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[Intervention Protocol]

Shorter versus longer duration antibiotic regimens for treatment of culture-positive neonatal sepsis

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the safety and effectiveness of shorter versus longer duration antibiotic regimens for the treatment of culture-positive neonatal sepsis with or without meningitis.

BACKGROUND

Description of the condition

Neonatal sepsis, occurring before 28 days' corrected age, is a leading cause of death globally (Lawn 2014). In adults and children, international consensus definitions of sepsis include multi-organ dysfunction and bacteraemia (Singer 2016). However, no international consensus definition for neonatal sepsis exists (Wynn 2016). In lieu, culture-positive or proven neonatal sepsis has been defined as clinical and laboratory criteria consistent with infection combined with the growth of bacteria in blood culture (Isaacs 1995). Despite significant improvements in global neonatal mortality rates (Liu 2016), an estimated 16% of global neonatal mortality was attributed to sepsis, meningitis or lower respiratory tract infections in 2019 (Perin 2022).

Neonates, in particular preterm infants, are at increased risk of sepsis due to immune system immaturity and reduced placental transfer of maternal antibodies (Camacho-Gonzalez 2013). Neonatal sepsis may be difficult to diagnose as the clinical manifestations may be non-specific (Camacho-Gonzalez 2013), and difficult to distinguish from those of non-infectious aetiology (Polin 2012). Culture-positive sepsis may be suspected by the presence of clinical signs that have been validated to predict bacteraemia, including signs of shock, abnormal body temperature and respiratory insufficiency (Okascharoen 2005; Okascharoen 2007). Laboratory tests including white cell count and acute-phase reactants are commonly used. However, they have limited diagnostic accuracy in predicting culture-positive sepsis (Wynn 2016). A diagnosis of culture-positive sepsis requires a positive blood culture, which has been reported to occur in 3.7% of all blood cultures processed in a high-income setting (Connell 2007), and in 47% of infants with early-onset sepsis (EOS) in a low-income setting (Kayange 2010). True positive results may be limited by resource availability and the volume of blood collected (Connell 2007).

The population estimate for neonatal sepsis is reported to be 28.2 per 1000 livebirths (Fleischmann 2021). There is a higher burden in low- and middle-income countries (Fleischmann-Struzek 2018), with the incidence of neonatal sepsis reported to be 39.3 to 46.9 per 1000 live births (Fleischmann 2021; Milton 2022), compared to 17.22 per 1000 livebirths in high-income countries (Fleischmann 2021). The reported mortality rate is variable, but most recent reports are between 11% and 19% (Fleischmann 2021). In addition to short-term neonatal mortality and longer-term death following discharge, neonatal sepsis carries significant morbidity with an increased risk of respiratory distress syndrome, intraventricular haemorrhage (IVH), meningitis, multi-organ failure, bronchopulmonary dysplasia (BPD) and poorer neurodevelopmental outcomes compared to controls without sepsis (Bakhuizen 2014; Schlapbach 2011).

Neonatal sepsis is categorised into EOS and late-onset sepsis (LOS) distinguished by timing and mode of infection acquisition, and therefore causative pathogens. EOS is commonly defined as sepsis occurring before 72 hours after birth (Cortese 2016; Korang 2021a; NICE 2021), and is a vertically acquired infection (mother to infant) from the antenatal or intrapartum period (Camacho-Gonzalez 2013). In high-income countries, the EOS incidence is reported to be between 0.7 and 0.79 per 1000 livebirths (Cailes 2018; Schrag 2016). In low- and middle-income countries, there is significant variability in reported incidence from 0.9 to 77 per 1000 livebirths (Sands 2022). Risk factors for EOS include prematurity, low birthweight, maternal *Group B streptococcus* (GBS) colonisation, chorioamnionitis, premature rupture of membranes and prolonged rupture of membranes (greater than 18 hours) (Camacho-Gonzalez 2013). The incidence of EOS is reported to have an inverse relationship to birthweight and gestational age (GA) (Fleischmann 2021).

The most common causative pathogens of EOS in high-income countries include GBS and *Escherichia coli* (*E coli*), and to a lesser extent *Listeria monocytogenes*, other *Streptococci* species, *Staphylococcus aureus* and *Haemophilus influenzae* (Stoll 2011; Vergnano 2011). *Klebsiella* species, *Staphylococcus aureus* and *E coli* are the most prevalent causative organisms in low- and middle-income countries, with far fewer infections caused by GBS (Vergnano 2005; Zaidi 2009).

LOS usually occurs after 72 hours of birth (Cortese 2016; Korang 2021b; NICE 2021). The overall incidence of LOS was reported as 9.5 per 1000 live births (Fleischmann 2021), with an incidence of 2.2 per 1000 live births reported in a high-income setting (Cailes 2018), and a variable incidence of 4.9 to 16.9 per 1000 live births in low- and middle-income settings (Al-Taiar 2013; Hammoud 2012). Risk factors for LOS include prematurity; low birthweight; delay in early breast milk feeding; prolonged use of parenteral nutrition; invasive interventions including intravascular catheterisation, mechanical ventilation and surgery; and underlying cardiac and respiratory disease (Boghossian 2013; Dong 2015; Leal 2012; Stoll 2002; Tsai 2014a). Central line-associated bloodstream infection (CLABSI) is a category of LOS defined by the Centers for Disease Control and Prevention as a primary bloodstream infection in a patient with a central line in situ 48 hours prior to development of the bloodstream infection, and not related to infection at another site (O'Grady 2011). *Coagulase negative staphylococci* (CoNS) is the predominant causative organism in high-income countries with an incidence of 8.25 per 1000 catheter-days (Zipursky 2019). Gram-negative or resistant organisms are more likely to be causative in resource-limited settings (Jenkins 2017), with an incidence of 2.6 to 60 per 1000 catheter-days reported (Rosenthal 2009).

CoNS is the predominant causative pathogen reported for LOS (particularly CLABSI), with *Staphylococcus aureus*, *E coli*, *Klebsiella* species, *Enterobacter* species, *Pseudomonas* species and *Candida* also commonly isolated (Dong 2015; Isaacs 1996; Vergnano 2005; Vergnano 2011). Some organisms are associated with a significantly increased risk of mortality, such as *Pseudomonas aeruginosa* with a mortality rate of up to 52.3% (Gordon 2006). Certain organisms such as *Serratia marcescans* cause increased morbidity such as increased home oxygen use and poorer neurodevelopmental outcomes associated with meningitis and subsequent brain abscess (Campbell 1992; Coggins 2023). Increased mortality rates are also seen with multiple-drug-resistant organisms. The mortality rate for infants with carbapenem-resistant gram-negative organisms has been documented to be significantly higher (34%) compared to non-carbapenem-resistant gram-negative organisms (13%) (Thomas 2022).

Meningitis is often included in the definition of neonatal sepsis as isolation of bacteria in cerebrospinal fluid (CSF) is often associated with bacteraemia (ANZNN 2023; Flannery 2022). The incidence of neonatal meningitis ranges from 0.1 to 6.1 per 1000 live births (El-Naggar 2019; Thaver 2009), with the most common causative organisms reported to be *E coli* and GBS (El-Naggar 2019). The

reported incidence of meningitis in association with sepsis is between 20% and 30% for EOS, and 10% for LOS (Isaacs 1995), and the presence of meningitis may impact the duration of antibiotics provided (Shane 2017). Given these reasons, this review will consider neonatal meningitis in association with bacteraemia.

However, differentiating neonatal sepsis from other morbidities such as respiratory disease can be challenging. Blood culture sensitivity is often low in neonates secondary to low colony count bacteraemia and limited blood volume available for culture (Connell 2007; Schelonka 1996). Suspected neonatal sepsis with negative blood culture results will be considered in the review titled "Shorter versus longer duration antibiotic regimens for treatment of suspected neonatal sepsis" (Legge 2023).

Description of the intervention

The appropriate use of antibiotics has resulted in a reduction in neonatal mortality from sepsis (Benitz 1999; Mukhopadhyay 2019; Zaidi 2011). Antibiotics are the most commonly prescribed medication for neonates in the hospital setting (Clark 2006; Stark 2022). Rates of antibiotic use in very low birth weight infants have been reported to be between 85% and 94% (Cordero 2003; Ting 2016). Neonates pose unique challenges that influence antibiotic use, including the diagnostic difficulty of identifying infection and frequent occurrence of clinical symptoms of sepsis in the absence of positive cultures (Gkentzi 2019). Adverse effects of antibiotics may be related to dose or duration of treatment, and include hypersensitivity reactions, nephrotoxicity or ototoxicity with aminoglycosides or vancomycin, and bone marrow suppression with cephalosporins (Mukhopadhyay 2019).

Treatment is usually commenced empirically when infection or sepsis is suspected. Targeted treatment is continued once the source of infection is confirmed or a causative pathogen is isolated. Choice of antibiotic is based on the clinical setting, timing of onset of symptoms, suspected site of infection, and geographical and antimicrobial resistance considerations. Two Cochrane reviews concluded that there is currently insufficient evidence to recommend one antibiotic regimen over another for both EOS (Korang 2021a), and LOS (Korang 2021b). EOS is commonly treated with a combination of a beta-lactam antibiotic (benzylpenicillin or ampicillin) and an aminoglycoside (gentamicin) (Dong 2015; Manan 2016; NICE 2021; Vergnano 2011). Third-generation cephalosporins are used for EOS in the instance of suspected meningitis, if aminoglycosides are contraindicated or if gram-negative bacteria are isolated (NICE 2021). Third-generation cephalosporins are generally not recommended as initial treatment due to their association with increased risk of *Candida* infection (Benjamin 2006), and emergence of antibiotic resistance (de Man 2000; Murki 2010). LOS has been recommended to be treated with narrow-spectrum antibiotics guided by local susceptibility and resistance data (Isaacs 2006). Common treatment regimens include a penicillin such as flucloxacillin plus gentamicin (Dong 2015; NICE 2021; Vergnano 2011). Alternatives include the use of vancomycin for resistant CoNS (Dong 2015), and cephalosporins (Al-Taiar 2013; Cortese 2016). In the instance of antibiotic-resistant organisms, targeted treatment with appropriate antibiotics such as carbapenems for treatment of extended spectrum beta-lactamase producing gram-negative bacilli is required (Shane 2017).

The recommended duration of antibiotic treatment is variable, commonly being between seven and 21 days (Camacho-Gonzalez 2013; Cortese 2016). Recommendations include a minimum of seven days for bloodstream infections, 14 days for gram-positive meningitis and 21 days for gram-negative meningitis (Shane 2017). Guidelines recommend evaluating duration of antibiotics for suspected EOS at 36 hours and continuing treatment for seven days or longer in culture-proven sepsis, or if sepsis has been strongly suspected (NICE 2021). For LOS, recommendations are to review at 48 hours, and recommended duration of ongoing treatment is variable from less than seven days to much longer treatment times depending on source and pathogen isolated (NICE 2021).

How the intervention might work

Optimising antibiotic treatment includes selecting the appropriate agent(s), route, dose and dosing regimen with regard to optimal pharmacokinetics (Mukhopadhyay 2019), and duration of therapy to both prevent antibiotic resistance and complications, and minimise the risk of infection recurrence.

A reduction in the duration of antibiotic treatment for management of neonatal infection may have significant benefits, including reduction in antibiotic resistance, healthcare costs, and complications associated with prolonged antibiotic use and intravascular access. Higher antibiotic use rates have been associated with higher rates of neonatal mortality, periventricular leukomalacia (PVL), chronic lung disease (CLD) and retinopathy of prematurity (ROP) in infants without culture-proven sepsis, with outcomes worse for those with the highest antibiotic use rates (Ting 2016). There is evidence to suggest that shorter antibiotic courses are appropriate for treatment of neonatal infection, with one retrospective observational study finding that five days of vancomycin for management of uncomplicated CoNS in very low birthweight infants is associated with satisfactory outcomes compared to longer treatment courses (Linder 2013). Additionally, there are studies in children indicating that four days of ceftriaxone for management of bacterial meningitis is a safe alternative to seven days of treatment (Roine 2000), and there is no difference in mortality or recurrence of infection between 10 and 14 days of intravenous antibiotics for uncomplicated gram-negative bacteraemia (Park 2014). Following a systematic review of the available literature, evidence-based recommendations for the duration of antibiotic therapy for bacteraemia, pneumonia, meningitis and other site infections are available for children (McMullan 2016). However, no such review exists for the neonatal population.

The liberal prescription of antibiotics has led to the emergence of global antibiotic resistance, which poses a major threat to human health (Antimicrobial Resistance Collaborators 2022). Globally, an estimated 214,000 neonatal sepsis deaths are attributable to resistant pathogens each year (Laxminarayan 2016). This is particularly true in neonatal units in low- and middle-income countries, with reports of between 40% and 80% of gram-negative organisms resistant to ampicillin, third-generation cephalosporins or gentamicin (Al-Taiar 2013; Viswanathan 2012). However, it is also a challenge in high-income countries. One cross-over trial carried out in two similar neonatal intensive care units using separate empirical antibiotic regimens demonstrated an 18-fold incidence of resistant bacteria in the ampicillin/cefotaxime group compared to the penicillin/tobramycin group (de Man 2000).

In addition to antimicrobial resistance, the prolonged and broad-spectrum use of antibiotics in neonates is associated with

increased risk of LOS, necrotising enterocolitis (NEC), fungal infections including invasive candidiasis, and mortality (Cotten 2006; Cotten 2009; Kuppala 2011; Lee 2013). While poorer neurodevelopmental outcomes including cerebral palsy, cognitive impairment as measured by Bayley Scales of Infant Development, hearing and visual impairment, are reported for infants with neonatal sepsis (Bakhuizen 2014), there was a higher risk of neurodevelopmental impairment reported for extremely preterm infants treated with antibiotics for five days or more for a blood culture-negative condition, compared to unaffected infants (Mukhopadhyay 2021), suggesting a negative impact due to antibiotic exposure. Recurrence rates of LOS have been reported to be 21% to 30% (Makhoul 2002; Stoll 2002; Tsai 2014b), and while uncommon, infections including septic arthritis, osteomyelitis and abscess occur secondary to haematogenous bacterial spread and are more likely in neonates who have had a central venous catheter (Isaacs 2014; Pittard 1976). In episodes of recurrent LOS, up to 70% of causative pathogens differ from the causative pathogen in the initial infection, suggesting that most recurrent infection is secondary to re-infection rather than relapse of the initial episode (Tsai 2014b). However, relapse of initial infection occurs particularly in the setting of gram-negative meningitis (Anderson 1990). It must be considered that a longer duration of antibiotic treatment may reduce relapse rates and recurrent infections from under treatment, and that duration of treatment may also be influenced by initial response to treatment.

The prolonged use of antibiotics requires longer periods of indwelling catheter use with associated complications. Peripheral intravenous extravasation occurs up to 70% of the time, while rates of peripherally inserted central catheter (PICC) infiltration range from 1% to 16% (Wu 2012). Severe extravasation causing necrosis or cellulitis is less common (Wu 2012). Phlebitis is reported to occur in 4% to 23% of newborns with PICC lines (Wu 2012). However, less common, more serious complications of central catheters include dysrhythmias, pleural or pericardial effusion, thromboembolism and occlusion (Wu 2012).

Antibiotic use in the neonatal period is also associated with altered gut microbiome (Reyman 2022), which is associated with an increased risk of wheezing and infantile colic in infancy (Alm 2008; Oosterloo 2018). The prolonged use of antibiotics may prolong hospital stays and increase healthcare costs.

Why it is important to do this review

Neonatal sepsis results in substantial morbidity and mortality. The vulnerability of the neonatal population and the diagnostic challenges associated with neonatal sepsis result in the empirical use of antibiotics. A conservative approach based on clinician experience is frequently taken with respect to the duration of antibiotic treatment. Reduction in the duration of antibiotic treatment may decrease antibiotic resistance, secondary fungal infections, NEC, duration of indwelling intravenous lines, and subsequent line complications, length of hospital stay and healthcare costs. However, it needs to be determined that this is not at the expense of safety, increased infection recurrence rates, and increased morbidity and mortality.

This Cochrane review will aim to assess the efficacy and safety of shorter versus longer duration antibiotic regimens for the treatment of culture-positive sepsis in neonates.

OBJECTIVES

To assess the safety and effectiveness of shorter versus longer duration antibiotic regimens for the treatment of culture-positive neonatal sepsis with or without meningitis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) comparing different durations of antibiotic therapy for treatment of culture-positive neonatal sepsis with or without meningitis. We will exclude cross-over RCTs as the design is inappropriate to the clinical context. We will exclude quasi-RCTs because they are inherently prone to bias, and cluster-RCTs as they are unlikely to have enough neonatal intensive care units of randomisation for reliable evidence.

We will include studies reported as full-text. We will consider unpublished studies or studies published as abstract only as eligible for inclusion in the review if the study author can confirm methods and data.

Types of participants

We will include term and preterm neonates admitted to a healthcare setting and receiving systemic antibiotic treatment (intravenous or intramuscular) for neonatal culture-positive sepsis with or without meningitis.

We will define a neonate as an infant aged up to and including 28 days' corrected age. We will include studies assessing antibiotic treatment of culture-positive sepsis with or without meningitis.

We will define neonatal culture-positive sepsis by clinical or laboratory criteria, or both, consistent with sepsis (as defined by study authors) combined with growth of bacteria in blood culture.

EOS will include infection occurring before 72 hours after birth and LOS will include infection occurring 72 hours or greater after birth (NICE 2021).

Meningitis as defined by the study authors.

We will define central line-associated bloodstream infection as a primary bacteraemia in a neonate with a central line in situ within the 48-hour period before development of the bacteraemia and not related to an infection at another site.

For studies that include only a subset of relevant participants, we will contact study authors to obtain relevant data. We will include the study if the majority of the participants are eligible.

We will exclude studies that include infants with sepsis secondary to fungaemia or viral infection.

Types of interventions

We will include any antibiotic regimens (intravenous or intramuscular administration), with or without the co-administration of antibiotic, antifungal or antiviral medications. Studies will only be eligible if co-administration of antibiotic, antifungal or antiviral medications is to both the treatment and

control groups. We will compare shorter versus longer duration regimens of antibiotic therapy, defined as a minimum difference in treatment time of two days.

We will consider studies in the following treatment time epochs for comparison.

1. Fewer than seven days versus seven days or greater to fewer than 10 days
2. Seven days or greater to fewer than 10 days versus 10 days or greater to fewer than 14 days
3. 10 days or greater to fewer than 14 days versus 14 days or greater to fewer than 21 days
4. 14 days or greater to fewer than 21 days versus 21 days or greater
5. We will report studies with duration of treatment for both groups within the same time epoch separately.

We will report all treatment arms of each study in the 'Characteristics of included studies' table.

Types of outcome measures

The following outcome measures do not form part of the eligibility criteria.

Primary outcomes

1. **All-cause mortality** prior to hospital discharge.
2. **Treatment failure** defined as either of the following within 14 days of ceasing antibiotics:
   a. recurrence of clinical sepsis (as defined by study authors) with recommencement of antibiotics; or
   b. growth of identical bacteria on blood culture.

Secondary outcomes

1. **Infant mortality** to 12 months of age (latest time reported).
2. **Days of hospital stay** to initial discharge.
3. **Secondary bacterial infection** may include septic arthritis, osteomyelitis, abscess or other as defined by the study authors during or after antibiotic treatment within three months of hospital discharge.
4. **New-onset fungal infection** is defined as growth of a pathogenic fungal organism in a sterile site (blood culture, urine or CSF) within three months of hospital discharge.
5. **Growth of extended spectrum resistance or multi-resistant bacteria** on blood, urine or CSF culture, or surface swab after commencement of antibiotic treatment and within three months of hospital discharge.
6. [a]**Necrotising enterocolitis (NEC)** (defined as Bell's stage II or greater, or any grade requiring surgery) (Bell 1978).
7. [a]**Severe complications of intravenous therapy** including extravasation injury and thromboembolism, as defined by study authors.
8. [a]**Complications of antibiotic therapy** including nephrotoxicity, ototoxicity, cytopenia, diarrhoea, fever or rash.
9. [a]**Duration (days) of respiratory support** including non-invasive respiratory support (e.g. continuous positive airway pressure) or mechanical ventilation.
10. [a]**Mechanical ventilation** defined as the requirement for mechanical ventilation by endotracheal tube.
11. **Neurosensory disability in survivors**; measured beyond one-year postmenstrual age (PMA) and defined as any of:
    a. cerebral palsy (Gross Motor Functioning Classification System (GMFCS) category 2 to 5);
    b. developmental delay more than two standard deviations below the population mean on standardised testing;
    c. blindness (visual acuity less than 6/60);
    d. deafness (hearing impairment requiring amplification).
12. **Chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD)** defined as the need for respiratory support (supplemental oxygen or assisted ventilation, or both) at 36 weeks' PMA.
13. [a]**Intraventricular haemorrhage (IVH)**, defined as grade III and IV (Papile 1978).
14. [a]**Cystic periventricular leukomalacia (PVL)** diagnosed on ultrasound or magnetic resonance imaging.
15. [a]**Retinopathy of prematurity (ROP)**, defined as stage 3 or greater.

[a]The outcomes will be reported up to hospital discharge unless otherwise specified.

Search methods for identification of studies

An Information Specialist (MF) wrote the search strategy for Ovid MEDLINE, which is presented in Appendix 1. This strategy will be translated for other databases, using appropriate syntax and controlled vocabulary. Methodological filters will be used to limit retrieval to RCTs and systematic reviews. Searches for systematic reviews on topics related to this review will be limited to the past two years. Searches for trials will be conducted without language, publication year, publication type or publication status restrictions.

We will document searches in sufficient detail to inform a study flow (PRISMA) diagram (Page 2021a; Page 2021b).

Electronic searches

We will search the following databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL), via CRS
2. Ovid MEDLINE(R) All
3. Ovid Embase (1974 to date of search)
4. Epistemonikos (www.epistemonikos.org)

Searching other resources

We will identify trial registration records using CENTRAL and by independent searches of:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov);
2. World Health Organization International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int/Default.aspx).

We will identify conference abstracts using CENTRAL and the following conference websites:

1. PAS (Pediatric Academic Societies) (www.pas-meeting.org/past-abstracts/);

2. European Society for Paediatric Infectious Diseases (www.espid.org/content.aspx?Group=archives&Page=archive_aem).

We will screen the reference lists of included studies and related systematic reviews for studies not identified by the database searches.

We will search for errata or retractions for included studies published on PubMed (www.ncbi.nlm.nih.gov/pubmed).

We will contact the corresponding investigator for information if we identify any relevant unpublished trials. We will consider unpublished studies or studies published as abstract only as eligible for inclusion in the review if the study author can confirm methods and data.

Data collection and analysis

We will collect information regarding the method of randomisation, blinding, intervention, stratification and whether the trial was single or multi-centre for each included study. We will note information regarding trial participants including GA, corrected GA, birthweight, diagnosis of sepsis, EOS, LOS, meningitis, CLABSI, Gram stain or type of pathogenic bacteria or both on culture (blood or CSF, or both), method of antibiotic administration, length of antibiotic administration (days) and low- or high-income country setting. We will analyse the clinical outcomes noted above in Types of outcome measures.

Where studies have multiple publications, we will collate the reports of the same study, so that each study, rather than each report, is the unit of interest for the review, and such studies have a single identifier with multiple references.

In the event we identify and include studies by review authors, we will have two independent review authors undertake the following: screening and selection, data extraction, risk of bias assessment and assess certainty of evidence. In the event multiple review authors are involved in an included study, we will recruit independent colleagues to undertake these tasks.

Selection of studies

We will manage search results using Endnote (Endnote). We will remove duplicates using both bibliographic management software and Covidence.

We will assess titles and abstracts in two ways: using Cochrane's Screen4Me (S4M) system (S4M), and by author screening. The S4M system includes three levels of assessment for identifying non-RCT records: Known Assessments, RCT Classifier, and Cochrane Crowd; assessments and further information on S4M are available in the literature (Marshall 2018; Noel-Storr 2020; Noel-Storr 2021; Thomas 2021). We will document the S4M process in the review.

Two review authors (AL, JM) will independently screen title and abstracts remaining after S4M classification. Two review authors (AL, JM) will independently screen the full-texts of any references included following title/abstract screening. We will resolve disagreements by discussion, or by consulting a third review author (AG).

We will document the reasons for excluding studies during full-text review in the 'Characteristics of excluded studies' table. We will also provide any information we can obtain about ongoing studies. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Page 2021a; Page 2021b).

Data extraction and management

Two review authors (AL and AG) will independently extract data using a data extraction form integrated with a modified version of the Cochrane Effective Practice and Organisation of Care Group data collection checklist (EPOC). We will pilot the form within the review team using a sample of included studies. We will extract the following characteristics from each included study.

1. Administrative details: study author(s); published or unpublished; year of publication; year in which study was conducted; presence of vested interests by study authors; details or other relevant papers cited.
2. Study characteristics: study registration, study design type, study setting, number of study centres and location, informed consent, ethics approval, completeness of follow-up (e.g. greater than 80%).
3. Participants: number randomised, number lost to follow-up/withdrawn, number analysed, mean GA, GA range, mean chronological age, chronological age range, sex, birthweight, bacterial organism culture results or Gram stain of bacterial organism isolated, or both, diagnosis of sepsis, meningitis or CLABSI, inclusion and exclusion criteria.
4. Interventions: mode of antibiotic administration, duration of administration, type of antibiotic(s), dose of antibiotic(s).
5. Outcomes as specified above under Types of outcome measures.

We will resolve any disagreements by discussion.

We will describe ongoing studies identified by our search and document available information such as the primary author, research question(s), methods and outcome measures, together with an estimate of the anticipated reporting date in the 'Characteristics of ongoing studies' table.

Should any queries arise, or in cases where additional data are required, we will contact study investigators/authors for clarification. Two review authors (AL and AG) will use Cochrane statistical software for data entry (RevMan 2024).

Assessment of risk of bias in included studies

Two of three review authors (AL or JM and AG) will independently assess the risk of bias (low, high or unclear) of all included trials using the Cochrane RoB 1 tool for the following domains (Higgins 2011).

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

We will resolve any disagreements by discussion or by consulting a third review author (AG). See Appendix 2 for a more detailed description of the risk of bias for each domain.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results using risk ratios (RR) and risk differences (RD) with 95% confidence intervals (CIs). We will calculate the number needed to treat for an additional beneficial outcome (NNTB), or the number needed to treat for an additional harmful outcome (NNTH) with 95% CIs if there is a significant reduction (or increase) in RD.

Continuous data

For continuous data, we will use the mean difference (MD) when trials measured outcomes in the same way. We will use the standardised mean difference (SMD) to combine trials that measured the same outcome but used different methods. Where trials reported continuous data as median and interquartile range (IQR) and data passed the test of skewness, we will convert median to mean and estimate the standard deviation as IQR/1.35.

If data are not reported in a format that can be entered directly into a meta-analysis, we will convert them to the required format using the information in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a).

Unit of analysis issues

We will perform the primary analysis per individual as randomised.

If any trials have multiple arms that are compared against the same control condition that will be included in the same meta-analysis, we will either combine groups to create a single pair-wise comparison, or select one pair of interventions and exclude the others.

Dealing with missing data

We intend to carry out analysis on an intention-to-treat basis for all included outcomes. Whenever possible, we will analyse all participants in the treatment group to which they were randomised, regardless of the actual treatment received. We will assess losses by performing sensitivity analysis according to risk of bias. We will address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We will describe the clinical diversity and methodological variability of the evidence narratively and in tables. Tables will include data on study characteristics such as design features, population characteristics and intervention details.

To assess statistical heterogeneity, we will visually inspect forest plots and describe the direction and magnitude of effects and the degree of overlap between CIs. We will also consider the statistics generated in forest plots that measure statistical heterogeneity. We will use the I^2 statistic to quantify inconsistencies between the trials in each analysis. We will also consider the P value from the Chi^2 test to assess if this heterogeneity is significant ($P < 0.1$). If we identify substantial heterogeneity, we will report the finding and explore possible explanatory factors using prespecified subgroup and sensitivity analysis.

We will grade the degree of heterogeneity as:

1. 0% to 40% might not represent important heterogeneity;
2. 30% to 60% may represent moderate heterogeneity;
3. 50% to 90% may represent substantial heterogeneity;
4. more than 75% may represent considerable heterogeneity.

We will use a rough guideline to interpret the I^2 value rather than a simple threshold, and our interpretation will take into account an understanding that measures of heterogeneity (I^2 statistic and Tau) will be estimated with high uncertainty when the number of studies is small (Deeks 2022).

Assessment of reporting biases

We will assess reporting bias by comparing the stated primary outcomes and secondary outcomes and reported outcomes. Where study protocols are available, we will compare these to the full publications to determine the likelihood of reporting bias. We will document studies using the interventions in a potentially eligible infant population but not reporting on any of the primary and secondary outcomes in the 'Characteristics of included studies' tables.

We will use funnel plots to screen for publication bias where there are a sufficient number of studies (10 or more) reporting the same outcome. If publication bias is suggested by a significant asymmetry of the funnel plot on visual assessment, we will incorporate this in our assessment of certainty of evidence (Egger 1997). If our review includes fewer than 10 studies, the ability to detect publication bias will be largely diminished, and we will simply note our inability to rule out possible publication bias or small-study effects.

Data synthesis

If we identify multiple studies that we consider to be sufficiently similar, we will perform meta-analysis using Review Manager (RevMan 2024). For categorical outcomes, we will calculate the typical estimates of RR and RD, each with its 95% CI; for continuous outcomes, we will calculate the MD or the SMD, each with its 95% CI. We will use a fixed-effect model to allow for weighting according to study size to combine data where it is reasonable to assume that studies were estimating the same underlying treatment effect. We will explore heterogeneity, and if present, we will try to explain this based on the different study characteristics and subgroup analyses. We will explore bias through sensitivity analyses. We will use forest plots to provide graphical representation of the study data. If we judge meta-analysis to be inappropriate, we will refer to methodological guidance from Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2023), and synthesis without meta-analysis (SWiM) reporting guidance (Campbell 2020). We will create a table with studies ordered by risk of bias, and calculate standardised effect estimates for each study. This table will be modelled on the worked example, Table 12.4.b from the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2023). A forest plot will be used to provide graphical representation of the data.

Subgroup analysis and investigation of heterogeneity

We will interpret tests for subgroup differences in effects with caution, given the potential for confounding with other study characteristics and the observational nature of the comparisons (Deeks 2022). In particular, subgroup analyses with fewer than

five studies per category are unlikely to be adequate to ascertain valid differences in effects and will not be highlighted in our results. When subgroup comparisons are possible, we will conduct stratified meta-analysis and a formal statistical test for interaction to examine subgroup differences that could account for effect heterogeneity (e.g. Cochran's Q test, meta-regression) (Deeks 2022).

We plan to carry out the following subgroup analyses of factors that may contribute to heterogeneity in the effects of the intervention.

1. Preterm infants (less than 37 weeks' GA) or low birthweight (less than 2500 g); term infants (37 weeks' GA or greater) or birthweight (2500 g or greater).
2. Type of organism: gram-positive bacteria; gram-negative bacteria.
3. Type of infection: neonatal culture-positive sepsis without meningitis; neonatal culture-positive sepsis with meningitis; CLABSI.
4. Timing of sepsis: EOS (before 72 hours); LOS (after 72 hours).

We will use the following outcomes in subgroup analyses if there are enough studies reporting to support valid subgroup comparisons (at least five studies per subgroup).

1. All-cause mortality prior to hospital discharge.
2. Treatment failure within 14 days of ceasing antibiotics.
3. Days of hospital stay to initial discharge.
4. New-onset fungal infection defined as growth of a pathogenic fungal organism in a sterile site (blood culture, urine or CSF) within three months of hospital discharge.
5. Growth of extended spectrum resistance or multi-resistant bacteria after commencement of antibiotic treatment and within three months of hospital discharge.
6. Severe complications of intravenous therapy prior to hospital discharge.
7. Neurosensory disability in survivors measured beyond one-year PMA.

Sensitivity analysis

We will explore methodological heterogeneity using sensitivity analyses. We will perform sensitivity analyses by excluding trials of lower quality based on a lack of any of the following: adequate randomisation, allocation concealment and less than 10% loss to follow-up. As the intervention is unlikely to be adequately blinded, we will not include blinding as a criterion in the sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence for the following (clinically relevant) outcomes.

1. All-cause mortality prior to hospital discharge.
2. Treatment failure within 14 days of ceasing antibiotics.
3. Days of hospital stay to initial discharge.
4. New-onset fungal infection defined as growth of a pathogenic fungal organism in a sterile site (blood culture, urine or CSF) within three months of hospital discharge.
5. Growth of extended spectrum resistance or multi-resistant bacteria after commencement of antibiotic treatment and within three months of hospital discharge.
6. Severe complications of intravenous therapy prior to hospital discharge.
7. Neurosensory disability in survivors measured beyond one-year PMA.

Two of three review authors (AL, AG or DO) will independently assess the certainty of evidence for each of the outcomes above. We will consider evidence from RCTs as high certainty, downgrading the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We will use GRADEpro GDT to create a summary of findings table to report the certainty of evidence for shorter versus longer duration antibiotic regimens for the following comparisons.

1. Fewer than seven days versus seven days or greater to fewer than 10 days
2. Seven days or greater to fewer than 10 days versus 10 days or greater to fewer than 14 days
3. 10 days or greater to fewer than 14 days versus 14 days or greater to fewer than 21 days
4. 14 days or greater to fewer than 21 days versus 21 days or greater
5. We will report studies with duration of treatment for both groups within the same time epoch separately

The GRADE approach results in an assessment of the certainty of a body of evidence in one of the following four grades.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We will report results with reference to Cochrane's MECIR Manual for the reporting of new Cochrane intervention reviews. We will report results in accordance with recommended narrative statements as described in Chapter 15, Table 15.6.b of the C*ochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022).

We will justify all decisions to downgrade the certainty of the evidence using footnotes and make comments to aid the reader's understanding of the review where necessary.

Conduct of the review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

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Editorial and peer-reviewer contributions

Cochrane Neonatal supported the authors in the development of this protocol.

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Mohan Pammi, Professor, Department of Pediatrics, Baylor College of Medicine
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Ben Ridley, Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Ben Ridley, Central Editorial Service
- Copy Editor (copy editing and production): Anne Lawson, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Katarzyna Wróblewska-Seniuk, MD, PhD, Assistant Professor; II Department of Neonatology, Poznan University of Medical Sciences (clinical/content review), Brian Duncan (consumer review), Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review), Yuan Chi, Beijing Health Technology Co, Ltd; McMaster University (search review). One additional peer reviewer provided clinical peer review but chose not to be publicly acknowledged.

REFERENCES

Additional references

Al-Taiar 2013

Al-Taiar A, Hammoud MS, Cuiqing L, Lee JK, Lui KM, Nakwan N, et al. Neonatal infections in China, Malaysia, Hong Kong and Thailand. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2013;**98**(3):F249-55. [DOI: 10.1136/archdischild-2012-301767] [PMID: 2942104]

Alm 2008

Alm B, Erdes L, Mollborg P, Pettersson R, Norvenius SG, Aberg N, et al. Neonatal antibiotic treatment is a risk factor for early wheezing. *Pediatrics* 2008;**121**(4):697-702. [DOI: 10.1542/peds.2007-1232] [PMID: 18381533]

Anderson 1990

Anderson SG, Gilbert GL. Neonatal gram negative meningitis: a 10-year review, with reference to outcome and relapse of infection. *Journal of Paediatrics and Child Health* 1990;**26**(4):212-6. [DOI: 10.1111/j.1440-1754.1990.tb02432.x] [PMID: 2257183]

Antimicrobial Resistance Collaborators 2022

Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022;**399**(10325):629-55. [DOI: 10.1016/S0140-6736(21)02724-0] [PMID: 35065702]

ANZNN 2023

Australian and New Zealand Neonatal Network. ANZNN 2023 Data Dictionary. Sydney, Australia, 2022. anznn.net/dataresources/datadictionaries (accessed prior to 17 June 2024).

Bakhuizen 2014

Bakhuizen SE, de Haan TR, Teune MJ, van Wassenaer-Leemhuis AG, van der Heyden JL, van der Ham DP, et al. Meta-analysis shows that infants who have suffered neonatal sepsis face an increased risk of mortality and severe complications. *Acta Paediatrica* 2014;**103**(12):1211-8. [DOI: 10.1111/apa.12764] [PMID: 25073543]

Bell 1978

Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Annals of Surgery* 1978;**187**(1):1-7. [DOI: 10.1097/00000658-197801000-00001] [PMID: 413500]

Benitz 1999

Benitz WE, Gould JB, Druzin ML. Antimicrobial prevention of early-onset group B streptococcal sepsis: estimates of risk reduction based on a critical literature review. *Pediatrics* 1999;**103**(6):e78. [PMID: 10353975]

Benjamin 2006

Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al, National Institute of Child Health, Human Development Neonatal Research Network. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics* 2006;**117**(1):84-92. [DOI: 10.1542/peds.2004-2292] [PMID: 16396864]

Boghossian 2013

Boghossian NS, Page GP, Bell EF, Stoll BJ, Murray JC, Cotten CM, et al, Eunice Kennedy Shriver National Institute of Child Health, Human Development Neonatal Research Network. Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. *Journal of Pediatrics* 2013;**162**(6):1120-4, 1124 e1. [DOI: 10.1016/j.jpeds.2012.11.089] [PMID: 23324523]

Cailes 2018

Cailes B, Kortsalioudaki C, Buttery J, Pattnayak S, Greenough A, Matthes J, et al, neonIN network. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2018;**103**(6):F547-53. [DOI: 10.1136/archdischild-2017-313203] [PMID: 29208666]

Camacho-Gonzalez 2013

Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. *Pediatric Clinics of North America* 2013;**60**(2):367-89. [DOI: 10.1016/j.pcl.2012.12.003] [PMID: 23481106]

Campbell 1992

Campbell JR, Diacovo T, Baker CJ. Serratia marcescens meningitis in neonates. *Pediatric Infectious Disease Journal* 1992;**11**(10):881-6. [DOI: 10.1097/00006454-199210000-00015] [PMID: 1408491]

Campbell 2020

Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;**368**:l6890. [DOI: 10.1136/bmj.l6890] [PMID: 31948937]

Clark 2006

Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics* 2006;**117**(6):1979-87. [DOI: 10.1542/peds.2005-1707] [PMID: 16740839]

Coggins 2023

Coggins SA, Edwards EM, Flannery DD, Gerber JS, Horbar JD, Puopolo KM. Serratia infection epidemiology among very preterm infants in the neonatal intensive care unit. *Pediatric Infectious Disease Journal* 2023;**42**(2):152-8. [DOI: 10.1097/INF.0000000000003736] [PMID: 36638403]

Connell 2007

Connell TG, Rele M, Cowley D, Buttery JP, Curtis N. How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. *Pediatrics* 2007;**119**(5):891-6. [DOI: 10.1542/peds.2006-0440] [PMID: 17473088]

Cordero 2003

Cordero L, Ayers LW. Duration of empiric antibiotics for suspected early-onset sepsis in extremely low birth weight infants. *Infection Control and Hospital Epidemiology* 2003;**24**(9):662-6. [DOI: 10.1086/502270] [PMID: 14510248]

Cortese 2016

Cortese F, Scicchitano P, Gesualdo M, Filaninno A, De Giorgi E, Schettini F, et al. Early and late infections in newborns: where do we stand? A review. *Pediatrics and Neonatology* 2016;**57**(4):265-73. [DOI: 10.1016/j.pedneo.2015.09.007] [PMID: 26750406]

Cotten 2006

Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K, Benjamin DK Jr, National Institute for Child Health, Human Development Neonatal Research Network. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. *Pediatrics* 2006;**118**(2):717-22. [DOI: 10.1542/peds.2005-2677] [PMID: 16882828]

Cotten 2009

Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sanchez PJ, et al, NICHD Neonatal Research Network. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics* 2009;**123**(1):58-66. [DOI: 10.1542/peds.2007-3423] [PMID: 19117861]

Covidence [Computer program]

Covidence. Version accessed 8 September 2023. Melbourne, Australia: Veritas Health Innovation. Available at covidence.org.

de Man 2000

de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacilli. *Lancet* 2000;**355**(9208):973-8. [DOI: 10.1016/s0140-6736(00)90015-1] [PMID: 10768436]

Deeks 2022

Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook/archive/v6.3.

Dong 2015

Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2015;**100**(3):F257-63. [DOI: 10.1136/archdischild-2014-306213] [PMID: 25425653]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34. [DOI: 10.1136/bmj.315.7109.629] [PMID: 9310563]

El-Naggar 2019

El-Naggar W, Afifi J, McMillan D, Toye J, Ting J, Yoon EW, et al, Canadian Neonatal Network Investigators II. Epidemiology of meningitis in Canadian neonatal intensive care units. *Pediatric Infectious Disease Journal* 2019;**38**(5):476-80. [DOI: 10.1097/INF.0000000000002247] [PMID: 30986789]

Endnote [Computer program]

Endnote. Version X9. Philadelphia (PA): Clarivate, 2023. Available at https://endnote.com/.

EPOC

Cochrane Effective Practice and Organisation of Care (EPOC). Cochrane Effective Practice and Organisation of Care Review Group. Data collection check list. methods.cochrane.org/sites/methods.cochrane.org.bias/files/uploads/EPOC%20Data%20Collection%20Checklist.pdf (accessed 8 September 2023).

Flannery 2022

Flannery DD, Edwards EM, Coggins SA, Horbar JD, Puopolo KM. Late-onset sepsis among very preterm infants. *Pediatrics* 2022;**150**(6):e2022058813. [DOI: 10.1542/peds.2022-058813] [PMID: 36366916.]

Fleischmann 2021

Fleischmann C, Reichert F, Cassini A, Horner R, Harder T, Markwart R, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. *Archives of Disease in Childhood* 2021;**106**(8):745-52. [DOI: 10.1136/archdischild-2020-320217] [PMID: 33483376]

Fleischmann-Struzek 2018

Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. *Lancet Respiratory Medicine* 2018;**6**(3):223-30. [DOI: 10.1016/S2213-2600(18)30063-8] [PMID: 29508706]

Gkentzi 2019

Gkentzi D, Dimitriou G. Antimicrobial stewardship in the neonatal intensive care unit: an update. *Current Pediatric Reviews* 2019;**15**(1):47-52. [DOI: 10.2174/1573396315666190118101953] [PMID: 30657041]

Gordon 2006

Gordon A, Isaacs D. Late onset neonatal gram-negative bacillary infection in Australia and New Zealand: 1992–2002. *Pediatric Infectious Disease Journal* 2006;**25**(1):25-9. [DOI: 10.1097/01.inf.0000195628.35980.2e] [PMID: 16395098]

GRADEpro GDT [Computer program]

GRADEpro GDT. Version accessed 8 September 2023. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at https://gradepro.org.

Hammoud 2012

Hammoud MS, Al-Taiar A, Thalib L, Al-Sweih N, Pathan S, Isaacs D. Incidence, aetiology and resistance of late-onset neonatal sepsis: a five-year prospective study. *Journal of Paediatrics and Child Health* 2012;**48**(7):604-9. [DOI: 10.1111/j.1440-1754.2012.02432.x] [PMID: 22404730]

Higgins 2011

Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). Cochrane, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Higgins 2022a

Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook/archive/v6.3.

Isaacs 1995

Isaacs D, Barfield CP, Grimwood K, McPhee AJ, Minutillo C, Tudehope DI. Systemic bacterial and fungal infections in infants in Australian neonatal units. *Medical Journal of Australia* 1995;**162**(4):198-201. [DOI: 10.5694/j.1326-5377.1995.tb126024.x] [PMID: 7877542]

Isaacs 1996

Isaacs D, Barfield C, Clothier T, Darlow B, Diplock R, Ehrlich J, et al. Late-onset infections of infants in neonatal units. *Journal of Paediatrics and Child Health* 1996;**32**(2):158-61. [DOI: 10.1111/j.1440-1754.1996.tb00914.x] [PMID: 9156527]

Isaacs 2006

Isaacs D. Unnatural selection: reducing antibiotic resistance in neonatal units. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2006;**91**(1):F72-4. [DOI: 10.1136/adc.2005.074963] [PMID: 16371394]

Isaacs 2014

Isaacs D. Evidence-Based Neonatal Infections. Hoboken (NJ): John Wiley & Sons, 2014. [PRINT ISBN: 9780470654606]

Jenkins 2017

Jenkins A, Geldenhuys C, Bekker A, Dramowski A. Central-line-associated bloodstream infections in a resource-limited South African neonatal intensive care unit. *South African Medical Journal* 2017;**107**(9):758-62. [DOI: 10.7196/SAMJ.2017.v107i9.12124] [PMID: 28875883]

Kayange 2010

Kayange N, Kamugisha E, Mwizamholya DL, Jeremiah S, Mshana SE. Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza-Tanzania. *BMC Pediatrics* 2010;**10**:39. [DOI: 10.1186/1471-2431-10-39] [PMID: 20525358]

Korang 2021a

Korang SK, Safi S, Nava C, Gordon A, Gupta M, Greisen G, et al. Antibiotic regimens for early-onset neonatal sepsis. *Cochrane Database of Systematic Reviews* 2021, Issue 5. Art. No: CD013837. [DOI: 10.1002/14651858.CD013837.pub2]

Korang 2021b

Korang SK, Safi S, Nava C, Greisen G, Gupta M, Lausten-Thomsen U, et al. Antibiotic regimens for late-onset neonatal sepsis. *Cochrane Database of Systematic Reviews* 2021, Issue 5. Art. No: CD013836. [DOI: 10.1002/14651858.CD013836.pub2]

Kuppala 2011

Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. *Journal of Pediatrics* 2011;**159**(5):720-5. [DOI: 10.1016/j.jpeds.2011.05.033] [PMID: 21784435]

Lawn 2014

Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, et al, Lancet Every Newborn Study Group. Every newborn: progress, priorities, and potential beyond survival. *Lancet* 2014;**384**(9938):189-205. [DOI: 10.1016/S0140-6736(14)60496-7] [PMID: 24853593]

Laxminarayan 2016

Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen JA, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016;**387**(10014):168-75. [DOI: 10.1016/S0140-6736(15)00474-2] [PMID: 26603918]

Leal 2012

Leal YA, Alvarez-Nemegyei J, Velazquez JR, Rosado-Quiab U, Diego-Rodriguez N, Paz-Baeza E, et al. Risk factors and prognosis for neonatal sepsis in southeastern Mexico: analysis of a four-year historic cohort follow-up. *BMC Pregnancy and Childbirth* 2012;**12**:48. [DOI: 10.1186/1471-2393-12-48] [PMID: 22691696]

Lee 2013

Lee JH, Hornik CP, Benjamin DK Jr, Herring AH, Clark RH, Cohen-Wolkowiez M, et al. Risk factors for invasive candidiasis in infants >1500 g birth weight. *Pediatric Infectious Disease Journal* 2013;**32**(3):222-6. [DOI: 10.1097/INF.0b013e3182769603] [PMID: 23042050]

Legge 2023

Legge A, Gordon A, Middleton JL, Fiander M, Cracknell J, Osborn DA. Shorter versus longer duration antibiotic regimens for treatment of suspected neonatal sepsis. Protocol under development. To be published in the Cochrane Database of Systematic Reviews: https://www.cochrane.library.com.

Linder 2013

Linder N, Lubin D, Hernandez A, Amit L, Ashkenazi S. Duration of vancomycin treatment for coagulase-negative Staphylococcus sepsis in very low birth weight infants. *British Journal of Clinical Pharmacology* 2013;**76**(1):58-64. [DOI: 10.1111/bcp.12053] [PMID: 23210694]

Liu 2016

Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development

Goals. *Lancet* 2016;**388**(10063):3027-35. [DOI: 10.1016/S0140-6736(16)31593-8] [PMID: 27839855]

Makhoul 2002

Makhoul IR, Sujov P, Smolkin T, Lusky A, Reichman B. Epidemiological, clinical, and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: a national survey. *Pediatrics* 2002;**109**(1):34-9. [DOI: 10.1542/peds.109.1.34] [PMID: 11773539]

Manan 2016

Manan MM, Ibrahim NA, Aziz NA, Zulkifly HH, Al-Worafi YM, Long CM. Empirical use of antibiotic therapy in the prevention of early onset sepsis in neonates: a pilot study. *Archives of Medical Science* 2016;**12**(3):603-13. [DOI: 10.5114/aoms.2015.51208] [PMID: 27279855]

Marshall 2018

Marshall IJ, Noel-Storr AH, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying randomized controlled trials: an evaluation and practitioner's guide. *Research Synthesis Methods* 2018;**9**(4):602-14. [DOI: 10.1002/jrsm.1287] [PMID: 29314757]

McKenzie 2023

McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions *V*ersion 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

McMullan 2016

McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, et al, ANZPID-ASAP group. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. *Lancet. Infectious Diseases* 2016;**16**(8):e139-52. [DOI: 10.1016/S1473-3099(16)30024-X] [PMID: 27321363]

Milton 2022

Milton R, Gillespie D, Dyer C, Taiyari K, Carvalho MJ, Thomson K, et al. Neonatal sepsis and mortality in low-income and middle-income countries from a facility-based birth cohort: an international multisite prospective observational study. *Lancet Global Health* 2022;**10**(5):e661-72. [DOI: 10.1016/S2214-109X(22)00043-2] [PMID: 35427523]

Mukhopadhyay 2019

Mukhopadhyay S, Wade KC, Puopolo KM. Drugs for the prevention and treatment of sepsis in the newborn. *Clinics in Perinatology* 2019;**46**(2):327-47. [DOI: 10.1016/j.clp.2019.02.012] [PMID: 31010563]

Mukhopadhyay 2021

Mukhopadhyay S, Puopolo KM, Hansen NI, Lorch SA, DeMauro SB, Greenberg RG, et al, NICHD Neonatal Research Network. Neurodevelopmental outcomes following neonatal late-onset sepsis and blood culture negative conditions. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2021;**106**(5):467-73. [PMID: 33478957]

Murki 2010

Murki S, Jonnala S, Mohammed F, Reddy A. Restriction of cephalosporins and control of extended spectrum beta-lactamase producing gram negative bacteria in a neonatal intensive care unit. *Indian Pediatrics* 2010;**47**(9):785-8. [DOI: 10.1007/s13312-010-0118-y] [PMID: 21048261]

NICE 2021

National Institute for Health and Care Excellence. Neonatal infection: antibiotics for prevention and treatment. 2021. Available from www.nice.org.uk/guidance/ng195.

Noel-Storr 2020

Noel-Storr AH, Dooley G, Wisniewski S, Glanville J, Thomas J, Cox S, et al. Cochrane Centralised Search Service showed high sensitivity identifying randomised controlled trials: a retrospective analysis. *Journal of Clinical Epidemiology* 2020;**127**:142-50. [DOI: 10.1016/j.jclinepi.2020.08.008] [PMID: 32798713]

Noel-Storr 2021

Noel-Storr AH, Dooley G, Elliott J, Steele E, Shemilt I, Mavergames C, et al. An evaluation of Cochrane Crowd found that crowdsourcing produced accurate results in identifying randomised trials. *Journal of Clinical Epidemiology* 2021;**4356**(21):130-9. [DOI: 10.1016/j.jclinepi.2021.01.006] [PMID: 33476769]

O'Grady 2011

O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al, Healthcare Infection Control Practices Advisory Committee. Guidelines for the prevention of intravascular catheter-related infections. *American Journal of Infection Control* 2011;**39**(4 Suppl 1):S1-34. [DOI: 10.1016/j.ajic.2011.01.003] [PMID: 21511081]

Okascharoen 2005

Oskascharoen C, Sirinavin S, Thakkinstian, Kitayaporn D, Supapanachart S. A bedside prediction-scoring model for late-onset neonatal sepsis. *Journal of Perinatology* 2005;**25**(12):778-83. [PMID: 16281050]

Okascharoen 2007

Okascharoen C, Hui C, Cairnie J, Morris AM, Kirpalani H. External validation of bedside prediction score for diagnosis of late-onset neonatal sepsis. *Journal of Perinatology* 2007;**27**(8):496-501. [PMID: 17568757]

Oosterloo 2018

Oosterloo BC, van Elburg RM, Rutten NB, Bunkers CM, Crijns CE, Meijssen CB, et al. Wheezing and infantile colic are associated with neonatal antibiotic treatment. *Pediatric Allergy and Immunology* 2018;**29**(2):151-8. [DOI: 10.1111/pai.12857] [PMID: 29314334]

Page 2021a

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71. [DOI: 10.1136/bmj.n71]

Page 2021b

Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;**372**:n160. [DOI: 10.1136/bmj.n160]

Papile 1978

Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *Journal of Pediatrics* 1978;**92**(4):529-34. [PMID: 305471]

Park 2014

Park SH, Milstone AM, Diener-West M, Nussenblatt V, Cosgrove SE, Tamma PD. Short versus prolonged courses of antibiotic therapy for children with uncomplicated gram-negative bacteraemia. *Journal of Antimicrobial Chemotherapy* 2014;**69**(3):779-85. [DOI: 10.1093/jac/dkt424] [PMID: 24159153]

Perin 2022

Perin J, Mulick A, Yeung D, Villavicencio F, Lopez G, Strong KL, et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the sustainable development goals. *Lancet. Child and Adolescent Health* 2022;**6**(2):106-15. [DOI: 10.1016/S2352-4642(21)00311-4] [PMID: 34800370]

Pittard 1976

Pittard WB, Thullen JD, Fanaroff AA. Neonatal septic arthritis. *Journal of Pediatrics* 1976;**68**(4):621-4. [DOI: 10.1016/s0022-3476(76)80022-4] [PMID: 943494]

Polin 2012

Polin RA, Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. *Pediatrics* 2012;**129**(5):1006-15. [PMID: 22547779]

RevMan 2024 [Computer program]

Review Manager (RevMan). Version 7.7.2. The Cochrane Collaboration, 2024. Available at https://revman.cochrane.org.

Reyman 2022

Reyman M, van Houten MA, Watson RL, Chu ML, Arp K, de Waal WJ, et al. Effects of early-life antibiotics on the developing infant gut microbiome and resistome: a randomized trial. *Nature Communications* 2022;**13**(1):893. [DOI: 10.1038/s41467-022-28525-z] [PMID: 35173154]

Roine 2000

Roine I, Ledermann W, Foncea LM, Banfi A, Cohen J, Peltola H. Randomized trial of four vs. seven days of ceftriaxone treatment for bacterial meningitis in children with rapid initial recovery. *Pediatric Infectious Disease Journal* 2000;**19**(3):219-22. [DOI: 10.1097/00006454-200003000-00009] [PMID: 10749463]

Rosenthal 2009

Rosenthal VD. Central line-associated bloodstream infections in limited-resource countries: a review of the literature. *Clinical Infectious Diseases* 2009;**49**(12):1899-907. [DOI: 19911941] [PMID: 10.1086/648439]

S4M

Cochrane. Screen4Me. https://training.cochrane.org/online-learning/good-practice-resources-cochrane-authors/screen4me (accessed 11 September 2023).

Sands 2022

Sands K, Spiller OB, Thomson K, Portal EA, Iregbu KC, Walsh TR. Early-onset neonatal sepsis in low- and middle-income countries: current challenges and future opportunities. *Infection and Drug Resistance* 2022;**15**:933-46. [DOI: 10.2147/IDR.S294156] [PMID: 35299860]

Schelonka 1996

Schelonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DP. Volume of blood required to detect common neonatal pathogens. *Journal of Pediatrics* 1996;**129**(2):275-8. [DOI: 10.1016/s0022-3476(96)70254-8] [PMID: 8765627]

Schlapbach 2011

Shlapbach LJ, Aebischer M, Adams M, Natalucci G, Bonhoeffer J, Latzin P, et al, Swiss Neonatal Network and Follow-Up Group. Impact of sepsis on neurodevelopmental outcome in a Swiss national cohort of extremely premature infants. *Pediatrics* 2011;**128**(2):e348-57. [DOI: 10.1542/peds.2010-3338] [PMID: 21768312]

Schrag 2016

Schrag SJ, Farley MM, Petit S, Reingold A, Weston EJ, Pondo T, et al. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. *Pediatrics* 2016;**138**(6):e20162013. [DOI: 10.1542/peds.2016-2013] [PMID: 27940705]

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from https://gdt.gradepro.org/app/handbook/handbook.html.

Schünemann 2022

Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Available from training.cochrane.org/handbook/archive/v6.3.

Shane 2017

Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. *Lancet* 2017;**390**(10104):1770-80. [DOI: 10.1016/S0140-6736(17)31002-4] [PMID: 2843465]

Singer 2016

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**(8):801-10. [DOI: 10.1001/jama.2016.0287] [PMID: 26903338]

Stark 2022

Stark A, Smith PB, Hornik CP, Zimmerman KO, Hornik CD, Pradeep S, et al. Medication use in the neonatal intensive care unit and changes from 2010 to 2018. *Journal of Pediatrics* 2022;**240**:66-71.e4. [DOI: 10.1016/j.jpeds.2021.08.075] [PMID: 34481808]

Stoll 2002

Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* 2002;**110**(2 Pt 1):285-91. [DOI: 10.1542/peds.110.2.285] [PMID: 12165580]

Stoll 2011

Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, van Meurs KP, et al, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics* 2011;**127**(5):817-26. [PMID: 10.1542/peds.2010-2217] [PMID: 21518717]

Thaver 2009

Thaver D, Zaidi AK. Burden of neonatal infections in developing countries: a review of evidence from community-based studies. *Pediatric Infectious Disease Journal* 2009;**28**(1 Suppl):S3-9. [DOI: 10.1097/INF.0b013e3181958755] [PMID: 19106760]

Thomas 2021

Thomas J, McDonald S, Noel-Storr AH, Shemilt I, Elliott J, Mavergames C, et al. Machine learning reduces workload with minimal risk of missing studies: development and evaluation of an RCT classifier for Cochrane reviews. *Journal of Clinical Epidemiology* 2021;**133**:140-51. [DOI: 10.1016/j.jclinepi.2020.11.003] [PMID: 33171275]

Thomas 2022

Thomas R, Ondongo-Ezhet C, Motsoaledi N, Sharland M, Clements M, Velaphi S. Incidence and all-cause mortality rates in neonates infected with carbapenem resistant organisms. *Frontiers in Tropical Diseases* 2022;**3**:832011. [DOI: 10.3389/fitd.2022.832011] [URL: https://www.frontiersin.org/articles/10.3389/fitd.2022.832011/full]

Ting 2016

Ting JY, Synnes A, Roberts A, Deshpandey A, Dow K, Yoon EW, et al, Canadian Neonatal Network Investigators. Association between antibiotic use and neonatal mortality and morbidities in very low-birth-weight infants without culture-proven sepsis or necrotizing enterocolitis. *JAMA Pediatrics* 2016;**170**(12):1181-7. [DOI: 10.1001/jamapediatrics.2016.2132] [PMID: 27775765]

Tsai 2014a

Tsai MH, Hsu JF, Chu SM, Lien R, Huang HR, Chiang MC, et al. Incidence, clinical characteristics and risk factors for adverse outcome in neonates with late-onset sepsis. *Pediatric Infectious Diseases Journal* 2014;**33**(1):e7-13. [DOI: 10.1097/INF.0b013e3182a72ee0] [PMID: 23899966]

Tsai 2014b

Tsai MH, Chu SM, Lee CW, Hsu JF, Huang HR, Chiang MC, et al. Recurrent late-onset sepsis in the neonatal intensive care unit: incidence, clinical characteristics and risk factors. *Clinical Microbiology and Infection* 2014;**20**(11):O928-35. [DOI: 10.1111/1469-0691.12661] [PMID: 24796697]

Vergnano 2005

Vergnano S, Sharland M, Kazembe P, Mwansambo C, Heath PT. Neonatal sepsis: an international perspective. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2005;**90**(3):F220-4. [DOI: 10.1136/adc.2002.022863] [PMID: 15846011]

Vergnano 2011

Vergnano S, Menson E, Kennea N, Embleton N, Russell AB, Watts T, et al. Neonatal infections in England: the NeonIN surveillance network. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2011;**96**(1):F9-14. [DOI: 10.1136/adc.2009.178798] [PMID: 20876594]

Viswanathan 2012

Viswanathan R, Singh AK, Basu S, Chatterjee S, Sardar S, Isaacs D. Multi-drug resistant gram negative bacilli causing early neonatal sepsis in India. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2012;**97**(3):F182-7. [PMID: 10.1136/archdischild-2011-300097] [PMID: 22155619]

Wu 2012

Wu J, Mu D. Vascular catheter-related complications in newborns. *Journal of Paediatrics and Child Health* 2012;**48**(2):E91-5. [DOI: 10.1111/j.1440-1754.2010.01934.x] [PMID: 21199061]

Wynn 2016

Wynn JL. Defining neonatal sepsis. *Current Opinion in Pediatrics* 2016;**28**(2):135-40. [DOI: 10.1097/MOP.0000000000000315] [PMID: 26766602]

Zaidi 2009

Zaidi AK, Thaver D, Ali SA, Khan TA. Pathogens associated with sepsis in newborns and young infants in developing countries. *Pediatric Infectious Disease Journal* 2009;**28**(1 Suppl):S10-8. [DOI: 10.1097/INF.0b013e3181958769] [PMID: 19106757]

Zaidi 2011

Zaidi AK, Ganatra HA, Syed S, Cousens S, Lee AC, Black, et al. Effect of case management on neonatal mortality due to sepsis and pneumonia. *BMC Public Health* 2011;**11**(Suppl 3):S13. [DOI: 10.1186/1471-2458-11-S3-S13] [PMID: 21501430]

Zipursky 2019

Zipursky AR, Yoon EW, Emberley J, Bertelle V, Kanungo J, Lee SK, et al, Canadian Neonatal Network Investigators. Central line-associated blood stream infections and non-central line-associated blood stream infections surveillance in Canadian tertiary care neonatal intensive care units. *Journal of Pediatrics* 2019;**208**:176-82.e. [DOI: 10.1016/j.jpeds.2018.12.011] [PMID: 30853200]

APPENDICES

Appendix 1. Search strategy MEDLINE

We will use the following search strategy for two related reviews:

Shorter versus longer duration antibiotic regimens for treatment of culture-positive neonatal sepsis (CD015555)

Shorter versus longer duration antibiotic regimens for treatment of suspected neonatal sepsis (CD016006)

The concept of treatment duration is not searchable in any reliable way, so we did not attempt it. Similarly, searching for culture-positive versus suspected sepsis is not possible; thus, sepsis (and related conditions) have been searched.

The selection of keywords and subject headings for selected drugs is based on input from a clinical author who provided names of drugs most frequently used to treat sepsis in the neonate population. We have not endeavoured to translate to keywords the names of every antibiotic found in the Anti-bacterial MeSH explosion.

We did not use the heading anti-infective agents after reviewing all narrower terms with a clinical author, we determined the substances were not antibiotics.

Some drug categories, such as quinolones do not fall under the anti-bacterial MeSH but, again, were named by clinicians as used in sepsis treatment.

Meningitis and strep infections have been used as cognate terms for sepsis because clinical authors considered these infections closely related to the occurrence of sepsis.

#	**Searches** Ovid MEDLINE(R) All
1	exp sepsis/ or exp bacteremia/ or exp fungemia/ or exp shock, septic/
2	(sepsis or septic* or bacter?emi* or candidemia* or endotox?emi* or fungemi* or pyemia* or pyohemia* or pyaemia*).ti,ab,kw,kf.
3	(Blood* adj3 (infect* or poison*)).ti,ab,kw,kf.
4	exp Meningitis, Bacterial/
5	(meningiti* adj2 bacterial*).ti,ab,kw,kf.
6	(Meningiti* adj2 (Escherichia* coli or Haemophilu* or Listeria* or Meningococca* or penicillin-resistant or pneumococca*)).ti,ab,kw,kf.
7	exp Streptococcal Infections/ or exp Streptococcus/
8	streptococc*.ti,ab,kw,kf.
9	Klebsiella/ or Enterobacter/ or exp Pseudomonas/
10	(Klebsiella* or Enterobacter* or Pseudomona*).ti,ab,kw,kf.
11	or/1-10 [Sepsis and associated]
12	exp anti-bacterial agents/
13	Anti-Infective Agents/ [Not exploding; MeSH says to prefer specifics-- which we have done; subterms are irrelevant per clinician review]
14	(antibiotic* or antibacterial* or anti-bacteria* or antiinfecti* or anti-infecti* or bactericid*).ti,ab,kw,kf.

(Continued)

15	exp Quinolines/
16	(quinolone? or quinoline?).ti,ab,kw,kf.
17	exp Sulfonamides/
18	sulfonamide*.ti,ab,kw,kf.
19	exp Penicillins/ or exp beta-Lactams/ or beta-Lactamase Inhibitors/
20	(penicillin* or ampicillin* or Pentrexyl or Polycillin* or Ukapen or Amcill or Amcill or omnipen or ((beta Lactamase* or beta-Lactamase) adj2 (inhibitor* or antagonist?))).ti,ab,kw,kf.
21	(Benzylpenicillin or Coliriocilina or Crystapen or "Or-pen" or Parcillin or Pekamin or Pengesod or Penibiot or Penilevel or Peniroger or Pfizerpen or Sodiopen or Sodipen or Unicilina or Ursopen or Van-Pen-G or Benpen or Floxacillin* or Fluorochloroxacillin* or Flucloxacillin* or beta lactamase? or beta-lactamase? or Carbapenem* or Cephalosporin* or Cefotaxim* or Cephotaxim* or Cefotax-im or Biosint or Cefradil or Taporin or Fotexina or Benaxima or Claforan or Primafen or Klaforan or Meropenem* or Merrem or ronem or penem or (Piperacillin adj2 Tazobactam) or Tazocin or Tazocillin or Zosyn or Tazocel or Monobactam*).ti,ab,kw,kf. [Selected pencillins/beta lactamase]
22	Aminoglycosides/
23	Aminoglycoside*.ti,ab,kw,kf.
24	Gentamicins/
25	(Gentamycin* or Garamycin or Gentacycol or Gentavet or Genticin or G-Myticin or G Myticin or GMyticin or Gentamicin).ti,ab,kw,kf.
26	Vancomycin/
27	(Vancomycin* or AB-Vancomycin* or Vanco Azupharma or Diatracin or VANCO-cell or Vanco-saar or Vancocin or Vancocine or Vancomicin*).ti,ab,kw,kf.
28	Metronidazole/
29	Metronidazol*.ti,ab,kw,kf.
30	Teicoplanin/ [glycopeptide]
31	(Teichomycin* or targocid?).ti,ab,kw,kf.
32	Glycopeptides/ [Proteins which contain carbohydrate groups attached covalently to the polypep-tide chain. The protein moiety is the predominant group with the carbohydrate making up only a small percentage of the total weight.]
33	Glycopeptid*.ti,ab,kw,kf.
34	or/12-33 [Antibiotics and related agents]
35	exp Infant, Newborn/ or Intensive Care, Neonatal/ or Intensive Care Units, Neonatal/ or Gestational Age/
36	(babe or babes or baby* or babies or gestational age? or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or neo-nat* or newborn* or new born? or newly born or pre-mature or pre-mature or pre-matures or prematures or prematurity or pre-maturity or preterm or

(Continued)

	preterms or pre term? or preemie or preemies or premies or premie or VLBW or VLBWI or VLBW-I or VLBWs or LBW or LBWI or LBWs or ELBW or ELBWI or ELBWs or NICU or NICUs).ti,ab,kw,kf.
37	or/35-36 [Filter: Neonatal Population 04-2022-MEDLINE]
38	randomized controlled trial.pt.
39	controlled clinical trial.pt.
40	randomized.ab.
41	placebo.ab.
42	clinical trials as topic.sh.
43	randomly.ab.
44	trial.ti.
45	or/38-44 [Cochrane HSSS-SP Maximizing RCT Filter]
46	(quasirandom* or quasi-random* or random*).ti,ab,kw,kf.
47	(control* adj2 (group? or trial? or study)).ti,ab,kw,kf.
48	or/46-47 [Additional terms to increase sensitivity]
49	exp animals/ not humans/
50	(or/45,48) not 49 [RCT Filter]
51	meta-analysis/ or "systematic review"/ or network meta-analysis/ [/ finds same as.pt. syntax]
52	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,k-f,kw.
53	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
54	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
55	(hand search* or handsearch*).ti,ab,kf,kw.
56	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,k-f,kw.
57	meta-analysis as topic/ or network meta-analysis/
58	(meta analy* or metanaly* or meta regression* or metaregression*).ti,ab,kf,kw.
59	(medline or cochrane or pubmed or medlars or embase or cinahl).ab.
60	(cochrane or systematic review?).jw.
61	or/51-60 [SR filter-Medline; based on CADTH https://searchfilters.cadth.ca]
62	11 and 34 and 37 and 50 [Sepsis AND Antibiotics AND Neonates AND RCT]

(Continued)

63	11 and 34 and 37 and 61 and ("2022" or "2023").yr. [SR Results]
64	or/62-63 [All results Medline]

Appendix 2. Risk of bias 1 tool

Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we will categorise the method used to generate the allocation sequence as:

1. low risk (any truly random process, e.g. random number table; computer random number generator);
2. high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
3. unclear risk.

Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we will categorise the method used to conceal the allocation sequence as:

1. low risk (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
2. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
3. unclear risk.

Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or class of outcomes. We will categorise the methods as:

1. low risk, high risk or unclear risk for participants; and
2. low risk, high risk or unclear risk for personnel.

Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorise the methods used to blind outcome assessment. We will assess blinding separately for different outcomes or class of outcomes. We will categorise the methods as:

1. low risk for outcome assessors;
2. high risk for outcome assessors; or
3. unclear risk for outcome assessors.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorise the methods as:

1. low risk (less than 20% missing data);
2. high risk (20% or greater missing data); or
3. unclear risk.

Selective reporting bias. Are reports of the study free of the suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

1. low risk (where it is clear that all the study's prespecified outcomes and all expected outcomes of interest to the review were reported);
2. high risk (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified outcomes of interest and were reported incompletely and so could not be used; the study failed to include results of a key outcome that would have been expected to have been reported); or
3. unclear risk.

Other sources of bias. Was the study apparently free of other problems that could put it at high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process).

We will assess whether each study was free of other problems that could put it at risk of bias as:

1. low risk;
2. high risk;
3. unclear risk.

If needed, we plan to explore the impact of the level of bias by undertaking sensitivity analyses.

CONTRIBUTIONS OF AUTHORS

DO and AG conceived the review.

AL, DO, AG, JM, JC and MF developed the protocol.

MF developed the search strategy.

All review authors provided feedback on the content of the protocol.

DECLARATIONS OF INTEREST

AL: none.

AG: is a member and past chair of the Sepsis Prevention quality improvement group in New South Wales, Australia.

DO: is a Senior Editor for Cochrane Neonatal; however, he did not participate in the editorial process for this protocol.

JM: is employed by a non-profit organisation, Royal Prince Alfred Hospital, NSW Health, as a research co-ordinator. Royal Prince Alfred Hospital, NSW Health, does not have an interest in the topic of interest.

MF: is a Managing Editor and Information Specialist for Cochrane Neonatal; however, she did not participate in the editorial process for this protocol.

JC: is a Managing Editor for Cochrane Neonatal; however, she did not participate in the editorial process for this protocol.

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