Cochrane Library

Cochrane Database of Systematic Reviews

Antibiotics for treatment of leptospirosis (Protocol)

Mukadi P, Tabei K, Edwards T, Brett-Major DM, Smith C, Kitashoji E, Win TZ

Mukadi P, Tabei K, Edwards T, Brett-Major DM, Smith C, Kitashoji E, Win TZ.
Antibiotics for treatment of leptospirosis (Protocol).
Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD014960.
DOI: 10.1002/14651858.CD014960.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Antibiotics for treatment of leptospirosis

Patrick Mukadi[1,2,3], Kozue Tabei[4], Tansy Edwards[5], David M Brett-Major[6], Chris Smith[4,7], Emi Kitashoji[1], Tin Zar Win[4]

[1]Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan. [2]Program for Nurturing Global Leaders in Tropical and Emerging Communicable Diseases, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan. [3]Institut National de Recherche Biomedicale (INRB), Kinshasa , DRC. [4]School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan. [5]Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK. [6]Department of Preventive Medicine and Biometrics, Uniformed Services University, Bethesda, Maryland, USA. [7]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK

Contact: Chris Smith, christopher.smith@lshtm.ac.uk.

Editorial group: Cochrane Hepato-Biliary Group.
Publication status and date: New, published in Issue 5, 2022.

Citation: Mukadi P, Tabei K, Edwards T, Brett-Major DM, Smith C, Kitashoji E, Win TZ.Antibiotics for treatment of leptospirosis (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 5. Art. No.: CD014960. DOI: 10.1002/14651858.CD014960.

ABSTRACT

Objectives

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

To assess the beneficial and harmful effects of antibiotics versus placebo, no intervention, or another antibiotic for the treatment of people with leptospirosis

BACKGROUND

Description of the condition

Leptospirosis is a zoonotic and waterborne disease caused by bacteria of the genus *Leptospira* and is distributed worldwide. Animals such as cattle, pigs, horses, dogs, and rodents carry *Leptospira* bacteria. It can be transmitted to humans through contact with water, soil, or food contaminated with the urine of infected animals. *Leptospira* bacteria generally enter the human body through mucous membranes and skin, especially through abraded skin (Bharti 2003; Levett 2001).

It is estimated that approximately 59,000 people die each year from leptospirosis and more than one million people are infected with it worldwide. However, there are no reliable global incidence data for leptospirosis as it may be under-reported (Costa 2015). Leptospirosis is widespread worldwide, especially in the tropics, where outbreaks following heavy rainfall and flooding cause considerable mortality and mobility (Suneth 2011). The global burden of leptospirosis is substantial. In 2015, leptospirosis was reported to have caused an estimated 2.90 million disability-adjusted life years (DALYs per year), with most instances occurring in low- and middle-income tropical countries (Torgerson 2015). The incidence of leptospirosis was highest in Oceania, South-East Asia, the Caribbean, and East Sub-Saharan Africa (Costa 2015).

The clinical picture of leptospirosis is broad and overlaps with the symptoms of several other diseases. It can have a 'biphasic' pattern, with an initial non-specific phase lasting one week, followed by a complicating immune phase in the second week (Farrar 2014). Most people with leptospirosis present with only mild, self-limiting influenza-like symptoms and may not seek medical attention. Symptoms can include headache, myalgia, backache, abdominal pain, conjunctival suffusion, chills, diarrhoea, anorexia, transient rash, cough, and sore throat. Severe leptospirosis causes multi-organ dysfunction affecting the liver, kidneys, lungs, and brain, and in some cases is associated with a haemorrhagic syndrome. Weil's disease, a severe form of leptospirosis first described in 1886, is associated with jaundice and kidney failure and remains one of the most clinically well-known forms of leptospirosis (Haake 2015; Weil 1886).

The clinical diagnosis of leptospirosis can be challenging because non-specific clinical signs can be similar to other tropical infectious diseases. The diagnosis of leptospirosis depends on laboratory tests that vary according to the evolutional stage of the disease. A laboratory diagnosis can be made using molecular methods (polymerase chain reaction (PCR) amplification and sequencing of the bacterial genome) during the first week of illness following the onset of fever, with or without serological methods (enzyme-linked immunosorbent assay (ELISA), ImmunoDOT, lateral flow tests, immunohistochemistry, microagglutination test) from the second week of illness. In some cases, laboratory diagnosis of leptospirosis will require a combination of diagnostic methods using appropriate specimens depending on the stage of illness (Budihal 2014; Koizumi 2020).

Leptospirosis is a treatable and preventable disease. Most instances of leptospirosis are self-limiting; however, some people with leptospirosis develop complications. The treatment of people with severe leptospirosis can require hospitalisation. Treatment includes medical resuscitation and early administration of antibiotics aiming to decrease the risk of complications. Doxycycline, azithromycin, cephalosporins, or penicillin are most often used, although the usefulness of antibiotic treatment has not been established, especially for severe forms of leptospirosis. For prevention, collective control measures based on deratting, control of industrial livestock effluents, and drainage of flooded areas are effective but difficult to implement. Vaccines have been developed for humans; all are serovar specific, developed for specific epidemiological circumstances, and are not widely available. The use of antibiotic prophylaxis in high-risk areas is also recommended as a preventive measure (Bhardwaj 2010; Brett-Major 2012; Vinetz 2020). In severe forms of leptospirosis, and especially in pulmonary and renal involvement, immunological therapies have been proposed because mediators of the immune system play a crucial role in the pathophysiology of these manifestations. Thus, corticosteroids and plasmapheresis have been used (Rodrigo 2014). However, there is currently insufficient evidence to support the utility of corticosteroids in severe leptospirosis, and the literature on this topic is sparse (Rodrigo 2014; Soler 2021).

Description of the intervention

The World Health Organization (WHO) guidelines strongly recommend treatment with effective antibiotics as soon as leptospirosis is considered a leading element of the differential diagnosis in a sick patient, preferably before the fifth day of onset (WHO 2003). According to the guideline, high doses of intravenous antibiotics should be used in severe cases of leptospirosis.

Although studies in vitro suggest high susceptibility of leptospires to many antibiotics (beta-lactams, tetracyclines, macrolides, fluoroquinolones) with no reported resistance, the relevance of the in vitro results to the clinical outcome of these agents has not been evaluated in clinical trials (Ressner 2008).

Antibiotic treatment of spirochaetal infections such as leptospirosis can be complicated by the Jarisch-Herxheimer reaction, characterised by shaking chills, fever, and intensification of skin rashes, and rarely in more severe reactions, multi-organ failure (Aronson 1976). The incidence of the Jarisch-Herxheimer reaction was reported to be 9% in one review of 976 leptospirosis cases treated with antibiotics (Butler 2017).

How the intervention might work

β-Lactam antibiotics, such as penicillin derivatives and cephalosporins, act by inhibiting the synthesis of bacterial cell walls. Penicillin-binding proteins (PBPs) are membrane-bound proteins that catalyse cell wall transpeptidation and carboxypeptidation reactions (Doi 2019). β-Lactam antibiotics produce their lethal effect on bacteria by inactivation of multiple PBPs simultaneously.

Cyclines class antibiotics act as inhibitors of bacterial protein synthesis. They bind to the 30S subunit of ribosomes, preventing the binding of aminoacyl-transfer ribonucleic acid (RNA) to the messenger RNA–ribosome complex, thus stopping the elongation phase of protein synthesis (Moffa 2019).

Macrolide antibiotics bind to the 50S ribosomal subunit of the bacteria and inhibit RNA-dependent protein synthesis at the step of chain elongation in susceptible prokaryotic organisms (Nesbitt 2019). The binding site is near the peptidyltransferase centre;

therefore, these antibiotics can prevent peptide chain elongation by blocking the polypeptide exit tunnel.

Quinolones inhibit the enzymatic activities of two members of the topoisomerase class of enzymes necessary for DNA syntheses such as DNA gyrase and topoisomerase IV, thereby inhibiting bacterial cell division and causing cell death (Hooper 2019).

However, the use of broad-spectrum antibiotics has the potential to lead to the development of resistance. It can happen through the misuse or overuse of drugs, or poor infection prevention and control (WHO 2020). *Leptospira* spp are naturally resistant to different classes of antimicrobials; however, there is limited evidence in the published literature on the mechanisms of development of those resistances (Trott 2018). The effectiveness of antimicrobials in the treatment of leptospirosis infections is also not well studied and continues to be a topic of controversy. Although there are few clinical trials and publications regarding the development of antibiotic resistance in *Leptospira*, it should not be taken for granted that pathogenic strains remain susceptible to currently used drugs (Karpagam 2020).

Why it is important to do this review

Although antibiotic treatment for leptospirosis is recommended and widely used in practice, there is insufficient evidence to determine its efficacy and whether it should be recommended. In 2012, one systematic review identified seven trials and assessed the evidence for antibiotic treatment in leptospirosis (Brett-Major 2012). In two of those trials, antibiotics shortened the duration of clinical illness by about two days compared to placebo (Brett-Major 2012). However, the outcome on the mortality benefit of antibiotic treatment was not statistically significant, especially in severe diseases. This systematic review has not been updated since 2012. Therefore, we plan to update this review based on the latest research and use the latest Cochrane methods during our review preparation. In addition, the spectrum, cost, dosing regimen, and adverse effects, including Jarisch-Herxheimer reaction, need to be considered to achieve the best balance between compliance and efficacy. There are no current systematic reviews on these topics.

OBJECTIVES

To assess the beneficial and harmful effects of antibiotics versus placebo, no intervention, or another antibiotic for the treatment of people with leptospirosis

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials studying antibiotic treatment for leptospirosis regardless of year, language, form of publication (including unpublished data), blinding or comparator, and outcomes reported. We will include cluster randomised trials and the first period of cross-over trials if found. We will determine the eligibility of data from such trials for inclusion in the meta-analysis.

We will exclude pseudo-randomised studies (i.e. quasi-randomised studies) as the method of allocation to the study groups is not truly random.

Types of participants

Individuals with suspected or confirmed leptospirosis infection by molecular (PCR amplification or sequencing of the bacterial genome) or serological methods (ELISA, ImmunoDOT, lateral flow tests, immunohistochemistry, microagglutination test) irrespective of clinical presentation (mild or severe cases), origin, sex, or age.

As published trial data for leptospirosis are likely to be limited, we will consider for inclusion trials with only a subset of eligible participants, while remaining faithful to the objectives of the review and rigorous Cochrane guidelines. If the outcome results of the subset of eligible participants are not presented separately in the identified trial publications or cannot be obtained directly from trial authors, we will consult with the advisory group and document difficult decisions in the review. We will apply sensitivity analyses to assess the impact of these decisions on the review's findings (McKenzie 2022a).

Types of interventions

Experimental intervention:

- antibiotics given for the treatment of leptospirosis, administered using any route, dosage, and schedule.

Control interventions:

- no intervention;
- placebo; or
- another antibiotic intervention.

We will allow any co-interventions if they are administered equally to the trial participants in the experimental and control groups.

Types of outcome measures

We will assess all the following dichotomous and continuous outcomes at maximum follow-up.

Primary outcomes

- All-cause mortality.
- Serious adverse events. We will consider an event as serious if it fulfilled the definition of serious adverse events of the International Council for Harmonisation (ICH) Guidelines (ICH-GCP 2016), that is, any event that leads to death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, congenital birth or anomaly, and any important medical event which may have jeopardised the patient or requires intervention to prevent it. A serious adverse reaction will be serious adverse events where the authors clearly stated a suspicion or confirmation that the event was due to the experimental or control intervention.

Secondary outcomes

Quality of life assessed by a validated questionnaire such as the World Health Organization Quality of Life Assessment (WHOQOL), 36-item Short-Form Health Survey (SF-36), 12-item Short-Form Health Survey (SF-12), Sickness Impact Profile, Nottingham Health Profile, EuroQol (EQ-5D), Short-Form Six-Dimension (SF-6D) (Nemeth 2006; Pequeno 2020).

- Proportion of people with non-serious adverse events.
  - Gastrointestinal symptoms such as abdominal cramps, nausea, vomiting, diarrhoea, or as defined by study authors, not included under the ICH Guidelines for serious adverse events (ICH-GCP 2016).
  - Other non-serious adverse events as defined by study authors (e.g. discolouration of teeth, photosensitivity, or transient hearing loss).

We will include studies regardless of whether these outcomes are reported.

Search methods for identification of studies

To minimise bias in our search results, we have followed the guidance in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2022) and in PRISMA-S, to plan and describe the search process for the review (Rethlefsen 2021).

Electronic searches

We will search the Cochrane Hepato-Biliary Group Controlled Trials Register, which will be searched internally by the Cochrane Hepato-Biliary Group Information Specialist via the Cochrane Register of Studies Web. We will also search the Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE Ovid, Embase Ovid (Excerpta Medica Database), LILACS (Bireme), Science Citation Index Expanded, and Conference Proceedings Citation Index – Science. The latter two databases will be searched simultaneously through the Web of Science.

Appendix 1 provides the preliminary search strategies for the databases, with the expected date range of the searches. We will provide the actual date of the electronic searches at the review stage.

Searching other resources

We will search the following clinical trials registries for ongoing or unpublished clinical trials, and for study information: WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp), US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov/), EU Clinical Trials Register (www.clinicaltrialsregister.eu/), European Medicines Agency (EMA; www.ema.europa.eu/ema/), and International Standard Randomised Controlled Trial Number Registry (ISRCTN; www.isrctn.com/). Appendix 1 provides the preliminary search strategies.

We will also search the following conference abstracts and proceedings: American Society of Tropical Medicine and Hygiene (ASTMH; 2005 to date of search), Infectious Diseases Society of America (IDSA; 2003 to date of search), and the International Society of Travel Medicine (ISTM; 2011 to date of search).

Once we decide to include a study, we will search its bibliography to seek other potential candidate studies or any relevant systematic reviews. We will use the PubMed/MEDLINE "similar articles search" tool on all included studies. We will also search for postpublication amendments and examine any relevant retraction statements and errata (e.g. through the Retraction Watch Database (retractionwatch.com/retraction-watch-database-user-guide/)), as errata can reveal important limitations or fatal flaws in included studies (Lefebvre 2022).

We will search for relevant grey literature sources such as reports, dissertations, theses, and conference abstracts in Google Scholar (scholar.google.com/).

We will contact authors of identified trials for additional published or unpublished trials. We will also contact relevant individuals and organisations for information about unpublished or ongoing studies.

We will provide the actual date of searching other sources at the review stage. We will use items from the PRISMA-S checklist that are relevant to our review to ensure that we have reported and documented our searches as advised (PRISMA-S Checklist; Rethlefsen 2021).

Data collection and analysis

We will follow the instructions in the *Cochrane Handbook for Systematic Reviews of Interventions* for data collection and analysis (Higgins 2022a). We will use Review Manager Web software to perform the meta-analyses (Review Manager Web 2020).

Selection of studies

Two review authors (PM, TZW) will independently review the list of all candidate studies obtained by the search. We will identify and 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 use Covidence software for study selection (Covidence). After screening titles and abstracts according to the inclusion criteria of our systematic review, we will obtain full-text papers of eligible studies and review full-text papers to identify whether the studies meet the eligibility criteria. We will contact authors of the selected publications by email to request any missing information that could help us determine the eligibility of a study. We will record the reasons for exclusion of studies not fulfilling the inclusion criteria in the characteristics of excluded studies table. We will resolve any disagreements with a third review author (CS). We will impose no language restrictions. We will include trials no matter if they report our outcomes of interest or not. We will record the selection process in sufficient detail to complete a PRISMA-S flow diagram (Page 2021a; Page 2021b).

For screening of non-English language publications, we will, in the first instance, use Google Translate (translate.google.com) to assist in eligibility assessment. If needed, we will seek translators, through the CHBG Editorial Team office, to assist with assessing eligibility of studies and, if eligible, assist with data extraction.

If we find observational studies (quasi-randomised studies, cohort studies, patient-reported) that report on adverse effects with antibiotics during our search for randomised clinical trials that meet the inclusion criteria for our review, we will extract and present relevant data on harms in a narrative or tabular way. This will be done regardless of the number of randomised clinical trials that are found to report on adverse events as we do not expect to identify numerous randomised clinical trials.

We recognise that not conducting separate systematic reviews for these observational studies may result in limited data on adverse events in the final systematic review. An additional systematic review of harms based on observational studies would be recommended if a benefit of the intervention is found (Storebø 2018).

Data extraction and management

We will use a prepiloted data extraction form before starting extracting trial data for the review. Two review authors (PM, TZW) will independently extract the study characteristics as below from included studies and complete a characteristics of included studies table. Any disagreements will be resolved with a third review author (CS).

- Study and publication identifiers.
- Ethics committee approval.
- Database index number.
- First author.
- Journal.
- Year of publication.
- Language.
- Location.
- Study methods.
- Study design.
- Number of trial arms.
- Randomisation and how randomised participants were allocated to groups.
- Description of interventions and control procedures.
- How blinded methods were conducted and how concealment was accomplished.
- Type of analysis.
- Study setting.
- Date of study.
- Total duration of study.
- Duration participants were followed.
- Details of any 'run-in' period.
- Location (country, prefecture/district)o
- Type and number of study centres and locations.
- Participants.
- Inclusion and exclusion criteria.
- Total number of participants and the number of participants in each group.
- Demographics characteristics.
- Severity of condition, comorbidity.
- Withdrawals and the reasons.
- Interventions.
- Details of intervention.
  - Type of antibacterial agent.
  - Route of admission.
  - Dose.
  - Timing of administration.
  - Duration of intervention.
- Definition of comparison, control groups.
- Concomitant treatment.
- Outcomes.
- Definition of primary and secondary outcomes and adverse effects.
- Outcomes measurements.
- Time points for follow-up reported.
- Notes.
- Funding source for trial.
- Notable conflicts of interest of trial authors.

We will record whether a trial measures adverse events as number of participants with an adverse event or measures multiple adverse events on the same participant.

Assessment of risk of bias in included studies

We will assess the effect of assignment to the intervention using the Cochrane RoB 2 tool, which is a revised tool to assess the risk of bias in randomised trials (Higgins 2022b; Sterne 2019). We will analyse participants in the intervention groups to which they were randomised, regardless of the intervention they actually received, and we will include all randomised participants in the outcome analyses (i.e. we will perform our analyses based on the intention-to-treat principle).

Two review authors (PM, TZW) will independently assess the risk of bias of all-cause mortality, serious adverse events, quality of life, and proportion of people with non-serious adverse events. We will assess these outcomes at maximum follow-up. We will resolve disagreements with a third review author (CS). We will assess the risk of bias in the included randomised parallel-group trials, based on the following domains (Higgins 2022b; Higgins 2022c; Lasserson 2016; Sterne 2019).

- Bias arising from the randomisation process: we will assess whether the allocation sequence was random and adequately concealed. We will also assess if the baseline differences between intervention groups suggest an issue with the randomisation process.
- Bias due to deviations from intended interventions: we will evaluate whether the participants were aware of their assigned interventions during the trial and if the carers and people delivering the interventions were aware of the participants' assigned intervention during the trial.
- Bias due to missing outcome data: we will analyse if the data for the studied outcome were available for all, or nearly all, participants randomised, if there was any evidence that the result was not biased by missing outcome data, and if the absence of the outcome was likely to depend on its true value.
- Bias in measurement of the outcome: we will evaluate if the method of measuring the outcome was inappropriate. We will also evaluate if the assessors of the outcome were aware of the intervention each study participant received, if the measurement of the outcome could have differed between intervention groups. We will also assess, if applicable, whether the assessment of the outcome was likely to have been influenced by knowledge of the intervention received.
- Bias in selection of the reported result: we will address whether the trial analysis was made in accordance with a predetermined plan before unblinded outcome data were available for analysis. We will also evaluate if the assessed numerical result is likely to have been selected from either multiple outcome measurements within the outcome domain or from the multiple analyses of the data.

We will answer signalling questions for each domain, using the algorithm proposed by the RoB 2 tool. The response options for the signalling questions are: yes, probably yes, probably no, no, and no information. Elaborations to these signalling questions can be

found in Higgins 2022c. Once these questions have been answered, the tool's algorithm reaches a risk of bias judgement and assigns one the following three levels to each domain.

- Low risk of bias.
- Some concerns.
- High risk of bias.

We will provide a justification for our judgments in the risk of bias tables, including reasons against the algorithm.

We will assess the risk of bias in the trials as follows (Higgins 2016; Sterne 2019).

- Low risk of bias: all the aforementioned domains are judged at low risk of bias.
- Some concerns: the trial raises some concerns in at least one domain, but there is no judgement of high risk of bias for any domain.
- High risk of bias: the trial is judged at risk of bias in at least one domain, or it has some concerns for multiple domains in a way that substantially lowers confidence in the result (Higgins 2022b).

For cluster-randomised clinical trials, we will consider an additional domain that specifically applies to the design of the cluster-randomised clinical trial, RoB 2 Domain 1b, 'Bias arising from the timing of identification and recruitment of individual participants within clusters in relation to timing of randomisation'. We will follow the suggested algorithm for reaching risk of bias judgements for bias arising from the timing of identification and recruitment of participants in a cluster-randomised trial (Eldridge 2020; Higgins 2020; Higgins 2022c). At the time of review preparation, we will use the most recent recommendations for assessing risk of bias in cluster-randomised trials.

For cross-over trials, we will use the data only from the period before cross-over, and therefore, we will use the standard version of RoB 2 (Sterne 2019).

The overall risk-of-bias assessment is the same as for the individual domains (i.e. low risk of bias, some concerns, or high risk of bias). Judging a result to be at a particular level of risk of bias for an individual domain implies that the result has an overall risk of bias at least this severe.

We will use the RoB 2 Excel tool (available at www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). We will store our RoB 2 data in Microsoft Excel files saved in Dropbox online storage. We will provide the link at the review stage.

The risk of bias assessments will feed into the risk of bias domain of the GRADE approach for assessing certainty of a body of evidence (Schünemann 2013; Schünemann 2022a). We will present the outcomes that we consider most relevant for clinical practice in summary of findings tables. These outcomes will be all-cause mortality, serious adverse events (hospitalisation and long-term disability), quality of life, and proportion of people with non-serious adverse events.

Measures of treatment effect

We will enter the outcome data for each trial into the data tables in Review Manager Web to calculate the treatment effects (Review Manager Web 2020). We will analyse dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs). We will measure continuous outcomes, such as quality of life, using the mean difference (MD) with 95% CI if trials used the same tool. We will use the standardised mean difference (SMD) with 95% CI to analyse quality of life if trials used different scales to measure it. The SMD expresses the size of the intervention effect when the MD between groups is divided by the standard deviation among participants (Higgins 2022b). We will interpret SMD as follows: SMD less than 0.40 for small intervention effects; SMD between 0.40 and 0.70 for moderate intervention effects; and SMD greater than 0.70 for large intervention effects (Schünemann 2022b). We will present medians and interquartile ranges for continuous data that are not normally distributed (skewed data), in a narrative format. We will present a forest plot to display effect estimates and CIs for individual trials (Lewis 2001). We will conduct meta-analyses only when the study group is sufficiently homogeneous (Deeks 2022).

Unit of analysis issues

We will consider the individual participant as the unit of analysis for randomised clinical trials. Where multiple trial arms are reported in a single trial, we will include only the treatment arms relevant to the review topic but list all treatment arms in the characteristics of included studies table, even if they are not used in the review. Our optimal approach will be to create a single pair-wise comparison. However, if there are trials with more than two arms, for example with the same participants in the placebo arm in both comparisons (e.g. antibiotic A versus placebo and antibiotic B versus placebo), we will follow the guidance in Section 6.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid double-counting of participants and arbitrary omission of relevant groups (Higgins 2022d).

If we find cluster-randomised clinical trials, then we will consider the cluster as unit of analysis, not the individual participants, in order to avoid unit-of-analysis error which may cause artificially narrow CIs and small P values, resulting in a false-positive result that leads to conclusions that the intervention had an effect (Higgins 2022c).

We do not expect to find clinical trials of antibiotics for leptospirosis using a cross-over design. If we do find them, we will include data from the first trial period to avoid residual effects of treatment (Higgins 2022c).

In order to avoid repeated observations of study participants, we will use trial data for the trial participants at the longest follow-up (Higgins 2022d).

If we identify trials that have also included participants with diseases other than leptospirosis, then we will contact trial authors to obtain individual participant data. However, this is not a likely scenario.

Dealing with missing data

We will contact investigators to verify key study characteristics and obtain missing numerical outcome data on the primary outcomes. If we are not successful, then we will calculate numerical outcome data that are still missing, such as standard deviations or correlation coefficients, from other available statistics such as P values, following the method described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). If

these calculations are not possible, we will assess the risk of bias due to missing outcome data as defined by the RoB 2 domain, undertake sensitivity analyses, and explore the impact of including these studies in the overall assessment of results (Page 2022). We will perform an intention-to-treat analysis as a primary analysis approach (available-case analysis, or modified intention-to-treat approach), as far as possible (Fergusson 2002). This approach assumes that missing data are missing at random.

We will conduct sensitivity analyses for binary outcomes assuming a worst-case scenario (missing data are assumed to be a 'negative' outcome) and a best-case scenario (missing data are assumed to be a 'positive' outcome) (Mavridis 2014). These two sensitivity analysis approaches can indicate the extent of uncertainty due to attrition bias. If the CIs and P value of the results of the primary meta-analysis and the results of the sensitivity analysis are similar, the validity of the results is increased (Jakobsen 2014). However, if they differ substantially, this suggests a risk of attrition bias. For continuous data, we will impute the mean value from available data. It is not expected that sufficient data will be available to impute missing data based on a more complex approach of using predicted values from a regression analysis. We will explicitly describe assumptions that we make during sensitivity analyses.

We will address the potential impact of all missing data on our findings of the review in the discussion section.

Assessment of heterogeneity

We will describe the clinical and methodological diversity of the evidence in the review text, considering the characteristics of the study, including design features, population characteristics, and details of the intervention.

We will visually check the forest plot and describe the direction and magnitude of the effect and the overlap of the CIs. We will evaluate statistical heterogeneity with the Chi^2 and I^2 statistics, using $P < 0.10$ as a cut-off point for statistical heterogeneity (Israel 2011). We will quantify heterogeneity using the I^2 statistic and interpret it as follows (Deeks 2022):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Interpretation of the value of the I^2 statistic will be based on consideration of the strength of evidence for heterogeneity and relation to the magnitude and direction of effects.

If we identify substantial heterogeneity, we will follow the strategies for handling heterogeneity given in the *Cochrane Handbook for Systematic Review of Interventions* to explore possible causes based on differences of population, intervention, comparison, and outcome, and difference in the quality of research (Deeks 2022). We will investigate possible reasons for heterogeneity via subgroup analyses where possible. If heterogeneity is considerable, we may decide not to perform a meta-analysis, and instead, we will present the outcome result in a narrative way.

Assessment of reporting biases

We will record biases (e.g. publication, time lag, multiple publications) at all points of data analysis and interpretation. If we identify 10 or more trials that can be included in a meta-analysis, we will create a funnel plot to analyse possible publication biases. If our search identifies any trial protocols, abstracts, or clinical trial registrations that indicate the existence of unpublished studies, we will try to contact the investigators to determine the status of these unpublished studies.

Data synthesis

We will pool data, such as RRs and MDs with 95% CIs, from trials that are judged clinically homogeneous. If we find multiple trials that provide usable data in any single comparison, we will perform a meta-analysis. However, if there is considerable heterogeneity, especially if the direction of effect is not consistent, we will not perform a meta-analysis, regardless of the number of trials found. We will present the results in a narrative or table format or both.

We will use the random-effects model as our primary analysis (DerSimonian 1986). We will use the fixed-effect model as our sensitivity analysis.

We will include all trials in the primary analysis and explore the effect of bias in a sensitivity analysis in which we will exclude small studies if there are systematic differences.

We will use Review Manager Web software to perform our meta-analyses (Review Manager Web 2020).

Given the likely limited number of studies meeting the eligibility criteria, we will include as much data as possible. We will perform a sensitivity analysis of just studies at low risk of bias in the meta-analyses if there are eligible studies at higher risk of bias.

If statistical pooling is not appropriate due to incomplete reported data in the primary studies, we will apply one of the acceptable synthesis methods (summarising effect estimates, combining P values, and vote counting based on direction of effect) depending on the circumstance (McKenzie 2022b).

Subgroup analysis and investigation of heterogeneity

We do not expect to perform subgroup analyses for two reasons. First, we do not think there will be many trials on the use of antibiotics for the treatment of leptospirosis. Second, because of the observational nature of subgroup analyses, which are not based on randomised comparisons, there is a risk of overestimating positive intervention effects and underestimating negative effects (Lagakos 2006; Wang 2007).

Potential subgroup differences in effectiveness of an intervention for leptospirosis might be hypothesised to occur if the same drug is given but according to a different regimen in terms of route, dosing, or duration. Differences by age might be observed, for example, if drug dosing is according to weight and the dose is suboptimal for younger participants with lower weight.

We will explore if subgroup analyses are possible, for all outcomes, to assess potential differences in effectiveness of the intervention where there is information available about intervention route, dosing, duration, and age. Should it be considered appropriate, outcomes in any subgroup analyses will be our two primary outcomes.

Where possible, we will assess subgroup differences by interaction tests available within Review Manager Web (Review Manager Web

2020). We will report the results of subgroup analyses using stratified forest plots quoting the Chi^2 statistic, P value, and interaction test I^2 value.

Sensitivity analysis

We will conduct the following three sensitivity analyses, for all outcomes, to assess the impact of heterogeneity and the effect of risk of bias in the included studies (Boutron 2022).

- Repeat all outcome analyses using the fixed-effect model (see Data synthesis).
- Repeat all outcome analyses excluding trials at an overall high risk of bias.
- Repeat all outcome analyses excluding unpublished studies (if there are any).

We will prepare a table, summarising the results of the sensitivity analyses.

In addition, we will perform a Trial Sequential Analysis to assess imprecision of our primary outcome results. We will then compare our evaluation of imprecision based on GRADE, an approach recommended in the *Cochrane Handbook for Systematic Review of Interventions* for assessing confidence of the evidence for pair-wise comparisons of interventions, with our choice of plausible relative risk reduction (RRR) and multiplicity correction to Trial Sequential Analysis, using similar choices of a plausible RRR and multiplicity correction.

In Trial Sequential Analysis, we will downgrade our assessment of imprecision by two levels if the accrued number of participants is below 50% of the diversity-adjusted required information size (DARIS), and by one level if between 50% and 100% of the DARIS. We will not downgrade if futility or DARIS is reached. A more detailed description of Trial Sequential Analysis, and the software programme, can be found at www.ctu.dk/tsa/ (Thorlund 2017).

Trial Sequential Analysis

We will use Trial Sequential Analysis as a sensitivity analysis to assess imprecision for the two primary outcomes (i.e. all-cause mortality and serious adverse events) (Castellini 2018; Gartlehner 2019; Jakobsen 2014). The underlying assumption of Trial Sequential Analysis is that testing for statistical significance may be performed each time a new trial is added to the meta-analysis. We will add the trials according to the year of publication, and, if more than one trial was published in a year, we will add the trials alphabetically according to the last name of the first author. For the random-effects meta-analyses, we will also calculate the DARIS (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Brok 2008; Brok 2009; Thorlund 2010; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). On the basis of the DARIS, we will construct the trial sequential monitoring boundaries for benefit, harm, and futility (Thorlund 2017; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). These boundaries determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the DARIS; if the trial sequential monitoring boundary for benefit or harm is crossed before the DARIS is reached, firm evidence may be established, and further evidence may be superfluous. However, if the boundaries for benefit or harm are not crossed, it is most probably necessary to continue conducting trials to detect or reject a certain intervention effect. If the cumulative Z-curve crosses the trial sequential monitoring boundaries for futility, no more trials will be needed.

In our Trial Sequential Analysis of the two primary outcomes (both dichotomous), we will base the DARIS on the event proportion in the control group; assuming a plausible RRR for all-cause mortality and serious adverse events of 10%; a risk of type I error of 3.3% due to two primary outcomes (Jakobsen 2014); a risk of type II error of 10%; and the diversity of the included trials in the meta-analysis. Trial Sequential Analysis considers the choice of statistical model (fixed-effect or random-effects) and diversity (Thorlund 2017; TSA 2017). We will use the random-effects model. We will also calculate the Trial Sequential Analysis-adjusted CIs (Thorlund 2017; Wetterslev 2017).

Summary of findings and assessment of the certainty of the evidence

We will use GRADEpro software to create summary of findings tables (GRADEpro GDT). Summary of findings tables provide information on comparative risk, relative risk, number of participants, number of trials, and certainty of the evidence for antibiotics use for the treatment of leptospirosis versus no intervention, placebo, or another antibiotic. We plan to create three summary of findings tables comparing: antibiotic treatment versus no intervention; antibiotic treatment versus placebo; and one antibiotic treatment versus another antibiotic treatment. We will present outcome results for all-cause mortality, serious adverse events, quality of life, and proportion of people with non-serious adverse events. We will use methods and recommendations described in Section 8.5 and Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b; Schünemann 2022b), and the GRADE Handbook (Schünemann 2013). We will provide the maximum follow-up and the mean or median, and their ranges of each outcome. Two review authors (PM and TZW) will independently grade the evidence of these outcomes. We will resolve disagreements through discussion, with arbitration from a third review author (CS) if necessary.

The assessment of GRADE approach is based on five factors which reduce the certainty of evidence in randomised clinical trials (risk of bias, inconsistency of results, indirectness of evidence, imprecision, and publication bias). It specifies four levels of the certainty of evidence as high, moderate, low, and very low (see definitions below). Through this approach, we will evaluate and form conclusions about the certainty of the evidence shown in the review (GRADEpro GDT).

The overall risk of bias from the overall risk of bias judgement will be used for each result to inform the GRADE assessment (see Assessment of risk of bias in included studies). We will justify all decisions to downgrade the certainty of evidence using footnotes, and we will create comments to help the reader understand the review if needed.

The four GRADE Working Group grades of evidence are:

- **high certainty:** we are very confident that the true effect lies close to that of the estimate of the effect;
- **moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;

- **low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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

ACKNOWLEDGEMENTS

The Cochrane Hepato-Biliary (CHB) Editorial Team supported the authors in the development of this review.

The following people from the CHB Editorial Team conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Christian Gluud, Co-ordinating Editor Cochrane Hepato-Biliary Group, Denmark;
- Contact Editor (provided editorial decision): Joshua Feinberg, Denmark;
- Statistical Editor (commented on statistics): Giovanni Casazza, Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Italy;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Dimitrinka Nikolova, Denmark;
- Information Specialist (database searches): Sarah Louise Klingenberg, Denmark;
- Peer-reviewers (provided clinical and content review comments): Christopher Parry, Liverpool School of Tropical Medicine, UK; Marta Ferreira Maia, KEMRI-Wellcome Trust Research Programme, Kenya; Cho Niang, James Cook University, Queensland, Australia; (Information Specialist review): Robin M Featherstone, Editorial & Methods Department, Cochrane Executive, London, UK;
- Associate Editor, Evidence Production and Methods Department, Cochrane: Rachel Richardson, UK;
- Copy Editor (copy editing and production): Anne Lawson, Copy Edit Support, Cochrane.

Cochrane Review Group funding acknowledgement: the Danish State is the largest single funder of the Cochrane Hepato-Biliary Group through its investment in the Copenhagen Trial Unit, Centre for Clinical Intervention Research, the Capital Region, Rigshospitalet, Copenhagen, Denmark. Disclaimer: the views and opinions expressed in this protocol are those of the authors and do not necessarily reflect those of the Danish State or the Copenhagen Trial Unit.

REFERENCES

Additional references

Aronson 1976

Aronson IK, Soltani K.The enigma of the pathogenesis of the Jarisch-Herxheimer reaction. *British Journal of Venereal Diseases* 1976;**52**(5):313-5.

Bhardwaj 2010

Bhardwaj P, Kosambiya JK, Vikas KD, Karan J.Chemoprophylaxis with doxycycline in suspected epidemic of leptospirosis during floods: does this really work? *African Health Sciences* 2010;**10**(2):199-200.

Bharti 2003

Bharti AR, Nally JE, Ricaldi JN, Matthias MA, Diaz MM, Lovett MA, et al.Leptospirosis: a zoonotic disease of global importance. *Lancet Infectious Diseases* 2003;**3**:757-71.

Boutron 2022

Boutron I, Page MJ, Higgins JP, Altman DG, Lundh A, Hrobjartsson A.Chapter 7: Considering bias and conflicts of interest among the included studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Brett-Major 2012

Brett-Major DM, Coldren R.Antibiotics for leptospirosis. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No: CD008264. [DOI: 10.1002/14651858.CD008264.pub2]

Brok 2008

Brok J, Thorlund K, Gluud C, Wetterslev J.Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. *Journal of Clinical Epidemiology* 2008;**61**:763-9.

Brok 2009

Brok J, Thorlund K, Wetterslev J, Gluud C.Apparently conclusive meta-analyses may be inconclusive – trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *International Journal of Epidemiology* 2009;**38**(1):287-98.

Budihal 2014

Budihal SV, Perwez K.Leptospirosis diagnosis: competancy of various laboratory tests. *Journal of Clinical and Diagnostic Research* 2014;**8**(1):199-202.

Butler 2017

Butler T.The Jarisch-Herxheimer reaction after antibiotic treatment of spirochetal infections: a review of recent cases and our understanding of pathogenesis. *American Journal of Tropical Medicine and Hygiene* 2017;**96**(1):46-52. [DOI: 10.4269/ajtmh.16-0434]

Castellini 2018

Castellini G, Bruschettini M, Gianola S, Gluud C, Moja L.Assessing imprecision in Cochrane systematic reviews: a comparison of GRADE and Trial Sequential Analysis. *Systematic Reviews* 2018;**7**(110):1-10.

Costa 2015

Costa F, Hagan JE, Calcagno J, Kane M, Torgerson P, Martinez-Silveira MS, et al.Global morbidity and mortality of leptospirosis: a systematic review. *PLoS Neglected Tropical Disease* 2015;**17**(9):9.

Covidence [Computer program]

Veritas Health Innovation Covidence systematic review software.Melbourne, Australia: Veritas Health Innovation, (accessed 5 January 2022). Available at www.covidence.org.

Deeks 2022

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

DerSimonian 1986

DerSimonian R, Laird N.Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177-88.

Doi 2019

Doi Y.Penicillins and β-lactamase inhibitors. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th edition. Philadelphia (PA): W.B. Saunders, 2019:251-68.

Eldridge 2020

Eldridge S, Campbell MK, Campbell MJ, Drahota AK, Giraudeau B, Reeves BC, et al.Revised Cochrane risk of bias tool for randomized trials (RoB 2). Additional considerations for cluster-randomized trials (RoB 2 CRT), 2020. Available from sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/rob-2-for-cluster-randomized-trials?authuser=0 (accessed prior to 18 May 2022).

Farrar 2014

Farrar J, Hotez PJ, Junghanss P, Kang G, Lalloo D, White NJ.Leptospirosis. In: Manson's Tropical Diseases. 23rd edition. Philadelphia (PA): W.B. Saunders Ltd, 2014:433-40. [DOI: 10.1016/C2010-0-66223-7]

Fergusson 2002

Fergusson D, Aaron SD, Guyatt G, Hebert P.Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ (Clinical Research Ed.)* 2002;**325**:625-4. [DOI: 10.1136/bmj.325.7365.652]

Gartlehner 2019

Gartlehner G, Nussbaumer-Streit B, Wagner G, Patel S, Swinson-Evans T, Dobrescu A, et al.Increased risks for random errors are

common in outcomes graded as high certainty of evidence. *Journal of Clinical Epidemiology* 2019;**106**:50-9. [DOI: 10.1016/j.jclinepi.2018.10.009]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT.Version accessed 5 January 2022. Hamilton (ON): McMaster University (developed by Evidence Prime), 2020. Available at gradepro.org.

Haake 2015

Haake DA, Levett PN.Leptospirosis in humans. *Current Topics in Microbiology and Immunology* 2015;**387**:65-97.

Higgins 2016

Higgins JP, Sterne JA, Savović J, Page MJ, Hróbjartsson A, Boutron I, et al.A revised tool for assessing risk of bias in randomized trials. In: Chandler J, McKenzie J, Boutron I, Welch V, editor(s). Cochrane Methods. Cochrane Database of Systematic Reviews 2016;(10 Suppl 1):29-31. [DOI: 10.1002/14651858.CD201601]

Higgins 2020

Higgins JP, Li T, Sterne J.Revised Cochrane 'Risk of bias' tool for randomized trials (RoB 2). Additional considerations for cross-over trials, 2020. drive.google.com/file/d/18Ek-uW8HYQsUja8Lakp1yOhoFk0EMfPO/view (accessed 7 January 2022).

Higgins 2022a

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s).Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022 . Available from www.training.cochrane.org/handbook.

Higgins 2022b

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA.Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Higgins 2022c

Higgins JP, Eldridge S, Li T.Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Higgins 2022d

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

Hooper 2019

Hooper DC, Strahilevitz J.Quinolones. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th edition. Philadelphia (PA): W.B. Saunders, 2019:426-49.

ICH-GCP 2016

International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH).ICH Harmonised Guideline. Integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2), 2016. database.ich.org/sites/default/files/E6_R2_Addendum.pdf (accessed 7 January 2022).

Israel 2011

Israel H, Richter RR.A guide to understanding meta-analysis. *Journal of Orthopaedic and Sports Physical Therapy* 2011;**41**(7):496-504. [DOI: 10.2519/jospt.2011.3333]

Jakobsen 2014

Jakobsen J, Wetterslev J, Winkel P, Lange T, Gluud C.Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. *BMC Medical Research Methodology* 2014;**14**:120.

Karpagam 2020

Karpagam KB, Ganesh B.Leptospirosis: a neglected tropical zoonotic infection of public health importance – an updated review. *European Journal of Clinical Microbiology & Infectious Diseases* 2020;**39**:835-46.

Koizumi 2020

Koizumi N.Laboratory diagnosis of leptospirosis. In: KoizumiN, PicardeauM, editors(s). Methods in Molecular Biology. Humana edition. Vol. **2134**. New York (NY): Humana, 2020:277-87.

Lagakos 2006

Lagakos SW.The NIH budget and the future of biomedical research. *New England Journal of Medicine* 2006;**354**(16):1665-7. [DOI: 10.1056/NEJMp068050]

Lasserson 2016

Lasserson T, Churchill R, Chandler J, Tovey D, Higgins JP.Standards for the reporting of protocols of new Cochrane Intervention Reviews. In: Higgins JP, Lasserson T, Chandler J, Tovey D, Churchill R. Methodological Expectations of Cochrane Intervention Reviews. community.cochrane.org/book_pdf/556 (accessed 24 May 2022).

Lefebvre 2022

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al.Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Levett 2001

Levett PN.Leptospirosis. *Clinical Microbiology Reviews* 2001;**14**(2):298-326.

Lewis 2001

Lewis S, Clarke M.Forest plots: trying to see the wood and the trees. *BMJ (Clinical Research Ed.)* 2001;**322**(7300):1479-80. [DOI: 10.1136/bmj.322.7300.1479]

Mavridis 2014

Mavridis D, Chaimani A, Efthimiou O, Leucht S, Salanti G.Addressing missing outcome data in meta-analysis. *Evidence-Based Mental Health* 2014;**17**(3):85-9. [DOI: 10.1136/eb-2014-101900]

McKenzie 2022a

McKenzie JE, Brennan SE, Ryan RE, Thomson HJ, Johnston RV, Thomas J.Chapter 3: Defining the criteria for including studies and how they will be grouped for the synthesis. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

McKenzie 2022b

McKenzie JE, Brennan SE.Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Moffa 2019

Moffa M, Brook I.Tetracyclines, glycylcyclines, and chloramphenicol. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th edition. Philadelphia (PA): W.B. Saunders, 2019:318-37.

Nemeth 2006

Nemeth G.Health related quality of life outcome instruments. *European Spine Journal* 2006;**15**:S44-S51. [DOI: 10.1007/s00586-005-1046-8]

Nesbitt 2019

Nesbitt WJ, Aronoff DM.Macrolides and clindamycin. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th edition. Philadelphia (PA): W.B. Saunders, 2019:359-75.

Page 2021a

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al.The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)* 2021;**372**:n71.

Page 2021b

Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al.PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ (Clinical Research Ed.)* 2021;**372**:n160.

Page 2022

Page MJ, Higgins JP, Sterne JA.Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Pequeno 2020

Pequeno NP, Cabral NL, Marchioni DM, Lima SC, Lyra CO.Quality of life assessment instruments for adults: a systematic review of population-based studies. *Health and Quality Life Outcomes* 2020;**18**(1):208. [DOI: 10.1186/s12955-020-01347-7]

Ressner 2008

Ressner RA, Griffith ME, Beckius ML, Pimentel G, Miller RS, Mende K, et al.Antimicrobial susceptibilities of geographically diverse clinical human isolates of Leptospira. *Antimicrobial Agents and Chemotherapy* 2008;**52**(8):2750-4.

Rethlefsen 2021

Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al, PRISMA-S Group.PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. *Systematic Reviews* 2021;**10**(1):39.

Review Manager Web 2020 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web).Version 1.22.0. The Cochrane Collaboration, 2020. Available at: revman.cochrane.org.

Rodrigo 2014

Rodrigo C, de Silva NL, Goonaratne R, Samarasekara K, Wijesinghe I, Parththipan B, et al.High dose corticosteroids in severe leptospirosis: a systematic review. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2014;**108**(12):743-50.

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s).GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook (accessed 24 May 2022).

Schünemann 2022a

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al.Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from training.cochrane.org/handbook.

Schünemann 2022b

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

Soler 2021

Soler MC, Mogliani S, Benítez ST, Cabillón LN, Rollié RD, Martins GM.Glucocorticoids in leptospira alveolar hemorrhage [Glucocorticoides en hemorragia alveolar por leptospira]. *Medicina* 2021;**81**:107-10.

Sterne 2019

Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al.RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research Ed.)* 2019;**366**:l4898. [DOI: 10.1136/bmj.l4898]

Storebø 2018

Storebø OJ, Pedersen N, Ramstad E, Kielsholm ML, Nielsen SS, Krogh HB, et al.Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents – assessment of adverse events in non-randomised studies. *Cochrane Database of Systematic Reviews* 2018, Issue 5. Art. No: CD012069. [DOI: 10.1002/14651858.CD012069.pub2]

Suneth 2011

Suneth BA, Sharon JP, Vasanthi T, Danaseela BN, Lee S, Janjira T, et al.Leptospirosis outbreak in Sri Lanka in 2008: lessons for assessing the global burden of disease. *American Journal of Tropical Medicine and Hygiene* 2011;**85**(3):471-8.

Thorlund 2010

Thorlund K, Anema A, Mills E.Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. *Clinical Epidemiology* 2010;**2**:57-66.

Thorlund 2017

Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C.User Manual for Trial Sequential Analysis (TSA); 2nd edition. Copenhagen Trial Unit, 2017. Available from ctu.dk/tsa/learn-more.

Torgerson 2015

Torgerson PR, Hagan JE, Costa F, Calcagno J, Kane M, Silveira MS, et al.Global burden of leptospirosis: estimated in terms of disability adjusted life years. *PLoS Neglected Tropical Diseases* 2015;**9**(10):e0004122. [DOI: 10.1371/journal.pntd.0004122]

Trott 2018

Trott DJ, Abraham S, Adler B.Antimicrobial resistance in leptospira, brucella, and other rarely investigated veterinary and zoonotic pathogens. *Microbiology Spectrum* 2018;**6**:4.

TSA 2017 [Computer program]

Copenhagen Trial Unit TSA – Trial Sequential Analysis.Version 0.9.5.10 Beta. Copenhagen: Copenhagen Trial Unit, 2017. ctu.dk/tsa/downloads/.

Vinetz 2020

Vinetz JM, Watt G.Chapter 79. Leptospirosis. In: RyanET, HillDR, SolomonT, AronsonNE, EndyTP, editors(s). Hunter's Tropical Medicine and Emerging Infectious Diseases. 10th edition. Edinburgh (UK): Elsevier, 2020:636-40.

Wang 2007

Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM.Statistics in medicine – reporting of subgroup analyses in clinical trials. *New England Journal of Medicine* 2007;**357**(21):2189-94. [DOI: 10.1056/NEJMsr077003]

Weil 1886

Weil A.On a strange, acute infectious disease, accompanied by swelling of the spleen, icterus, and nephritis [Ueber eine eigenthümliche, mit Milztumor, Icterus und Nephritis einhergehende, acute Infectionskrankheit]. *Deutsches Archiv für klinische Medizin* 1886;**39**:209.

Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C.Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75.

Wetterslev 2009

Wetterslev J, Thorlund K, Brok J, Gluud C.Estimating required information size by quantifying diversity in a random-effects meta-analysis. *BMC Medical Research Methodology* 2009;**9**:86.

Wetterslev 2017

Wetterslev J, Jakobsen JC, Gluud C.Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Medical Research Methodology* 2017;**17**(1):39.

WHO 2003

World Health Organization.Human leptospirosis: guidance for diagnosis, surveillance and control. *Revista do Instituto de Medicina Tropical de São Paulo* 2003;**45**(5):292. [DOI: 10.1590/S0036-46652003000500015]

WHO 2020

World Health Organization.Antibiotic resistance, 2020. www.who.int/news-room/fact-sheets/detail/antibiotic-resistance (accessed 13 October 2021).

APPENDICES

Appendix 1. Search strategies

Database	Timespan	Search strategy
Cochrane Hepato-Biliary Group Controlled	Date of search will be given at review stage	(antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bac-

(Continued)

Trials Register (via the Cochrane Register of Studies Web)		teriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*) AND (leptospir* or ((weil* or Swineherd*) and disease*) or "Stuttgart disease*" or "hemorrhagic jaundice" or "spirochetal jaundice" or (("cane cutter" or canicola or icterohemorrhagic or mud or "rice field" or swamp) and fever))
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 MeSH descriptor: [Anti-Bacterial Agents] explode all trees #2 (antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*) #3 #1 or #2 #4 MeSH descriptor: [Leptospirosis] explode all trees #5 (leptospir* or ((weil* or Swineherd*) and disease*) or (Stuttgart next disease*) or (hemorrhagic next jaundice) or (spirochetal next jaundice) or (((cane next cutter) or canicola or icterohemorrhagic or mud or (rice next field) or swamp) and fever)) #6 #4 or #5 #7 #3 and #4
MEDLINE Ovid	1946 to date of search	1. exp Anti-Bacterial Agents/ 2. (antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*).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 Leptospirosis/ 5. (leptospir* or ((weil* or Swineherd*) and disease*) or Stuttgart disease* or hemorrhagic jaundice or spirochetal jaundice or ((cane cutter or canicola or icterohemorrhagic or mud or rice field or swamp) and fever)).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] 6. 4 or 5 7. 3 and 6 8. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. 9. clinical trials as topic.sh. 10. (random* or placebo*).ab. or trial.ti. 11. 8 or 9 or 10

(Continued)

		12. exp animals/ not humans.sh. 13. 11 not 12 14. 7 and 13
Embase Ovid	1974 to date of search	1. exp antibiotic agent/ 2. (antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 3. 1 or 2 4. exp leptospirosis/ 5. (leptospir* or ((weil* or Swineherd*) and disease*) or Stuttgart disease* or hemorrhagic jaundice or spirochetal jaundice or ((cane cutter or canicola or icterohemorrhagic or mud or rice field or swamp) and fever)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 6. 4 or 5 7. 3 and 6 8. Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or retracted article/ 9. (random$ or placebo or parallel group$1 or crossover or cross over or assigned or allocated or volunteer or volunteers).ti,ab. 10. (compare or compared or comparison or trial).ti. 11. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 12. (open adj label).ti,ab. 13. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 15. (controlled adj7 (study or design or trial)).ti,ab. 16. (erratum or tombstone).pt. or yes.ne. 17. or/8-16 18. (random$ adj sampl$ adj7 ('cross section$' or questionnaire$ or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) 19. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

(Continued)

		20. (((case adj control$) and random$) not randomi?ed controlled).ti,ab. 21. (Systematic review not (trial or study)).ti. 22. (nonrandom$ not random$).ti,ab. 23. 'Random field$'.ti,ab. 24. (random cluster adj3 sampl$).ti,ab. 25. (review.ab. and review.pt.) not trial.ti. 26. 'we searched'.ab. and (review.ti. or review.pt.) 27. 'update review'.ab. 28. (databases adj4 searched).ab. 29. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 30. Animal experiment/ not (human experiment/ or human/) 31. or/18-30 32. 17 not 31 33. 7 and 32
LILACS (Bireme)	1982 to date of search	(antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$ or antibacterial$ or anti-bacterial$ or antimycobacterial$ or anti-mycobacterial$ or bacteriocid$ or Chloramphenicol$ or Penicillin$ or Benzylpenicillin$ or Doxycyclin$ or Cefotaxim$ or Ceftriaxon$ or Azithromycin$ or Oxytetracyclin$ or Cephalosporin$ or Amoxycillin$ or Cefotaxim$ or quinolone$) [Words] and (leptospir$ or ((weil$ or Swineherd$) and disease$) or Stuttgart disease$ or hemorrhagic jaundice or spirochetal jaundice or ((cane cutter or canicola or icterohemorrhagic or mud or rice field or swamp) and fever)) [Words]
Science Citation Index Expanded (Web of Science)	1900 to date of search	#5 #3 AND #4 #4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=(leptospir* or ((weil* or Swineherd*) and disease*) or “Stuttgart disease*” or “hemorrhagic jaundice” or “spirochetal jaundice” or ((“cane cutter” or canicola or icterohemorrhagic or mud or “rice field” or swamp) and fever)) #1 TS=(antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*)
Conference Proceedings Citation Index – Science (Web of Science)	1990 to date of search	#5 #3 AND #4 #4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1

(Continued)

		#2 TS=(leptospir* or ((weil* or Swineherd*) and disease*) or "Stuttgart disease*" or "hemorrhagic jaundice" or "spirochetal jaundice" or (("cane cutter" or canicola or icterohemorrhagic or mud or "rice field" or swamp) and fever)) #1 TS=(antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*)
World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp)	Date of search will be given at review stage	leptospirosis OR leptospira OR leptospir*
ClinicalTrial.gov (clinicaltrials.gov/)	Date of search will be given at review stage	Condition: leptospirosis OR leptospira OR leptospir* OR leptospira infection
EU Clinical Trials Register, European Medicines Agency (www.clinicaltrialsregister.eu/ctr-search/)	Date of search will be given at review stage	leptospirosis OR leptospira OR leptospir*
International Standard Randomised Controlled Trial Number Registry (ISRCTN) (www.isrctn.com/)	Date of search will be given at review stage	leptospirosis OR leptospira
American Society of Tropical Medicine and Hygiene (ASTMH) (www.astmh.org/)	Presented abstract programmes, national meetings from 2005 to date of search	Abstract search engine and PDF search, dependent upon year of meeting, with "leptospir"
Infectious Diseases Society of America (IDSA) (idsa.confex.com/idsa/)	Presented abstract programmes, national meetings from 2003 to date of search	PDF search "leptospir*"
International Society of Travel Medicine (ISTM) (www.istm.org/)	Presented abstract programmes, international meetings from 2011 to date of search	Abstract search engine with "leptospir*" and use the search box with "leptospir", dependent upon year of meeting

CONTRIBUTIONS OF AUTHORS

CS, KT, TZW, PM, TE, EK, and DB specified the scope of the different components of the PICO (population, intervention, comparison, and outcomes) questions.

KT, PM, TZW, TE, EK, and CS drafted the protocol.

KT, DB, PM, TZW, EK, and CS drafted the background section.

KT, TE, TZW, PM, and CS specified statistical aspects of the protocol.

KT and CS designed the search strategy.

CS revised the protocol critically.

All authors read and approved the final version of the protocol.

DECLARATIONS OF INTEREST

PM: none.

KT: none.

TE: none.

DB: none.

CS: none.

EK: none.

TZW: none.

SOURCES OF SUPPORT

Internal sources

- Internal sources of support, Japan

  This work is in part funded by Nagasaki University (salary support for CS, TW, and TE).

External sources

- No funding sources to report, Other

  No funding sources to report

NOTES

We share common authors in three leptospirosis protocols for systematic review of interventions and, therefore, our text may overlap.