500 mg, diluted with 5% dextrose to obtain a final concentration of 5 mg/dl as recommended in the Neofax manual. Loading dose of 10 mg/kg followed by a total daily dose infused slowly over 24 hours by a constant infusion pump set. Total daily dose was calculated from the Neofax manual, based on gestational age and postnatal age

Split between study groups	36
Loss to follow-up	0
% Female	48%
Condition specific characteristics	Gestational age (weeks) Mean (SD): 28.6 (2.9) Birth weight (g) Mean (SD): 1026 (364)

Risk of bias

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably yes *(Study was developed because of potential dosing errors with intermittent infusion)*
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Probably no
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information

Section	Question	Answer
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information *(Limited information about analysis methods)*
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information *(Limited information about analysis methods)*
	Risk of bias judgement for confounding	Serious *(Limited information about analysis methods. Study was developed because of potential dosing errors with intermittent infusion which may affect results compared to the continuous group)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no

Section	Question	Answer
	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
	4.3. Were important co-interventions balanced across intervention groups?	No information
	4.4. Was the intervention implemented successfully for most participants?	No information
	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Probably yes
	5.2 Were participants excluded due to missing data on intervention status?	No
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no

Section	Question	Answer
	6.2 Were outcome assessors aware of the intervention received by study participants?	No information
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(Limited information about analysis methods. Study was developed because of potential dosing errors with intermittent infusion but not information if similar errors occurred during the study)*
	Directness	Partially Applicable *(Not based in the UK so bacteria that cause infection may differ.*

Section	Question	Answer
		Babies with suspected or well-established sepsis. Results not reported separately)

Patel, 2020

Bibliographic Reference	Patel, P.D.; Bhagat, P.; Bartlett, A.H.; Bondi, D.S.; Comparison of neonatal outcomes with the use cefotaxime versus ceftazidime in a neonatal intensive care unit; Journal of Pediatric Pharmacology and Therapeutics; 2020; vol. 25 (no. 2); 117-123

Study details

Study type	Retrospective cohort study
Study location	USA
Study setting	NICU at the University of Chicago Medicine Comer Children's Hospital
Study dates	April 2015 - August 2017
Duration of follow-up	Not reported

Sources of funding	None
Inclusion criteria	Received at least 24 hours of cefotaxime or ceftazidime within pre-specified time frames in the NICU
Exclusion criteria	Received the alternative study antibiotic for more than 24 hours during the same admission
Sample size	101
Interventions	Cefotaxime Ceftazidime
Outcome measures	Antibiotic resistance If an isolate tested resistant to an agent in at least 3 antimicrobial classes.If the baby had polymicrobial bacteremia from a single blood culture, only 1 of the isolates was required to be resistant for it to be considered a resistant infection

Study arms

Cefotaxime (N = 43)

No information about doses and timing

Split between study groups	43
% Female	41.9%
Condition specific characteristics	Median gestational age (IQR) 32.3 weeks (26.9-37.4)

	Median birth weight (IQR) 1670 g (972-3057)

Ceftazidime (N = 58)

No information about doses and timing

% Female	44.8%
Condition specific characteristics	Median gestational age (IQR) 28.1 weeks (25-36.6) Median birth weight (IQR) 990 g (716.3-2318.8)

Risk of bias

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Probably yes
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Probably yes

Section	Question	Answer
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Not applicable
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Not applicable
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
	Risk of bias judgement for confounding	Moderate *(Groups separated by type of antibiotic given but no information on dose or timing. Results not stratified by dosing strategy)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No

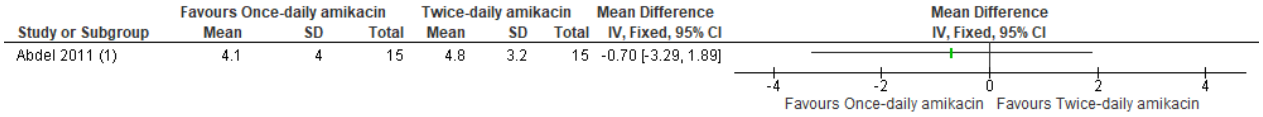
Section	Question	Answer
	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
	4.3. Were important co-interventions balanced across intervention groups?	Yes
	4.4. Was the intervention implemented successfully for most participants?	Yes
	4.5. Did study participants adhere to the assigned intervention regimen?	Yes
	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
	5.2 Were participants excluded due to missing data on intervention status?	Yes
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Yes
	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably no
	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes

Section	Question	Answer
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No
	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(No information about doses or timing of doses in either treatment arm)*
	Directness	Directly applicable

Appendix E – Forest plots

Amikacin

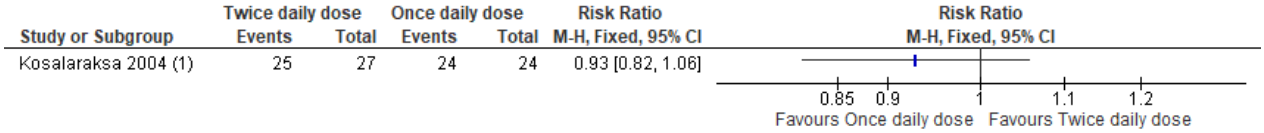
Once versus twice daily: Duration to culture negative (days)



Footnotes
(1) Mean time to normalisation of leukocytes, neutrophils and band forms of CBC

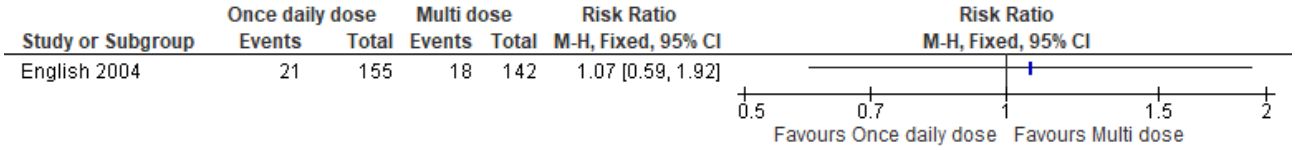
Gentamicin

Once versus twice daily dose: Responders



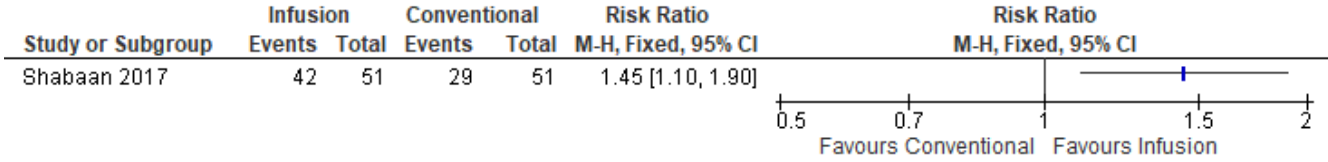
Footnotes
(1) Clinical response (improvement within 72 hours of treatment)

Once daily versus multi dose gentamicin: Neonatal mortality (timepoint not specified)

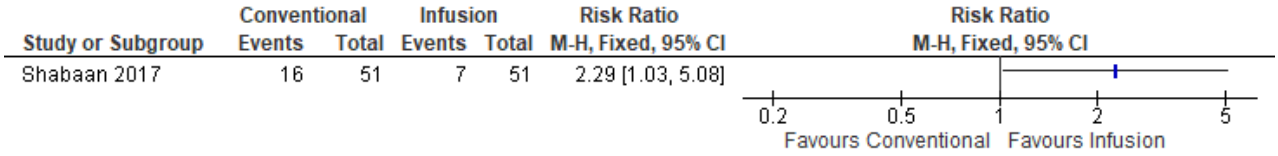


Meropenem

Conventional versus infusion therapy: Culture negative 7 days after starting therapy

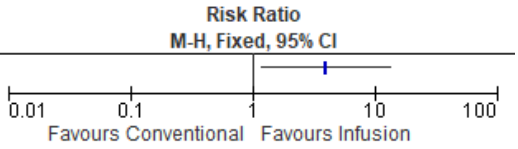


Conventional versus infusion therapy: Neonatal mortality (timepoint not specified)



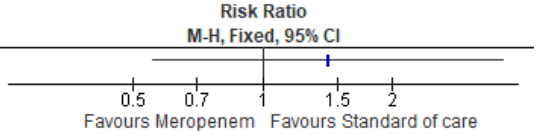
Conventional versus infusion therapy: Adverse drug reactions (acute kidney injury)

Study or Subgroup	Conventional Events	Conventional Total	Infusion Events	Infusion Total	Risk Ratio M-H, Fixed, 95% CI
Shabaan 2017	12	51	3	51	4.00 [1.20, 13.34]



Meropenem versus standard of care: Mortality at 28 days

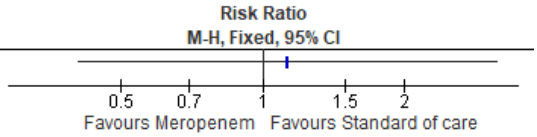
Study or Subgroup	Meropenem Events	Meropenem Total	Standard of care Events	Standard of care Total	Risk Ratio M-H, Fixed, 95% CI
Lutsar 2020 (1)	10	136	7	135	1.42 [0.56, 3.62]



Footnotes
(1) Standard of care: Ampicillin-gentamicin or Cefotaxme-gentamicin

Meropenem versus standard of care: Relapse by 28 days

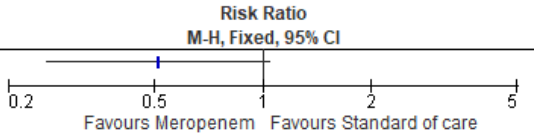
Study or Subgroup	Meropenem Events	Meropenem Total	Standard of care Events	Standard of care Total	Risk Ratio M-H, Fixed, 95% CI
Lutsar 2020 (1)	8	44	5	31	1.13 [0.41, 3.12]



Footnotes
(1) Standard of care: Ampicillin-gentamicin or Cefotaxme-gentamicin

Meropenem versus standard of care: Adverse drug reactions (hearing impairment) at 28 days

Study or Subgroup	Meropenem Events	Meropenem Total	Standard of care Events	Standard of care Total	Risk Ratio M-H, Fixed, 95% CI
Lutsar 2020 (1)	9	61	20	70	0.52 [0.25, 1.05]

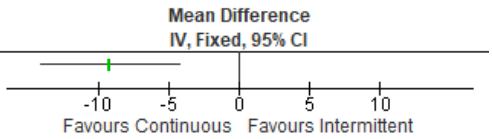


Footnotes
(1) Standard of care: Ampicillin-gentamicin or Cefotaxme-gentamicin

Vancomycin

Continuous versus intermittent infusion: Time to culture negative (days)

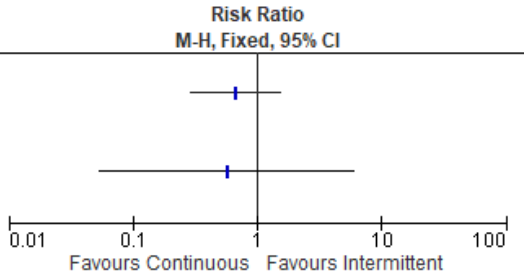
Study or Subgroup	Continuous Mean	Continuous SD	Continuous Total	Intermittent Mean	Intermittent SD	Intermittent Total	Mean Difference IV, Fixed, 95% CI
Gwee 2019 (1)	46.1	10.3	53	55.3	14.9	51	-9.20 [-14.14, -4.26]



Footnotes
(1) Mean time to clearance of bacteraemia

Continuous versus intermittent infusion: Methicillin-resistant staphylococcus infections

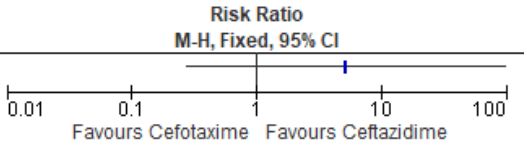
Study or Subgroup	Continuous Events	Total	Intermittent Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Beginning of treatment					
Demirel 2015	7	36	12	41	0.66 [0.29, 1.50]
4.2.2 48th hour of treatment					
Demirel 2015	1	36	2	41	0.57 [0.05, 6.02]



Cefotaxime versus Ceftazidime

Antibiotic resistance (multidrug resistant organism after initial antibiotic course)

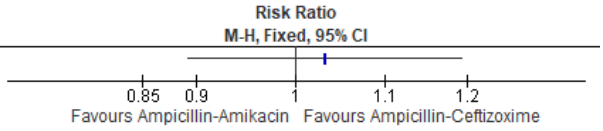
Study or Subgroup	Cefotaxime Events	Total	Ceftazidime Events	Total	Risk Ratio M-H, Fixed, 95% CI
Patel 2020	3	58	0	43	5.22 [0.28, 98.49]



Ampicillin-Amikacin versus Ampicillin-Ceftizoxime

Responders

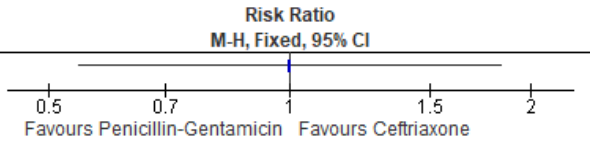
Study or Subgroup	Ampicillin-Ceftizoxime Events	Total	Ampicillin-Amikacin Events	Total	Risk Ratio M-H, Fixed, 95% CI
Taheri 2011	60	70	54	65	1.03 [0.89, 1.19]



Benzylpenicillin-Gentamicin versus Ceftriaxone

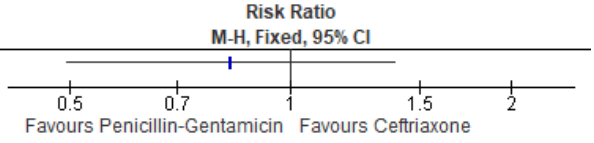
Neonatal mortality (inpatient)

Study or Subgroup	Penicillin-Gentamicin Events	Total	Ceftriaxone Events	Total	Risk Ratio M-H, Fixed, 95% CI
Molyneux 2017	18	161	19	170	1.00 [0.54, 1.84]



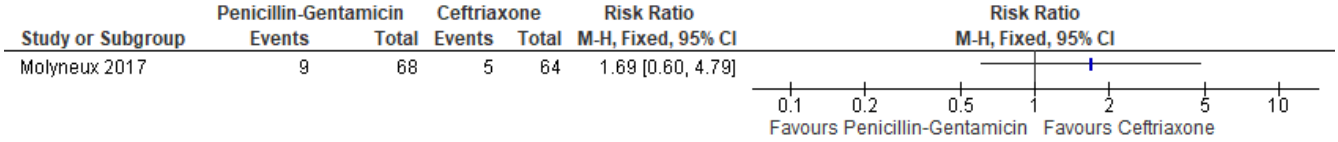
Neonatal mortality (6-month follow up)

Study or Subgroup	Penicillin-Gentamicin Events	Total	Ceftriaxone Events	Total	Risk Ratio M-H, Fixed, 95% CI
Molyneux 2017 (1)	22	161	28	170	0.83 [0.50, 1.39]



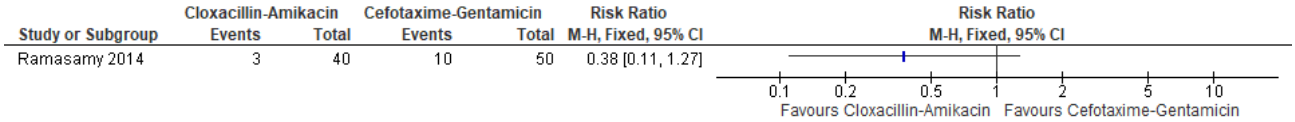
Footnotes
(1) Loss to long-term follow-up: Penicillin-Gentamicin = 15; Ceftriaxone = 17

Adverse drug reactions (hearing loss)



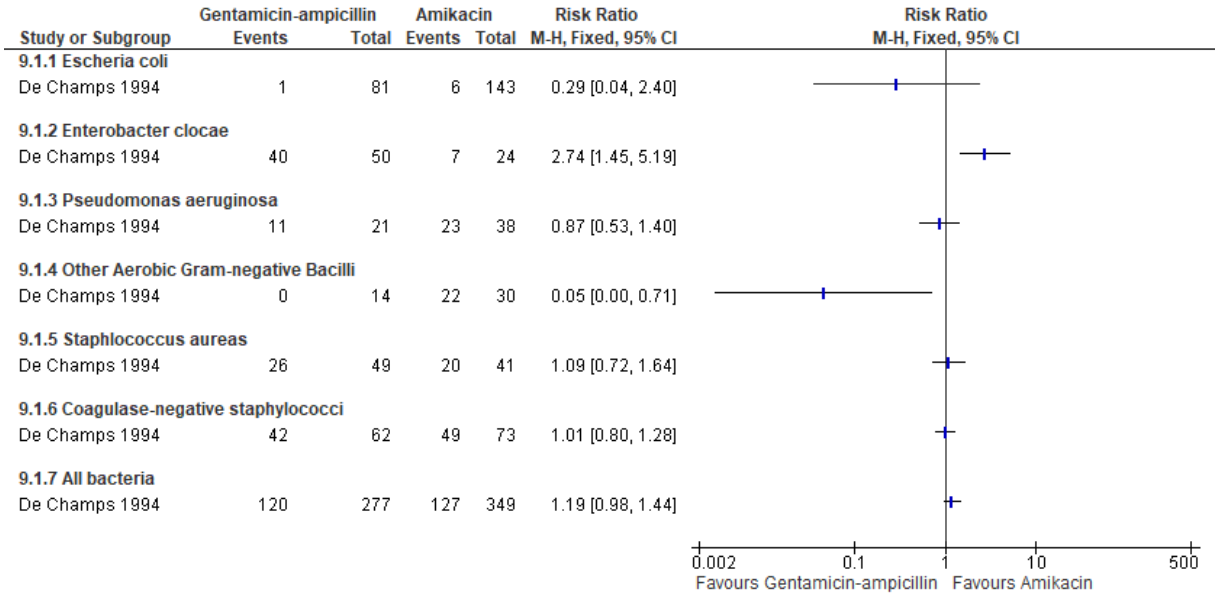
Cloxacillin-Amikacin versus Cefotaxime-Gentamicin

Neonatal mortality (before hospital discharge)

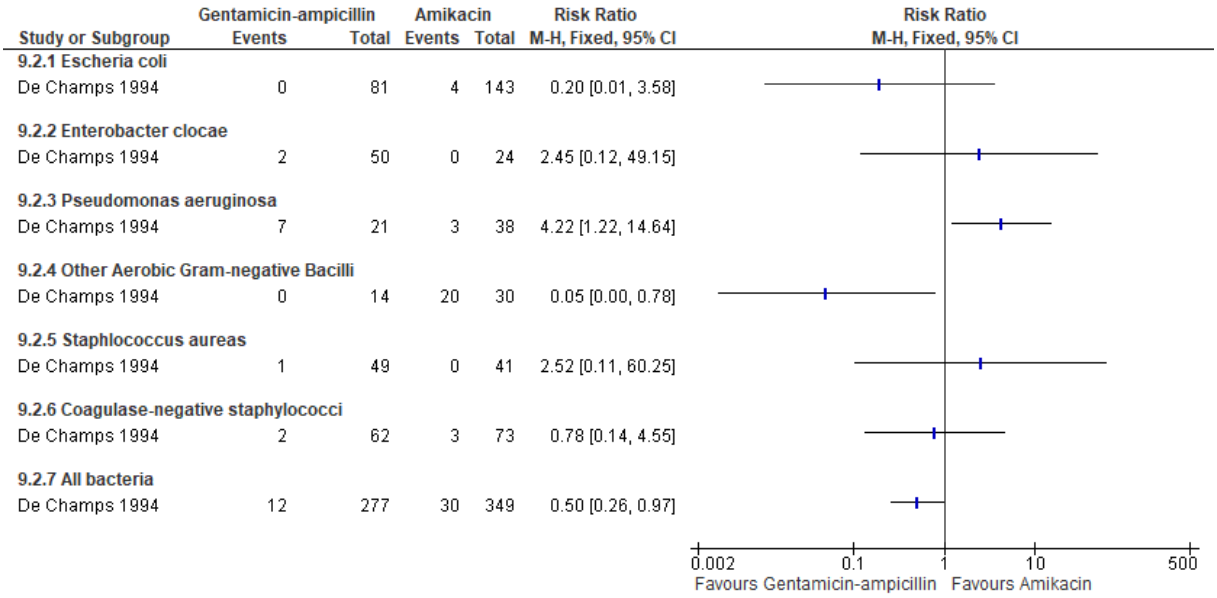


Gentamicin-Ampicillin versus Amikacin

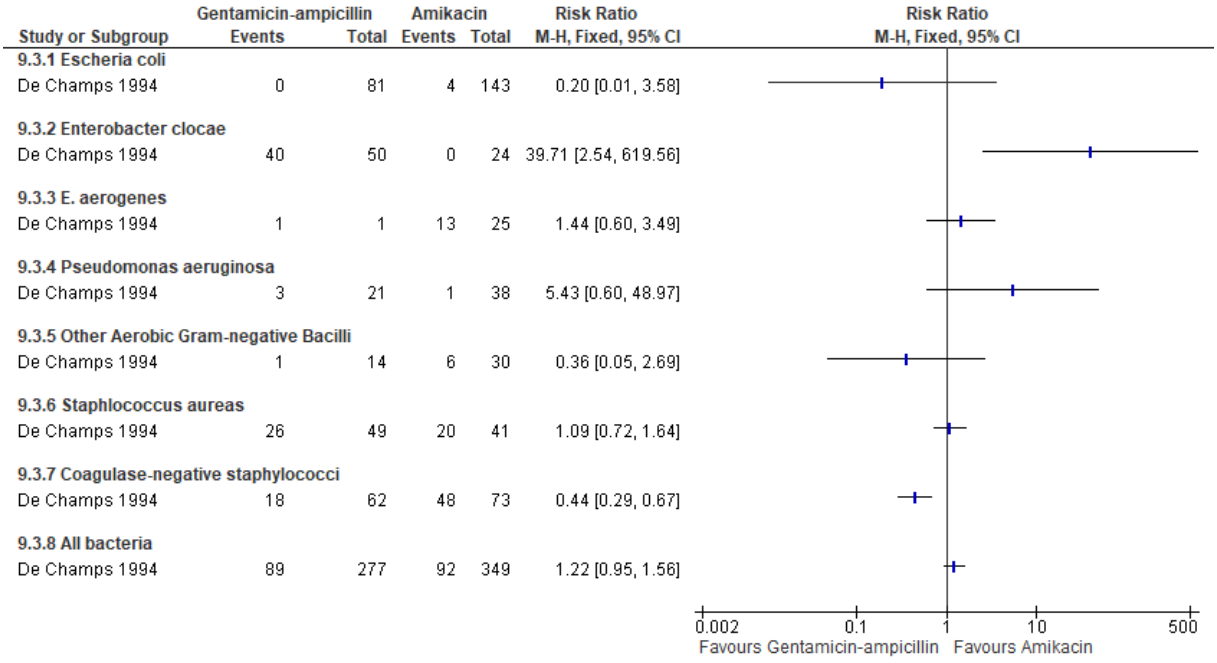
Gentamicin resistance



Amikacin resistance



Ceftazidime resistance



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.

Amikacin

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Once versus twice daily dose: Duration to culture negative (days) (MD <0 favours once daily dose)									
1 (Abdel-Hady 2011)	Parallel RCT	30	MD -0.70 (-3.29, 1.89)	-	-	Very serious[1]	N/A[2]	Serious[3]	Very low

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

Gentamicin

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Once versus twice daily dose: Number of responders (RR <1 favours once daily dose)									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (Kosalaraksa 2004)	Parallel RCT	51	RR 0.93 (0.82, 1.06)	100 per 100	93 per 100 (82, 100)	Very serious[1]	N/A[2]	Serious[3]	Very low
Once daily versus multi dose: Neonatal mortality (timepoint not specified) (RR <1 favours once daily dose)									
1 (English 2004)	Parallel RCT	297	RR 1.07 (0.59, 1.92)	14 per 100	14 per 100 (8, 26)	Not serious	N/A[2]	Serious[3]	Moderate

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

Meropenem

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Culture negative 7 days after starting therapy (RR <1 favours conventional dose)									
1 (Shabaan 2017)	Parallel RCT	102	RR 1.45 (1.10, 1.90)	82 per 100	57 per 100 (43, 75)	Serious[1]	N/A[2]	Serious[3]	Low
Conventional dose versus infusion: Neonatal mortality (timepoint not specified) (RR <1 favours conventional dose)									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (Shabaan 2017)	Parallel RCT	102	RR 2.29 (1.03, 5.08)	14 per 100	31 per 100 (14, 70)	Serious[1]	N/A[2]	Serious[3]	Low
Conventional dose versus infusion: Adverse drug reactions (acute kidney injury) (RR <1 favours conventional dose)									
1 (Shabaan 2017)	Parallel RCT	102	RR 4.00 (1.20, 13.34)	6 per 100	24 per 100 (7, 78)	Serious[1]	N/A[2]	Serious[3]	Low
Meropenem versus standard of care (Ampicillin-gentamicin or Cefotaxime-gentamicin): Mortality at 28 days (RR <1 favours meropenem)									
1 (Lutsar 2020)	Parallel RCT	271	RR 1.42 (0.56, 3.62)	5 per 100	7 per 100 (3, 19)	Not serious	N/A[2]	Serious[3]	Moderate
Meropenem versus standard of care (Ampicillin-gentamicin or Cefotaxime-gentamicin): Relapse by 28 days (RR <1 favours meropenem)									
1 (Lutsar 2020)	Parallel RCT	75	RR 1.13 (0.41, 3.12)	16 per 100	18 per 100 (7, 50)	Not serious	N/A[2]	Serious[3]	Moderate
Meropenem versus standard of care (Ampicillin-gentamicin or Cefotaxime-gentamicin): Adverse drug reactions (hearing impairment) at 28 days (RR <1 favours meropenem)									
1 (Lutsar 2020)	Parallel RCT	131	RR 0.52 (0.25, 1.05)	29 per 100	15 per 100 (7, 30)	Not serious	N/A[2]	Serious[3]	Moderate

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

Vancomycin

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Continuous versus intermittent infusion: Time to culture negative (hours) (MD<0 favours continuous infusion)									
1 (Gwee 2019)	RCT	111	MD -9.20 (-14.14, -4.26)	-	-	Serious[3]	N/A[4]	Serious[1]	Low
Continuous versus intermittent infusion: Antibiotic resistance - Methicillin-resistant staphylococcus infections (beginning of treatment) (RR <1 favours continuous infusion)									
1 (Demirel 2015)	Retrospective cohort	77	RR 0.66 (0.29, 1.50)	29 per 100	19 per 100 (8, 44)	Very serious[2]	N/A[4]	Serious[1]	Very low
Continuous versus intermittent infusion - Antibiotic resistance: Methicillin-resistant staphylococcus infections (48th hour of treatment) (RR <1 favours continuous infusion)									
1 (Demirel 2015)	Retrospective cohort	77	RR 0.57 (0.05, 6.02)	5 per 100	3 per 100 (0, 29)	Very serious[2]	N/A[4]	Serious[1]	Very low

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

Cefotaxime versus Ceftazidime

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Antibiotic resistance (multidrug resistant organism after initial antibiotic course – no specific timepoint) (RR<0 favours cefotaxime)									
1 (Patel 2020)	Retrospective cohort	101	RR 5.22 (0.28, 98.49)	1 per 100	6 per 100 (0, 100)	Very serious[1]	N/A[2]	Not serious	Low

1. Single study at high risk of bias. Quality downgraded 2 levels
2. Single study. Inconsistency not applicable

Ampicillin-Amikacin versus Ampicillin-Ceftizoxime

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Number of responders (RR <1 favours ampicillin-amikacin)									
1 (Taheri 2011)	Parallel RCT	135	RR 1.03 (0.89, 1.19)	86 per 100	83 per 100 (72, 96)	Very serious[1]	N/A[2]	Serious[3]	Very low

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

Benzylpenicillin-gentamicin vs Ceftriaxone

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Neonatal mortality: inpatients (RR <1 favours benzylpenicillin-gentamicin)									
1 (Molyneux 2017)	Parallel RCT	331	RR 1.00 (0.54, 1.84)	11 per 100	11 per 100 (6, 21)	Serious[1]	N/A[2]	Serious[2]	Low
Neonatal mortality: 6 months follow-up (RR <1 favours benzylpenicillin-gentamicin)									
1 (Molyneux 2017)	Parallel RCT	331	RR 0.83 (0.50, 1.39)	16 per 100	14 per 100 (8, 23)	Serious[1]	N/A[2]	Serious[2]	Low
Adverse drug reactions: hearing loss (RR <1 favours benzylpenicillin-gentamicin)									
1 (Molyneux 2017)	Parallel RCT	132	RR 1.69 (0.60, 4.79)	8 per 100	13 per 100 (5, 37)	Serious[1]	N/A[2]	Serious[3]	Low

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

Cloxacillin-amikacin vs Cefotaxime-gentamicin

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Neonatal mortality (before hospital discharge) (RR <1 favours cloxacillin-amikacin)									
1 (Ramasamy 2014)	Parallel RCT	90	RR 0.38 (0.11, 1.27)	20 per 100	8 per 100 (2, 25)	Serious[1]	N/A[2]	Serious[3]	Low

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

Gentamicin-ampicillin vs Amikacin

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Gentamicin resistance (no specific timepoint) (RR <1 favours gentamicin-ampicillin)									
Escheria coli bacteria									
1 (De Champs 1994)	Retrospective cohort	224	RR 0.29 (0.04, 2.40)	4 per 100	1 per 100 (0, 10)	Very serious[1]	N/A[2]	Serious[3]	Very low
Enterobacter clocae bacteria									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (De Champs 1994)	Retrospective cohort	74	RR 2.74 (1.45, 5.19)	29 per 100	80 per 100 (42, 100)	Very serious[1]	N/A[2]	Serious[3]	Very low
Pseudomonas aeruginosa bacteria									
1 (De Champs 1994)	Retrospective cohort	59	RR 0.87 (0.53, 1.40)	61 per 100	53 per 100 (32, 85)	Very serious[1]	N/A[2]	Serious[3]	Very low
Other aerobic Gram-negative bacilli									
1 (De Champs 1994)	Retrospective cohort	44	RR 0.05 (0.00, 0.71)	73 per 100	4 per 100 (0, 52)	Very serious[1]	N/A[2]	Serious[3]	Very low
Staphylococcus aureas bacteria									
1 (De Champs 1994)	Retrospective cohort	90	RR 1.09 (0.72, 1.64)	49 per 100	53 per 100 (35, 80)	Very serious[1]	N/A[2]	Serious[3]	Very low
Coagulase-negative staphylococci bacteria									
1 (De Champs 1994)	Retrospective cohort	135	RR 1.01 (0.80, 1.28)	67 per 100	68 per 100 (54, 86)	Very serious[1]	N/A[2]	Serious[3]	Very low
All bacteria									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (De Champs 1994)	Retrospective cohort	626	RR 1.19 (0.98, 1.44)	36 per 100	43 per 100 (36, 52)	Very serious[1]	N/A[2]	Serious[3]	Very low
Amikacin resistance (no specific timepoint) (RR <1 favours gentamicin-ampicillin)									
Escheria coli bacteria									
1 (De Champs 1994)	Retrospective cohort	224	RR 0.20 (0.01, 3.58)	3 per 100	1 per 100 (0, 10)	Very serious[1]	N/A[2]	Serious[3]	Very low
Enterobacter clocae bacteria									
1 (De Champs 1994)	Retrospective cohort	74	RR 2.45 (0.12, 49.15)	2 per 100	5 per 100 (0, 100)	Very serious[1]	N/A[2]	Serious[3]	Very low
Pseudomonas aeruginosa bacteria									
1 (De Champs 1994)	Retrospective cohort	59	RR 4.22 (1.22, 14.64)	8 per 100	33 per 100 (10, 100)	Very serious[1]	N/A[2]	Serious[3]	Very low
Other aerobic Gram-negative bacilli									
1 (De Champs 1994)	Retrospective cohort	44	RR 0.05 (0.00, 0.78)	67 per 100	3 per 100 (0, 52)	Very serious[1]	N/A[2]	Serious[3]	Very low

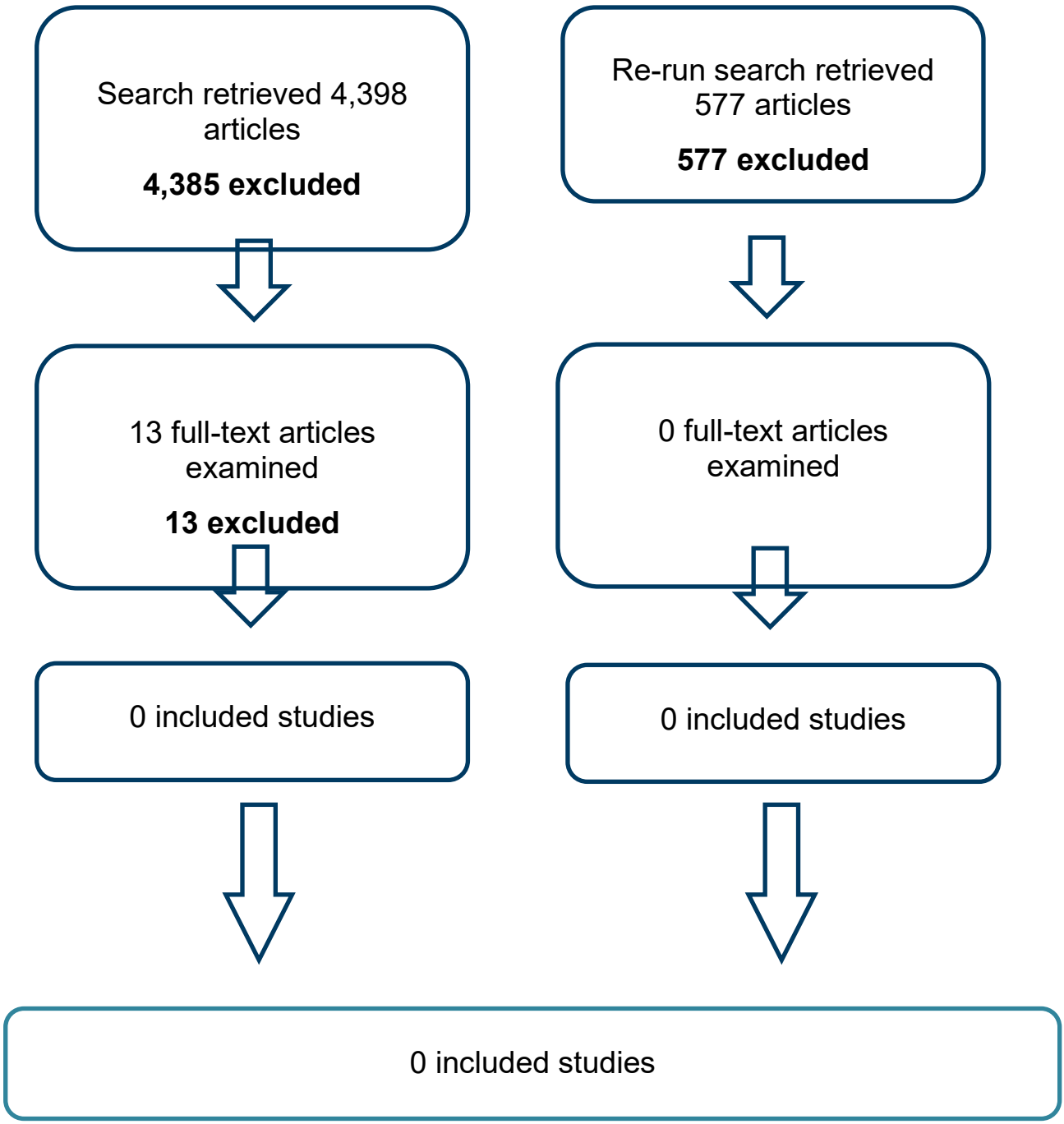
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
Staphylococcus aureas bacteria									
1 (De Champs 1994)	Retrospective cohort	90	RR 2.52 (0.11, 60.25)	1 per 100	3 per 100 (0, 73)	Very serious[1]	N/A[2]	Serious[3]	Very low
Coagulase-negative staphylococci bacteria									
1 (De Champs 1994)	Retrospective cohort	135	RR 0.78 (0.14, 4.55)	4 per 100	3 per 100 (1, 19)	Very serious[1]	N/A[2]	Serious[3]	Very low
All bacteria									
1 (De Champs 1994)	Retrospective cohort	626	RR 0.50 (0.26, 0.97)	9 per 100	4 per 100 (2, 8)	Very serious[1]	N/A[2]	Serious[3]	Very low
Ceftazidime resistance (no specific timepoint) (RR <1 favours gentamicin-ampicillin)									
Escheria coli bacteria									
1 (De Champs 1994)	Retrospective cohort	224	RR 0.20 (0.01, 3.58)	3 per 100	1 per 100 (0, 10)	Very serious[1]	N/A[2]	Serious[3]	Very low
Enterobacter clocae bacteria									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (De Champs 1994)	Retrospective cohort	74	RR 39.71 (2.54, 619.56)	2 per 100	83 per 100 (5, 100)	Very serious[1]	N/A[2]	Serious[3]	Very low
E. aerogenes bacteria									
1 (De Champs 1994)	Retrospective cohort	26	RR 1.44 (0.60, 3.49)	52 per 100	75 per 100 (31, 100)	Very serious[1]	N/A[2]	Serious[3]	Very low
Pseudomonas aeruginosa bacteria									
1 (De Champs 1994)	Retrospective cohort	59	RR 5.43 (0.60, 48.97)	3 per 100	14 per 100 (2, 100)	Very serious[1]	N/A[2]	Serious[3]	Very low
Other aerobic Gram-negative bacilli									
1 (De Champs 1994)	Retrospective cohort	44	RR 0.36 (0.05, 2.69)	20 per 100	7 per 100 (1, 54)	Very serious[1]	N/A[2]	Serious[3]	Very low
Staphylococcus aureas bacteria									
1 (De Champs 1994)	Retrospective cohort	90	RR 1.09 (0.72, 1.64)	49 per 100	53 per 100 (35, 80)	Very serious[1]	N/A[2]	Serious[3]	Very low
Coagulase-negative staphylococci bacteria									

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk (control)	Absolute risk (intervention)	Risk of bias	Inconsistency	Indirectness	Quality
1 (De Champs 1994)	Retrospective cohort	135	RR 0.44 (0.29, 0.67)	66 per 100	29 per 100 (19, 44)	Very serious[1]	N/A[2]	Serious[3]	Very low
All bacteria									
1 (De Champs 1994)	Retrospective cohort	626	RR 1.22 (0.95, 1.56)	26 per 100	32 (25, 41)	Very serious[1]	N/A[2]	Serious[3]	Very low

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

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

Although this question was prioritised for original economic analysis, as detailed in 1.1.8 Economic model, no de novo modelling was performed.

Appendix J – Excluded studies

Clinical studies

Study	Code [Reason]
Adelman, R D; Wirth, F; Rubio, T (1987) A controlled study of the nephrotoxicity of mezlocillin and amikacin in the neonate. American journal of diseases of children (1960) 141(11): 1175-8	- Study does not include population of interest *[States infants with suspected infection but does not reported age]*
Adelman, R D; Wirth, F; Rubio, T (1987) A controlled study of the nephrotoxicity of mezlocillin and gentamicin plus ampicillin in the neonate. The Journal of pediatrics 111(6pt1): 888-93	- Study does not include population of interest *[Study does not state age of neonates]*
African Neonatal Sepsis Trial (AFRINEST), group, Tshefu, Antoinette, Lokangaka, Adrien et al. (2015) Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: a randomised, open-label, equivalence trial. Lancet (London, England) 385(9979): 1767-1776	- Community-based antibiotic regimes. Not relevant to UK practice
Agarwal, Ghanshyam, Rastogi, Alok, Pyati, Suma et al. (2002) Comparison of once-daily versus twice-daily gentamicin dosing regimens in infants > or = 2500 g. Journal of perinatology : official journal of the California Perinatal Association 22(4): 268-74	- Study does not contain outcomes of interest
Alinejad, S., Yousefichaijan, P., Rezagholizamenjany, M. et al. (2018) Nephrotoxic effect of gentamicin and amikacin in neonates with infection. Nephro-Urology Monthly 10(2): e58580	- Study does not contain outcomes of interest
Allen, T.R. and Da Silva, O.P. (2003) Choice of antibiotics in late neonatal sepsis in the extremely low birth weight infant. Canadian Journal of Infectious Diseases 14(1): 28-31	- Not a relevant study design *[Observational study that does not report information on antibiotic resistance]*
Alsaedi, SA (2003) Once daily gentamicin dosing in full term neonates. Saudi medical journal 24(9): 978-981	- Study does not contain outcomes of interest

Study	Code [Reason]
Aydemir, Cumhur, Oguz, Serife Suna, Dizdar, Evrim Alyamac et al. (2011) Randomised controlled trial of prophylactic fluconazole versus nystatin for the prevention of fungal colonisation and invasive fungal infection in very low birth weight infants. Archives of disease in childhood. Fetal and neonatal edition 96(3): f164-8	- Study does not include population of interest *[Babies <72 hours of age]*
Baqui, Abdullah H, Saha, Samir K, Ahmed, A S M Nawshad Uddin et al. (2015) Safety and efficacy of alternative antibiotic regimens compared with 7 day injectable procaine benzylpenicillin and gentamicin for outpatient treatment of neonates and young infants with clinical signs of severe infection when referral is not possible: a randomised, open-label, equivalence trial. The Lancet. Global health 3(5): e279-87	- Community-based antibiotic regimes. Not relevant to UK practice
Baqui, Abdullah H, Saha, Samir Kumar, Ahmed, A S M Nawshad Uddin et al. (2013) Safety and efficacy of simplified antibiotic regimens for outpatient treatment of serious infection in neonates and young infants 0-59 days of age in Bangladesh: design of a randomized controlled trial. The Pediatric infectious disease journal 32suppl1: 12-8	- Community-based antibiotic regimes. Not relevant to UK practice
Batra, A and Kler, N (2009) Antibiotic therapy in neonatal sepsis: cochrane reviews. Journal of neonatology 23(1): 78-79	- Not a relevant study design *[Summary of systematic reviews]*
Benjamin Jr., D.K., Hudak, M.L., Duara, S. et al. (2014) Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: A randomized clinical trial. JAMA - Journal of the American Medical Association 311(17): 1742-1749	- RCT for antifungal treatment that does not meet the methods stated in the protocol *[Use of antifungals for preterm babies. Babies did not need to be receiving antibiotic treatment for suspected infection]*
Bennet, R, Eriksson, M, Nord, CE et al. (1986) Fecal bacterial microflora of newborn infants during intensive care management and treatment with five antibiotic regimens. Pediatric infectious disease 5(5): 533-539	- Not a relevant study design *[Observational study that does not report antibiotic resistance outcomes]*
Bordbar, A., Mazouri, A., Kashaki, M. et al. (2017) Standard multiple and single daily dosing	- Study does not contain outcomes of interest

Study	Code [Reason]
of amikacin in premature infants. Iranian Journal of Neonatology 8(4): 57-64	
Burman, L G, Berglund, B, Huovinen, P et al. (1993) Effect of ampicillin versus cefuroxime on the emergence of beta-lactam resistance in faecal Enterobacter cloacae isolates from neonates. The Journal of antimicrobial chemotherapy 31(1): 111-6	- Study does not include population of interest *[States infants being discharged from neonatal unit but age is not reported]*
Cailes, B., Kortsalioudaki, C., Buttery, J. et al. (2018) Epidemiology of UK neonatal infections: The neonIN infection surveillance network. Archives of Disease in Childhood: Fetal and Neonatal Edition 103(6): F547-F553	- Not a relevant study design *[Observational study that does not report antibiotic resistance outcomes]*
Cailes, Benjamin, Kortsalioudaki, Christina, Buttery, Jim et al. (2018) Antimicrobial resistance in UK neonatal units: neonIN infection surveillance network. Archives of disease in childhood. Fetal and neonatal edition 103(5): f474-f478	- Not a relevant study design *[Non-comparative observational study]*
Ceriani Cernadas, Jose M, Fernandez Jonusas, Silvia, Marquez, Maritza et al. (2014) Clinical outcome of neonates with nosocomial suspected sepsis treated with cefazolin or vancomycin: a non-inferiority, randomized, controlled trial. Archivos argentinos de pediatria 112(4): 308-14	- Study not reported in English
Chaudhari, Sudha, Suryawanshi, Pradeep, Ambardekar, Shrikant et al. (2004) Safety profile of ciprofloxacin used for neonatal septicemia. Indian pediatrics 41(12): 1246-51	- Not a relevant study design *[Observational study that does not report antibiotic resistance outcomes]*
Chotigeat, U; Narongsanti, A; Ayudhya, D P (2001) Gentamicin in neonatal infection: once versus twice daily dosage. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 84(8): 1109-15	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Coscia, A, Maiorca, D, Martano, C et al. (2008) Use of netilmicin once or twice daily in preterm newborns: evaluation of nephrotoxicity by urinary alpha1-microglobulin and retinol binding protein. Journal of chemotherapy (florence, italy) 20(3): 324-326	- Not a relevant study design *[Non-RCT study]*

Study	Code [Reason]
de Louvois, J; Dagan, R; Tessin, I (1992) A comparison of ceftazidime and aminoglycoside based regimens as empirical treatment in 1316 cases of suspected sepsis in the newborn. European Society for Paediatric Infectious Diseases--Neonatal Sepsis Study Group. European journal of pediatrics 151(12): 876-84	- Study does not include population of interest *[Median age was within the range for early-onset infection. No information about how many babies with late-onset infection were included]*
Degefie Hailegebriel, Tedbabe, Mulligan, Brian, Cousens, Simon et al. (2017) Effect on Neonatal Mortality of Newborn Infection Management at Health Posts When Referral Is Not Possible: A Cluster-Randomized Trial in Rural Ethiopia. Global health, science and practice 5(2): 202-216	- Community-based antibiotic regimes. Not relevant to UK practice
Demirel, Gamze, Celik, Istemi Han, Erdeve, Omer et al. (2013) Prophylactic Saccharomyces boulardii versus nystatin for the prevention of fungal colonization and invasive fungal infection in premature infants. European journal of pediatrics 172(10): 1321-6	- Study does not include population of interest *[Babies aged <72 hours]*
Duby, Jessica; Lassi, Zohra S; Bhutta, Zulfiqar A (2019) Community-based antibiotic delivery for possible serious bacterial infections in neonates in low- and middle-income countries. The Cochrane database of systematic reviews 4: cd007646	- Community-based antibiotic regimes. Not relevant to UK practice *[Systematic review of community-based antibiotics]*
El-barbary, M.N.; Ismail, R.I.H.; Ibrahim, A.A.A. (2015) Gentamicin extended interval regimen and ototoxicity in neonates. International Journal of Pediatric Otorhinolaryngology 79(8): 1294-1298	- Not a relevant study design *[Non-RCT study of effectiveness]*
Engle, W D, Jackson, G L, Sendelbach, D et al. (2000) Neonatal pneumonia: comparison of 4 vs 7 days of antibiotic therapy in term and near-term infants. Journal of perinatology : official journal of the California Perinatal Association 20(7): 421-6	- Study does not include population of interest *[Babies with symptoms of early-onset infection]*
Engle, William D, Jackson, Gregory L, Sendelbach, Dorothy M et al. (2003) Pneumonia in term neonates: laboratory studies and duration of antibiotic therapy. Journal of	- Study does not include population of interest *[Babies with symptoms of early-onset infection]*

Study	Code [Reason]
perinatology : official journal of the California Perinatal Association 23(5): 372-7	
Fjalstad, Jon Widding, Esaiassen, Eirin, Juvet, Lene Kristine et al. (2018) Antibiotic therapy in neonates and impact on gut microbiota and antibiotic resistance development: a systematic review. The Journal of antimicrobial chemotherapy 73(3): 569-580	- Systematic review. Reference list checked for possible includes
Giapros, VI, Andronikou, S, Cholevas, VI et al. (1995) Renal function in premature infants during aminoglycoside therapy. Pediatric nephrology (Berlin, Germany) 9(2): 163-166	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Giustardi, A and Coppola, G (1992) Comparison of plasma concentrations of amoxicillin administered by oral and venous routes in neonatal bacterial colonizations. Pediatria medica e chirurgica [Medical and surgical pediatrics] 14(4): 447-449	- Study not reported in English
Gordon Adrienne, Jeffery Heather E (2005) Antibiotic regimens for suspected late onset sepsis in newborn infants. Cochrane Database of Systematic Reviews: Reviews issue3	- Systematic review. Reference list checked for possible includes
Gordon, A and Jeffery, H E (2005) Antibiotic regimens for suspected late onset sepsis in newborn infants. The Cochrane database of systematic reviews: cd004501	- Systematic review. Reference list checked for possible includes
Grosso, A., Neves De Faria, R.I., Bojke, L. et al. (2020) Cost-effectiveness of strategies preventing late-onset infection in preterm infants. Archives of Disease in Childhood 105(5): 452-457	- Health economics analysis
Guadalupe Vasquez-Mendoza, Ma, Vargas-Origel, Arturo, Del Carmen Ramos-Jimenez, Aurelia et al. (2007) Efficacy and renal toxicity of one daily dose of amikacin versus conventional dosage regime. American journal of perinatology 24(2): 141-6	- Study does not include population of interest *[Mean age was within the time period for early-onset infection]*

Study	Code [Reason]
Hagen, I and Oymer, K (2009) Pharmacological differences between once and twice daily gentamicin dosage in newborns with suspected sepsis. Pharmacy world and science 31: 18-23	- Not a relevant study design *[Observational study that does not reported antibacterial resistance outcomes]*
Hall, M A, Ducker, D A, Lowes, J A et al. (1988) A randomised prospective comparison of cefotaxime versus netilmicin/penicillin for treatment of suspected neonatal sepsis. Drugs 35suppl2: 169-77	- Study does not include population of interest *[Included babies with suspected infection but mean age was within the time period for early-onset infection in both groups]*
Hammerberg, O, Elder, D, Richardson, H et al. (1986) Staphylococcal resistance to aminoglycosides before and after introduction of amikacin in two teaching hospitals. Journal of clinical microbiology 24(4): 629-32	- Study does not include population of interest *[Observational study reporting antimicrobial resistance but results are for neonatal and adult wards combined]*
Hayani, K C, Hatzopoulos, F K, Frank, A L et al. (1997) Pharmacokinetics of once-daily dosing of gentamicin in neonates. The Journal of pediatrics 131(1pt1): 76-80	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Hemels, Marieke A C, van den Hoogen, Agnes, Verboon-Maciolek, Malgorzata A et al. (2012) Shortening the antibiotic course for the treatment of neonatal coagulase-negative staphylococcal sepsis: fine with three days?. Neonatology 101(2): 101-5	- Not a relevant study design *[Observational study which does not report antibacterial resistance outcomes]*
Hill, L.F., Turner, M.A., Lutsar, I. et al. (2020) An optimised dosing regimen versus a standard dosing regimen of vancomycin for the treatment of late onset sepsis due to Gram-positive microorganisms in neonates and infants aged less than 90 days (NeoVanc): Study protocol for a randomised controlled trial. Trials 21(1): 329	- Study protocol
Holton, A F; Hall, M A; Lowes, J A (1989) Antibiotic exposure delays intestinal colonization by Clostridium difficile in the newborn. The Journal of antimicrobial chemotherapy 24(5): 811-7	- Study does not include population of interest *[States that neonates were included but no information about their age]*
Howell, A., Barfield, C., Bourchier, D. et al. (2009) Oral nystatin prophylaxis and neonatal fungal infections. Archives of Disease in	- Not a relevant study design *[Observational study that does not report resistance outcomes]*

Study	Code [Reason]
Childhood: Fetal and Neonatal Edition 94(6): f429-f433	
Jaiswal, Nishant, Singh, Meenu, Kondel, Ritika et al. (2016) Feasibility and efficacy of gentamicin for treating neonatal sepsis in community-based settings: a systematic review. World journal of pediatrics : WJP 12(4): 408-414	- Community-based antibiotic regimes. Not relevant to UK practice *[Systematic review of community-based antibiotics]*
Kaguelidou, Florentia, Turner, Mark A, Choonara, Imti et al. (2013) Randomized controlled trials of antibiotics for neonatal infections: a systematic review. British journal of clinical pharmacology 76(1): 21-9	- Systematic review. Reference list checked for possible includes
Kaufman, D., Boyle, R., Hazen, K.C. et al. (2001) Fluconazole prophylaxis against fungal colonization and infection in preterm infants. New England Journal of Medicine 345(23): 1660-1666	- Study does not include population of interest *[Babies treated with antifungals but mean age at enrollment was within the time period for early-onset infection]*
Kaufman, D., Boyle, R., Hazen, K.C. et al. (2005) Twice weekly fluconazole prophylaxis for prevention of invasive Candida infection in high-risk infants of <1000 grams birth weight. Journal of Pediatrics 147(2): 172-179	- Study does not include population of interest *[Babies given antifungal treatment but median age was within the time period for early-onset infection]*
Kaufman, D.A., Morris, A., Gurka, M.J. et al. (2014) Fluconazole prophylaxis in preterm infants: A multicenter case-controlled analysis of efficacy and safety. Early Human Development 90(suppl1): 87-s90	- Not a relevant study design *[Non-RCT study of effectiveness]*
Keij, F.M., Kornelisse, R.F., Hartwig, N.G. et al. (2019) RAIN study: A protocol for a randomised controlled trial evaluating efficacy, safety and cost-effectiveness of intravenous-to-oral antibiotic switch therapy in neonates with a probable bacterial infection. BMJ Open 9(7): e026688	- Not a peer-reviewed publication *[Protocol for RAIN study]*
Keij, Fleur M, Kornelisse, Rene F, Hartwig, Nico G et al. (2019) RAIN study: a protocol for a randomised controlled trial evaluating efficacy, safety and cost-effectiveness of intravenous-to-oral antibiotic switch therapy in neonates with a probable bacterial infection. BMJ open 9(7): e026688	- Comparator in study does not match that specified in protocol *IV antibiotics - specific antibiotic regimen not specified*

Study	Code [Reason]
Kicklighter, S.D., Springer, S.C., Cox, T. et al. (2001) Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. Pediatrics 107(2): 293-298	- Study does not include population of interest *[Excluded babies admitted to the NICU over 72 hours of age]*
Kirpal, Harita, Gathwala, Geeta, Chaudhary, Uma et al. (2016) Prophylactic fluconazole in very low birth weight infants admitted to neonatal intensive care unit: randomized controlled trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 29(4): 624-8	- Study does not include population of interest *[Babies with suspected early-onset infection. Must have already been given antibiotics before starting antifungals]*
Kotze, A.; Bartel, P.R.; De Sommers, K. (1999) Once versus twice daily amikacin in neonates: Prospective study on toxicity. Journal of Paediatrics and Child Health 35(3): 283-286	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Krediet, T G; Fleer, A; Gerards, L J (1993) Development of resistance to aminoglycosides among coagulase-negative staphylococci and enterobacteriaceae in a neonatal intensive care unit. The Journal of hospital infection 24(1): 39-46	- Study does not include population of interest *[Study includes babies admitted to a NICU but no information about age]*
Krishnan, L and George, S A (1997) Gentamicin therapy in preterms: a comparison of two dosage regimens. Indian pediatrics 34(12): 1075-80	- Study does not include population of interest *[Median age was within the time period for early-onset infection]*
Le, Jennifer, Nguyen, Thuy, Okamoto, Mark et al. (2008) Impact of empiric antibiotic use on development of infections caused by extended-spectrum beta-lactamase bacteria in a neonatal intensive care unit. The Pediatric infectious disease journal 27(4): 314-8	- Study does not contain outcomes of interest
Lee, SJ and Park, EA (2005) Efficacy and Safety of Amoxicillin-sulbactam and Ampicillin-sulbactam in Full Term Neonates. Journal of the korean society of neonatology 12(1): 17-24	- Study not reported in English

Study	Code [Reason]
Levin, GS, Jesurun, CA, Ipsen, MA et al. (2003) Neonatal suspected sepsis: a cost comparison of 2 vs. 3 days of antibiotic therapy. Pediatric research 53: 137	- Conference abstract
Lokangaka, A., Bauserman, M., Coppieters, Y. et al. (2018) Simplified antibiotic regimens for treating neonates and young infants with severe infections in the Democratic Republic of Congo: A comparative efficacy trial. Maternal Health, Neonatology and Perinatology 4(1): 8	- Community-based antibiotic regimes. Not relevant to UK practice
Lönnerholm, G; Bengtsson, S; Ewald, U (1982) Oral pivampicillin and amoxycillin in newborn infants. Scandinavian journal of infectious diseases 14(2): 127-130	- Not a relevant study design *[Non-RCT study of effectiveness]*
Manzoni, P., Arisio, R., Mostert, M. et al. (2006) Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: A single-center, 6-year, retrospective cohort study. Pediatrics 117(1): e22-e32	- Not a relevant study design *[Non-comparative observational study]*
Manzoni, P., Farina, D., Leonessa, M.L. et al. (2006) Use of prophylactic fluconazole in a neonatal intensive care unit: Efficacy is similar to that described in adult high-risk surgical patients. Critical Care 10(1): 402	- Not a peer-reviewed publication *[Letter to the editor]*
Manzoni, P., Stolfi, I., Pugni, L. et al. (2007) A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. New England Journal of Medicine 356(24): 2483-2495	- Study does not include population of interest *[Babies with suspected early-onset infection]*
Marks, S, Marks, M I, Dupont, C et al. (1978) Evaluation of three antibiotic programs in newborn infants. Canadian Medical Association journal 118(6): 659-62	- Study does not contain outcomes of interest
Mathur, N B; Kharod, Prarthana; Kumar, Surinder (2015) Evaluation of duration of antibiotic therapy in neonatal bacterial meningitis: a randomized controlled trial. Journal of tropical pediatrics 61(2): 119-25	- Study does not contain a relevant intervention *[Examines use of antibiotics for neonatal infection but does not state which antibiotics and doses were used in the trial]*

Study	Code [Reason]
Mathur, N B and Murugesan, A (2018) Comparison of Four Days Versus Seven Days Duration of Antibiotic Therapy for Neonatal Pneumonia: A Randomized Controlled Trial. Indian journal of pediatrics 85(11): 963-967	- Study does not include population of interest *[Neonates with pneumonia without positive blood culture]*
McCracken, G H Jr; Mize, S G; Threlkeld, N (1980) Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy. Report of the Second Neonatal Meningitis Cooperative Study Group. Lancet (London, England) 1(8172): 787-91	- Study does not include population of interest *[Includes neonates and children up to 1 year. Results for neonates not reported separately]*
McCracken, G H Jr, Threlkeld, N, Mize, S et al. (1984) Moxalactam therapy for neonatal meningitis due to gram-negative enteric bacilli. A prospective controlled evaluation. JAMA 252(11): 1427-32	- Study does not include population of interest *[Children up to 1 year. Results for neonates not reported separately]*
McCracken, GJ, Threlkeld, N, Mize, S et al. (1984) Moxalactam therapy for neonatal meningitis due to gram-negative enteric bacilli. JAMA 252: 1427-1432	- Study does not include population of interest *[Children up to 1 year. Results for neonates not reported separately]*
McCrossan, Brian A, McHenry, Elaine, O'Neill, Fiona et al. (2007) Selective fluconazole prophylaxis in high-risk babies to reduce invasive fungal infection. Archives of disease in childhood. Fetal and neonatal edition 92(6): f454-8	- Study does not include population of interest *[Babies given antifungals but not necessarily when given antibiotics]* - Not a relevant study design *[Observational study which does not report antifungal resistance outcomes]*
Miall-Allen, V M; Whitelaw, A G; Darrell, J H (1988) Ticarcillin plus clavulanic acid (Timentin) compared with standard antibiotic regimes in the treatment of early and late neonatal infections. The British journal of clinical practice 42(7): 273-9	- Study does not contain outcomes of interest
Miller, Jamie L, Johnson, Peter N, White, Bryan P et al. (2019) Impact of Ceftazidime Use on Susceptibility Patterns in the Neonatal Intensive Care Unit. The Pediatric infectious disease journal 38(6): 605-607	- Not a relevant study design *Non-comparative study*

Study	Code [Reason]
Narang, A; Dutta, S; Choudhard, G (2005) Randomized Controlled Trial of 7-Day Versus 14-Day Antibiotic Regimes for Neonatal Sepsis. Pediatric academic societies annual meeting; 2005 may 14-17; washington DC, united states	- Study does not include population of interest
Nelson, JD and McCracken, GH (1973) Clinical pharmacology of carbenicillin and gentamicin in the neonate and comparative efficacy with ampicillin and gentamicin. Pediatrics 52(6): 801-812	- Study does not contain outcomes of interest *[Observational study which does not report antibiotic resistance outcomes]*
Nestaas, E., Bangstad, H.-J., Sandvik, L. et al. (2005) Aminoglycoside extended interval dosing in neonates is safe and effective: A meta-analysis. Archives of Disease in Childhood: Fetal and Neonatal Edition 90(4): f294-f300	- Systematic review. Reference list checked for possible includes
Pacifici, G.M. (2009) Peak and trough concentrations of gentamicin in the neonate: A review of the literature. Current Pediatric Reviews 5(1): 2-7	- Study does not contain outcomes of interest *[Systematic review which did not cover the outcomes of interest]*
Pawlotsky, F, Thomas, A, Kergueris, M F et al. (1998) Constant rate infusion of vancomycin in premature neonates: a new dosage schedule. British journal of clinical pharmacology 46(2): 163-7	- Not a relevant study design *[Non-RCT study]*
Peixoto, P.B., Massinhani, F.H., dos Santos, K.R.N. et al. (2020) Methicillin-resistant Staphylococcus epidermidis isolates with reduced vancomycin susceptibility from bloodstream infections in a neonatal intensive care unit. Journal of Medical Microbiology 69(1): 41-45	- Not a relevant study design *Non-comparative study*
Rajchgot, P, Prober, CG, Soldin, S et al. (1984) Aminoglycoside related nephrotoxicity in the premature newborn. Clinical pharmacology and therapeutics 35: 394-401	- Study does not contain outcomes of interest
Rao Shripada C, Srinivasjois Ravisha, Hagan Ronald, Ahmed Mohmed (2011) One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven	- Systematic review. Reference list checked for possible includes

Study	Code [Reason]
sepsis in neonates. Cochrane Database of Systematic Reviews: Reviews issue11	
Rao, Shripada C; Srinivasjois, Ravisha; Moon, Kwi (2016) One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. The Cochrane database of systematic reviews 12: cd005091	- Systematic review. Reference list checked for possible includes
Reed, MD, Kliegman, RM, Yamashita, TS et al. (1990) Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. Antimicrobial agents and chemotherapy 34(6): 1172-1177	- Not a relevant study design *[Non-randomised trial]*
Saini, Shiv Sajan, Dutta, Sourabh, Ray, Pallab et al. (2011) Short course versus 7-day course of intravenous antibiotics for probable neonatal septicemia: a pilot, open-label, randomized controlled trial. Indian pediatrics 48(1): 19-24	- Study does not include population of interest *[Babies with suspected infection but median age was within the time period for early-onset infection]*
Seale, Josephine V, Hutchinson, Richard A, Fleming, Paul F et al. (2018) Does antibiotic choice for the treatment of suspected late-onset sepsis in premature infants determine the risk of developing necrotising enterocolitis? A systematic review. Early human development 123: 6-10	- Study does not contain outcomes of interest *[Systematic review that does not contain outcomes of interest]*
Shabuj, MKH, Moni, SC, Shaha CK et al. (2017) Gentamicin in newborn sepsis: once-daily versus twice-daily dose. Bangladesh medical research council bulletin 43(2): 82-86	- Not a relevant study design *[non-RCT trial]*
Shah Sachin S, Ohlsson Arne, Shah Vibhuti S (2012) Intraventricular antibiotics for bacterial meningitis in neonates. Cochrane Database of Systematic Reviews: Reviews issue7	- Systematic review. Reference list checked for possible includes
Shah, Sachin S; Ohlsson, Arne; Shah, Vibhuti S (2012) Intraventricular antibiotics for bacterial meningitis in neonates. The Cochrane database of systematic reviews: cd004496	- Duplicate reference
Skopnik, H, Wallraf, R, Nies, B et al. (1992) Pharmacokinetics and antibacterial activity of	- Study does not include population of interest *[Babies with suspected early-onset infection]*

Study	Code [Reason]
daily gentamicin. Archives of disease in childhood 67(1specno): 57-61	
Solomon, R, Kuruvilla, K A, Job, V et al. (1999) Randomized controlled trial of once vs. twice daily gentamicin therapy in newborn. Indian pediatrics 36(2): 133-7	- Study does not include population of interest *[States babies in 'early neonatal life' but does not report age]*
Sorsa, Abebe, Fruh, Jonas, Stotter, Loraine et al. (2019) Blood culture result profile and antimicrobial resistance pattern: a report from neonatal intensive care unit (NICU), Asella teaching and referral hospital, Asella, south East Ethiopia. Antimicrobial resistance and infection control 8: 42	- Not a relevant study design *Non-compariative study*
Steele, R W and Bradsher, R W (1983) Comparison of ceftriaxone with standard therapy for bacterial meningitis. The Journal of pediatrics 103(1): 138-41	- Study does not include population of interest *[Includes neonates and children up to 14 years. Results for neonates not reported separately]*
Tessin, I, Thiringer, K, Trollfors, B et al. (1988) Comparison of serum concentrations of ceftazidime and tobramycin in newborn infants. European journal of pediatrics 147(4): 405-7	- Study does not include population of interest *[Study includes babies with suspected early-onset infection. Mean age is within the criteria for early-onset]*
Tessin, I, Trollfors, B, Bergmark, J et al. (1987) Enzymuria in neonates during treatment with gentamicin or tobramycin. Pediatric infectious disease journal 6(9): 870-871	- Study does not include population of interest *[One study arm only has babies with suspected early-onset infection]*
Tessin, I, Trollfors, B, Thiringer, K et al. (1991) Ampicillin-aminoglycoside combinations as initial treatment for neonatal septicaemia or meningitis. A retrospective evaluation of 12 years' experience. Acta paediatrica Scandinavica 80(10): 911-6	- Not a relevant study design *[Non-comparative observational study]*
Tessin, I, Trollfors, B, Thiringer, K et al. (1989) Concentrations of ceftazidime, tobramycin and ampicillin in the cerebrospinal fluid of newborn infants. European journal of pediatrics 148(7): 679-81	- Study does not contain outcomes of interest *[Non-RCT which does not report antibiotic resistance outcomes]*
Tiwari, Soumya, Rehan, H S, Chandra, Jagdish et al. (2009) Efficacy and safety of a single daily dose of gentamicin in hospitalized Indian	- Study does not include population of interest

Study	Code [Reason]
children: a quasi-randomized trial. The Journal of antimicrobial chemotherapy 64(5): 1096-101	*[Included neonates and children up to 11 years of age. Results not reported separately]*
Tullus, K and Burman, L G (1989) Ecological impact of ampicillin and cefuroxime in neonatal units. Lancet (London, England) 1(8652): 1405-7	- Study does not include population of interest *[No information about age of neonates]* - Study does not contain outcomes of interest *[Antibiotic resistance based on faecal culture]*
Umana, M A, Odio, C M, Castro, E et al. (1990) Evaluation of aztreonam and ampicillin vs. amikacin and ampicillin for treatment of neonatal bacterial infections. The Pediatric infectious disease journal 9(3): 175-80	- Study does not include population of interest *[Babies without proven infection excluded from analysis]*
Vergnano, Stefania, Menson, Esse, Kennea, Nigel et al. (2011) Neonatal infections in England: the NeonIN surveillance network. Archives of disease in childhood. Fetal and neonatal edition 96(1): f9-f14	- Not a relevant study design *[Non-comparative observational study]*
Violaris, Kimon, Carbone, Tracy, Bateman, David et al. (2010) Comparison of fluconazole and nystatin oral suspensions for prophylaxis of systemic fungal infection in very low birthweight infants. American journal of perinatology 27(1): 73-8	- RCT for antifungal treatment that does not meet the methods stated in the protocol *[Babies given antifungal treatment but no information about how many were also being given antibiotics]*
Vucicevic, K., Rakonjac, Z., Miljkovic, B. et al. (2014) Pharmacokinetic variability of amikacin after once-daily and twice-daily dosing regimen in full-term neonates. Journal of Pharmacological Sciences 124(2): 138-143	- Study does not contain outcomes of interest
Vucicevic, K.M., Rakonjac, Z.M., Jankovic, B.Z. et al. (2014) Clinical pharmacokinetics in optimal gentamicin dosing regimen in neonates. Central European Journal of Medicine 9(3): 485-490	- Study does not contain outcomes of interest
Wainer, S., Cooper, P.A., Funk, E. et al. (1992) Prophylactic miconazole oral gel for the prevention of neonatal fungal rectal colonization and systemic infection. Pediatric Infectious Disease Journal 11(9): 713-716	- Study does not include population of interest *[Babies with suspected early-onset infection]*

Study	Code [Reason]
Wiese, G (1988) Treatment of neonatal sepsis with ceftriaxone/gentamicin and with azlocillin/gentamicin: a clinical comparison of efficacy and tolerability. Chemotherapy 34(2): 158-63	- Study does not include population of interest *[States that neonates were included but no information about age]*
Zaidi, Anita K M, Tikmani, Shiyam Sundar, Sultana, Shazia et al. (2013) Simplified antibiotic regimens for the management of clinically diagnosed severe infections in newborns and young infants in first-level facilities in Karachi, Pakistan: study design for an outpatient randomized controlled equivalence trial. The Pediatric infectious disease journal 32suppl1: 19-25	- Community-based antibiotic regimes. Not relevant to UK practice
Zaidi, Anita K M, Tikmani, Shiyam Sundar, Warraich, Haider J et al. (2012) Community-based treatment of serious bacterial infections in newborns and young infants: a randomized controlled trial assessing three antibiotic regimens. The Pediatric infectious disease journal 31(7): 667-72	- Community-based antibiotic regimes. Not relevant to UK practice

Economic studies

Study	Code [Reason]
Andrews RE. Audit of single daily dose gentamicin versus a variable frequency lower dose regimen in term and preterm neonates. BRITISH JOURNAL OF INTENSIVE CARE. 2000;10(2):42-6.	- Exclude overall. No health economic information relevant for this review question.
Blyth CC, Barzi F, Hale K, Isaacs D. Chemoprophylaxis of neonatal fungal infections in very low birthweight infants: efficacy and safety of fluconazole and nystatin. Journal of paediatrics and child health. 2012 Sep;48(9):846-51.	- Study is not an economic evaluation.
Chen S, Sun KY, Feng XW, Ran X, Lama J, Ran YP. Efficacy and safety of itraconazole use in infants. World Journal of Pediatrics. 2016 Nov 1;12(4):399-407.	- Exclude overall. No health economic information relevant for this review question.

Study	Code [Reason]
De Cock RF, Smits A, Allegaert K, de Hoon J, Saegeman V, Danhof M, Knibbe CA. Population pharmacokinetic modelling of total and unbound cefazolin plasma concentrations as a guide for dosing in preterm and term neonates. Journal of Antimicrobial Chemotherapy. 2014 May 1;69(5):1330-8.	- Study is not an economic evaluation.
Gordon A, Jeffery HE. Antibiotic regimens for suspected late onset sepsis in newborn infants. Cochrane Database of Systematic Reviews. 2005(3).	- Study is not an economic evaluation
Ng TB, Cheung RC, Ye XJ, Fang EF, Chan YS, Pan WL, Dan XL, Yin CM, Lam SK, Lin P, Kui Ngai PH. Pharmacotherapy approaches to antifungal prophylaxis. Expert opinion on pharmacotherapy. 2012 Aug 1;13(12):1695-705.	- Exclude overall. No health economic information relevant for this review question.
Leonart LP, Tonin FS, Ferreira VL, da Silva Penteado ST, de Araújo Motta F, Pontarolo R. Fluconazole doses used for prophylaxis of invasive fungal infection in neonatal intensive care units: A network meta-analysis. The Journal of Pediatrics. 2017 Jun 1;185:129-35.	- Study is not an economic evaluation.
Mersal A, Alzahrani I, Azzouz M, Alsubhi A, Alsawaigh H, Albshri N, Bajammal M, Avand G, Almahbosh A. Oral nystatin versus intravenous fluconazole as neonatal antifungal prophylaxis: non-inferiority trial. Journal of clinical neonatology. 2013 Apr;2(2):88.	- Study only contains costs.
Ramasamy S, Biswal N, Bethou A, Mathai B. Comparison of two empiric antibiotic regimen in late onset neonatal sepsis—a randomized controlled trial. Journal of tropical pediatrics. 2014 Feb 1;60(1):83-6.	- Study is not an economic evaluation
Reynolds LF, Mailman TL, McMillan DD. Gentamicin in neonates at risk for sepsis–peak serum concentrations are not necessary. Paediatrics & child health. 2012 Jun 1;17(6):310-2.	- Exclude overall. No health economic information relevant for this review question.
Swanson JR, Vergales J, Kaufman DA, Sinkin RA. Cost analysis of fluconazole prophylaxis for	- Different decision problem. Not relevant to this review question.

Study	Code [Reason]
prevention of neonatal invasive candidiasis. The Pediatric Infectious Disease Journal. 2016 May 1;35(5):519-23.	
Thureen PJ, Reiter PD, Gresores A, Stolpman NM, Kawato K, Hall DM. Once-versus twice-daily gentamicin dosing in neonates≥ 34 weeks' gestation: cost-effectiveness analyses. Pediatrics. 1999 Mar 1;103(3):594-8.	- Different decision problem. Not relevant to this review question.
Yang YC, Mao J. Value of platelet count in the early diagnosis of nosocomial invasive fungal infections in premature infants. Platelets. 2018 Jan 2;29(1):65-70.	- Study is not an economic evaluation.

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

What is the optimal antibiotic treatment regimen for suspected late-onset neonatal infection?

K.1.2 Why this is important

Nine RCTs and three retrospective cohort studies were identified which compared different antibiotic regimens for the treatment of babies with late-onset neonatal infection. The evidence base was low quality, with small sample sizes and reported few of the outcomes considered most important to determine the effectiveness of antibiotics.

UK-based RCTs are needed which examine both the effectiveness and safety of different antibiotics for a baby who develops late-onset neonatal infection. Research in this area is essential to understand which antibiotic regimens can help a baby recover from neonatal infection quickly, thereby reducing the potential harmful effects associated with infection as well as minimising the time a baby is exposed to antibiotics.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Neonatal infection can have serious consequences for the health of a baby. Currently, little is known about the most effective antibiotic, or combination of antibiotics, to treat babies who develop late-onset infection. Increased understanding of the effects of antibiotics to treat late-onset neonatal infection will mean that babies can be given the most effective treatment options, helping them to recover as quickly as possible, and minimising the time they are exposed to antibiotics.
Relevance to NICE guidance	The committee have made recommendations on antibiotic treatment for babies with late-onset infection, based primarily on local antibiotic prescribing guidelines. An increased understanding of whether there is a particular antibiotic, or combination of antibiotics, that would most benefit babies being treated for late-onset infection will help the committee make more specific recommendations in future updates of this guideline.
Relevance to the NHS	A greater understanding of the most effective antibiotics for treating babies with suspected late-onset neonatal infection will help give clinicians confidence when prescribing treatment. If the most effective antibiotic regimens can be identified, then the duration of treatment may be reduced which will reduce the costs of treatment, as well as the costs

	associated with any side effects of infection that can develop if infection is not treated quickly.
National priorities	Medium
Current evidence base	This review identified 9 RCTs and 3 retrospective cohort studies reporting data on antibiotics for babies with late-onset neonatal infection. These studies reported on a range of antibiotics, but the evidence base for each antibiotic regimen was limited and low quality and reported few of the outcomes needed to judge effectiveness and safety.
Equality considerations	No specific equality concerns are relevant to this research recommendation.

K.1.4 Modified PICO table

PICO	**Population:** Babies with suspected late-onset neonatal bacterial infection (from 72 hours to 28 days after birth) **Interventions:** Antibiotics (and combinations of antibiotics, including intra and inter-class combinations) **Comparator:** • Head-to-head comparison with any other antibiotics (including combinations of antibiotics) • Different treatment durations • Placebo • No treatment / usual care **Outcomes:** Neonatal outcomes: • Culture-proven infection from sample taken between 72 hours and 28 days of age (term babies) or 28 days corrected gestational age (preterm babies) • Relapse • Mortality • Hospital length of stay • Duration to culture negative • Adverse drug reactions specifically related to antibiotics • Neurodevelopmental outcomes (measured using a validated tool) • Antimicrobial resistance (culture proven) Maternal/family outcomes: • psychological distress in baby's family as measured using a validated scale
Current evidence base	9 RCTs and 3 retrospective cohort studies
Study design	RCTs

Other comments	Study should be adequately powered, based in the UK, and should collect data on both effectiveness and safety. Studies should use quantitative methods of data collection