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PhD Thesis

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Interventions for neonatal and pediatric sepsis

Four systematic reviews with meta-analysis

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PREFACE

This PhD thesis was carried out from October 2018 to the present, at the Copenhagen Trial Unit, Centre for Clinical Intervention Research, at Copenhagen University Hospital − Rigshospitalet. Before the PhD, I made a knowledge gap analysis for the treatment of pediatric sepsis. I identified Cochrane reviews which have not been updated for 14-15 year. I reviewed treatment guidelines for adults and children to identify gaps that need further investigation.

The primary aim of the PhD was to evaluate the clinical effects of different interventions commonly used for neonatal and pediatric sepsis. These include the choice of empirical antibiotics and glucocorticosteroids.

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Finally, I would like to thank my fiancé Christine Esmann Mulvad for the endless support and understanding throughout my PhD. I dedicate this thesis to my children Zoe, Audrina, and Zion.

List of publications

This thesis is based on the results reported in the following publications:

Project I: Antibiotics for neonatal sepsis

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

Paper Ib: **Korang SK**, Safi S, Nava C, Greisen G, Gupta M, Lausten-Thomsen U, Jakobsen JC. Antibiotic regimens for late-onset neonatal sepsis. Cochrane Database of Systematic Reviews 2021, Issue 5. Art. No.:CD013836. DOI: 10.1002/14651858.CD013837.pub2.

Project II: Antibiotics for hospital-acquired pneumonia in neonates and children

Paper II: **Korang SK**, Nava C, Nygaard U, Jakobsen JC. Antibiotics for hospital-acquired pneumonia in neonates and children. Cochrane Database of Systematic Reviews TBD, Issue TBD. Art. No.: CD013864. DOI: 10.1002/14651858.CD013864

Project III: **Glucocorticosteroids for paediatric sepsis**

Paper III: **Korang SK**, Safi S, Gluud C, Jakobsen JC. The effects of adding glucocorticosteroids to standard care for children with sepsis. A systematic review of randomized clinical trials with meta-analysis and Trial Sequential Analysis [Internet]. 2021 [cited 2021 Apr 18]. Available from: https://www.researchsquare.com/article/rs-275296/v1

All publications are available in the supplementary material.

Abstract

Background

Sepsis is defined as life-threatening organ dysfunction presumed to be caused by a dysregulated host response to infection. Sepsis can lead to significant morbidity and mortality. In children, sepsis is a common cause of critical illness and is one of the ten leading causes of death.

Antibiotics are used to treat the underlying bacterial cause of sepsis and hence, a vital part of the first-line treatment for children with sepsis. Other potential add-on therapies for treating the dysregulated host response include fluid therapy, oxygen, and glucocorticosteroids. The latter are thought to block some of the immunological pathways involved in the progression from infection to sepsis. Despite being a relatively common disease, the effects of different antibiotic regimens for neonates with sepsis had not been systematically evaluated since 2005. In addition, glucocorticosteroids have been thoroughly assessed for adults, but the focus on these drugs for children has been lacking.

Therefore, the purpose of this PhD was to conduct several systematic reviews to assess the evidence for the clinical effects of some of these interventions used to treat neonates and children with sepsis.

Methods

We conducted three Cochrane reviews and a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials. We included trials that compared; antibiotic regimens for neonatal sepsis; glucocorticosteroids with placebo for children with sepsis; and antibiotic regimens for children with hospital-acquired pneumonia.

We searched electronic databases such as the Cochrane Central Register of Controlled Trials, MEDLINE Ovid (PubMed), Embase Ovid, CINAHL, LILACS, Science Citation Index EXPANDED, and Conference Proceedings Citation Index.

Our outcomes varied between the reviews, but we always assessed all-cause mortality and serious adverse events.

Published protocols preceded all the systematic reviews according to the Cochrane Handbook and the PRISMA guidelines. These protocols thoroughly describe our planned methods for all the reviews.

Results

Our three Cochrane reviews only included up to five trials each, randomising between 84 and 865 participants to different antibiotic regimens for early-onset neonatal sepsis, late-onset neonatal sepsis, and hospital-acquired pneumonia. All trials were underpowered (at risks of random errors). All trials were at an overall high risk of bias (at risks of systemic errors). As the included trials made different comparisons of antibiotic regimens, it was not possible to pool the data of two or more trials, and therefore not possible to conduct the planned meta-analyses and Trial Sequential Analysis.

Our systematic review assessing the effects of adding glucocorticosteroids to standard care for sepsis in children found that dexamethasone might result in a large reduction of serious adverse events (relative risk (RR) 0.68, 95% confidence interval (CI) 0.53 to 0.86; P = 0.001, very low certainty of evidence) and ototoxicity (RR 0.63, 95% CI 0.45 to 0.88; P = 0.007, low certainty of evidence) for children with meningitis. However, the cumulative Z curves in the Trial Sequential Analyses did not reach the trial sequential monitoring boundaries of the diversity-adjusted required information size. Meta-analyses showed that the effects of adding glucocorticosteroids for children with sepsis with a mixed focus were very uncertain for any of our outcomes.

Conclusions

Our systematic reviews concluded that we did not have enough evidence from randomised clinical trials to suggest that one antibiotic regimen was superior to another for the empirical treatment of neonatal sepsis and hospital-acquired pneumonia in children.

All the included trials were underpowered and, therefore, not able to detect realistic differences between antibiotic regimens on clinically important outcomes such as all-cause mortality and serious adverse events.

Therefore, current treatment guidelines for children with sepsis cannot be based solely on evidence from existing randomised clinical trials. Until further trials are conducted, guidelines could also be based on observational studies and local antibiotic resistance patterns.

Randomised clinical trials represent the highest level of evidence. But since the most probable bacteria and resistance pattern varies over time and between geographical regions, the results of such trials may become outdated and inappropriate when finished. Therefore, it might not be possible for such trials to show one superior antibiotic regimen for the empirical treatment of sepsis. Future guidelines will consequently also need to rely on recent observational data to determine the most appropriate empirical treatment for sepsis in children. Due to many potential empirical antibiotic regimens, pair-wise comparisons might not be a feasible method of determining which antibiotic regimen should be the first-line treatment. Network meta-analysis and methods for combining observational data with evidence from randomised clinical trials could potentially provide more pragmatic guidance for future trials and guidelines.

Although glucocorticosteroids are being widely used for septic shock, current evidence from randomised clinical trials does not support the use of glucocorticosteroids for children sepsis or septic shock. The glucocorticosteroid, dexamethasone, may decrease serious adverse events and ototoxicity for children with sepsis due to meningitis. The theoretical benefit of glucocorticosteroids is thought to be for children with septic shock. The trials assessing glucocorticosteroids for septic shock in children are, however, significantly underpowered. Based on our results, the use of glucocorticosteroids for sepsis in children still needs to be examined in well-powered randomised placebo-controlled clinical trials.

Resumé

Baggrund

Sepsis defineres som livstruende organdysfunktion forårsaget af en dysreguleret værtsreaktion på infektion. Sepsis kan medføre betydelig morbiditet og mortalitet. Sepsis en af de ti vigtigste dødsårsager hos børn.

Antibiotika anvendes til behandling af den underliggende årsag til sepsis og er dermed en vigtig del af førstevalgsbehandlingen af nyfødte og børn med sepsis. Andre supplerende behandlinger for det dysreguleret værtsreaktion omfatter væsketerapi, ilt og glukokortikosteroider. Sidstnævnte menes at blokere nogle af de immunologiske mekanismer, der er involveret i udviklingen fra infektion til sepsis.

Selv om sepsis er en relativt almindelig sygdom, er virkningerne af forskellige antibiotikabehandlinger til nyfødte med sepsis ikke blevet evalueret siden 2005. Glukokortikosteroider er blevet grundigt undersøgt for voksne, men der har manglet fokus på anvendelsen af denne intervention hos børn.

Derfor var formålet med denne ph.d.-afhandling at foretage flere systematiske reviews for at vurdere de kliniske virkninger af nogle af disse vigtige interventioner, der anvendes til behandling af nyfødte og børn med sepsis og hospitals-erhvervet lungebetændelse.

Metoder

Vi sammenlignede antibiotikabehandlinger for neonatal sepsis, glukokortikosteroider med placebo til børn med sepsis, og antibiotikabehandlinger til børn med hospitals-erhvervet lungebetændelse.

Vi gjorde dette ved hjælp af tre Cochrane-reviews og et systematiske review med meta-analyse og Trial Sequential Analysis. Alle de systematiske reviews blev forudgået af publicerede protokoller i overensstemmelse med Cochrane Handbook og PRISMA-retningslinjerne. Disse protokoller beskriver detaljeret vores planlagte metoder for alle reviews.

Resultater

Vores tre Cochrane reviews inkluderede kun op til fem forsøg per review som i alt randomiserede mellem 84 og 865 deltagere til forskellige antibiotikabehandlinger. Alle de inkluderede forsøg var således med utilstrækkelig power (med risiko for tilfældige fejl) og havde generelt en høj risiko for bias (med risiko for systematiske fejl). Da de inkluderede forsøg sammenlignede forskellige antibiotikaregimer, var det ikke muligt at gennemføre de planlagte meta-analyser og Trial Sequential Analyser på grund af manglende relevante data.

Vores systematiske gennemgang, der vurderede virkningerne af at tilføje glukokortikosteroider til standardbehandling af sepsis hos børn, viste, at dexamethason kunne medføre en stor reduktion af alvorlige hændelser (relativ risiko (RR) 0,68, 95% konfidensinterval (CI) 0,53 til 0,86; P = 0,001, meget lav evidenssikkerhed) og høretab (RR 0,63, 95% CI 0,45 til 0,88; P = 0,007, lav evidenssikkerhed) for børn med meningitis. Vores Trial Sequential Analyser viste at de foreliggende forsøg ikke nåede op på den krævede informationsstørrelse. Meta-analyser viste ingen evidens for en effekt af at tilføje glukokortikosteroider til børn med sepsis med blandet fokus for nogen af vores udfald. Disse forsøg var alle med utilstrækkelig power.

Konklusion

Vores systematiske undersøgelser konkluderede, at vi ikke havde tilstrækkelig dokumentation fra randomiserede kliniske forsøg til at konkludere, om et antibiotikaregime var bedre end et andet til empirisk behandling af neonatal sepsis og hospitals-erhvervet lungebetændelse hos børn. Alle de inkluderede forsøg havde for lidt power og var derfor ikke i stand til at påvise forskelle mellem antibiotikaregimer med hensyn til klinisk vigtige resultater som fx dødelighed af alle årsager og alvorlige uønskede hændelser.

Derfor kan de nuværende retningslinjer for behandling af børn med sepsis ikke udelukkende baseres på dokumentation fra eksisterende randomiserede kliniske forsøg. I afventningen af sådanne forsøg bliver retningslinier også nød til at baseres på observationelle studier og lokale antibiotikaresistensmønstre.

Randomiserede kliniske forsøg repræsenterer det højeste evidensniveau. Men da de mest sandsynlige bakterier og resistensmønstre varierer over tid og mellem geografiske regioner, kan resultaterne af sådanne forsøg blive forældede når de er afsluttet. Derfor vil det måske aldrig

være muligt for sådanne forsøg at påvise ét overlegent antibiotikaregime til empirisk behandling af sepsis. Fremtidige retningslinjer vil derfor også skulle baseres på nyere observationel data for at fastlægge den mest hensigtsmæssige empiriske behandling af sepsis hos børn. På grund af de mange potentielle empiriske antibiotikabehandlinger er parvise sammenligninger måske ikke en gennemførlig metode til at bestemme, hvilken antibiotikabehandling der bør være førstevalg. Netværks meta-analyse og metoder til at kombinere observationel data med evidens fra randomiserede kliniske forsøg kunne potentielt give mere pragmatisk vejledning til fremtidige retningslinjer.

Selv om glukokortikosteroider anvendes i vid udstrækning til behandling af septisk chok, understøtter den nuværende dokumentation fra randomiserede kliniske forsøg ikke brugen af glukokortikosteroider til børn med sepsis eller septisk chok. Glukokortikosteroidet dexamethason kan mindske alvorlige bivirkninger og høretab hos børn med sepsis som følge af meningitis. Den teoretiske fordel ved glukokortikosteroider menes dog at være til børn med septisk chok. De forsøg, der vurderer glukokortikosteroider til behandling af septisk chok hos børn, er imidlertid betydeligt underdimensionerede til at kunne svare sufficient på spørgsmålet. På baggrund af vores resultater skal brugen af glukokortikosteroider ved sepsis hos børn stadig undersøges i randomiserede placebo-kontrollerede kliniske forsøg.

List of abbreviations

CI: Confidence interval

DARIS: diversity-adjusted required information size

MD: Mean difference

NEC: Necrotising enterocolitis

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines

RCT: Randomised clinical trials

RR: Risk ratio

RRR: Relative risk reduction

TSA: Trial Sequential Analysis

Objectives

The overall objective of this PhD project was to summarize the current evidence for some of the commonly used interventions for sepsis and hospital-acquired pneumonia in neonates and children. These included antibiotics and glucocorticosteroids for the empirical treatment of sepsis.

Project I

The objective of this project was to compare different antibiotic regimens for the empirical treatment of early-onset and late-onset neonatal sepsis.

Project II

The objective of this project was to compare different antibiotic regimens for the empirical treatment of children with hospital-acquired pneumonia.

Project III

To assess the benefits and harms of adding glucocorticosteroids to standard care for sepsis in children.

Introduction

Infections can span from being a self-limiting disease to life-threatening sepsis with multiorgan failure (1). Infections in childhood are very common (2). Although most infections are asymptomatic or are self-limiting, some infections develop into more severe infections (2). When a child presents with fever or other signs of infection, one of the fears among parents is a serious progression of the infection. For clinicians, this would mean the progression to sepsis.

A report from 2013 showed that each year 2.3 million children under the age of five years lost their lives to infections globally (3). The incidence of sepsis and the risk of mortality are highest in neonates, young children, and the elderly (4–6). Geographical regions also play a role, as the morbidity and mortality are higher in low- and middle-income countries. Still, sepsis is also an important challenge in high-income countries sepsis (3). This has caused WHO to list the burden of sepsis as a key issue for global health (7).

The definition of sepsis for adults has recently changed to become “life-threatening organ dysfunction caused by a dysregulated host response to infection” (8). In addition to the deleterious effects of the pathogen, sepsis is characterized as a condition in which the immune system responds to the infection in a way that injures the hosts' tissues and organs (8). A clear consensus definition has not been established for neonates and children. Similar definitions are most likely underway for children and neonates (9).

Sepsis is more common in neonates than older children (3). This may be due to not fully developed innate and adaptive immune systems in neonates, especially in preterm neonates (10–14). Sepsis can be caused by a lot of different pathogens such as bacteria, viruses, fungi, and parasites (7). It is a potential complication of preventable infection with a primary focus in the airways, gastrointestinal tract, urinary tract, skin, central nerve system, or a bloodstream infection. Observational studies have shown that the lungs are the most common focus of infection among children with sepsis, followed by bloodstream, abdominal, central nerve system, genitourinary, and skin foci (15,16).

An infection might start as a localized infection and progress from a mild systemic disease to sepsis and potentially septic shock (15).

Septic shock is a subcategory of sepsis, characterized by increased mortality due to underlying circulatory and cellular/metabolic abnormalities (8). This progression from a localized infection to sepsis or septic shock is thought to be mediated by a complex activation of pro-inflammatory and anti-inflammatory host responses (17). The activation of this host response is started by an interaction between pattern recognition receptors expressed by cells of the immune system and either pathogen-associated molecular patterns expressed by the pathogen or endogenous danger-associated molecular patterns (17).

Examples of organ dysfunction seen in sepsis are haemodynamic instability, adrenal insufficiency, acute lung injury, acute kidney injury, hepatic dysfunction, gastrointestinal dysfunction, and more (15,18).

In children and especially neonates, it can be challenging to distinguish between a severe infection (such as pneumonia, meningitis, osteomyelitis, pyelonephritis) and sepsis (10,19). This thesis will therefore also focus on hospital-acquired pneumonia. Hospital-acquired pneumonia is usually caused by bacteria from the pharynx, oral cavity, or the upper gastrointestinal tract entering the lower airways (20).

Hospital-acquired pneumonia children constitute 6.8% to 32.3% of all nosocomial infections in neonates and children (21,22). Most patients with hospital-acquired pneumonia are classified as ventilator-associated pneumonia, defined as pneumonia occurring 48 hours or more after endotracheal intubation (23,24). Intubation with endotracheal tubes bypasses parts of the innate host barrier defence mechanisms, which may explain the increased risk for these patients (20).

The most common bacteria causing hospital-acquired pneumonia in children worldwide are *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (25–27).

Risk factors for sepsis and hospital-acquired pneumonia

Both sepsis and hospital-acquired pneumonia have a number of overlapping risk factors. The time of onset of the infection is an important risk factor for both neonatal sepsis and ventilator-associated pneumonia.

Neonatal sepsis is usually divided into early-onset and late-onset sepsis. Early-onset sepsis is defined as onset before 72 hours after birth and is more likely to be an infection acquired through transmission from the mother to the neonate. Late-onset sepsis is more likely to be caused by nosocomial or community-acquired infection.

For ventilator-associated pneumonia, the onset of the infection is also associated with the causative bacteria and prognosis (28,29). Early-onset ventilator-associated pneumonia (< four days of hospitalisation) is associated with a better prognosis than late-onset ventilator-associated pneumonia (> four days of hospitalisation) (28,30,31).

As the onset is associated with different pathogens, some guidelines recommend different types of first-line antibiotics for early-onset and late-onset (30,32,33).
For early-onset neonatal sepsis, maternal risk factors include intrapartum fever, chorioamnionitis, urinary tract infection, preterm rupture of the membrane (PROM), multiple gestations, prolonged labour and meconium aspiration (34,35). Prematurity and low birth weight are major risk factors due to immature innate and adaptive immune systems (11,12,36–38).

Essential risk factors for late-onset neonatal sepsis include intubation, intravascular catheterisation, parenteral nutrition, surgical procedures, respiratory and cardiovascular comorbidities, and hospitalisation (39–41).

Risk factors for hospital-acquired pneumonia included long hospitalisation, respiratory disease, immune deficiencies, immunosuppression, recent antibiotic therapy, use of glucocorticosteroids, genetic syndromes, reintubation, self-extubation, and bronchoscopy (42,43). Usage of endotracheal tubes, orogastric tubes, and exposure to broad-spectrum antibiotic agents in neonatal intensive care units (NICUs) and pediatric care units (PICUs) also serves as important risk factors (42,44).

Treatment

The treatment of sepsis is primarily focused on the eradication of the pathogen causing the infection (e.g. antibiotics) or support organ function (such as vasopressors, fluid resuscitation, oxygen therapy) (45–48). No therapy has successfully been shown to inhibit the pathways responsible for the initiation and progression of sepsis (47).

The most isolated pathogens for patients with sepsis are bacteria (15,49). The bacteria most isolated depend on multiple variables such as geographical region, age, the primary focus, and whether the infection is community-acquired or hospital-acquired (50–53). The types of pathogens that cause these infections and their antibiotic resistance patterns also change over time (50–53). Some common bacteria include the Gram-positive bacteria group B *Streptococcus*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and the Gram-negative bacteria *Escherichia coli*, *Klebsiella species*, and *Pseudomonas aeruginosa* (54). Antibiotics are therefore the primary choice of treatment. Antivirals, antifungals, or antiparasitics are chosen if a viral, fungal, or parasitic infection is suspected (46).

Although it would be ideal to know what pathogen is treated, current diagnostic tools might require up to three days to determine what the potential causative organism is (55). Unfortunately, the treatment of sepsis cannot wait that long. Although most (96%) positive cultures appear within the first 24 hours, evidence from observational studies suggests that time is precious (56). Evidence from adult studies shows that the mortality increases for every hour the antibiotic treatment is delayed (56). Recent observational studies on children also find increased mortality associated with delayed antimicrobial treatment (57,58).

Consequently, the treatment of sepsis relies on empirical treatment, which refers to the initiation of treatment before the causative pathogen is unknown (46,48). The treatment should cover the most likely pathogen to cause the infection and consider patient-specific risk factors (46). If the pathogen causing the infection is not susceptible to the empirical antibiotics given, the patient is likely to deteriorate, and the risk of mortality increases (59–61). Therefore, it is essential that the initial treatment is up to date and evidence-based to target the causative pathogen appropriately (59–61).

The empirical treatment of sepsis in neonates and children usually includes antibiotics such as beta-lactam antibiotics, aminoglycosides, and glycopeptides (62).

For neonatal sepsis, the empirical treatment is commonly a beta-lactam antibiotic (ampicillin, penicillin, cephalosporine, and flucloxacillin) combined with an aminoglycoside or a glycopeptide (62). The length of the treatment varies, depending on the suspected focus of infection, response to treatment, and type of pathogen (46,48).

Targeting the pathogen responsible for the infection is not the only goal when treating sepsis. Besides treating the organ dysfunction present in the patient, it could also involve inhibition of the immune response seen in patients with sepsis (63). No treatment has successfully been able to inhibit the immune response causing sepsis (47). One of the candidates is glucocorticosteroids. Glucocorticosteroids (e.g. hydrocortisone, dexamethasone, methylprednisolone, etc.) are known for their anti-inflammatory effects (64,65). They might be able to inhibit some of the pathways responsible for the inflammatory response in sepsis (65,66). The glucocorticosteroids' ability to raise the blood pressure and correct potential adrenal insufficiency are also mechanisms through which they might be beneficial for patients with sepsis (18,66–69). For these reasons, glucocorticosteroids have been widely used in pediatric intensive care units for children with sepsis or septic shock (16,70). Prior guidelines have recommended the use of hydrocortisone for children with fluid refractory and catecholamine-resistant septic shock (48,71). More recent guidelines state that they "*suggest that either IV hydrocortisone or no hydrocortisone may be used if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability (weak recommendation, low quality of evidence)*" (46). The glucocorticosteroid, hydrocortisone, is therefore only recommended if the patient has septic shock and is not responding to vasopressor and fluid therapy (46).

The focus of this thesis will be on antibiotics as well as glucocorticosteroids.

The rationale for the projects

Since both the causative agents, comorbidities, and pharmacokinetics differ between children and adults, it is necessary to assess antibiotic therapy and glucocorticosteroids separately for children (72). Especially neonates with sepsis are at risk of complications unlikely to be seen in older children and adults, such as periventricular leukomalacia, intraventricular haemorrhage, cerebral palsy, cognitive and psychomotor delay and bronchopulmonary dysplasia (73–77).

If the treatment guidelines are based on studies performed on adults, it will decrease the certainty of the evidence due to the indirectness caused by assuming that the effects in children are similar to the effects seen in adults (78).

Research conducted in pediatric populations is usually scarce compared to research in adult populations (79). This has led to fewer and more uncertain recommendations for pediatric guidelines compared to adult recommendations (79). Nevertheless, without relevant evidence from high-quality research studies such as randomised clinical trials, the construction of new recommendations will be a challenge.

The projects described in this thesis, therefore, focus on the assessment of the evidence from randomised clinical trials. The aim was to systematically summarize the randomised clinical trials comparing different antibiotic regimens for sepsis and hospital-acquired pneumonia and trials assessing the effects of adding glucocorticosteroids to standard care for children with sepsis and severe infections.

The goal was to provide updated evidence to support relevant treatment guidelines and to identify what the next steps should be for future clinical research within this field.

Methods

All the included studies are systematic reviews. We published protocols for all the reviews (80–84) and followed the Cochrane Handbook (85) and PRISMA guidelines (86,87). As the methodology used in all the reviews are similar, this method section will collectively describe the methods used in the reviews. An exhaustive description of our planned methodology can be found in our publish protocols for the individual systematic reviews (80–82,84).

We included randomised clinical trials assessing the relevant comparisons in the study populations predefined in our protocols. Our reviews included neonates (< 28 days old) and children (< 18 years of age) suspected of sepsis (Project I and III) and hospital-acquired pneumonia (Project II).

For Project I and II, we included trials comparing two different antibiotic regimens. Our inclusion criteria were thereby not limited to any particular comparison. We used the same broad principle in project III, where we included any glucocorticosteroids added to standard care.

We pre-specified all outcomes in the protocols. We always included all-cause mortality and serious adverse events. The remaining outcomes depended on the scope of the review. We chose outcomes based on clinical relevance and what would be important to the patients and their caretakers. We tried to avoid using surrogate outcomes unless editors or peer-reviewers insisted (see **Table 1**).

Table 1. Pre-specified outcomes in the different reviews

REVIEW	PRIMARY OUTCOMES	SECONDARY OUTCOMES
PAPER IA AND IB	All-cause mortality	Serious adverse events, respiratory support, circulatory support, nephrotoxicity, neurological developmental and sensory impairment, necrotising enterocolitis, and ototoxicity

PAPER II	All-cause mortality, serious adverse events	Quality of life, pneumonia-related mortality, non-serious adverse events, and treatment failure
PAPER III	All-cause mortality, serious adverse events	Quality of life, shock reversal, organ failure, ototoxicity, and non-serious adverse events

Search methods

We developed search strategies in cooperation with an information specialist from either the Cochrane Neonatal Group, Cochrane Acute Respiratory Infections Group, or Cochrane Hepato-Biliary Group (affiliated with the Copenhagen Trial Unit). We searched electronic databases such as Cochrane Central Register of Controlled Trials, MEDLINE Ovid (PubMed), Embase Ovid, CINAHL, LILACS, Science Citation Index EXPANDED, and Conference Proceedings Citation Index.

Data collections

The author of this thesis and another review author (usually the second author) independently screened the titles and abstracts of records identified by the search for inclusion in the reviews. We retrieved selected full-text articles, and two review authors independently screened the full-texts and identified relevant trials for inclusion. We also recorded reasons for excluding studies that did not live up to our inclusion criteria.

We used data collection forms for trial characteristics and outcome data. Two review authors extracted trial characteristics from included trials according to our pre-specified protocols. Two review authors independently extracted outcome data from included trials. We resolved disagreements by consensus or by involving a third author.

Assessment of risk of bias in the reviews

We assessed the risk of bias according to the previous Cochrane Handbook 5.1 (88). We thereby evaluated the risk of bias by the domains 'generation of allocation sequence', 'allocation concealment', 'blinding of participants and treatment providers', 'blinding of outcome assessment', 'incomplete outcome data', 'selective outcome reporting', 'for-profit bias' and 'other bias sources'.

Measures of treatment effects

We calculated the risk ratio (RR) with the 95% confidence interval (CI) for dichotomous outcomes. If we had included any continuous outcomes, we planned to calculate the mean differences or the standardised mean difference with the 95% CI.

Assessment of heterogeneity

We inspected forest plots to identify visual signs of heterogeneity. Then we explored possible heterogeneity in our pre-specified subgroup analyses if we had enough relevant data. We also assessed statistical heterogeneity I^2 statistic with significance set at $P < 0.10$ (89,90). We inspect trial characteristics across trials to identify clinical heterogeneity.

Assessment of reporting biases

We used a funnel plot to detect reporting bias if ten or more trials were included. This was only the case for paper III (91). We inspected funnel plots for asymmetry to assess the risk of reporting bias. For dichotomous outcomes, we tested asymmetry with the Harbord test (92).

Data synthesis

We planned to pool data from trials we judge to be clinically homogeneous. Hence, we only performed meta-analysis if more than one trial provided relevant data in any single comparison.

Meta-analysis

We undertook meta-analyses according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (85,88). We used Review Manager 5 software (93). In Project I, we used the fixed-effect model in accordance with the Neonatal Cochrane Group instructions (80,81). In project II and III, we assessed our intervention effects with both fixed-effect meta-analyses and random-effects meta-analyses (82–84,94,95). We used the more conservative point estimate of the two.

As we choose one and two primary outcomes in the different reviews, we considered P-values 0.05 and 0.033 or less as the threshold for evidence of a difference (80–82). We did this to account for the multiplicity.

Trial Sequential Analysis

We performed Trial Sequential Analyses (TSA) on our outcomes, and when possible, we calculated the diversity-adjusted required information size (DARIS) (91). The results of our TSAs and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries guided our GRADE assessment on imprecision and thereby the certainty of our results.

For our dichotomous outcomes, we estimated the required information size based on the proportion of participants with an outcome in the control group, a predefined relative risk reduction (usually 20%), an alpha (adjusted according to the number of primary outcomes), a beta of 10% or 20%, and diversity as suggested by the trials in the meta-analysis (80–84).

Network meta-analysis

For paper II we planned to perform network meta-analysis if a connected network of trials could be conducted (84,96). This was not possible due to a lack of comparable antibiotic regimens in the included trials. We planned to use Stata 16.1 under the frequentist framework (97). A detailed description of our planned methodology can be found in paper II (84).

Subgroup analyses

We planned several sub-group analyses to explore potential heterogeneity among the trials and their participants. We always included subgroups that compared trials at overall high risk of bias to trials

at overall low risk of bias. For all the reviews comparing antibiotic regimens, we also had subgroups that compared trials from different geographical regions. All reviews also had sub-groups that compared trials with different types of sepsis (e.g., focus of infection or with compared to without septic shock). The remaining sub-groups were tailored to the respected reviews.

Sensitivity analyses

To explore the possible impact of the missing data, we planned sensitivity analyses on our primary outcomes for all our reviews.

First, we planned a 'best-worst-case' scenario: we planned to assume that all participants lost to follow-up in the intervention group had a beneficial event (survived or no serious adverse event), and all those participants with missing outcomes in the control group had had a harmful event (died or had a serious adverse event).
Then we conducted a 'worst-best-case' scenario: we planned to assume that all participants lost to follow-up in the intervention group harmful event and that all those participants lost to follow-up in the control group had a beneficial event.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (98), to assess the certainty of evidence of our primary outcomes and the secondary outcomes we deemed the most important and clinically relevant in the protocols. Two review authors independently assessed the certainty of the evidence for each of the outcomes. We downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies (heterogeneity), directness of the evidence (external validity), precision of estimates (risks of random type I and II errors), and presence of publication bias.

For Project II, we also planned to assess confidence in network meta-analysis results using CINeMA (Confidence in Network Meta-Analysis) (99,100).

Results

Project I - Antibiotics for neonatal sepsis

The two reviews each included five randomised clinical trials assessing different antibiotic regimens for early-onset (Paper Ia) and late-onset neonatal sepsis (Paper Ib) (101,102).
The five trials in paper Ia compared (101):

- ampicillin plus gentamicin versus benzylpenicillin plus gentamicin
- piperacillin plus tazobactum versus amikacin
- ticarcillin plus clavulanic acid versus piperacillin plus gentamicin
- piperacillin versus ampicillin plus amikacin
- ceftazidime versus benzylpenicillin plus gentamicin.

The five trials in paper Ib compared (102):

- cefazolin plus amikacin versus vancomycin plus amikacin
- ticarcillin plus clavulanic acid versus flucloxacillin plus gentamicin
- cloxacillin plus amikacin versus cefotaxime plus gentamicin
- vancomycin plus gentamicin versus vancomycin plus aztreonam
- meropenem versus standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin).

As none of the trials assessed similar comparisons, none of their results could be pooled for our planned meta-analyses on any of our outcomes. The two reviews included a total of 865 (paper Ia) and 580 participants (paper Ib), with the individual trials randomising between 28 and 396 participants (101,102).
All the comparisons were very imprecise and at high risk of bias for all outcomes.
We calculated the optimal information size for all the comparisons on our included outcomes. This confirmed that the trials were highly underpowered to detect any clinically meaningful difference between the different antibiotic regimens. All comparisons were assessed to be of very low certainty of evidence when using the GRADE assessment.

As it was not possible to meta-analyse any results in the two reviews, we reported single-trial results only (see **Table 2 and 3)**.
None of the trials reported respiratory support and ototoxicity.

We could not conduct our planned sensitivity analyses, subgroup analyses, or funnel plots as we only included one trial in all the comparisons.

Table 2: Results from paper Ia comparing different antibiotic regimens for neonates with early-onset sepsis (101).

Trial	**Comparison**	**Participants with early-onset sepsis**	**All-cause mortality RR (95%CI)**	**Serious adverse events RR (95%CI)**	**Circulatory support RR (95%CI)**	**Neurological developmental impairment RR (95%CI)**	**Nephrotoxicity RR (95%CI)**	**NEC RR (95%CI)**	**Risk of bias**
Metsvaht 2010	**Ampicillin plus gentamicin versus penicillin plus gentamicin**	283	**RR 0.56** (0.30 to 1.06)	**RR 0.93** (0.72 to 1.21)	**RR 0.93** (0.72 to 1.21)	**RR 0.81** (0.40 to 1.61)	NA	**RR 1.24** (0.50 to 3.05)	High
Tewari 2014	**Piperacillin plus tazobactam versus amikacin**	59	**RR 0.32** (0.01 to 7.61)	**RR 0.97** (0.15 to 6.41)	NA	NA	NA	NA	High
Miall-Allen 1988	**Ticarcillin + clavulanic acid versus piperacillin + gentamicin**	72	**RR 0.75** (0.19 to 2.90)	**RR 0.75** (0.19 to 2.90)	NA	NA	NA	NA	High
Hammerberg 1989	**Piperacillin versus ampicillin plus amikacin**	396	**RR 0.62** (0.35 to 1.10)	**RR 0.62** (0.35 to 1.10)	NA	NA	**RR 1.14** (0.80 to 1.61)	NA	High
Snelling 1983	**Ceftazidime versus benzylpenicillin plus gentamicin**	55	NA	NA	NA	NA	NA	NA	High

Table 3: Results from paper Ib comparing different antibiotic regimens for neonates with late-onset sepsis (102).

Trial	**Comparison**	**Participants with Early onset sepsis**	**All-cause mortality RR (95%CI)**	**Serious adverse events RR (95%CI)**	**Circulatory support RR (95%CI)**	**Neurological developmental impairment RR (95%CI)**	**Nephrotoxicity RR (95%CI)**	**NEC RR (95%CI)**	**Risk of bias**
Cefriani 2014	Cefazolin plus amikacin versus vancomycin plus amikacin	109	**0.70** (0.29 to 1.66)	**0.70** (0.29 to 1.66)	NA	NA	NA	NA	High
Miall-Allen 1988	Flucloxacillin plus gentamycin versus ticarcillin plus clavulanic acid	28	**0.20** (0.01 to 3.82)	**0.20** (0.01 to 3.82)	NA	NA	NA	NA	High
Ramasamy 2014	Cloxacillin plus amikacin versus cefotaxime plus gentamicin	90	**0.38** (0.11 to 1.27)	**0.50** (0.17 to 1.48)	**0.50** (0.17 to 1.48)	NA	**0.25** (0.03 to 2.05)	NA	High
Lutsfar 2020	Meropenem versus standard care (ampicillin + gentamicin or cefotaxime + gentamicin)	271	**1.42** (0.56 to 3.62)	**1.54** (0.90 to 2.66)	NA	**0.87** (0.51 to 1.48)	NA	**0.68** (0.33 to 1.42)	High
Millar 1992	Vancomycin plus gentamicin versus vancomycin plus aztreonam	81	**0.65** (0.20 to 2.13)	**0.65** (0.20 to 2.13)	NA	NA	NA	**12.69** (0.74 to 218.09)	High

Project II - Antibiotics for hospital-acquired pneumonia in neonates and children

This review included four randomised clinical trials comparing different antibiotic regimens for hospitalized-acquired pneumonia (104). Three trials compared two different beta-lactam antibiotic regimens (103,105,106), and one trial compared an oxazolidinone (linezolid) with a glycopeptide (vancomycin) (107). The four trials compared:

- cefepime versus ceftazidime
- linezolid versus vancomycin
- ceftobiprole versus standard of care (cephalosporin)
- meropenem versus cefotaxime.

As no one of the trials assessed similar comparisons, none of their results could be pooled for our planned meta-analyses on any of our outcomes. The four trials randomised between 6 and 32 participants. In two of the trials the children with hospital-acquired pneumonia, constituted only subgroups of the total study population.
One of the trials did not report any of our selected outcomes (105). Another trial did not clearly describe the intervention given in the control group (106).
All the comparisons were very imprecise and at high risk of bias for all outcomes.

We calculated the optimal information size for all the comparisons on our included outcomes. The sample sizes corresponded to an optimal information size from 0.7% to 2.4%, indicating that the trials were highly underpowered to detect any clinically meaningful difference between the different antibiotic regimens. All comparisons were assessed to be of very low certainty of evidence when using the GRADE assessment (104).

As no meta-analysis was performed, the single-trial results are presented individually in **Table 4**. None of the trials reported health-related quality of life, pneumonia-related mortality, or non-serious adverse events for participants with hospital-acquired pneumonia. As we only included one trial in all the comparisons, we did not perform our planned sensitivity analyses, subgroup analyses, or funnel plots (104).

Table 4: Results from paper II comparing different antibiotic regimens for neonates and children with hospital-acquired pneumonia (104).

Trial	**Comparison**	**Participants with hospital-acquired pneumonia**	**All-cause mortality RR (95%CI)**	**Serious adverse events**	**Treatment failure**	**Risk of bias**
Shahid 2008 (103)	Cefepime versus ceftazidime	30	0.14 (0.01 to 2.55)	0.14 (0.01 to 2.55)	0.50 (0.15 to 1.64)	High
Jantausch 2003	Linezolid versus vancomycin	32	NA	NA	2.05 (0.49 to 8.63)	High
Bosheva 2021	Ceftobiprole versus standard of care (cephalosporin)	10	NA	NA	NA	High
Schuler 1995	Meropenem versus cefotaxime	6	NA	NA	1.80 (0.10-31.52)	High

Project III - Glucocorticosteroids for paediatric sepsis

This review included 24 trials assessing glucocorticosteroids as an add-on therapy to standard care for children with sepsis (91).

Of the 24 trials, 20 trials randomising a total of 2866 participants were included for our meta-analyses. These trials compared the glucocorticosteroids, hydrocortisone, dexamethasone, and methylprednisolone, with either placebo or no intervention. All the trials assessed glucocorticosteroids as add-on therapy of standard care for sepsis. The included trials randomised infants (< 1 year) and children (age >1 year and < 12 years) with sepsis (mixed focus of infection) or meningitis.

The follow-up in the trials was between one to 12 months. Most trials reported our primary outcomes all-cause mortality (19 trials) and serious adverse events (20 trials). Whereas only two trials reported shock reversal, eleven trials reported ototoxicity, and nine trials reported non-serious adverse events.
Twelve trials reported neurological complications, which we decided to include as a post-hoc outcome. None of the trials reported quality of life or organ failure.
The certainty of evidence ranged from very low to low, according to GRADE.

We found substantial heterogeneity and subgroup difference (P = 0.02) between trials randomising participants with meningitis and trials randomising participants with sepsis when performing the meta-analysis on our primary outcome, serious adverse events. We could therefore not justify pooling trials that only included children with meningitis with trials including children with sepsis. We, therefore, reported results for trials including children with meningitis and trials including children with sepsis, separately.

Glucocorticosteroids for sepsis with mixed focus

Primary outcomes

Five trials randomising 358 participants reported all-cause mortality and serious adverse events. Meta-analysis showed that the effects of glucocorticosteroids were very uncertain when assessing all-cause mortality (RR 1.24, 95% CI 0.80 to 1.92; P = 0.34; I^2 = 0%; very low certainty) and serious adverse events (RR 1.24, 95% CI 0.82 to 1.87; P = 0.31; I^2 = 0%; very low certainty). TSA showed that the results of these meta-analyses were very imprecise for mortality (TSA-adjusted CI 0.21 to 7.39) and serious adverse events (TSA-adjusted CI 0.23 to 6.62).

We did not identify any signs of heterogeneity from visual inspection of the forest plot or tests for statistical heterogeneity.
Our planned subgroup analyses assessing age, type of steroids, risk of bias, and presence of shock showed no evidence of a subgroup difference.

Secondary outcomes

Two trials randomising 97 participants reported shock reversal. Meta-analysis showed the effects of glucocorticosteroids were uncertain when assessing shock reversal (RR 0.91, 95% CI 0.52 to 1.59; P = 0.74; I^2 = 68%; very low certainty of evidence).

Non-serious adverse events

Three trials randomising 159 participants reported non-serious adverse events. Meta-analysis showed the effects of glucocorticosteroids were uncertain when assessing non-serious adverse events (RR 0.68, 95% CI 0.45 to 1.04; P = 0.08; I^2 = 0%, very low certainty of evidence).

None of the included trials assessed quality of life, organ failure, or ototoxicity.

Dexamethasone for meningitis

Fourteen trials randomising 2449 participants reported all-cause mortality. Meta-analysis showed little to no effect of glucocorticosteroids when assessing all-cause mortality (RR 0.97, 95% CI 0.78 to 1.21; P = 0.77; I^2 = 7%; low certainty of evidence). We did not identify any signs of heterogeneity from visual inspection of the forest plot or tests for statistical heterogeneity.
Our sensitivity analyses showed that missing data did not have the potential to change the conclusions of the results. We found no clear signs of asymmetry by visual inspection of the funnel plot. Our planned subgroup analyses assessing age, risk of bias, and dose showed no evidence of a subgroup difference.

Fourteen trials randomising 2379 participants reported serious adverse events. The trials mainly reported serious adverse events such as neurological complications and ototoxicity. Meta-analysis showed that dexamethasone might have a large reduction of serious adverse events

when added to standard care (RR 0.68, 95% CI 0.53 to 0.86; P = 0.001; I^2 = 64%; very low certainty of evidence). We found evidence of statistical heterogeneity (I^2 = 64%; P = 0.0006), but the heterogeneity was not confirmed by visually inspection of the forest plot did. TSA showed that the result of our meta-analysis was too imprecise to confirm the beneficial effect (TSA-adjusted CI 0.25 to 1.80).
Our sensitivity analyses showed that missing data did not have the potential to change the conclusions of the results. Both the visual inspection of the funnel plots and the Harbord test (P = 0.0009) indicated risk of publication bias. Our planned subgroup analyses assessing age, risk of bias, and dose showed no evidence of a subgroup difference.

Eleven trials randomising 1825 participants reported hearing loss or ototoxicity. Meta-analysis showed that dexamethasone may have a large reduction of ototoxicity when added to standard care (RR 0.63, 95% CI 0.45 to 0.88; P = 0.007; I^2 = 44%; low certainty of evidence). TSA showed that the result of our meta-analysis was too imprecise to confirm the beneficial effect (TSA-adjusted CI 0.16 to 2.48).

Five trials randomising 582 participants reported non-serious adverse events. Meta-analysis showed that the effects of dexamethasone on non-serious adverse events were very uncertain (RR 1.15, 95% CI 0.76 to 1.75; P = 0.52; I^2 = 69%; very low certainty of evidence).

None of the included trials assessed quality of life, shock reversal, and organ failure.

As neurological complications were reported by most of the trials including children with meningitis, we decided to analyse that outcome separately as well.
Twelve trials randomising 1866 participants reported neurological complications.
Meta-analysis showed that dexamethasone might reduce neurological complications, but the confidence interval was compatible with no effect (RR 0.79, 95% CI 0.58 to 1.05; P = 0.12; I^2 = 20%; low certainty of evidence).

Discussion

I will summarize our main findings of the three projects included in my thesis and put our findings into perspective with regard to current guidelines. I also seek to discuss the challenges for future research and present my suggestions to deal with some of them.

Systematic reviews

A review from 2013 assessing randomised clinical trials in pediatric critical care highlighted the issue that the number of randomised clinical trials in pediatric critical care is sparse and that the existing evidence from such trials is not easily accessible to clinicians not trained in literature searches (79). With the systematic reviews included in this thesis, we summarized the existing evidence for some of the commonly used interventions for sepsis and hospital-acquired pneumonia in neonates and children. Systematic reviews with meta-analysis have the potential to identify differences between interventions that may have been discarded due to a type II error. In addition, the systematic reviews could also provide results that aid the pathway for future research. For our antibiotic reviews (Project I-II), the trials included were so small that none of the included antibiotic regimens stood out as been more or less promising than any other regimen included. What was striking in both reviews was that both neonatal sepsis reviews (Paper Ia and Ib) excluded a lot of trials that did not make distinctions between early-onset and late-onset neonatal sepsis. The evidence from these trials could potentially provide valuable evidence. We have, therefore, already started a review that will assess antibiotic regimens for neonatal sepsis regardless of onset (62).

Our review on glucocorticosteroids for sepsis in children did not expose any prior type II errors, but it did suggest that the focus of the new trials should be on children with septic shock.

Summary of findings in the reviews

Our two Cochrane reviews (Paper 1a and 1b) assessing the effects of different antibiotics identified five trials, including participants with early-onset neonatal sepsis (randomising 865 participants) (101) and five trials, including participants with late-onset neonatal sepsis (randomising 580 participants) (102). Despite five trials contributing data to our predefined

outcomes for both reviews, none of the trials assessed the same comparison of antibiotic regimens. It was therefore not possible to conduct any meta-analysis of pooled data. All the included trials in the two reviews were underpowered to detect any clinically relevant difference between the antibiotic regimens on our outcomes (101,102).
Furthermore, all the included trials were at high risk of bias and very underpowered. The high risk of bias and the imprecision of our results makes the certainty of the evidence summarized in the reviews very low (101,102).

Our Cochrane review assessing the effects of different antibiotics for hospital-acquired pneumonia included four trials randomising a total of 84 participants (Paper II). As it was the case in Paper 1a and 1b, these trials were also at high risks of bias and substantially underpowered. None of the included trials assessed the same comparison of antibiotic regimens, hence we could not conduct any meta-analyses.

Both Project I and Project II were, thus, characterized by a lack of well-powered trials to assess the beneficial and harmful effects of different antibiotic regimens. The evidence from randomised trials is, therefore, insufficient to favour any particular antibiotic regimen for neonatal sepsis and hospital-acquired pneumonia.
As so many neonates and children are receiving antibiotics for suspected neonatal sepsis and hospital-acquired pneumonia, it is important to evaluate which regimens are the most effective and most safe. We planned to evaluate safety through our planned outcomes such as serious adverse events, adverse events, nephrotoxicity, ototoxicity, and necrotising enterocolitis. Our failure to identify differences in safety is most likely also due to the lack of power in our reviews.

The findings of our systematic review (paper III) assessing the effects glucocorticosteroids as an add-on therapy was a bit more complex. We initially chose to pool trials assessing participants with meningitis and sepsis because we hypothesised that the effects of glucocorticosteroids would be comparable (82). However, based on the results of our subgroup analysis, we concluded that pooling trials randomising children with meningitis and children with sepsis would not be valid as the effects seem to differ (91).
For children with sepsis, our meta-analyses only included a number of participants that corresponded to 2.6% to 7.1% of the required information size.

The included trials were thus very underpowered, making our results very imprecise. We could, consequently, neither confirm or reject any effect of glucocorticosteroids when assessing any of our outcomes (all-cause mortality, serious adverse events, shock reversal, or adverse events).
The most common indication for corticosteroids in children with sepsis is septic shock. But only two minor trials randomising a total of 97 participants assessed the effects of glucocorticosteroids for septic shock in children. With so few participants we can not expect to find any clinically relevant effect of the glucocorticosteroids.
Some studies suggest that pediatric sepsis could be divided into subgroups based on RNA expression (108,109). It is thought that glucocorticosteroids may have different effects on these different subgroups (108). A large multicentred trial assessing the use of hydrocortisone for children with septic shock is currently ongoing (110). This trial will not only provide more robust result on the effects of glucocorticosteroids, it will also explore the effects of hydrocortisone on the different subgroups of septic shock (110).

For children with meningitis, our review showed that the glucocorticosteroid, dexamethasone, may decrease the risk having a serious adverse events and ototoxicity. Both bayes factor and our sensitivity analysis on missing data supported these findings. But TSA showed that we did not have sufficient evidence to confirm these findings. The certainty of evidence was low for both outcomes. Our meta-analyses showed that the effects of dexamethasone for children with meningitis were still uncertain for our remaining outcomes (all-cause mortality, adverse events, and neurological complications).

Perspective to guidelines

The recommended empirical antibiotic treatment for neonatal sepsis, according to guidelines, is benzylpenicillin or ampicillin combined with gentamicin for early-onset and narrow-spectrum antibiotics (e.g. flucloxacillin) with gentamicin for late-onset (111,112). Our reviews did not find any evidence from randomised clinical trials to support these recommendations.

Guidelines for hospital-acquired pneumonia propose to base the choice of empirical antibiotics on the local distribution of pathogens and antibiograms, individual risk factors, likelihood of *Pseudomans aeruginosa,* and multidrug resistant pathogens (30,113). The results of our review on hospital-acquired pneumonia did not add further evidence to support stronger

recommendations.

The most recent Surviving Sepsis Campaign guidelines suggest that hydrocortisone may be used for children with septic shock not responding to fluid resuscitation and vasopressor therapy (46). The results of our review show that the evidence to support this recommendation is too sparse (91). The only glucocorticosteroid that showed beneficial effects on clinically important outcomes was dexamethasone. However, that was for children with meningitis and not children with septic shock.

The challenge of randomised clinical trials for assessment of different antibiotic regimens

Let us assume a closed setting where sepsis and hospital-acquired pneumonia are caused by pathogens with no or low antibiotic resistance and no temporal change in resistance or types of pathogens. Trials conducted in such settings could provide the necessary evidence to determine which antibiotic regimens are superior under the given assumptions. Especially if we only have to choose between two possible antibiotic regimens. If the choice is to find the optimal antibiotic regimen out of nine different antibiotic regimens (the number of different antibiotic regimens included in paper Ia), it would require 36 well-powered trials to compare all the different antibiotic regimens with each other. Even if we decided to narrow it down to five antibiotic regimens of interest, it would require ten trials to make all possible comparisons. As only five underpowered trials have been conducted globally until this date for early-onset and late-onset neonatal sepsis (80,81), even ten trials could be a challenge.

A pragmatic solution could be to conduct the number of trials necessary to create a closed network (for network meta-analysis) (96). The minimum number of trials required to make a closed network is equal to the number of antibiotic regimens, thus 9 and 5 trials instead of 36 and 10 in the examples above. Although indirect evidence has its own limitations, coordinating the comparison chosen for future trials could prove to be a faster and more realistic pathway towards conclusive evidence. Another option could be to conduct a large multicentred trial with multiple intervention arms, thus assessing many antibiotic regimens in the same trial. This could be organised as some of the COVID-19 trials are organised: as a platform trial (114). A prerequisite for this is that the necessary funding should be available and that weaknesses of the platform design can be avoided, e.g. secure blinding of parents, participants, care givers, data managers,

and statistical analyses; blinded independent data monitoring committees; sufficient control of multiplicity; compliance with randomised intervention; etc.

All the options would most likely require coordination by an international research network such as the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network (16).

The efficacy of antibiotic regimens in treating infections is more complicated. If we assumed that all the included participants had the same causative pathogen, it could be evaluated which regimens most effectively cleared the infection and prevented death and serious adverse events associated with disease progression. This is, however, not the case. The most common pathogens and their antibiotic resistance change over time and between geographical areas (50–53). The optimal antibiotic regimen is therefore likely to depend on the area and change over time. Observational studies suggest that inappropriate antibiotic regimens may cause higher mortality (60,61). Inappropriate is defined as an empirical antibiotic regimen that is ineffective towards the causative pathogen (60,61).

A given antibiotic could therefore turn out to be appropriate during the period of the trial but end up being inappropriate if one changes the time and place of the trial. One could argue that the solution would be to increase the number of trials to cover different geographical areas and to repeat the trials after a certain period to confirm or reject that the prior results and conclusions are still valid. This may not be feasible.

Well-conducted randomised clinical trials is considered the highest quality of evidence (115–117). Despite this, randomised clinical trials are sometimes being criticised for having strictly experimental settings and inclusion criteria that may limit their ability to predict results in real-world clinical practice (118). In the case of antibiotics for sepsis, that criticism might actually be justified. Not due to strict inclusion criteria, but rather due to the diversity and changing nature of sepsis.

All our three reviews only identified trials comparing the empirical antibiotic treatment of sepsis and hospital-acquired pneumonia. This initial treatment might be subjected to changes based on the results of the culture and the resistance of the bacteria. So, answering the question of which

empirical antibiotic is superior, does not answer which antibiotic regimen to choose if the microbiology results suggest that the bacteria are susceptible to several. Randomised clinical trials comparing different antibiotic regimens for the targeted therapy (after the bacteria and its resistance pattern has been identified) should also be conducted (46). Such trials should include subgroup analyses comparing the effects on different types of bacteria and different focus of infections.

Diagnostic challenges

If future research is to utilise the network meta-analysis, we have to address another limitation found in all the included publications of our reviews: the lack of consensus regarding diagnosis. To uphold the transitivity assumption for network meta-analysis, we need to make sure that future trials use similar inclusion criteria and definitions of sepsis (96). The diagnostic methods are a major challenge for both neonatal sepsis and hospital-acquired pneumonia in children with the lack of a gold standard (9,24,119–121). This is not only an issue for the recognition of these patients. The lack of standardised diagnostic criteria also makes clinical research for these conditions difficult. If different studies do not use the same diagnostic methods and definitions, it becomes challenging to compare the findings across studies (9). Different inclusion criteria could potentially explain discrepancies in epidemiology and outcomes between studies. Getting a consensus on the diagnostic criteria of sepsis is an important first step optimized the generalisability of individual trials (9,120).

The use of observational studies

Observational studies such cohort studies, case-control studies, or case-series are generally more susceptible to bias than randomised clinical trials (115,117,122).

Although the intervention groups appear similar in characteristics, results of observational studies sometimes differ from results of randomised studies of the same comparison (123). As several meta-epidemiological studies suggest, the data from non-randomised studies might produce misleading results (123). A recent meta-epidemiological survey showed that a third of routinely collected data studies showed results that differed from randomised clinical trials

assessing the same research question (124). The same study also found that non-randomised studies had a tendency to overestimate the treatment effects (124). This may be due to selection bias or residual confounding.

As it is difficult to spot and account for selection bias, it is recommended only to conduct non-randomised studies when randomised clinical trials are either not ethical or not feasible (123). Caution should therefore be made if observational data is used to form health care policies (117).

Let us revisit our theoretical setting with no antibiotic resistance and fixed pathogens. The reality is that the most likely pathogen and their suspected antibiotic resistance are suspectable to change over time and between regions. Observational studies regularly updated could provide the necessary evidence to detect these changes and complement data from randomised clinical trials. The results from our systematic reviews show that we do not even have sufficient evidence from randomised clinical trials to determine which antibiotic regimen that would be superior in a simplified setting. Given the complexity of reality with temporal changes, a globalized world, and changing pathogens, we are even further from an answer. If current data should enable us to determine what antibiotic regimen that would be superior in the simplified setting, we might need to combine data from randomised clinical trials with data from observational studies. Methods to combine data from randomised clinical trials and well-conducted observational studies have recently been developed (118,125). These methods might be a pragmatic solution to aid decision-making in the midst of sparse randomised clinical trials (118,125,126).

In summary, network meta-analysis and methods to combine data from randomised clinical trials and observational data might be possible solutions to determine which antibiotic regimens that should be first-line treatments for neonatal sepsis and hospital-acquired pneumonia.

Conclusions

The current evidence from randomised clinical trials does not allow confirmation or rejection of one antibiotic regimen being superior to another for early-onset neonatal sepsis, late-onset neonatal sepsis, or hospital-acquired pneumonia. Future research needs to be able to develop an

international consensus definition of neonatal sepsis and hospital-acquired pneumonia. This would ensure that future trials have comparable participants. The next step is to conduct high-quality randomised clinical trials to assess the effects of different antibiotic regimens for sepsis in neonates, infants and children with hospital-acquired pneumonia. These trials should randomise a sufficient number of participants to demonstrate a reliable result. Assess outcomes important to the patient (e.g. all-cause mortality, serious adverse events, and quality of life); be conducted at low risk of bias; adhere to consensus definitions of early- and late-onset neonatal and hospital-acquired pneumonia when such emerge; measure antibiotic resistance among the culture-positive participants; be conducted in areas know to have different microbial risk factors. A coordinated effort by an international network should be established to ensure that sensible prioritized comparisons are assessed.

As the data coming from randomised clinical trials are so sparse, current guidelines might have to rely on observational studies as a pragmatic approach to create evidence-based treatment guidelines.

Glucocorticosteroids are being widely used for septic shock, but current evidence from randomised clinical trials does not support the use of glucocorticosteroids for children sepsis or septic shock. The glucocorticosteroid, dexamethasone, may decrease serious adverse events and ototoxicity for children with sepsis due to meningitis. The theoretical benefit of glucocorticosteroids is thought to be for children with septic shock. The trials assessing glucocorticosteroids for septic shock in children are, however, significantly underpowered. Based on our results, the use of glucocorticosteroids for sepsis in children still needs to be examined in well-powered randomised placebo-controlled clinical trials. These trials should focus on children with septic shock and assess differences between subsets of septic shock.

Overall conclusions

The projects included in this PhD thesis highlight a challenge to pediatric critical care: the paucity of evidence from randomised clinical trials. Important therapies for sepsis, such as antibiotics and glucocorticosteroids, lack the necessary evidence to support strong recommendations in guidelines. Evidence from randomised clinical trials cannot support the choice of a specific antibiotic as the first-line empirical treatment for sepsis or hospital-acquired

pneumonia in children. Neither can the use of corticosteroids for children with septic shock be supported by randomised clinical trials.

There is, therefore, a need to increase the number of randomised clinical trials, including children with sepsis and hospital-acquired pneumonia. For the assessment of antibiotics, it will be important to establish an international network to facilitate a coordinated effort to create multicentred trials. Due to the changing nature of pathogens causing sepsis and hospital-acquired pneumonia, observational studies might be a necessity to answer research questions that are infeasible to answer through randomised clinical trials.

Future trials assessing glucocorticosteroids versus placebo should primarily include children with septic shock.

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Supplementary material

Project I: Antibiotics for neonatal sepsis

Paper Ia: Antibiotic regimens for early-onset neonatal sepsis.

Paper Ib: Antibiotic regimens for late-onset neonatal sepsis.

Project II: Antibiotics for hospital-acquired pneumonia in neonates and children

Paper II: Antibiotics for hospital-acquired pneumonia in neonates and children.

Project III: **Glucocorticosteroids for paediatric sepsis**

Paper III: The effects of adding glucocorticosteroids to standard care for children with sepsis.

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Antibiotic regimens for early-onset neonatal sepsis (Review)

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[Intervention Review]

Antibiotic regimens for early-onset neonatal sepsis

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ABSTRACT

Background

Neonatal sepsis is a major cause of morbidity and mortality. It is the third leading cause of neonatal mortality globally constituting 13% of overall neonatal mortality. Despite the high burden of neonatal sepsis, high-quality evidence in diagnosis and treatment is scarce. Possibly due to the diagnostic challenges of sepsis and the relative immunosuppression of the newborn, many neonates receive antibiotics for suspected sepsis. Antibiotics have become the most used therapeutics in neonatal intensive care units. The last Cochrane Review was updated in 2004. Given the clinical importance, an updated systematic review assessing the effects of different antibiotic regimens for early-onset neonatal sepsis is needed.

Objectives

To assess the beneficial and harmful effects of different antibiotic regimens for early-onset neonatal sepsis.

Search methods

We searched the following electronic databases: CENTRAL (2020, Issue 8); Ovid MEDLINE; Embase Ovid; CINAHL; LILACS; Science Citation Index EXPANDED and Conference Proceedings Citation Index – Science on 12 March 2021. We searched clinical trials databases and the reference lists of retrieved articles for randomised controlled trials (RCTs) and quasi-RCTs.

Selection criteria

We included RCTs comparing different antibiotic regimens for early-onset neonatal sepsis. We included participants from birth to 72 hours of life at randomisation.

Data collection and analysis

Three review authors independently assessed studies for inclusion, extracted data, and assessed risk of bias. We used the GRADE approach to assess the certainty of evidence. Our primary outcome was all-cause mortality, and our secondary outcomes were: serious adverse events, respiratory support, circulatory support, nephrotoxicity, neurological developmental impairment, necrotising enterocolitis, and ototoxicity. Our primary time point of interest was at maximum follow-up.

Main results

We included five RCTs (865 participants). All trials were at high risk of bias. The certainty of the evidence according to GRADE was very low. The included trials assessed five different comparisons of antibiotics.

We did not conduct any meta-analyses due to lack of relevant data.

Of the five included trials one trial compared ampicillin plus gentamicin with benzylpenicillin plus gentamicin; one trial compared piperacillin plus tazobactam with amikacin; one trial compared ticarcillin plus clavulanic acid with piperacillin plus gentamicin; one trial compared piperacillin with ampicillin plus amikacin; and one trial compared ceftazidime with benzylpenicillin plus gentamicin.

None of the five comparisons found any evidence of a difference when assessing all-cause mortality, serious adverse events, circulatory support, nephrotoxicity, neurological developmental impairment, or necrotising enterocolitis; however, none of the trials were near an information size that could contribute significantly to the evidence of the comparative benefits and risks of any particular antibiotic regimen.

None of the trials assessed respiratory support or ototoxicity.

The benefits and harms of different antibiotic regimens remain unclear due to the lack of well-powered trials and the high risk of systematic errors.

Authors' conclusions

Current evidence is insufficient to support any antibiotic regimen being superior to another. Large RCTs assessing different antibiotic regimens in early-onset neonatal sepsis with low risk of bias are warranted.

PLAIN LANGUAGE SUMMARY

Antibiotic regimens for early-onset neonatal sepsis

Review question

We reviewed available evidence on different antibiotic regimens for newborns (from birth to 72 hours of life), with early-onset sepsis (as defined by trialists).

Background

Sepsis in newborns is a severe and potential lethal condition, caused by the body's response to an infection. Neonatal sepsis is the third leading cause of neonatal death globally. Despite the high burden of sepsis in newborns, high-quality evidence in diagnosis and treatment is scarce. This Cochrane Review was originally published in 2004. To identify the most appropriate antibiotic policies for neonatal sepsis, there is a need to base these policies on an updated well-conducted review. Given the clinical importance, such a review assessing the effects of different antibiotic regimens for early-onset neonatal sepsis is needed.

Study characteristics

The evidence is current to August 2020. We included five trials randomising 865 participants. The included trials compared five different antibiotic regimens.

Key results

We included five trials: one trial compared ampicillin plus gentamicin with benzylpenicillin plus gentamicin; one trial compared piperacillin plus tazobactam with amikacin; one trial compared ticarcillin plus clavulanic acid with piperacillin plus gentamicin; one trial compared piperacillin with ampicillin plus amikacin; and one trial compared ceftazidime with benzylpenicillin plus gentamicin.

None of the five comparisons showed any difference when assessing death from all causes, serious adverse events (i.e. major complications), respiratory support, circulatory support, nephrotoxicity (toxicity in the kidneys), neurological developmental impairment (disabilities in the functioning of the brain that affect a child's behaviour, memory, or ability to learn), necrotising enterocolitis (tissues in the gut become inflamed and start to die), or ototoxicity (toxic to the ear). Current evidence cannot confirm or reject one antibiotic regimen being superior to another.

Quality of the evidence

The evidence behind our conclusions is very-low quality. The five trials had high risk of bias (i.e. the trials were conducted in a way that may have skewed results to the positive side). In addition, the five trials included few participants, making the results of this review imprecise.

SUMMARY OF FINDINGS

Summary of findings 1. Ampicillin plus gentamicin compared with penicillin plus gentamicin for early-onset neonatal sepsis

Ampicillin + gentamicin compared with penicillin + gentamicin for early-onset neonatal sepsis

Patient or population: neonates with early-onset sepsis

Settings: neonatal intensive care unit in Estonia

Intervention: ampicillin + gentamicin

Comparison: penicillin + gentamicin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Penicillin + gentamicin	Ampicillin + gentamicin				
All-cause mortality maximum follow-up	163 per 1000	91 per 1000 (49 to 173)	**RR 0.56** (0.30 to 1.06)	283 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 3898 (RR 0.80, α 0.05, β 0.20)
Serious adverse events maximum follow-up	461 per 1000	428 per 1000 (332 to 558)	**RR 0.93** (0.72 to 1.21)	283 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 992 (RR 0.80, α 0.05, β 0.20) The serious adverse events were need for vasoactive drugs.
Circulatory support maximum follow-up	461 per 1000	428 per 1000 (332 to 558)	**RR 0.93** (0.72 to 1.21)	283 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 992 (RR 0.80, α 0.05, β 0,20)
Neurological developmental impairment maximum follow-up	113 per 1000	92 per 1000 (45 to 183)	**RR 0.81** (0.40 to 1.61)	283 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 5592 (RR 0.80, α 0.05, β 0.20) Participants with intraventricular haemorrhage type III to IV.
Necrotising enterocolitis maximum follow-up	57 per 1000	70 per 1000 (28 to 173)	**RR 1.24** (0.50 to 3.05)	283 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 11822 (RR 0.80, α 0.05, β 0.20)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OIS:** optimal information size; **RR:** risk ratio.

GRADE Working Group grades of evidence

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.

[a]Downgraded three levels because of very serious risk of bias, very serious imprecision of results, and serious risk of indirectness.

Summary of findings 2. Piperacillin plus tazobactam compared with amikacin for early-onset neonatal sepsis

Piperacillin + tazobactam compared with amikacin for early-onset neonatal sepsis

Patient or population: neonates with early-onset sepsis

Settings: neonatal intensive care unit in India

Intervention: piperacillin + tazobactam

Comparison: amikacin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Amikacin	Piperacillin + tazobactam				
All-cause mortality maximum follow-up	34 per 1000	11 per 1000 (0 to 262)	**RR 0.32** (0.01 to 7.61)	59 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 20142 (RR 0.80, α 0.05, β 0.20)
Serious adverse events maximum follow-up	69 per 1000	67 per 1000 (10 to 442)	**RR 0.97** (0.15 to 6.41)	59 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 9602 (RR 0.80, α 0.05, β 0.20) The serious adverse events were treatment failures.

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Summary of findings 3. Ticarcillin plus clavulanic acid compared with piperacillin plus gentamicin for early-onset neonatal sepsis

Ticarcillin + clavulanic acid compared with piperacillin + gentamicin for early-onset neonatal sepsis

Patient or population: neonates with early-onset sepsis

Settings: neonatal intensive care unit in England

Intervention: ticarcillin + clavulanic acid

Comparison: piperacillin + gentamicin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Piperacillin + gentamicin	Ticarcillin + clavulanic acid				
All-cause mortality maximum follow-up	125 per 1000	94 per 1000 (24 to 363)	**RR 0.75** (0.19 to 2.90)	72 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 5014 (RR 0.80, α 0.05, β 0.20)
Serious adverse events maximum follow-up	125 per 1000	94 per 1000 (24 to 363)	**RR 0.75** (0.19 to 2.90)	72 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 5014 (RR 0.80, α 0.05, β 0.20) The serious adverse events were deaths.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OIS:** optimal information size; **RR:** risk ratio.

GRADE Working Group grades of evidence

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[a]Downgraded three levels because of very serious risk of bias, very serious imprecision of results, and serious risk of indirectness.

Summary of findings 4. Piperacillin compared with ampicillin plus amikacin for early-onset neonatal sepsis

Piperacillin compared with ampicillin + amikacin for early-onset neonatal sepsis

Patient or population: neonates with early-onset sepsis

Settings: NICU in Canada

Intervention: piperacillin

Comparison: ampicillin + amikacin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Ampicillin + amikacin	Piperacillin				
All-cause mortality maximum follow-up	138 per 1000	85 per 1000 (48 to 152)	**RR 0.62** (0.35 to 1.10)	396 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 4518 (RR 0.80, α 0.05, β 0.20)
Serious adverse events	138 per 1000	85 per 1000 (48 to 152)	**RR 0.62** (0.35 to 1.10)	396 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 4518 (RR 0.80, α 0.05, β 0.20) The serious adverse events were deaths.

maximum follow-up						
Nephrotoxicity maximum follow-up	229 per 1000	250 per 1000 (186 to 353)	**RR 1.14** (0.80 to 1.61)	396 (1)	⊕⊖⊖⊖ **Very low** [a]	OIS: 4518 (RR 0.80, α 0.05, β 0.20) There might have been a lower number of participants in this outcome as only participants who received antibiotics for > 1 day were included. The exact number was unclear.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OIS:** optimal information size; **RR:** risk ratio.

GRADE Working Group grades of evidence

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[a]Downgraded three levels because of very serious risk of bias, very serious imprecision of results, and serious risk of indirectness.

Summary of findings 5. Ceftazidime compared with benzylpenicillin plus gentamicin for early-onset neonatal sepsis

Ceftazidime compared with benzylpenicillin + gentamicin for early-onset neonatal sepsis

Patient or population: neonates with early-onset sepsis

Settings: neonatal intensive care unit in the UK

Intervention: ceftazidime

Comparison: penicillin + gentamicin

Outcomes	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
All-cause mortality maximum follow-up	Not estimable	55 (1)	⊕⊖⊖⊖ **Very low** [a]	There were no deaths in either group.

Serious adverse events maximum follow-up	Not estimable	55 (1)	⊕⊖⊖⊖ **Very low** [a]	There were no serious adverse events in either group.

CI: confidence interval; **OIS:** optimal information size; **RR:** risk ratio.

GRADE Working Group grades of evidence

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.
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BACKGROUND

Description of the condition

Definition

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer 2016). There are internationally agreed diagnostic criteria for sepsis in both adults and children (Singer 2016; Wynn 2014), but currently there is no international consensus on specific criteria for neonatal sepsis (Wynn 2014; Wynn 2016). The most used neonatal sepsis criteria used in clinical trials are based on a combination of clinical and laboratory parameters (see Table 1) (Morris 2016; Wynn 2014).

Sepsis that occurs before 28 days after birth is termed neonatal sepsis (Bakhuizen 2014; Camacho-Gonzalez 2013). Depending on the time of onset, neonatal sepsis is referred to as either early- or late-onset sepsis. The most commonly accepted distinction between these two subgroups is before and after 72 hours of age, although other definitions also exist such as 48 hours and seven days of age (Bakhuizen 2014; Bizzarro 2008; Camacho-Gonzalez 2013; Manan 2016; NICE 2012; Shah 2014; Shane 2013; Shane 2014; Tripathi 2012; Zaidi 2009; Zea-Vera 2015). This distinction is based on the different aetiologies and pathophysiology of pathogens typically seen before and after 72 hours (Camacho-Gonzalez 2013; Shah 2014; Shane 2013).

It is generally accepted that the infection in early-onset sepsis usually is *vertically* acquired from the mother (either because the mother is infected, or simply colonised with commonly occurring vaginal or gut bacteria), and that the infection in late-onset sepsis is usually horizontally acquired (e.g. from the community or a nosocomial (hospital-acquired) infection) (Park 2013; Shane 2013; Stoll 2002; Weston 2011; Zea-Vera 2015). As some of these clinical manifestations can be non-specific, it can be difficult to clinically distinguish between sepsis and severe infections, such as meningitis, osteomyelitis, and necrotising enterocolitis (Camacho-Gonzalez 2013; Zea-Vera 2015).

Epidemiology

The incidence of neonatal sepsis is estimated to be between 1 per 1000 and 12 per 1000 live births in high-income countries (Bakhuizen 2014; Stoll 2011). The incidence in low- and middle-income countries (LMICs) is higher. Reported incidences are estimated to be 7.1 per 1000 to 38 per 1000 live births in Asia, 6.5 per 1000 to 23 per 1000 live births in Africa, and 3.5 per 1000 to 8.9 per 1000 live births in South America and the Caribbean (Karunasekera 1999; Lim 1995; Moreno 1994; Robillard 1993; Tallur 2000; WHO 1999).

Early-onset sepsis is reported to be less frequent than late-onset sepsis. Studies from the USA and Australia suggest that early-onset sepsis ranges from 1.5 per 1000 to 3.5 per 1000 live births, while late-onset sepsis constitutes up to 6 per 1000 live births (Isaacs 1999; Schuchat 2000; Vergnano 2005). However, as there is no consensus on criteria for neonatal sepsis and no agreement on the cut-off between early- and late-onset sepsis (48 hours, 72 hours, or 7 days) (see 'Definition' section above), it is difficult to estimate the exact incidence of neonatal sepsis (Bakhuizen 2014). The incidence of early-onset sepsis is higher for neonates with very low birthweight (less than 1500 g) than for term neonates, with an incidence of 4 per 1000 for low birthweight versus 0.4 per 1000 for term neonates (Bedford Russell 2015). The incidence of early-onset sepsis is around 1 per 1000 live births in high-income countries (Stoll 2011; Vergnano 2011), but increases with decreasing gestational age and birthweight up to approximately 11 per 1000 live births in neonates weighing 401 g to 1500 g (Stoll 2011).

Neonatal sepsis is a major cause of morbidity and mortality. Neonatal sepsis is the third leading cause of neonatal mortality globally, constituting 13% of overall neonatal mortality, only surpassed by intrapartum-related complications (23%) and preterm birth complications (35%) (Lawn 2005; Liu 2012). In high-income countries, the mortality rate in neonatal sepsis ranges from 5% to 20% and results in major disability or death in 39% of all cases despite initiation of conventional treatment. Mortality rates higher than 70% can be observed in some LMICs (Bakhuizen 2014; Kabwe 2016; Weston 2011; Wynn 2014).

Sepsis in the neonatal period can result in several complications, such as multiple organ failure, cerebral haemorrhage, periventricular leukomalacia, meningitis, and respiratory distress syndrome (Sharma 2007; Stoll 2010). In survivors, sepsis is associated with serious long-term morbidity, such as cerebral palsy, cognitive and psychomotor delay, auditory and visual impairment, and bronchopulmonary dysplasia (Bakhuizen 2014; Benjamin 2006; Klinger 2010; Schlapbach 2011; Stoll 2004). Most of these associations are based on observational cohort studies and, therefore, do not distinguish between causality and association. It remains uncertain whether it is possible to prevent these subsequent sequela by treating neonatal sepsis with an appropriate empirical antibiotic regimen (Bakhuizen 2014).

Aetiology

In high-income countries, the most common aetiological agents responsible for early-onset sepsis are group B *Streptococcus* (38% to 58% of cases) and *Escherichia coli* (18% to 29% of cases), and together they constitute 62% to 72% of all cases of early-onset sepsis (Bizzarro 2005; Bizzarro 2008; Stoll 2011; Vergnano 2011; Weston 2011). One study from the USA showed that most (73%) infants with group B *Streptococcus* isolates were term, and most (81%) with *E coli* were preterm infants (Stoll 2011). Other agents prevalent in early-onset sepsis are *Listeria monocytogenes*, other streptococci species than group B *Streptococcus* (*Streptococcus pyogenes*, viridans group streptococci, *Streptococcus pneumoniae*), enterococci, staphylococci, *Bacillus* species, and *Haemophilus influenzae* (Stoll 2011; Vergnano 2011). Studies from the USA and Australia have shown a reduced incidence of early-onset neonatal sepsis after the implementation of antenatal screening for group B *Streptococcus* and intrapartum antibiotic prophylaxis offered to colonised women who are group B *Streptococcus* positive (Isaacs 1999; Shane 2014; Stoll 2011). This preventive effect of intrapartum antibiotic prophylaxis is not seen in late-onset sepsis (Ohlsson 2014).

The distribution of pathogens is quite different in LMICs with pathogens such as *Klebsiella* species and *Staphylococcus aureus* being the most prevalent causes of neonatal sepsis while group B *Streptococcus* infection is rare (Breurec 2016; Vergnano 2005; Zaidi 2005). Estimations suggest that Gram-negative rod-shaped bacteria (most commonly *Klebsiella* species) constitute approximately 60% of positive blood cultures in LMICs (Zaidi 2005).

Several risk factors are associated with an increased risk of developing early-onset sepsis (Manan 2016). Commonly recognised risk factors are maternal intrapartum fever, urinary tract infection, prolonged labour, preterm rupture of the membrane (PROM), prolonged PROM of greater than 18 hours, meconium aspiration, multiple gestation, and chorioamnionitis (Naher 2011; Shah 2014). Prematurity (defined as neonates born before the 37th gestational week) and low birthweight are major risk factors, as one multicentre observational study showed that neonatal sepsis was most common in preterm (82%) and low birthweight neonates (81%) (Stoll 2011). This might be influenced by the fact that the risk factor intrauterine infection (e.g. chorioamnionitis and amnionitis) is a major contributor to spontaneous preterm delivery (Goldenberg 2000).

Furthermore, neonates are immunocompromised as several components of the immune system are not fully developed at birth (Camacho-Gonzalez 2013; Kumar 2016). Preterm neonates are especially immunocompromised due to even more immature innate and adaptive immune systems (Kan 2016; Rogosch 2012; Walker 2011; Ygberg 2012; Zemlin 2007).

Description of the intervention

Treatment of neonatal sepsis is aimed at:

- treating the underlying infectious cause of sepsis (i.e. the bacterial infection), which in turn depends on the presumed aetiology (Deutschman 2014; Singer 2016); and
- correcting the associated organic dysfunction via, for example, respiratory support, maintenance of central and peripheral perfusion (often requiring intravenous fluids and inotropes), and correction of metabolic, temperature, and glucose derangements (Seale 2015; WHO 2013).

Antibiotics are antimicrobial drugs that are used to either kill or inhibit the growth of the bacteria and, accordingly, they are paramount in treatment of sepsis (Waksman 1947). Early initiation of antibiotic therapy in neonates with suspected sepsis reduces both mortality and morbidity (Bakhuizen 2014). According to guidelines, the treatment should be given as soon as possible and always within one hour of the decision to treat (NICE 2012; WHO 2013).

The choice of the empirical antibiotic used is based on several factors, such as age at onset, likely pathogens, and antibiotic susceptibility patterns with a special focus on group B *Streptococcus*, *E coli*, other Gram-negative organisms, and *Listeria monocytogenes* (Manan 2016; NICE 2014). Most neonates who receive antibiotics have negative blood cultures (Klingenberg 2018); therefore, trials that assess empirical antibiotics need to consider, in design and analysis, the issue that neonates with true sepsis will be pooled with non-infected neonates due to the lack of specific early diagnostic criteria. With the current diagnostic tools, the inclusion of non-infected neonates will be inevitable, when assessing empirical antibiotics. This may potentially cause type II errors as the event rate of clinically import outcomes would be lower in a study population including healthy neonates.

Most guidelines recommend a beta-lactam antibiotic (most commonly benzylpenicillin or ampicillin) together with an aminoglycoside (most commonly gentamicin) for empirical treatment of all cases of early-onset neonatal sepsis (Cortese 2016; Manan 2016; NICE 2014; Vergnano 2005; WHO 2013). Beta-lactam antibiotics are divided into four classes: penicillins, cephalosporins, monobactams, and carbapenems (Golan 2011; Katzung 2009).

Ampicillin is also frequently combined with a third-generation cephalosporin drug (most commonly cefotaxime) (Cantey 2015; Clark 2006a; Stoll 2011; Tzialla 2015; Vergnano 2011). Other regimens, such as cephalosporins (as monotherapy) are also used (NICE 2012). However, most national and international guidelines recommend the use of a penicillin combined with an aminoglycoside, as the use of cephalosporins are thought to cause a higher incidence of drug resistance (Cortese 2016; Manan 2016; NICE 2012; NICE 2014; WHO 2013).

The duration of treatment is adjusted according to the type of pathogen, treatment response, and the possibility of the antibiotic to penetrate to the site of infection in case of, for example, meningitis (inflammation of the protective membranes covering the brain and spinal cord), encephalitis (infection of the brain), osteomyelitis (infection in a bone), or endocarditis (inflammation of the inner layer of the heart). When the pathogen is identified by cultures, the antibiotic therapy might be changed according to the antibiotic susceptibility of the pathogen. However, causative bacteria are identified only in about one-third of the patients with presumed sepsis (Dellinger 2013; Gaieski 2010; Kumar 2006). One study found that the empirical antibiotic regimen was changed in 44% of the cases when the pathogen and susceptibility was identified, and the most frequently added antibiotics were vancomycin, cefotaxime, and penicillin (Stoll 2011). It is recommended to stop the antibiotic treatment when there are no signs and symptoms of infection and no pathogen identified (Camacho-Gonzalez 2013; Cortese 2016).

Antibiotic susceptibility

Antibiotic resistance is a growing problem which increases the morbidity, mortality, and healthcare costs associated with infections globally (Cohen 1992; Foster 2006; Huynh 2016; Vergnano 2005). Studies indicate that bacterial resistance to antibiotics results primarily from the selective pressure exerted by the use and overuse of antibiotics (Foster 2006; Kunin 1990; McGowan 1994; Murray 1994; Sáez-Llorens 2000). Studies that compare antibiotic susceptibility over time in the same unit show increased resistance to the most-used antibiotics (Vergnano 2005). The spread of antibiotic-resistant organisms within hospitals is a recognised problem, although neonates admitted from the community may also carry antibiotic-resistant pathogens (Bhutta 1996).

The pathogens that cause neonatal infections and their antibiotic susceptibility patterns change over time and differ between countries, cities, and hospitals (Breurec 2016; Isaacs 2003; May 2005; Stoll 2003; Stoll 2005; Vergnano 2011). Furthermore, the definition and epidemiology of neonatal sepsis differ between countries, which may make the comparison of antibiotic susceptibility between countries difficult (Vergnano 2005). When comparing the epidemiology of neonatal sepsis in LMICs with high-income countries, some important differences emerge in the pattern of aetiological pathogens and their antibiotic resistance (Khatua 1986; Tallur 2000; Tessin 1990; Vesikari 1985).

For example, data from the UK showed that 95% of the identified pathogens were susceptible to the most used empirical

antibiotic regimens of penicillin and gentamicin (Vergnano 2011). One multicentre observational study from the USA showed that all group B *Streptococcus* isolates tested were sensitive to penicillin, ampicillin, and vancomycin, while 46% were resistant to erythromycin and 20% to clindamycin. With regards to *E coli*, 78% were ampicillin-resistant, 4% were gentamicin-resistant, and 3% were resistant to third-generation cephalosporins (Stoll 2011).

Two multicentre studies from the USA showed an increased proportion of *E coli* strains resistant to ampicillin, especially among preterm neonates (Baltimore 2001; Hyde 2002). The emergence of intrapartum ampicillin exposure is thought to be a significant independent risk factor for ampicillin resistance (Bizzarro 2008). Some neonatal units have changed antibiotic policies to include a third-generation cephalosporin in exchange for ampicillin due to a growing resistance of Gram-negative bacteria to ampicillin and gentamicin (Camacho-Gonzalez 2013; Meyer 2010; Sáez-Llorens 2000; Vergnano 2005). However, several reports have also shown an emerging reduced susceptibility to third-generation cephalosporin (Meyer 2010; Musoke 2000; Rahman 2002).

In LMICs, estimations suggest that up to 70% of pathogens isolated from neonatal sepsis may not be covered by the recommended empirical antibiotic regimen of ampicillin and gentamicin (Zaidi 2005). Some studies in LMICs have shown almost universal resistance (92% to 100% resistant) among the most common pathogens (Gram-negative rods) to first-line (often ampicillin and gentamicin) and second-line antibiotics, such as third-generation cephalosporins (Kabwe 2016; WHO 2013; Zaidi 2005). In addition, some LMICs face widespread dissemination of resistant bacterial strains, including extended-spectrum-lactamase-producing bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA) (Cotton 2000; Gonzalez-Vertiz 2001; Shenoy 2007; Zaidi 2005).

Adverse events

Use of ampicillin has been associated in some studies with adverse events, such as rashes, diarrhoea, nausea, and nephrotoxicity (Golan 2011; Katzung 2009; Mrvos 2013). Contrary to these findings, one systematic review of randomised controlled trials (RCTs) only found an significant increased incidence of candidiasis with no significant increase in rashes, diarrhoea, nausea, or nephrotoxicity (Gillies 2015). Nephrotoxicity has been estimated to be rare (0.03%) (Mrvos 2013).

Aminoglycosides (e.g. gentamicin) have been shown to be toxic (nephrotoxicity and ototoxicity) in adults, whereas its toxicity in neonates remains unclear (Huth 2011; Jackson 1971; Mattie 1989; McGlone 2008; Mingeot-Leclercq 1999; Musiime 2015; Schultze 1971; Selimoglu 2007; Wargo 2014). Regarding ototoxicity in neonates, trials have presented conflicting results showing ototoxicity in 0% to 26% of neonates exposed to aminoglycoside (Agarwal 2002; Finitzo-Hieber 1979; Itsarayoungyuen 1982; Lundergan 1999; Mercado 2004; Rastogi 2002). One meta-analysis showed that 3% of neonates had hearing loss after treatment with gentamicin (Musiime 2015).

With regards to nephrotoxicity in neonates, the literature shows a large discrepancy between the degree of nephrotoxicity seen in neonates after gentamicin exposure (Kent 2014; Martinková 2010; McWilliam 2017). Studies span from showing no nephrotoxicity to showing the development of nephrotoxicity in 33% of the cases after aminoglycoside exposure (Martinková 2010; McWilliam 2017; Rhone 2014). In comparison, it is estimated that almost 25% of all adults who received aminoglycoside therapy develop nephrotoxicity (Lopez-Novoa 2011; Wargo 2014).

How the intervention might work

Antibiotics are antimicrobial drugs that treat and prevent bacterial infections by either killing or inhibiting the growth of the bacteria (Waksman 1947). They can be classified based on:

- their mechanism of action (bactericidal or bacteriostatic);
- bacterial spectrum (broad or narrow); and
- chemical structure (e.g. penicillins, macrolides, quinolones, tetracyclines, or aminoglycosides) (Bérdy 2005).

A combination of different antibiotics might have several advantages. The rational of combination therapy is to broaden the spectrum of antibiotic coverage when used empirically to increase the chance of covering the alleged causative bacteria. Theoretically, combination therapy might also suppress the development of subpopulations of micro-organisms resistant to antibiotic (Allan 1985; Milatovic 1987; Tamma 2012).

However, it is theoretically possible that the optimal empirical antibiotic treatment should not be chosen solely based on the presumed pathogen and cultures. Antibiotics might have different effects in the human body compared to the pattern they show in vitro (e.g. cell cultures).

Why it is important to do this review

The previous version of this review (Mtitimila 2004), included two small trials and showed no evidence of a difference in effect between the compared antibiotic regimens on mortality, treatment failure, and bacteriological resistance (Mtitimila 2004). The two trials compared ticarcillin plus clavulanic acid versus piperacillin plus gentamicin (Miall-Allen 1988), and ceftazidime versus combination therapy (benzylpenicillin and gentamicin) (Snelling 1983).

Despite the high burden of neonatal sepsis, high-quality evidence in diagnosis and treatment is scarce (Zea-Vera 2015). In adults, appropriate empirical antibiotic treatment reduces mortality rates by up to 50% associated with sepsis (Ibrahim 2000; Leibovici 1998; Paul 2010). Accordingly, it is currently recommended that the antibiotic empirical treatment should be broad to ensure coverage of any likely pathogen, which typically results in a composite antibiotic therapy (Cawcutt 2014; Dellinger 2013). Due to the diagnostic challenges of sepsis and the relative immunosuppression of the newborn, many neonates receive antibiotics for suspected sepsis. In fact, antibiotics have become the most used therapeutics in neonatal intensive care units (Clark 2006b), and observational studies in high-income countries suggest that 83% to 94% of newborns treated with antibiotics for suspected sepsis have negative blood cultures (Klingenberg 2018). This presumed inappropriate use of antibiotics seems to contribute to the development and spread of resistant pathogens in neonatal intensive care units and seems to be associated with adverse events (e.g. invasive candidiasis, increased antimicrobial resistance, necrotising enterocolitis) (Clark 2006a; Cordero 2003; Cotten 2006; Cotten 2009; Foster 2006; Kuppala 2011). Adverse events of antibiotic exposure in infants is believed to be minimised

through appropriate antibiotic choice and duration of treatment (Tripathi 2012).

Finally, the overuse of antibiotics has an important impact on health economic budgets. The cost of antimicrobials in children's hospitals in the USA has amounted to USD 192.9 million annually, corresponding to 17.1% of the total pharmacy budget (USD 1.13 billion) (Ross 2015). One Cochrane Review showed that the implementation of antibiotic policies/antimicrobial stewardship programmes effectively reduces the use of antibiotics (Davey 2017). To create the most appropriate antibiotic policies for neonatal sepsis, there is a need to base these policies on an updated systematic review with meta-analysis.

In conclusion, there is a need for an updated systematic review assessing the effects of different antibiotic regimens for early-onset neonatal sepsis.

OBJECTIVES

To assess the beneficial and harmful effects of different antibiotic regimens for early-onset neonatal sepsis.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs, quasi-RCTs, and cluster-RCTs regardless of publication type, publication status, publication date, and language. We excluded crossover trials.

Types of participants

We included neonates (from birth to 72 hours of life at randomisation) clinically suspected of or diagnosed with early-onset sepsis (as defined by trialists), severe/deep-seated infections such as meningitis, osteomyelitis, endocarditis, or necrotising enterocolitis.

We excluded trials where the suspicion of sepsis was solely based on risk factors with no clinical signs of sepsis.

Types of interventions

We accepted any type of antibiotic or combination of antibiotics such as the following:

- broad-spectrum beta-lactam antibiotics defined as broad-spectrum penicillins (e.g. ampicillin, amoxicillin, piperacillin, ticarcillin, carbenicillin, and mezlocillin), cephalosporins (e.g. cefazolin, cephalexin, cefuroxime, cefotetan, cefoxitin, ceftriaxone, cefotaxime, ceftazidime, cefepime, cefazolin, ceftobiprole, ceftolozane, and cefoperazone), carbapenems (e.g. imipenem, meropenem, doripenem, and ertapenem), and monobactams (e.g. aztreonam);
- narrow-spectrum antibiotics including narrow-spectrum penicillins (e.g. oxacillin, cloxacillin, dicloxacillin, nafcillin, methicillin, and penicillin G);
- beta-lactam antibiotics with beta-lactamase inhibitors (e.g. avibactam, clavulanic acid, sulbactam, and tazobactam);
- combinations of beta-lactam with aminoglycoside (e.g. gentamicin);
- combinations of beta-lactam with glycopeptide (e.g. vancomycin and teicoplanin);
- combinations of glycopeptide with aminoglycoside.

We planned to assess the following comparisons:

- aminoglycoside added to any type of antibiotic versus antibiotic (same antibiotic as in the experimental group);
- broad-spectrum antibiotic and aminoglycoside versus narrower-spectrum antibiotic (defined in the above description, e.g. penicillins) and aminoglycoside (same aminoglycoside as in the experimental group);
- any other used antibiotic regimen (not included in the above-mentioned comparisons) versus any other used antibiotic regimen (not included in the above-mentioned comparisons).

Types of outcome measures

Primary outcomes

- All-cause mortality.

Secondary outcomes

- Proportion of participants with one or more serious adverse event. We defined a serious adverse event as any untoward medical occurrence that resulted in death; was life-threatening; jeopardised the participant; was persistent; or led to significant disability, hospitalisation, or prolonged hospitalisation (ICH-GCP 2015). As we expected the reporting of serious adverse events in many trials to be very heterogeneous and not strictly according to the recommendations regarding good clinical practice from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP) (ICH-GCP 2015), we included the event as a serious adverse event if the trial authors either:
  * used the term 'serious adverse event' but not referred to ICH-GCP; or
  * reported the proportion of participants with an event we considered fulfil the ICH-GCP definition. If studies reported several such events, we chose the highest proportion reported in each trial to avoid double-counting.
- Respiratory support, defined as the need for respiratory support, such as non-invasive ventilation (e.g. continuous positive airway pressure (CPAP)) or invasive ventilation (e.g. respirator).
- Circulatory support, defined as the need for circulatory support such as fluid bolus or vasoactive medication (e.g. inotropic agents or vasopressors).
- Nephrotoxicity (as defined by the trial author(s)).
- Presence of moderate-to-severe neurological developmental and sensory impairment (defined as a functional abnormality in the function of the brain, spinal cord, muscles, nerves, eyes or ears; or as any significant lag in a child's physical or motor, cognitive, behavioural, emotional, or social development, in comparison with other children of the same age and sex within similar environments. If formal evaluation tools were used to assess neurodevelopmental impairment, we used a threshold of –2 standard deviations (SDs) of the normal. Furthermore, severe brain injury per se is included, such as intraventricular haemorrhage grade 3 and 4 (Papile 1978; Volpe 2008), and periventricular leukomalacia.

- Necrotising enterocolitis during or after treatment, defined by Bell's criteria 2 (Bell 1978).
- Ototoxicity as defined by trial author(s).

We assessed all dichotomised outcomes as proportions.

We used the trial results reported at maximum follow-up (our primary time point of interest).

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialised register; neonatal.cochrane.org/resources-review-authors). We searched for errata or retractions 12 March 2021 from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and we found none.

Electronic searches

We conducted a comprehensive literature search including: the Cochrane Central Register of Controlled Trials (CENTRAL 2021, Issue 3) in the Cochrane Library; Ovid MEDLINE (1946 to 12 March 2021); Embase via Ovid (1974 to 12 March 2021); CINAHL (EBSCOhost; 12 March 2021); LILACS (Bireme; 1982 to 12 March 2021) and Science Citation Index EXPANDED and Conference Proceedings Citation Index – Science (1990 to 12 March 2021). We have included the search strategies for each database in Appendix 1.

We searched ZETOC for abstracts of scientific conferences or symposia (zetoc.jisc.ac.uk/).

We searched clinical trial registries for ongoing or recently completed trials. We searched the World Health Organization's International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/), and the U.S. National Library of Medicine's ClinicalTrials.gov (clinicaltrials.gov), via Cochrane CENTRAL. Additionally, we searched the ISRCTN Registry for any unique trials not identified through the Cochrane CENTRAL search (www.isrctn.com/).

We applied no language restrictions. If we identified any papers in a language not known by the review author group, we sought translation assistance and acknowledged the translators in the Acknowledgements section of the review.

Searching other resources

We searched the reference lists of any articles selected for inclusion in this review to identify additional relevant articles.

We searched clinical trial registers of Europe and the USA, websites of pharmaceutical companies, the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) websites, to identify unpublished trials.

Data collection and analysis

Selection of studies

Three review authors working in pairs (SKK, CN, and SS) independently screened titles and abstracts. We retrieved all relevant full-text study reports/publications. Two review authors (SKK and SS) independently screened the full text and identified trials for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a third review author (JCJ). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and a Characteristics of excluded studies table.

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

Data extraction and management

We used validated data collection forms for trial characteristics and outcome data. Three review authors working in pairs (SKK, CN, and SS) extracted trial characteristics from included trials. We extracted the following trials characteristics:

- methods: trial design, total duration of the trial, number of trial centres and location, trial setting, withdrawals, and date of the trial;
- participants: number of participants in each intervention group, mean age, age range, gender, diagnostic criteria, inclusion criteria, and exclusion criteria;
- interventions: intervention (including dosage, route of administration, and length of empirical treatment) and comparison;
- outcomes: primary and secondary outcomes specified and collected, and time points reported;
- notes: funding for trial and notable conflicts of interest of trial authors.

Three review authors (SKK, CN, and SS) independently extracted outcome data from included trials. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We resolved disagreements by discussion, or by involving a third review author (JCJ). One review author (SKK) transferred data into Review Manager 5 (Review Manager 2020). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SS) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (SKK and SS) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2020), for the following domains.

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

We resolved any disagreements through discussion or by consulting a third review author (JCJ). See Appendix 2 for a more detailed description of risk of bias for each domain.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Korang 2021), and planned to report any deviations from it in the Differences between protocol and review section of the review.

Measures of treatment effect

Dichotomous outcomes

We calculated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials and the neonatal unit (or subunit) for cluster-RCTs. For cluster-RCTs, we undertook analyses at the level of the individual while accounting for the clustering in the data using the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

Dealing with missing data

We did not impute missing values for any outcomes in our primary analysis.

We contacted trial investigators and sponsors to verify key trial characteristics and obtain missing numerical outcome data where possible (e.g. when we identified a study as an abstract only).

Assessment of heterogeneity

We planned to visually inspect forest plots to assess for signs of heterogeneity and explore possible heterogeneity in our prespecified subgroup analyses. We also planned to inspect trial characteristics across trials to identify clinical heterogeneity. We planned to assess the presence of statistical heterogeneity using the Chi^2 test (threshold $P < 0.10$) and measure the quantities of heterogeneity using the I^2statistic (Higgins 2002; Higgins 2003). If we detected moderate or high heterogeneity (I^2 statistic of 50% or greater), we planned to explore the possible causes (i.e. differences in study design, participants, interventions, or completeness of outcome assessments). Ultimately, we decided that a meta-analysis should be avoided (Higgins 2002; Higgins 2003).

Assessment of reporting biases

We planned to use a funnel plot to assess publication bias if 10 or more trials met the inclusion criteria. We planned to visually inspect funnel plots to assess the risk of bias. We tested asymmetry using the Harbord test (Harbord 2006).

Data synthesis

Meta-analysis

We planned to undertake this meta-analysis according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). We used Review Manager 5 to analyse data (Review Manager 2020).

We planned to assess our intervention effects using fixed-effect meta-analyses (Demets 1987), in accordance with the policies of Cochrane Neonatal. We had one primary outcome and, therefore, we considered a P value of 0.05 or less as the threshold for statistical significance (Jakobsen 2014). We planned to use the eight-step procedure to assess if the threshold for significance was crossed (Jakobsen 2014). Where data were only available from one trial, we planned to use Fisher's exact test for dichotomous data (Fisher 1922).

Where a trial reported multiple trial arms, we planned to only include the relevant trial arms. If two comparisons were combined in the same meta-analysis, we would halve the control group to avoid double-counting.

Trial sequential analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. Therefore, we planned to perform trial sequential analysis (TSA) on the outcomes to calculate the required information size and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries (Brok 2008; Brok 2009; Thorlund 2009; Thorlund 2010; Thorlund 2011; TSA 2017; Wetterslev 2008; Wetterslev 2009). We wished to control the risks of type I errors and type II errors. A more detailed description of TSA can be found at www.ctu.dk/tsa/. We planned to assess our TSA intervention effects with both a random-effects model (DerSimonian 1986), and a fixed-effect model (Demets 1987). We planned to use the more conservative point estimate of the two (Jakobsen 2014). The more conservative point estimate would be the estimate closest to zero effect. If the two estimates were similar, we used the estimate with the widest CI.

For dichotomous outcomes, we planned to estimate the required information size based on the observed, unweighted proportion of neonates with an outcome in the control group (the cumulative proportion of participants with an event in the control groups relative to all participants in the control groups), a relative risk reduction of 20%, an alpha of 5%, a beta of 20%, and diversity as suggested by the trials in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses for our primary outcome.

- High risk of bias trials compared to low risk of bias trials.
- Gestational age: term (37 weeks or greater) compared to preterm.
- Trials from high-income countries compared to trials from LMICs, as defined by the World Bank (World Bank 2019).
- Early-onset sepsis defined as onset within 48 hours, within 72 hours, within one week, or as defined by the trial authors.
- Clinically suspected sepsis compared to culture-supported suspicion of severe bacterial infection.

We planned to use the formal test for subgroup interactions in Review Manager 5 (Review Manager 2020).

Sensitivity analysis

To assess the potential impact of the missing data, we planned to perform the following two sensitivity analyses on the primary outcome.

- 'Best-worst-case' scenario: we planned to assume that all participants lost to follow-up in the experimental group had

survived; and all those participants with missing outcomes in the control group had not survived.
- 'Worst-best-case' scenario: we planned to assume that all participants lost to follow-up in the experimental group had not survived and that all those participants lost to follow-up in the control group had survived.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence of the following (clinically relevant) outcomes: our primary outcome (all-cause mortality), and five secondary outcomes (serious adverse event, circulatory support, nephrotoxicity, neurological developmental impairment, and necrotising enterocolitis).

Two review authors (SKK and SS) independently assessed the certainty of the evidence for each of the outcomes above. We considered evidence from RCTs as high certainty but downgraded 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 used the GRADEpro GDT Guideline Development Tool to create five 'Summary of findings' tables to report the certainty of the evidence for the following five comparisons of antibiotic regimens.

- Ampicillin plus gentamicin compared with penicillin plus gentamicin.
- Piperacillin plus tazobactam compared with amikacin.
- Ticarcillin plus clavulanic acid compared with piperacillin plus gentamicin.
- Piperacillin compared with ampicillin plus amikacin.
- Ceftazidime compared with benzylpenicillin plus gentamicin.

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

- High certainty: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low certainty: we are very uncertain about the estimate.

RESULTS

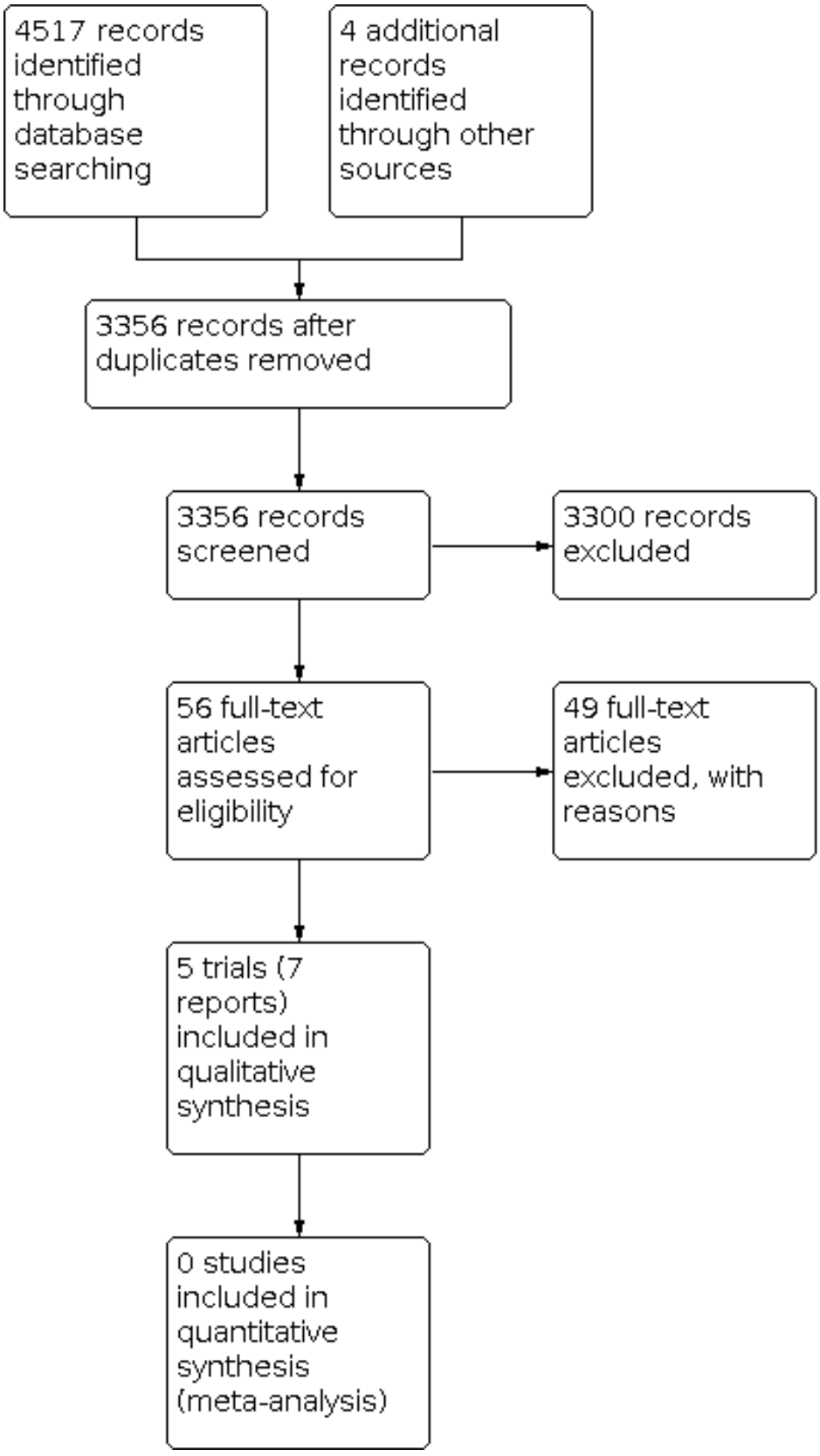
Description of studies

We assessed all studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020), and the protocol for this review (Korang 2021). Characteristics of each study can be found in the Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies tables.

Results of the search

Our initial search identified 3356 references. We deemed 56 studies relevant and obtained full texts for further evaluation (see Figure 1). Of these, we included five completed trials (Hammerberg 1989; Metsvaht 2010; Miall-Allen 1988; Snelling 1983: Tewari 2014). We identified no ongoing trials relevant for the review.

Figure 1. Study flow diagram.



Included studies

Five trials met our inclusion criteria (Hammerberg 1989; Metsvaht 2010; Miall-Allen 1988; Snelling 1983; Tewari 2014). For detailed descriptions, see the Characteristics of included studies table. Two additional papers were included as secondary publications (Metsvaht 2011; Parm 2010), to Metsvaht 2010. Four were single centre trials (Hammerberg 1989; Miall-Allen 1988; Snelling 1983; Tewari 2014), and one trial was a cluster-RCT conducted at two centres (Metsvaht 2010).

Participants

The five included trials randomised 865 participants. The mean proportion of girls was 43% among the trials that reported the participant's gender.

Interventions

The five trials compared different antibiotic regimens.

- Metsvaht 2010 compared ampicillin plus gentamicin with benzylpenicillin plus gentamicin.
- Tewari 2014 compared piperacillin plus tazobactam with amikacin.
- Miall-Allen 1988 compared ticarcillin plus clavulanic acid with piperacillin plus gentamicin.
- Hammerberg 1989 compared piperacillin with ampicillin plus amikacin.
- Snelling 1983 compared ceftazidime with benzylpenicillin plus gentamicin.

Co-interventions

Participants in all five included trials received standard care in addition to the allocated antibiotic regimen.

Outcomes

All five included trials reported all-cause mortality. Five trials reported serious adverse events. None of the trials reported serious adverse events according to the ICH-GCP, neither did they report serious adverse events as a composite outcome. Therefore, we reported the proportion of participants with an event we considered fulfilled the ICH-GCP definition (e.g. need for vasoactive drugs or death). As there were several such events, we chose the highest proportion reported in each trial to avoid double-counting. One trial reported circulatory support (Metsvaht 2010), nephrotoxicity (Hammerberg 1989), necrotising enterocolitis (Metsvaht 2010), and neurological developmental impairment (Metsvaht 2010). None of the trials reported respiratory support and ototoxicity.

Antibiotic resistance in included trials

One trial (from Estonia) reported three cases of resistance (to ampicillin) out of the six participants with positive cultures in the ampicillin plus gentamicin group, and five cases of resistance (to both penicillin and gentamicin) out of the eight participants with positive cultures in the penicillin plus gentamicin group (Metsvaht 2010).

One trial (from the USA) reported a single case of resistance (towards piperacillin) out of the 12 participants with positive cultures in the piperacillin group, but no resistance was reported among the 15 participants with positive cultures in the ampicillin plus amikacin group (Hammerberg 1989).

One trial (from Iran) reported one case of resistance out of the three participants with positive cultures in the piperacillin plus tazobactam group, but there was no resistance among the two participants with positive cultures in the amikacin group (Tewari 2014).

One trial (from the USA) comparing ceftazidime with benzylpenicillin plus gentamicin reported that none of the six participants with positive cultures grew any resistant isolates to the allocated antibiotics (Snelling 1983).

One trial (from the USA) reported two cases of resistance to ticarcillin out of the five participants with positive cultures in the ticarcillin plus clavulanic acid group, but no cases of resistance out of the seven participants with positive cultures in the piperacillin plus gentamicin group. (Miall-Allen 1988).

Excluded studies

We assessed 49 trials as relevant on review of the abstract, but later excluded them upon review of the full publication.

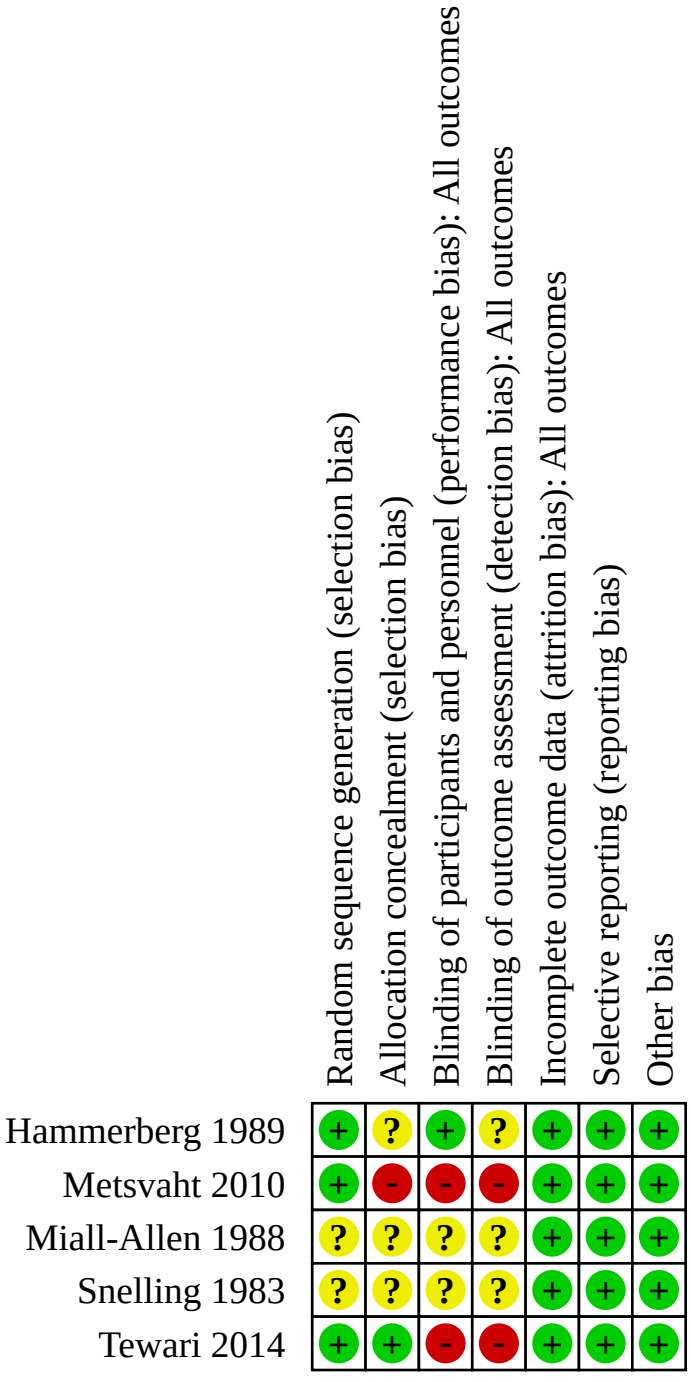
- We excluded 23 trials due to being a mix of early-onset and late-onset neonatal sepsis (Adelman 1987a; Adelman 1987b; Baqui 2013; Begue 1998; De Louvois 1992; Faix 1988; Fogel 1983; Gokalp 1991; Haffejee 1984; Hall 1988; Lee 2005; Marks 1978; Mir 2017; Molyneux 2017; Odio 1987; Taheri 2011; Tessin 1988; Tessin 1989; Tshefu 2015a; Tshefu 2015b; Umana 1990; Wiese 1988; Zaidi 2013).
- In eight trials, both groups received the same antibiotics (Auriti 2005; Chowdhary 2006; Gathwala 2010; Hansen 1980; Langhendries 1993; McCracken 1976; Mulubwa 2020; Rohatgi 2017).
- Three trials included only late-onset neonatal sepsis (Ceriani 2014; Lutsar 2020; Millar 1992).
- One trial included adults (Bassetti 1991).
- Three trials were not randomised (Ebrahim 1969; Odio 1995; Oral 1998).
- Eleven trials did not include neonates with early-onset sepsis (Alinejad 2018; Aronoff 1984; Chartrand 1984; Collins 1998; Deville 2003; Feigin 1976; Jantausch 2003; Kaplan 2003; Lonnerholm 1982; Viganó 1995; Wells 1984).

When the participant age was unclear or separate data were not available for early-onset sepsis, we contacted the trial authors. However, we obtained no additional information on these trials.

Risk of bias in included studies

We assessed all the included trials at overall high risk of bias (Figure 2). We contacted the authors for clarification, as some data were missing and several bias domains were unclear.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Two trials did not describe how allocation sequence generation was performed resulting in unclear risk of bias (Miall-Allen 1988; Snelling 1983). Three trials used a computer generated sequence, flipped a coin, or used an online randomisation service resulting in low risk of bias (Hammerberg 1989; Metsvaht 2010; Tewari 2014).

One trial used serially numbered opaque sealed envelopes to conceal allocation and was at low risk of bias (Tewari 2014). Three trials did not describe allocation concealment and were at unclear risk of bias (Hammerberg 1989; Miall-Allen 1988; Snelling 1983). One trial was a cluster-RCT resulting in assessment of high risk of bias (Metsvaht 2010).

Blinding

Two trials did not blind participants, treatment providers, or outcome assessors resulting in high risk of bias. Two trials did not describe blind participants, treatment providers, or outcome assessors resulting in unclear risk of bias. One trial did blind treatment providers and participants, but did not describe the blinding of outcome assessors resulting in 'low' and 'unclear' risk of bias respectively.

Incomplete outcome data

All five included trials used either intention-to-treat analysis or had no/few dropouts resulting in low risk of attrition bias.

Selective reporting

All five included trials reported mortality resulting in low risk of reporting bias.

Other potential sources of bias

We observed no other biases.

Effects of interventions

See: **Summary of findings 1** Ampicillin plus gentamicin compared with penicillin plus gentamicin for early-onset neonatal sepsis; **Summary of findings 2** Piperacillin plus tazobactam compared with amikacin for early-onset neonatal sepsis; **Summary of findings 3** Ticarcillin plus clavulanic acid compared with piperacillin plus gentamicin for early-onset neonatal sepsis; **Summary of findings 4** Piperacillin compared with ampicillin plus amikacin for early-onset neonatal sepsis; **Summary of findings 5** Ceftazidime compared with benzylpenicillin plus gentamicin for early-onset neonatal sepsis

Five trials met the inclusion criteria (Hammerberg 1989; Metsvaht 2010; Miall-Allen 1988; Snelling 1983; Tewari 2014). We were able to assess in part all-cause mortality as our primary outcome and the secondary outcomes serious adverse events, circulatory support, neurological developmental impairment, nephrotoxicity, and necrotising enterocolitis. However, the five trials assessed comparisons with different antibiotic regimens. Hence, we performed no meta-analyses, TSAs, or subgroup analyses. We estimated the optimal information size for all outcomes and the optimal information size was not reached for any of the comparisons (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).

Ampicillin plus gentamicin compared with benzylpenicillin plus gentamicin

We found one trial comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin (Summary of findings 1).

Primary outcome

All-cause mortality

One trial randomising 283 participants comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin showed no evidence of a difference in all-cause mortality (RR 0.56, 95% CI 0.30 to 1.06; very low-certainty evidence; Analysis 1.1) (Metsvaht 2010).

Secondary outcomes

Serious adverse events

One trial randomising 283 participants comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin showed no evidence of a difference in serious adverse events (RR 0.93, 95% CI 0.72 to 1.21; very low-certainty evidence; Analysis 1.2) (Metsvaht 2010).

Respiratory support

The trial did not report respiratory support.

Circulatory support

One trial randomising 283 participants comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin showed no evidence of a difference in circulatory support (RR 0.93, 95% CI 0.72 to 1.21; very low-certainty evidence; Analysis 1.3) (Metsvaht 2010).

Nephrotoxicity

The trial did not report nephrotoxicity.

Neurological developmental impairment

One trial randomising 283 participants comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin showed no evidence of a difference in neurological developmental impairment (RR 0.81, 95% CI 0.40 to 1.61; very low-certainty evidence; Analysis 1.4) (Metsvaht 2010).

Necrotising enterocolitis

One trial randomising 283 participants comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin showed no evidence of a difference in necrotising enterocolitis (RR 1.24, 95% CI 0.50 to 3.05; very low-certainty evidence; Analysis 1.5) (Metsvaht 2010).

Ototoxicity

The trial did not report ototoxicity.

Piperacillin plus tazobactam compared with amikacin

We found one trial comparing piperacillin plus tazobactam with amikacin (Summary of findings 2).

Primary outcome

All-cause mortality

One trial randomising 59 participants comparing piperacillin plus tazobactam with amikacin showed no evidence of a difference in all-cause mortality (RR 0.32, 95% CI 0.01 to 7.61; very low-certainty evidence; Analysis 2.1) (Tewari 2014).

Secondary outcomes

Serious adverse events

One trial randomising 59 participants comparing piperacillin plus tazobactam with amikacin showed no evidence of a difference in serious adverse events (RR 0.97, 95% CI 0.15 to 6.41; very low-certainty evidence; Analysis 2.2) (Tewari 2014).

Respiratory support

The trial did not report respiratory support.

Circulatory support

The trial did not report circulatory support.

Nephrotoxicity

The trial did not report nephrotoxicity.

Neurological developmental impairment

The trial did not report neurological developmental impairment.

Necrotising enterocolitis

The trial did not report necrotising enterocolitis.

Ototoxicity

The trial did not report ototoxicity.

Ticarcillin plus clavulanic acid compared with piperacillin plus gentamicin

We found one trials comparing ticarcillin plus clavulanic acid compared with piperacillin (Summary of findings 3).

Primary outcome

All-cause mortality

One trial randomising 72 participants comparing ticarcillin plus clavulanic acid with piperacillin plus gentamicin showed no evidence of a difference in all-course mortality (RR 0.75, 95% CI 0.19 to 2.90; very low-certainty evidence; Analysis 3.1) (Miall-Allen 1988).

Secondary outcomes

Serious adverse events

One trial randomising 72 participants comparing ticarcillin plus clavulanic acid with piperacillin plus gentamicin showed no evidence of a difference in serious adverse events (RR 0.75, 95% CI 0.19 to 2.90; very low-certainty evidence; Analysis 3.2) (Miall-Allen 1988).

Respiratory support

The trial did not report respiratory support.

Circulatory support

The trial did not report circulatory support.

Nephrotoxicity

The trial did not report nephrotoxicity.

Neurological developmental impairment

The trial did not report neurological developmental impairment.

Necrotising enterocolitis

The trial did not report necrotising enterocolitis.

Ototoxicity

The trial did not report ototoxicity.

Piperacillin compared with ampicillin plus amikacin

We found one trial comparing piperacillin with ampicillin plus amikacin (Summary of findings 4).

Primary outcome

All-cause mortality

One trial randomising 396 participants comparing piperacillin with ampicillin plus amikacin showed no evidence of a difference in all-course mortality (RR 0.62, 95% CI 0.35 to 1.10; very low-certainty evidence; Analysis 4.1) (Hammerberg 1989).

Secondary outcomes

Serious adverse events

One trial randomising 396 participants comparing piperacillin with ampicillin plus amikacin showed no evidence of a difference in serious adverse events (RR 0.62, 95% CI 0.35 to 1.10; very low-certainty evidence; Analysis 4.2) (Hammerberg 1989).

Respiratory support

The trial did not report respiratory support.

Circulatory support

The trial did not report circulatory support.

Nephrotoxicity

One trial randomising 396 participants comparing piperacillin with ampicillin plus amikacin showed no evidence of a difference in nephrotoxicity (RR 1.14, 95% CI 0.80 to 1.63; very low-certainty evidence; Analysis 4.3) (Hammerberg 1989).

Neurological developmental impairment

The trial did not report neurological developmental impairment.

Necrotising enterocolitis

The trial did not report necrotising enterocolitis.

Ototoxicity

The trial did not report ototoxicity.

Ceftazidime compared with benzylpenicillin plus gentamicin

We found one trial comparing ceftazidime compared with benzylpenicillin plus gentamicin (Summary of findings 5).

Primary outcome

All-cause mortality

One trial randomising 55 participants comparing ceftazidime with benzylpenicillin plus gentamicin reported no deaths (Analysis 5.1) (Snelling 1983).

Secondary outcomes

Serious adverse events

One trial randomising 55 participants comparing ceftazidime with benzylpenicillin plus gentamicin reported no serious adverse events (Analysis 5.2) (Snelling 1983).

Respiratory support

The trial did not report respiratory support.

Circulatory support

The trial did not report circulatory support.

Nephrotoxicity

The trial did not report nephrotoxicity.

Neurological developmental impairment

The trial did not report neurological developmental impairment.

Necrotising enterocolitis

The trial did not report necrotising enterocolitis.

Ototoxicity

The trial did not report ototoxicity.

DISCUSSION

Summary of main results

Evidence from five RCTs including 865 participants contributed data to our prespecified outcomes. We found insufficient information to assess the relative effects of any of the antibiotics compared. Furthermore, these trials had high risk of bias. In summary, we graded the level of evidence as very-low certainty.

We conducted no meta-analyses due to a lack of relevant data. The optimal information size was not reached for any of the comparisons (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).

When assessing all-cause mortality, one trial randomising 283 participants found no evidence of a difference when comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin (RR 0.56, 95% CI 0.30 to 1.06; very low-certainty evidence) (Metsvaht 2010); one trial randomising 59 participants found no evidence of a difference when comparing piperacillin plus tazobactam with amikacin (RR 0.32, 95% CI 0.01 to 7.61; very low-certainty evidence) (Tewari 2014); one trial randomising 72 participants found no evidence of a difference when comparing ticarcillin plus clavulanic acid with piperacillin plus gentamicin (RR 0.75, 95% CI 0.19 to 2.90; very low-certainty evidence) (Miall-Allen 1988); one trial randomising 396 participants found no evidence of a difference when comparing piperacillin with ampicillin plus amikacin (RR 0.62, 95% CI 0.35 to 1.10; very low-certainty evidence) (Hammerberg 1989); and one trial randomising 55 participants comparing ceftazidime with benzylpenicillin plus gentamicin reported no deaths (Snelling 1983).

When assessing serious adverse events, one trial randomising 283 participants found no evidence of a difference when comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin (RR 0.93, 95% CI 0.72 to 1.21; very low-certainty evidence) (Metsvaht 2010); one trial randomising 59 participants found no evidence of a difference when comparing piperacillin plus tazobactam with amikacin (RR 0.97, 95% CI 0.15 to 6.41; very low-certainty evidence) (Tewari 2014); one trial randomising 72 participants found no evidence of a difference when comparing ticarcillin plus clavulanic acid with piperacillin plus gentamicin (RR 0.75, 95% CI 0.19 to 2.90; very low-certainty evidence) (Miall-Allen 1988); one trial randomising 396 participants found no evidence of a difference when comparing piperacillin with ampicillin plus amikacin (RR 0.62, 95% CI 0.35 to 1.10; very low-certainty evidence) (Hammerberg 1989); and one trial randomising 55 participants comparing ceftazidime or benzylpenicillin plus gentamicin reported no serious adverse events (Snelling 1983).

None of the trials reported respiratory support.

When assessing circulatory support, one trial randomising 283 participants found no evidence of a difference when comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin (RR 0.93, 95% CI 0.72 to 1.21; very low-certainty evidence) (Metsvaht 2010).

When assessing nephrotoxicity, one trial randomising 396 participants found no evidence of a difference when comparing piperacillin with ampicillin plus amikacin (RR 1.14, 95% CI 0.80 to 1.63; very low-certainty evidence) (Hammerberg 1989).

When assessing neurological developmental impairment, one trial randomising 283 participants found no evidence of a difference when comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin (RR 0.81, 95% CI 0.40 to 1.61; very low-certainty evidence) (Metsvaht 2010).

When assessing necrotising enterocolitis, one trial randomising 283 participants found no evidence of a difference when comparing ampicillin plus gentamicin with benzylpenicillin plus gentamicin (RR 1.24, 95% CI 0.50 to 3.05; very low-certainty evidence) (Metsvaht 2010).

None of the trials reported ototoxicity.

The benefits and harms of different antibiotic regimens remain unclear owing to the lack of well-powered trials and the high risks of bias.

Overall completeness and applicability of evidence

We were unable to perform any meta-analyses due to lack of relevant data and the identified trials were underpowered. Therefore, it was not possible to conclude whether one antibiotic regimen was superior to another in neonates with early-onset sepsis. More and larger RCTs with low risk of bias are needed.

Quality of the evidence

Heterogeneity

As no meta-analysis was performed, we did not assess heterogeneity.

Risk of systematic error ('bias')

We found no trials and no outcome results at low risk of bias.

It was not possible to assess publication bias, as we included only five studies.

Risk of random error ('play of chance')

It was not possible to perform TSA, as we performed no meta-analyses.

GRADE

We assessed the certainty of the evidence for each outcome using the GRADE approach. The GRADE assessment generally showed that evidence was of very-low certainty. The reasons for the GRADE assessment are given in the footnotes of the tables (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; and Summary of findings 5).

Potential biases in the review process

The main limitation of this review was the low number of randomised participants and hence paucity of evidence for the use of different antibiotic regimens. Another limitation was that some trials did not distinguish between early-onset and late-onset neonatal sepsis, which resulted in exclusion of a large number of potentially relevant trials. Most included trials were from before 1990.

We used the broadest possible definition of early-onset sepsis as there is no internationally agreed-upon consensus definition of neonatal sepsis. This could potentially have caused the inclusion of trials with very a heterogeneous population. The consequence was that some trials included participants with suspected early-onset sepsis may have included participants that did not have sepsis. We decided to use a broad definition to potentially include more trials and obtain more power. However, despite this broad approach, we only found five trials.

If we had found trials with different sepsis definitions, we would have explored the statistical and clinical heterogeneity (according to our protocol (Korang 2021)), and considered whether meta-analysis could be justified.

As indicated in our Background section, there might be substantial differences between the pathogens across countries. The optimal antibiotic regimen might, therefore, vary according to country and local risks of antibiotic resistance. We did not include enough trials to confirm or reject that this was the case. Despite the anticipated differences between the antibiotic resistance at different sites, there could still be important differences between antibiotic regimens on clinical outcomes that would lead to generalised recommendations (Paul 2010). Furthermore, adverse events of the antibiotics are presumably similar across different populations.

For future updates, we will systematically assess the clinical heterogeneity (Barbateskovic 2021).

Agreements and disagreements with other studies or reviews

The additional trials included in this review update did not change the overall conclusions and recommendations of the former review (Mtitimila 2004).

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence does not allow confirmation or rejection of one antibiotic regimen being superior to another.

Implications for research

The primary focus should be to develop an international consensus definition of neonatal sepsis (McGovern 2020; Wynn 2014; Wynn 2016). Then high-quality randomised controlled trials are needed to assess the effects of different antibiotic regimens for sepsis in newborn infants. Such trials should:

- randomise a sufficient number of participants to demonstrate reliable results;
- assess all-cause mortality and serious adverse events;
- be conducted with low risk of bias;
- adhere to consensus definitions of suspected and diagnosed early-onset neonatal when such emerge;
- measure antibiotic resistance among the culture-positive participants;
- assess differences between sites, countries, and regions included.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Hammerberg 1989

Study characteristics	
Methods	Randomised controlled trial Duration: at the discretion of the attending neonatologist. Maximum duration 10 days Date: NA Location: NICU in Canada
Participants	396 infants suspected of early-onset sepsis Inclusion criteria: had combination of risk factors or clinical signs (or both) compatible with sepsis; aged < 7 days of life Gender (boy/girl): NA Age: median gestational age 31.5 weeks. 97% were < 72 hours at randomisation. Exclusion criteria: previously received antibiotics, had underlying congenital conditions incompatible with life or were known to be septic.
Interventions	**Intervention 1:** piperacillin 50 mg/kg and placebo (5% dextrose in water) every 12 hours **Intervention 2:** ampicillin 50 mg/kg and amikacin 7.5 mg/kg every 12 hours Co-interventions: not described
Outcomes	**Primary outcome** • All-cause mortality **Secondary outcomes** • Mortality due to infection • Duration of treatment • Renal impairment (nephrotoxicity) defined as > 100 µmol/L • Hepatic impairment defined as total serum bilirubin > 20 µmol/L **Follow-up** • Not described
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used computer-generated randomised sequence.
Allocation concealment (selection bias)	Unclear risk	Not described.

Hammerberg 1989 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as being blinded and used placebo.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	Low risk	Reported mortality.
Other bias	Low risk	No other bias observed.

Metsvaht 2010

Study characteristics	
Methods	Cluster randomised trial Duration: NA Date: 2 August 2006 to 30 November 2007 Location: 2 tertiary NICUs in Estonia
Participants	283 neonates admitted within 72 hours of life, needing early empiric antibiotic treatment for early-onset neonatal sepsis or risk factors of infection according to the CDC criteria (e.g. maternal chorioamnionitis or maternal risk factors of infection or preterm labour in < 35 weeks of gestation, or a combination of these). Gender (boy/girl): 163/120 Age: median gestational age 31 weeks. < 72 hours at randomisation Exclusion criteria: prior administration of a different antibiotic regimen for > 24 hours or presence of suspected or confirmed meningitis, NEC, peritonitis, severe sepsis, or septic shock with isolation of micro-organisms resistant to the study regimen in maternal urinary tract or birth canal or other situations that required different antibacterial treatment
Interventions	**Intervention 1:** gentamicin (4–5 mg/kg 24–48 hourly, based on gestational age and postnatal age) + ampicillin (25 mg/kg 8–12 hourly, based on gestational age and postnatal age) **Intervention 2:** gentamicin (4–5 mg/kg 24–48 hourly, based on gestational age and postnatal age) + penicillin G (25 000 IU/kg 8–12 hourly, based on gestational age and postnatal age) Co-interventions: not described
Outcomes	**Primary outcome** • Treatment failure **Secondary outcomes** • 28-day and NICU mortality

Metsvaht 2010 *(Continued)*

- NICU and hospital stay
- Duration of early empiric antibiotic treatment
- Duration of respiratory support and vasoactive treatment
- Rate of LOS and use of additional antibacterial therapy
- Presence of NEC stage II–III
- Patent arterial duct requiring surgery
- Threshold retinopathy of prematurity requiring laser therapy
- Severe IVH (stage III–IV)
- Severe bronchopulmonary dysplasia

Follow-up

- Until discharge from NICU or 60 days of life

Notes	The study was supported by Estonian Science Foundation Grant No 6984; Estonian Target Financing No 2726, and ESPID Small Grant Award.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Cluster randomised trial. Was assigned randomly by flipping a coin.
Allocation concealment (selection bias)	High risk	Whole unit was treated the same.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment was not performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	Low risk	Reported mortality and serious adverse events.
Other bias	Low risk	No other biases were identified.

Miall-Allen 1988

Study characteristics

Methods	Randomised controlled trial Duration: maximum 10 days, but until 48 hours if participants were asymptomatic and afebrile Date: NA Location: Hammersmith Hospital, London, UK

Miall-Allen 1988 *(Continued)*

Participants	72 neonates with suspected infection up to 48 hours of age Gender (boys/girls): 39/33 Age: < 48 hours at randomisation Inclusion criteria: < 48 hours after birth with confirmed sepsis, signs highly suggestive of sepsis, or who were at particular high risk of developing sepsis Exclusion criteria: not described
Interventions	**Intervention 1:** ticarcillin + clavulanic acid 80 mg/kg 12 hourly or 8 hourly if > 2 kg (n = 32) **Intervention 2:** piperacillin 100 mg/kg 12 hourly + gentamicin 2.5 mg/kg 12 hourly (n = 40)
Outcomes	• Mortality • Treatment failure • Bacteriological resistance **Follow-up** • 4–6 weeks after end of treatment
Notes	It was not possible to contact the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only described as randomised.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	Low risk	Reported mortality and serious adverse events.
Other bias	Low risk	No other biases identified.

Snelling 1983

Study characteristics

Snelling 1983 *(Continued)*

Methods	Randomised controlled trial Duration: 7–10 days, but 48 hours if participants were asymptomatic and had negative blood cultures Date: NA Location: Liverpool Maternity Hospital, Liverpool, UK
Participants	55 neonates with suspected serious infection within 48 hours of birth Gender (boys/girls): NA Age: < 48 hours at randomisation Inclusion criteria: < 48 hours after birth with confirmed sepsis, signs highly suggestive of sepsis or who were at particular high risk of developing sepsis Exclusion criteria: not described
Interventions	**Intervention 1:** ceftazidime 50 mg/kg 12 hourly (n = 31) **Intervention 2:** gentamicin 3 mg/kg + benzylpenicillin 15 mg/kg 12 hourly (n = 24)
Outcomes	• Mortality • Treatment failure • Bacteriological resistance **Follow-up** • Not reported
Notes	Not possible to contact the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of intervention and outcome measurements not reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of intervention and outcome measurements not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	Low risk	Reported mortality and serious adverse events.
Other bias	Low risk	No other biases were identified.

Tewari 2014

Study characteristics	
Methods	Randomised controlled trial Duration: ≥ 48 hours Date: 1 May 2009 to 30 April 2011 Location: Neonatal Unit, Department of Pediatrics, Kerala Institute of Medical Sciences, Trivandrum, India
Participants	59 neonates with suspected early-onset neonatal sepsis Gender (boys/girls): NA Mean age: 1 day Diagnostic criteria: risk factors were maternal fever (> 37.8 °C) between onset of labour to delivery, prolonged rupture of membranes > 18 hours, spontaneous preterm (< 37 weeks) onset of labour, preterm (< 37 weeks) premature rupture of membranes, maternal sepsis, urinary infection or diarrhoea within 7 days to date of delivery, and features of clinical chorioamnionitis. Enrolled newborns were stratified within 1 hour of birth as asymptomatic or symptomatic based on presence of respiratory distress, apnoea, vomiting, abdominal distention, hypotension, hypoperfusion, hypoglycaemia, or hyperglycaemia. Exclusion criteria: babies with life-threatening congenital anomalies, surgical illnesses, and indicated preterm birth for a maternal cause not associated with risk of early-onset sepsis
Interventions	**Intervention 1:** piperacillin + tazobactam 100 mg/kg IV infusion 12 hourly in 5% dextrose over 30 minutes **Intervention 2:** amikacin in 5% dextrose by IV infusion over 30 minutes with dose adjusted for the postmenstrual age in weeks and postnatal age in days Co-interventions: routine and supportive care was provided using similar methods to participants in both groups as per unit guidelines.
Outcomes	**Primary outcome** • Treatment failure **Secondary outcome** • Mortality • Second infection • Fungal infection **Follow-up** • Days 7 and 28
Notes	Authors contacted by email: docvvt_13@hotmail.com Data for symptomatic participants were obtained from trialist.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Tewari 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation using an online randomisation service.
Allocation concealment (selection bias)	Low risk	Allocation concealment done using serially numbered opaque sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used intention-to-treat.
Selective reporting (reporting bias)	Low risk	Reported mortality and serious adverse events.
Other bias	Low risk	No other biases identified.

CDC: Centers for Disease Control; IQR: interquartile range; IV: intravenous; IVH: intraventricular haemorrhage; LOS: length of stay; n: number of participants; NA: not applicable; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; SD: standard deviation.

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

Study	Reason for exclusion
Adelman 1987a	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Adelman 1987b	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Alinejad 2018	Participants did not have early-onset neonatal sepsis.
Aronoff 1984	Did not include neonates with sepsis.
Auriti 2005	Both groups received amoxicillin.
Baqui 2013	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Bassetti 1991	Participants were adults.
Begue 1998	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Ceriani 2014	Included only late-onset neonatal sepsis.
Chartrand 1984	Did not include neonates with sepsis.

Study	Reason for exclusion
Chowdhary 2006	Both groups received the same antibiotics.
Collins 1998	Participants did not have early-onset neonatal sepsis.
De Louvois 1992	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Deville 2003	Did not have sepsis.
Ebrahim 1969	Not a randomised controlled trial.
Faix 1988	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Feigin 1976	Participants did not have early-onset neonatal sepsis.
Fogel 1983	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Gathwala 2010	Both groups received the same antibiotics.
Gokalp 1991	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Haffejee 1984	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Hall 1988	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Hansen 1980	Both groups received ampicillin and gentamicin.
Jantausch 2003	Did not have early-onset sepsis.
Kaplan 2003	Did not have early-onset sepsis.
Langhendries 1993	Both groups received the same antibiotic.
Lee 2005	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Lonnerholm 1982	Participants were not suspected of having sepsis, a severe infection or deep-seated infection.
Lutsar 2020	Only included participants with late-onset neonatal sepsis.
Marks 1978	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
McCracken 1976	Both groups received the same antibiotic.
Millar 1992	Only included participants with late-onset neonatal sepsis.
Mir 2017	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.

Study	Reason for exclusion
Molyneux 2017	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Mulubwa 2020	Both groups received the same antibiotic.
Odio 1987	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Odio 1995	Not a randomised controlled trial.
Oral 1998	Not a randomised controlled trial.
Rohatgi 2017	Both groups received the same antibiotics
Taheri 2011	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Tessin 1988	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Tessin 1989	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Tshefu 2015a	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Tshefu 2015b	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Umana 1990	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Viganó 1995	Did not have early-onset sepsis.
Wells 1984	Did not have early-onset sepsis.
Wiese 1988	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.
Zaidi 2013	Included both early-onset and late-onset neonatal sepsis. Unable to provide separate data for early onset.

DATA AND ANALYSES

Comparison 1. Ampicillin plus gentamicin compared with benzylpenicillin plus gentamicin

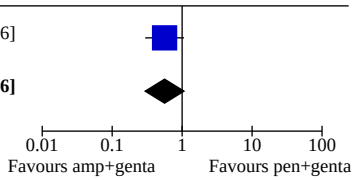
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	1	283	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.30, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Serious adverse events	1	283	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.21]
1.3 Circulatory support	1	283	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.21]
1.4 Neurological developmental impairment	1	283	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.40, 1.61]
1.5 Necrotising enterocolitis	1	283	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.50, 3.05]

Analysis 1.1. Comparison 1: Ampicillin plus gentamicin compared with benzylpenicillin plus gentamicin, Outcome 1: All-cause mortality

Study or Subgroup	Ampicillin + gentamicin Events	Total	Penicillin + gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Metsvaht 2010	13	142	23	141	100.0%	0.56 [0.30 , 1.06]
Total (95% CI)		**142**		**141**	**100.0%**	**0.56 [0.30 , 1.06]**
Total events:	13		23			

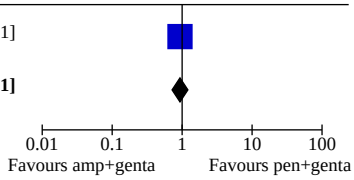
Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Ampicillin plus gentamicin compared with benzylpenicillin plus gentamicin, Outcome 2: Serious adverse events

Study or Subgroup	Ampicillin + gentamicin Events	Total	Penicillin + gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Metsvaht 2010	61	142	65	141	100.0%	0.93 [0.72 , 1.21]
Total (95% CI)		**142**		**141**	**100.0%**	**0.93 [0.72 , 1.21]**
Total events:	61		65			

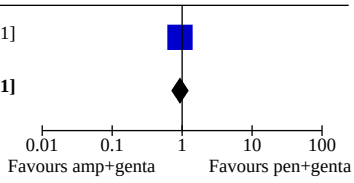
Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Ampicillin plus gentamicin compared with benzylpenicillin plus gentamicin, Outcome 3: Circulatory support

Study or Subgroup	Ampicillin + gentamicin Events	Total	Penicillin + gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Metsvaht 2010	61	142	65	141	100.0%	0.93 [0.72 , 1.21]
Total (95% CI)		**142**		**141**	**100.0%**	**0.93 [0.72 , 1.21]**
Total events:	61		65			

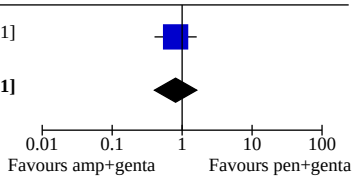
Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Ampicillin plus gentamicin compared with benzylpenicillin plus gentamicin, Outcome 4: Neurological developmental impairment

Study or Subgroup	Ampicillin + gentamicin Events	Total	Penicillin + gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Metsvaht 2010	13	142	16	141	100.0%	0.81 [0.40 , 1.61]
Total (95% CI)		**142**		**141**	**100.0%**	**0.81 [0.40 , 1.61]**
Total events:	13		16			

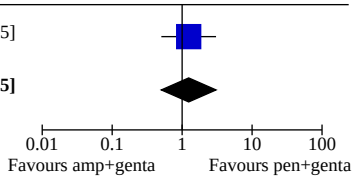
Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Ampicillin plus gentamicin compared with benzylpenicillin plus gentamicin, Outcome 5: Necrotising enterocolitis

Study or Subgroup	Ampicillin + gentamicin Events	Total	Penicillin + gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Metsvaht 2010	10	142	8	141	100.0%	1.24 [0.50 , 3.05]
Total (95% CI)		**142**		**141**	**100.0%**	**1.24 [0.50 , 3.05]**
Total events:	10		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable



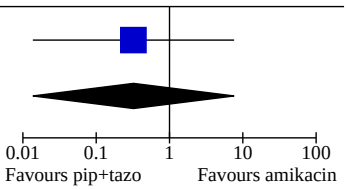
Comparison 2. Piperacillin plus tazobactum compared with amikacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.61]
2.2 Serious adverse events	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.15, 6.41]

Analysis 2.1. Comparison 2: Piperacillin plus tazobactum compared with amikacin, Outcome 1: All-cause mortality

Study or Subgroup	Piperacillin + tazobactum Events	Total	Amikacin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tewari 2014	0	30	1	29	100.0%	0.32 [0.01 , 7.61]
Total (95% CI)		**30**		**29**	**100.0%**	**0.32 [0.01 , 7.61]**
Total events:	0		1			

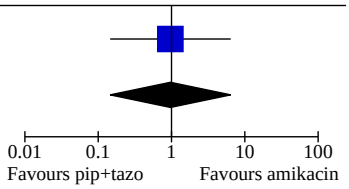
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Piperacillin plus tazobactum compared with amikacin, Outcome 2: Serious adverse events

Study or Subgroup	Piperacillin + tazobactum Events	Total	Amikacin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tewari 2014	2	30	2	29	100.0%	0.97 [0.15 , 6.41]
Total (95% CI)		**30**		**29**	**100.0%**	**0.97 [0.15 , 6.41]**
Total events:	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



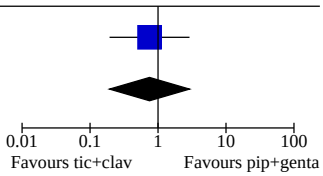
Comparison 3. Ticarcillin plus clavulanic acid compared with piperacillin plus gentamicin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.19, 2.90]
3.2 Serious adverse events	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.19, 2.90]

Analysis 3.1. Comparison 3: Ticarcillin plus clavulanic acid compared with piperacillin plus gentamicin, Outcome 1: All-cause mortality

Study or Subgroup	Ticarcillin + clavulanic acid Events	Total	Piperacillin + gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Miall-Allen 1988	3	32	5	40	100.0%	0.75 [0.19 , 2.90]
Total (95% CI)		**32**		**40**	**100.0%**	**0.75 [0.19 , 2.90]**
Total events:	3		5			

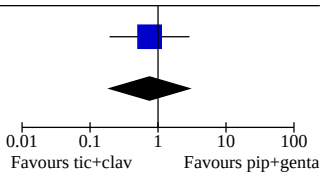
Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Ticarcillin plus clavulanic acid compared with piperacillin plus gentamicin, Outcome 2: Serious adverse events

Study or Subgroup	Ticarcillin + clavulanic acid Events	Total	Piperacillin + gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Miall-Allen 1988	3	32	5	40	100.0%	0.75 [0.19 , 2.90]
Total (95% CI)		**32**		**40**	**100.0%**	**0.75 [0.19 , 2.90]**
Total events:	3		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)
Test for subgroup differences: Not applicable



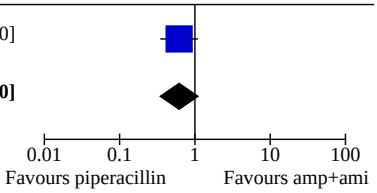
Comparison 4. Piperacillin compared with ampicillin plus amikacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality	1	396	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.35, 1.10]
4.2 Serious adverse events	1	396	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.35, 1.10]
4.3 Nephrotoxicity	1	396	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.80, 1.63]

Analysis 4.1. Comparison 4: Piperacillin compared with ampicillin plus amikacin, Outcome 1: All-cause mortality

Study or Subgroup	Piperacillin Events	Piperacillin Total	Ampicillin + amikacin Events	Ampicillin + amikacin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hammerberg 1989	17	200	27	196	100.0%	0.62 [0.35 , 1.10]
Total (95% CI)		**200**		**196**	**100.0%**	**0.62 [0.35 , 1.10]**
Total events:	17		27			

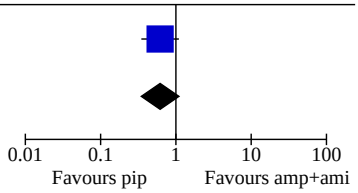
Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Piperacillin compared with ampicillin plus amikacin, Outcome 2: Serious adverse events

Study or Subgroup	Piperacillin Events	Piperacillin Total	Ampicillin + amikacin Events	Ampicillin + amikacin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hammerberg 1989	17	200	27	196	100.0%	0.62 [0.35 , 1.10]
Total (95% CI)		**200**		**196**	**100.0%**	**0.62 [0.35 , 1.10]**
Total events:	17		27			

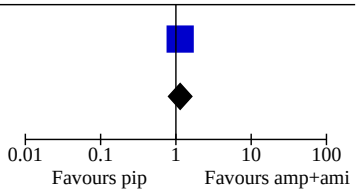
Heterogeneity: Not applicable
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Piperacillin compared with ampicillin plus amikacin, Outcome 3: Nephrotoxicity

Study or Subgroup	Piperacillin Events	Piperacillin Total	Ampicillin + amikacin Events	Ampicillin + amikacin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hammerberg 1989	50	200	43	196	100.0%	1.14 [0.80 , 1.63]
Total (95% CI)		**200**		**196**	**100.0%**	**1.14 [0.80 , 1.63]**
Total events:	50		43			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable

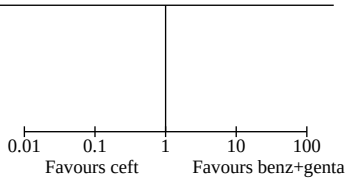


Comparison 5. Ceftazidime compared with benzylpenicillin plus gentamicin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 All-cause mortality	1	55	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 Serious adverse events	1	55	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

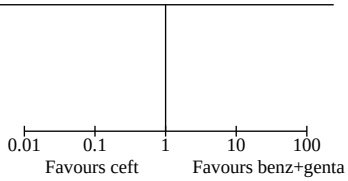
Analysis 5.1. Comparison 5: Ceftazidime compared with benzylpenicillin plus gentamicin, Outcome 1: All-cause mortality

	Ceftazidime		Benzylpenicillin+gentamicin			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Snelling 1983	0	31	0	24		Not estimable	
Total (95% CI)		**31**		**24**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Analysis 5.2. Comparison 5: Ceftazidime compared with benzylpenicillin plus gentamicin, Outcome 2: Serious adverse events

	Ceftazidime		Benzylpenicillin+gentamicin			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Snelling 1983	0	31	0	24		Not estimable	
Total (95% CI)		**31**		**24**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



ADDITIONAL TABLES

Table 1. Commonly used clinical and laboratory criteria of sepsis

Clinical criteria	Laboratory criteria
• Abdominal distension • Skin and subcutaneous lesions (such as petechial rash, abscesses, sclerema) • Cardiovascular signs (tachycardia/bradycardia, hypotension, poor perfusion) • Respiratory signs (apnoea, cyanosis, tachypnoea, need for ventilator, increased oxygen requirement) • Abnormal temperature (fever or hypothermia) • Central nervous system signs (lethargy, hypotonia, seizure) • Feeding problems	• WBC • Immature WBC:total WBC ratio • Platelet count • C-reactive protein • Metabolic acidosis • Neutropenia • Abnormal fibrinogen • Hyperglycaemia and hypoglycaemia

WBC: white blood cell.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 3) in the Cochrane Library

#1 MeSH descriptor: [Infant] explode all trees

#2 (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

#3 #1 or #2

#4 MeSH descriptor: [Neonatal Sepsis] explode all trees

#5 (sepsis NEAR/3 (neonat* or neo nat*))

#6 (sepsis NEAR/3 (newborn* or new born* or newly born*))

#7 (septic* NEAR/3 (neonat* or neo nat*))

#8 (septic* NEAR/3 (newborn* or new born* or newly born*))

#9 (infect* NEAR/3 (neonat* or neo nat*))

#10 (infect* NEAR/3 (newborn* or new born* or newly born*))

#11 (bacter* NEAR/3 (neonat* or neo nat*))

#12 (bacter* NEAR/3 (newborn* or new born* or newly born*))

#13 (gram NEAR/2 negative)

#14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13

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

#16 (antibiot* OR antimicrob* OR lactam* OR aminoglycoside* OR glycoprotein OR penicillin OR oxacillin OR cloxacillin OR dicloxacillin OR nafcillin OR methicillin OR ampicillin OR amoxicillin OR piperacillin OR ticarcillin OR carbenicillin OR mezlocillin OR cephalosporins OR cefazolin OR cephalexin OR cefuroxime OR cefotetan OR cefoxitin OR ceftriaxone OR cefotaxime OR ceftazidime OR cefepime OR cefazolin OR ceftobiprole OR cefoperazone OR carbapenems OR imipenem OR meropenem OR doripenem OR ertapenem OR monobactams OR aztreonam)

#17 #15 OR #16

#18 #3 and #14 and #17

MEDLINE Ovid (1946 to March 2021)

1. exp Infant/

2. (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. 1 or 2

4. exp Neonatal Sepsis/

5. (sepsis adj3 (neonat$ or neo nat$)).ti,ab.

6. (sepsis adj3 (newborn$ or new born$ or newly born$)).ti,ab.

7. (septic$ adj3 (neonat$ or neo nat$)).ti,ab.

8. (septic$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

9. (infect$ adj3 (neonat$ or neo nat$)).ti,ab.

10. (infect$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

11. (bacter$ adj3 (neonat$ or neo nat$)).ti,ab.

12. (bacter$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

13. (gram adj2 negative).ti,ab.

14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. exp Anti-Bacterial Agents/

16. (antibiot* or antimicrob* or lactam* or aminoglycoside* or glycoprotein or penicillin or oxacillin or cloxacillin or dicloxacillin or nafcillin or methicillin or ampicillin or amoxicillin or piperacillin or ticarcillin or carbenicillin or mezlocillin or cephalosporins or cefazolin or cephalexin or cefuroxime or cefotetan or cefoxitin or ceftriaxone or cefotaxime or ceftazidime or cefepime or cefazolin or ceftobiprole or cefoperazone or carbapenems or imipenem or meropenem or doripenem or ertapenem or monobactams or aztreonam).ti,ab.

17. 15 or 16

18. 3 and 14 and 17

19. (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or trial.ti.

20. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

21. 18 and (19 or 20)

Embase Ovid (1974 to March 2021)

1. exp infant/

2. (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

3. 1 or 2

4. exp newborn sepsis/

5. (sepsis adj3 (neonat$ or neo nat$)).ti,ab.

6. (sepsis adj3 (newborn$ or new born$ or newly born$)).ti,ab.

7. (septic$ adj3 (neonat$ or neo nat$)).ti,ab.

8. (septic$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

9. (infect$ adj3 (neonat$ or neo nat$)).ti,ab.

10. (infect$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

11. (bacter$ adj3 (neonat$ or neo nat$)).ti,ab.

12. (bacter$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

13. (gram adj2 negative).ti,ab.

14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. exp antiinfective agent/

16. (antibiot* or antimicrob* or lactam* or aminoglycoside* or glycoprotein or penicillin or oxacillin or cloxacillin or dicloxacillin or nafcillin or methicillin or ampicillin or amoxicillin or piperacillin or ticarcillin or carbenicillin or mezlocillin or cephalosporins or cefazolin or cephalexin or cefuroxime or cefotetan or cefoxitin or ceftriaxone or cefotaxime or ceftazidime or cefepime or cefazolin or ceftobiprole or cefoperazone or carbapenems or imipenem or meropenem or doripenem or ertapenem or monobactams or aztreonam).ti,ab.

17. 15 or 16

18. 3 and 14 and 17

19. Randomized controlled trial/ or Controlled clinical study/ or trial.ti.

20. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

21. 18 and (19 or 20)

CINAHL (EBSCOhost; March 2021)

S14 S10 AND S13

S13 S11 OR S12

S12 TX (random* or blind* or placebo* or meta-analys*) OR TI trial

S11 PT randomized controlled trial OR PT controlled clinical trial

S10 S3 AND S6 AND S9

S9 S7 OR S8

S8 TI ((antibiot* or antimicrob* or lactam* or aminoglycoside* or glycoprotein or penicillin or oxacillin or cloxacillin or dicloxacillin or nafcillin or methicillin or ampicillin or amoxicillin or piperacillin or ticarcillin or carbenicillin or mezlocillin or cephalosporins or cefazolin or cephalexin or cefuroxime or cefotetan or cefoxitin or ceftriaxone or cefotaxime or ceftazidime or cefepime or cefazolin or ceftobiprole or cefoperazone or carbapenems or imipenem or meropenem or doripenem or ertapenem or monobactams or aztreonam)

S7 MH antibiotics

S6 S4 OR S5

S5 TI ((((sepsis or septic* or infect* or bacter*) N3 (neonat* or neo nat* or newborn* or new born* or newly born*)) or (gram N2 negative))) OR AB ((((sepsis or septic* or infect* or bacter*) N3 (neonat* or neo nat* or newborn* or new born* or newly born*)) or (gram N2 negative)))

S4 MH Neonatal Sepsis

S3 S1 OR S2

S2 TX (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

S1 MH infant

LILACS (Bireme; 1982 to March 2021)

(infan$ or newborn or neonat$ or premature or preterm or very low birth weight or low birth weight or VLBW or LBW) and (((sepsis or septic$ or infect$ or bacter$) and (neonat$ or neo nat$ or newborn$ or new born$ or newly born$)) or (gram near negative)) and (antibiot$ OR antimicrob$ OR lactam$ OR aminoglycoside$ OR glycoprotein OR penicillin OR oxacillin OR cloxacillin OR dicloxacillin OR nafcillin OR methicillin OR ampicillin OR amoxicillin OR piperacillin OR ticarcillin OR carbenicillin OR mezlocillin OR cephalosporins OR cefazolin OR cephalexin OR cefuroxime OR cefotetan OR cefoxitin OR ceftriaxone OR cefotaxime OR ceftazidime OR cefepime OR cefazolin OR ceftobiprole OR cefoperazone OR carbapenems OR imipenem OR meropenem OR doripenem OR ertapenem OR monobactams OR aztreonam) [Words] and (random$ or blind$ or placebo$ or meta-analys$) [Words]

Science Citation Index EXPANDED (1900 to August 2020) and Conference Proceedings Citation Index – Science (1990 to March 2021) (Web of Science)

#5 #4 AND #3 AND #2 AND #1

#4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*)

#3 TS=(antibiot* OR antimicrob* OR lactam* OR aminoglycoside* OR glycoprotein OR penicillin OR oxacillin OR cloxacillin OR dicloxacillin OR nafcillin OR methicillin OR ampicillin OR amoxicillin OR piperacillin OR ticarcillin OR carbenicillin OR mezlocillin OR cephalosporins OR cefazolin OR cephalexin OR cefuroxime OR cefotetan OR cefoxitin OR ceftriaxone OR cefotaxime OR ceftazidime OR cefepime OR cefazolin OR ceftobiprole OR cefoperazone OR carbapenems OR imipenem OR meropenem OR doripenem OR ertapenem OR monobactams OR aztreonam)

#2 TS=(((sepsis or septic* or infect* or bacter*) and (neonat* or neo nat* or newborn* or new born* or newly born*)) or (gram near negative))

#1 TS=(infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. 'Risk of bias' tool

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

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

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

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

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

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- 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 categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low, high, or unclear risk for participants; and
- low, high, 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 categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- 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 described the completeness of data including attrition and exclusions from the analysis. We noted 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 was reported or supplied by the trial authors, we reincluded missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

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

For each included study, we described 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 compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it was clear that all the study's prespecified outcomes and all expected outcomes of interest to the review were reported);
- 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; study failed to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

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

For each included study, we described 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 assessed whether each study was free of other problems that could have put it at risk of bias as:

- low risk;
- high risk;
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
12 March 2021	Amended	Prior to updating, the authors rewrote the protocol. The protocol and subsequent review will update the previously published review of "Antibiotic regimens for suspected early neonatal sepsis" (Mtitimila 2004).

HISTORY

Protocol first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

SKK: conceived, designed, and drafted the review. He extracted, analysed, and interpreted the data.

SS: extracted data, and commented on and revised the review.

CN: extracted data, and commented on and revised the review.

MG: provided general advice and revised the review.

AG: provided general advice and revised the review.

GG: provided general advice and revised the review.

ULT: provided general advice and revised the review.

JCJ: conceived, designed, provided general advice and revised the review. He analysed and interpreted the data.

All authors agreed on the final review version.

DECLARATIONS OF INTEREST

The project received no funding.

SKK: none.

SS: none.

CN: none.

MG: none.

AG: none.

GG: none.

ULT: none.

JCJ: none.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Vermont Oxford Network, USA

  Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We decided to describe the antibiotic resistance occurring within the included trials towards the allocated antibiotic regimens narratively. We did this to further strengthen the review as recommended by Leibovici and colleagues (Leibovici 2016).
- We decided to include a subgroup assessing the different inclusion criteria for sepsis.

Cochrane Library

Cochrane Database of Systematic Reviews

Antibiotic regimens for late-onset neonatal sepsis (Review)

Korang SK, Safi S, Nava C, Greisen G, Gupta M, Lausten-Thomsen U, Jakobsen JC

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

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[Intervention Review]

Antibiotic regimens for late-onset neonatal sepsis

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Editorial group: Cochrane Neonatal Group.
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ABSTRACT

Background

Neonatal sepsis is a major cause of morbidity and mortality. It is the third leading cause of neonatal mortality globally constituting 13% of overall neonatal mortality. Despite the high burden of neonatal sepsis, high-quality evidence in diagnosis and treatment is scarce. Due to the diagnostic challenges of sepsis and the relative immunosuppression of the newborn, many neonates receive antibiotics for suspected sepsis. Antibiotics have become the most used therapeutics in neonatal intensive care units, and observational studies in high-income countries suggest that 83% to 94% of newborns treated with antibiotics for suspected sepsis have negative blood cultures. The last Cochrane Review was updated in 2005. There is a need for an updated systematic review assessing the effects of different antibiotic regimens for late-onset neonatal sepsis.

Objectives

To assess the beneficial and harmful effects of different antibiotic regimens for late-onset neonatal sepsis.

Search methods

We searched the following electronic databases: CENTRAL (2021, Issue 3); Ovid MEDLINE; Embase Ovid; CINAHL; LILACS; Science Citation Index EXPANDED and Conference Proceedings Citation Index – Science on 12 March 2021. We also searched clinical trials databases and the reference lists of retrieved articles for randomised controlled trials (RCTs) and quasi-RCTs.

Selection criteria

We included RCTs comparing different antibiotic regimens for late-onset neonatal sepsis. We included participants older than 72 hours of life at randomisation, suspected or diagnosed with neonatal sepsis, meningitis, osteomyelitis, endocarditis, or necrotising enterocolitis. We excluded trials that assessed treatment of fungal infections.

Data collection and analysis

Three review authors independently assessed studies for inclusion, extracted data, and assessed risk of bias. We used the GRADE approach to assess the certainty of evidence. Our primary outcome was all-cause mortality, and our secondary outcomes were: serious adverse events, respiratory support, circulatory support, nephrotoxicity, neurological developmental impairment, necrotising enterocolitis, and ototoxicity. Our primary time point of interest was at maximum follow-up.

Main results

We included five RCTs (580 participants). All trials were at high risk of bias, and had very low-certainty evidence.

The five included trials assessed five different comparisons of antibiotics.

We did not conduct a meta-analysis due to lack of relevant data.

Of the five included trials one trial compared cefazolin plus amikacin with vancomycin plus amikacin; one trial compared ticarcillin plus clavulanic acid with flucloxacillin plus gentamicin; one trial compared cloxacillin plus amikacin with cefotaxime plus gentamicin; one trial compared meropenem with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin); and one trial compared vancomycin plus gentamicin with vancomycin plus aztreonam.

None of the five comparisons found any evidence of a difference when assessing all-cause mortality, serious adverse events, circulatory support, nephrotoxicity, neurological developmental impairment, or necrotising enterocolitis; however, none of the trials were near an information size that could contribute significantly to the evidence of the comparative benefits and risks of any particular antibiotic regimen.

None of the trials assessed respiratory support or ototoxicity.

The benefits and harms of different antibiotic regimens remain unclear due to the lack of well-powered trials and the high risk of systematic errors.

Authors' conclusions

Current evidence is insufficient to support any antibiotic regimen being superior to another. RCTs assessing different antibiotic regimens in late-onset neonatal sepsis with low risks of bias are warranted.

PLAIN LANGUAGE SUMMARY

Antibiotic regimens for late-onset neonatal sepsis

Review question

We reviewed the available evidence on different antibiotic regimens for newborns (from 72 hours of life to one month of life) with late-onset sepsis.

Background

Sepsis in newborns is a severe and potential lethal condition, caused by the body's response to an infection. Neonatal sepsis is the third leading cause of neonatal death globally. Despite this high burden of sepsis in newborns, high-quality evidence in diagnosis and treatment is scarce. This Cochrane Review was originally published in 2005. To identify the most appropriate antibiotic policies for neonatal sepsis, there is a need to base these policies on an updated well-conducted review. Therefore, there is a need for such a review assessing the effects of different antibiotic regimens for late-onset neonatal sepsis.

Study characteristics

The evidence is current to March 2021. We included five trials randomising 580 participants. The five trials compared five different antibiotic regimens.

Key results

We included five trials: one trial compared cefazolin plus amikacin with vancomycin plus amikacin; one trial compared ticarcillin plus clavulanic acid with flucloxacillin plus gentamicin; one trial compared cloxacillin plus amikacin with cefotaxime plus gentamicin; one trial compared meropenem with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin); and one trial compared vancomycin plus gentamicin with vancomycin plus aztreonam.

None of the five antibiotic comparisons showed that the choice of antibiotics influenced the effects on death from all-causes, serious adverse events (i.e. major complications), circulatory support, nephrotoxicity (toxicity in the kidneys), neurological developmental impairment (disabilities in the functioning of the brain that affect a child's behaviour, memory, or ability to learn), or necrotising enterocolitis (tissues in the gut become inflamed and start to die). Current evidence cannot confirm or reject, one antibiotic regimen being superior to another due to scarce data.

Quality of the evidence

Our conclusions are based on very low-quality evidence. The five trials were at high risk of bias (i.e. the trials were conducted in a way that may have skewed results to the positive side). In addition, the five trials included few participants, making the results of this review imprecise.

SUMMARY OF FINDINGS

Summary of findings 1. Cefazolin plus amikacin compared with vancomycin plus amikacin for late-onset neonatal sepsis

Cefazolin + amikacin compared with vancomycin + amikacin for late-onset neonatal sepsis

Patient or population: newborns with late-onset sepsis

Settings: neonatal intensive care unit in Argentina

Intervention: cefazolin + amikacin

Comparison: vancomycin + amikacin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Vancomycin + amikacin	Cefazolin + amikacin				
All-cause mortality maximum follow-up	135 per 1000	94 per 1000 (39 to 223)	**RR 0.70** (0.29 to 1.66)	109 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 3022 (RR 0.80, α 0.05, β 0.20)
Serious adverse events maximum follow-up	135 per 1000	94 per 1000 (39 to 223)	**RR 0.70** (0.29 to 1.66)	109 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 3022 (RR 0.80, α 0.05, β 0.20) Serious adverse events were deaths.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OIS:** optimal information size; **RR:** risk ratio.

GRADE Working Group grades of evidence

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.

[a]Downgraded three levels because of very serious risk of bias, very serious imprecision of results, and serious risk of indirectness.

Summary of findings 2. Ticarcillin plus clavulanic acid compared with flucloxacillin and gentamicin for late-onset neonatal sepsis

Ticarcillin + clavulanic acid compared with flucloxacillin + gentamicin for late-onset neonatal sepsis

Patient or population: newborns with late-onset sepsis

Settings: neonatal intensive care unit in England

Intervention: ticarcillin + clavulanic acid

Comparison: flucloxacillin + gentamicin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Flucloxacillin + gentamicin	Ticarcillin + clavulanic acid				
All-cause mortality maximum follow-up	143 per 1000	28 per 1000 (1 to 546)	**RR 0.20** (0.01 to 3.82)	28 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 4306 (RR 0.80, α 0.05, β 0.20)
Serious adverse events maximum follow-up	143 per 1000	28 per 1000 (1 to 546)	**RR 0.20** (0.01 to 3.82)	28 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 4306 (RR 0.80, α 0.05, β 0.20) Serious adverse events were deaths.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OIS:** optimal information size; **RR:** risk ratio.

GRADE Working Group grades of evidence

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.

[a]Downgraded three levels because of very serious risk of bias, very serious imprecision of results, and serious risk of indirectness.

Summary of findings 3. Cloxacillin plus amikacin compared with cefotaxime plus gentamicin for neonatal late-onset sepsis

Cloxacillin + amikacin compared with cefotaxime + gentamicin for neonatal late-onset sepsis

Patient or population: newborns with late-onset sepsis

Settings: neonatal intensive care unit in India

Intervention: cloxacillin + amikacin

Comparison: cefotaxime + gentamicin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Cefotaxime + gentamicin	Cloxacillin + amikacin				
All-cause mortality maximum follow-up	200 per 1000	76 per 1000 (22 to 254)	**RR 0.38** (0.11 to 1.27)	90 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 2894 (RR 0.80, α 0.05, β 0.20)
Serious adverse events maximum follow-up	200 per 1000	100 per 1000 (34 to 296)	**RR 0.50** (0.17 to 1.48)	90 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 2894 (RR 0.80, α 0.05, β 0.20) Serious adverse events were participants who developed shock.
Circulatory support maximum follow-up	200 per 1000	100 per 1000 (34 to 296)	**RR 0.50** (0.17 to 1.48)	90 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 2894 (RR 0.80, α 0.05, β 0.20)
Nephrotoxicity maximum follow-up	100 per 1000	25 per 1000 (3 to 205)	**RR 0.25** (0.03 to 2.05)	90 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 6428 (RR 0.80, α 0.05, β 0.20)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OIS:** optimal information size; **RR:** risk ratio.

GRADE Working Group grades of evidence

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.

[a]Downgraded three levels because of very serious risk of bias, very serious imprecision of results, and serious risk of indirectness.

Summary of findings 4. Meropenem compared with standard care for neonatal late-onset sepsis

Meropenem compared with standard care for neonatal late-onset sepsis

Patient or population: newborns with late-onset sepsis

Settings: neonatal intensive care units in Europe

Intervention: meropenem

Comparison: standard care (ampicillin + gentamicin or cefotaxime + gentamicin)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Meropenem	Standard care				
All-cause mortality maximum follow-up	52 per 1000	74 per 1000 (29 to 188)	**RR 1.42** (0.56 to 3.62)	271 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 12976 (RR 0.80, α 0.05, β 0.20)
Serious adverse events maximum follow-up	133 per 1000	205 per 1000 (120 to 355)	**RR 1.54** (0.90 to 2.66)	271 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 4662 (RR 0.80, α 0.05, β 0.20)
Neurological developmental impairment maximum follow-up	178 per 1000	155 per 1000 (91 to 263)	**RR 0.87** (0.51 to 1.48)	271 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 3336 (RR 0.80, α 0.05, β 0.20) This outcome was number of participants with intracranial bleeding.
Necrotising enterocolitis maximum follow-up	119 per 1000	81 per 1000 (39 to 168)	**RR 0.68** (0.33 to 1.42)	271 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 5324 (RR 0.80, α 0.05, β 0.20)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CIS:** optimal information size; **RR:** risk ratio.

GRADE Working Group grades of evidence

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.

[a]Downgraded three levels because of very serious risk of bias, very serious imprecision of results, and serious risk of indirectness.

Summary of findings 5. Vancomycin plus gentamicin compared with vancomycin plus aztreonam for late-onset neonatal sepsis

Vancomycin + gentamicin compared with vancomycin + aztreonam for late-onset neonatal sepsis

Patient or population: newborns with late-onset sepsis

Settings: neonatal intensive care units in England

Intervention: vancomycin + gentamicin

Comparison: vancomycin + aztreonam

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Vancomycin + aztreonam	Vancomycin + gentamicin				
All-cause mortality maximum follow-up	150 per 1000	98 per 1000 (30 to 320)	**RR 0.65** (0.20 to 2.13)	81 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 4072 (RR 0.80, α 0.05, β 0.20)
Serious adverse events maximum follow-up	150 per 1000	98 per 1000 (30 to 320)	**RR 0.65** (0.20 to 2.13)	81 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: 4072 (RR 0.80, α 0.05, β 0.20)
Necrotising enterocolitis maximum follow-up	NA	NA	**RR 12.69** (0.74 to 218.09)	81 (1)	⊕⊖⊖⊖[a] **Very low**	OIS: NA

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NA:** not available; **OIS:** optimal information size; **RR:** risk ratio.

GRADE Working Group grades of evidence

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.

[a]Downgraded three levels because of very serious risk of bias, very serious imprecision of results, and serious risk of indirectness.

BACKGROUND

Description of the condition

Definition

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer 2016). There is currently no international consensus on specific criteria for neonatal sepsis (Wynn 2014; Wynn 2016). The most used neonatal sepsis criteria in clinical trials are based on a combination of clinical and laboratory parameters (see Table 1) (Morris 2016; Wynn 2014).

Sepsis that occurs before 28 days after birth is termed neonatal sepsis (Bakhuizen 2014; Camacho-Gonzalez 2013). Depending on the time of onset, neonatal sepsis is termed either early-onset sepsis or late-onset sepsis. The most accepted distinction between these two subgroups is cases occurring before 72 hours after birth and after 72 hours after birth, but other definitions exist (e.g. 48 hours and seven days after birth (Bakhuizen 2014; Bizzarro 2008; Camacho-Gonzalez 2013; Manan 2016; Metsvaht 2010; Shah 2014; Shane 2013; Shane 2014; Tripathi 2012; Zaidi 2009; Zea-Vera 2015). This distinction is based on the different aetiologies and pathophysiology of pathogens typically seen before and after 72 hours of age (Camacho-Gonzalez 2013; Metsvaht 2010; Shah 2014; Shane 2013).

Late-onset sepsis frequently presents with clinical deterioration including apnoea, tachypnoea, increased ventilatory requirement, hypotension, abnormal heart rate, hyperglycaemia, abnormal temperature (hypothermia or hyperthermia), cyanosis, acidosis, feeding intolerance, abdominal distension, lethargy, and skin mottling (Craft 2000; Tsai 2014). As some of these clinical manifestations can be non-specific, it can be difficult to clinically distinguish between sepsis and deep-seated infections, such as meningitis, osteomyelitis, and necrotising enterocolitis (NEC) (Camacho-Gonzalez 2013; Zea-Vera 2015).

Epidemiology

Since there is neither consensus on criteria for neonatal sepsis nor agreement on the cut-off between early-onset and late-onset sepsis (48 hours, 72 hours, or seven days) (see 'Definition' section above), it is difficult to estimate the exact incidence of neonatal sepsis (Bakhuizen 2014). Studies from the USA and Australia suggest that late-onset sepsis constitutes 3 per 1000 to 6 per 1000 live births, while early-onset sepsis ranges from 0.9 per 1000 to 3.5 per 1000 live births (Isaacs 1999; Schuchat 2000; Vergnano 2005; Vergnano 2011).

Late-onset sepsis is believed to be more common in preterm (less than 37 weeks' gestation) and low birthweight (less than 2500 g) neonates (Stoll 2011; Tsai 2014). Large non-randomised studies suggest that late-onset sepsis has decreased significantly in recent decades in high-income countries (Horbar 2017; Stoll 2015).

Neonatal sepsis is a major cause of morbidity and mortality. It is the third leading cause of neonatal mortality globally, constituting 13% of overall neonatal mortality (Lawn 2005; Liu 2012). In high-income countries, the mortality rate due to neonatal sepsis ranges from 5% to 20%, and neonatal sepsis results in major disability or death in 39% of all cases despite initiation of conventional treatment. Mortality rates higher than 70% can be observed in some low- and middle-income countries (LMICs) (Bakhuizen 2014; Kabwe 2016; Weston 2011; Wynn 2014).

Sepsis during the neonatal period can result in several complications, such as multiple organ failure, cerebral haemorrhage, periventricular leukomalacia, meningitis, and respiratory distress syndrome (Sharma 2007; Stoll 2010). In survivors, sepsis is associated with serious long-term morbidity, such as cerebral palsy, cognitive and psychomotor delay, auditory and visual impairment, and bronchopulmonary dysplasia (Bakhuizen 2014; Benjamin 2006; Klinger 2010; Schlapbach 2011). Most of these associations are based on observational cohort studies and therefore do not distinguish between causality and association. It remains uncertain whether it is possible to prevent these subsequent sequela by treating neonatal sepsis with an appropriate empirical antibiotic regimen (Bakhuizen 2014).

Aetiology

The pathogens that cause late-onset sepsis include Gram-positive and Gram-negative bacteria, as well as fungal infections (Boghossian 2013). The mortality and the distribution pattern of pathogens that cause late-onset infection differ between LMICs and high-income countries. Important variations may be observed within and between individual neonatal intensive care units (NICUs) in each country. The predominant organisms responsible for neonatal sepsis within regions have also changed over time (Dong 2015; Stoll 1996).

The most common aetiological pathogen responsible for late-onset sepsis is coagulase-negative staphylococci, constituting 53% to 78% of all cases of late-onset sepsis in high-income countries (Bizzarro 2005; Bizzarro 2008; Dong 2015; Isaacs 1996; Rubin 2002; Stoll 2011; Weston 2011). However, since coagulase-negative staphylococci are skin commensals, these organisms are also common blood culture contaminants and there is a lack of consensus regarding how to interpret blood cultures that are positive for coagulase-negative staphylococci (Rubin 2002; Weinstein 2003). Other bacteria prevalent in late-onset sepsis are *Escherichia coli*, group B *Streptococcus*, *Klebsiella pneumoniae*, *Enterococcus*, *Candida*, and *Pseudomonas* (Isaacs 1996; Rubin 2002; Stoll 2011; Vergnano 2011).

In LMICs, coagulase-negative staphylococci are still very common, constituting 36% to 47% of all cases of late-onset sepsis (Dong 2015; Hammoud 2012). The second most common Gram-positive pathogen is *Staphylococcus aureus* (Dong 2015; Zaidi 2005). Gram-negative pathogens are relatively more common in LMICs (Dong 2015; Zaidi 2005). The most frequent Gram-negative pathogens are *Klebsiella* species, *E coli*, *Pseudomonas*, and *Salmonella* species (Breurec 2016; Hammoud 2012; Vergnano 2005; WHO 1999; Zaidi 2005). The pathogen with the highest case fatality ratio is considered to be *Pseudomonas aeruginosa* (Hammoud 2012; Tsai 2014).

Late-onset sepsis has several risk factors. Major risk factors are immaturity, mechanical ventilation, intravascular catheterisation, failure of early enteral feeding with breast milk, prolonged duration of parenteral nutrition, surgery, underlying respiratory and cardiovascular diseases, and hospitalisation (Boghossian 2013; Leal 2012; Stoll 2002; Tröger 2014; Tsai 2014). Furthermore, neonates are theoretically immunocompromised as several components of the immune system are not fully developed at birth (Camacho-Gonzalez 2013; Kumar 2016). Preterm neonates are especially immunocompromised due to even more immature

innate and adaptive immune systems (Kan 2016; Rogosch 2012; Walker 2011; Ygberg 2012; Zemlin 2007).

Description of the intervention

Antibiotics are antimicrobial drugs that treat and prevent bacterial infections by either killing the bacteria or inhibiting their growth (Waksman 1947). Early initiation of antibiotic therapy on neonates with suspected sepsis reduces both mortality and morbidity (Bakhuizen 2014). The choice of antibiotic used is often empirical and based on several factors, such as age at onset, likely pathogens, and antibiotic susceptibility patterns (Dong 2015; Manan 2016; Rubin 2002).

The most used first-line treatment is a beta-lactam antibiotic (most commonly ampicillin, flucloxacillin, or penicillin) combined with an aminoglycoside (most commonly gentamicin) (Dong 2015; Vergnano 2011). However, there has been an increased use of alternatives, such as vancomycin and cephalosporins, due to increased drug resistance among the most common pathogen (e.g. coagulase-negative staphylococci) (Dong 2015; Rubin 2002).

Most guidelines recommend a penicillin plus an aminoglycoside for all cases of neonatal sepsis (Cortese 2016; Manan 2016; Muller-Pebody 2011; Vergnano 2005; Vergnano 2011; WHO 2013). However, other protocols exist where a cephalosporin or a glycopeptide is used as a first-line option to treat late-onset sepsis (Fernando 2008; Marchant 2013; Stockmann 2014). Guidelines may differ due to local antibiotic resistance of the most common pathogens or whether the empirical regimen is supposed to cover the common but low virulence coagulase-negative staphylococci (Bizzarro 2015; Marchant 2013). Vancomycin is to be considered if staphylococcal infection is suspected (Stockmann 2014).

Antibiotic susceptibility

Antibiotic resistance is a growing problem that increases the morbidity, mortality, and costs associated with infections globally (Cohen 1992; Foster 2006; Huynh 2016; Vergnano 2005). Studies indicate that bacterial resistance to antibiotics results primarily from the selective pressure exerted by the use and overuse of antibiotics (Foster 2006; Kunin 1990; McGowan 1994; Murray 1994; Sáez-Llorens 2000). The spread of drug-resistant organisms in hospitals is a recognised problem, although neonates admitted from the community may also carry drug-resistant pathogens (Bhutta 1996). Studies that compare antibiotic susceptibility over time in the same unit show increased resistance to the most used antibiotics (Vergnano 2005).

The pathogens that cause neonatal infections and their antibiotic susceptibility patterns change over time and may differ between countries (Breurec 2016; Isaacs 2003; May 2005; Stoll 2003; Stoll 2005; Vergnano 2011). Furthermore, the definition and epidemiology of neonatal sepsis differs between countries (Vergnano 2005). This makes the comparison of antibiotic susceptibility between countries difficult. When comparing the epidemiology of neonatal sepsis in LMICs with high-income countries, some important differences emerge in the pattern of aetiological pathogens and their antibiotic resistance (Khatua 1986; Tallur 2000; Tessin 1990; Vesikari 1985).

In high-income countries, most pathogens that cause late-onset sepsis (84%) were susceptible to the commonly used empiric antibiotics (penicillin/gentamicin and flucloxacillin/gentamicin) (Vergnano 2011).

In LMICs, estimations suggest that up to 70% of pathogens isolated from neonatal sepsis may not be covered by the recommended empirical regimen of ampicillin and gentamicin (Zaidi 2005). Some studies in LMICs have shown almost universal resistance (92% to 100% resistance) among some of the most common pathogens to first- and second-line antibiotics (Dagnew 2013; Kabwe 2016; Zaidi 2005).

In addition to antibiotic coverage, supportive care aiming to reverse the life-threatening organ dysfunction caused by a dysregulated host response to infection is also part of the care for neonates with sepsis. This includes respiratory support, maintenance of peripheral perfusion (intravenous fluids and inotropics), phototherapy, temperature, and glucose regulation (Seale 2015; WHO 2013).

Adverse events

Use of ampicillin has been associated in some studies with adverse events, such as rashes, diarrhoea, nausea, and nephrotoxicity (Golan 2011; Katzung 2009; Mrvos 2013). Contrary to these findings, one systematic review of randomised controlled trials (RCTs) showed that ampicillin only increased the incidence of candidiasis with no significant increase in rashes, diarrhoea, nausea, or nephrotoxicity (Gillies 2015).

Aminoglycosides (e.g. gentamicin) have been shown to be toxic (nephrotoxicity and ototoxicity) in adults. However, their toxicity in neonates remains unclear (Huth 2011; Jackson 1971; Mattie 1989; McGlone 2008; Mingeot-Leclercq 1999; Musiime 2015; Schultze 1971; Selimoglu 2007; Wargo 2014).

The most common adverse effects caused by vancomycin are fever, phlebitis, and, in rare cases, nephrotoxicity and ototoxicity (Rybak 2009). However, in addition to the development of resistance towards vancomycin, one must also consider that observational studies suggest a three- to four-fold increase in nephrotoxicity when aminoglycosides are combined with vancomycin (Farber 1983; Hailemeskel 1999; Rybak 2009; Sorrell 1985).

Cefotaxime, which is considered an alternative first-line antibiotic, might have a broad spectrum of activity. However, cefotaxime is also associated with increased risk of death and invasive candidiasis in non-randomised studies (Clark 2006a; Cotten 2006; Stockmann 2014).

In addition to the specific adverse effects of each antibiotic, extended use of antibiotics is also associated with higher risk of neonatal candidaemia (Filioti 2007; Spiliopoulou 2012).

How the intervention might work

Antibiotics are antimicrobial drugs that treat and prevent bacterial infections by either killing or inhibiting the growth of the bacteria (Waksman 1947). They can be classified based on:

- their mechanism of action (bactericidal or bacteriostatic);
- bacterial spectrum (broad or narrow); and
- chemical structure (e.g. penicillins, macrolides, quinolones, tetracyclines, or aminoglycosides) (Bérdy 2005).

A combination of different antibiotics might have several advantages. First, it is thought to provide an enhanced effect beyond the additive effects of the individual therapies (Allan 1985). Second, it can be used to broaden the spectrum of antibiotic coverage when used empirically to increase the chances of covering the alleged causative bacteria. Third, a combination therapy is thought to suppress the development of subpopulations of micro-organisms resistant to antibiotics (Allan 1985; Milatovic 1987; Tamma 2012).

Why it is important to do this review

Despite the high burden of neonatal sepsis, high-quality evidence in diagnosis and treatment is scarce (Zea-Vera 2015). Yet, in adults, appropriate empirical antibiotic treatment halves the fatality associated with sepsis (Ibrahim 2000; Leibovici 1998; Paul 2010). Due to the diagnostic challenges of sepsis, and the relative immunosuppression of the newborn, many neonates receive antibiotics for suspected sepsis. In fact, antibiotics have become the most used therapeutics in NICUs (Clark 2006b). Studies suggest that up to 95% of newborns treated with antibiotics for suspected sepsis prove to have no evidence of infection (Bedford Russell 2015; Cantey 2015; Luck 2003). This presumed inappropriate use of antibiotics seems to contribute to the development and spread of resistant pathogens in NICUs, and seems to be associated with adverse events (e.g. invasive candidiasis and increased antimicrobial resistance) (Clark 2006a; Cordero 2003; Cotten 2006; Cotten 2009; Foster 2006; Kuppala 2011).

The Cochrane Review published in 2005 concluded that there was inadequate evidence from RCTs in favour of any particular antibiotic regimen for the treatment of suspected late-onset neonatal sepsis (Gordon 2005). No other systematic review has been conducted to date to assess the effects of different antibiotic regimens for suspected late-onset sepsis. Therefore, there is a need for an updated systematic review that assesses the effects of different antibiotic regimens for late-onset sepsis.

OBJECTIVES

To assess the beneficial and harmful effects of different antibiotic regimens for late-onset neonatal sepsis.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs, quasi-RCTs, and cluster-RCTs. We included trials regardless of publication type (e.g. full-text or abstract), publication status (e.g. preprint or published), publication date, and language. We excluded crossover trials.

Types of participants

We included participants suspected of or diagnosed with late-onset sepsis (as defined by trial authors).

We included participants if described as newborns or 72 hours of life or more (at randomisation), suspected or diagnosed with neonatal sepsis, meningitis, osteomyelitis, endocarditis, or NEC.

We excluded trials that assessed treatment of fungal infections.

Types of interventions

We accepted any type of antibiotic or combination of antibiotics, such as the following.

- Broad-spectrum beta-lactam antibiotics, defined as broad-spectrum penicillins (e.g. ampicillin, amoxicillin, piperacillin, ticarcillin, carbenicillin, and mezlocillin), cephalosporins (e.g. cefazolin, cephalexin, cefuroxime, cefotetan, cefoxitin, ceftriaxone, cefotaxime, ceftazidime, cefepime, cefazolin, ceftobiprole, ceftolozane, and cefoperazone), carbapenems (e.g. imipenem, meropenem, doripenem, and ertapenem), and monobactams (e.g. aztreonam). Narrow-spectrum antibiotics included narrow-spectrum penicillins (e.g. oxacillin, cloxacillin, dicloxacillin, nafcillin, methicillin, and penicillin G).
- Beta-lactam antibiotics with beta-lactamase inhibitors such as avibactam, clavulanic acid, sulbactam, and tazobactam.
- Combination of beta-lactam with aminoglycoside (e.g. gentamicin).
- Combination of beta-lactam with glycopeptide (e.g. vancomycin and teicoplanin).
- Combination of glycopeptide with aminoglycoside.

We planned to assess the following comparisons.

- Aminoglycoside added to any type of antibiotic versus any type of antibiotic (same antibiotic as in the experimental group).
- Broad-spectrum beta-lactam antibiotic and aminoglycoside versus narrow-spectrum beta-lactam antibiotic (as defined in the above) and aminoglycoside (same aminoglycoside as in the experimental group).
- Beta-lactam antibiotic (as defined in the above) and aminoglycoside versus beta-lactam antibiotic and glycopeptide.
- Any other used antibiotic regimen (not included in the above-mentioned comparisons) versus any other used antibiotic regimen (not included in the above-mentioned comparisons).

Types of outcome measures

Primary outcomes

- All-cause mortality.

Secondary outcomes

- Proportion of participants with one or more serious adverse events. We defined a serious adverse event as any untoward medical occurrence that resulted in death, was life-threatening, jeopardised the participant, was persistent, led to significant disability, hospitalisation, or prolonged hospitalisation (ICH-GCP 2015). As we expected the reporting of serious adverse events in many trials to be very heterogeneous and not strictly according to the recommendations regarding good clinical practice from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP) (ICH-GCP 2015), we included the event as a serious adverse event if the trial authors either: used the term 'serious adverse event' but not refer to ICH-GCP, or reported the proportion of participants with an event we consider fulfilled the ICH-GCP definition (e.g. death or developed shock). If several such events were reported, we chose the highest proportion reported in each trial to avoid double-counting.

- Respiratory support, defined as the need for respiratory support, such as non-invasive ventilation (e.g. continuous positive airway pressure (CPAP)) or invasive ventilation (e.g. respirator).
- Circulatory support, defined as the need for circulatory support such as fluid bolus or vasoactive medication (e.g. inotropes or vasopressors).
- Nephrotoxicity measured as decreased urine output, decreased estimated creatine clearance, or increase in S-creatinine according to guidelines (such as "Paediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease (pRIFLE) system", "Acute Kidney Injury Network (AKIN) guideline", and "Kidney Disease: Improving Global Outcomes (KDIGO) guideline") (McWilliam 2017) or as defined by the trial author.
- Presence of moderate-to-severe neurological developmental and sensory impairment (defined as a functional abnormality in the function of the brain, spinal cord, muscles, nerves, eyes, or ears, or as any significant lag in a child's physical or motor, cognitive, behavioural, emotional or social development, in comparison with other children of the same age and sex within similar environments. If formal evaluation tools were used to assess neurodevelopmental impairment, we planned to use a threshold of –2 standard deviations (SDs) of the normal. Furthermore, severe brain injury per se is included, such as intraventricular haemorrhage grade 3 and 4 (Papile 1978; Volpe 2008), and periventricular leukomalacia.
- NEC during or after treatment, defined by Bell's criteria 2 (Bell 1978) (participants with NEC at baseline were not included in the analysis of this outcome).
- Ototoxicity as defined by the trial authors.

We assessed all dichotomised outcomes as proportions.

We used the trial results reported at maximum follow-up (our primary time point of interest).

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for Specialized Register; neonatal.cochrane.org/resources-review-authors). We searched for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Electronic searches

We conducted a comprehensive literature search including: the Cochrane Central Register of Controlled Trials (CENTRAL 2021, Issue 3) in the Cochrane Library; Ovid MEDLINE (1946 to 12 March 2021); Embase via Ovid (1974 to 12 March 2021); CINAHL (EBSCOhost; 12 March 2021); LILACS (Bireme; 1982 to 12 March 2021); and Science Citation Index EXPANDED and Conference Proceedings Citation Index – Science (1990 to 12 March 2021). We have included the search strategies for each database in Appendix 1.

We searched ZETOC for abstracts of scientific conferences or symposia (zetoc.jisc.ac.uk/).

We searched clinical trial registries for ongoing or recently completed trials. We searched the World Health Organization's International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/), and the U.S. National Library of Medicine's ClinicalTrials.gov (clinicaltrials.gov), via Cochrane CENTRAL. Additionally, we searched the ISRCTN Registry for any unique trials not identified through the Cochrane CENTRAL search (www.isrctn.com/).

We applied no language restrictions. If we identified any papers in a language not known by the review author group, we sought translation assistance and acknowledged the translators in the Acknowledgements section of the review.

Searching other resources

We checked the reference lists of all relevant primary trials and reviews for additional references.

To identify unpublished trials we also searched clinical trial registers of Europe and the USA, websites of pharmaceutical companies, and websites of the US Food and Drug Administration (FDA) and the European Medicines Agency.

Data collection and analysis

Selection of studies

Three review authors (SKK, CN, and SS) independently screened titles and abstracts. We retrieved all relevant full-text study reports/publication and three review authors (SKK, CN, and SS) independently screened the full texts and identified trials for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion or, if required, by consulting another review author (JCJ). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and a Characteristics of excluded studies table.

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

Data extraction and management

We used data collection forms for trial characteristics and outcome data that we piloted on at least one trial included in the review. Three review authors (SKK, CN, and SS) extracted trial characteristics from included trials. We extracted the following trials characteristics.

- Methods: trial design, total duration of the trial, number of trial centres and location, trial setting, withdrawals, and date of the trial.
- Participants: number of participants in each intervention group, mean age, age range, gender, diagnostic criteria, inclusion criteria, and exclusion criteria.
- Interventions: intervention and comparison.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for trial, and notable conflicts of interest of trial authors.

Three review authors (SKK, CN and SS) independently extracted outcome data from included trials. We noted in the Characteristics of included studies table if the trial authors did not report outcome data in a usable way. We resolved disagreements by consensus or

by involving another review author (JCJ). One review author (SKK) transferred data into the Review Manager 5 (Review Manager 2020). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (SS) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (SKK and SS) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2011).

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

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

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Korang 2021), and reported any deviations from it in the Differences between protocol and review section.

Measures of treatment effect

Dichotomous outcomes

We calculated risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials and the neonatal unit (or subunit) for cluster-RCTs. For cluster-RCTs, we planned to undertake analyses at the level of the individual while accounting for the clustering in the data using the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Dealing with missing data

We did not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses, we planned to impute data (see Sensitivity analysis).

We contacted investigators and trial sponsors to verify key trial characteristics and obtain missing numerical outcome data when possible (e.g. when we identified a study as an abstract only).

Assessment of heterogeneity

We planned to visually inspect forest plots to assess signs of heterogeneity, and we planned to explore possible heterogeneity in our prespecified subgroup analyses. We inspected trial characteristics across trials to identify clinical heterogeneity. We assessed the presence of statistical heterogeneity using the Chi^2 test (threshold $P < 0.10$) and measured the quantities of heterogeneity using the I^2 statistic (Higgins 2002; Higgins 2003). If we had detected moderate or high heterogeneity (I^2 statistic of 50% or greater), we planned to explore the possible causes (e.g. differences in study design, participants, interventions, or completeness of outcome assessments).

Assessment of reporting biases

We planned to use a funnel plot to assess publication bias if 10 or more trials met the inclusion criteria. We also planned to visually inspect funnel plots to assess the risk of bias. As we planned to report results when we analysed dichotomous outcomes using RRs, we did not use any tests to assess funnel plot asymmetry when analysing dichotomous outcomes (Higgins 2019).

Data synthesis

Meta-analysis

We planned to undertake this meta-analysis according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We planned to use Review Manager 5 to analyse data (Review Manager 2020).

We planned to assess our intervention effects using fixed-effect meta-analyses (Demets 1987), in accordance with the policies of Cochrane Neonatal. We used one primary outcome and, therefore, we considered a P value of 0.05 or less as the threshold for statistical significance (Jakobsen 2014). We used the eight-step procedure to assess if the thresholds for significance were crossed (Jakobsen 2014). Where data were only available from one trial, we planned to use Fisher's exact test for dichotomous data (Fisher 1922).

Where a trial reported multiple trial arms, we planned to include only the relevant trial arms. If two comparisons were combined in the same meta-analysis, we would halve the control group to avoid double-counting.

Trial sequential analysis

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. Therefore, we planned to perform trial sequential analysis (TSA) on the outcomes, to calculate the required information size and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries (Brok 2008; Brok 2009; Thorlund 2009; Thorlund 2011; TSA 2011; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). We wished to control the risks of type I errors and type II errors. A more detailed description of TSA can be found at www.ctu.dk/tsa/. We planned to assess our TSA intervention effects with both a random-effects model (DerSimonian 1986), and a fixed-effect model (Demets 1987).

For dichotomous outcomes, we planned to estimate the required information size based on the observed, unweighted proportion of participants with an outcome in the control group (the cumulative proportion of participants with an event in the control groups relative to all participants in the control groups), a relative risk reduction of 20%, an alpha of 5%, a beta of 20%, and diversity as suggested by the trials in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses for our primary outcome.

- High risk of bias trials compared with low risk of bias trials.
- Gestational age: term (37 weeks or greater) compared with preterm.
- Trials from high-income countries compared with trials from LMICs, as defined by the World Bank (World Bank 2017).
- Late-onset sepsis defined by: onset after 48 hours, after 72 hours, after one week, or as defined by the trial authors.
- Clinically suspected sepsis compared with culture-supported suspicion of severe bacterial infection.
- Trials including participants with coagulase-negative staphylococci versus trials excluding participants with coagulase-negative staphylococci.

We planned to use the formal test for subgroup interactions in Review Manager 5 (Review Manager 2020). We did not perform any of the above subgroups due to a lack of data.

Sensitivity analysis

To assess the potential impact of the missing data, we planned to perform the two following sensitivity analyses on the primary outcome and the secondary outcome serious adverse events.

- 'Best-worst-case' scenario: we planned to assume that all participants lost to follow-up in the experimental group had survived and had no serious adverse event; and all those participants with missing outcomes in the control group had not survived and had a serious adverse event.
- 'Worst-best-case' scenario: we planned to assume that all participants lost to follow-up in the experimental group had not survived and had a serious adverse event; and that all those participants lost to follow-up in the control group had survived and had no serious adverse event.

We planned to present results of both scenarios in our review, but we did not perform any of the sensitivity analyses due to a lack of data.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence of the following (clinically relevant) outcomes: all-cause mortality (primary outcome), and five secondary outcomes (serious adverse events, circulatory failure, nephrotoxicity, neurological developmental impairment, and NEC) at maximum follow-up.

Three review authors (SKK, SS, and CN) independently assessed the certainty of the evidence for each of the outcomes above. We considered evidence from RCTs as high certainty but downgraded 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 used GRADEpro GDT to create five 'Summary of findings' tables to report the certainty of the evidence.

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

- High certainty: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low certainty: we are very uncertain about the estimate.

RESULTS

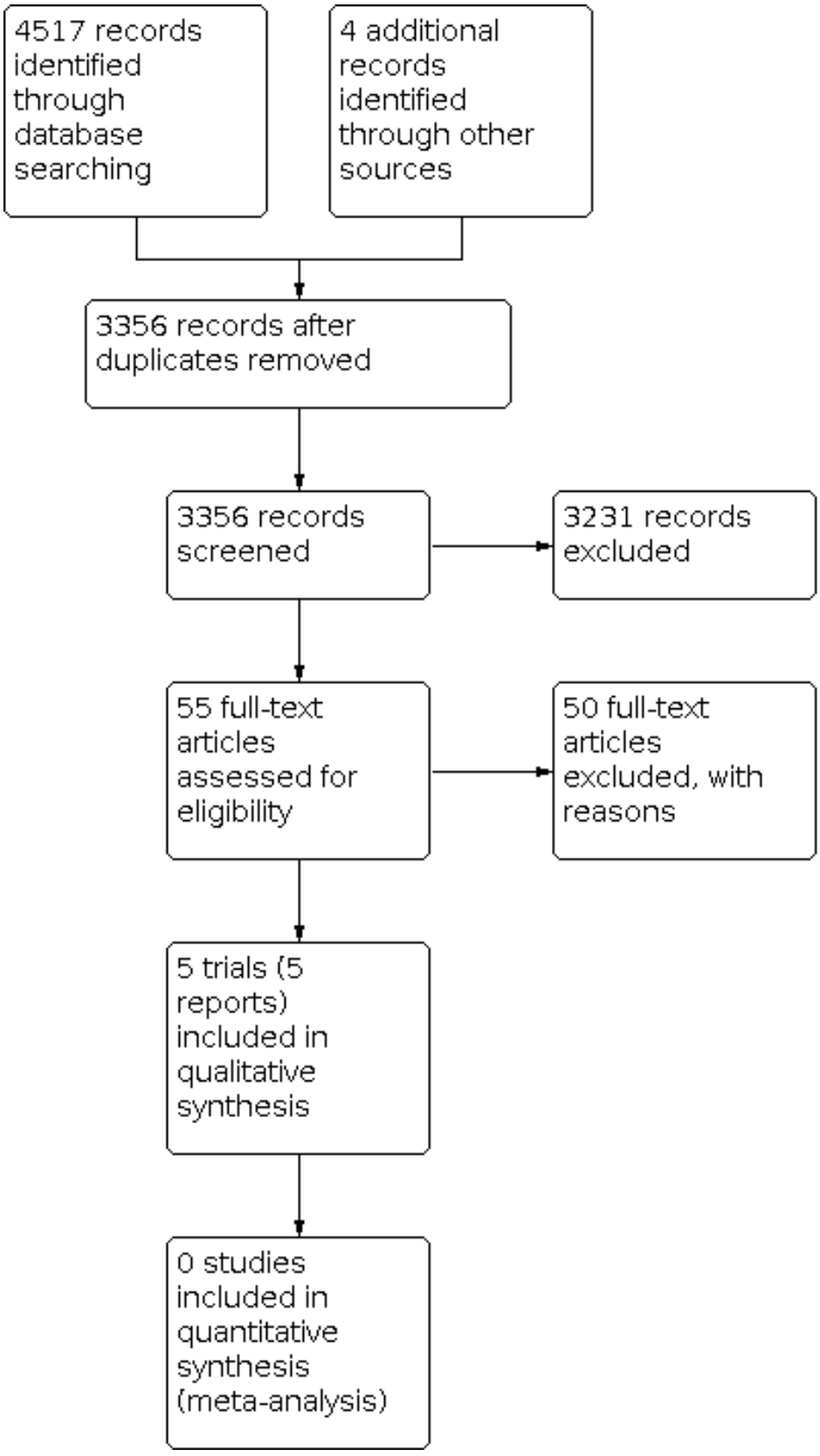
Description of studies

We assessed all studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019), and the protocol for this review (Korang 2021). Characteristics of each study can be found in the Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

Our initial search identified 3356 references. We deemed 55 studies relevant and obtained full texts for further evaluation (see Figure 1). Of these, we included five trials (Ceriani 2014; Lutsar 2020; Miall-Allen 1988; Millar 1992; Ramasamy 2014). We identified no ongoing trials relevant to the review.

Figure 1. Study flow diagram.



Included studies

Five trials met our inclusion criteria (Ceriani 2014; Lutsar 2020; Miall-Allen 1988; Millar 1992; Ramasamy 2014). For detailed descriptions, see the Characteristics of included studies table. Four of the trials were single centre, and one was multicentre.

Participants

The five trials included 580 participants. The mean proportion of girls was 46% among the trials that reported gender.

Interventions

The trials reported five different antibiotic regimens.

- One trial assessed cefazolin plus amikacin compared with vancomycin plus amikacin (Ceriani 2014).
- One trial assessed ticarcillin plus clavulanic acid compared with flucloxacillin plus gentamicin (Miall-Allen 1988).
- One trial assessed cloxacillin plus amikacin compared with cefotaxime plus gentamicin (Ramasamy 2014).
- One trial assessed meropenem compared with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin) (Lutsar 2020).
- One trial assessed vancomycin plus gentamicin compared with vancomycin plus aztreonam (Millar 1992).

Co-interventions

Participants in all five trials received standard care in addition to the allocated antibiotic regimen.

Outcomes

All five included trials reported all-cause mortality and serious adverse events. None of the trials reported serious adverse events according to the ICH-GCP, neither did they report serious adverse events as a composite outcome. Therefore, we reported the proportion of participants with an event we considered fulfilled the ICH-GCP definition (e.g. shock or death). As there were several such events, we chose the highest proportion reported in each trial to avoid double-counting. One trial reported circulatory support (Ramasamy 2014), neurological developmental impairment (Lutsar 2020), and nephrotoxicity (Ramasamy 2014). Two trials reported NEC (Lutsar 2020; Millar 1992). None of the trials reported respiratory support or ototoxicity.

Antibiotic resistance in included trials

One trial (from different countries in Europe) reported 31 cases of resistance (towards meropenem) out of the 63 participants with positive cultures in the meropenem group, compared with 45 cases of resistance (towards one of the allocated antibiotics) out of the 75 participants with positive cultures in the standard care group (Lutsar 2020).

One trial (from England) reported one case of resistance (towards gentamicin) out of the four participants with positive cultures in the flucloxacillin plus gentamicin group, but there was no resistance among the five participants with positive cultures in the ticarcillin plus clavulanic acid group (Miall-Allen 1988).

The remaining three trials (from Argentina, England, and India) did not report resistance among the included participants towards the allocated antibiotics (Ceriani 2014; Millar 1992; Ramasamy 2014).

Excluded studies

We assessed 50 trials as relevant upon review of the abstract, but later excluded them upon review of the full publication.

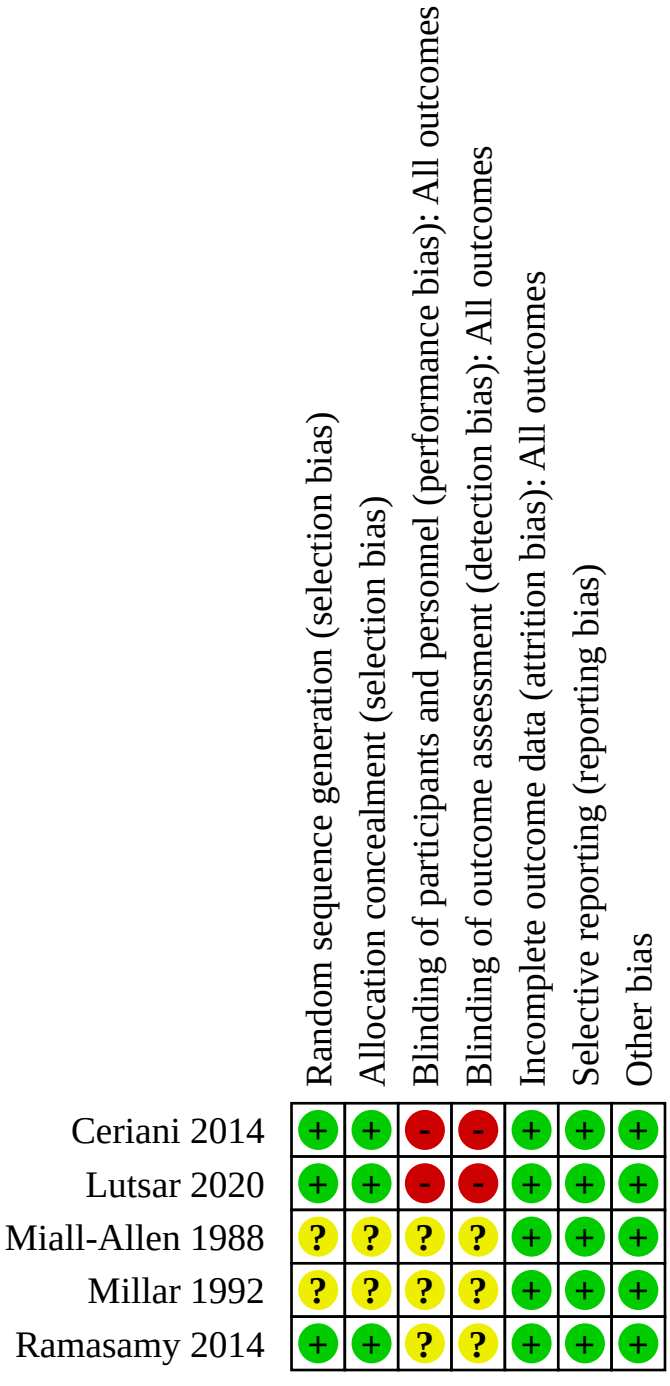
- We excluded 24 trials because they were a mix of early- and late-onset neonatal sepsis (Adelman 1987a; Adelman 1987b; Baqui 2013; Begue 1998; De Louvois 1992; Faix 1988; Fogel 1983; Gokalp 1991; Haffejee 1984; Hall 1988; Lee 2005; Marks 1978; Mir 2017; Molyneux 2017; Odio 1987; Odio 1995; Taheri 2011; Tessin 1988; Tessin 1989; Tshefu 2015a; Tshefu 2015b; Umaña 1990; Wiese 1988; Zaidi 2013).
- In eight trials both groups received the same antibiotics (Auriti 2005; Chowdhary 2006; Gathwala 2010; Hansen 1980; Langhendries 1993; McCracken 1976; Mulubwa 2020; Rohatgi 2017).
- Four trials included only early-onset neonatal sepsis (Hammerberg 1989; Metsvaht 2010; Snelling 1983; Tewari 2014).
- One trial included adults (Bassetti 1991).
- Two trials were not randomised (Ebrahim 1969; Oral 1998).
- Eleven trials did not include neonates with late-onset sepsis (Alinejad 2018; Aronoff 1984; Chartrand 1984; Collins 1998; Deville 2003; Feigin 1976; Jantausch 2003; Kaplan 2003; Lönnerholm 1982; Viganò 1995; Wells 1984).

When the participant age was unclear or separate data were not available for late-onset sepsis, we contacted the study authors. However, we obtained no additional information on these trials.

Risk of bias in included studies

We assessed all the included studies at overall high risk of bias (Figure 2). We contacted the authors for clarification, as some data were missing and several bias domains were unclear.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Three trials used a computer program to generate the sequence resulting in assessment of low risk (Ceriani 2014; Lutsar 2020; Ramasamy 2014). Two trials did not describe how allocation sequence generation was performed resulting in assessment of unclear (Miall-Allen 1988; Millar 1992).

Three trials allocated with concealment using serially numbered opaque sealed envelopes or had the randomisation list kept confidential and were at low risk of bias (Ceriani 2014; Lutsar 2020; Ramasamy 2014). Two trials did not describe allocation concealment and were at unclear risk of bias (Miall-Allen 1988; Millar 1992).

Blinding

Two trials did not blind participants or treatment providers resulting in assessment of high risk of performance bias (Ceriani 2014; Lutsar 2020). Two trials did not describe methods of blinding (Miall-Allen 1988; Millar 1992), and one trial was only described as single-blinded (without specifications) (Ramasamy 2014), resulting in unclear risk of performance bias.

Two trials did not blind outcome assessors resulting in assessment of high risk of detection bias (Ceriani 2014; Lutsar 2020). Three trials did not describe whether outcome assessors were blinded resulting in unclear risk of detection bias (Miall-Allen 1988; Millar 1992; Ramasamy 2014).

Incomplete outcome data

All trials used either intention-to-treat analysis or had no or few dropouts resulting in assessment of low risk of attrition bias.

Selective reporting

All trials reported mortality resulting in assessment of low risk of reporting bias.

Other potential sources of bias

Review authors observed no other biases.

Effects of interventions

See: **Summary of findings 1** Cefazolin plus amikacin compared with vancomycin plus amikacin for late-onset neonatal sepsis; **Summary of findings 2** Ticarcillin plus clavulanic acid compared with flucloxacillin and gentamicin for late-onset neonatal sepsis; **Summary of findings 3** Cloxacillin plus amikacin compared with cefotaxime plus gentamicin for neonatal late-onset sepsis; **Summary of findings 4** Meropenem compared with standard care for neonatal late-onset sepsis; **Summary of findings 5** Vancomycin plus gentamicin compared with vancomycin plus aztreonam for late-onset neonatal sepsis

We included five trials (580 participants) that met all the inclusion criteria (Ceriani 2014; Lutsar 2020; Miall-Allen 1988; Millar 1992; Ramasamy 2014). We were able to assess in part all-cause mortality, serious adverse events, circulatory support, nephrotoxicity, neurological developmental impairment, and NEC as primary and secondary outcomes. However, the five trials assessed comparisons with different antibiotic regimens. Hence, we performed no meta-analyses, no TSA, and no subgroup analysis on any outcomes. We estimated the optimal information size for all of the outcomes and the optimal information size was not reached for any of the comparisons (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).

Cefazolin plus amikacin compared with vancomycin plus amikacin

We found one trial comparing cefazolin plus amikacin with vancomycin plus amikacin (Summary of findings 1).

Primary outcome

All-cause mortality

One trial randomising 109 participants comparing cefazolin plus amikacin with vancomycin plus amikacin showed no evidence of a difference in all-cause mortality (RR 0.70, 95% CI 0.29 to 1.66; very low-certainty evidence; Analysis 1.1) (Ceriani 2014).

Secondary outcomes

Serious adverse events

One trial randomising 109 participants comparing cefazolin plus amikacin with vancomycin plus amikacin showed no evidence of a difference in serious adverse events (RR 0.70, 95% CI 0.29 to 1.66; very low-certainty evidence; Analysis 1.2) (Ceriani 2014).

Respiratory support

The trial did not report respiratory support.

Circulatory support

The trial did not report circulatory support.

Nephrotoxicity

The trial did not report nephrotoxicity.

Neurological developmental impairment

The trial did not report neurological developmental impairment.

Necrotising enterocolitis

The trial did not report NEC.

Ototoxicity

The trial did not report ototoxicity.

Ticarcillin plus clavulanic acid compared with flucloxacillin plus gentamicin

We found one trial comparing ticarcillin plus clavulanic acid with flucloxacillin plus gentamicin (Summary of findings 2).

Primary outcome

All-cause mortality

One trial randomising 28 participants comparing ticarcillin plus clavulanic acid with flucloxacillin plus gentamicin showed no evidence of a difference in all-cause mortality (RR 0.20, 95% CI 0.01 to 3.82; very low-certainty evidence; Analysis 2.1) (Miall-Allen 1988).

Secondary outcomes

Serious adverse events

One trial randomising 28 participants comparing ticarcillin plus clavulanic acid with flucloxacillin plus gentamicin showed no evidence of a difference in serious adverse events (RR 0.20, 95% CI 0.01 to 3.82; Analysis 2.2; very low-certainty evidence) (Miall-Allen 1988).

Respiratory support

The trial did not report respiratory support.

Circulatory support

The trial did not report circulatory support.

Nephrotoxicity

The trial did not report nephrotoxicity.

Neurological developmental impairment

The trial did not report neurological developmental impairment.

Necrotising enterocolitis

The trial did not report NEC.

Ototoxicity

The trial did not report ototoxicity.

Cloxacillin plus amikacin compared with cefotaxime plus gentamicin

We found one study comparing cloxacillin plus amikacin with cefotaxime plus gentamicin (Summary of findings 3).

Primary outcome

All-cause mortality

One trial randomising 90 participants comparing cloxacillin plus amikacin with cefotaxime plus gentamicin showed no evidence of a difference in all-cause mortality (RR 0.38, 95% CI 0.11 to 1.27; very low-certainty evidence; Analysis 3.1) (Ramasamy 2014).

Secondary outcomes

Serious adverse events

One trial randomising 90 participants comparing cloxacillin plus amikacin with cefotaxime plus gentamicin showed no evidence of a difference in serious adverse events (RR 0.50, 95% CI 0.17 to 1.48; very low-certainty evidence; Analysis 3.2) (Ramasamy 2014).

Respiratory support

The trial did not report respiratory support.

Circulatory support

One trial randomising 90 participants comparing cloxacillin plus amikacin with cefotaxime plus gentamicin showed no evidence of a difference in circulatory support (RR 0.50, 95% CI 0.17 to 1.48; very low-certainty evidence; Analysis 3.3) (Ramasamy 2014).

Nephrotoxicity

One trial randomising 90 participants comparing cloxacillin plus amikacin with cefotaxime plus gentamicin showed no evidence of a difference in nephrotoxicity (RR 0.25, 95% CI 0.03 to 2.05; very low-certainty evidence; Analysis 3.4) (Ramasamy 2014).

Neurological developmental impairment

The trial did not report neurological developmental impairment.

Necrotising enterocolitis

The trial did not report NEC.

Ototoxicity

The trial did not report ototoxicity.

Meropenem compared with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin)

We found one trial comparing meropenem compared with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin) (Summary of findings 4).

Primary outcome

All-cause mortality

One trial randomising 271 participants comparing meropenem with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin) showed no evidence of a difference in all-cause mortality (RR 1.42, 95% CI 0.56 to 3.62; very low-certainty evidence; Analysis 4.1) (Lutsar 2020).

Secondary outcomes

Serious adverse events

One trial randomising 271 participants comparing meropenem with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin) showed no evidence of a difference in serious adverse events (RR 1.54, 95% CI 0.90 to 2.66; very low-certainty evidence; Analysis 4.2) (Lutsar 2020).

Respiratory support

The trial did not report respiratory support.

Circulatory support

The trial did not report circulatory support.

Nephrotoxicity

The trial did not report nephrotoxicity.

Neurological developmental impairment

One trial randomising 271 participants comparing meropenem with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin) showed no evidence of a difference in neurological developmental impairment (RR 0.87, 95% CI 0.51 to 1.48; very low-certainty evidence; Analysis 4.3) (Lutsar 2020).

Necrotising enterocolitis

One trial randomising 271 participants comparing meropenem with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin) showed no evidence of a difference in NEC (RR 0.68, 95% CI 0.33 to 1.42; very low-certainty evidence; Analysis 4.4) (Lutsar 2020).

Ototoxicity

The trial did not report ototoxicity.

Vancomycin plus gentamicin compared with vancomycin plus aztreonam

We found one trial comparing vancomycin plus gentamicin compared with vancomycin plus aztreonam (Summary of findings 5).

Primary outcome

All-cause mortality

One trial randomising 81 participants comparing vancomycin plus gentamicin with vancomycin plus aztreonam showed no evidence of a difference in all-cause mortality (RR 0.65, 95% CI 0.20 to 2.13; very low-certainty evidence; Analysis 5.1) (Millar 1992).

Secondary outcomes

Serious adverse events

One trial randomising 81 participants comparing vancomycin plus gentamicin with vancomycin plus aztreonam showed no evidence of a difference in serious adverse events (RR 0.65, 95% CI 0.20 to 2.13; very low-certainty evidence; Analysis 5.2) (Millar 1992).

Respiratory support

The trial did not report respiratory support.

Circulatory support

The trial did not report circulatory support.

Nephrotoxicity

The trial did not report nephrotoxicity.

Neurological developmental impairment

The trial did not report neurological developmental impairment.

Necrotising enterocolitis

One trial randomising 81 participants comparing vancomycin plus gentamicin with vancomycin plus aztreonam showed no evidence of a difference in NEC (RR 12.69, 95% CI 0.74 to 218.09; very low-certainty evidence; Analysis 5.3) (Millar 1992).

Ototoxicity

The trial did not report ototoxicity.

DISCUSSION

Summary of main results

Evidence from five RCTs including 580 participants contributed data to our predefined outcomes. There is insufficient information to assess the relative effects of any of the antibiotics compared. Furthermore, these trials had high risk of bias. In summary, the certainty of the evidence was very low.

We conducted no meta-analyses due to a lack of relevant data. The optimal information size was not reached for any of the comparisons (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).

When assessing all-cause mortality: one trial randomising 109 participants showed no evidence of a difference when comparing cefazolin plus amikacin with vancomycin plus amikacin (RR 0.70, 95% CI 0.29 to 1.66; very low-certainty evidence) (Ceriani 2014); one trial randomising 28 participants showed no evidence of a difference when comparing ticarcillin plus clavulanic acid with flucloxacillin plus gentamicin (RR 0.20, 95% CI 0.01 to 3.82; very low-certainty evidence) (Miall-Allen 1988); one trial randomising 90 participants showed no evidence of a difference when comparing cloxacillin plus amikacin with cefotaxime plus gentamicin (RR 0.38, 95% CI 0.11 to 1.27; very low-certainty evidence) (Ramasamy 2014); one trial randomising 71 participants showed no evidence of a difference when comparing meropenem with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin) (RR 1.42, 95% CI 0.56 to 3.62; very low-certainty evidence) (Lutsar 2020); one trial randomising 81 participants showed no evidence of a difference when comparing vancomycin plus gentamicin with vancomycin plus aztreonam (RR 0.65, 95% CI 0.20 to 2.13; very low-certainty evidence) (Millar 1992).

When assessing serious adverse events: one trial randomising 109 participants showed no evidence of a difference when comparing cefazolin plus amikacin with vancomycin plus amikacin (RR 0.70, 95% CI 0.29 to 1.66; very low-certainty evidence) (Ceriani 2014); one trial randomising 28 participants showed no evidence of a difference when comparing ticarcillin plus clavulanic acid with flucloxacillin plus gentamicin (RR 0.20, 95% CI 0.01 to 3.82; very low-certainty evidence) (Miall-Allen 1988); one trial randomising 90 participants showed no evidence of a difference when comparing cloxacillin plus amikacin with cefotaxime plus gentamicin (RR 0.50, 95% CI 0.17 to 1.48; very low-certainty evidence) (Ramasamy 2014); one trial randomising 271 participants showed no evidence of a difference when comparing meropenem with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin) (RR 1.54, 95% CI 0.90 to 2.66; very low-certainty evidence) (Lutsar 2020); one trial randomising 81 participants showed no evidence of a difference when comparing vancomycin plus gentamicin with vancomycin plus aztreonam (RR 0.65, 95% CI 0.20 to 2.13; very low-certainty evidence) (Millar 1992).

None of the trials reported respiratory support.

When assessing circulatory support, one trial randomising 90 participants showed no evidence of a difference when comparing cloxacillin plus amikacin with cefotaxime plus gentamicin (RR 0.50, 95% CI 0.17 to 1.48; very low-certainty evidence) (Ramasamy 2014).

When assessing nephrotoxicity, one trial randomising 90 participants showed no evidence of a difference when comparing cloxacillin plus amikacin with cefotaxime plus gentamicin (RR 0.25, 95% CI 0.03 to 2.05; very low-certainty evidence) (Ramasamy 2014).

When assessing neurological developmental impairment, one trial randomising 271 participants showed no evidence of a difference when comparing meropenem with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin) (RR 0.87, 95% CI 0.51 to 1.48; very low-certainty evidence) (Lutsar 2020).

When assessing NEC: one trial randomising 271 participants showed no evidence of a difference when comparing meropenem with standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin) (RR 0.68, 95% CI 0.33 to 1.42; very low-certainty evidence) (Lutsar 2020); one trial randomising 81 participants showed no evidence of a difference when comparing vancomycin plus gentamicin with vancomycin plus aztreonam (RR 12.69, 95% CI 0.74 to 218.09; very low-certainty evidence) (Millar 1992).

None of the trials reported ototoxicity.

The benefits and harms of different antibiotic regimens remain unclear owing to the lack of well-powered trials, and the high risk of systematic errors.

Overall completeness and applicability of evidence

We were unable to perform any meta-analyses due to lack of relevant data and the identified trials were underpowered. Therefore, it was not possible to conclude whether one antibiotic regimen was superior to another in neonates with late-onset sepsis. More and larger RCTs with low risk of bias are needed.

Quality of the evidence

Heterogeneity

As no meta-analysis was performed, we did not assess heterogeneity.

Risk of systematic error ('bias')

We found no trials and no outcome results at low risk of bias.

It was not possible to assess publication bias, as we were only able to include five studies.

Risk of random error ('play of chance')

It was not possible to perform TSA, as we performed no meta-analyses.

GRADE

We assessed the certainty of the evidence for each outcome by using the GRADE approach (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5). The GRADE assessment generally showed that the evidence was of very-low certainty.

Potential biases in the review process

The main limitation of this review was the low number of randomised participants and hence paucity of evidence for the use of different antibiotic regimens. Another limitation was that some trials did not distinguish between early-onset and late-onset neonatal sepsis, which resulted in a large number of potentially relevant trials that were excluded. We used the broadest possible definition of late-onset sepsis and the broadest choice of possible antibiotic regimens. This could potentially have caused the inclusion of trials with very a heterogeneous population and many different interventions. Despite this broad approach, we only found five trials.

If that had been the case, we would have considered whether meta-analysis could be justified.

As indicated in our Background section, there might be substantial differences between the pathogens across countries. The optimal antibiotic regimen might, therefore, vary according to country and local risks of antibiotic resistance. We did not include enough trials to confirm that this was the case.

Despite the anticipated differences between antibiotic resistance at different sites, there could still be important differences between antibiotic regimens on clinical outcomes that would lead to generalised recommendations (Paul 2010).

For future updates, we will systematically assess the clinical heterogeneity (Barbateskovic 2021).

Agreements and disagreements with other studies or reviews

The additional trials included in this version did not change the overall conclusions and recommendations of the former review (Gordon 2005). The largest included trial only randomised 271 participants and compared meropenem with standard care (Lutsar 2020). The authors found no evidence to suggest that meropenem was superior to standard care. Although the largest of our included trials, this sample size is presumably underpowered to detect any evidence of a difference between two antibiotic regimens on clinically important outcomes such as mortality and serious adverse events.

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence does not allow confirmation, or rejection, of one antibiotic regimen being superior to another.

Implications for research

The primary focus should be to develop an international consensus definition of neonatal sepsis (McGovern 2020; Wynn 2014; Wynn 2016).

Then high-quality randomised controlled trials are needed to assess the effects of different antibiotic regimens for sepsis in newborn infants. Such trials should:

- randomise a sufficient number of participants to demonstrate a reliable result;
- assess all-cause mortality and serious adverse events;
- be conducted with low risk of bias;
- adhere to consensus definitions of suspected and diagnosed late-onset neonatal when such emerge;
- measure antibiotic resistance among the culture-positive participants;
- Assess differences between sites, countries, and regions included.

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As Cochrane Neonatal Associate Editors, Jeffrey Horbar and Vibhuti Shah peer reviewed and offered feedback for this review.

The Methods section of this review was based on a standard template used by Cochrane Neonatal.

We thank the Danish/Spanish nurse Cindy Bustamante for her help in translating Ceriani 2014 .

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References to studies included in this review

Ceriani 2014 *{published data only}*

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CHARACTERISTICS OF STUDIES

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

Ceriani 2014

Study characteristics	
Methods	Design: randomised controlled trial, single centre Duration: 7 days; however, if pretreatment cultures were positive or there was a lack of clinical improvement, treatment continued to 10 days Date: March 2006 to August 2010 Location: La División de Neonatologia del Hospital Italiano de Buenos Aires, Argentina
Participants	109 neonates aged > 3 days of life with suspected or confirmed neonatal sepsis Gender (boys/girls): not specified Age: not specified Diagnostic criteria: confirmed sepsis defined when, before a clinical picture compatible with sepsis, the blood culture or CSF were positive. Sepsis was most likely described when cultures were negative and the newborn presented clinical signs of sepsis and ≥ 2 of the following test results diagnostics: < 5000 white blood cells/mm^3, < 1500 neutrophils/mm^3, NI/NT ≥ 0.2, C-reactive protein > 10 mg/L, and number of platelets < 100,000/mm^3. Nosocomial or late-onset sepsis was considered when the clinical signs of bacterial infection showed up after the 3rd day of life and even before discharge. Assessed by physicians to have neonatal sepsis and indicated to get vancomycin. Exclusion criteria: received vancomycin or other antibiotics prior to arrival or randomisation.
Interventions	**Intervention 1:** cefazolin + amikacin **Intervention 2:** vancomycin + amikacin Antibiotics were administered intravenously at doses and intervals according to gestational and postnatal age (not specified).
Outcomes	**Primary outcomes** • Clinical cure (normalised blood test, normal clinical assessment, food tolerance, normal temperature, negative blood cultures/CSF culture, normalisation of initial abnormal blood tests) • Treatment failure

Ceriani 2014 *(Continued)*

	Follow-up: 7-10 days after end of treatment
Notes	In Spanish, translated with help from Spanish nurse Cindy Bustamante and Translated with www.DeepL.com/Translator. Funded by Carlos A Gia. Email: jose.ceriani@hospitalitaliano.org.ar

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used a computer program to perform sequence generation.
Allocation concealment (selection bias)	Low risk	Allocation details stored in opaque envelopes with sequential numbering.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	Low risk	Reported all-cause mortality.
Other bias	Low risk	Appeared free of other components that could have put it at risk of bias.

Lutsar 2020

Study characteristics

Methods	Design: randomised clinical trial, multicentre Duration: 8–14 days to allocated treatment Date: September 2012 to November 2014 Location: 18 NICUs in Estonia, Greece, Italy, Lithuania, Spain, and Turkey
Participants	272 neonates aged > 3 days of life with clinical or culture confirmed late-onset neonatal sepsis Gender (boys/girls): 53% boys in both groups Age (median in days): 16 in both groups Diagnostic criteria: postnatal age between 72 hours and 90 days and clinical or culture confirmed late-onset sepsis. Culture-confirmed late-onset sepsis defined as the presence of ≥ 1 positive culture from a

Lutsar 2020 *(Continued)*

	normally sterile site and ≥ 1 abnormal clinical or laboratory parameter within the 24 hours prior to randomisation. If postmenstrual age > 44 weeks, the International Paediatric Sepsis Consensus Conference criteria had to be met (Goldstein 2005). For neonates with postmenstrual age < 44 weeks, the criteria defined by the European Medicines Agency Expert Meeting on Neonatal and Paediatric Sepsis were used (Oeser 2013) and the presence of ≥ 2 clinical and 2 laboratory parameters within the 24 hours prior to randomisation. Exclusion criteria: administration of any systemic antibiotics for > 24 hours within the 7 days prior to randomisation unless the change was driven by lack of efficacy, late-onset sepsis caused by micro-organisms suspected or known to be resistant to study antibiotics, severe congenital malformations if the baby was not expected to survive > 3 months, presence of renal failure or requirement of haemofiltration or peritoneal dialysis (or a combination) and known intolerance of study medication.
Interventions	**Intervention 1:** meropenem 20 mg/kg 8 hourly with the exception of those with gestational age (GA) < 32 weeks or postnatal age < 2 weeks who received the same dose 12 hourly. **Intervention 2:** standard care (ampicillin + gentamicin or cefotaxime + gentamicin depending on site)
Outcomes	**Composite primary endpoint** • Treatment success (survival, no modification of allocated therapy, resolution/improvement of clinical and laboratory markers, no need of additional antibiotics and presumed/confirmed eradication of pathogens) **Secondary outcomes** • Safety, clinical and laboratory response on day 3 • Survival at day 28 • Time to NICU discharge • Presence of hearing disturbances and abnormalities in brain ultrasound • Acquisition of meropenem-resistant Gram-negative organisms in rectal swabs and occurrence of relapses or new infections after successful outcome Resolution or improvement of clinical and laboratory parameters was evaluated by the study statistician using predefined algorithms. Clinical relapses were defined as recurrence of late-onset sepsis 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 neonate with signs of infection. An adverse event was defined as any untoward medical occurrence or deviation of laboratory parameters of any causality in a neonate receiving study treatment. **Follow-up:** 28 days after start of treatment
Notes	Email: Irja.lutsar@ut.ee

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation using a computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	Randomisation list was kept confidential to trial team and sites received automated treatment assignment centrally via the e-CRF.

Lutsar 2020 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout in the standard care group.
Selective reporting (reporting bias)	Low risk	Followed the prepublished protocol, and reported mortality.
Other bias	Low risk	Appeared free of other components that could have put it at risk of bias.

Miall-Allen 1988

Study characteristics	
Methods	Design: randomised controlled study Duration: maximum 10 days, but until 48 hours after participant were asymptomatic and afebrile Date: not specified Location: Hammersmith Hospital, London, UK
Participants	28 neonates with suspected infection after 48 hours of age Gender (boys/girls): 13/15 Age (mean in days): 17.5 (intervention 1), 18.2 (intervention 2) Inclusion criteria: > 48 hours after birth with confirmed sepsis, signs highly suggestive of sepsis or who were at particular high risk of developing sepsis Exclusion criteria: administration of any systemic antibiotics in the 24 hours preceding entry to the trial
Interventions	**Intervention 1:** ticarcillin + clavulanic acid 80 mg/kg 12 hourly or 8 hourly if neonate weighed > 2 kg **Intervention 2:** flucloxacillin 25 mg/kg 12 hourly + gentamicin 2.5 mg/kg 12 hourly
Outcomes	• Mortality • Treatment failure • Bacteriological resistance **Follow-up:** 4–6 weeks after end of treatment
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Miall-Allen 1988 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout in the ticarcillin + clavulanic acid group. The reason was clearly stated.
Selective reporting (reporting bias)	Low risk	Trial reported all-cause mortality.
Other bias	Low risk	No other biases identified

Millar 1992

Study characteristics	
Methods	Design: randomised controlled study Duration: median duration of antibiotic treatment in both groups was 5 days Date: February 1989 and April 1990 Location: Peter Congdon Regional Neonatal Unit in Leeds, UK
Participants	81 neonates with suspected sepsis after the first week of life Gender: not reported Age: not reported Inclusion criteria: neonates < 33 weeks' gestational age with episodes of suspected bacterial infection occurring after the 1st week of life. Diagnosis of suspected infection was made clinically and the clinical signs included apnoea, bradycardia, metabolic acidosis, hypotension, unstable temperature, and poor peripheral perfusion. Exclusion criteria: not reported
Interventions	**Intervention 1:** intravenous vancomycin 22 mg/kg every 12 hours with gentamicin 3 mg/kg every 12 hours (41 neonates) **Intervention 2:** intravenous vancomycin 22 mg/kg every 12 hours with aztreonam 15 mg/kg every 12 hours (40 neonates)
Outcomes	• Mortality • Faecal colonisation

Millar 1992 *(Continued)*

- Incidence of necrotising enterocolitis
- Incidence of chronic lung disease
- Median hospital stay

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	Low risk	Reported mortality.
Other bias	Low risk	No other biases identified.

Ramasamy 2014

Study characteristics

Methods	Design: randomised controlled trial Duration: all neonates were given antibiotics for ≥ 10 days. Duration of antibiotics was extended if required depending on clinical response and repeat blood culture report Date: not described Location: extramural nursery of the Paediatrics Department, JIPMER, Pondicherry, a tertiary care teaching hospital in India
Participants	90 neonates with suspected late-onset neonatal sepsis Gender (boys/girls): 56/34 Age: not reported Inclusion criteria: neonates aged 3–28 days with the evidence of late-onset sepsis by both clinical and laboratory parameters. The clinical parameters used were poor feeding, poor activity, seizures, apnoea, respiratory distress, umbilical discharge and abdominal distension, whereas the septic screen tests included microerythrocyte sedimentation rate, C-reactive protein, absolute neutrophil count, and

Ramasamy 2014 *(Continued)*

	band cell count. Neonates with ≥ 1 of the above clinical parameters and 2 positive septic screen tests were included in the study. Exclusion criteria: babies with major congenital anomalies, extreme prematurity (< 28 weeks), very low birthweight (< 1500 g), congenital heart disease, severe asphyxia (5-minute Apgar < 5), and who had received antibiotics before admission
Interventions	**Intervention 1:** cefotaxime + gentamicin (50 neonates) **Intervention 2:** cloxacillin + amikacin (40 neonates) Antibiotics were administered intravenously but doses and intervals were not specified.
Outcomes	**Primary outcomes** • Mortality before discharge from hospital • Complications including: shock, DIC, acidosis, renal failure, and rehospitalisation within 2 weeks of discharge **Secondary outcomes** • Treatment failure • Subsequent fungal infections • Duration of hospital stay • Cost analysis • Problems on follow-up **Follow-up:** 2 weeks and 1 month after discharge
Notes	Email: drnbiswal@yahoo.com

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Allocations kept in sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as single-blinded but it was unclear in what way.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as single-blinded but it was unclear in what way.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	Low risk	Reported all-cause mortality.
Other bias	Low risk	No other biases identified.

CSF: cerebrospinal fluid; DIC: disseminated intravascular coagulation; e-CRF: electronic case report form; NICU: neonatal intensive care unit; NI/NT: neutrophil ratio immature on total neutrophils.

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

Study	Reason for exclusion
Adelman 1987a	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Adelman 1987b	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Alinejad 2018	Participants did not have late-onset neonatal sepsis.
Aronoff 1984	Did not included neonates with sepsis.
Auriti 2005	Both groups received amoxicillin.
Baqui 2013	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Bassetti 1991	Participants were adults.
Begue 1998	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Chartrand 1984	Did not included neonates with sepsis.
Chowdhary 2006	Both groups received the same antibiotics.
Collins 1998	Participants did not have late-onset neonatal sepsis.
De Louvois 1992	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Deville 2003	Did not have late-onset sepsis.
Ebrahim 1969	Not a randomised controlled trial.
Faix 1988	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Feigin 1976	Participants did not have late-onset neonatal sepsis.
Fogel 1983	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Gathwala 2010	Both groups received the same antibiotics.
Gokalp 1991	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Haffejee 1984	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.

Study	Reason for exclusion
Hall 1988	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Hammerberg 1989	Only included participants with early-onset neonatal sepsis.
Hansen 1980	Both groups received ampicillin + gentamycin.
Jantausch 2003	Did not have late-onset sepsis.
Kaplan 2003	Did not have late-onset sepsis.
Langhendries 1993	Both groups received the same antibiotic.
Lee 2005	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Lönnerholm 1982	Participants were not suspected for sepsis, a severe infection or deep-seated infection.
Marks 1978	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
McCracken 1976	Both groups received the same antibiotic.
Metsvaht 2010	Included only participants with early-onset sepsis.
Mir 2017	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Molyneux 2017	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Mulubwa 2020	Both groups received the same antibiotic.
Odio 1987	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Odio 1995	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Oral 1998	Not a randomised controlled trial.
Rohatgi 2017	Both groups received the same antibiotics.
Snelling 1983	Included only participants with early-onset sepsis.
Taheri 2011	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Tessin 1988	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Tessin 1989	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Tewari 2014	Included only participants with early-onset sepsis.

Study	Reason for exclusion
Tshefu 2015a	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Tshefu 2015b	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Umaña 1990	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Viganò 1995	Did not have late-onset sepsis.
Wells 1984	Did not have late-onset sepsis.
Wiese 1988	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.
Zaidi 2013	Included a mix of early- and late-onset neonatal sepsis. Unable to provide separate data for late-onset.

DATA AND ANALYSES

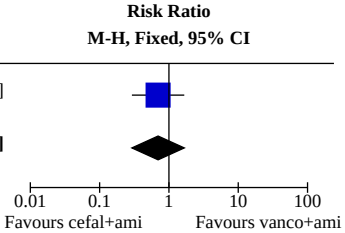
Comparison 1. Cefazolin plus amikacin versus vancomycin plus amikacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.29, 1.66]
1.2 Serious adverse events	1	109	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.29, 1.66]

Analysis 1.1. Comparison 1: Cefazolin plus amikacin versus vancomycin plus amikacin, Outcome 1: All-cause mortality

Study or Subgroup	Cefalozin plus amikacin Events	Total	Amikacin plus amikacin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ceriani 2014	7	52	11	57	100.0%	0.70 [0.29 , 1.66]
Total (95% CI)		**52**		**57**	**100.0%**	**0.70 [0.29 , 1.66]**
Total events:	7		11			

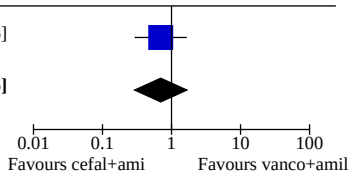
Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Cefazolin plus amikacin versus vancomycin plus amikacin, Outcome 2: Serious adverse events

Study or Subgroup	Cefalozin plus amikacin Events	Total	Amikacin plus amikacin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ceriani 2014	7	52	11	57	100.0%	0.70 [0.29 , 1.66]
Total (95% CI)		**52**		**57**	**100.0%**	**0.70 [0.29 , 1.66]**
Total events:	7		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



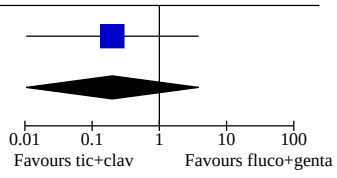
Comparison 2. Ticarcillin plus clavulanic acid versus flucloxacillin plus gentamicin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 3.82]
2.2 Serious adverse events	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 3.82]

Analysis 2.1. Comparison 2: Ticarcillin plus clavulanic acid versus flucloxacillin plus gentamicin, Outcome 1: All-cause mortality

Study or Subgroup	Ticarcillin+clavulanic acid Events	Total	Flucloxacillin+gentamycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Miall-Allen 1988	0	14	2	14	100.0%	0.20 [0.01 , 3.82]
Total (95% CI)		**14**		**14**	**100.0%**	**0.20 [0.01 , 3.82]**
Total events:	0		2			

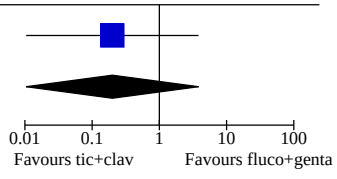
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Ticarcillin plus clavulanic acid versus flucloxacillin plus gentamicin, Outcome 2: Serious adverse events

Study or Subgroup	Ticarcillin+clavulanic acid Events	Total	Flucloxacillin+gentamycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Miall-Allen 1988	0	14	2	14	100.0%	0.20 [0.01 , 3.82]
Total (95% CI)		**14**		**14**	**100.0%**	**0.20 [0.01 , 3.82]**
Total events:	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)
Test for subgroup differences: Not applicable



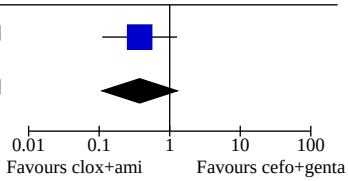
Comparison 3. Cloxacillin plus amikacin versus cefotaxime plus gentamicin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.11, 1.27]
3.2 Serious adverse events	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.17, 1.48]
3.3 Circulatory support	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.17, 1.48]
3.4 Nephrotoxicity	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.05]

Analysis 3.1. Comparison 3: Cloxacillin plus amikacin versus cefotaxime plus gentamicin, Outcome 1: All-cause mortality

Study or Subgroup	Cloxacillin+amikacin Events	Total	Cefotaxime+gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ramasamy 2014	3	40	10	50	100.0%	0.38 [0.11 , 1.27]
Total (95% CI)		**40**		**50**	**100.0%**	**0.38 [0.11 , 1.27]**
Total events:	3		10			

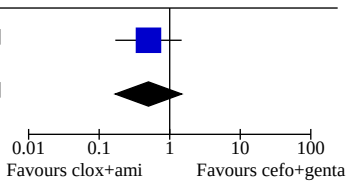
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Cloxacillin plus amikacin versus cefotaxime plus gentamicin, Outcome 2: Serious adverse events

Study or Subgroup	Cloxacillin+amikacin Events	Total	Cefotaxime+gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ramasamy 2014	4	40	10	50	100.0%	0.50 [0.17 , 1.48]
Total (95% CI)		**40**		**50**	**100.0%**	**0.50 [0.17 , 1.48]**
Total events:	4		10			

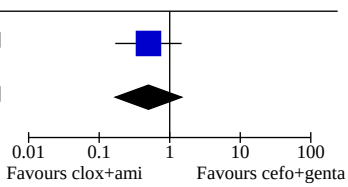
Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



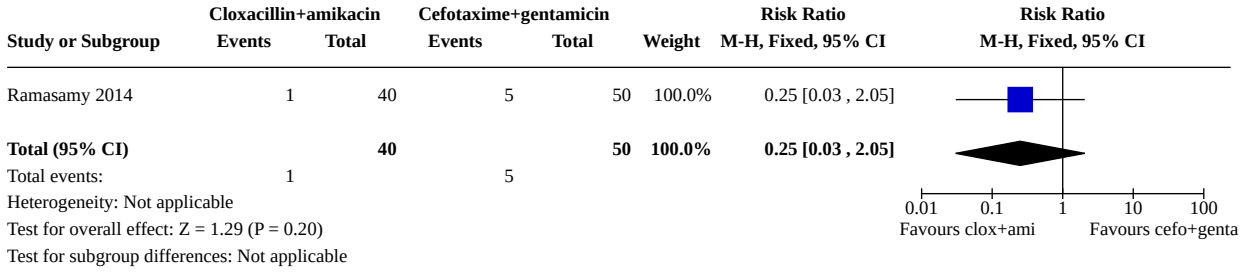
Analysis 3.3. Comparison 3: Cloxacillin plus amikacin versus cefotaxime plus gentamicin, Outcome 3: Circulatory support

Study or Subgroup	Cloxacillin+amikacin Events	Total	Cefotaxime+gentamicin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ramasamy 2014	4	40	10	50	100.0%	0.50 [0.17 , 1.48]
Total (95% CI)		**40**		**50**	**100.0%**	**0.50 [0.17 , 1.48]**
Total events:	4		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



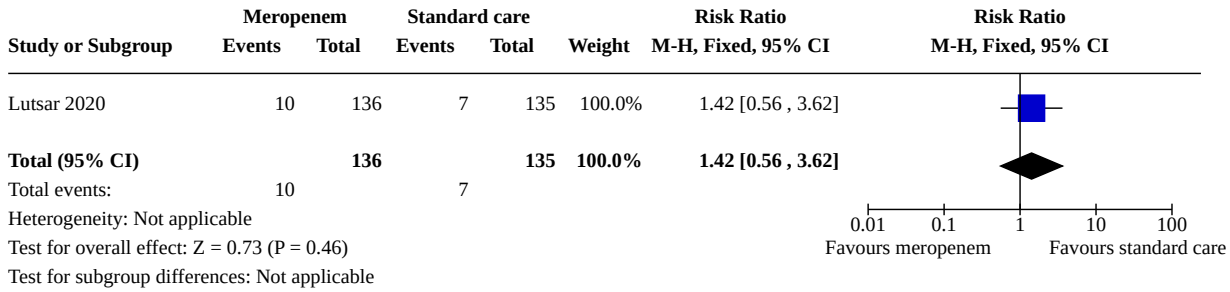
Analysis 3.4. Comparison 3: Cloxacillin plus amikacin versus cefotaxime plus gentamicin, Outcome 4: Nephrotoxicity



Comparison 4. Meropenem versus standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality	1	271	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.56, 3.62]
4.2 Serious adverse events	1	271	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.90, 2.66]
4.3 Neurological developmental impairment	1	271	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.51, 1.48]
4.4 Necrotising enterocolitis	1	271	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.33, 1.42]

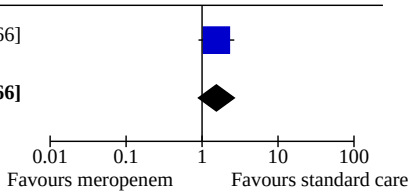
Analysis 4.1. Comparison 4: Meropenem versus standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin), Outcome 1: All-cause mortality



Analysis 4.2. Comparison 4: Meropenem versus standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin), Outcome 2: Serious adverse events

Study or Subgroup	Meropenem Events	Meropenem Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lutsar 2020	28	136	18	135	100.0%	1.54 [0.90 , 2.66]
Total (95% CI)		**136**		**135**	**100.0%**	**1.54 [0.90 , 2.66]**
Total events:	28		18			

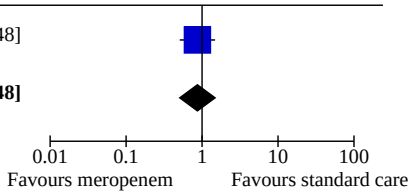
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: Meropenem versus standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin), Outcome 3: Neurological developmental impairment

Study or Subgroup	Meropenem Events	Meropenem Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lutsar 2020	21	136	24	135	100.0%	0.87 [0.51 , 1.48]
Total (95% CI)		**136**		**135**	**100.0%**	**0.87 [0.51 , 1.48]**
Total events:	21		24			

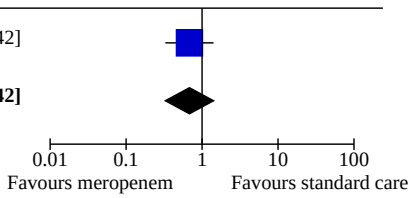
Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.61)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Meropenem versus standard care (ampicillin plus gentamicin or cefotaxime plus gentamicin), Outcome 4: Necrotising enterocolitis

Study or Subgroup	Meropenem Events	Meropenem Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lutsar 2020	11	136	16	135	100.0%	0.68 [0.33 , 1.42]
Total (95% CI)		**136**		**135**	**100.0%**	**0.68 [0.33 , 1.42]**
Total events:	11		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



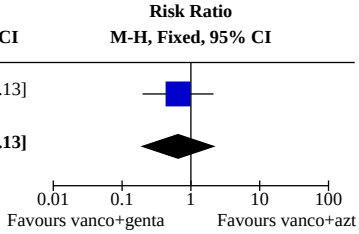
Comparison 5. Vancomycin plus gentamicin versus vancomycin plus aztreonam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 All-cause mortality	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.20, 2.13]
5.2 Serious adverse events	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.20, 2.13]
5.3 Necrotising enterocolitis	1	81	Risk Ratio (M-H, Fixed, 95% CI)	12.69 [0.74, 218.09]

Analysis 5.1. Comparison 5: Vancomycin plus gentamicin versus vancomycin plus aztreonam, Outcome 1: All-cause mortality

Study or Subgroup	Vancomycin+gentamicin Events	Total	Vancomycin+aztreonam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Millar 1992	4	41	6	40	100.0%	0.65 [0.20 , 2.13]
Total (95% CI)		**41**		**40**	**100.0%**	**0.65 [0.20 , 2.13]**
Total events:	4		6			

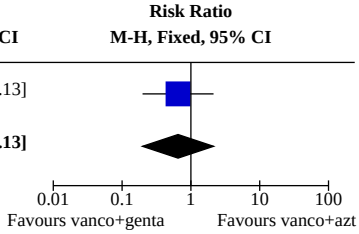
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Vancomycin plus gentamicin versus vancomycin plus aztreonam, Outcome 2: Serious adverse events

Study or Subgroup	Vancomycin+gentamicin Events	Total	Vancomycin+aztreonam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Millar 1992	4	41	6	40	100.0%	0.65 [0.20 , 2.13]
Total (95% CI)		**41**		**40**	**100.0%**	**0.65 [0.20 , 2.13]**
Total events:	4		6			

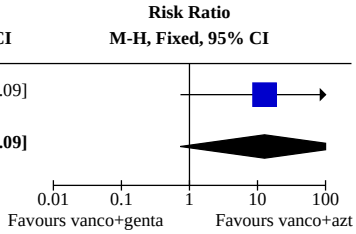
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable



Analysis 5.3. Comparison 5: Vancomycin plus gentamicin versus vancomycin plus aztreonam, Outcome 3: Necrotising enterocolitis

Study or Subgroup	Vancomycin+gentamicin Events	Total	Vancomycin+aztreonam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Millar 1992	6	41	0	40	100.0%	12.69 [0.74 , 218.09]
Total (95% CI)		**41**		**40**	**100.0%**	**12.69 [0.74 , 218.09]**
Total events:	6		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Commonly used clinical and laboratory criteria of sepsis

Clinical criteria	Laboratory criteria
• Abdominal distension • Skin and subcutaneous lesions such as petechial rash, abscesses, sclerema • Cardiovascular signs (tachycardia/bradycardia, hypotension, poor perfusion) • Respiratory signs (apnoea, cyanosis, tachypnoea, need for ventilator, increased oxygen requirement) • Abnormal temperature (fever or hypothermia) • Central nervous system signs (lethargy, hypotonia, seizure) • Feeding problems	• WBC • Immature WBC:total WBC ratio • Platelet count • C-reactive protein • Metabolic acidosis • Neutropenia • Abnormal fibrinogen

Table 1. Commonly used clinical and laboratory criteria of sepsis *(Continued)*

	• Hyperglycaemia and hypoglycaemia

WBC: white blood cell.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 3) in the Cochrane Library

#1 MeSH descriptor: [Infant] explode all trees

#2 (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

#3 #1 or #2

#4 MeSH descriptor: [Neonatal Sepsis] explode all trees

#5 (sepsis NEAR/3 (neonat* or neo nat*))

#6 (sepsis NEAR/3 (newborn* or new born* or newly born*))

#7 (septic* NEAR/3 (neonat* or neo nat*))

#8 (septic* NEAR/3 (newborn* or new born* or newly born*))

#9 (infect* NEAR/3 (neonat* or neo nat*))

#10 (infect* NEAR/3 (newborn* or new born* or newly born*))

#11 (bacter* NEAR/3 (neonat* or neo nat*))

#12 (bacter* NEAR/3 (newborn* or new born* or newly born*))

#13 (gram NEAR/2 negative)

#14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13

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

#16 (antibiot* OR antimicrob* OR lactam* OR aminoglycoside* OR glycoprotein OR penicillin OR oxacillin OR cloxacillin OR dicloxacillin OR nafcillin OR methicillin OR ampicillin OR amoxicillin OR piperacillin OR ticarcillin OR carbenicillin OR mezlocillin OR cephalosporins OR cefazolin OR cephalexin OR cefuroxime OR cefotetan OR cefoxitin OR ceftriaxone OR cefotaxime OR ceftazidime OR cefepime OR cefazolin OR ceftobiprole OR cefoperazone OR carbapenems OR imipenem OR meropenem OR doripenem OR ertapenem OR monobactams OR aztreonam)

#17 #15 OR #16

#18 #3 and #14 and #17

MEDLINE Ovid (1946 to March 2021)

1. exp Infant/

2. (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. 1 or 2

4. exp Neonatal Sepsis/

5. (sepsis adj3 (neonat$ or neo nat$)).ti,ab.

6. (sepsis adj3 (newborn$ or new born$ or newly born$)).ti,ab.

7. (septic$ adj3 (neonat$ or neo nat$)).ti,ab.

8. (septic$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

9. (infect$ adj3 (neonat$ or neo nat$)).ti,ab.

10. (infect$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

11. (bacter$ adj3 (neonat$ or neo nat$)).ti,ab.

12. (bacter$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

13. (gram adj2 negative).ti,ab.

14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. exp Anti-Bacterial Agents/

16. (antibiot* or antimicrob* or lactam* or aminoglycoside* or glycoprotein or penicillin or oxacillin or cloxacillin or dicloxacillin or nafcillin or methicillin or ampicillin or amoxicillin or piperacillin or ticarcillin or carbenicillin or mezlocillin or cephalosporins or cefazolin or cephalexin or cefuroxime or cefotetan or cefoxitin or ceftriaxone or cefotaxime or ceftazidime or cefepime or cefazolin or ceftobiprole or cefoperazone or carbapenems or imipenem or meropenem or doripenem or ertapenem or monobactams or aztreonam).ti,ab.

17. 15 or 16

18. 3 and 14 and 17

19. (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or trial.ti.

20. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

21. 18 and (19 or 20)

Embase Ovid (1974 to March 2021)

1. exp infant/

2. (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

3. 1 or 2

4. exp newborn sepsis/

5. (sepsis adj3 (neonat$ or neo nat$)).ti,ab.

6. (sepsis adj3 (newborn$ or new born$ or newly born$)).ti,ab.

7. (septic$ adj3 (neonat$ or neo nat$)).ti,ab.

8. (septic$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

9. (infect$ adj3 (neonat$ or neo nat$)).ti,ab.

10. (infect$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

11. (bacter$ adj3 (neonat$ or neo nat$)).ti,ab.

12. (bacter$ adj3 (newborn$ or new born$ or newly born$)).ti,ab.

13. (gram adj2 negative).ti,ab.

14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. exp antiinfective agent/

16. (antibiot* or antimicrob* or lactam* or aminoglycoside* or glycoprotein or penicillin or oxacillin or cloxacillin or dicloxacillin or nafcillin or methicillin or ampicillin or amoxicillin or piperacillin or ticarcillin or carbenicillin or mezlocillin or cephalosporins or cefazolin or cephalexin or cefuroxime or cefotetan or cefoxitin or ceftriaxone or cefotaxime or ceftazidime or cefepime or cefazolin or ceftobiprole or cefoperazone or carbapenems or imipenem or meropenem or doripenem or ertapenem or monobactams or aztreonam).ti,ab.

17. 15 or 16

18. 3 and 14 and 17

19. Randomized controlled trial/ or Controlled clinical study/ or trial.ti.

20. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

21. 18 and (19 or 20)

CINAHL (EBSCOhost; March 2021)

S14 S10 AND S13

S13 S11 OR S12

S12 TX (random* or blind* or placebo* or meta-analys*) OR TI trial

S11 PT randomized controlled trial OR PT controlled clinical trial

S10 S3 AND S6 AND S9

S9 S7 OR S8

S8 TI ((antibiot* or antimicrob* or lactam* or aminoglycoside* or glycoprotein or penicillin or oxacillin or cloxacillin or dicloxacillin or nafcillin or methicillin or ampicillin or amoxicillin or piperacillin or ticarcillin or carbenicillin or mezlocillin or cephalosporins or cefazolin or cephalexin or cefuroxime or cefotetan or cefoxitin or ceftriaxone or cefotaxime or ceftazidime or cefepime or cefazolin or ceftobiprole or cefoperazone or carbapenems or imipenem or meropenem or doripenem or ertapenem or monobactams or aztreonam)

S7 MH antibiotics

S6 S4 OR S5

S5 TI ((((sepsis or septic* or infect* or bacter*) N3 (neonat* or neo nat* or newborn* or new born* or newly born*)) or (gram N2 negative))) OR AB ((((sepsis or septic* or infect* or bacter*) N3 (neonat* or neo nat* or newborn* or new born* or newly born*)) or (gram N2 negative)))

S4 MH Neonatal Sepsis

S3 S1 OR S2

S2 TX (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

S1 MH infant

LILACS (Bireme; 1982 to March 2021)

(infan$ or newborn or neonat$ or premature or preterm or very low birth weight or low birth weight or VLBW or LBW) and (((sepsis or septic$ or infect$ or bacter$) and (neonat$ or neo nat$ or newborn$ or new born$ or newly born$)) or (gram near negative)) and (antibiot$ OR antimicrob$ OR lactam$ OR aminoglycoside$ OR glycoprotein OR penicillin OR oxacillin OR cloxacillin OR dicloxacillin OR nafcillin OR methicillin OR ampicillin OR amoxicillin OR piperacillin OR ticarcillin OR carbenicillin OR mezlocillin OR cephalosporins OR cefazolin OR cephalexin OR cefuroxime OR cefotetan OR cefoxitin OR ceftriaxone OR cefotaxime OR ceftazidime OR cefepime OR cefazolin OR ceftobiprole OR cefoperazone OR carbapenems OR imipenem OR meropenem OR doripenem OR ertapenem OR monobactams OR aztreonam) [Words] and (random$ or blind$ or placebo$ or meta-analys$) [Words]

Science Citation Index EXPANDED (1900 to March 2021) and Conference Proceedings Citation Index – Science (1990 to March 2021) (Web of Science)

#5 #4 AND #3 AND #2 AND #1

#4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*)

#3 TS=(antibiot* OR antimicrob* OR lactam* OR aminoglycoside* OR glycoprotein OR penicillin OR oxacillin OR cloxacillin OR dicloxacillin OR nafcillin OR methicillin OR ampicillin OR amoxicillin OR piperacillin OR ticarcillin OR carbenicillin OR mezlocillin OR cephalosporins OR cefazolin OR cephalexin OR cefuroxime OR cefotetan OR cefoxitin OR ceftriaxone OR cefotaxime OR ceftazidime OR cefepime OR cefazolin OR ceftobiprole OR cefoperazone OR carbapenems OR imipenem OR meropenem OR doripenem OR ertapenem OR monobactams OR aztreonam)

#2 TS=(((sepsis or septic* or infect* or bacter*) and (neonat* or neo nat* or newborn* or new born* or newly born*)) or (gram near negative))

#1 TS=(infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. 'Risk of bias' tool

We used the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the included trials. For each included trial, we sought information regarding the method of randomisation, blinding, and reporting of all outcomes of all infants enrolled in the trial. We assessed each criterion as being at low, high, or unclear risk of bias. Three review authors independently assessed each study. We resolved any disagreement by discussion. We added this information to the 'Characteristics of included studies' table. We evaluated the following issues and entered the findings into the 'Risk of bias' table.

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

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

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

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

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

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

3. 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 categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

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

4. 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 categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. 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 described the completeness of data including attrition and exclusions from the analysis. We noted 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 was reported or supplied by the trial authors, we reincluded missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or

- unclear risk.

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

For each included study, we described 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 compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

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

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

For each included study, we described 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 assessed whether each study was free of other problems that could have put it at risk of bias as:

- low risk;
- high risk;
- unclear risk.

If needed, we planned to explore the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
12 March 2021	Amended	The authors have revised the protocol prior to conducting the updated review (Korang 2021). This protocol and the subsequent review will replace the review of "Antibiotic regimens for suspected late onset sepsis in newborn infants" (Gordon 2005).

HISTORY

Protocol first published: Issue 12, 2020
Review first published: Issue 4, 2021

Date	Event	Description
7 July 2016	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

SKK: conceived, designed, and drafted the review. He extracted, analysed and interpreted the data.

SS: extracted data, commented on, and revised the review.

CN: extracted data, commented on, and revised the review.

MG: provided general advice and revised the review.

GG: provided general advice and revised the review.

ULT: provided general advice and revised the review.

JCJ: conceived, designed, provided general advice, and revised the review. He analysed and interpreted the data.

All authors agreed on the final review version.

DECLARATIONS OF INTEREST

The project received no funding.

SKK: none.

SS: none.

CN: none.

MG: none.

GG: none.

ULT: none.

JCJ: none.

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- National Institute for Health Research (NIHR), UK

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- Vermont Oxford Network, USA

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We decided to describe the antibiotic resistance occurring within the included trials towards the allocated antibiotic regimens narratively. We did this to further strengthen the review as recommended by Leibovici and colleagues (Leibovici 2016).
- We decided to include two subgroups assessing the different inclusion criteria for sepsis (primarily for future updates).

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Antibiotics for hospital-acquired pneumonia in neonates and children (Review)

Korang SK, Nava C, Mohana SP, Nygaard U, Jakobsen JC

Korang SK, Nava C, Mohana SP, Nygaard U, Jakobsen JC.
Antibiotics for hospital-acquired pneumonia in neonates and children.
Cochrane Database of Systematic Reviews TBD, Issue TBD. Art. No.: CD013864.
DOI: 10.1002/14651858.CD013864.

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[Intervention Review]

Antibiotics for hospital-acquired pneumonia in neonates and children

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ABSTRACT

Background

Hospital-acquired pneumonia is one of the most common hospital-acquired infections in children worldwide. Most of our understanding of hospital-acquired pneumonia in children is derived from adult studies. To our knowledge, no systematic review with meta-analysis has assessed the benefits and harms of different antibiotic regimens in neonates and children with hospital-acquired pneumonia.

Objectives

To assess the beneficial and harmful effects of different antibiotic regimens for hospital-acquired pneumonia in neonates and children.

Search methods

We searched CENTRAL, MEDLINE, Embase, three other databases, and two trial registers to February 2021, together with reference checking, citation searching, and contact with study authors to identify additional studies.

Selection criteria

We included randomised clinical trials comparing one antibiotic regimen with any other antibiotic regimen for hospital-acquired pneumonia in neonates and children.

Data collection and analysis

Three review authors independently assessed studies for inclusion, extracted data, and assessed risk of bias. We assessed the certainty of the evidence using the GRADE approach. Our primary outcomes were all-cause mortality and serious adverse events; our secondary outcomes were health-related quality of life, pneumonia-related mortality, non-serious adverse events, and treatment failure. Our primary time point of interest was at maximum follow-up.

Main results

We included four randomised clinical trials (84 participants). We assessed all trials as having high risk of bias.

We did not conduct any meta-analyses, as the included trials did not compare similar antibiotic regimens.

Each of the four trials assessed a different comparison, as follows: cefepime versus ceftazidime; linezolid versus vancomycin; meropenem versus cefotaxime; and ceftobiprole versus cephalosporin.

Only one trial reported our primary outcomes of all-cause mortality and serious adverse events. Three trials reported our secondary outcome of treatment failure. Two trials primarily included community-acquired pneumonia and hospitalised children with bacterial infections, hence the children with hospital-acquired pneumonia constituted subgroups of the total sample sizes.

Where outcomes were reported, the certainty of the evidence was very low for each of the comparisons. We are unable to draw meaningful conclusions from the numerical results.

None of the included trials assessed health-related quality of life, pneumonia-related mortality, or non-serious adverse events.

Authors' conclusions

The relative beneficial and harmful effects of different antibiotic regimens remain unclear due to the very low certainty of the available evidence. The current evidence is insufficient to support any antibiotic regimen being superior to another. Randomised clinical trials assessing different antibiotic regimens for hospital-acquired pneumonia in children and neonates are warranted.

PLAIN LANGUAGE SUMMARY

Antibiotics for hospital-acquired pneumonia in newborns and children

Review question

Which antibiotic regimen is safer and more effective in treating neonates (newborns) and children with hospital-acquired pneumonia?

Background

Hospital-acquired pneumonia is an inflammation of the tissue of one or both lungs caused by an infection that occurs during a hospital stay (i.e. 48 hours or more after hospital admission). It is one of the most common hospital-acquired infections in children worldwide, and is associated with a high death rate. Most of our understanding of hospital-acquired pneumonia in children is drawn from adult studies. To our knowledge this is the first review with meta-analysis that assesses the benefits and harms of different antibiotic regimens in newborns and children with hospital-acquired pneumonia.

Search date

The evidence is current to February 2021.

Study characteristics

We included four trials randomising 84 children with hospital-acquired pneumonia to different antibiotic regimens. Three trials were multicentre trials from the USA, Latin America, Europe, and South Africa. The South African trial included one site in Malaysia. Each of the four included trials compared different antibiotic regimens, as follows: cefepime versus ceftazidime; linezolid versus vancomycin; meropenem versus cefotaxime; and ceftobiprole versus cephalosporin.

Study funding sources

Three trials were funded by pharmaceutical companies (Zeneca Pharmaceuticals, Pharmacia Corp, and Basilea Pharmaceutica International Ltd.), indicating a possible risk of bias related to vested interest risk.

Key results

Each of the four included trials compared different antibiotic regimens, as follows: cefepime versus ceftazidime; linezolid versus vancomycin; meropenem versus cefotaxime; and ceftobiprole versus cephalosporin.

Only one trial reported our primary outcomes of death from all causes and serious adverse events (major complications). Three trials reported our secondary outcome of treatment failure. Two trials primarily included community-acquired pneumonia and hospitalised children with bacterial infections, hence the children with hospital-acquired pneumonia constituted only subgroups of the total study populations.

Where outcomes were reported, the certainty of the evidence was very low for each of the comparisons. We were unable to draw any meaningful conclusions from the numerical results.

None of the included trials assessed health-related quality of life, pneumonia-related death, or non-serious adverse events (minor complications).

Conclusions

The available evidence does not suggest that one antibiotic regimen is safer and more effective than another in treating newborns and children with hospital-acquired pneumonia. Further research is needed.

Certainty of the evidence

The certainty of evidence is very low. All four included trials had high risk of bias (i.e. the studies were designed in such a way that the results may have been skewed). In addition, the included trials involved few participants, which is likely to have led to inaccurate results.

SUMMARY OF FINDINGS

Summary of findings 1. Cefepime compared with ceftazidime for hospital-acquired pneumonia in neonates and children

Cefepime compared with ceftazidime for hospital-acquired pneumonia in neonates and children

Patient or population: neonates and children with hospital-acquired pneumonia

Settings: hospital

Intervention: cefepime

Comparison: ceftazidime

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Ceftazidime	Cefepime				
All-cause mortality Maximum follow-up (Time point was not described.)	**200 per 1000**	**28 per 1000** (2 to 510)	**RR 0.14** (0.01 to 2.55)	30 (1 study)	⊕⊖⊖⊖ Very low[a]	OIS: 3262 (RR 0.80, α 0.033, β 0.20, Pc 20%)
Serious adverse events Maximum follow-up (Time point was not described.)	**200 per 1000**	**28 per 1000** (2 to 510)	**RR 0.14** (0.01 to 2.55)	30 (1 study)	⊕⊖⊖⊖ Very low[a]	OIS: 3262 (RR 0.80, α 0.033, β 0.20, Pc 20%) Serious adverse events were deaths.
Treatment failure Maximum follow-up (Time point was not described.)	**400 per 1000**	**200 per 1000** (60 to 656)	**RR 0.50** (0.15 to 1.64)	30 (1 study)	⊕⊖⊖⊖ Very low[a]	OIS: 1272 (RR 0.80, α 0.033, β 0.20, Pc 40%)
Health-related quality of life Maximum follow-up	-	-	-	-	-	This outcome was not reported.
Pneumonia-related mortality	-	-	-	-	-	This outcome was not reported.

Maximum follow-up						
Non-serious adverse events Maximum follow-up	-	-	-	-	-	This outcome was not reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OIS**: optimal information size; **RR:** risk ratio; **Pc:** Percentage in control group

GRADE Working Group grades of evidence
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.

[a]Downgraded by 1 level for study limitations due to serious risk of bias, and two levels for imprecision due to very small information size.

Summary of findings 2. Linezolid compared with vancomycin for hospital-acquired pneumonia in neonates and children

Linezolid compared with vancomycin for hospital-acquired pneumonia in neonates and children

Patient or population: neonates and children with hospital-acquired pneumonia

Settings: hospital

Intervention: linezolid

Comparison: vancomycin

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Vancomycin	**Linezolid**				
All-cause mortality Maximum follow-up (up to 35 days)	-	-	-	-	-	This outcome was not reported.

Serious adverse events Maximum follow-up (up to 35 days)	-	-	-	-	-	This outcome was not reported.
Treatment failure Maximum follow-up (up to 35 days)	**154 per 1000**	**315 per 1000** (75 to 1000)	**RR 2.05** (0.49 to 8.63)	32 (1 study)	⊕⊖⊖⊖ Very low[a]	OIS: 4438 (RR 0.80, α 0.033, β 0.20, Pc 15.4%)
Health-related quality of life Maximum follow-up	-	-	-	-	-	This outcome was not reported.
Pneumonia-related mortality Maximum follow-up	-	-	-	-	-	This outcome was not reported.
Non-serious adverse events Maximum follow-up	-	-	-	-	-	This outcome was not reported.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OIS**: optimal information size; **RR:** risk ratio; **Pc:** Percentage in control group

GRADE Working Group grades of evidence
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.

[a]Downgraded by 1 level for study limitations due to serious risk of bias, and 2 levels for imprecision due to very small information size.

BACKGROUND

Description of the condition

Hospital-acquired pneumonia (also known as nosocomial pneumonia) is defined as pneumonia that occurs 48 hours or more after hospital admission (Eccles 2014; Kalil 2016; Torres 2017).

Epidemiology

Hospital-acquired infection is a serious complication of hospitalisation worldwide in adults and children (Polin 2012; Zingg 2017). The incidence of hospital-acquired infections is between 0.17% and 36% of hospitalised paediatric patients (Polin 2012; Vijay 2018). Variations in incidence may be due to differences in diagnostic criteria as well as differences in local risk factors for the development of hospital-acquired infections (Polin 2012; Vijay 2018). The highest incidences are seen in neonatal intensive care units (NICUs) and paediatric intensive care units (PICUs) (Iosifidis 2018; Polin 2012; Stein 1994; Zingg 2017). European studies suggest that the incidence of hospital-acquired infections is higher in paediatric surgical wards (17%) compared with general paediatrics wards (2.5%) (Li 2019).

Hospital-acquired pneumonia is one of the most common hospital-acquired infections in children worldwide (Alvares 2019). Hospital-acquired pneumonia in neonates and children accounts for 6.8% to 32.3% of all hospital-acquired infections (Polin 2012; Stein 1994; Zingg 2017). It is therefore a frequent cause of hospital-acquired infection in patients in the NICU or PICU, only surpassed by catheter-associated bloodstream infections (Bigham 2009; Cernada 2013; Polin 2012; Richards 1999; Zingg 2017). The incidence is particularly high amongst premature neonates or neonates with low birth weight (Apisarnthanarak 2003; Tan 2014). Paediatric hospital-acquired pneumonia has been shown to be associated with increased mortality (Bigham 2009; Iosifidis 2018). Hospital-acquired pneumonia is associated with even higher mortality and morbidity in preterm neonates (Apisarnthanarak 2003).

The vast majority of hospital-acquired pneumonia is ventilator-associated pneumonia, a subtype of hospital-acquired pneumonia. Ventilator-associated pneumonia is defined as "pneumonia that occurs 48 hours or more after endotracheal intubation" (Cernada 2013; Iosifidis 2018; Joram 2012; Kalil 2016; Torres 2017). The incidence of ventilator-associated pneumonia is reported to be 2.9 to 11.6 cases per 1000 ventilator days (de Neef 2019; Jarvis 1991; Joram 2012).

Even though most research is focused on ventilator-associated pneumonia, non-ventilatory hospital-acquired pneumonia has similar, or even higher mortality rates and financial costs than ventilator-associated pneumonia, whilst its incidence could be underestimated (Davis 2012; Giuliano 2018).

Risk factors

Risk factors for hospital-acquired pneumonia are prolonged hospitalisation, mechanical ventilation, serious underlying illnesses (e.g. lung disease, immune deficiency), bloodstream infections, recent antimicrobial therapy, genetic syndromes, immunosuppression, use of steroids, prematurity, low birth weight, reintubation or self-extubation, and bronchoscopy (Aelami 2014; Liu 2013; Stein 1994). Newborns, preterms, and infants are especially prone to infections, due to a developmental deficiency in the innate, adaptive immune systems, usage of endotracheal and orogastric tubes, exposure to broad-spectrum antibiotic agents, and parenteral nutrition (Aelami 2014; Polin 2012; Tan 2014). This broad range of risk factors increases the risk of hospital-acquired pneumonia; however, they are associated with different kinds of pathogens (Mourani 2017; Polin 2012), therefore one antibiotic regimen for all patients might not be warranted.

The onset of ventilator-associated pneumonia is also a risk factor associated with specific pathogens and prognosis (Ewig 1999; Kalil 2016; Safdar 2005). Early-onset ventilator-associated pneumonia and late-onset ventilator-associated pneumonia are distinguished by whether the ventilator-associated pneumonia occurs before or after the first four days of hospitalisation (Langer 1987). Early-onset ventilator-associated pneumonia is associated with a better prognosis than late-onset ventilator-associated pneumonia (Kalil 2016; Safdar 2005).

Pathophysiology

Hospital-acquired pneumonia is most often caused by aspiration of bacteria from the pharynx, oral cavity, or the upper gastrointestinal tract (Polin 2012). The increased risk of ventilator-associated pneumonia after intubation is caused by endotracheal tubes bypassing the initial host barrier defence mechanisms (Polin 2012). In the absence of the endotracheal tube as a direct portal of entry for pathogens, non-ventilatory hospital-acquired pneumonia could be caused by the contiguous spread of a primary infection at a distant site (Polin 2012), or by specific conditions of susceptibility of the patient. For example, hospital-acquired pneumonia is more frequent in patients who are subjected to several emergency procedures, or who have skin and mucous lesions, which cause a disruption of natural membrane defences, with an increased risk of the infection spreading. Hence, there is a higher rate of hospital-acquired pneumonia in paediatric patients hospitalised for an injury including the head and neck, and those with firearm or pulmonary injuries (Cutler 2017). Moreover, the trauma itself generates an impairment of immunological defences of the patients, making them more prone to infections (Pories 1991).

Microbiology

The most common pathogens involved in hospital-acquired pneumonia worldwide are *Enterobacteriaceae, Pseudomonas aeruginosa*, and *Staphylococcus aureus* (Jones 2010; Patel 2000; Srinivasan 2009; van der Zwet 2005; Weiner-Lastinger 2020). Gram-negative bacteria cause 67.5% of hospital-acquired pneumonia in children, whereas gram-positive bacteria and respiratory viruses cause 13% and 12.6% of hospital-acquired pneumonia in children, respectively (Wang 2010). However, when comparing different geographical regions, the pathogens, their antibiotic susceptibility, the burden of disease, and diagnostic methods vary (Bigham 2009; Iosifidis 2018; van der Zwet 2005). In particular, some studies show that viruses such as rhinovirus, influenza, and parainfluenza could be as common as bacterial pathogens in causing hospital-acquired pneumonia in non-ventilated children and adults (Shorr 2017; Zinna 2016). Several observational studies show that infections caused by multidrug-resistant (MDR) pathogens increase the risk of death, length of hospital stay, and healthcare costs (Su 2020).

Furthermore, rhinovirus and enterovirus are the most commonly recognised pathogens causing hospital-acquired viral respiratory

infection in both adults and paediatric patients (Chow 2017; Zinna 2016).

Diagnosis

The diagnosis of hospital-acquired pneumonia and ventilator-associated pneumonia is based upon a combination of imaging test evidence of a lung disease plus clinical evidence that the infiltrate is of an infectious origin (Kalil 2016).

- Radiological test (e.g. X-ray image) could show a new and persistent or progressive and persistent lung infiltrate, consolidation, cavitation, or pneumatocele (in infants younger than one year old) (Gunalan 2021; Magill 2013).
- Sign and symptoms may vary depending on the age of the patient, as follows.
  - **"For children > 1 year old or ≤ 12 years old**: fever, leukocytosis, new onset of purulent sputum or change in character of sputum, increased respiratory secretions or increased suctioning requirements, new onset or worsening cough, dyspnoea, apnoea, or tachypnoea, rales or bronchial breath sounds, worsening gas exchange" (Gunalan 2021; Magill 2013).
  - **"For children < 1 year old** worsening of gas exchange with increased oxygen requirements is the most common presentation, in association with temperature instability, leukopenia (≤ 4000 WBC/mm^3) or leukocytosis (≥ 15,000 WBC/mm^3), new onset of purulent sputum or change in character of sputum, increased respiratory secretions or increased suctioning requirements, apnoea, tachypnoea, nasal flaring, wheezing, cough, bradycardia (< 100 beats/min) or tachycardia (> 170 beats/min)" (Gunalan 2021; Magill 2013).

The clinical symptoms of hospital-acquired pneumonia are non-specific, and no combination of signs and symptoms has been found to be highly sensitive or specific for the diagnosis (Fabregas 1999; Ferrer 2019). Nevertheless, no gold standard exists for the diagnosis of hospital-acquired pneumonia (Chang 2016; Iosifidis 2018).

Description of the intervention

The treatment of hospital-acquired pneumonia can be either empirical (initiation of an antibiotic regimen before the aetiological pathogen is known) or based on the results of microbiologic studies. The decision to treat empirically is based primarily on the clinical presentation of the patient (Kalil 2016; Torres 2017). Early initiation and appropriate antimicrobial therapy of hospital-acquired pneumonia has been shown to significantly reduce morbidity and mortality in adults (Kelly 2019). Current guidelines for adults recommend that the choice of antibiotics should be based on local antibiograms, local distribution of pathogens, and individual risk factors for serious infection, MDR pathogens, or if *P aeruginosa* is suspected (Kalil 2016; Kelly 2019; Torres 2017).

Patients assessed as being at low risk of antibiotic resistance and early-onset hospital-acquired pneumonia or ventilator-associated pneumonia are recommended for initial empiric therapy with a narrow-spectrum antibiotic, whereas high-risk patients will require broader therapy with a combination of different classes of antimicrobials (Kelly 2019; NICE 2019; Torres 2017).

In the case of low risk of methicillin-resistant *S aureus* (MRSA), the American Thoracic Society guidelines recommend piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem for *S aureus*, *P aeruginosa*, and other gram-negative bacilli (the last only for patients suspected of having ventilator-associated pneumonia) (Kalil 2016).

If there is a risk of MRSA, the American Thoracic Society guidelines recommend vancomycin or linezolid (Kalil 2016). Whether to initiate monotherapy or combination therapy depends on the risk of gram-negative bacteria or risk of antimicrobial resistance, or both (Kalil 2016; Weiss 2020).

Antibiotics such as aminoglycoside and colistin are not recommended, unless alternative agents with adequate gram-negative activity are unavailable (Kalil 2016).

The role of viruses in causing hospital-acquired pneumonia in neonates and children might also be taken into account. The confirmation of a viral organism when routine cultures are negative might facilitate antibiotic discontinuation (Shorr 2017).

Guidelines for the treatment of hospital-acquired pneumonia focus primarily on adults (Kalil 2016; Kelly 2019; NICE 2019; Torres 2017); however, it should be noted that children differ from adults with hospital-acquired pneumonia due to differences in pathogenesis, pharmacokinetics, and types of pathogens (Fernandez 2011; Jain 2015; Stephenson 2005). Consequently, evidence from adult studies cannot be directly transmitted to treatment regimens in children.

How the intervention might work

Hospital-acquired pneumonia could be both a viral or bacterial infection. Considering that viral pneumonia does not require antibiotic therapy unless a mixed infection or secondary bacterial infection is suspected, one of the main objectives of empirical treatment of hospital-acquired pneumonia is to kill the bacteria. Antibiotics are therefore an essential part of the treatment of hospital-acquired pneumonia.

Antibiotics may be classified by their: "1) mechanism of action (bactericidal or bacteriostatic); 2) bacterial spectrum (broad or narrow); and 3) chemical structure (e.g. penicillins, aminoglycosides, macrolides, glycopeptides, or quinolones)" (Bérdy 2005; Korang 2021b; Korang 2021c).

The empirical treatment for suspected hospital-acquired pneumonia should provide coverage for the most likely bacteria. This may result in antibiotic combination therapy if there is a suspicion of either MDR pathogens or severe infection (Kalil 2016; Weiss 2020). The rationale of combination therapy is to widen the spectrum of the empirical antibiotic regimen to increase the likelihood of covering the causative bacteria. Theoretically, combination therapy might also suppress the occurrence of resistant subpopulations (Allan 1985; Milatovic 1987). A recent guideline has been created to determine whether to continue or stop the empirical antibiotic after 48 to 72 hours of treatment (Shein 2019)

An optimal empirical antibiotic treatment would ideally reduce disease progression of the pneumonia and avoid the development of sepsis and septic shock (Chang 2016; Weiss 2020). This would in turn reduce the risk of death and complications (Chang 2016). By

clearing the pathogen, an optimal antibiotic regimen would also speed up the recovery and thereby reduce the discomfort and work of breathing that a child may experience during such an infection.

Why it is important to do this review

Hospital-acquired pneumonia is one of the most common nosocomial infections amongst neonates and children (Cernada 2013; Polin 2012). Current guidelines are directed solely towards adults (Kelly 2019; Martin-Loeches 2018). Most of our understanding of hospital-acquired pneumonia in children is derived from adult studies; however, there exist many differences between neonates/children and adults with respect to hospital-acquired pneumonia (such as the pattern of causative agents isolated, risk factors, and diagnostic methods) (Iosifidis 2018; Vijay 2018). The certainty of evidence from adult studies will also generally tend to be downgraded due to the indirectness of the evidence (Guyatt 2011a; Weiss 2020). No previous systematic review with meta-analysis has assessed the benefits and harms of different antibiotic regimens for children with hospital-acquired pneumonia. There is a need for a systematic review with meta-analysis to provide the necessary evidence for the effects of antibiotics in children with hospital-acquired pneumonia.

OBJECTIVES

To assess the beneficial and harmful effects of different antibiotic regimens for hospital-acquired pneumonia in neonates and children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials reported as full text, abstract only, and unpublished data. We excluded trials with a cross-over design and cluster-randomised trials.

Types of participants

We included neonates (< 28 days old) and children (< 18 years of age) suspected of, or diagnosed with, hospital-acquired pneumonia (as defined by the trialists).

Types of interventions

We included trials comparing one antibiotic regimen with any other antibiotic regimen or placebo. We included the following antibiotic groups.

1. Beta-lactam antibiotics
   a. Narrow-spectrum penicillins (penicillin G, oxacillin, dicloxacillin, cloxacillin, nafcillin, and methicillin).
   b. Broad-spectrum penicillins (e.g. amoxicillin, ampicillin, piperacillin, ticarcillin, mezlocillin, and carbenicillin).
   c. Penicillins combined with beta-lactamase inhibitors (e.g. piperacillin/tazobactam and amoxicillin/clavulanic acid).
   d. Cephalosporins (e.g. cefuroxime, cefotaxime, ceftazidime, cefazolin, cefalexin, cefotetan, cefoxitin, ceftriaxone, cefepime, cefazolin, ceftobiprole, and cefoperazone).
   e. Carbapenems (e.g. meropenem, imipenem, doripenem, and ertapenem).
   f. Monobactams (aztreonam).
2. Aminoglycosides (e.g. amikacin, tobramycin, and gentamicin).
3. Quinolones (e.g. ciprofloxacin, ofloxacin, temafloxacin, garenoxacin, gatifloxacin, grepafloxacin, sparfloxacin, levofloxacin, and moxifloxacin).
4. Macrolides (e.g. azithromycin, clarithromycin, and erythromycin).
5. Glycopeptides (e.g. vancomycin and teicoplanin).
6. Lincosamides (e.g. clindamycin).
7. Antibacterial oxazolidinone agents (e.g. linezolid).
8. Nitroimidazoles (e.g. metronidazole) (Korang 2019).

We also planned to assess any antibiotic regimen (such as either piperacillin-tazobactam, cefepime, levofloxacin, or meropenem/imipenem) that covers patients at low risk of having an MDR pathogen compared to an antibiotic regimen (such as a combination of either piperacillin-tazobactam, cefepime/ceftazidime, levofloxacin/ciprofloxacin, meropenem/imipenem, or amikacin/gentamicin/tobramycin plus either vancomycin or linezolid) that covers patients at high risk of having an MDR pathogen.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Proportion of participants with one or more serious adverse events. We used the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP) definition of a serious adverse event, which is any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolonging of existing hospitalisation, and resulted in persistent or significant disability or jeopardised the participant (ICH-GCP 2016). If the trialists did not use the ICH-GCP definition, we included the data if the trialists used the term 'serious adverse event'. If the trialists did not use the ICH-GCP definition or this term, then we included the data if the event clearly fulfilled the ICH-GCP definition for a serious adverse event. We planned to assess each type of serious adverse event separately (Korang 2021b; Korang 2021c).

Secondary outcomes

1. Health-related quality of life (any continuous scale used by the trialists).
2. Pneumonia-related mortality (as defined by trialists).

3. Proportion of participants with one or more non-serious adverse event (any adverse event which was not classified as "serious" or which did not clearly fulfilled the ICH-GCP definition for a serious adverse event). We planned to assess each reported adverse event separately.
4. Proportion of participants with treatment failure. We defined treatment failure as clinical deterioration or recurrence of clinical signs leading to any modification of the assigned empirical antibiotic treatment (we accepted similar definitions as defined by the trialists).

We used the trial results reported closest to one month as our primary time point of interest for all outcomes.

Search methods for identification of studies

Electronic searches

We searched the following databases from inception to present.

1. The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (1 February 2021, Issue 2).
2. MEDLINE Ovid (from 1946 to 1 February 2021).
3. Embase Ovid (from 1974 to 1 February 2021).

We also searched the following databases.

1. CINAHL via EBSCOhost (Cumulative Index to Nursing and Allied Health Literature) (from 1961 to 1 February 2021).
2. PsycINFO via EBSCOhost (from 1967 to 1 February 2021).
3. Science Citation Index Expanded (Web of Science) (from 1900 to 1 February 2021) and Conference Proceedings Citation Index – Science (Web of Science) (from 1990 to 1 February 2021).
4. LILACS (Latin American and Caribbean Health Science Information database) (from 1982 to 1 February 2021).

We used the search strategy described in Appendix 1 to search MEDLINE. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for randomised trials: sensitivity and precision-maximising version (2008 revision) (Lefebvre 2011).

We also conducted a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (1 February 2021)and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) (1 February 2021).

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We contacted experts in the field to identify additional unpublished materials.

In an effort to identify unpublished trials, we searched clinical trial registers of Europe and the USA and the websites of pharmaceutical companies, the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA).

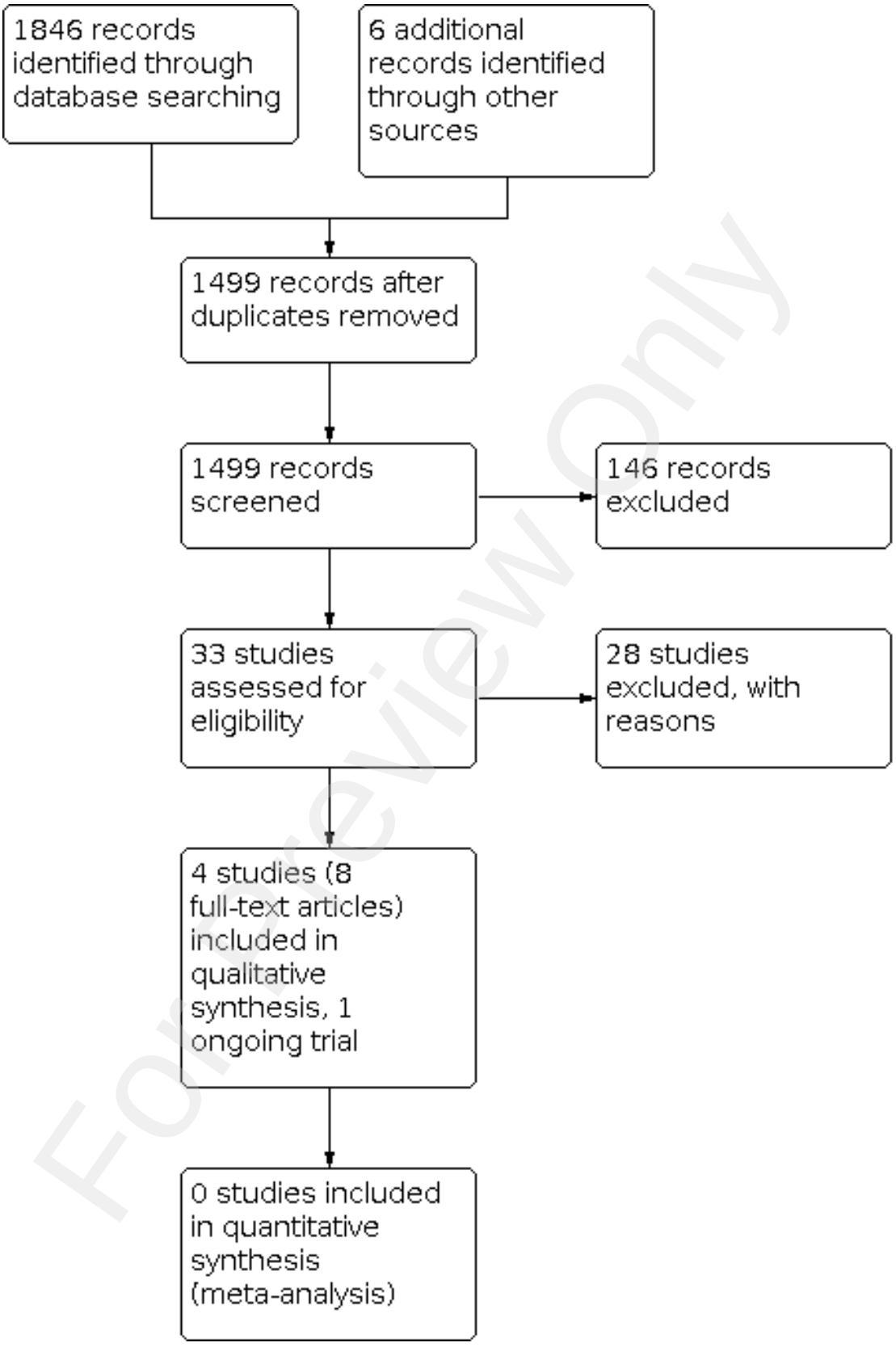
We searched for errata or retractions from the included studies published in full text on PubMed (23 March 2021) (www.ncbi.nlm.nih.gov/pubmed).

Data collection and analysis

Selection of studies

Three review authors (SKK, CN, SPM) independently screened the titles and abstracts of records identified by the search for potential inclusion in the review. We retrieved selected full-text study reports/publications, and three review authors (SKK, CN, SPM) independently screened the full-texts and identified trials for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. Any disagreements were resolved through discussion or by consulting a fourth review author (JCJ) if required. We excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and Characteristics of excluded studies table (Moher 2009). We did not impose any language or publication restrictions.

Figure 1. Study flow diagram.



Data extraction and management

We used a data collection form to record study characteristics and outcome data that we piloted on at least one study in the review. One review author (SKK or CN or SPM) extracted trial characteristics from the included trials. We extracted the following trial characteristics.

1. Methods: trial design, total duration of trial, number of trial centres and location, trial setting, withdrawals, and date of trial.
2. Participants: number of participants, mean age, age range, sex, microbial agent isolated, severity of condition, diagnostic criteria, baseline lung function, smoking history (of participants or parents, or both), inclusion criteria, and exclusion criteria.
3. Interventions: intervention (including dosage, route of administration, and length of empirical treatment), comparison, co-interventions, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Three review authors (SKK, CN, SPM) independently extracted outcome data from the included trials. We noted in the Characteristics of included studies table if outcome data were not reported in a useable way. Any disagreements were resolved by consensus or by consulting a fourth review author (JCJ). One review author (SKK) entered the data into Review Manager 5 software (Review Manager 2020). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports.

Assessment of risk of bias in included studies

Three review authors (SKK, CN, SPM) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). Any disagreements were resolved by discussion or by involving another review author (JCJ). We assessed risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as low, high, or unclear and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered the domains blinding of outcome assessment, incomplete outcome data, and selective outcome reporting separately for different key outcomes, where necessary. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the risk of bias table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Overall risk of bias

We assessed overall risk of bias as follows.

1. Low risk of bias: we classified the outcome of a trial as overall 'low risk of bias' only if all domains were classified as at low risk of bias.
2. Unclear risk of bias: we classified the outcome of a trial as overall 'unclear' risk of bias if one or more domains were classified as unclear, and no domain was at high risk of bias.
3. High risk of bias: we classified the outcome of a trial as overall 'high risk of bias' if at least one domain was classified as high risk of bias.

See Appendix 2 for further details.

We planned to assess confidence in network meta-analysis results using CINeMA (Confidence in Network Meta-Analysis) (Nikolakopoulou 2020; Papakonstantinou 2020).

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Korang 2021a), and reported any deviations from it in the Differences between protocol and review section.

Measures of treatment effect

We entered the outcome data for each trial into the data tables in Review Manager 5 to calculate the treatment effects (Review Manager 2020).

Dichotomous outcomes

We calculated risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes.

Continuous outcomes

We planned to calculate the mean differences (MDs) and the standardised mean difference (SMD) with 95% CI for continuous outcomes.

We planned to perform meta-analysis only if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

Unit of analysis issues

The unit of analysis was the participating children in individually randomised trials.

Dealing with missing data

We contacted trial investigators to obtain missing outcome data where possible. If the missing data were unobtainable, we explored the impact of the missing data in a sensitivity analysis (Sensitivity analysis).

If numerical outcome data such as standard deviations or correlation coefficients were missing, and they could not be obtained from the trial authors, we would calculate them from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

We did not impute missing values for any outcomes in our primary analysis. We planned to impute data in two sensitivity analyses.

Assessment of heterogeneity

We planned to visually inspect forest plots for signs of heterogeneity, and to explore possible heterogeneity in our prespecified subgroup analyses. We inspected trial characteristics across trials to identify clinical heterogeneity. We planned to assess the presence of statistical heterogeneity by the Chi^2 test (threshold $P < 0.10$) and to measure the quantities of heterogeneity using the I^2 statistic (Higgins 2002; Higgins 2003). If we detected moderate or high heterogeneity, we explored possible causes (e.g. differences in study design, participants, interventions, or completeness of outcome assessments) (Korang 2019).

We defined the level of heterogeneity as:

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity; and
4. 75% to 100%: may represent considerable heterogeneity.

We would evaluate whether a meta-analysis should be avoided if the level of heterogeneity indicated that pooling of data was not justified (Higgins 2021).

Assessment of reporting biases

We planned to use a funnel plot to assess publication bias only if we included 10 or more trials. We planned to visually inspect funnel plots to assess risk of bias. We planned to test asymmetry with the Harbord test (Harbord 2006).

Data synthesis

We planned to pool data from trials that we judged to be clinically homogeneous. We planned to perform meta-analysis only if more than one trial provided relevant data in any single comparison.

Meta-analysis

We planned to undertake meta-analyses according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*, Higgins 2021, and our protocol (Korang 2021a). We used Review Manager 5 software (Review Manager 2020).

We planned to assess our intervention effects with both fixed-effect and random-effects meta-analyses (DeMets 1987; DerSimonian 1986). We planned to use the more conservative point estimate of the two. We considered the point estimate closest to zero effect as the more conservative point (Jakobsen 2014). As we have chosen two primary outcomes, we considered a P value of 0.033 or less as the threshold for evidence of a difference (Jakobsen 2014). We planned to use the eight-step procedure provided by Jakobsen and colleagues to assess if the threshold for any evidence of a difference was crossed (Jakobsen 2014). Where data were available from only one trial, we planned to use Fisher's exact test for dichotomous data (Fisher 1922).

We planned that if the ranking of the identified interventions was unclear based on aggregating the meta-analysis results, we would perform a network meta-analysis (see Appendix 3).

In addition to the primary meta-analysis, we planned to use Trial Sequential Analysis (TSA) as a secondary analysis (see Appendix 4).

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses.

1. Trials at high risk of bias compared to trials at low risk of bias.
2. Age: newborn (less than 1 month), infants (1 month to 1 year), children of preschool age (1 to 5 years), children of school age (5 to 12 years), adolescents (older than 12 years).
3. Trials from high-income countries compared to trials from low- and middle-income countries, as defined by the World Bank (World Bank 2020).
4. Suspected hospital-acquired pneumonia without radiological verification or culture of respiratory specimens compared to hospital-acquired pneumonia with radiological verification or culture of respiratory specimens at randomisation.
5. Empirical compared to targeted treatment based on bacterial cultures, if possible.
6. Hospital-acquired pneumonia compared to ventilator-associated pneumonia.
7. Early-onset compared to late-onset, defined as onset of ventilator-associated pneumonia before or after four days.
8. Length of antibiotic treatment: three days or shorter, four to seven days, or longer than seven days.
9. Participants without underlying diseases compared to participants with underlying diseases such as genetic syndromes, lung disease, or immune deficiency.

We planned to use the Chi^2 test to test for subgroup interactions in Review Manager 5 (Review Manager 2020).

Sensitivity analysis

To assess the potential impact of missing data, we planned to perform two sensitivity analyses on the primary outcomes, as follows.

1. 'Best-worst-case' scenario: we assumed that all participants lost to follow-up in the experimental group survived and had no serious adverse event. We assumed that all of those with missing outcomes in the control group did not survive and had a serious adverse event.
2. 'Worst-best-case' scenario: we assumed that all participants lost to follow-up in the experimental group did not survive and had a serious adverse event. We assumed that all participants lost to follow-up in the control group survived and had no serious adverse event (Jakobsen 2014).

Summary of findings and assessment of the certainty of the evidence

We created two summary of findings tables (Summary of findings 1; Summary of findings 2) reporting our primary and secondary outcomes. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used the methods and recommendations in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro

GDT). We justified all decisions to down- or upgrade the quality of the evidence using footnotes and made comments to aid the reader's understanding of the review where necessary.

Had we performed a network meta-analysis, we would also have used CINeMA to assess the certainty of a body of evidence (Guyatt 2008; Guyatt 2011b; Schünemann 2003).

RESULTS

Description of studies

For study details, see Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies.

We based our assessment of the included trials on the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions*, Higgins 2021, and our protocol (Korang 2021a).

Results of the search

We searched seven databases (see Electronic searches) and retrieved 1846 records. Our searches of the trial registers identified four further studies. Our searches of other resources identified no additional studies appearing to meet the inclusion criteria. Screening reference lists of the included publications revealed two potentially relevant studies. We therefore retrieved a total of 1852 records, which amounted to 1499 records after de-duplication. We excluded 1466 records based on title and abstract, and obtained the full texts of the remaining 33 records. We excluded 28 studies (see Characteristics of excluded studies). We identified one ongoing trial that might include children with hospital-acquired pneumonia (Shahrin 2020).

We included four trials reported in eight articles. Our screening process is illustrated in a PRISMA flow diagram (see Figure 1).

Included studies

Four trials met our inclusion criteria (Bosheva 2021; Jantausch 2003; Schuler 1995; Shahid 2008). Four additional papers were included as secondary publications to Jantausch 2003 (Deville 2003; Kaplan 2003; Meissner 2003; Saiman 2003). For study details, see Characteristics of included studies. Three trials were multicentre trials and included 59 sites in the USA and Latin America (Jantausch 2003), 12 sites in Europe (Bosheva 2021), 22 sites in Europe and South Africa (Schuler 1995), and one site in Malaysia (Shahid 2008). Three trials included children with different infections, of which a minor portion was hospital-acquired pneumonia (Bosheva 2021; Jantausch 2003; Schuler 1995). Two trials primarily included community-acquired pneumonia, Bosheva 2021, and hospitalised children with bacterial infections (Schuler 1995), hence the children with hospital-acquired pneumonia constituted only subgroups of the total sample sizes. One trial included participants with late-onset ventilator-associated pneumonia only (Shahid 2008).

Participants

The four trials randomised a total of 84 participants. The studies included participants of the following age groups:

1. under one year (Shahid 2008);
2. birth to 12 years (Jantausch 2003);
3. 3 months to 12 years (Schuler 1995);
4. 3 months to 18 years (Bosheva 2021).

Interventions

The four trials compared four different antibiotic regimens, as follows:

1. cefepime versus ceftazidime (Shahid 2008);
2. linezolid versus vancomycin (Jantausch 2003);
3. ceftobiprole versus standard of care (cephalosporin) (Bosheva 2021);
4. meropenem versus cefotaxime (Schuler 1995).

One trial administered metronidazole in cases of mixed aerobic/anaerobic infection, but only for the control group (Schuler 1995). One trial described the use of vancomycin in the control group when MRSA was confirmed or suspected, and similarly amikacin, gentamicin, or tobramycin was administered in the control groups when infection by *P aeruginosa* was confirmed or suspected (Bosheva 2021).

Co-interventions

One trial provided concomitant treatment in both groups with amikacin, vancomycin, gentamicin, or tobramycin for confirmed or suspected infection caused by *P aeruginosa*, which could be added at the discretion of the blinded investigator (Bosheva 2021). The remaining trials did not report co-interventions (Jantausch 2003; Schuler 1995; Shahid 2008).

Outcomes

Only one trial reported sparse data on all-cause mortality and serious adverse events (Shahid 2008). This trial did not report serious adverse events according to the ICH-GCP, but reported the number of deaths in each group. Three trials reported treatment failure (Jantausch 2003; Schuler 1995; Shahid 2008). None of the included trials assessed health-related quality of life, pneumonia-related mortality, or non-serious adverse events.

Antibiotic resistance in included trials

One trial reported that resistance to study medications was not found in pathogens isolated at baseline in either group (Jantausch 2003). The remaining trials did not report on antibiotic resistance amongst the culture-positive participants having hospital-acquired pneumonia (Bosheva 2021; Schuler 1995; Shahid 2008)

Excluded studies

We assessed 28 trials as potentially relevant upon review of the abstract, but that were later excluded after full-text review. The reasons for exclusion were as follows.

1. Wrong participant population, such as adults or participants that did not have hospital-acquired pneumonia (25 trials) (Agweyu 2015; Amonova 2011; Awad 2014; Barradas 1989; Bassetti 1991; Begue 1998; Bhavnani 2012; Chaudhary 2008; Chuchalin 1997; Cometta 1994; Dickstein 2016; Giamarellos-Bourboulis 2014; Grudinina 2002; Iakovlev 2000; Iakovlev 2006; Joshi 1999; Kollef 2012; Lacy 2015; Mohamed 2018; Muscedere 2012; Nassar 2018; Norrby 1993; Rodloff 1996; Straneo 1990; Tucker 2017).

2. Not randomised (1 trial) (Berman 2004).
3. The same antibiotic assessed in the intervention and control groups (2 trials) (Fatehi 2019; Patel 2015).

For details, see Characteristics of excluded studies.

Risk of bias in included studies

We assessed all of the included trials as at overall high risk of bias (see Figure 2; Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

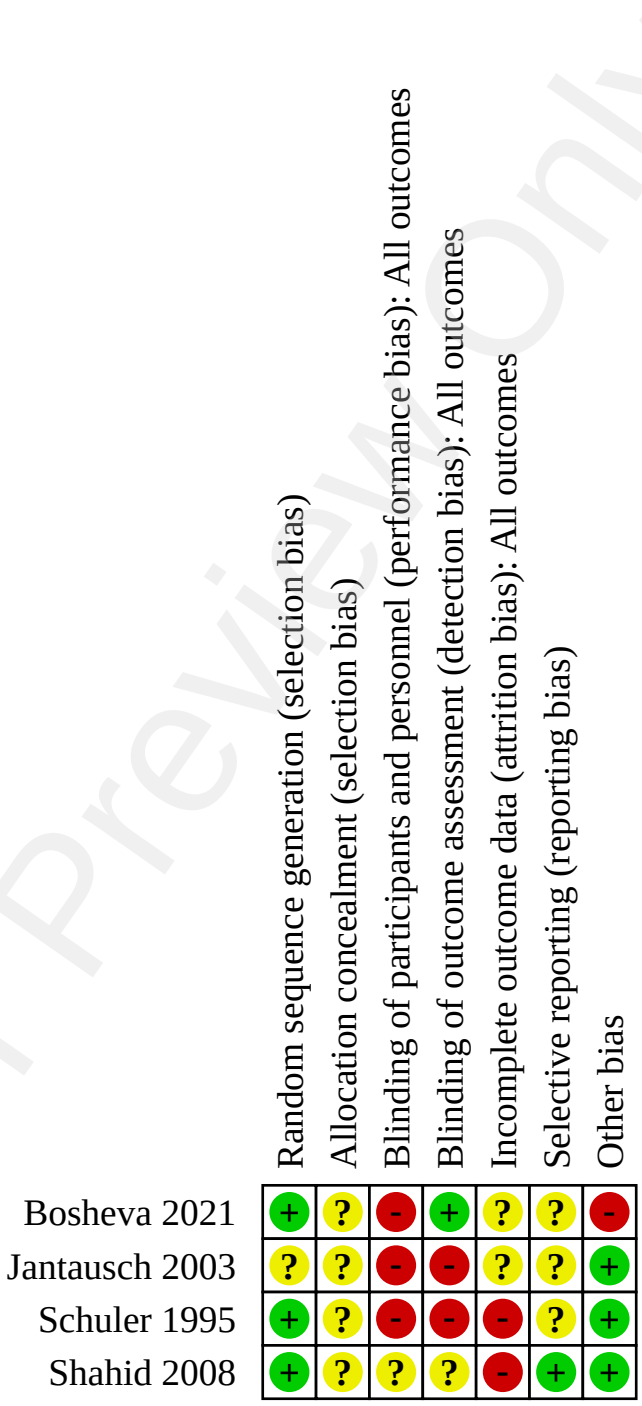
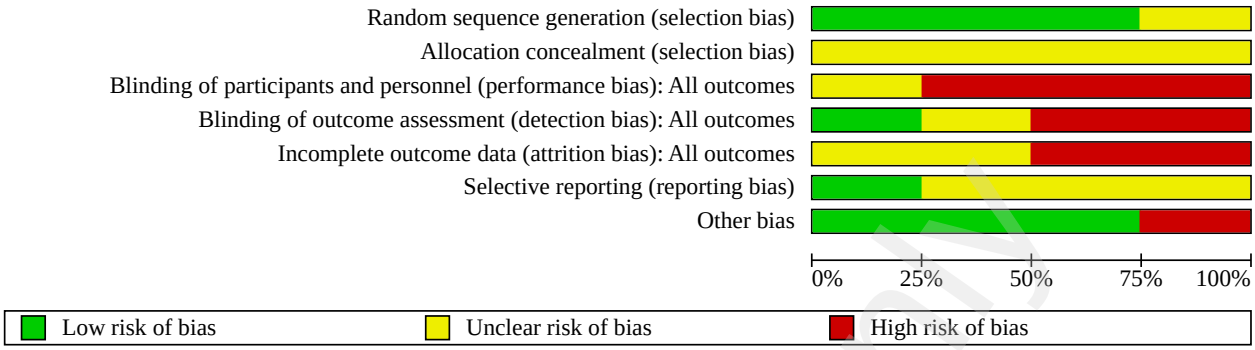


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Three trials used a computer-generated assignment sequence resulting in 'low risk of bias' (Bosheva 2021; Schuler 1995; Shahid 2008). One trial did not describe how allocation sequence generation was performed and was therefore judged as 'unclear risk of bias' (Jantausch 2003).

None of the trials described allocation concealment, therefore we judged all four trials as 'unclear risk of bias' (Bosheva 2021; Jantausch 2003; Schuler 1995; Shahid 2008).

Blinding

Two trials were unblinded and were assessed as 'high risk of bias' in both domains (Jantausch 2003; Schuler 1995). One trial did not describe blinding and was assessed as 'unclear risk of bias' in both domains (Shahid 2008). The remaining trial blinded the investigators but not the treatment providers/participants, resulting in a judgement of 'low risk of bias' for blinding of outcome assessment and 'high risk of bias' for blinding of participants and personnel (Bosheva 2021).

Incomplete outcome data

Two trials had a high number of dropouts and were assessed as 'high risk of bias' (Schuler 1995; Shahid 2008). Two trials did not describe dropouts and were assessed as 'unclear risk of bias' (Bosheva 2021; Jantausch 2003).

Selective reporting

One trial reported both mortality and serious adverse events, resulting in a judgement of 'low risk of bias' (Shahid 2008). Three trials did not have a protocol, nor did they report mortality and serious adverse events, resulting in a judgement of 'unclear risk of bias' (Bosheva 2021; Jantausch 2003; Schuler 1995).

Other potential sources of bias

We found that three trials were funded by the pharmaceutical companies that produce the studied antibiotics (Jantausch 2003; Schuler 1995; Bosheva 2021). Among those, we found one trial to be at high risk of other bias due to for-profit bias (Bosheva 2021) as the pharmaceutical company had a major involvement in designing the study and in the acquisition of data, statistical analysis, and article preparation. The other two (Jantausch 2003; Schuler 1995) were funded and may be influenced by vested interests, but no involvement of the funders was described. We found no other potential sources of bias in the remaining trials (Jantausch 2003; Schuler 1995; Shahid 2008).

Effects of interventions

See: **Summary of findings 1** Cefepime compared with ceftazidime for hospital-acquired pneumonia in neonates and children; **Summary of findings 2** Linezolid compared with vancomycin for hospital-acquired pneumonia in neonates and children

The four trials assessed different comparisons of antibiotic regimens, therefore we did not perform any meta-analyses, trials sequential analyses, or subgroup analyses on any our outcomes. Of the two trials that had under 10 participants, one did not report our prespecified outcomes (Bosheva 2021), and the other trial had an unclear comparison (Schuler 1995); we therefore decided not to include a summary of findings table for these two comparisons.

Three trials compared two beta-lactam antibiotics (Bosheva 2021; Schuler 1995; Shahid 2008), and one trial compared a glycopeptide with an antibacterial agent (oxazolidinone) (Jantausch 2003).

Cefepime compared with ceftazidime for late-onset ventilator-associated pneumonia

Primary outcomes

All-cause mortality

One trial showed that the effect of cefepime on mortality compared to ceftazidime is very uncertain (risk ratio (RR) 0.14, 95% confidence interval (CI) 0.01 to 2.55; 1 trial, 30 participants; very low-certainty evidence; Analysis 1.1) (Shahid 2008). We calculated the optimal information size based on a relative risk reduction (RRR) of 20%, an alpha of 3.3%, a beta of 20%, and the observed incidence in the control group (15.4%) (Guyatt 2011c; Higgins 2011). Calculation of the optimal information size showed that we did not have sufficient information to confirm or reject that cefepime compared with ceftazidime reduced the risk of death by 20% or more.

This outcome was assessed as high risk of bias (Figure 2), and the certainty of the evidence was very low (Summary of findings 1).

Proportion of participants with one or more serious adverse events

One trial showed that the effect of cefepime on serious adverse events compared to ceftazidime is very uncertain (RR 0.14, 95% CI 0.01 to 2.55; 1 trial, 30 participants; very low-certainty evidence; Analysis 1.2) (Shahid 2008). We calculated the optimal information size based on an RRR of 20%, an alpha of 3.3%, a beta of 20%, and the observed incidence in the control group (15.4%) (Guyatt 2011c; Higgins 2011). Calculation of the optimal information size showed that we did not have sufficient information to confirm or reject that cefepime versus ceftazidime reduced the risk of having a serious adverse event by 20% or more.

This outcome was assessed as high risk of bias (Figure 2), and the certainty of the evidence was very low (Summary of findings 1).

Secondary outcomes

Shahid 2008 did not report health-related quality of life, pneumonia-related mortality, or non-serious adverse events for participants with hospital-acquired pneumonia.

Proportion of participants with treatment failure

One trial showed that the effect of cefepime on serious adverse events compared to ceftazidime is very uncertain (RR 0.50, 95% CI 0.15 to 1.64; 1 trial, 30 participants; very low-certainty evidence; Analysis 1.3) (Shahid 2008). We calculated the optimal information size based on an RRR of 20%, an alpha of 3.3%, a beta of 20%, and the observed incidence in the control group (40%) (Guyatt 2011c; Higgins 2011). Calculation of the optimal information size showed that we did not sufficient information to confirm or reject that cefepime versus ceftazidime reduced the risk of having treatment failure by 20% or more.

This outcome was assessed as high risk of bias (Figure 2), and the certainty of the evidence was very low (Summary of findings 1).

As we only included one trial in this comparison, we did not perform a subgroup analysis, sensitivity analysis, or funnel plot.

Linezolid compared with vancomycin for hospital-acquired pneumonia

Primary outcomes

Jantausch 2003 did not report all-cause mortality or the proportion of participants with one or more serious adverse events for hospital-acquired pneumonia.

Secondary outcomes

Jantausch 2003 did not report health-related quality of life, pneumonia-related mortality, or non-serious adverse events for participants with hospital-acquired pneumonia.

Proportion of participants with treatment failure

One trial showed that the effect of linezolid on treatment failure compared to vancomycin is very uncertain (RR 2.05, 95% CI 0.49 to 8.63; 1 trial, 32 participants; very low-certainty evidence; Analysis 2.1) (Jantausch 2003). We defined treatment failure as participants not being clinically cured. We calculated the optimal information size based on an RRR of 20%, an alpha of 3.3%, a beta of 20%, and the observed incidence in the control group (15.4%) (Guyatt 2011c; Higgins 2011). Calculation of the optimal information size showed that we did not have sufficient information to confirm or reject that linezolid versus vancomycin reduced the risk of having treatment failure by 20% or more.

This outcome was assessed as high risk of bias (Figure 2), and the certainty of the evidence was very low (Summary of findings 2).

As we only included one trial in this comparison, we did not perform a subgroup analysis, sensitivity analysis, or funnel plot.

Ceftobiprole compared with standard of care (cephalosporin) for hospital-acquired pneumonia

Primary outcomes

Bosheva 2021 did not report all-cause mortality or the proportion of participants with one or more serious adverse events for hospital-acquired pneumonia.

Secondary outcomes

Bosheva 2021 did not report health-related quality of life, pneumonia-related mortality, the proportion of participants with one or more non-serious adverse events, or the proportion of participants with treatment failure for hospital-acquired pneumonia.

As we only included one trial in this comparison, we did not perform a subgroup analysis, sensitivity analysis, or funnel plot.

Meropenem compared with cefotaxime for hospital-acquired pneumonia

Primary outcomes

Schuler 1995 did not report all-cause mortality or the proportion of participants with one or more serious adverse events for hospital-acquired pneumonia.

Secondary outcomes

Schuler 1995 did not report health-related quality of life, pneumonia-related mortality, or non-serious adverse events for participants with hospital-acquired pneumonia.

Proportion of participants with treatment failure

One trial showed that the effect of meropenem on treatment failure compared to cefotaxime is very uncertain (RR 1.80, 95% CI 0.10 to 31.52; 1 trial, 6 participants; very low-certainty evidence; Analysis 3.1) (Schuler 1995). We defined treatment failure as participants not being clinically cured. It was not possible to calculate the optimal information size, as we did not observe any incidence in the control group (Guyatt 2011c; Higgins 2011). However, as the trial included only six participants, it is fair to assume that there was insufficient information to confirm or reject that meropenem versus cefotaxime reduced the risk of having treatment failure by 20% or more.

This outcome was assessed as high risk of bias (Figure 2), and the certainty of the evidence was very low.

As we only included one trial in this comparison, we did not perform any subgroup analysis, sensitivity analysis, or funnel plot.

DISCUSSION

Summary of main results

We included four trials randomising a total of 84 participants. We assessed all trials as having high risk of bias.

We did not conduct any meta-analyses as the included trials all compared different antibiotic regimens. None of the comparisons reached the optimal information size (Summary of findings 1; Summary of findings 2).

Where outcomes were reported, the certainty of the evidence was very low for each of the comparisons. We were unable to draw any meaningful conclusions from the numerical results. None of the included trials assessed health-related quality of life, pneumonia-related mortality, or non-serious adverse events.

Overall completeness and applicability of evidence

The relative beneficial and harmful effects of different antibiotic regimens remain unclear due to a lack of well-powered trials and high risk of systematic errors. The current evidence is insufficient to support any antibiotic regimen being superior to another. Large randomised clinical trials assessing different antibiotic regimens for hospital-acquired pneumonia in children and neonates are warranted.

Quality of the evidence

Heterogeneity

We did not perform a meta-analysis, therefore we did not assess heterogeneity.

Risk of systematic error ('bias')

All of the included trials were at high risk of bias.

It was not possible to assess publication bias, as only four trials were included in the review.

Risk of random error ('play of chance')

None of the trial results reached the optimal information size. It was not possible to perform trial sequential analysis, as we performed no meta-analysis.

GRADE

We assessed the certainty of the evidence for each of the outcomes using the GRADE approach (Summary of findings 1; Summary of findings 2). The evidence for each reported outcome was of very low certainty. The rationale for the GRADE assessment is given in footnotes (Summary of findings 1; Summary of findings 2).

Potential biases in the review process

The main limitation of this review is the low number of randomised participants, and the very low certainty of the available evidence. A further limitation is that we could not perform a meta-analysis, as none of the trials compared similar antibiotics.

There might also be a difference between the pathogens and their antibiotic susceptibility in different countries. The optimal antibiotic regimen will therefore vary according to country and local risks of antibiotic resistance. The number of included trials was insufficient to confirm or reject this presumption.

The lack of a gold standard for the diagnosis of hospital-acquired pneumonia could result in clinical heterogeneity between studies. Some participants may have had an unrecognised viral aetiology of hospital-acquired pneumonia. Although these cases of viral infection must be assumed to be equally distributed in the intervention groups, they might lead to an underestimation of the differences between different antibiotic regimens.

Agreements and disagreements with other studies or reviews

Although hospital-acquired pneumonia is one of the most common nosocomial infections amongst the paediatric population, we are not aware of any other reviews assessing the effects of different antibiotic regimens in paediatric patients with hospital-acquired pneumonia.

In the latest review conducted by the National Institute for Health and Care Excellence to develop the therapeutic guideline for hospital-acquired pneumonia (NICE 2019), studies with a mixed population of hospital-acquired pneumonia and community-acquired pneumonia were excluded, unless ≥ 75% were a hospital-acquired pneumonia population. Moreover, NICE 2019 excluded studies with a mixed population of ventilator- and non-ventilator-associated pneumonia where data could not be analysed separately. As such, no studies involving children were identified and included, even if they were recognised as a subgroup of interest in the study protocol. Instead, the authors decided to make recommendations for paediatric therapy on the basis of higher-quality evidence on adults.

Overall, whilst including six randomised clinical trials and one post hoc analysis, the NICE 2019 authors did not find any difference in their analysis of the effectiveness of antibiotic regimens in adults (NICE 2019). Likewise, they did not find any statistical difference in adverse effects between antibiotics or classes of antibiotics in people with hospital-acquired pneumonia.

Although there are similarities between children and adults with hospital-acquired pneumonia (e.g. pathogenesis), evidence from adult studies cannot be transmitted to treatment regimens in children with certainty. The spectrum of responsible bacteria may differ, as colonisation in the pharynx and trachea varies, particularly in young children, who are less commonly colonised with *S aureus*, *P aeruginosa*, and MDR pathogens, compared to adults (Jain 2015). Furthermore, antibiotic pharmacokinetics vary between adults and children (Fernandez 2011; Stephenson 2005), and children have less frequent underlying lung diseases and known risk factors such as chronic lung disease and chronic renal failure, which may influence the severity and treatment response (Sopena 2014). Choice of antibiotics, as well as dosing and treatment duration, should thus be evaluated in children with hospital-acquired pneumonia.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the currently available evidence, we were unable to confirm or reject whether one antibiotic regimen is superior to another.

Implications for research

Randomised clinical trials are needed to assess the effects of different antibiotic regimens for hospital-acquired pneumonia. Such trials should:

1. randomise a sufficient number of participants to demonstrate reliable results;
2. assess treatment failure, all-cause mortality, and serious adverse events; and
3. be conducted such that there is a low risk of bias.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bosheva 2021

Study characteristics	
Methods	Design: randomised, multicentre trial Duration: 27 November 2017 to 16 March 2020 Country: 12 sites in Europe (Bulgaria, Georgia, Hungary, and Romania) Setting: hospital (no detail as to which unit or department) Date of publication: 21 January 2021
Participants	Randomised 138 participants with pneumonia (8 children with nosocomial pneumonia) to either cefto-biprole or standard of care (cephalosporin). Mean age (range): not reported

Bosheva 2021 *(Continued)*

	Sex (M/F): NA Type of HAP: HAP Inclusion criteria: individuals 3 months to 18 years of age with a body weight of ≥ 5 kg and a diagnosis of HAP (pneumonia acquired after ≥ 48 hours of hospitalisation). Exclusion criteria: use of systemic antibacterial treatment for > 24 hours in the 48 hours before randomisation for the current episode of pneumonia (except patients with CAP who failed to improve after at least 48 hours of prior antibiotic therapy and required a change in treatment), mechanical ventilation for > 48 hours, viral pneumonia without bacterial superinfection, and known resistance to study antibiotic treatments.
Interventions	Intervention group: ceftobiprole Control group: cephalosporin Co-interventions: vancomycin (10 to 15 mg/kg as an IV infusion every 6 hours) was also administered when MRSA was confirmed or suspected. Concomitant treatment with amikacin, gentamicin, or tobramycin for confirmed or suspected infection caused by *Pseudomonas aeruginosa* could be added at the discretion of the blinded investigator. Length of intervention: 7 to 14 days.
Outcomes	Primary outcomes: the cumulative incidence of adverse events during the first 3 days of study treatment and at the end of treatment, test-of-cure, and last follow-up visits. Secondary outcomes: comparison of early clinical response at day 4 and clinical cure rates at the end of treatment. Clinical and microbiologic relapse rates at the last follow-up visit were also compared (all efficacy populations). Microbiologic eradication rates at the test-of-cure visit, duration of IV antibiotic treatment, time to oral antibiotic switch, and duration of hospitalisation. Follow-up: up to 35 days
Notes	Missing data: mean age and gender distribution for HAP participants exclusively. Email: kamal.hamed@basilea.com ClinicalTrials.gov ID: NCT03439124

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out using a central interactive web-based response system based on a computer-generated randomisation schedule.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	All other study site staff, including the principal investigator, pharmacists, and nursing staff, were unblinded. The participant and their parent/guardian were also unblinded and were reminded at each interaction with the blinded investigator not to disclose the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The blinded investigator was also responsible for determining the duration of IV treatment, the decision to discontinue IV treatment, and the time point to switch to an oral antibiotic. To maintain blinding, the blinded investigator did not observe the participant at times when the study antibiotics were being administered.

Bosheva 2021 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts were unclear.
Selective reporting (reporting bias)	Unclear risk	They did not have a protocol and did not report outcome data on HAP participants separately.
Other bias	High risk	The study was supported by Basilea Pharmaceutica International Ltd., Basel, Switzerland. Basilea Pharmaceutica International Ltd. designed the study and aided in the acquisition of data, statistical analysis, and article preparation. Under the direction of the authors, medical writing support for the article was provided by Stephanie Carter of Arc, a division of Spirit Medical Communications Group Limited, funded by Basilea Pharmaceutica International Ltd.

Jantausch 2003

Study characteristics	
Methods	Design: randomised, open-label, multicentre trial Duration: February to December 2001 Country: the USA and Latin America Setting: hospital (no detail regarding which unit or department) Date of publication: 9 April 2003
Participants	Randomised 40 children with nosocomial pneumonia to either linezolid or vancomycin. Mean age (range): NA Sex (M/F): NA Type of HAP: antibiotic-resistant gram-positive HAP Inclusion criteria: nosocomial pneumonia as defined by local institutions or PRSP (penicillin MIC 2 g/mL). Chest radiograph at baseline consistent with a diagnosis of pneumonia. At least 2 of the following: cough, new/worsened purulent sputum production, rales, pulmonary consolidation, or signs of respiratory distress (e.g. dyspnoea, tachypnoea, cyanosis, intercostal retractions, laboured breathing, grunting, or nasal flaring). Exclusion criteria: previous treatment for > 24 h with a potentially effective antibiotic within 48 h of study enrolment (unless the treatment failed or the pathogen showed resistance to the antibiotic). Furthermore, patients with pulmonary conditions such as cystic fibrosis or general underlying conditions such ischaemic ulcers, necrotising fasciitis, gas gangrene, etc., were excluded.
Interventions	Intervention group: linezolid Control group: vancomycin Co-interventions: not reported Length of intervention: 10 to 21 days
Outcomes	Primary outcomes: clinical status at the test-of-cure follow-up visit (cured, failure, indeterminate or missing). Secondary outcomes: pathogen eradication rates and changes in clinical signs and symptoms of infection.

Jantausch 2003 *(Continued)*

	Follow-up: up to 35 days
Notes	Missing data: mean age and gender distribution for HAP participants exclusively. We (the review authors) defined treatment failure as participants who did not experience clinical cure. Funded by Pharmacia Corp.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as being randomised, but did not specify the sequence generation.
Allocation concealment (selection bias)	Unclear risk	Described as being randomised, but did not specify the allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants in the linezolid group were excluded in the ITT analysis.
Selective reporting (reporting bias)	Unclear risk	They did not have a protocol and did not report all-cause mortality and serious adverse events for participants with HAP.
Other bias	Low risk	No other biases were identified.

Schuler 1995

Study characteristics	
Methods	Design: randomised, multicentre trial Duration: 7.1 days (mean) in each group Country: 22 sites in Europe (Belgium, the Czech Republic, France, and Hungary) and South Africa Setting: hospital (no detail regarding which unit or department) Date of publication: 1995
Participants	Randomised 119 hospitalised children with bacterial infections (6 children with nosocomial pneumonia) to either meropenem or cefotaxime. Mean age (range): not reported Sex (M/F): NA Type of HAP: HAP

Schuler 1995 *(Continued)*

	Inclusion criteria: hospitalised children aged 3 months to 12 years, with clinical signs and symptoms of a bacterial infection requiring a parenteral antibiotic. Exclusion criteria: body weight < 5 to 6 kg in order to exclude neonates; hypersensitivity to any beta-lactam antibiotic; administration of another antibiotic within the 3 days before enrolment (unless the pathogen was resistant or persisted) or another investigational drug within the 30 days before enrolment; clinically manifest hepatic failure or hepatic coma; renal function impairment (creatinine clearance rate ≤51 mL/min); history of seizures, meningitis, or cystic fibrosis; neutrophil count < 1 x 10^9/L; and the presence of severe underlying disease likely to prevent completion of at least 48 hours of study drug therapy.
Interventions	Intervention group: meropenem (10 or 20 mg/kg up to a maximum of 1 g) Control group: cefotaxime 100 to 150 mg/kg/day divided into 2 to 4 equal doses. Metronidazole (7.5 mg/kg every 8 hours) was added to the cefotaxime regimen in cases of suspected mixed aerobic/anaerobic infection. Amikacin (15 mg/kg/day in 2 to 3 equal doses) was added to the cefotaxime regimen for the treatment of UTI in France, according to local guidelines, but only for the control group. Co-interventions: not reported Length of intervention: maximum 28 days Follow-up: up to 6 weeks
Outcomes	Primary outcomes: safety Secondary outcomes: clinical and bacteriological efficacy
Notes	Missing data: mean age and gender distribution for HAP participants exclusively. Funded by Zeneca Pharmaceuticals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated code used.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	High number of dropouts
Selective reporting (reporting bias)	Unclear risk	They did not have a protocol and only reported on clinical cure/treatment failure for HAP participants.
Other bias	Low risk	No other biases were identified.

Shahid 2008

Study characteristics	
Methods	Design: randomised, single-centre clinical trial Duration: from April 2004 to August 2005 Country: Malaysia Setting: hospital (no detail regarding which unit or department) Date of publication: 2 April 2007
Participants	Randomised 30 children with late-onset VAP to either cefepime or ceftazidime Mean age (SE): 1.56 year (0.7) Sex (M/F): 11/19 Type of HAP: late-onset VAP Inclusion criteria: age < 1 year and late-onset VAP. New or progressive pulmonary infiltrates and at least 2 of the following: a body temperature of > 38 °C or < 36 °C; > 10,000 or < 4000 leucocytes/uL blood; purulent tracheo-bronchial secretions; and/or a decrease in the partial pressure of oxygen. Exclusion criteria: disseminated intravascular coagulation, organ failure, immunosuppression, or known hypersensitivity to cephalosporins and preterm newborns.
Interventions	Intervention group: cefepime Control group: ceftazidime Co-interventions: not reported
Outcomes	Primary outcomes: clinical response (cure, improvement, failure, or death) Secondary outcomes: microbiological response (eradication, persistence, superinfection, or unable to determine) Follow-up: not reported
Notes	The mean age of VAP participants seems to conflict with the age limit mentioned in the inclusion criteria. Email: sukhbir5@lycos.com

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random table used.
Allocation concealment (selection bias)	Unclear risk	Did not describe allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Did not describe blinding.

Shahid 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Did not describe blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	8/40 participants had missing data for the only outcome (treatment failure) we were able to extract.
Selective reporting (reporting bias)	Low risk	They did not have a protocol. However, all-cause mortality and serious adverse events were reported.
Other bias	Low risk	No other biases were observed.

AEs: adverse events
CAP: community-acquired pneumonia
EOT: end of treatment
HAP: hospital-acquired pneumonia
ITT: intention-to-treat
IV: intravenous
MIC: minimal inhibitory concentration
MRSA: methicillin-resistant *Staphylococcus aureus*
NA: not available
PRSP: penicillin-resistant *Streptococcus pneumoniae*
SE: standard error
UTI: upper tract infection
VAP: ventilator-associated pneumonia

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

Study	Reason for exclusion
Agweyu 2015	Unclear if children had HAP. Authors did not respond to our request for this information.
Amonova 2011	Only included adult participants
Awad 2014	Only included adult participants
Barradas 1989	Only included adult participants
Bassetti 1991	Only included adult participants
Begue 1998	Did not include participants with HAP
Berman 2004	Not randomised
Bhavnani 2012	Only included adult participants
Chaudhary 2008	Only included adult participants
Chuchalin 1997	Only included adult participants
Cometta 1994	Only included adult participants
Dickstein 2016	Only included adult participants

Study	Reason for exclusion
Fatehi 2019	Same antibiotic (colistin) in both intervention groups
Giamarellos-Bourboulis 2014	Only included adult participants
Grudinina 2002	Only included adult participants
Iakovlev 2000	Only included adult participants
Iakovlev 2006	Only included adult participants
Joshi 1999	Only included adult participants
Kollef 2012	Only included adult participants
Lacy 2015	Only included adult participants
Mohamed 2018	Only included adult participants
Muscedere 2012	Only included adult participants
Nassar 2018	Only included adult participants
Norrby 1993	Only included adult participants
Patel 2015	Same antibiotic (amoxicillin) in both intervention groups
Rodloff 1996	Only included adult participants
Straneo 1990	Only included adult participants
Tucker 2017	Only included adult participants

HAP: hospital-acquired pneumonia

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

Shahrin 2020

Study name	Injectable amoxicillin versus injectable ampicillin plus gentamicin in the treatment of severe pneumonia in children aged 2 to 59 months: protocol for an open-label randomised controlled trial
Methods	This randomised, controlled, open-label, non-inferiority trial is being conducted in Dhaka Hospital of the International Centre for Diarrheal Disease Research, Bangladesh. A sample size of 308 children with severe pneumonia will give adequate power to this study. Children aged 2 to 59 months are randomised to either IV ampicillin or IV amoxicillin, plus IV gentamicin in both study arms. The monitoring of patients is carried out according to the WHO protocol for the treatment of severe pneumonia. The primary objective is the rate of treatment failure, defined as the persistence of danger signs of severe pneumonia beyond 48 hours or deterioration within 24 hours of initiation of therapy. The secondary objectives are: 1. improvement in or the resolution of danger signs since enrolment; 2. length of hospital stay; 3. death during hospitalisation; 4. rate of nosocomial infections.

Shahrin 2020 *(Continued)*

Participants	Children aged 2 to 59 months are eligible for study enrolment upon meeting clinical criteria of severe pneumonia, as defined by the WHO classification updated in 2014.
Interventions	In the ampicillin arm, the participant receives a 50 mg/kg dose of IV ampicillin every 6 hours and a 7.5 mg/kg dose of IV gentamicin once daily for 5 to 7 days. In the intervention arm (amoxicillin arm), the participant receives a 40 mg/kg dose of IV amoxicillin every 12 hours and a 7.5 mg/kg dose of IV gentamicin once daily for 5 to 7 days.
Outcomes	Primary outcome variable: the percentage of children with treatment failure, as determined either by the persistence of danger signs over 48 hours or by the appearance of new danger signs within 24 hours of the study intervention. Secondary outcome variables: 1. time to resolution of danger signs of severe pneumonia; 2. length of hospital stay; 3. rate of nosocomial infections; 4. death during or after discharge. The secondary outcome measurement variables are the time (in hours) of disappearance of danger signs, time (in days) to discharge from the acute phase, and rate of suspected nosocomial infections (a nosocomial infection will be diagnosed based on the appearance of new signs of infection, such as fever, cough, or respiratory distress, diarrhoea, or crying during urination, after 48 hours of admission or within 72 hours of discharge from the hospital).
Starting date	1 January 2018
Contact information	Email: lubabashahrin@icddrb.org
Notes	ClinicalTrials.gov ID: NCT03369093

IV: intravenous
WHO: World Health Organization

DATA AND ANALYSES

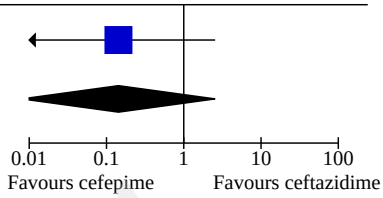
Comparison 1. Cefepime compared with ceftazidime

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.55]
1.2 Serious adverse events	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.55]
1.3 Treatment failure	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.15, 1.64]

Analysis 1.1. Comparison 1: Cefepime compared with ceftazidime, Outcome 1: All-cause mortality

Study or Subgroup	Cefepime Events	Cefepime Total	Ceftazidime Events	Ceftazidime Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Shahid 2008	0	15	3	15	100.0%	0.14 [0.01 , 2.55]
Total (95% CI)		**15**		**15**	**100.0%**	**0.14 [0.01 , 2.55]**
Total events:	0		3			

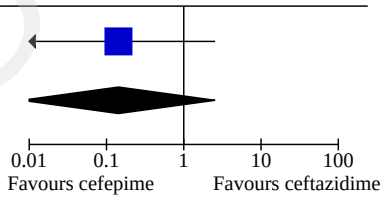
Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Cefepime compared with ceftazidime, Outcome 2: Serious adverse events

Study or Subgroup	Cefepime Events	Cefepime Total	Ceftazidime Events	Ceftazidime Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Shahid 2008	0	15	3	15	100.0%	0.14 [0.01 , 2.55]
Total (95% CI)		**15**		**15**	**100.0%**	**0.14 [0.01 , 2.55]**
Total events:	0		3			

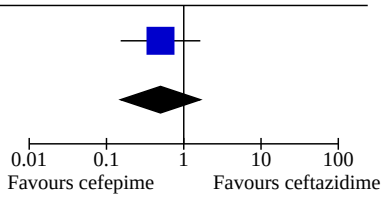
Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Cefepime compared with ceftazidime, Outcome 3: Treatment failure

Study or Subgroup	Cefepime Events	Cefepime Total	Ceftazidime Events	Ceftazidime Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Shahid 2008	3	15	6	15	100.0%	0.50 [0.15 , 1.64]
Total (95% CI)		**15**		**15**	**100.0%**	**0.50 [0.15 , 1.64]**
Total events:	3		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable



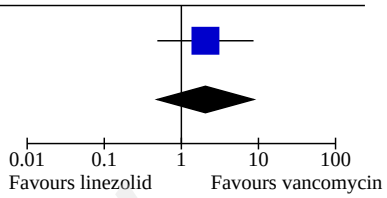
Comparison 2. Linezolid compared with vancomycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Treatment failure	1	32	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.49, 8.63]

Analysis 2.1. Comparison 2: Linezolid compared with vancomycin, Outcome 1: Treatment failure

Study or Subgroup	Linezolid Events	Linezolid Total	Vancomycin Events	Vancomycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jantausch 2003	6	19	2	13	100.0%	2.05 [0.49 , 8.63]
Total (95% CI)		**19**		**13**	**100.0%**	**2.05 [0.49 , 8.63]**
Total events:	6		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)
Test for subgroup differences: Not applicable



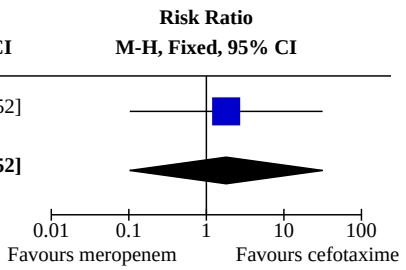
Comparison 3. Meropenem compared with cefotaxime

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Treatment failure	1	6	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.10, 31.52]

Analysis 3.1. Comparison 3: Meropenem compared with cefotaxime, Outcome 1: Treatment failure

Study or Subgroup	Meropenem Events	Meropenem Total	Cefotaxime Events	Cefotaxime Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schuler 1995	1	4	0	2	100.0%	1.80 [0.10 , 31.52]
Total (95% CI)		**4**		**2**	**100.0%**	**1.80 [0.10 , 31.52]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategy

Cochrane Central Register of Controlled Trials in the Cochrane Library (CENTRAL; 2021, Issue 2) :

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

#2 (antibiot* or antimicrob*)

#3 MeSH descriptor: [Aminoglycosides] explode all trees

#4 MeSH descriptor: [Carbapenems] explode all trees

#5 MeSH descriptor: [Cephalosporins] explode all trees

#6 MeSH descriptor: [Glycopeptides] explode all trees

#7 MeSH descriptor: [Lincosamides] explode all trees

#8 MeSH descriptor: [Macrolides] explode all trees

#9 MeSH descriptor: [Monobactams] explode all trees

#10 MeSH descriptor: [Nitroimidazoles] explode all trees

#11 MeSH descriptor: [Penicillins] explode all trees

#12 MeSH descriptor: [Quinolones] explode all trees

#13 (Aminoglycosides or Antibacerial oxazolidinone agents or Beta-lactam antibiotics or Carbapenems or Cephalosporins or Glycopeptides or Lincosamides or Macrolides or Monobactams or Nitroimidazoles or Penicillins or Quinolones or amikacin or amoxicillin or ampicillin or azithromycin or aztreonam or carbenicillin or cefazolin or cefepime or cefoperazone or cefotaxime or cefotetan or cefoxitin or ceftazidime or ceftobiprole or ceftriaxone or cefuroxime or cephalexin or ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or Cloxacillin or Dicloxacillin or doripenem or ertapenem or erythromycin or garenoxacin or gatifloxacin or gentamycin or grepafloxacin or imipenem or levofloxacin or linezolid or meropenem or Methicillin or metronidazole or mezlocillin or moxifloxacin or Nafcillin or ofloxacin or Oxacillin or penicillin G or piperacillin or sparfloxacin or tazobactam or teicoplanin or temafloxacin or ticarcillin or tobramycin or vancomycin)

#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 MeSH descriptor: [Healthcare-Associated Pneumonia] explode all trees

#16 MeSH descriptor: [Pneumonia, Ventilator-Associated] explode all trees

#17 ((pneumonia* and (((hospital or ventilator or health-care or health care) and (aquired or associated)) or nosocomial)) or HAP or VAP)

#18 #15 or #16 or #17

#19 MeSH descriptor: [Adolescent] explode all trees

#20 MeSH descriptor: [Child] explode all trees

#21 MeSH descriptor: [Infant] explode all trees

#22 (child* or P*ediat* or infant* or bab* or pre*school or lactant* or neonat* or adolesc* or school*child or youth* or toddler* or teen* or boy* or girl* or student* or juvenile* or minor* or pubescen* or young* or newborn)

#23 #19 or #20 or #21 or 322

#24 #14 and #18 and #23

MEDLINE Ovid (1946 to February 2021)

1. exp Anti-Bacterial Agents/

2. (antibiot* or antimicrob*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. exp Aminoglycosides/

4. exp Carbapenems/

5. exp Cephalosporins/

6. exp Glycopeptides/

7. exp Lincosamides/

8. exp Macrolides/

9. exp Monobactams/

10. exp Nitroimidazoles/

11. exp Penicillins/

12. exp Quinolones/

13. (Aminoglycosides or Antibacerial oxazolidinone agents or Beta-lactam antibiotics or Carbapenems or Cephalosporins or Glycopeptides or Lincosamides or Macrolides or Monobactams or Nitroimidazoles or Penicillins or Quinolones or amikacin or amoxicillin or ampicillin or azithromycin or aztreonam or carbenicillin or cefazolin or cefepime or cefoperazone or cefotaxime or cefotetan or cefoxitin or ceftazidime

or ceftobiprole or ceftriaxone or cefuroxime or cephalexin or ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or Cloxacillin or Dicloxacillin or doripenem or ertapenem or erythromycin or garenoxacin or gatifloxacin or gentamycin or grepafloxacin or imipenem or levofloxacin or linezolid or meropenem or Methicillin or metronidazole or mezlocillin or moxifloxacin or Nafcillin or ofloxacin or Oxacillin or penicillin G or piperacillin or sparfloxacin or tazobactam or teicoplanin or temafloxacin or ticarcillin or tobramycin or vancomycin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. exp Healthcare-Associated Pneumonia/

16. exp Pneumonia, Ventilator-Associated/

17. ((pneumonia* and (((hospital or ventilator or health-care or health care) and (aquired or associated)) or nosocomial)) or HAP or VAP).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

18. 15 or 16 or 17

19. exp Adolescent/ or exp Child/ or exp Infant/

20. (child* or P*ediat* or infant* or bab* or pre*school or lactant* or neonat* or adolesc* or school*child or youth* or toddler* or teen* or boy* or girl* or student* or juvenile* or minor* or pubescen* or young* or newborn).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

21. 19 or 20

22. 14 and 18 and 21

23. (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or trial.ti.

24. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

25. 22 and (23 or 24)

Embase Ovid (1974 to February 2021)

1. exp antiinfective agent/

2. (antibiot* or antimicrob*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

3. exp aminoglycoside/

4. exp carbapenem derivative/

5. exp cephalosporin derivative/

6. exp glycopeptide/

7. exp lincosamide/

8. exp macrolide/

9. exp monobactam derivative/

10. exp nitroimidazole derivative/

11. exp penicillin derivative/

12. exp quinolone derivative/

13. (Aminoglycosides or Antibacterial oxazolidinone agents or Beta-lactam antibiotics or Carbapenems or Cephalosporins or Glycopeptides or Lincosamides or Macrolides or Monobactams or Nitroimidazoles or Penicillins or Quinolones or amikacin or amoxicillin or ampicillin or azithromycin or aztreonam or carbenicillin or cefazolin or cefepime or cefoperazone or cefotaxime or cefotetan or cefoxitin or ceftazidime or ceftobiprole or ceftriaxone or cefuroxime or cephalexin or ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or Cloxacillin or Dicloxacillin or doripenem or ertapenem or erythromycin or garenoxacin or gatifloxacin or gentamycin or grepafloxacin or imipenem or levofloxacin or linezolid or meropenem or Methicillin or metronidazole or mezlocillin or moxifloxacin or Nafcillin or ofloxacin or Oxacillin or penicillin G or piperacillin or sparfloxacin or tazobactam or teicoplanin or temafloxacin or ticarcillin or tobramycin or vancomycin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. exp health care associated pneumonia/

16. exp ventilator associated pneumonia/

17. ((pneumonia* and (((hospital or ventilator or health-care or health care) and (aquired or associated)) or nosocomial)) or HAP or VAP).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

18. 15 or 16 or 17

19. exp Adolescent/ or exp Child/ or exp Infant/

20. (child* or P*ediat* or infant* or bab* or pre*school or lactant* or neonat* or adolesc* or school*child or youth* or toddler* or teen* or boy* or girl* or student* or juvenile* or minor* or pubescen* or young* or newborn).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

21. 19 or 20

22. 14 and 18 and 21

23. Randomized controlled trial/ or Controlled clinical study/ or trial.ti.

24. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

25. 22 and (23 or 24)

LILACS (Bireme; 1982 to February 2021)

(antibiot$ or antimicrob$) or (Aminoglycosides or Antibacterial oxazolidinone agents or Beta-lactam antibiotics or Carbapenems or Cephalosporins or Glycopeptides or Lincosamides or Macrolides or Monobactams or Nitroimidazoles or Penicillins or Quinolones or amikacin or amoxicillin or ampicillin or azithromycin or aztreonam or carbenicillin or cefazolin or cefepime or cefoperazone or cefotaxime or cefotetan or cefoxitin or ceftazidime or ceftobiprole or ceftriaxone or cefuroxime or cephalexin or ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or Cloxacillin or Dicloxacillin or doripenem or ertapenem or erythromycin or garenoxacin or gatifloxacin or gentamycin or grepafloxacin or imipenem or levofloxacin or linezolid or meropenem or Methicillin or metronidazole or mezlocillin or moxifloxacin or Nafcillin or ofloxacin or Oxacillin or penicillin G or piperacillin or sparfloxacin or tazobactam or teicoplanin or temafloxacin or ticarcillin or tobramycin or vancomycin) [Words] and ((pneumonia$ and (((hospital or ventilator or health-care or health care) and (aquired or associated)) or nosocomial)) or HAP or VAP) [Words] and (child$ or P$ediat$ or infant$ or bab$ or pre$school or lactant$ or neonat$ or adolesc$ or school$child or youth$ or toddler$ or teen$ or boy$ or girl$ or student$ or juvenile$ or minor$ or pubescen$ or young$ or newborn) [Words]

Science Citation Index EXPANDED (1900 to February 2021) and Conference Proceedings Citation Index – Science (1990 to February 2021) (Web of Science)

#8 #7 AND #6

#7 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*)

#6 #5 AND #4 AND #3

#5 TS=(child* or P*ediat* or infant* or bab* or pre*school or lactant* or neonat* or adolesc* or school*child or youth* or toddler* or teen* or boy* or girl* or student* or juvenile* or minor* or pubescen* or young* or newborn)

#4 TS=((pneumonia* and (((hospital or ventilator or health-care or health care) and (aquired or associated)) or nosocomial)) or HAP or VAP)

#3 #2 OR #1

#2 TS=(Aminoglycosides or Antibacerial oxazolidinone agents or Beta-lactam antibiotics or Carbapenems or Cephalosporins or Glycopeptides or Lincosamides or Macrolides or Monobactams or Nitroimidazoles or Penicillins or Quinolones or amikacin or amoxicillin or ampicillin or azithromycin or aztreonam or carbenicillin or cefazolin or cefepime or cefoperazone or cefotaxime or cefotetan or cefoxitin or ceftazidime or ceftobiprole or ceftriaxone or cefuroxime or cephalexin or ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or Cloxacillin or Dicloxacillin or doripenem or ertapenem or erythromycin or garenoxacin or gatifloxacin or gentamycin or grepafloxacin or imipenem or levofloxacin or linezolid or meropenem or Methicillin or metronidazole or mezlocillin or moxifloxacin or Nafcillin or ofloxacin or Oxacillin or penicillin G or piperacillin or sparfloxacin or tazobactam or teicoplanin or temafloxacin or ticarcillin or tobramycin or vancomycin)

#1 TS=(antibiot* or antimicrob*)

CINAHL (Ebsco host; February 2021) (317 hits)

S11 S9 AND S10

S10 TX (random* or blind* or placebo* or meta-analys*)

S9 S4 AND S8

S8 S5 OR S6 OR S7

S7 TX ((pneumonia* and (((hospital or ventilator or health-care or health care) and (aquired or associated)) or nosocomial)) or HAP or VAP)

S6 MH pneumonia, ventilator-associated

S5 MH healthcare-associated pneumonia

S4 S1 OR S2 OR S3

S3 TX (Aminoglycosides or Antibacerial oxazolidinone agents or Beta-lactam antibiotics or Carbapenems or Cephalosporins or Glycopeptides or Lincosamides or Macrolides or Monobactams or Nitroimidazoles or Penicillins or Quinolones or amikacin or amoxicillin or ampicillin or azithromycin or aztreonam or carbenicillin or cefazolin or cefepime or cefoperazone or cefotaxime or cefotetan or cefoxitin or ceftazidime or ceftobiprole or ceftriaxone or cefuroxime or cephalexin or ciprofloxacin or clarithromycin or clavulanic acid or clindamycin or Cloxacillin or Dicloxacillin or doripenem or ertapenem or erythromycin or garenoxacin or gatifloxacin or gentamycin or grepafloxacin or imipenem or levofloxacin or linezolid or meropenem or Methicillin or metronidazole or mezlocillin or moxifloxacin or Nafcillin or ofloxacin or Oxacillin or penicillin G or piperacillin or sparfloxacin or tazobactam or teicoplanin or temafloxacin or ticarcillin or tobramycin or vancomycin)

S2 TX (antibiot* or antimicrob*)

S1 MH antibiotics

Appendix 2. Risk of bias assessment

Allocation sequence generation

1. Low risk: if sequence generation was achieved using a computer random number generator or a random numbers table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are also considered adequate if performed by an independent adjudicator.
2. Unclear risk: if the method of randomisation was not specified, but the trial is still presented as being randomised.
3. High risk: if the allocation sequence was not randomised or was only quasi-randomised.

Allocation concealment

1. Low risk: if the allocation of participants was performed by a central, independent unit, onsite locked computer, identical-looking numbered, sealed envelopes, drug bottles or containers prepared by an independent pharmacist or investigator.
2. Unclear risk: if the trial was classified as randomised, but the allocation concealment process was not described.
3. High risk: if the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

1. Low risk: if the participants and the treatment providers were blinded to intervention allocation, and this was described.
2. Unclear risk: if the blinding procedure was insufficiently described.
3. High risk: if blinding of participants and treatment providers was not performed.

Blinding of outcome assessment

1. Low risk of bias: if it was mentioned that outcome assessors were blinded, and this was described.
2. Unclear risk of bias: if blinding of outcome assessors was not mentioned, or the extent of blinding is insufficiently described.
3. High risk of bias: if no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

1. Low risk of bias: if missing data were unlikely to make treatment effects depart from plausible values. This could be either:
   a. there were no dropouts or withdrawals for all outcomes; or
   b. the numbers and reasons for the withdrawals and dropouts for all outcomes were clearly stated and are similar between groups. Generally, the trial was judged as at low risk of bias due to incomplete outcome data if dropouts were less than 5%; however, this cut-off was not definitive.
2. Unclear risk of bias: if there was insufficient information to assess whether missing data were likely to introduce bias into the results.
3. High risk of bias: if the results were likely to be biased due to missing data, either because the pattern of dropouts could be described as differing between the two intervention groups, or the trial used improper methods in dealing with the missing data (e.g. 'last observation carried forward').

Selective outcome reporting

1. Low risk of bias: if a protocol was published before or at the time the trial was begun, and the outcomes specified in the protocol were reported on. If there is no protocol, or the protocol was published after the trial was begun, reporting of all-cause mortality and serious adverse events granted the trial a grade of low risk of bias.
2. Unclear risk of bias: if no protocol was published, and the outcomes all-cause mortality and serious adverse events were not reported.
3. High risk of bias: if the outcomes in the protocol were not reported on.

Other bias

1. Low risk of bias: if the trial appears to be free of other components that could put it at risk of bias (e.g. academic bias or for-profit bias).
2. Unclear risk of bias: if the trial may or may not be free of other components that could put it at risk of bias.
3. High risk of bias: if there are other factors in the trial that could put it at risk of bias (e.g. the authors have conducted trials on the same topic, for-profit bias, etc.).

Overall risk of bias

1. Low risk of bias: we classified the outcome of a trial as overall 'low risk of bias' only if all domains were classified as at low risk of bias.
2. Unclear risk of bias: we classified the outcome of a trial as overall 'unclear' risk of bias if one or more domains were classified as unclear, and no domain was at high risk of bias.
3. High risk of bias: we classified the outcome of a trial as overall 'high risk of bias' if at least one domain was classified as high risk of bias.

We graded each potential source of bias as low, high, or unclear, and provided a justification for our judgement in the risk of bias table. We planned to perform a sensitivity analysis considering trials with domains at unclear risk of bias as overall high risk of bias because meta-epidemiologic studies suggest that they tend to overestimate positive intervention effects and underestimate negative effects in the same way as domains with high risk of bias (Hróbjartsson 2012; Hróbjartsson 2013; Hróbjartsson 2014; Moustgaard 2020; Savovic 2018). We summarised the risk of bias judgements across different trials for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the risk of bias table. When considering treatment effects, we took into account the risk of bias for the trials that contributed to that outcome.

Appendix 3. Network meta-analysis

We planned to obtain information about the antibiotic regimens of interest either from head-to-head trials, or from trials comparing an antibiotic regimen with another antibiotic regimen, or placebo. Hence, the synthesis comparator set consisted of all the antibiotic regimens listed in Types of interventions as well as a placebo. We analysed each specific antibiotic regimen separately.

We generated descriptive statistics for each treatment comparison describing important clinical and methodological characteristics (e.g. publication year, participant age). Each outcome data set would be presented in a different network diagram, where the size of the nodes was proportional to the total number of randomised participants, and the width of each edge was weighted according to the number of studies comparing the connected treatments. We planned to additionally plot the edges of each network according to the average risk of bias per treatment comparison, using green for low, yellow for moderate, and red for high risk of bias. We anticipated that any participant who met the inclusion criteria was, in principle, equally likely to be randomised to any of the interventions in the synthesis comparator set. We would perform network meta-analysis using Stata 16.1 (command: mvmeta) under the frequentist framework (Stata 2019), using the network suite of commands (White 2015). The network meta-analysis synthesises evidence for the comparative effectiveness of more than two alternative interventions for the same condition (Korang 2020; Shim 2017).

We planned only to perform network meta-analysis if a connected network of trials could be conducted (Mills 2013).

If network meta-analysis was possible, we would assess a priori the two prerequisite assumptions: transitivity and consistency. We planned to assess for the transitivity assumption across treatment comparisons in the network using box plots, and evaluate the assumption of consistency using the design-by-treatment interaction model as a global test (Higgins 2003; Shim 2017). Effect modifiers would be age, ethnicity (based on country of participants), type of pneumonia (hospital-acquired pneumonia or ventilator-associated pneumonia), onset of pneumonia (early or late onset), existence of underlying diseases (e.g. genetic syndromes, lung disease, or immune deficiency), length of treatment (3 days or shorter, 4 to 5 days, 6 to 7 days, or longer than 7 days). We planned to evaluate the transitivity assumption for carrying out a network meta-analysis using these effect modifiers. We would also explore these through network subgroup meta-analyses. If we concluded that the transitivity and consistency assumptions were not met, we would not perform network meta-analysis, but would present direct and indirect evidence separately.

We would report the estimation of each treatment comparison separately using the relevant effect size (risk ratio), a 95% confidence interval, and a 95% prediction interval. We planned to use the network forest plot to illustrate the summary effect size of the comparative effectiveness amongst the antibiotic regimens. Along the estimated effect sizes, we would present the ranking probabilities for each antibiotic regimen being at each possible rank, as well as the surface under the cumulative ranking curve (SUCRA) (Räcker 2015; Salanti 2011). We planned to use a rank-heat plot to depict the SUCRA values (and their 95% confidence interval) across all outcomes (Veroniki 2016).

We planned to conduct a random-effects network meta-analysis, assuming a common within-network heterogeneity for each analysis, since the nature of the antibiotic regimens in the network is similar (Mills 2013; White 2015).

Appendix 4. Trial Sequential Analysis

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data (Brok 2008; Brok 2009; Higgins 2011; Pogue 1997; Thorlund 2009; Wetterslev 2009; Wetterslev 2017). Trial Sequential Analysis (TSA), CTU 2011, can be applied to control these random errors and to assess the risks of imprecision (Castellini 2018; Gartlehner 2019; Jakobsen 2014; Thorlund 2011). The required information size calculated by TSA takes into account the event proportion in the control group, the assumption of a plausible relative risk reduction (RRR), and the heterogeneity of the meta-analysis (Turner 2013; Wetterslev 2009).

For dichotomous outcomes, we have not identified valid previous data on effect sizes, so we have chosen an RRR of 20% as anticipated intervention effect. We estimated the required information size based on the proportion of participants with an outcome in the control group and an RRR of 20%, an alpha of 2.5%, a beta of 20%, and a variance suggested by the trials in a random-effects meta-analysis (diversity-adjusted required information size) (Jakobsen 2014; Wetterslev 2009). In case there is some evidence of effect of the intervention, a supplementary TSA used the limit of the confidence interval closest to 1.00 as the anticipated intervention effect (Jakobsen 2014). We additionally calculated the TSA-adjusted confidence interval.

For continuous outcomes, we have not identified valid previous data on effect sizes on quality of life, so we have chosen to use standard deviation (SD)/2 as anticipated intervention effect. Hence, we estimated the required information size based on the SD observed in the control group of trials with low risk of bias or lower risk of bias and a minimal relevant difference of the observed SD/2, an alpha of 2.5%, a beta of 20%, and a diversity suggested by the trials in the meta-analysis (Jakobsen 2014; Wetterslev 2009). In case there is some evidence of effect of the intervention, a supplementary TSA used the limit of the confidence interval closest to 0.00 as the anticipated intervention effect (Jakobsen 2014). We additionally calculated the TSA-adjusted confidence interval.

HISTORY

Protocol first published: Issue 1, 2021

CONTRIBUTIONS OF AUTHORS

Steven Kwasi Korang (SKK), Chiara Nava (CN), Sutharshini Punniyamoorthy Mohana (SPM), Ulrikka Nygaard (UN), Janus C Jakobsen (JCJ)
Conceiving the protocol/review: SKK and CN
Co-ordinating the protocol/review: SKK
Writing the review: SKK, CN, and SPM
Designing the protocol: SKK, CN, and JCJ
Guarantor for the review (one author): SKK
Revising the review: SKK, CN, SPM, UN, and JCJ
Responsible for reading and checking the review before submission: SKK, CN, SPM, UN, and JCJ

All authors agreed on the final version of the review.

DECLARATIONS OF INTEREST

The performance of this review is free of any real or perceived bias introduced by receipt of any benefit in cash or kind, on any subsidy derived from any source that may have or be perceived to have an interest in the outcomes of the review.

Steven Kwasi Korang: has declared that they have no conflict of interest.
Chiara Nava: has declared that they have no conflict of interest.
Sutharshini Punniyamoorthy Mohana: has declared that they have no conflict of interest.
Ulrikka Nygaard: has declared that they have no conflict of interest.
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences between the protocol, Korang 2021a, and the review.

The effects of adding glucocorticosteroids to standard care for children with sepsis. A systematic review of randomized clinical trials with meta-analysis and Trial Sequential Analysis

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Research Article

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Abstract

Background: Glucocorticosteroids are widely used to treat severe sepsis in pediatric intensive care units. However, the evidence on the clinical effects is unclear.

Objective: To assess the benefits and harms of glucocorticosteroids for children with sepsis.

Data Sources: We conducted a systematic review of randomized clinical trials with meta-analysis and Trial Sequential Analysis (TSA) (PROSPERO CRD42017054341). We searched CENTRAL, MEDLINE, Embase, LILACS, SCI-Expanded, and more.

Study Selection: Randomized clinical trials assessing the effects of adding glucocorticosteroids to standard care for children with sepsis.

Data Extraction: Two independent reviewers screened studies and extracted data. Evidence was assessed by GRADE according to our published protocol.

Data Synthesis: We included 24 trials randomizing 3073 participants.

Meta-analyses showed no evidence of an effect of adding glucocorticosteroids for children with sepsis with a mixed focus for any of our outcomes.

Meta-analyses suggested evidence of a beneficial effect of dexamethasone for children with meningitis when assessing serious adverse events (risk ratio (RR) 0.68, 95% confidence interval (CI) 0.53 to 0.86; P = 0.001, very low certainty of evidence) and ototoxicity (RR 0.63, 95% CI 0.45 to 0.88; P = 0.007, low certainty of evidence). TSAs showed that we did not have sufficient data to confirm or reject these results. We found insufficient evidence to confirm or reject an effect on mortality or our other outcomes.

No trials reported quality of life or organ failure. Most trials were at high risks of bias. We found high clinical heterogeneity between participants. None of our TSAs showed benefits, harms or futility.

Conclusions: Generally, we found no evidence of an effect of glucocorticosteroids for children with sepsis without meningitis. Dexamethasone for sepsis in children due to meningitis may decrease serious adverse events and ototoxicity.

Background

Sepsis is a leading cause of death in infants and children worldwide (1). Guidelines suggest that the glucocorticosteroid, hydrocortisone, might be used for children with fluid refractory and vasopressor-resistant septic shock, but the recommendation is based on unclear evidence (2, 3). The use of glucocorticosteroids for sepsis has been controversial for decades (4). A study from the UK suggested that 76% of pediatric intensive care units used steroids for septic shock (5). A worldwide cross-sectional study showed that the use of glucocorticosteroids was at 45% for children with severe sepsis (6).

Glucocorticosteroids seem to slightly reduce 28-day mortality in adults with sepsis (7). Important differences exist between children and adults with regard to sepsis and septic shock (8, 9). There is, therefore, a need to conduct an up-to-date review to address the benefits and harm of treatment with glucocorticosteroids in children with sepsis.

Methods

We detailed our predefined methodology in our pre-published protocol (10, 11) according to international guidelines (12). In accordance with our protocol, we conducted our systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) (13), The Cochrane Handbook for Systematic Reviews of Interventions (12), Keus and colleagues (14), and the eight-step assessment suggested by Jakobsen and colleagues for better validation of meta-analytic results in systematic reviews (15). Review Manager 5.3 was used for all meta-analyses (16).

We searched for trials assessing the effects of adding any glucocorticosteroid to standard care versus standard care for hospitalized children (age < 18 years) with a diagnosis of sepsis based on the current international consensus (SIRS) or similar terms (as defined by trialists) (17). We also included participants suspected of or diagnosed with severe/deep-seated infections such as meningitis, osteomyelitis, endocarditis, and necrotizing enterocolitis (11). We searched for eligible trials published before February 2021 in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, Science Citation Index Expanded on Web of Science, BIOSIS, Google Scholar, clinicaltrials.gov, Trip Medical Database (TRIP), EU Clinical Trial Register (EUCTR), and WHO International Clinical Trials Registry Platform (ICTRP). The search strategy can be found in **Supplementary material**. Trials were included irrespective of trial design, setting, publication status, publication year, language, and the reporting of our outcomes.

Two authors (SKK and SS) independently selected relevant trials, extracted data using a standardized data extraction sheet, and systematically assessed risks of bias (12). We contacted trial authors if relevant data were unclear or missing.

Our primary outcomes were all-cause mortality and serious adverse events (10, 11). Our secondary outcomes were quality of life, shock reversal, organ failure, hearing loss or ototoxicity, and adverse events not considered serious. For all outcomes, we used the trial results reported at maximal follow-up.

We planned several subgroup analyses including subgroups based on risk of bias, type of glucocorticosteroids, dose, age, and presence of shock (10, 11).

We used risk ratios (RR) for dichotomous outcomes. We performed both random-effects (Der Simonian-Laird) and fixed-effect (Mantel-Haenszel) meta-analyses and chose the most conservative result as our primary result (11). We used Trial Sequential Analysis (TSA) to control random errors and reported TSA-adjusted confidence interval (CI) if the cumulative Z-curves did not reach the futility area or passed the diversity-adjusted required information size (DARIS) (11, 15, 18–25). We assessed two primary outcomes

and, hence, considered a P-value of 0.033 or less as the threshold for statistical significance for the primary outcomes to account for multiplicity (11, 15). We assessed five secondary outcomes and considered a P-value of 0.05 as the threshold for statistical significance for the secondary outcomes. We used 'best-worst' and 'worst-best' case analyses to assess the potential impact of missing data (15). We calculated Bayes factor to quantify the likelihood of the meta-analysis results being more or less compatible with either the null hypothesis or the anticipated intervention effects (15). We used GRADE to assess the certainty of the body of evidence (26).

Results

Included trials

Our literature search identified a total of 9133 studies. 1929 duplicates were excluded. 7204 studies were excluded based on the title or abstract. 21 studies were excluded based on the full text assessment. 24 trials met our inclusion criteria randomizing 3073 participants (27-50), of which 20 trials randomizing 2866 participants provided data for our predefined meta-analyses (27-43, 45, 47, 48). See **PRISMA flowchart (Figure 1)** for details regarding the literature search and the selection of trials.

The age groups of the randomized participants were infants (< 1 year) (38, 43, 44, 47) and children (age > 1 year and < 12 years) (27-37, 39-42, 45, 47, 48). All the trials assessed glucocorticosteroids as add on therapy of standard care. The glucocorticosteroids included were hydrocortisone (8 trials) (27, 42, 43, 46-50); dexamethasone (15 trials) (28-41, 43); and methylprednisolone (1 trial) (45) (**Table 1**). 18 trials used placebo plus standard care (27-31, 33, 35-37, 40-43, 45, 46, 48, 49) and 6 trials used only standard care as control intervention (16, 25, 32, 34, 38, 47). The follow-up ranged from one to 12 months. 19 trials reported all-cause mortality (27-43, 45, 47, 48); 20 trials reported serious adverse events (27-43, 45, 47, 48); 2 trials reported shock reversal (37, 42); 11 trials reported ototoxicity (29-31, 33-36, 39-41, 43); 9 trials reported adverse events not considered serious (29, 32, 35-37, 42, 43, 45, 48); and 12 trials reported neurological complications (28-34, 36, 38-41). No trials reported quality of life or organ failure. We created a 'Summary of findings' table (**Table 2**) using the prespecified outcomes all-cause mortality, serious adverse events, shock reversal, ototoxicity, and adverse events not considered serious. We also assessed neurological complications as a post-hoc analysis for trials including children with meningitis.

Six trials were assessed to be at overall low risk of bias (30, 36, 39, 41, 47, 48) whereas 18 trials were assessed to be at overall high risk of bias (27-29, 31-35, 37, 38, 40, 42-46, 49, 50) (**Figure 2**). The certainty of evidence according to GRADE ranged from very low to low.

The visual inspection of the forest plot and test for subgroup difference (P = 0.02) in the meta-analysis on our primary outcome serious adverse events showed that the effects of glucocorticosteroids seemed to differ between trials randomising participants with meningitis and trials randomising participants with sepsis of mixed focus (**Figure 3 and 4**). It was therefore not justifiable to pool trials including only children with meningitis with trials including children with difference underlying infections. Hence, we

chose to report results separately for each group of trials (children with mixed focus of infection and children with meningitis). We have attached the results of the overall analyses in **Appendix 1**.

Effects of interventions

Glucocorticosteroids for sepsis with mixed focus

All-cause mortality

A total of 5/9 trials (55.6%), randomizing 358 participants, reported all-cause mortality. In the glucocorticosteroid group, 33/184 (17.9%) participants died compared with 27/174 (15.5%) participants in the control group. Meta-analysis showed no evidence of a difference when assessing all-cause mortality (RR 1.24, 95% CI 0.80 to 1.92; P = 0.34; I^2 = 0%; 358 participants; 5 trials; very low certainty of evidence; **Figure 5**). Neither visual inspection of the forest plot nor tests for statistical heterogeneity (I^2 = 0 %; P = 0.83) showed signs of heterogeneity.

Trial Sequential Analysis showed that we did not have sufficient data to confirm or reject that adding glucocorticosteroids to standard care reduced the risk of death by 20% and that the accrued information was compatible with either a reduced risk of death by 79% or an increased risk of death by 639% (TSA-adjusted CI 0.21 to 7.39) (**Figure 6)**. Bayes factor (4.31) was above the Bayes factor threshold for significance of 0.1. Hence, the result confirmed the meta-analysis result showing no difference. We assessed the risk of bias of this outcome as high risk of bias. There were no missing data, so we did not perform 'best-worst' and 'worst-best' case meta-analyses on this outcome. As we only included five trials, no funnel plot was constructed.

Subgroup analyses

None of the planned subgroup analyses assessing risk of bias, age, type of steroids, and presence of shock showed evidence of a difference (**Figure 7-10).**

Serious adverse events

A total of 5/9 trials (55.5%), randomizing 358 participants, reported serious adverse events. In the glucocorticosteroid group, 37/184 (20.1%) participants experienced one or more serious adverse events compared with 30/174 (17.2%) participants in the control group. The trials including children with sepsis and mixed focus did not report any neurological events. The majority (80%) of these trials administered hydrocortisone (See Table 2). Meta-analysis showed no evidence of a difference when assessing serious adverse events (RR 1.24, 95% CI 0.82 to 1.87; P = 0.31; I^2 = 0%; 358 participants; 5 trials; very low certainty of evidence; **Figure 11**). Neither visual inspection of the forest plot nor tests for statistical heterogeneity (I^2 = 0%; P = 0.96) showed clear signs of heterogeneity. Trial Sequential Analysis showed that we did not have sufficient data to confirm or reject that adding glucocorticosteroids to standard care reduced serious adverse events by 20% and that the accrued information was compatible with either a decrease of serious adverse events by 77% or an increase of serious adverse events by 562% (TSA-adjusted CI 0.23 to

6.62) (**Figure 12)**. Bayes factor (5.20) was above the Bayes factor threshold for significance of 0.1. Hence, the result confirmed the meta-analysis result showing no difference. We assessed the risk of bias of this outcome as high risk of bias. There were no dropouts, so we did not perform 'best-worst' and 'worst-best' case meta-analyses on this outcome. As we only included five trials, no funnel plot was constructed.

Subgroup analyses

None of the planned subgroup analyses assessing risk of bias, age, type of steroids, and presence of shock showed evidence of a difference (**Figure 13-16).**

Secondary outcomes

Shock reversal

A total of 2/9 (22.2%) trials, randomizing 97 participants, reported shock reversal. In the glucocorticosteroid group 23/48 (47.9%) participants experienced shock reversal compared with 28/49 (57.1%) participants in the control group. Meta-analysis showed no evidence of a difference (RR 0.91, 95% CI 0.52 to 1.59; P = 0.74; I^2 = 68%; 97 participants; 2 trials; very low certainty of evidence; **Figure 17**).

Adverse events

A total of 3/9 trials (33.3%), randomizing 159 participants, reported adverse events. In the glucocorticosteroid group 21/78 (26.9%) participants experienced one or more adverse events compared with 32/81 (39.5%) participants in the control group. Meta-analysis showed no evidence of a difference (RR 0.68, 95% CI 0.45 to 1.04; P = 0.08; I^2 = 0%, 159 participants; 3 trials; very low certainty of evidence; **Figure 18**).

No trials assessed quality of life, organ failure, or ototoxicity. Hence, no meta-analysis was performed.

Dexamethasone for meningitis

Primary outcomes

All-cause mortality

A total of 14/14 trials (100%), randomizing 2449 participants, reported all-cause mortality. In the dexamethasone group, 193/1243 (15.5%) participants died compared with 191/1206 (15.8%) participants in the control group. Meta-analysis showed no evidence of a difference when assessing all-cause mortality (RR 0.97, 95% CI 0.78 to 1.21; P = 0.77; I^2 = 7%; 2449 participants; 14 trials; low certainty of evidence; **Figure 19**). Neither visual inspection of the forest plot nor tests for statistical heterogeneity (I^2 = 0 %; P = 0.58) showed signs of heterogeneity. Trial Sequential Analysis showed that we had did not have sufficient data to confirm or reject that adding glucocorticosteroids to standard care reduced the risk of death by 20% and that the accrued information was compatible with either a reduced risk of death by

41% or an increased risk of death by 58% (TSA-adjusted CI 0.59 to 1.58) (**Figure 20)**. Bayes factor (4.23) was above the Bayes factor threshold for significance of 0.1. Hence, the Bayes factor result confirmed the meta-analysis result showing no difference. We assessed the risk of bias of this outcome as high risk of bias. The 'best-worst' and 'worst-best' case meta-analyses showed that incomplete outcome data bias did not have the potential to influence the results (**Figure 21** and **Figure 22**). Visual inspection of the funnel plots showed no clear signs of asymmetry (**Figure 23**).

Subgroup analyses

None of the planned subgroup analyses assessing risk of bias, age, and dose showed evidence of a difference (**Figure 24-26).**

Serious adverse events

A total of 14/14 trials (100%), randomizing 2379 participants, assessed serious adverse events. In the dexamethasone group, 370/1210 (30.6%) participants experienced one or more serious adverse events compared with 435/1169 (37.2%) participants in the control group. The trials primarily reported neurological complications, hearing loss/ ototoxicity, or a combination of both (see **Table 1**). Meta-analysis showed evidence of a difference when assessing serious adverse events (RR 0.68, 95% CI 0.53 to 0.86; P = 0.001; I^2 = 64%; 2379 participants; 14 trials; very low certainty of evidence; **Figure 27**). There were signs of statistical heterogeneity (I^2 = 64%; P = 0.0006), however, visual inspection of the forest plot did not show clear signs of heterogeneity. Trial Sequential Analysis showed that we did not have sufficient data to confirm or reject that adding glucocorticosteroids to standard care reduced serious adverse events by 20% and that the accrued information was compatible with either a decrease of serious adverse events by 75% or an increase of serious adverse events by 80% (TSA-adjusted CI 0.25 to 1.80) (**Figure 28)**. Bayes factor (0.02) was under the Bayes factor threshold for significance of 0.1. Hence, the result confirmed the meta-analysis result suggesting a difference. We assessed the risk of bias of this outcome as high risk of bias. The 'best-worst' and 'worst-best' case meta-analyses showed that incomplete outcome data bias did not have the potential to influence the results (**Figure 29** and **Figure 30**). Visual inspection of the funnel plots showed clear signs of asymmetry (**Figure 31**) confirmed by Harbord test (P=0.0009).

Subgroup analyses

None of the planned subgroup analyses assessing risk of bias, age, and dose showed evidence of a difference in intervention effects (**Figure 32-34).**

Secondary outcomes

Hearing loss or ototoxicity

A total of 11/14 (78.6%), randomizing 1825 participants, reported hearing loss or ototoxicity. In the dexamethasone group 130/941 (13.8%) participants experienced ototoxicity compared with 174/884

(19.7%) participants in the control group. Meta-analysis showed evidence of a beneficial effect of adding dexamethasone to standard care (RR 0.63, 95% CI 0.45 to 0.88; P = 0.007; I^2 = 44%; 1825 participants; 11 trials; low certainty of evidence; **Figure 35**). Trial Sequential Analysis showed that we did not have sufficient data to confirm or reject that adding glucocorticosteroids to standard care reduced serious adverse events by 20% and that the accrued information was compatible with either a reduced the risk of ototoxicity by 84% or an increased the risk of ototoxicity by 148% (TSA-adjusted CI 0.16 to 2.48) (**Figure 36**).

Adverse events

A total of 5/14 trials (35.7%), randomizing 582 participants, reported adverse events. In the dexamethasone group 126/293 (43.0%) participants experienced one or more adverse events compared with 97/289 (33.6%) participants in the control group. Meta-analysis showed no evidence of a difference (RR 1.15, 95% CI 0.76 to 1.75; P = 0.52; I^2 = 69%, 582 participants; 5 trials; very low certainty of evidence; **Figure 37**).

No trials assessed quality of life, organ failure or shock reversal. Hence, no meta-analysis was performed.

Post-hoc analysis of neurological complications

The trials including children with meningitis reported many neurological complications as serious adverse events. We therefore decided to analyze that outcome separately as well.

A total of 12/14 (85.7%) trials, randomizing a total of 1866 participants, assessed neurological complications. In the dexamethasone group 123/950 (12.9%) participants experienced neurological complications compared with 140/916 (15.3%) participants in the control group. Meta-analysis showed no evidence of a difference (RR 0.79, 95% CI 0.58 to 1.05; P = 0.12; I^2 = 20%; 1866 participants; 12 trials; low certainty of evidence; **Figure 38**).

Discussion

We included 24 trials randomizing a total of 3073 infants or children below 12 years. Six trials were assessed at overall ‘low risk of bias’, and 18 trials were assessed at overall ‘high risk of bias’. The certainty of evidence according to GRADE ranged from very low to low. The trials included a heterogeneous group of children with different underlying infections such as pneumonia, meningitis, and a mix of different foci; the trials were conducted in both high-income countries and low-income countries. The types of glucocorticosteroids were hydrocortisone, dexamethasone, or methylprednisolone. Eighteen trials used placebo and six trials only used standard care as control intervention.

When meta-analyzing the trial results, visual inspection of the forest plots and test for subgroup differences showed that the effects of glucocorticosteroids seemed to differ between trials randomising

participants with meningitis and trials randomising participants with sepsis of mixed focus. Hence, we chose to report results separately for each group of trials.

Meta-analysis showed no evidence of an effect of adding glucocorticosteroids to standard care for children with sepsis with a mixed focus when assessing all-cause mortality, serious adverse events, shock reversal, or adverse events. None of the trials assessed quality of life, ototoxicity, or organ failure for children with sepsis with mixed focus.

Meta-analyses suggested evidence of a beneficial effect of adding dexamethasone to standard care for children with meningitis on serious adverse events and ototoxicity. Bayes factor supported these findings. However, Trial Sequential Analysis showed that we did not have sufficient evidence to confirm that dexamethasone reduced serious adverse events by 20% or more and GRADE assessment indicated of low certainty of evidence. Meta-analyses showed no evidence of an effect of adding dexamethasone to standard care for children with meningitis when assessing all-cause mortality, adverse events, and neurological complications. No trials assessed quality of life, organ failure, or shock reversal for children with meningitis.

Dexamethasone is thought to suppress crucial inflammatory pathways responsible for meningitis (51). Accordingly, it was the glucocorticosteroid chosen in all the trials including only children with meningitis.

Our review has several strengths.
Our methodology was described in detail in a protocol that was published before the literature search was initiated (10, 11). We systematically assessed the risks of systematic errors through bias risk assessments, we conducted Trial Sequential Analyses to guide our GRADE assessments of levels of downgrade for imprecision, and we adjusted our thresholds for statistical significance to control the risks of random errors (15). We systematically used our eight–step procedure to assess if the thresholds for statistical and clinical significance were crossed (15). This added further robustness to our results and conclusions. Furthermore, we included a larger number of both trials and participants than any previous review (52), which gives us increased precision and power. We included enough participants to reject that adding glucocorticosteroids to standard care would reduce the risk of death by 20% or more. Moreover, the two most recent systematic reviews assessing the use of corticosteroids for sepsis among adults and children did not identify enough pediatric trials to perform meta-analysis for the pediatric population (7, 52). One review included participants with community acquired pneumonia that might not have sepsis (53) and excluded trials assessing children with meningitis (7).

Our review also has several limitations.
First, we chose to both include participants with sepsis and meningitis because we hypothesized that the effects of glucocorticosteroids might be similar in these two types of patients (5, 6). However, based on the present results, we reached to the conclusion that pooling trials randomizing children with sepsis and children with meningitis would not be valid since the effects seem to differ. Another limitation is that most trials were at ‘high risk of bias’. For all outcomes, a varying proportion of trials did not report on the patient-relevant outcomes we had prespecified in our protocol (5, 6). This makes our analyses open to

outcome reporting bias (54). The types of participants and choice of glucocorticosteroids differed between the included trials, which leads to a certain degree of clinical heterogeneity. Neither did we distinct between children with different degrees of severity (e.g. PRISM, PIM, PELOD, SOFA scores). We did not reach a sufficient information size for most of our outcomes to confirm or reject a beneficial or harmful effect of glucocorticosteroids. A large ongoing multicenter trial, that is planning to randomize 1032 participants, will likely be an important contribution to the assessment of the effects of glucocorticosteroids, but results are not expected before 2024 (55).

Guidelines suggest that one might use hydrocortisone for children with fluid refractory and vasopressor-resistant septic shock (3), but we found no evidence from randomized clinical trials to support this recommendation. No beneficial effects of glucocorticosteroids were found in children with septic shock, but only few children were randomized. Dexamethasone was the only glucocorticosteroids that seemed to show a beneficial effect for children with meningitis, however, the evidence was of low certainty.

Conclusions

Generally, we found no evidence of an effect of glucocorticosteroids for children with sepsis without meningitis.

Glucocorticosteroids (dexamethasone) seems to reduce serious adverse events and ototoxicity for children with meningitis but does not seem to have any effect on all-cause mortality. The clinical effects of glucocorticosteroids on shock reversal, and adverse events considered non-serious are unclear based on current evidence. No trials assessed quality of life and organ failure.

Based on our results, the guidelines need updating and the use of glucocorticosteroids for sepsis in children should be examined in randomized placebo-controlled clinical trials conducted at low risk of bias and low risk of systematic errors. Such trials ought to be designed according to the SPIRIT statement (56) and reported according to the CONSORT statement (57).

List Of Abbreviations

CI: Confidence interval. DARIS: diversity-adjusted required information size. MD: Mean difference.PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. RR: Risk ratio. TSA: Trial Sequential Analysis.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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Authors' contributions

Dr. Korang: Drafted the protocol, extracted data, co-ordinated the review, conceived the review, designed the review, analyzed the data, interpreted the data providing a methodological and clinical view, and revised the review.

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Tables

Table 1: Characteristics of included trials

	Type of glucocorticosteriod	Focus of infection	Septic shock	Country (income)	Age (infants (age <1 year), children (age >1 year and < 12 years), or adolescents (age > 12 years)
l	Hydrocortisone	Mixed	Yes	Brasil (Upper middle)	Children
	Dexamethasone	Meningitis	No	USA (High)	NA
	Hydrocortisone	Mixed	No	USA (High)	NA
	Hydrocortisone	Mixed	No	Brasil (Middle)	Infants
	Dexamethasone	Meningitis	No	Mosambique (Low)	Infants and children
f	Hydrocortisone	Mixed	Yes	UK (High)	Children
	Hydrocortisone	Mixed	Yes	Egypt (Middle)	Infants
	Dexamethasone	Meningitis	No	Turkey (Upper middle)	Children
	Dexamethasone	Meningitis	No	Finland (High)	Infants and children
	Dexamethasone	Meningitis	No	USA (High)	Children
	Hydrocortisone	Mixed	Yes	India (Lower middle)	Infants
	Dexamethasone	Meningitis	No	India (Lower middle)	Infants
	Hydrocortisone	Mixed	Yes	Canada (High)	Children
x	Dexamethasone	Meningitis	No	Malawi (Low)	NA
	Methylprednisolon	Pneumonia	No	Hungary (High)	Children
	Dexamethasone	Meningitis	No	Costa Rica (Upper middle)	Children
	Dexamethasone	Meningitis	No	Latin America (Middle)	NA
	Dexamethasone	Meningitis	No	Pakistan (Lower middle)	Infants and children
	Dexamethasone	Meningitis	No	India	Children

				(Lower middle)	
	Dexamethasone	Meningitis	No	Scaad (High)	Children
sh	Dexamethasone	Meningitis	No	Libya (Upper middle)	Infants
	Dexamethasone	Mixed	No	Kenya and Nigeria (Lower middle)	Children
	Hydrocortisone	Mixed	Yes	India (Lower middle)	Children
	Dexamethasone	Meningitis	No	USA (High)	Infants

Table 2: Summary of findings table.

Glucocorticosteroids compared with placebo or no intervention for sepsis in children

Patient or population: Children with sepsis

Settings: Hospital

Intervention: Glucocorticosteroids

Comparison: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Glucocorticosteroids				
All-cause mortality maximum follow-up	**Study population**		**RR** 1.24, (95% CI 0.80 to 1.92)	358 (5)	⊕⊖⊖⊖ **Very low**	Downgraded for bias and imprecision. DARIS: 5810 (RRR 20; alpha 3.33%; beta 10%; Pc 15.5% diversity 0.0%)
	155 per 1000	**192 per 1000** (124 to 295)				
Serious adverse events maximum follow-up	**Study population**		**RR** 1.24 (95% CI 0.82 to 1.87)	358 (5)	⊕⊖⊖⊖ **Very low**	Downgraded for bias, imprecision and indirectness. DARIS: 5143 (RRR 20; alpha 3.33%; beta 10%; Pc 17.2% diversity 0.0%)
	172 per 1000	**213 per 1000** (141 to 322)				
Shock reversal maximum follow-up	**Study population**		**RR** 0.91 (95% CI 0.52 to 1.59)	97 (2)	⊕⊖⊖⊖ **Very low**	Downgraded for bias, indirectness, imprecision, and inconsistency DARIS: 3787
	571 per	**520 per 1000**				

	1000	(297 to 907)				(RRR 20%; alpha 5%; beta 10%; Pc 57.1%; diversity 78.72%)
Adverse events not considered serious maximum follow-up	**Study population**		**RR** 0.68 (95% CI 0.45 to 1.04)	159 (3)	⊕⊖⊖⊖ **Very low**	Downgraded for bias, indirectness, imprecision, and inconsistency DARIS: 1543 (RRR 20%; alpha 5%; beta 10%; Pc 39.5%; diversity 0.0%)
	363 per 1000	**315 per 1000** (210 to 471)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio **DARIS**: Diversity-adjusted required information size

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Dexamethasone compared with placebo or no intervention for meningitis in children

Patient or population: Children with meningitis

Settings: Hospital

Intervention: Dexamethasone

Comparison: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Glucocorticosteroids				
All-cause mortality maximum follow-up	Study population		**RR** 0.97, (95% CI 0.78 to 1.21)	2449 (14)	⊕⊕⊖⊖ **Low**	Downgraded for bias and imprecision. DARIS: 9412 (RRR 20%; alpha 3.33%; beta 10%; Pc 15.8%; diversity 39.51%)
	155 per 1000	**150 per 1000** (121 to 188)				
Serious adverse events maximum follow-up	Study population		**RR** 0.68 (95% CI 0.53 to 0.86)	2379 (14)	⊕⊖⊖⊖ **Very low**	Downgraded for bias, publication bias and indirectness. DARIS: 1422 (RRR 20%; alpha 3.33%; beta 10%; Pc 37.2%; diversity 84.48%)
	372 per 1000	**253 per 1000** (197 to 320)				
Ototoxicity maximum follow-up	Study population		**RR** 0.63 (95% CI 0.45 to 0.88)	1825 (11)	⊕⊕⊖⊖ **Low**	Downgraded for bias and imprecision. DARIS: 10515 (RRR 20%; alpha 5.0%; beta 10%; Pc 19.7%;
	197 per 1000	**124 per 1000** (89 to 173)				

						diversity 62.48%)
Adverse events not considered serious maximum follow-up	**Study population**		**RR** 1.15 (95% CI 0.76 to 1.75)	582 (5)	⊕⊖⊖⊖ **Very low**	Downgraded one level for bias, indirectness and two levels for very serious imprecision. DARIS: 7936 (RRR 20%; alpha 5%, beta 10%; Pc 33.6%; diversity 75.25%)
	336 per 1000	**386 per 1000** (255 to 588)				
Neurological complications maximum follow-up	**Study population**		**RR** 0.79 (95% CI 0.58 to 1.05)	1866 (12)	⊕⊕⊖⊖ L**ow**	Downgraded for bias and imprecision. DARIS 10131 (RRR 20%; alpha 5%; beta 10%; Pc 15.3%; diversity 47.38%)
	153 per 1000	**121 per 1000** (89 to 160)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio **DARIS**: Diversity-adjusted required information size

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Figures

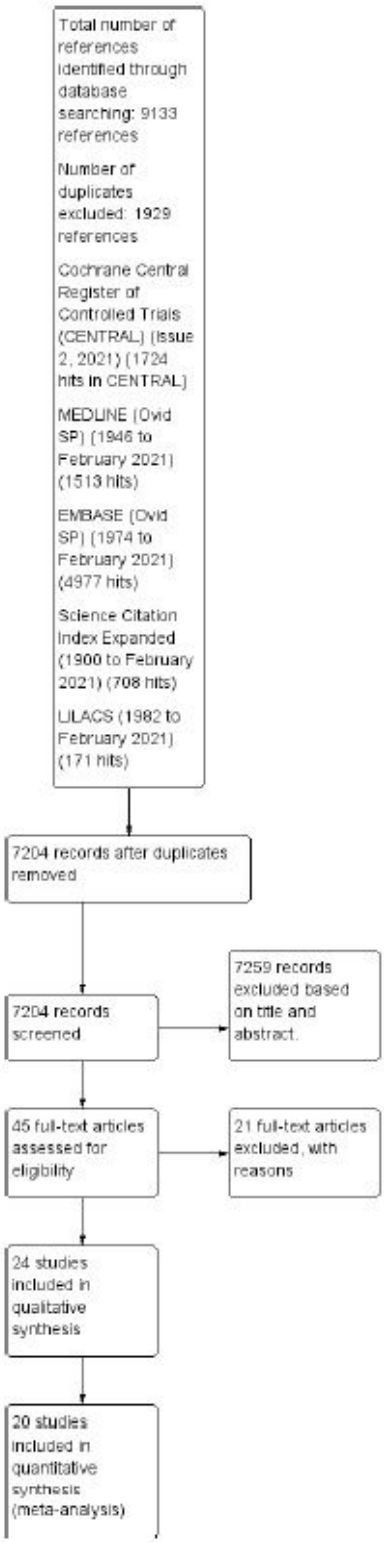

Figure 1

PRISMA flowchart

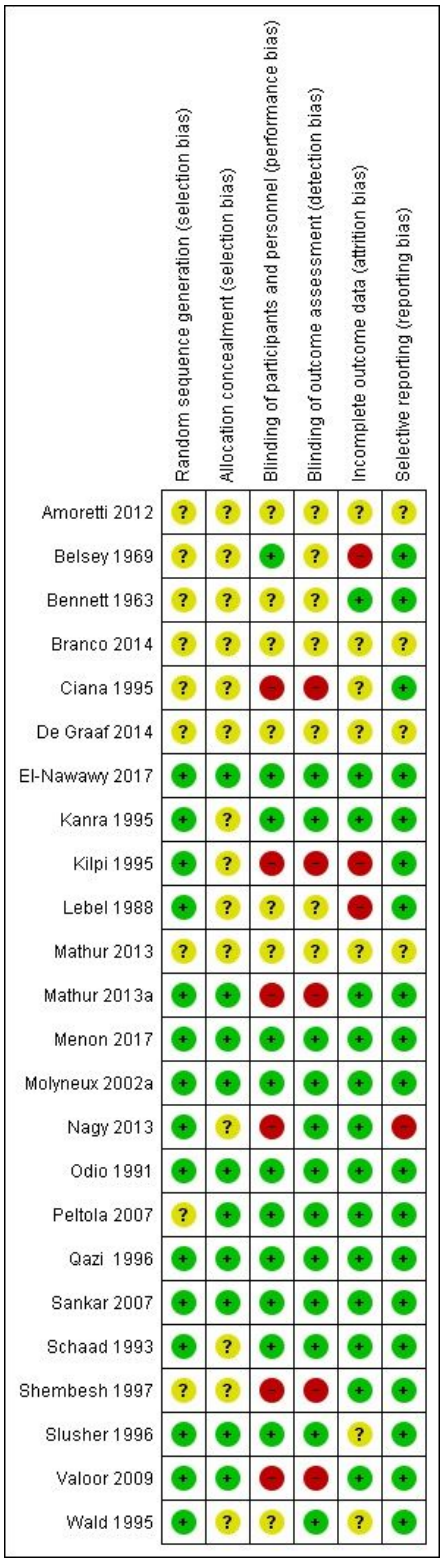

Figure 2

Risk of bias assessment

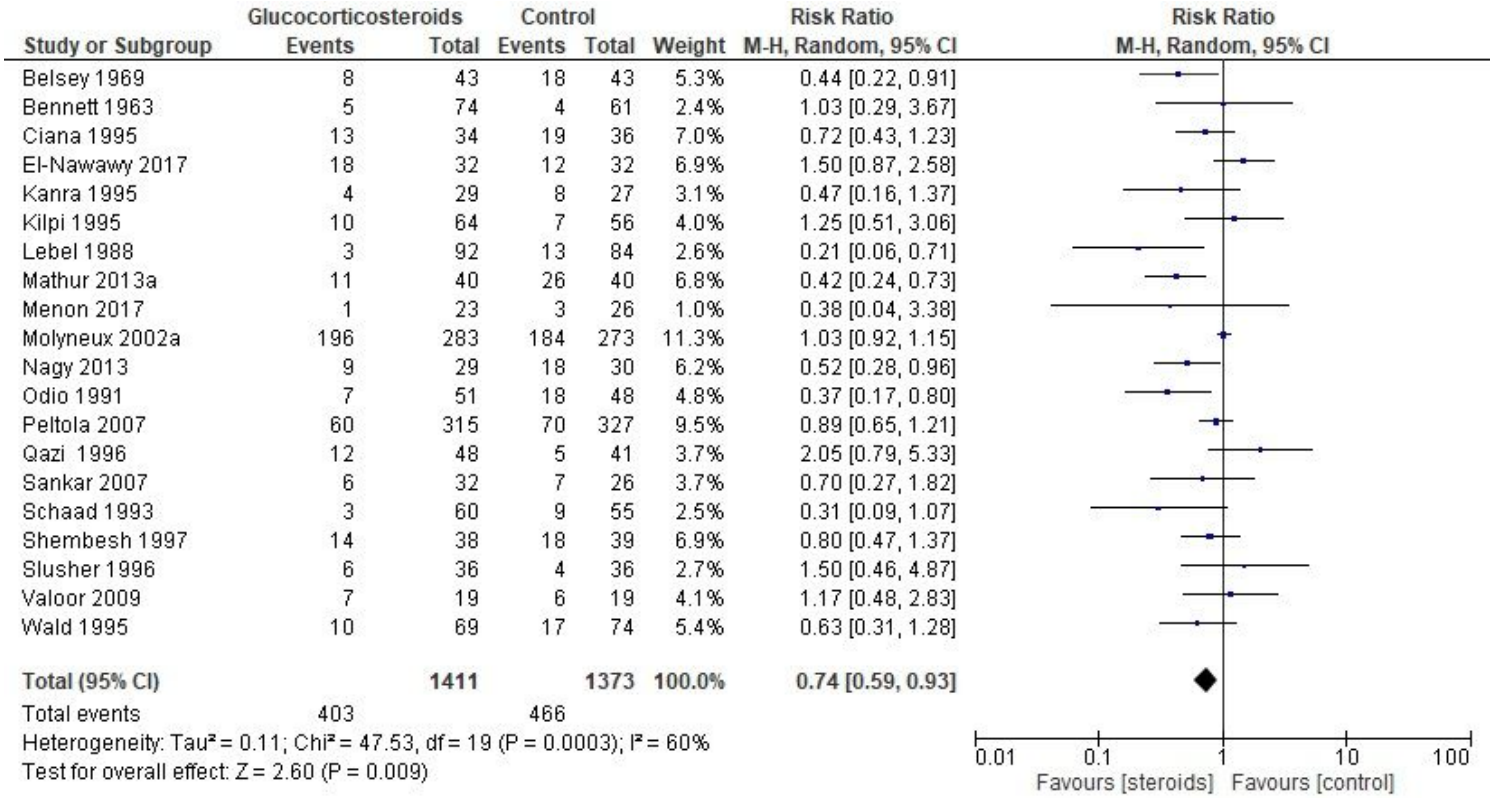

Figure 3

Serious adverse events overall analysis (Random effects model)

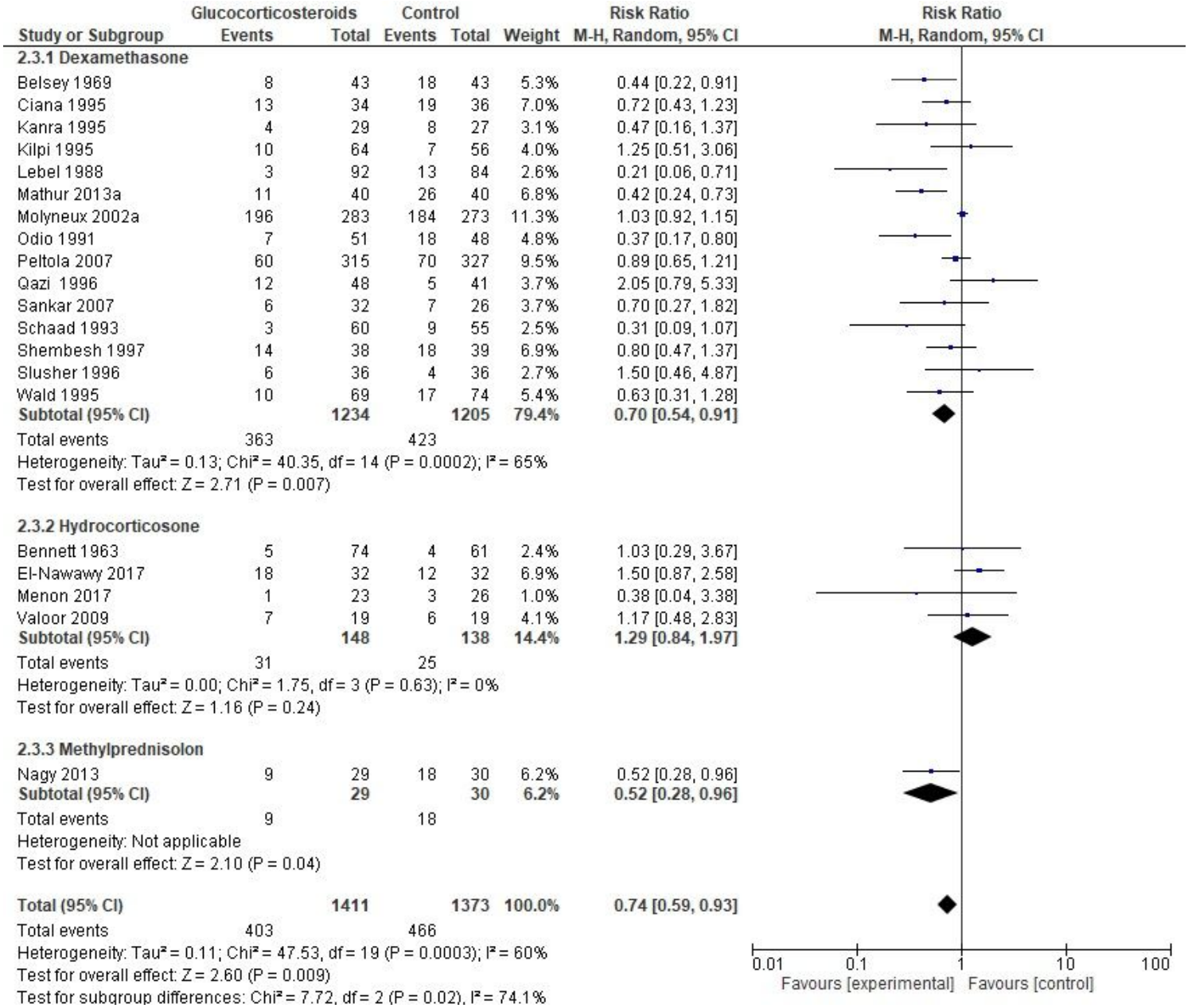

Figure 4

Serious adverse events (overall) - Subgroup based on type of steroid

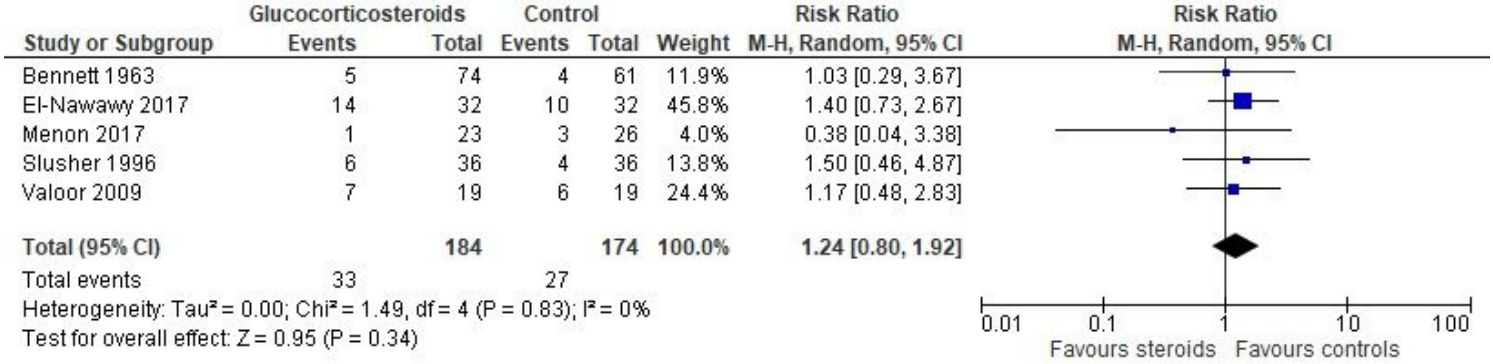

Figure 5

All-cause mortality (Sepsis- mixed focus)

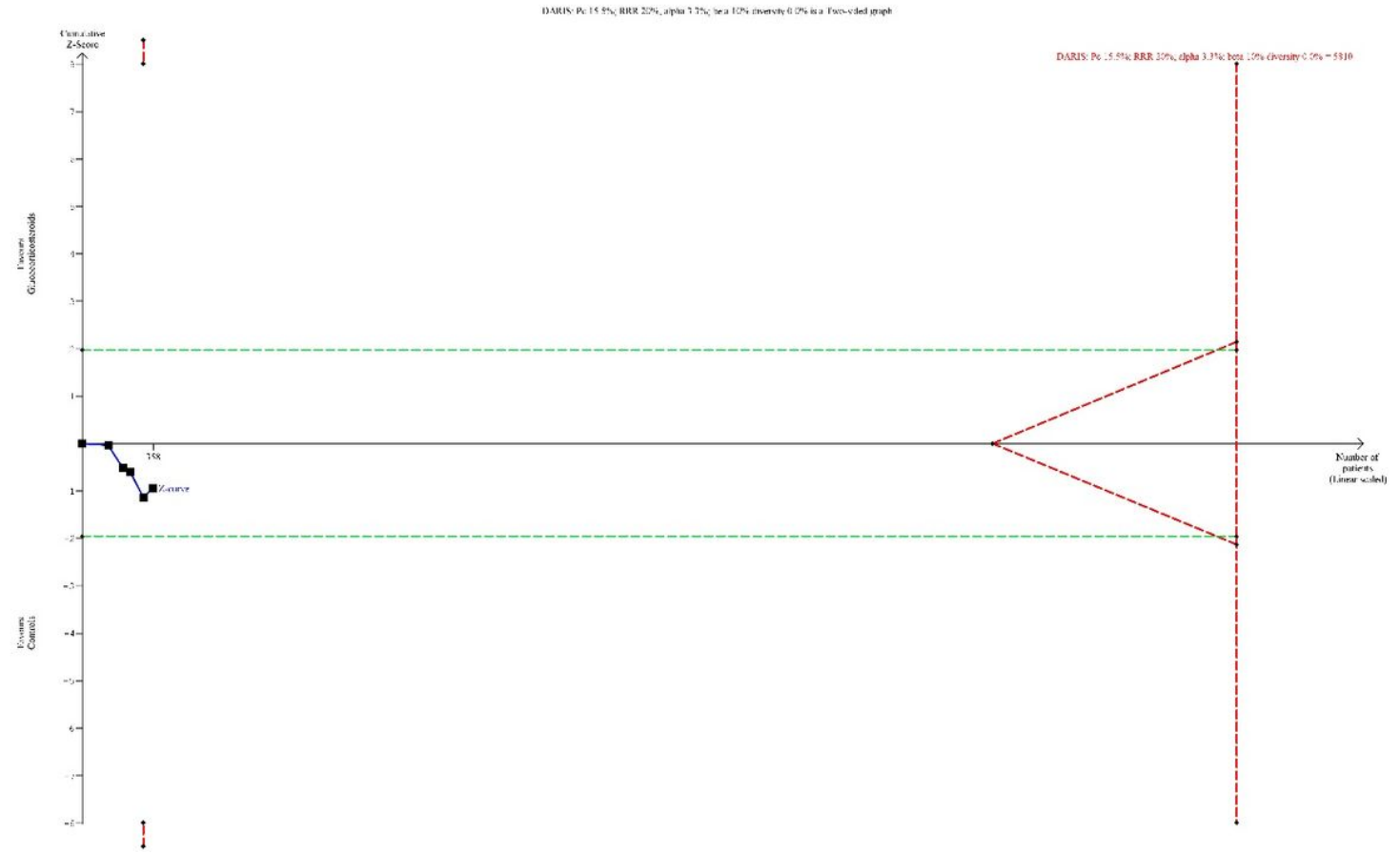

Figure 6

TSA All-cause mortality (Sepsis-mixed focus)

Study or Subgroup	Steroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Low risk of bias						
El-Nawawy 2017	14	32	10	32	45.8%	1.40 [0.73, 2.67]
Menon 2017	1	23	3	26	4.0%	0.38 [0.04, 3.38]
Subtotal (95% CI)		**55**		**58**	**49.8%**	**1.10 [0.40, 3.03]**
Total events	15		13			
Heterogeneity: Tau² = 0.21; Chi² = 1.32, df = 1 (P = 0.25); I² = 24%						
Test for overall effect: Z = 0.19 (P = 0.85)						
1.12.2 High risk of bias						
Bennett 1963	5	74	4	61	11.9%	1.03 [0.29, 3.67]
Slusher 1996	6	36	4	36	13.8%	1.50 [0.46, 4.87]
Valoor 2009	7	19	6	19	24.4%	1.17 [0.48, 2.83]
Subtotal (95% CI)		**129**		**116**	**50.2%**	**1.21 [0.65, 2.25]**
Total events	18		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)		**184**		**174**	**100.0%**	**1.24 [0.80, 1.92]**
Total events	33		27			
Heterogeneity: Tau² = 0.00; Chi² = 1.49, df = 4 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						

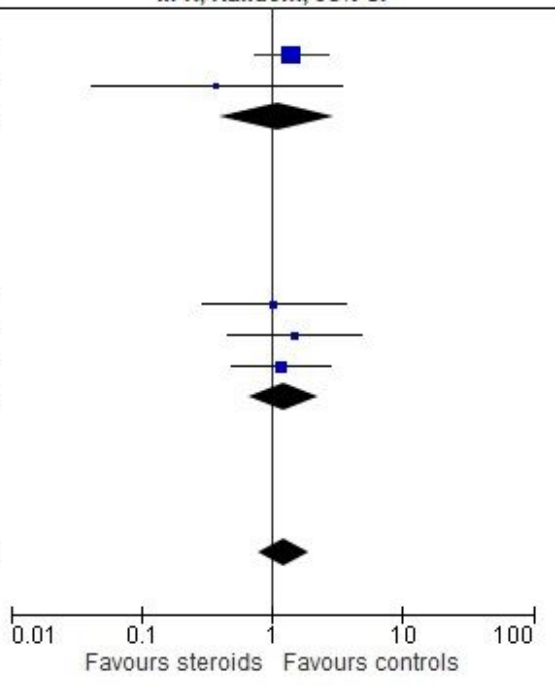

Figure 7

All-cause mortality (Sepsis- mixed focus) – Subgroup based on risk of bias

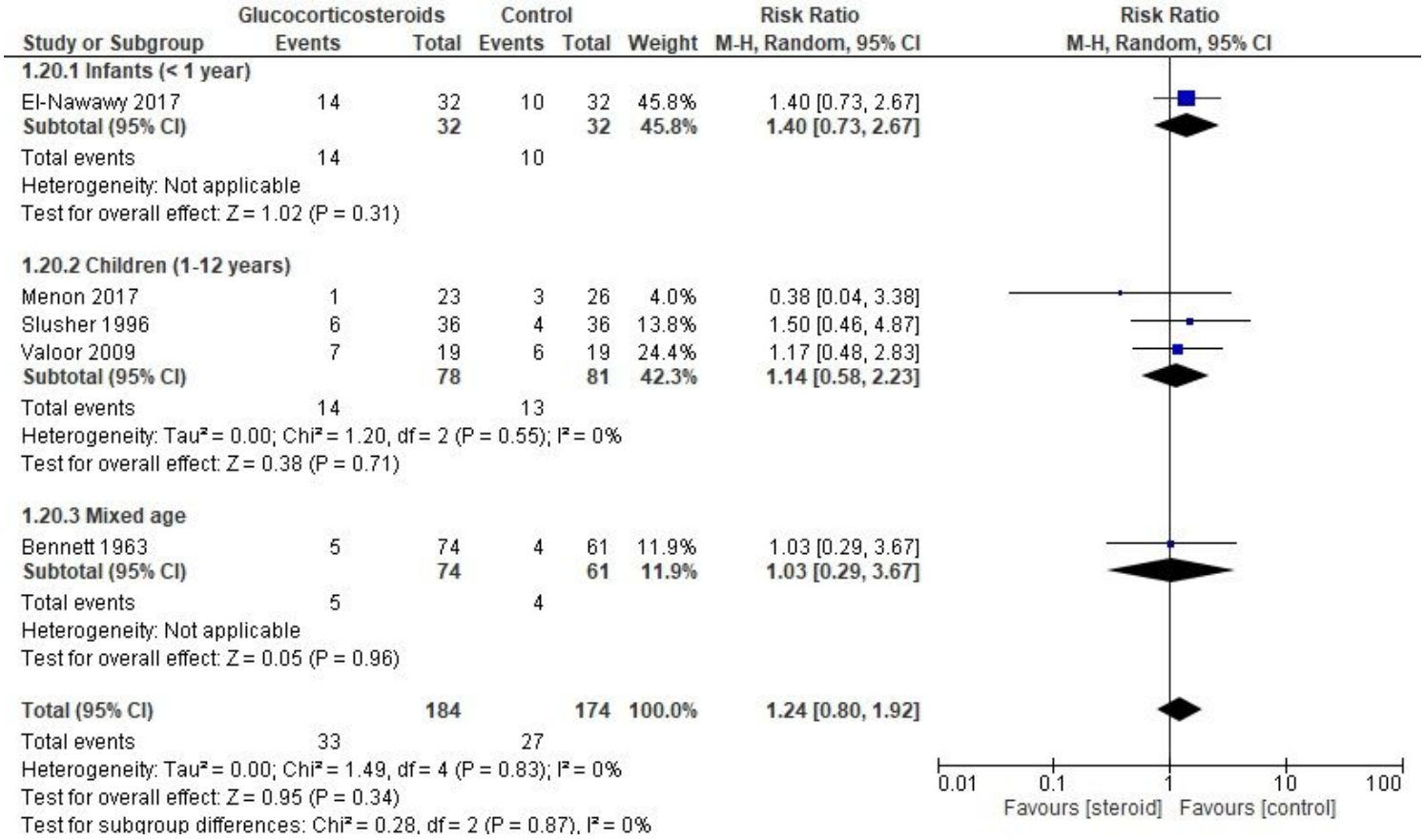

Figure 8

All-cause mortality (Sepsis- mixed focus) – Subgroup based on age

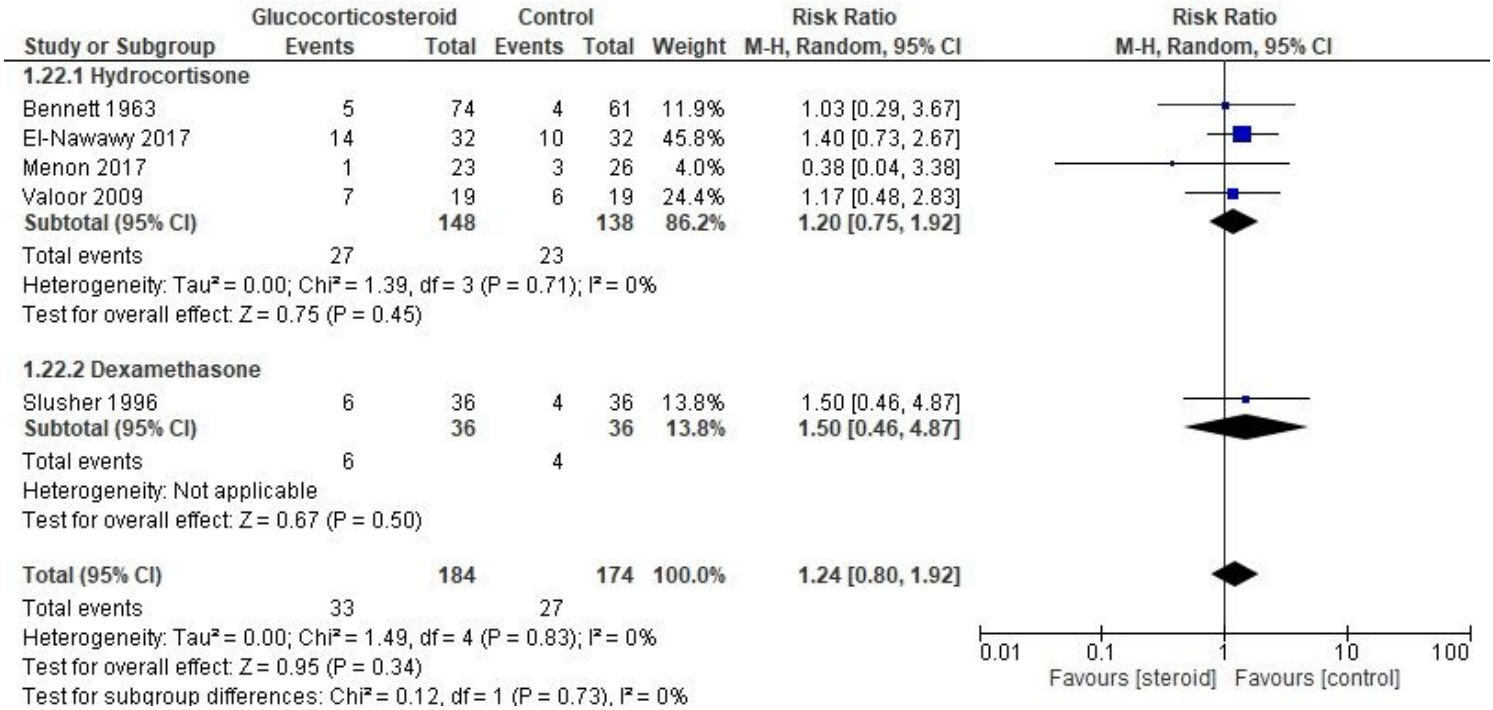

Figure 9

All-cause mortality (Sepsis- mixed focus) – Subgroup based on type of steroid

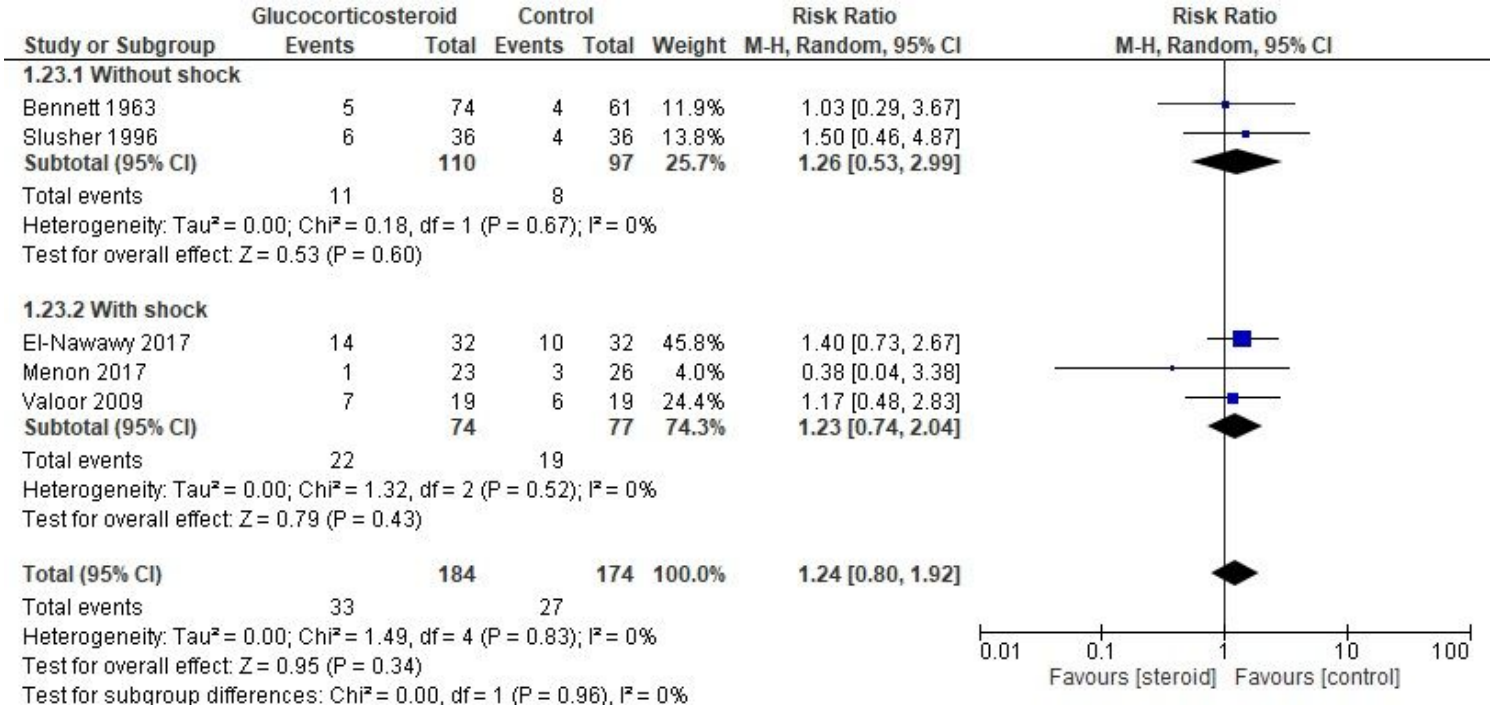

Figure 10

All-cause mortality (Sepsis- mixed focus) – Subgroup based on presence of shock

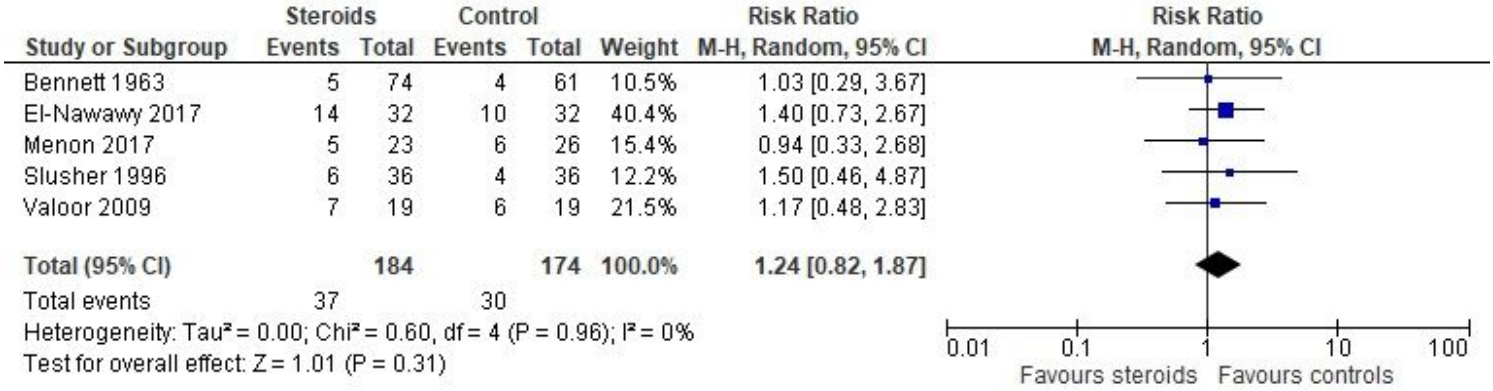

Figure 11

Serious adverse events (Sepsis – mixed focus)

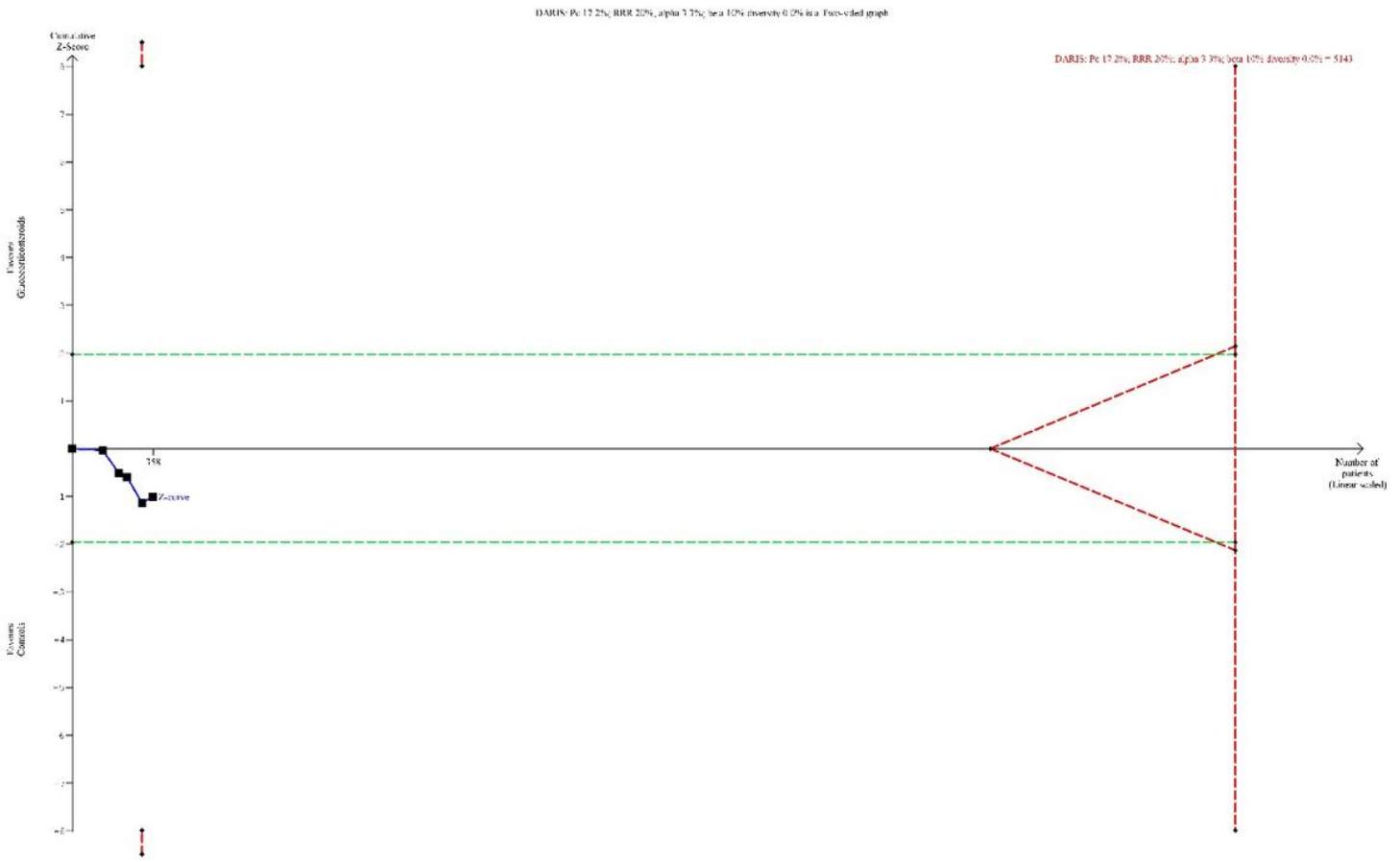

Figure 12

TSA Serious adverse events (Sepsis-mixed focus)

Study or Subgroup	Glucocorticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.13.1 Low risk of bias						
El-Nawawy 2017	14	32	10	32	40.4%	1.40 [0.73, 2.67]
Menon 2017	5	23	6	26	15.4%	0.94 [0.33, 2.68]
Subtotal (95% CI)		**55**		**58**	**55.8%**	**1.25 [0.72, 2.17]**
Total events	19		16			
Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.81 (P = 0.42)						
2.13.2 High risk of bias						
Bennett 1963	5	74	4	61	10.5%	1.03 [0.29, 3.67]
Slusher 1996	6	36	4	36	12.2%	1.50 [0.46, 4.87]
Valoor 2009	7	19	6	19	21.5%	1.17 [0.48, 2.83]
Subtotal (95% CI)		**129**		**116**	**44.2%**	**1.21 [0.65, 2.25]**
Total events	18		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)		**184**		**174**	**100.0%**	**1.24 [0.82, 1.87]**
Total events	37		30			
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 4 (P = 0.96); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%						

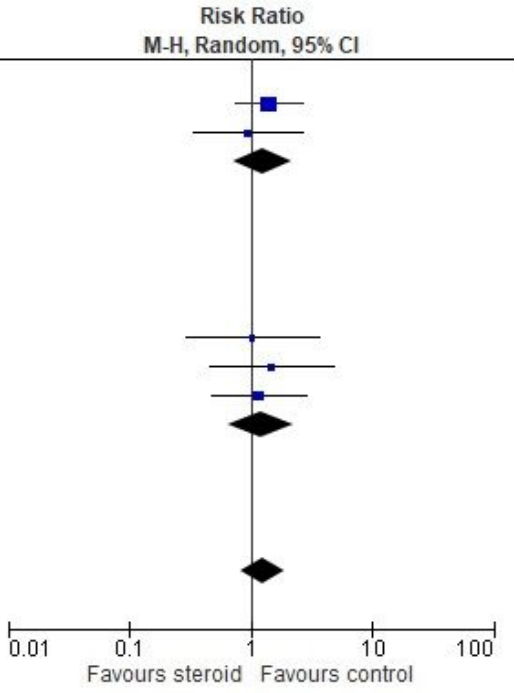

Figure 13

Serious adverse events (meningitis) – Subgroup based on risk of bias

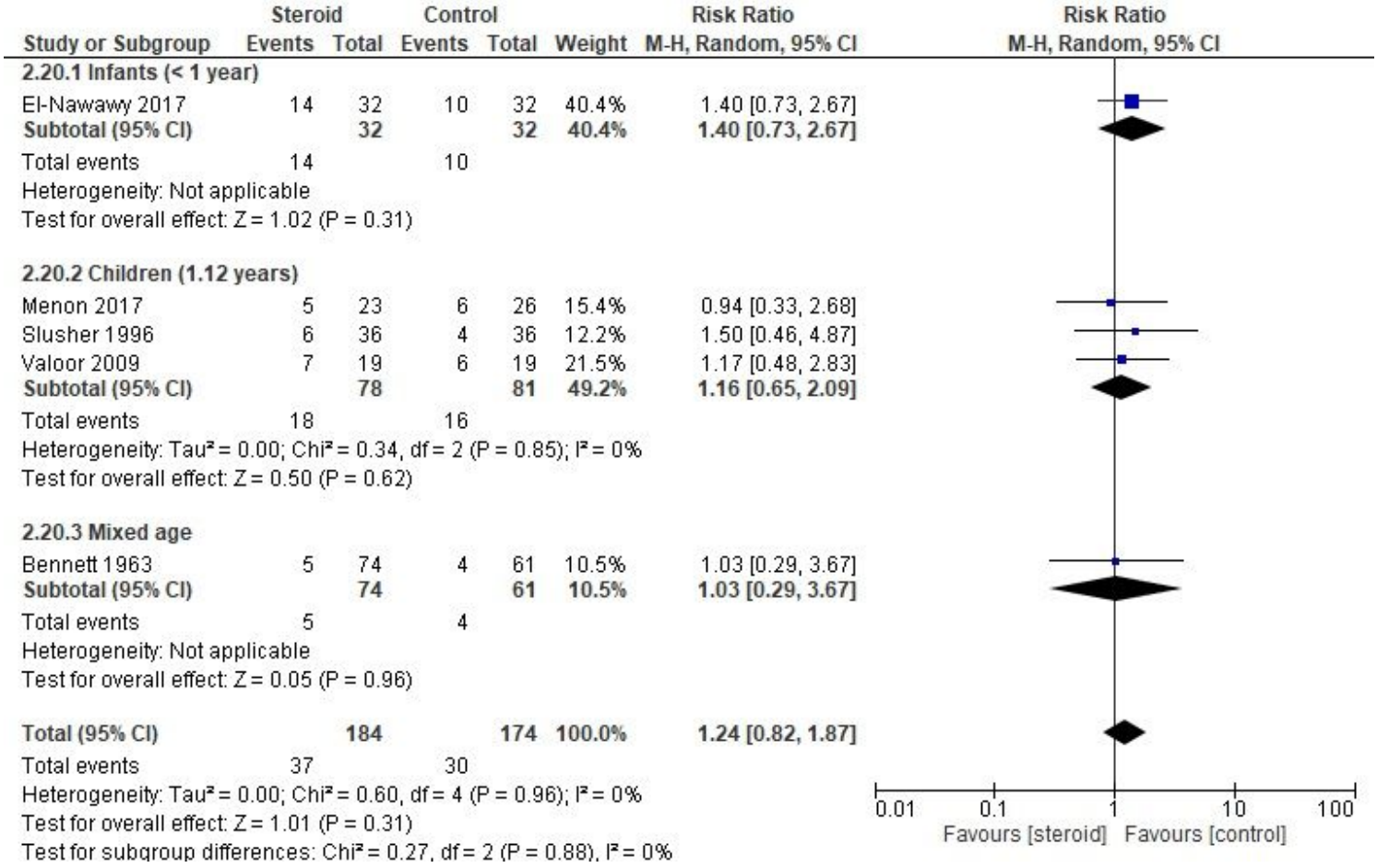

Figure 14

Serious adverse events (Sepsis – mixed focus) – Subgroup based on age

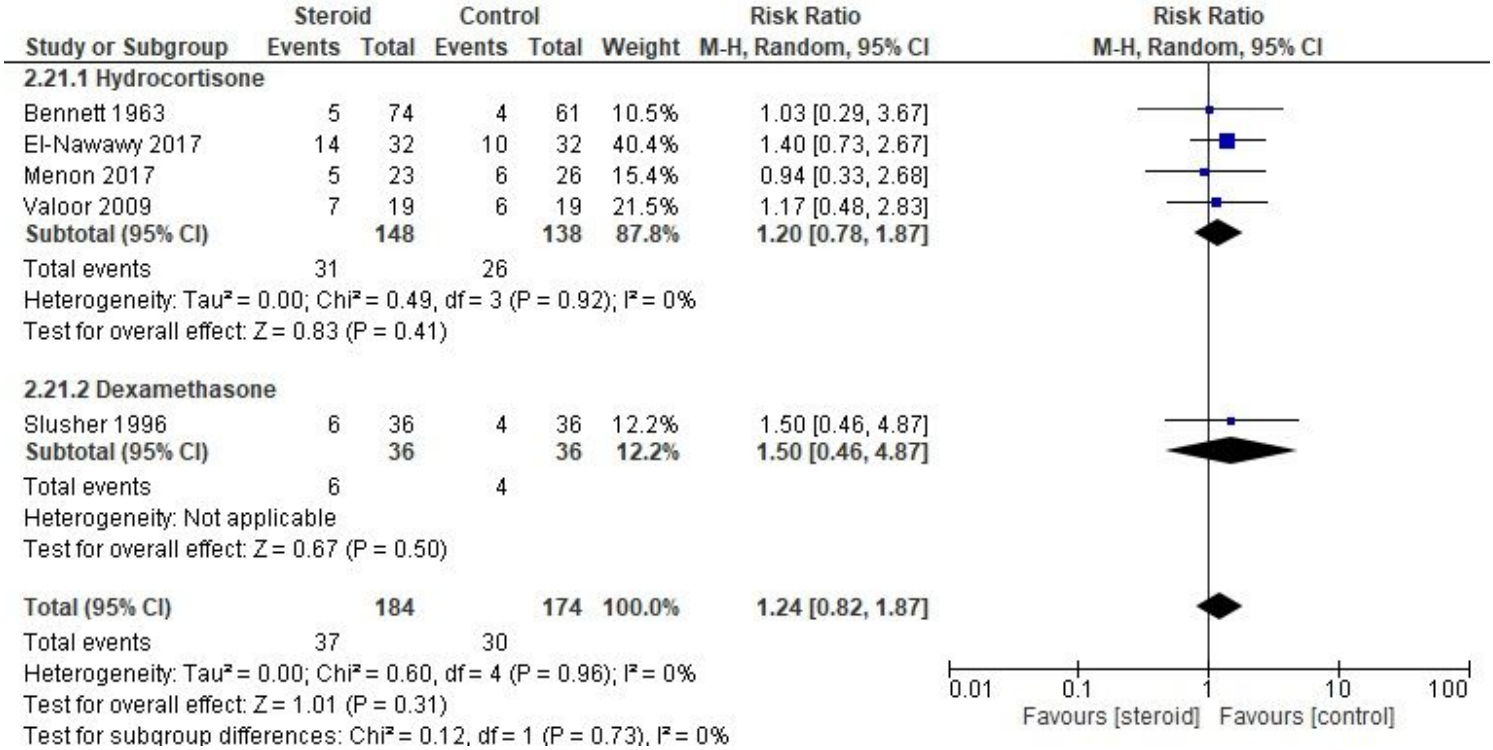

Figure 15

Serious adverse events (Sepsis- mixed focus) – Subgroup based on risk of type of steroid

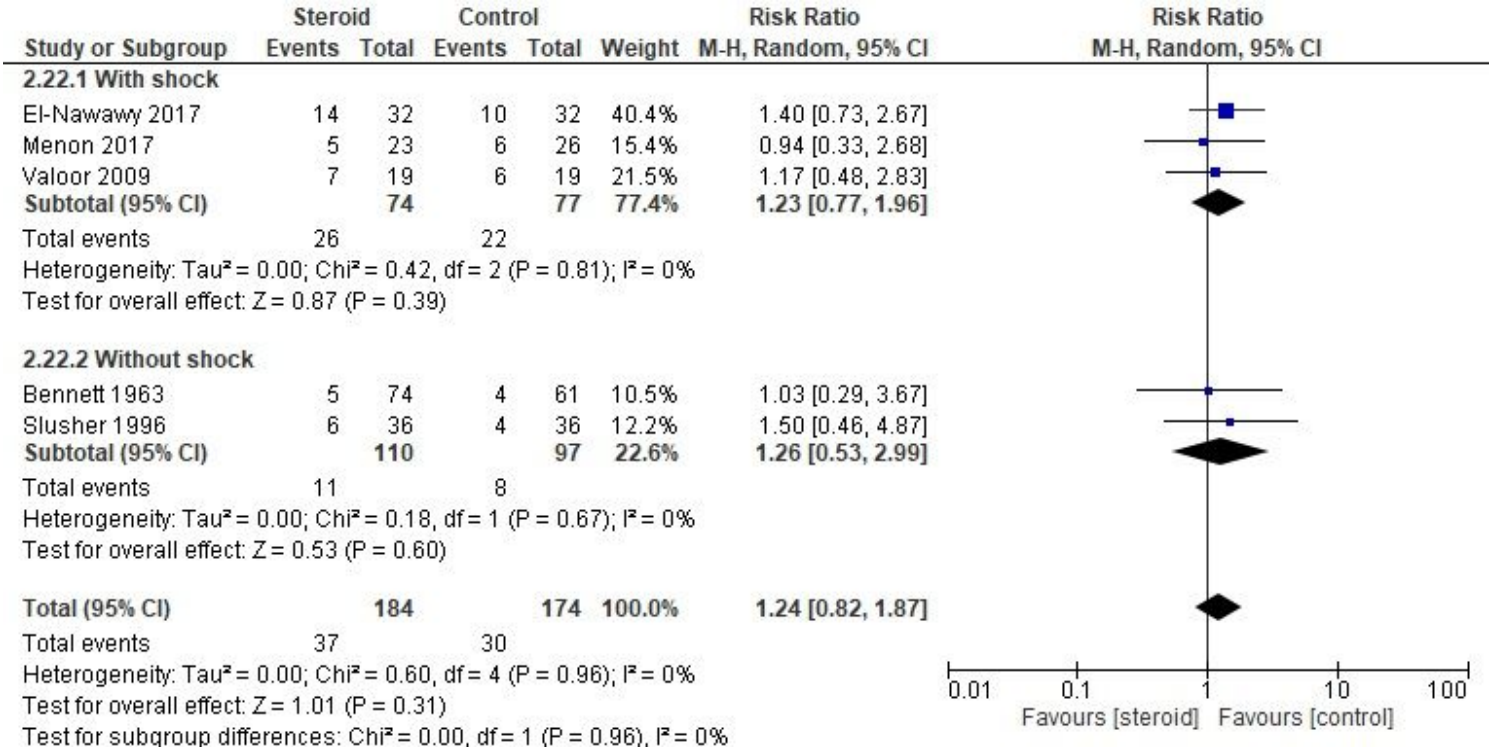

Figure 16

Serious adverse events (Sepsis- mixed focus) – Subgroup based on the presence of shock

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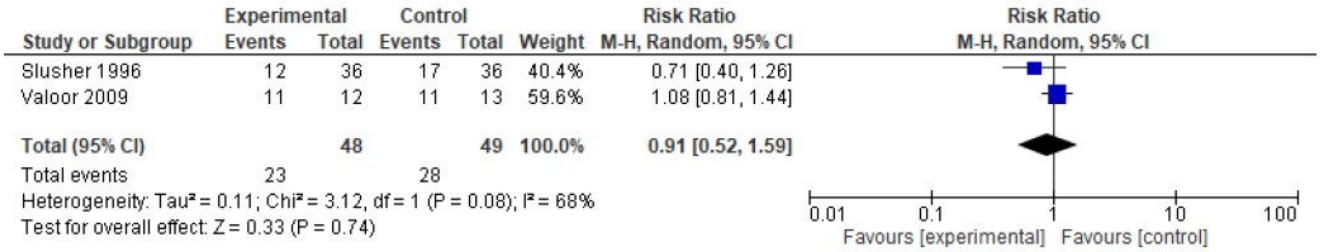

B:

Figure 17

Shock reversal (Random effect) mixed focus

Figure 18

Forest plot for adverse events (Sepsis – mixed focus)

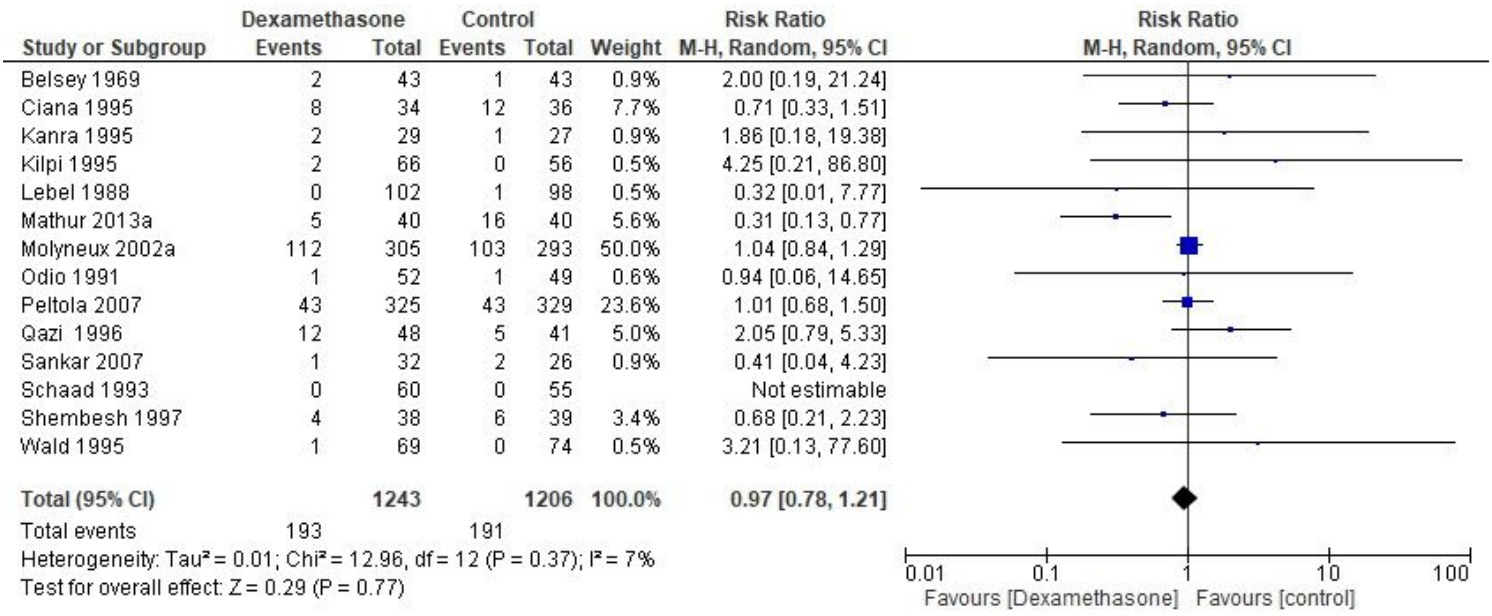

Figure 19

All-cause mortality (meningitis)

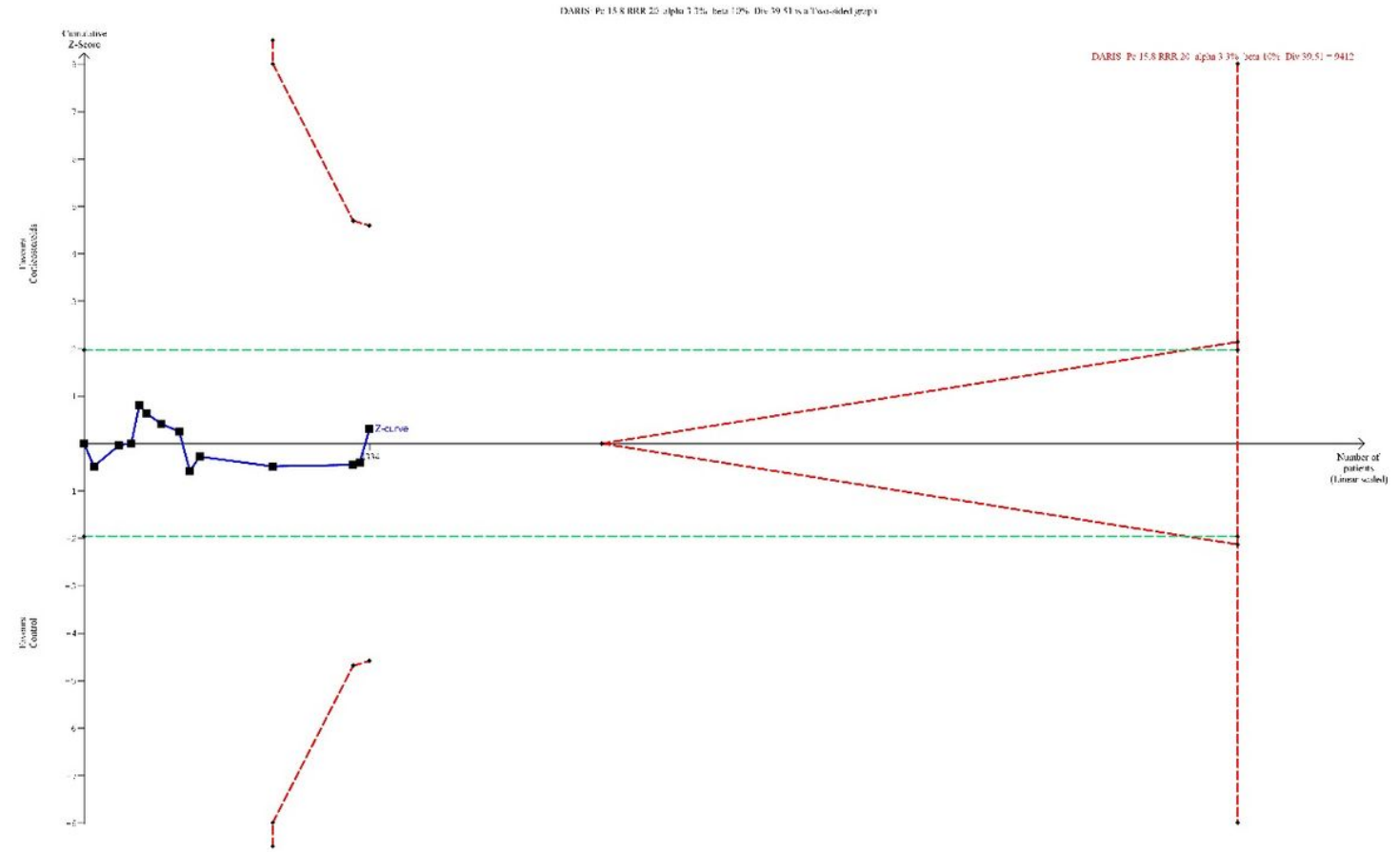

Figure 20

TSA All-cause mortality (meningitis)

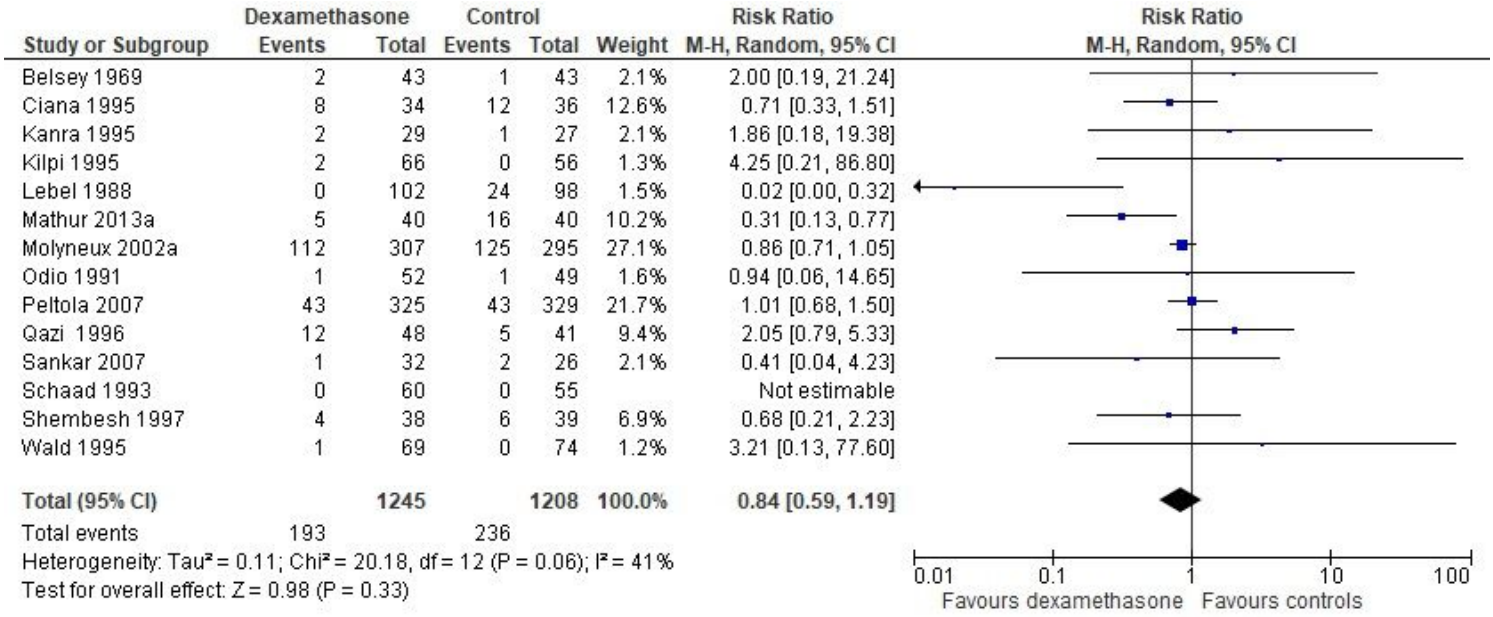

Figure 21

All-cause mortality (meningitis) – Subgroup based on best / worse

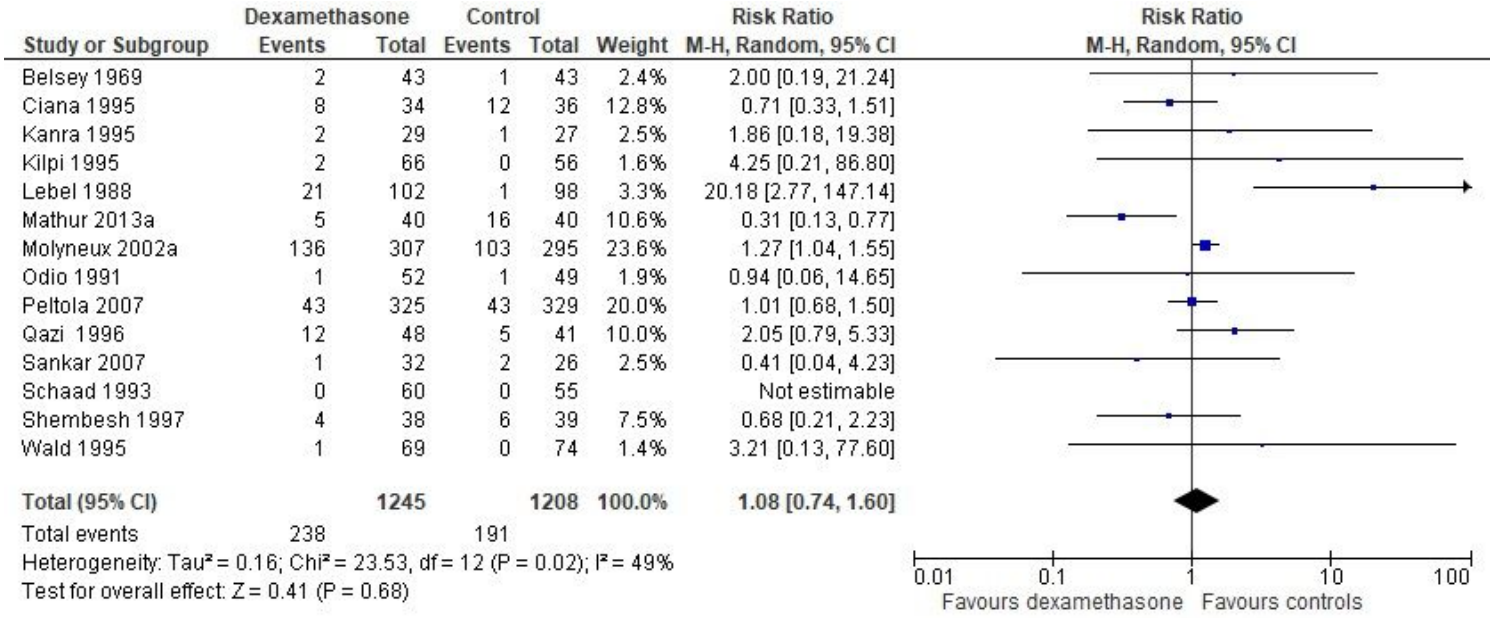

Figure 22

All-cause mortality (meningitis) – Subgroup based on worse - best

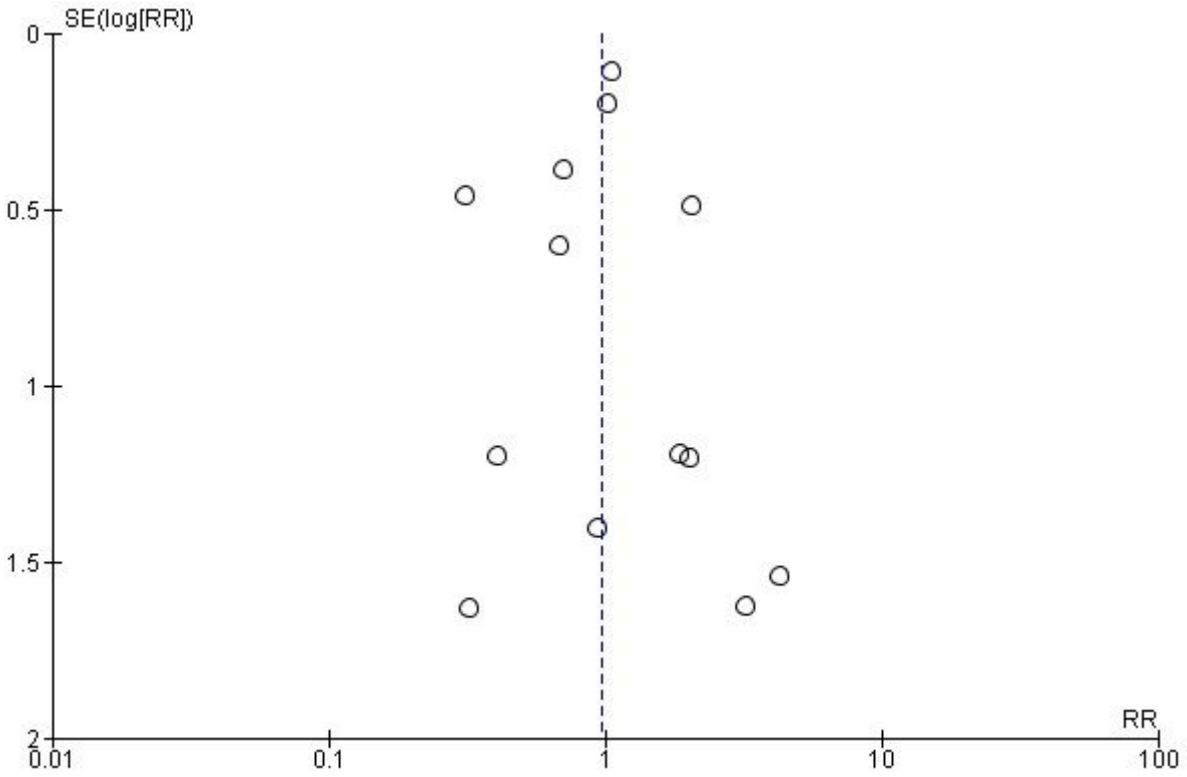

Figure 23

Funnel plot for All-cause mortality (Dexamethasone for meningitis)

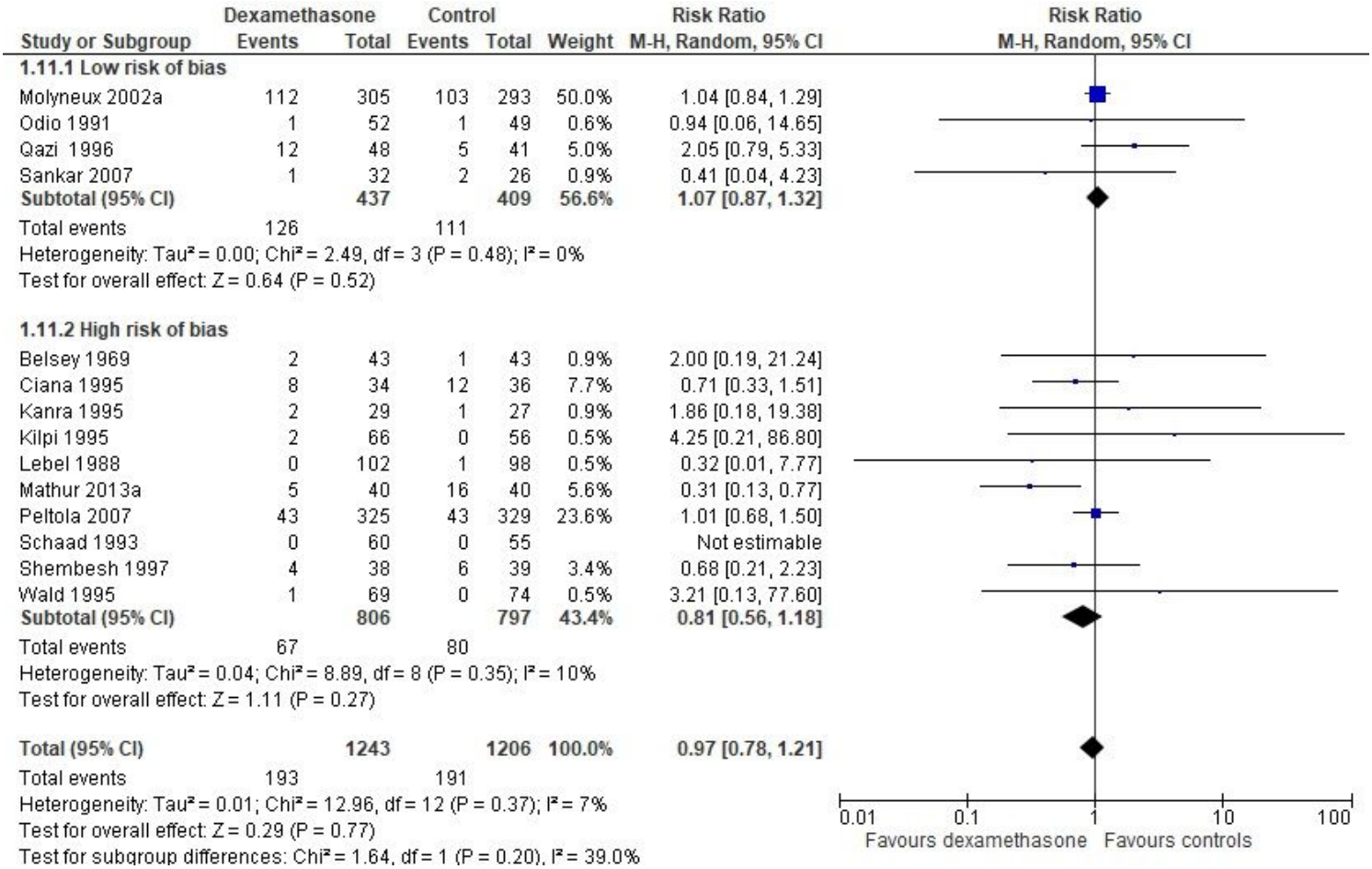

Figure 24

All-cause mortality (meningitis) – Subgroup based on risk of bias

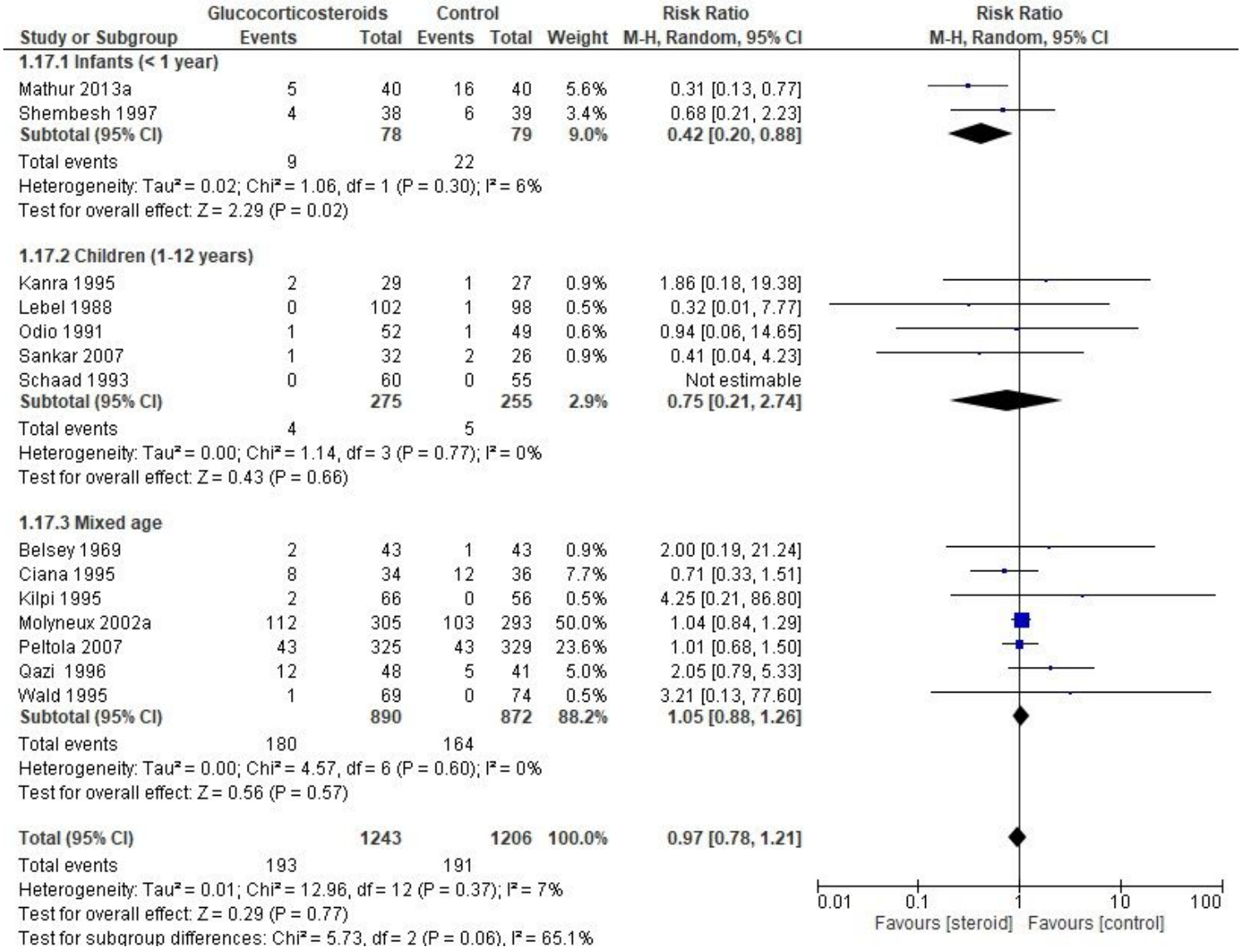

Figure 25

All-cause mortality (meningitis) – Subgroup based on age

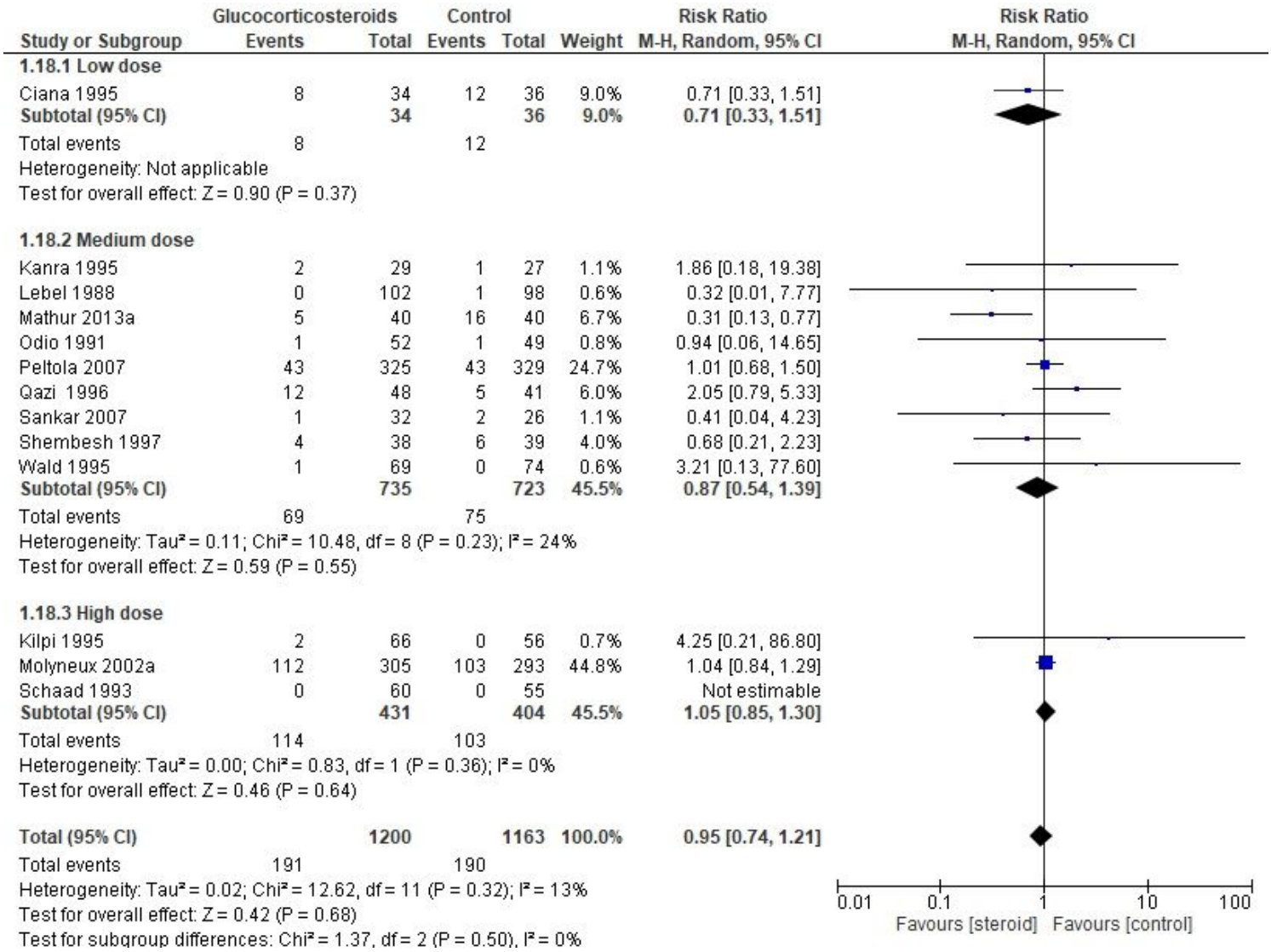

Figure 26

All-cause mortality (meningitis) – Subgroup based on dose

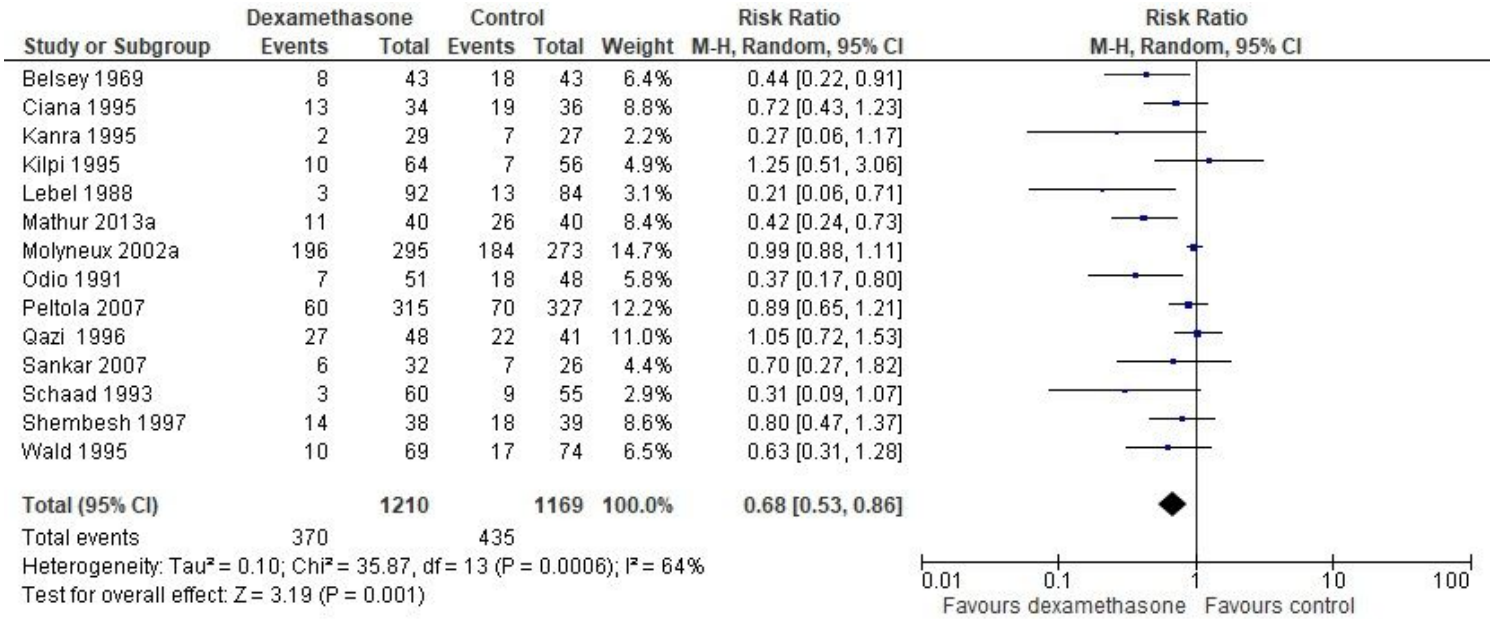

Figure 27

Serious adverse events (Meningitis)

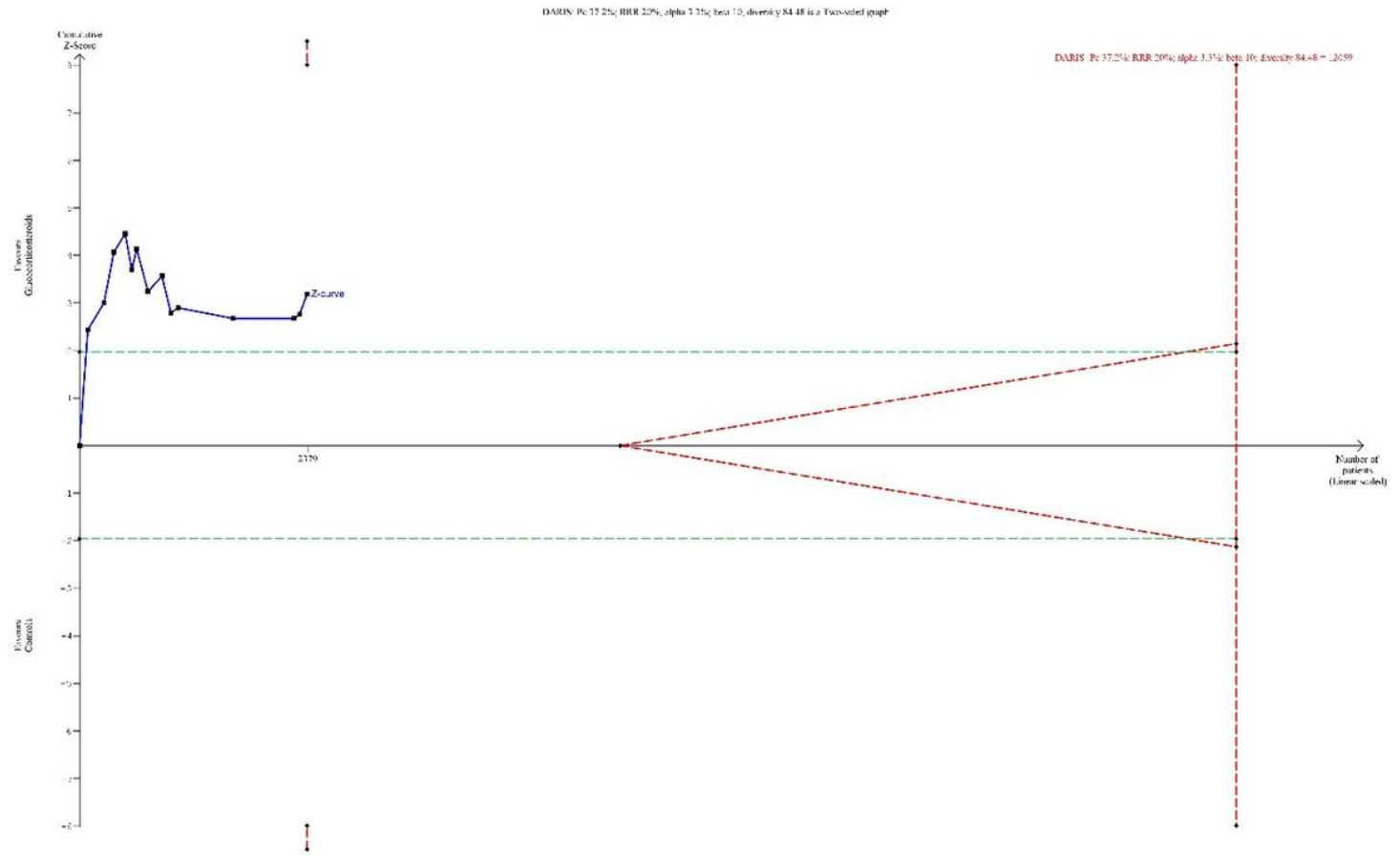

Figure 28

TSA Serious adverse events (meningitis)

Study or Subgroup	Dexamethasone Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Belsey 1969	8	43	18	43	6.6%	0.44 [0.22, 0.91]
Ciana 1995	13	34	19	36	8.7%	0.72 [0.43, 1.23]
Kanra 1995	2	29	7	27	2.4%	0.27 [0.06, 1.17]
Kilpi 1995	10	66	7	56	5.1%	1.21 [0.49, 2.97]
Lebel 1988	3	102	27	98	3.6%	0.11 [0.03, 0.34]
Mathur 2013a	11	40	26	40	8.4%	0.42 [0.24, 0.73]
Molyneux 2002a	198	307	208	295	13.7%	0.91 [0.82, 1.02]
Odio 1991	7	52	19	49	6.1%	0.35 [0.16, 0.75]
Peltola 2007	60	325	72	329	11.7%	0.84 [0.62, 1.15]
Qazi 1996	27	48	22	41	10.7%	1.05 [0.72, 1.53]
Sankar 2007	6	32	7	26	4.7%	0.70 [0.27, 1.82]
Schaad 1993	3	60	9	55	3.2%	0.31 [0.09, 1.07]
Shembesh 1997	14	38	18	39	8.6%	0.80 [0.47, 1.37]
Wald 1995	10	69	17	74	6.7%	0.63 [0.31, 1.28]
Total (95% CI)		**1245**		**1208**	**100.0%**	**0.64 [0.49, 0.82]**
Total events	372		476			

Heterogeneity: Tau² = 0.12; Chi² = 41.15, df = 13 (P < 0.0001); I² = 68%
Test for overall effect: Z = 3.50 (P = 0.0005)

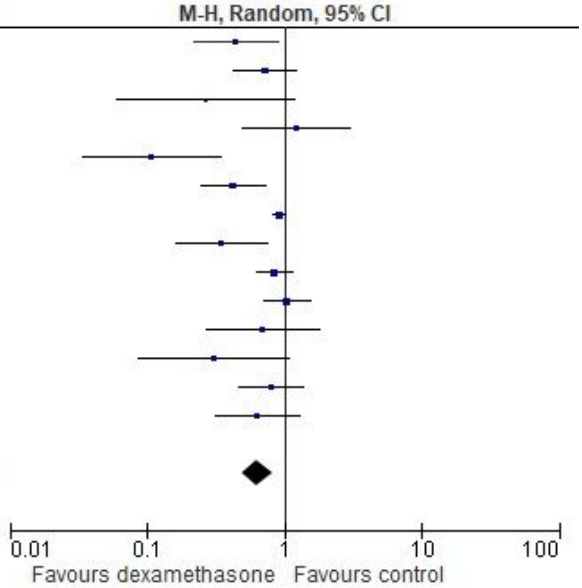

Figure 29

Serious adverse events (Meningitis) – Best-Worst

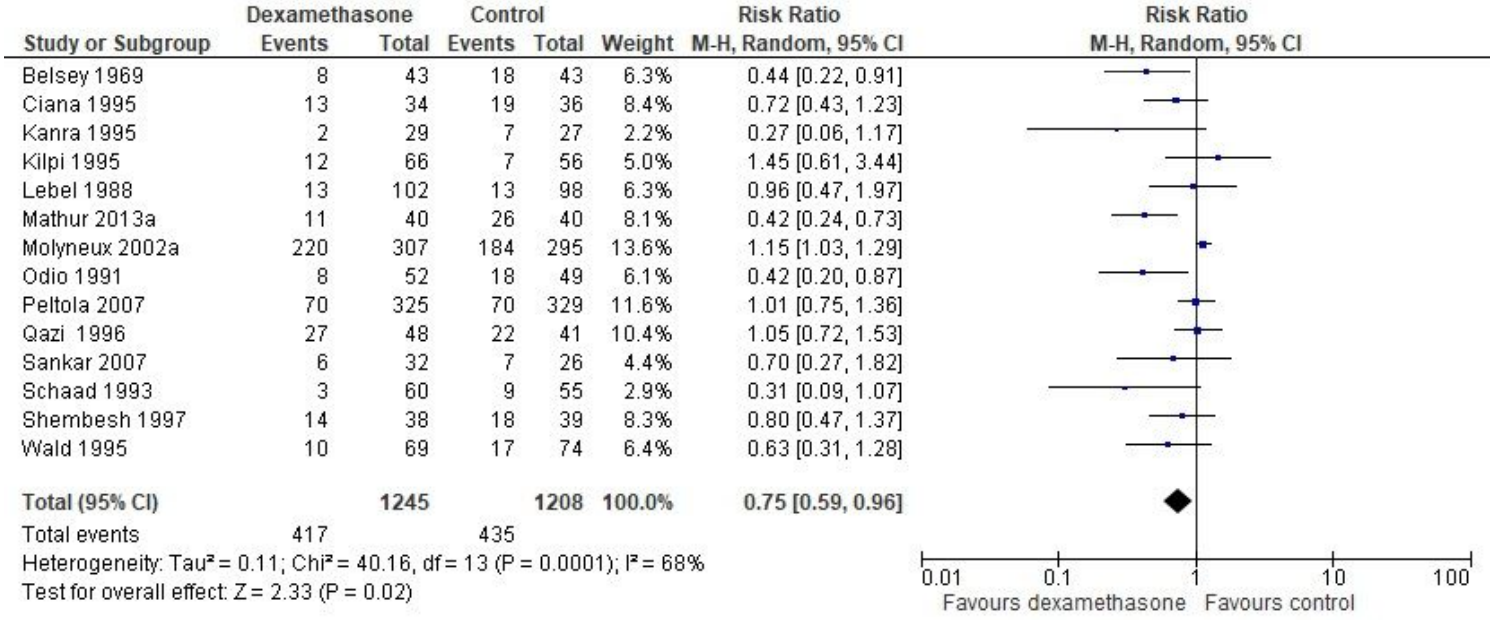

Figure 30

Serious adverse events (Meningitis) – Worst- Best

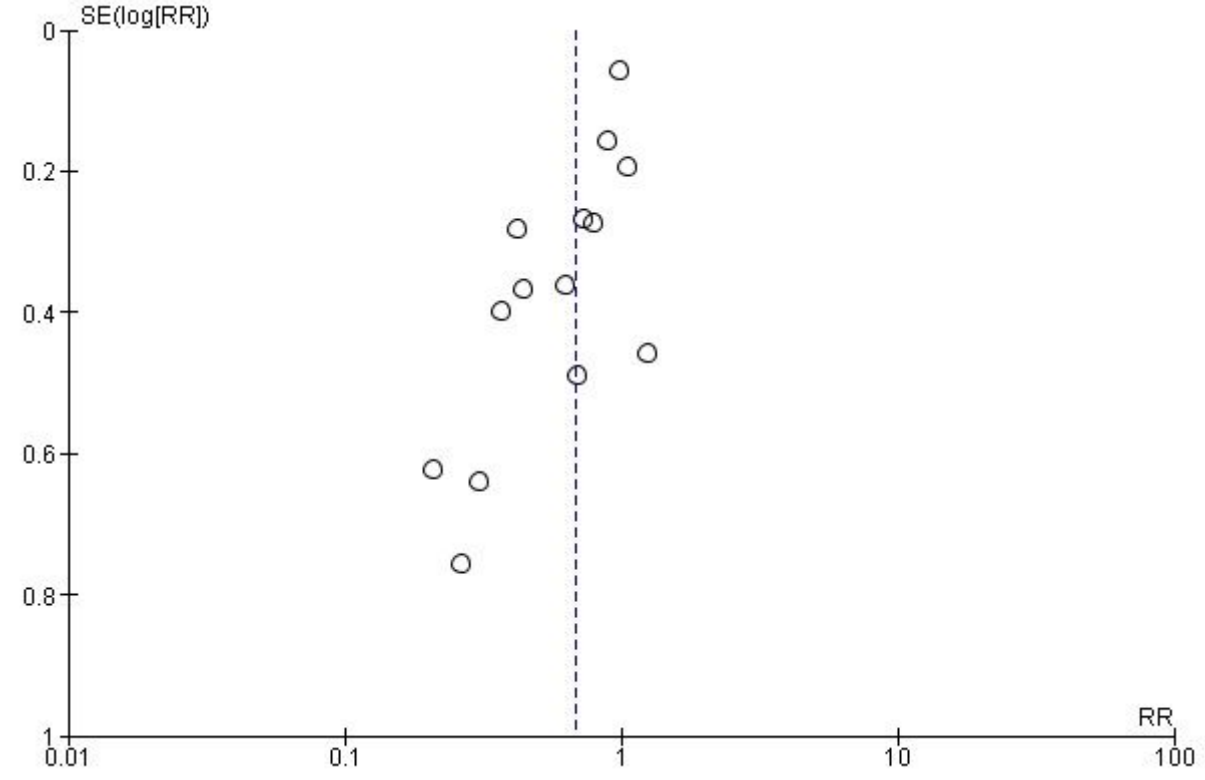

Figure 31

Funnel plot for Serious adverse events (Meningitis)

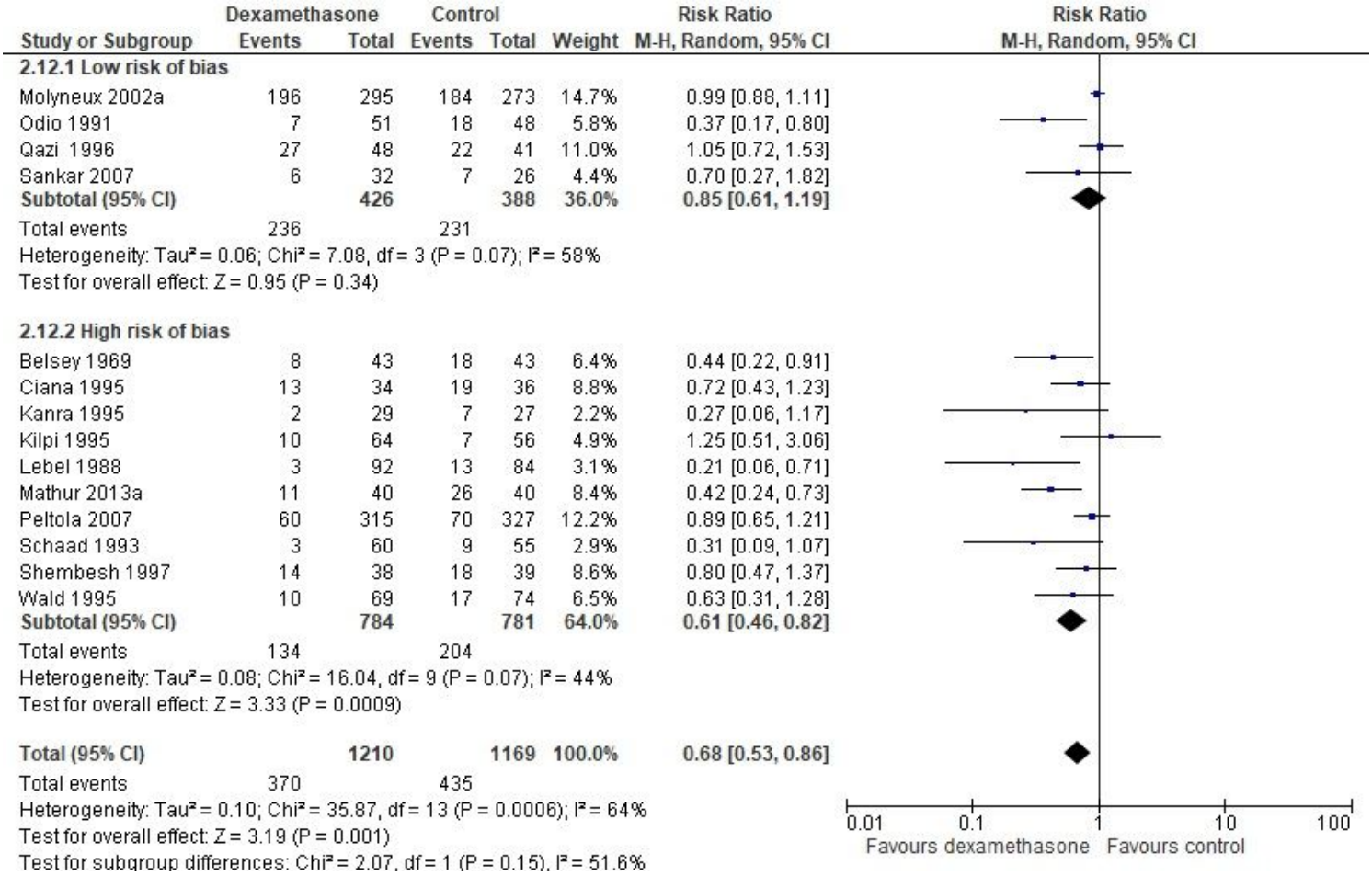

Figure 32

Serious adverse events (meningitis) – Subgroup based on risk of bias

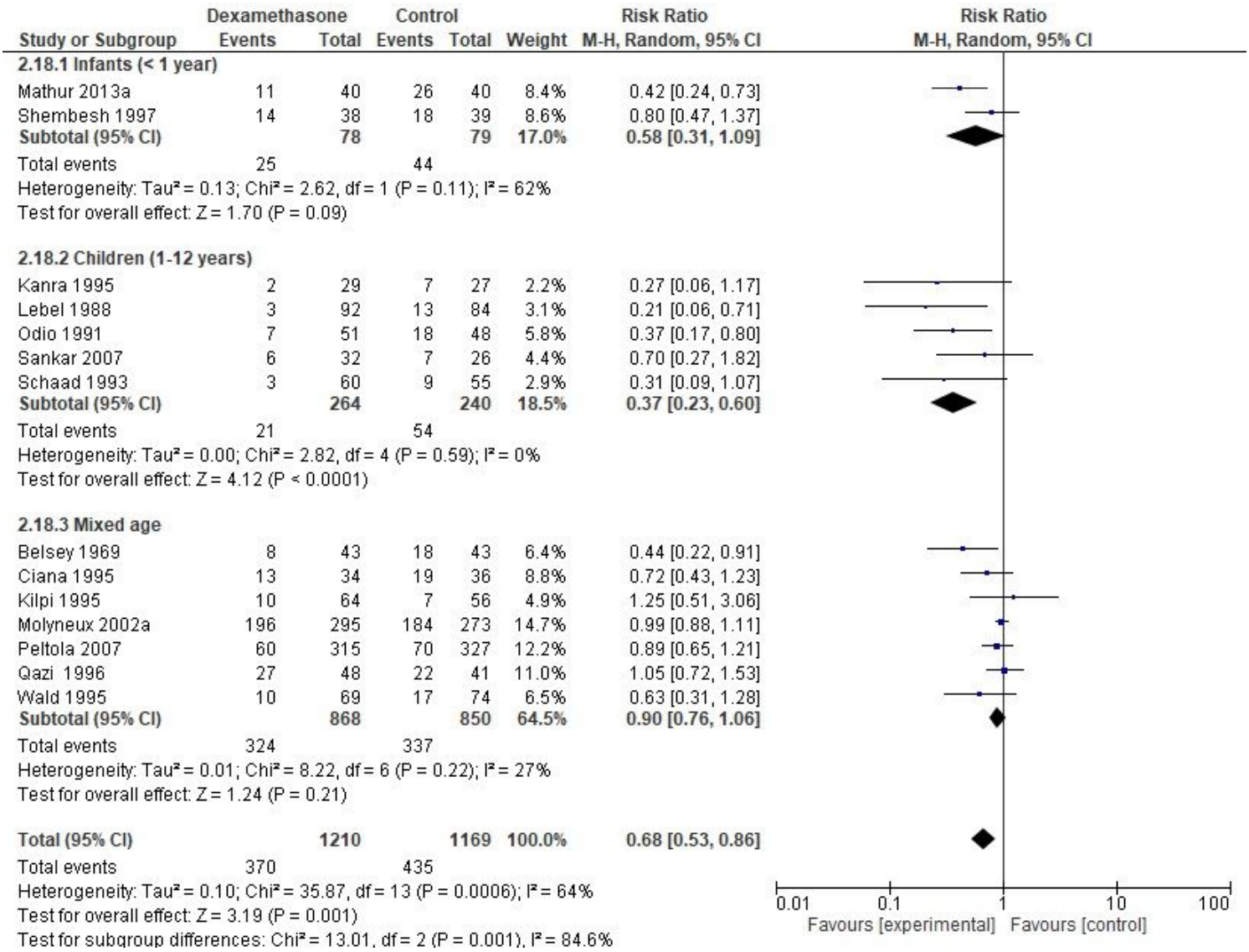

Figure 33

Serious adverse events (meningitis) – Subgroup based on age

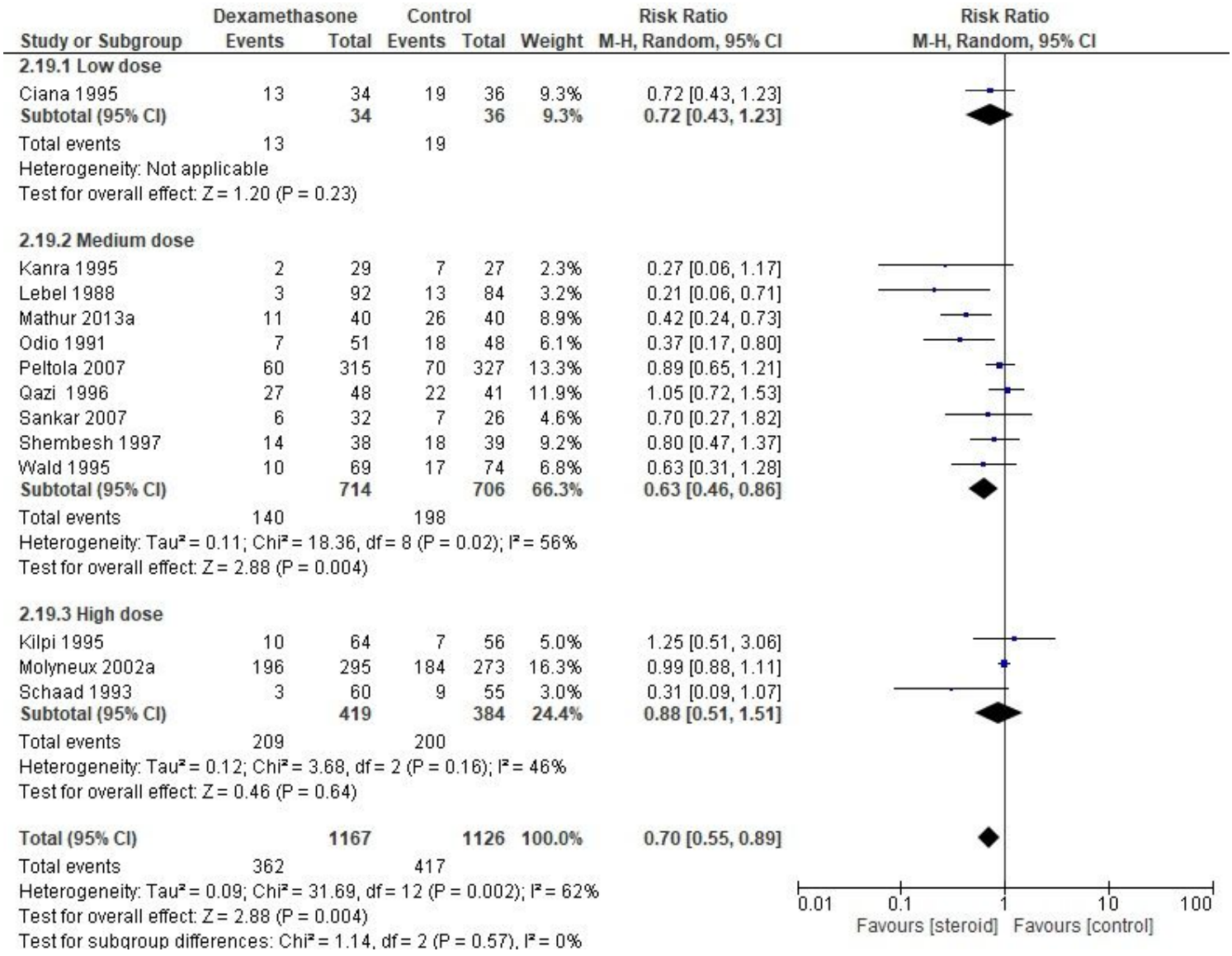

Figure 34

Serious adverse events (meningitis) – Subgroup based on dose

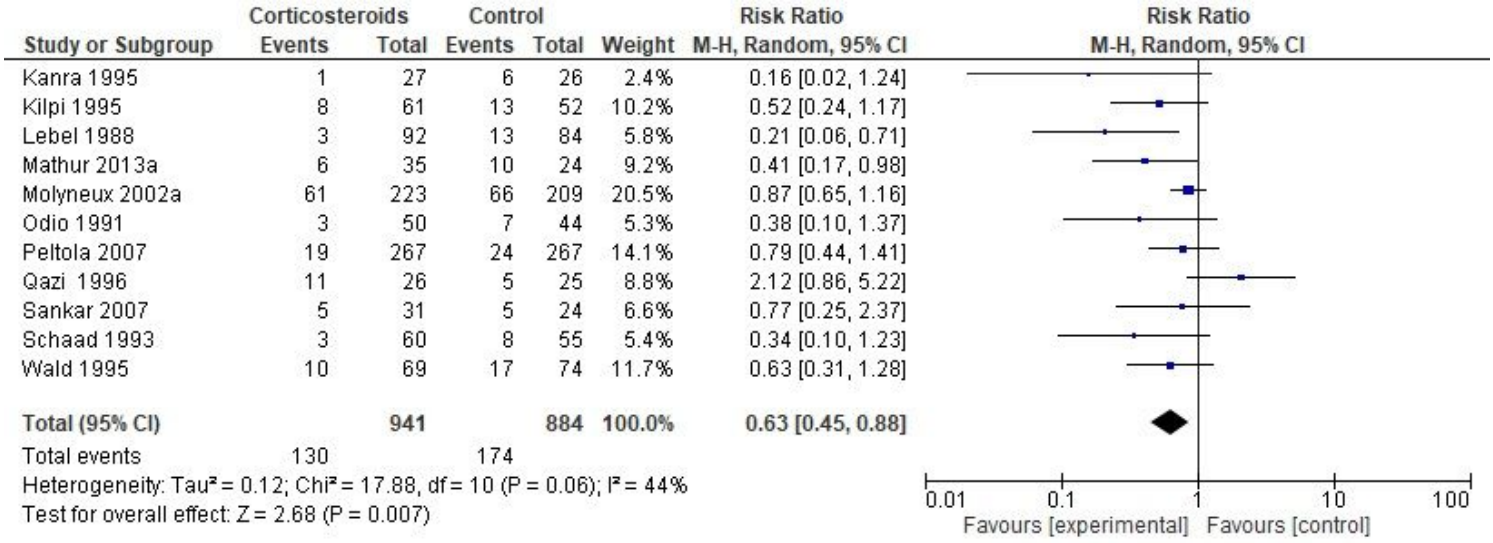

Figure 35

Forest plot of Ototoxicity (Random effects model)

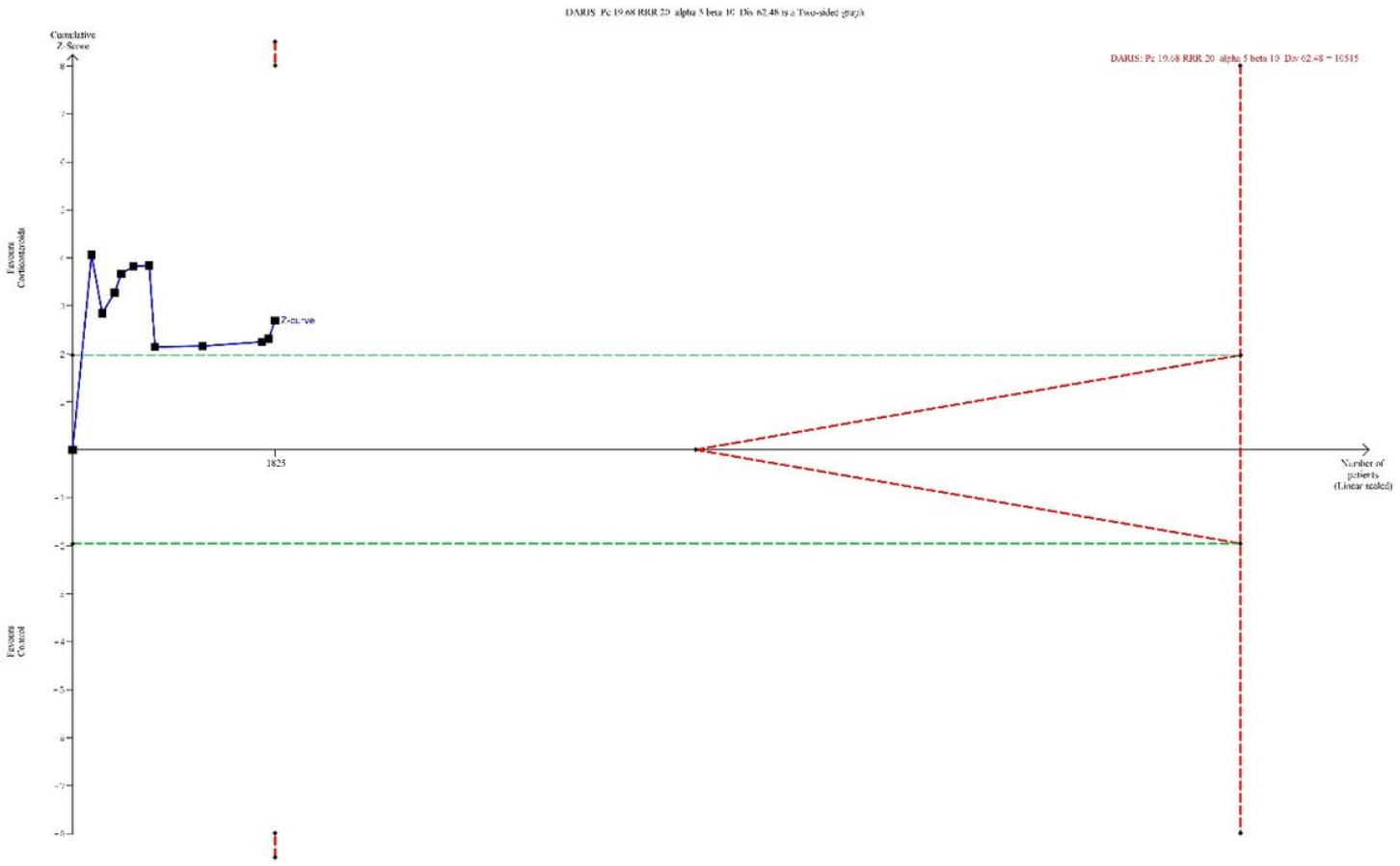

Figure 36

TSA Ototoxicity

Study or Subgroup	Dexamethasone Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ciana 1995	9	34	6	36	12.5%	1.59 [0.63, 3.99]
Lebel 1988	63	102	34	98	26.9%	1.78 [1.30, 2.43]
Molyneux 2002a	15	40	21	40	21.9%	0.71 [0.43, 1.17]
Qazi 1996	8	48	11	41	14.5%	0.62 [0.28, 1.40]
Wald 1995	31	69	25	74	24.2%	1.33 [0.88, 2.01]
Total (95% CI)		**293**		**289**	**100.0%**	**1.15 [0.76, 1.75]**
Total events	126		97			

Heterogeneity: Tau² = 0.15; Chi² = 12.89, df = 4 (P = 0.01); I² = 69%
Test for overall effect: Z = 0.65 (P = 0.52)

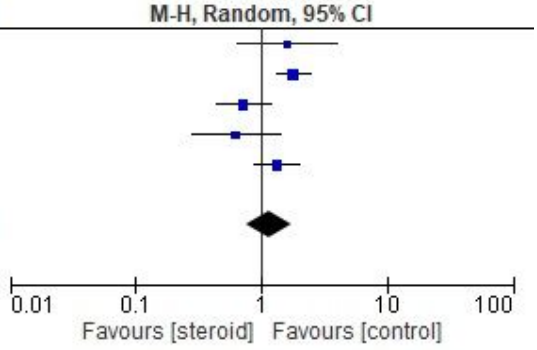

Figure 37

Adverse events (meningitis)

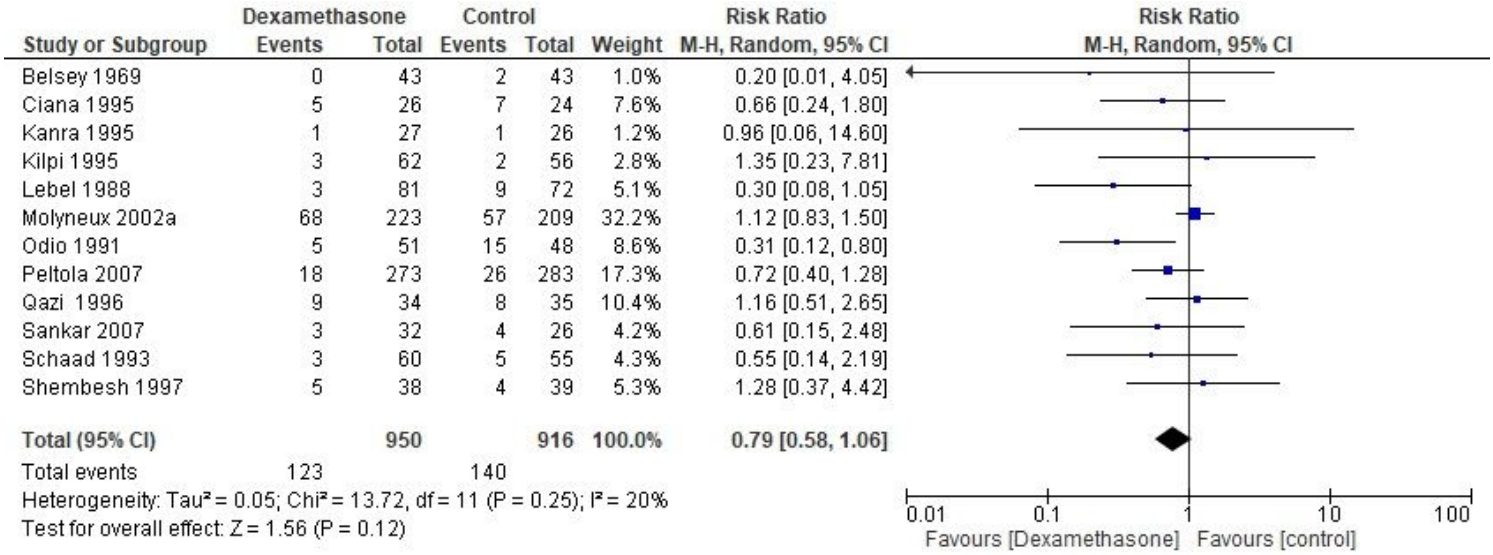

Figure 38

Forest plot of Neurological complications (Random effect)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009ChecklistBMC.doc
- SupplementarymaterialSearchstrategies.pdf
- Appendix1.pdf

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The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Steven Kwasi Korang
E-mail	Steven.korang@ctu.dk
Name of principal supervisor	Gorm Greisen
Title of the PhD thesis	Interventions for neonatal and pediatric sepsis

2. The declaration applies to the following article	
Title of article	Antibiotic regimens for early-onset neonatal sepsis
Article status	
Published ☒ Date: 17/5-2021	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	Korang SK, Safi S, Nava C, Gordon A, Gupta M, Greisen G, et al. Antibiotic regimens for early-onset neonatal sepsis. Cochrane Database Syst Rev [Internet]. 2021 [cited 2021 May 18];(5). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013837.pub2/full

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	A

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.[i] I drafted the protocol and review, extracted data, co-ordinated the review, conceived the review, designed the review, analyzed the data, interpreted the data providing a methodological and clinical view, and revised the review.	

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authors[iii]				
	Date	**Name**	**Title**	**Signature**

5. Signatures of the co-authors[iii]				
1.	29. jun. 2021	Janus Christian Jakobsen	Professor	Janus Jakobsen (29. Jun 2021 12:41 GMT+2)
2.	29. jun. 2021	Sanam Safi	Medical student	Sanam safi (29. Jun 2021 08:20 EDT)
3.	29. jun. 2021	Chiara Nava	MD	Chiara Nava (29. Jun 2021 16:47 GMT+2)
4.	1. jul. 2021	Ulrik Lausten-Thomsen	MD, PhD	Ulrik Lausten-Thomsen (1. Jul 2021 17:29 GMT+2)
5.	1. jul. 2021	Adrienne Gordon	Professor	
6.	1. jul. 2021	Munish Gupta	MD	Munish Gupta
7.	1. jul. 2021	Gorm Greisen	Professor	
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 1. jul. 2021

Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 2. jul. 2021

PhD student: Steven Kwasi Korang

Steven Kwasi Korang (2. Jul 2021 23:53 GMT+2)

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."

[iii] If more signatures are needed please add an extra sheet.

DECLARATION OF CO-AUTHORSHIP

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1. Declaration by	
Name of PhD student	Steven Kwasi Korang
E-mail	Steven.korang@ctu.dk
Name of principal supervisor	Gorm Greisen
Title of the PhD thesis	Interventions for neonatal and pediatric sepsis

2. The declaration applies to the following article	
Title of article	Antibiotic regimens for late-onset neonatal sepsis
Article status	
Published ☒ Date: 8/5-2021	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	Korang SK, Safi S, Nava C, Greisen G, Gupta M, Lausten-Thomsen U, et al. Antibiotic regimens for late-onset neonatal sepsis. Cochrane Database Syst Rev [Internet]. 2021 [cited 2021 May 18];(5). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013836.pub2/full

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
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2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.[i] I drafted the protocol and review, extracted data, co-ordinated the review, conceived the review, designed the review, analyzed the data, interpreted the data providing a methodological and clinical view, and revised the review.	

4. Material from another thesis / dissertation[ii]	
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If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

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2.	29. jun. 2021	Sanam Safi	Medical student	Sanam Safi (29. Jun 2021 08:21 EDT)
3.	29. jun. 2021	Chiara Nava	MD	Chiara Nava (29. Jun 2021 16:48 GMT+2)
4.	30. jun. 2021	Ulrik Lausten-Thomsen	MD, PhD	Ulrik Lausten-Thomsen (30. Jun 2021 16:28 GMT+2)
5.	29. jun. 2021	Munish Gupta	MD	Munish Gupta
6.	2. jul. 2021	Gorm Greisen	Professor	
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 2. jul. 2021

Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 2. jul. 2021

PhD student: Steven Kwasi Korang

Steven Kwasi Korang (2. Jul 2021 23:52 GMT+2)

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[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

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Name of PhD student	Steven Kwasi Korang
E-mail	Steven.korang@ctu.dk
Name of principal supervisor	Gorm Greisen
Title of the PhD thesis	Interventions for neonatal and pediatric sepsis

2. The declaration applies to the following article	
Title of article	The effects of adding glucocorticosteroids to standard care for children with sepsis. A systematic review of randomized clinical trials with meta-analysis and Trial Sequential Analysis
Article status	
Published ☒ Date: 11/3-2021	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	Korang SK, Safi S, Gluud C, Jakobsen JC. The effects of adding glucocorticosteroids to standard care for children with sepsis. A systematic review of randomized clinical trials with meta-analysis and Trial Sequential Analysis [Internet]. 2021 [cited 2021 Apr 18]. Available from: https://www.researchsquare.com

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1. Formulation/identification of the scientific problem	A

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2. Development of the key methods	A
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.[i] I drafted the protocol and review, extracted data, co-ordinated the review, conceived the review, designed the review, analyzed the data, interpreted the data providing a methodological and clinical view, and revised the review.	

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If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	

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	Date	**Name**	**Title**	**Signature**

5. Signatures of the co-authors[iii]				
1.	29. jun. 2021	Janus Christian Jakobsen	Professor	Janus Jakobsen (29. Jun 2021 12:42 GMT+2)
2.	29. jun. 2021	Christian Gluud	Professor	C Gluud (29. Jun 2021 17:17 GMT+2)
3.	29. jun. 2021	Sanam Safi	Medical student	Sanam Safi (29 Jun 2021 08:23 EDT)
4.				
5.				
6.				
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 30. jun. 2021

Principal supervisor:

7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.

Date: 30. jun. 2021

PhD student: Steven Kwasi Korang
Steven Kwasi Korang (30. Jun 2021 00:27 GMT+2)

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."

[iii] If more signatures are needed please add an extra sheet.