

Antibiotics for hospital-acquired pneumonia in neonates and children

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Antibiotics for hospital-acquired pneumonia in neonates and children (Protocol)

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[Intervention Protocol]

Antibiotics for hospital-acquired pneumonia in neonates and children

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ABSTRACT

Objectives

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

To assess the beneficial and harmful effects of different antibiotic regimens for hospital-acquired pneumonia in neonates and children.

BACKGROUND

Description of the condition

Hospital-acquired pneumonia (also known as nosocomial pneumonia) is defined as pneumonia that occurs 48 hours or more after admission to hospital and that was not present at the time of 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 (Ford-Jones 1989; Polin 2012; Richards 1999; 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) (Brown 1985; Iosifidis 2018; Milliken 1988; Polin 2012; Stein 1994; Zingg 2017). The incidence of hospital-acquired infections in medical and surgical paediatric patients seems to be similar (Stein 1994).

Hospital-acquired pneumonia is one of the most common hospital-acquired infections in children worldwide (Richards 2000). Hospital-acquired pneumonia in neonates and children accounts for 6.8% to 32.3% of all hospital-acquired infections (Jarvis 1991; 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). Paediatric hospital-acquired pneumonia infections have been shown to be associated with increased mortality (Bigham 2009; Iosifidis 2018; Milliken 1988).

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 reported incidence of ventilator-associated pneumonia in the PICU setting ranges from 2.9 to 11.6 ventilator-associated pneumonia 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).

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).

The most common pathogens involved in hospital-acquired pneumonia worldwide are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterobacteriaceae* (Jones 2010; Patel 2000; Srinivasan 2009; van der Zwet 2005; Weiner-Lastinger 2020). 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). Several observational studies show that infections caused by multidrug-resistant (MDR) pathogens increase the risk of death, length of stay, and healthcare costs (Cosgrove 2006; Maragakis 2008).

Risk factors for hospital-acquired pneumonia are prolonged hospitalisation, serious underlying illnesses (e.g. lung disease, immune deficiency), recent antimicrobial therapy, immunosuppression, genetic syndromes, steroid use, reintubation or self-extubation, bloodstream infection, and bronchoscopy (Aelami 2014; Liu 2013; Stein 1994). Newborns, pretermes, and infants are especially prone to infections, due to a developmental deficiency in the innate, adaptive immune systems, usage of endotracheal tubes 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, but they are associated with different kinds of pathogens (Mourani 2017; Polin 2012). One antibiotic regimen for all patients might therefore not be warranted.

The onset of ventilator-associated pneumonia is also a risk factor associated with specific pathogens and prognosis (Ewig 1999; 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).

Diagnosis

The diagnosis of hospital-acquired pneumonia and ventilator-associated pneumonia is based upon a new lung infiltrate (e.g. x-ray image) plus clinical evidence that the infiltrate is of an infectious origin, which may include the new onset of fever, leukocytosis, purulent sputum, and a decline in oxygenation (Kalil 2016). 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/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; Torres 2017).

When there is a 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).

When 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 aminoglycosides and colistin are not recommended, unless alternative agents with adequate gram-negative activity are unavailable (Kalil 2016).

How the intervention might work

As hospital-acquired pneumonia is a bacterial infection, one of the main objectives of treatment 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 2019b).

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). The current guidelines are directed solely towards adults (Kelly 2019; Martin-Loeches 2018). Most of our understanding of hospital-acquired pneumonia in children has derived from adult studies, but there exists many differences between neonates/children and adults regarding 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 former 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 will include randomised clinical trials reported as full text, abstract only, and unpublished data. We will exclude trials with cross-over design and cluster-randomised trials.

Types of participants

We will include 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 will include trials comparing one antibiotic regimen with any other antibiotic regimen or placebo. We will include 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, ceftoxitin, ceftriaxone, cefepime, ceftazidime, ceftobiprole, and cefoperazone).
 - e. Carbapenems (e.g. meropenem, imipenem, doripenem, and ertapenem).
 - f. Monobactams (aztreonam).
2. Aminoglycosides (e.g. amikacin, tobramycin, and gentamycin).
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 2019a](#)).

We also plan 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 will use 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 do not use the ICH-GCP definition, we will include the data if the trialists use the term 'serious adverse event'. If the trialists do not use the ICH-GCP definition or this term, then we will include the data if the event clearly fulfils the ICH-GCP definition for a serious adverse event. We will exploratorily assess each type of serious adverse event separately ([Korang 2020](#)).

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 (see above). We will assess each reported adverse event separately.
4. Proportion of participants with treatment failure. We will define treatment failure as clinical deterioration or recurrence of clinical signs leading to any modification of the assigned empirical antibiotic treatment (we will accept similar definitions as defined by the trialists).

We will use the trial results reported at closest to one month as our primary time point of interest for all outcomes.

Search methods for identification of studies

Electronic searches

We will search the following databases from inception to present.

1. the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (latest issue).
2. MEDLINE Ovid (PubMed) (from 1946 to present).
3. Embase Ovid (from 1974 to present).

We will also search the following databases, if relevant.

1. CINAHL via EBSCOhost (Cumulative Index to Nursing and Allied Health Literature) (from 1961 to present).
2. PsycINFO via EBSCOhost (from 1967 to present).
3. Science Citation Index Expanded (Web of Science) (from 1900 to present) and Conference Proceedings Citation Index – Science (Web of Science) (from 1990 to present).
4. LILACS (Latin American and Caribbean Health Science Information database) (from 1982 to present).

We will use the search strategy described in [Appendix 1](#) to search MEDLINE. We will combine the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for randomised trials: sensitivity and precision-maximising version (2008 revision) ([Lefebvre 2011](#)).

We will also conduct a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

Searching other resources

We will check the reference lists of all primary studies and review articles for additional references. We will contact experts in the field to identify additional unpublished materials.

In order to identify unpublished trials, we will search clinical trial registers of Europe and the USA, websites of pharmaceutical companies, and the websites of the US Food and Drug Administration (FDA) and the European Medicines Agency.

We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and report the date this was searched in the review.

Data collection and analysis

Selection of studies

Two review authors (SKK, CN) will independently screen the titles and abstracts of records identified by the search for potential

inclusion in the review. We will retrieve selected full-text study reports/publications, and two review authors (SKK, CN) will independently screen the full-texts and identify trials for inclusion, and identify and record reasons for exclusion of the ineligible studies. Any disagreements will be resolved through discussion or by consulting a third review author (JCJ) if required. We will exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009). We will not impose any language or publication restrictions.

Data extraction and management

We will use a data collection form to record study characteristics and outcome data which we will pilot on at least one study in the review. One review author (SKK or CN) will extract trial characteristics from the included trials. We will extract the following trial characteristics (see Table 1):

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.

Two review authors (SKK, CN) will independently extract outcome data from the included trials. We will note in the 'Characteristics of included studies' table if outcome data are not reported in a useable way. Any disagreements will be resolved by consensus or by consulting a third review author (JCJ). One review author (SKK) will enter the data into Review Manager 5 software (Review Manager 2020). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports.

Assessment of risk of bias in included studies

Two review authors (SKK, CN) will independently assess the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). Any disagreements will be resolved by discussion or by involving another review author (JCJ). We will assess 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 will grade each potential source of bias as low, high, or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider the domains of blinding of outcome assessment, incomplete outcome data, and selective outcome reporting separately for different key outcomes, where necessary. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Overall risk of bias

We will assess overall risk of bias in three groups, as follows.

1. Low risk of bias: we will classify the outcome result of a trial as overall 'low risk of bias' only if all domains are classified as at low risk of bias.
2. Unclear risk of bias: we will classify the outcome result of a trial as overall 'unclear' risk of bias if one or more domains are classified as unclear, and no domain is at high risk of bias.
3. High risk of bias: we will classify the outcome result of a trial as overall 'high risk of bias' if at least one domain is classified as high risk of bias.

See Appendix 2 for further details.

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

Measures of treatment effect

We will enter 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 will calculate risk ratios (RRs) with 95% confidence interval (CI) for dichotomous outcomes.

Continuous outcomes

We will calculate the mean differences (MDs) and the standardised mean difference (SMD) with 95% CI for continuous outcomes.

We will only perform meta-analysis if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.

Unit of analysis issues

The unit of analysis will be the participating children in individually randomised trials.

Dealing with missing data

We will contact investigators to obtain missing outcome data where possible. If this is not possible, we will explore the impact of missing data in a sensitivity analysis (Sensitivity analysis).

If numerical outcome data such as standard deviations or correlation coefficients are missing, and they cannot be obtained from the authors, we will 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 2020).

We will not impute missing values for any outcomes in our primary analysis. We will impute data in two of our sensitivity analyses (see Sensitivity analysis).

Assessment of heterogeneity

We will visually inspect forest plots to evaluate signs of heterogeneity, and we will explore possible heterogeneity in our prespecified subgroup analyses. We will also inspect trial characteristics across trials to identify clinical heterogeneity. We will assess the presence of statistical heterogeneity by the χ^2 test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the I^2 statistic (Higgins 2002; Higgins 2003). If we detect moderate or high heterogeneity, we will explore the possible causes (e.g. differences in study design, participants, interventions, or completeness of outcome assessments) (Korang 2019a).

We will define 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 may ultimately decide that a meta-analysis should be avoided if the level of heterogeneity indicates that the pooling of data is not justified (Higgins 2020).

Assessment of reporting biases

We will use a funnel plot to assess publication bias only if we include 10 or more trials. We will visually inspect funnel plots to assess the risk of bias. We will test asymmetry with the Harbord test (Harbord 2006).

Data synthesis

We will pool data from trials we judge to be clinically homogeneous. We will only perform meta-analysis if more than one trial provides relevant data in any single comparison.

Meta-analysis

We will undertake meta-analyses according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020). We will use Review Manager 5 software (Review Manager 2020).

We will assess our intervention effects with both fixed-effect meta-analyses and random-effects meta-analyses (DeMets 1987; DerSimonian 1986). We will use the more conservative point estimate of the two. We will consider the point estimate closest to zero effect as the more conservative point (Jakobsen 2014).

As we have chosen two primary outcomes, we will consider a P value of 0.033 or less as the threshold for evidence of a difference (Jakobsen 2014). We plan to use the eight-step procedure provided by Jakobsen and colleagues to assess if the threshold for any evidence of a difference is crossed (Jakobsen 2014). Our primary conclusion will be based on results with low risk of bias (Jakobsen 2014). Where data are available from only one trial, we will use Fisher's exact test for dichotomous data (Fisher 1922).

If multiple comparisons are reported in a single trial, we will only include the relevant comparisons. If two comparisons are used in the same meta-analysis, we will halve the control group to avoid double-counting.

If the ranking of the identified interventions is unclear based on aggregating the meta-analysis results, we will perform a network meta-analysis.

Network meta-analysis

We will 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 consists of all the antibiotic regimens listed in Types of interventions as well as a placebo. We will analyse each specific antibiotic regimen separately.

We will generate descriptive statistics for each treatment comparison describing important clinical and methodological characteristics (e.g. publication year, participant age). Each outcome data set will be presented in a different network diagram, where the size of the nodes will be proportional to the total number of randomised participants, and the width of each edge will be weighted according to the number of studies comparing the connected treatments. We will 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 anticipate that any participant who meets the inclusion criteria is, in principle, equally likely to be randomised to any of the interventions in the synthesis comparator set. Network meta-analysis will be performed 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 will only perform network meta-analysis if a connected network of trials can be conducted (Mills 2013).

If network meta-analysis is possible, we will assess a priori the two prerequisite assumptions: transitivity and consistency. We will assess for the transitivity assumption across treatment comparisons in the network using box plots, and will evaluate the assumption of consistency using the design-by-treatment interaction model as a global test (Higgins 2003; Shim 2017). Effect modifiers will 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). The transitivity assumption for carrying out a network meta-analysis

will be evaluated using these effect modifiers. We will also explore these through network subgroup meta-analyses. If we conclude that the transitivity and consistency assumptions are not met, we will not perform network meta-analysis, but will present direct and indirect evidence separately.

The estimation of each treatment comparison will be reported separately using the relevant effect size (RR), a 95% CI, and a 95% prediction interval. We will 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 will 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 will use a rank-heat plot to depict the SUCRA values (and their 95% CI) across all outcomes (Veroniki 2016).

We will 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).

In addition to the primary meta-analysis, we plan to use Trial Sequential Analysis (TSA) as a secondary analysis (see Appendix 3).

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. High risk of bias trials compared to low risk of bias trials.
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 versus diagnosed pneumonia (verified by radiological findings or culture of respiratory specimens) at randomisation.
5. Empirical compared to targeted treatment based on bacterial cultures.
6. Hospital-acquired pneumonia compared to ventilator-associated pneumonia.
7. Early-onset compared to late-onset, defined as onset of pneumonia before or after four days.
8. Length of antibiotic treatment: 3 days or shorter, 4 to 5 days, 6 to 7 days, or longer than 7 days.
9. Participants without underlying diseases compared to participants with underlying diseases such as genetic syndromes, lung disease, or immune deficiency.

We will use the Chi² test to test for subgroup interactions in Review Manager 5 (Review Manager 2020).

Sensitivity analysis

To assess the potential impact of missing data, we will perform two sensitivity analyses on the primary outcomes, as follows.

1. 'Best-worst-case' scenario: we will assume that all participants lost to follow-up in the experimental group survived and had no serious adverse event. We will assume 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 will assume that all participants lost to follow-up in the experimental group did not survive and had a serious adverse event. We will assume that all those participants lost to follow-up in the control group survived and had no serious adverse event (Jakobsen 2014).

We will present the results of both scenarios in our review.

Summary of findings and assessment of the certainty of the evidence

We will create a 'Summary of findings' table reporting our primary outcomes of all-cause mortality and serious adverse events, and secondary outcomes of health-related quality of life, pneumonia-related mortality, non-serious adverse events, and treatment failure. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality 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 will use 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 will justify all decisions to down- or upgrade the quality of studies using footnotes and will make comments to aid the reader's understanding of the review where necessary.

If we perform a network meta-analysis, we will also use CINeMA to assess the quality of a body of evidence (Guyatt 2008; Guyatt 2011b; Schünemann 2003).

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ADDITIONAL TABLES
Table 1. 'Characteristics of included studies' table template

Methods	Study design (e.g. parallel RCT) Study duration: date of first recruitment to last follow-up Date of trial:
Participants	Inclusion criteria Setting: e.g. outpatient, inpatient, multicentre, national/international Country: list all countries Relevant health status: Number: treatment (N = x); control (N = x) Withdrawals/lost to follow-up: Age (mean, SD/median, range) Treatment group: Control group:

Table 1. 'Characteristics of included studies' table template *(Continued)*

	Sex (M/F): treatment (N/N M/F); control (N/N M/F) Any other relevant info, such as comorbidities Exclusion criteria <list>
Interventions	Treatment group Intervention Dose, duration, frequency, administration Other relevant info Control group Intervention (e.g. placebo, no treatment) Dose, duration, frequency, administration Other relevant info
Outcomes	Primary outcomes <list> Secondary outcomes <list> Note: describe the methods used to measure the outcomes Time points reported:
Notes	Declarations of interest: Funding source: Contact with study authors for additional information: Other:

m/f: male/female

N: number

RCT: randomised controlled trial

SD: standard deviation

APPENDICES

Appendix 1. Search strategy

Cochrane Central Register of Controlled Trials in the Cochrane Library:

#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 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 ceftazidime or ceftobiprole or ceftriaxone or cefuroxime or cephalixin 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

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 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 ceftazidime or ceftobiprole or ceftriaxone or cefuroxime or cephalixin 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

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 ceftazidime or ceftobiprole or ceftriaxone or cefuroxime or cephalixin 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

(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 ceftazidime or ceftobiprole or ceftriaxone or cefuroxime or cephalixin 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]

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#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 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 ceftazidime or cefepime or cefoperazone or cefotaxime or cefotetan or ceftazidime or ceftazidime or ceftobiprole or ceftriaxone or cefuroxime or cephalixin 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*)

Appendix 2. 'Risk of bias' assessment

Allocation sequence generation

1. Low risk: if sequence generation was achieved using 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 was 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, on-site locked computer, identical-looking numbered, sealed envelopes, drug bottles or containers prepared by an independent pharmacist or investigator.
2. Uncertain 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 (except the one prescribing the interventions to adjust the blood pressure) were blinded to intervention allocation, and this was described.
2. Uncertain 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. Uncertain risk of bias: if it was not mentioned if the outcome assessors in the trial were blinded, or the extent of blinding was 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 could be described as being similar in both 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. Uncertain 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 will grant the trial a grade of low risk of bias.
2. Uncertain 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

We will assess overall risk of bias in three groups, defined as follows.

1. Low risk of bias: we will classify the outcome result of a trial as overall 'low risk of bias' only if all domains are classified as at low risk of bias.
2. Unclear risk of bias: we will classify the outcome result of a trial as overall 'unclear' risk of bias if one or more domains are classified as unclear, and no domain is at high risk of bias.
3. High risk of bias: we will classify the outcome result of a trial as overall 'high risk of bias' if at least one domain is classified as high risk of bias.

We will grade each potential source of bias as low, high, or unclear and provide a quote from the trial report together with a justification for our judgement in the 'Risk of bias' table. We will 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 will summarise 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 will note this in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for the trials that contribute to that outcome.

Appendix 3. Trial Sequential Analysis

Trial Sequential Analysis (TSA)

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, and the heterogeneity of the meta-analysis (Turner 2013; Wetterslev 2009).

For dichotomous outcomes, previous data suggest the effect size to be a relative risk reduction of 20%. However, we will estimate the required information size based on the proportion of participants with an outcome in the control group and a relative RR of 7.5% (a bit more conservative than the existing data), 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 will use the limit of the confidence interval closest to 1.00 as the anticipated intervention effect (Jakobsen 2014). Additionally, we will calculate 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 will estimate 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 will use the limit of the confidence interval closest to 0.00 as the anticipated intervention effect (Jakobsen 2014). Additionally, we will calculate TSA-adjusted confidence interval.

HISTORY

Protocol first published: Issue 1, 2021

CONTRIBUTIONS OF AUTHORS

Steven Kwasi Korang (SKK), Chiara Nava (CN), Ulrikka Nygaard (UN), Janus C Jakobsen (JCJ)

Conceiving the protocol: SKK and CN

Co-ordinating the protocol: SKK

Writing the protocol: SKK and CN

Designed the protocol: SKK, CN, and JCJ

Guarantor for the protocol (one author): SKK

Revising the protocol: SKK, CN, UN, and JCJ

Person responsible for reading and checking protocol before submission: SKK, CN, UN, and JCJ

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: none known

Chiara Nava: none known

Ulrikka Nygaard: none known

Janus C Jakobsen: none known