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[Intervention Protocol]

Antibiotic prophylaxis for leptospirosis

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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 antibiotics for the prevention of leptospirosis

BACKGROUND

Description of the condition

Leptospirosis is a worldwide zoonotic and waterborne disease caused by bacteria of the genus *Leptospira*. The pathogen's primary reservoirs include several mammalian species such as rodents, dogs, cattle, and swine; however, rodents are most commonly discussed when typical leptospirosis outbreaks occur. Humans are infected when they come into contact with water, soil, or food contaminated with the urine of infected animals. *Leptospira* bacteria typically enter the human body through mucous membranes and skin abrasions (Levett 2001; Bharti 2003).

Even though leptospirosis is treatable and preventable, it is considered an important emerging global public health problem due to its epidemic proportions and increasing incidence in countries around the world (Vijayachari 2008). A systematic review on global morbidity and mortality documented that annually 1.03 million people become infected (95% confidence interval (CI) 0.43 to 1.75 million) and 58,900 deaths occur (95% CI 23,800 to 95,900). Of these, a large proportion of those infected (48%, 95% CI 40 to 61%) and of deaths (42%, 95% CI 34 to 53%) were adults aged 20 years to 49 years (Costa 2015). Leptospirosis is widespread and common, particularly in the tropics, where outbreaks initiated by heavy rain and flooding cause significant morbidity and mortality (Suneth 2011). Leptospirosis has a significant global impact. In 2015, it was estimated that leptospirosis caused 2.90 million disability-adjusted life years (DALYs), with most occurring in low- and middle-income tropical countries (Torgerson 2015). The highest occurrences of leptospirosis were found in Oceania, South-East Asia, the Caribbean, and East Sub-Saharan Africa (Costa 2015). Climate change (heavy rain, floods, and cyclones), poor sanitation, growing populations, and unplanned urbanisation are all global risk factors for the emergence of leptospirosis. People living in urban slums and farmers engaged in subsistence farming (rural settings) are particularly vulnerable (Karpagam 2020). People in rural endemic areas are exposed to *Leptospira* during childhood, and significant asymptomatic seroconversion occurs (Thai 2008). Outbreaks occur in immune-naive individuals exposed to changing environmental conditions, the introduction of new *Leptospira* species, travel, or occupational or recreational activities (Bharti 2003).

Leptospirosis has a broad range of symptoms that overlap with those of several other diseases. It can have a 'biphasic' pattern, with a non-specific phase lasting one week, and a complicating immune phase lasting the second week (Chierakul 2014). The vast majority of patients experience mild, self-limiting flu-like symptoms, and do not seek medical attention. Symptoms include headache, myalgia, backache, abdominal pain, conjunctival suffusion, chills, diarrhoea, anorexia, transient rash, cough, and sore throat. Severe leptospirosis causes multi-organ dysfunction in the liver, kidneys, lungs, and brain and is occasionally associated with pulmonary haemorrhage. Weil's disease, which was first described in 1886 and is characterised by jaundice and renal failure, is still one of the most clinically recognised severe forms of leptospirosis (Haake 2015). According to a systematic study of leptospirosis outbreaks worldwide from 1970 to 2012, the overall case fatality rate (CFR) was 5% (Munoz-Zanzi 2020). According to the U.S. Centre for Disease Control and Prevention (CDC), the CFR is roughly 5% to 15% among severely affected patients and more than 50% among patients with severe pulmonary haemorrhagic syndrome (CDC 2018). The majority of deaths occur between the tenth and fifteenth days of sickness, but can happen as early as the fifth day (Kobayashi 2001).

Leptospirosis can be harder to diagnose in clinical practice because non-specific clinical signs can mimic those of other tropical infectious diseases. The diagnosis of leptospirosis is based on laboratory tests that vary depending on the disease's stage of evolution. Molecular methods (polymerase chain reaction (PCR) amplification and bacterial genome sequencing) can be used to make a laboratory diagnosis during the first week of illness after fever onset, and/or serological methods (enzyme-linked immunosorbent assay (ELISA), lateral flow tests, immunohistochemistry, or microagglutination test) can be used at the beginning of the second week of illness. In some patients, laboratory diagnosis of leptospirosis may 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. The vast majority of leptospirosis infections are self-limiting; however, complications do occur in some patients. Severe illness may necessitate admission to a hospital for treatment. To reduce the risk of complications, medical resuscitation and early antibiotic administration are used. Although the efficacy of antibiotic treatment for severe forms of leptospirosis has not been proven, the most commonly used antibiotics are doxycycline, azithromycin, cephalosporins, or penicillin. Immunologic therapies have been proposed in severe forms of leptospirosis, particularly with pulmonary and renal involvement, because immune system mediators play a critical role in the pathophysiology of these manifestations. As a result, corticosteroids and plasmapheresis have been employed. However, there is currently insufficient evidence to support the use of corticosteroids in severe leptospirosis, and the literature on the subject is limited (Rodrigo 2014; Soler 2021).

Collective control measures based on deratting, control of industrial livestock effluents, and drainage of flooded areas are effective but difficult to implement in terms of prevention. Vaccines for humans have been developed; however, they are all serovar-specific, that is, developed according to the circulating serovars in a particular region, and are not widely available. Antibiotic prophylaxis has also been recommended as a preventive measure in high-risk areas (Bhardwaj 2010; Brett-Major 2012; Vinetz 2020).

Description of the intervention

Early diagnosis and treatment are recommended for leptospirosis in order to improve prognosis and fatality (Levett 2001). However, because leptospirosis is often associated with heavy rains or flooding, such natural disasters may block roads and may damage health systems and services, making access to health facilities difficult or impossible (WHO 2020). The World Health Organization (WHO) guidelines recommend antibiotic prophylaxis for leptospirosis as a possible preventive intervention, particularly for travellers and high-risk groups (WHO 2003; Galloway 2020). Prophylaxis for leptospirosis is an approach in which an individual takes an antibiotic to reduce the likelihood of infection, either before or after potential exposure, such as through water, soil, or food contaminated with the urine from infected animals, especially during the rainy or harvest seasons (Bhardwaj 2010). Prophylaxis may be done once or more than once, depending on the protocol. Population-based mass prophylaxis has been used before or after

floods and during occupational or recreational activities where there is a risk of exposure (Bhardwaj 2010). While doxycycline is the most commonly used antibiotic in the literature, others may have been used (Bharti 2003; Illangasekera 2008; Chierakul 2014). However, the use of antibiotic prophylaxis for leptospirosis must be carefully considered because of the adverse effects and unclear benefits of prophylaxis. A systematic review concluded that weekly use of oral doxycycline 200 mg significantly increases the incidence of adverse effects such as nausea and vomiting, while the benefits in terms of reducing *Leptospira* seroconversion and clinical sequelae of infection are unclear (Brett-Major 2009).

How the intervention might work

Antimicrobial prophylaxis can be primary (prevention of an initial infection) or secondary (prevention of infection recurrence or reactivation), or it can be used to prevent infection by removing a colonising organism (Enzler 2011). Oral doxycycline is the most commonly used antibiotic for leptospirosis prevention (Schneider 2017). Doxycycline is a tetracycline-class antibiotic that is administered intravenously for severe leptospirosis infections and orally for less severe infections. By binding to the 30S ribosomal subunits, tetracycline inhibits bacterial protein synthesis (Moffa 2019). This binding prevents aminoacyl transfer RNA from binding to the acceptor site on the new amino acids to form the peptide chain. Other antibiotics such as penicillin, azithromycin, and cephalosporin are also believed to act as antibacterial prophylactic agents against *Leptospiral* and could interrupt disease progression after infection (Griffith 2006; Illangasekera 2008; Alikhani 2018).

Why it is important to do this review

Many factors, such as recent flooding, dense urban populations, and occupational or recreational exposures continue to pose a predictably high risk for leptospirosis. Antibiotic prophylaxis has been proposed as a method of preventing leptospirosis in humans. Mass antibiotic prophylaxis can provide protection by reducing the overall number of leptospirosis infected patients following high-risk exposure, decreasing the incidence and prevalence of the disease, and preventing morbidity and mortality (Goarant 2016; Abd Rahim 2018). Further, antibiotic prophylaxis for leptospirosis has been shown to have minimal adverse effects. A 2009 Cochrane systematic review examined the evidence for antibiotic prophylaxis with oral doxycycline against leptospirosis (Brett-Major 2009). This review identified three studies conducted in Brazil, Panama, and the northern Andaman Islands (Takafuji 1984; Gonsalez 1988; Sehgal 2000). It concluded that taking 200 mg of doxycycline once a week increased the risk of nausea and vomiting but did not seem to have an effect on the incidence of leptospirosis. Although the use of antibiotics for leptospirosis prophylaxis is generally recommended, data on its effectiveness are limited. This systematic review has not been updated since 2009. It is therefore important to conduct a comprehensive assessment of all available data on the benefits and harms of antibiotic prophylaxis for leptospirosis. The results of this systematic review may provide a sound basis for policymakers and public health authorities in formulating guidelines for the prevention and control of leptospirosis.

OBJECTIVES

To assess the beneficial and harmful effects of antibiotics for the prevention of leptospirosis

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials studying antibiotic prophylaxis for leptospirosis regardless of year, language, form of publication, blinding, comparator, and outcomes reported. We will include cluster randomised trials and cross-over trials, if found. We will initially consider eligible for inclusion any published cross-over randomised trials due to the likelihood of limited published trial data for leptospirosis. We will evaluate suitability of data from such studies for inclusion in meta-analysis.

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

Types of participants

- Agricultural workers in endemic regions and veterinarians
- Those with other high-risk occupations due to contact with water or animals
- High-risk activity travellers, such as troops and eco-tourists
- Those experiencing emergencies resulting in potential exposure to contaminated water with *Leptospira* such as flood, heavy rain, or tsunami

As published trial data for leptospirosis are likely to be limited, we will consider for inclusion studies with only a subset of eligible participants, while remaining faithful to the objectives of the review and rigorous Cochrane guidelines. 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 (Joanne 2021).

Types of interventions

Experimental intervention

- Antibiotics given for the prevention of leptospirosis, administered using any route, dosage, and schedule

Control interventions

- Placebo or no intervention
- Another antibiotic or another dose or schedule

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

Types of outcome measures

We aim to assess all outcomes, irrespective of original study design, at the longest follow-up.

Primary outcomes

- Proportion of people with all-cause mortality

- Proportion of people with leptospirosis
  - Laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome
  - Clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation
  - Clinical diagnosis of leptospirosis confirmed by laboratory diagnosis
- Serious adverse events (proportion of participants with serious adverse events.

We will consider an event as a serious adverse event if it fulfils the definition of serious adverse events of the International Council for Harmonisation's (ICH) Guidelines (ICH-GCP 2016), that is, any event that leads to death; is life-threatening; requires in-patient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability, congenital birth defect, or anomaly; and any important medical event which may have jeopardised the patient or requires intervention to prevent permanent damage. A serious adverse reaction will be a serious adverse event where the study authors clearly state 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 (WHOQOL), SF-36, SF-12, Sickness Impact Profile, Nottingham Health Profile, EuroQol (EQ-5D), or 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
  - 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 were reported.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Hepato-Biliary Group (CHBG) Controlled Trials Register (searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web; we will provide the date of search at the review stage), the Cochrane Central Register of Controlled Trials (latest issue) in the Cochrane Library, MEDLINE Ovid (1946 to the date of the search), Embase Ovid (1974 to the date of the search), LILACS (Bireme; 1982 to the date of the search), Science Citation Index Expanded (Web of Science; 1900 to the date of the search), and Conference Proceedings Citation Index-Science (Web of Science; 1990 to the date of the search). Appendix 1 gives the preliminary search strategies with the expected time spans of the searches.

Searching other resources

We will search the following clinical trials registries for ongoing clinical trials (search strategies are provided in Appendix 1): World Health Organization International Clinical Trials Registry Platform (WHO 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/). We will provide the date of search at the review stage.

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

Once we decide to include a study, we will screen its bibliography to seek other potential candidate studies. We will also search for post-publication amendments and examine any relevant retraction statements and errata, as errata can reveal important limitations or even fatal flaws in included studies (Lefebvre 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 2021a). We will use Review Manager Web software to perform the meta-analysis (RevMan Web 2020).

Selection of studies

Two review authors (PM and TZW) will independently review titles and abstracts of candidate studies obtained by the electronic search to determine if they meet the inclusion criteria of our systematic review. We will obtain full-text papers of all studies that appear eligible after the screening, and review them to identify the studies that meet the eligibility criteria. We will record the reasons for exclusion for studies that do not match the inclusion criteria. We will resolve disagreements with a third review author (CS). We will not impose any language restrictions.

We will use Covidence software for study screening (Covidence 2020). We will record the selection process in sufficient detail to complete a PRISMA-S flow diagram (Rethlefsen 2021).

During the selection of randomised clinical trials, we will note, and extract data on adverse effects from, observational studies such as quasi-randomised studies, cohort studies, or patient reports. We will not run a separate search for observational studies. We will present the data in a narrative or table format. We recognise that not conducting a separate systematic search for observational studies will limit the data that we will be able to collect on adverse events. If we find a benefit of antibiotic prophylaxis, a systematic review of harms based on observational studies will be required (Storebø 2018).

Data extraction and management

We will use a pre-piloted data extraction form to extract trial data for the review. Two review authors (PM and TZW) will independently extract the following characteristics from included studies. A third review author (CS) will resolve any disagreements.

- Study and publication identifiers
- Database index number
- First author
- Journal
- Year of publication

- Language
- Location
- Study methods
- Study design
- Number of arms or groups
- 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
- The total duration of the study
- Duration participants were followed
- Details of any 'run-in' period
- Location (country, prefecture/district)
- 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, co-morbidity
- 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 and control groups
- Concomitant treatment
- Outcomes
- Definition of primary and secondary outcomes (including details on diagnostic laboratory assays employed) and adverse effects
- Outcomes measurements
- Time points for follow-up reported
- Notes
- Funding source for trial
- Notable conflicts of interest of trial authors

Assessment of risk of bias in included studies

We plan to assess the effect of assignment to the intervention using the Cochrane 'Risk of bias' tool (RoB 2) which is a revised tool to assess the risk of bias in randomised trials (Sterne 2019; Higgins 2021b). 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 and TZW) will independently assess the risk of bias of all-cause mortality, proportion of people with leptospirosis, serious adverse events (hospitalisation and long-term disability); 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 (Lasserson 2016; Sterne 2019; Higgins 2021b; Higgins 2021c).

- 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 careers 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 patients randomised, if there was any evidence that the result was not biased by missing outcome data and also 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: (1) Yes; (2) Probably yes; (3) Probably no; (4) No; and (5) No information. Elaborations to these signalling questions can be found in Higgins 2021c. 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 to be at low risk of bias.

- Some concerns: the trial raises some concerns in at least one of the domains, but there is no judgement of high risk of bias for any domain.
- High risk of bias: the trial is judged to be 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 2021b).

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 (Higgins 2020; Eldridge 2020; Higgins 2021c). 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 plan to use the data only from the first period of the 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 https://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). In summary of findings tables, we will present the outcomes which we consider most relevant for clinical practice. These outcomes are all-cause mortality; proportion of people with leptospirosis; serious adverse events (hospitalisation and long-term disability); and quality of life.

Measures of treatment effect

We will collect and upload the outcome data for each study into the data tables in Review Manager Web so that we can calculate the treatment effects (RevMan Web 2020). We will analyse dichotomous outcome data as risk ratios (RR) with 95% CIs, and continuous data as mean differences (MD) and 95% CIs or standardised MD (SMD) and 95% CIs when different scales are used to measure the same outcome. We will present medians and interquartile ranges in a narrative format for continuous data that are skewed. We will present a forest plot that displays effect estimates and CIs for individual studies (Lewis 2001). A meta-analysis will only be conducted when the study group is sufficiently homogeneous (Deeks 2021).

We will focus on a hybrid approach (including both a pre-specified set of adverse events and any other adverse events identified during the conduct of the review) in order to maximise the inclusion of available safety data. We will apply the same eligibility criteria for intended (benefit) and unintended effects (harm). We will use the RoB 2 tool for randomised trials to assess risk of bias for all studies. Before comparing or synthesising adverse effects data across studies, we will evaluate the consistency and similarity of case definitions and methods of ascertainment for harms outcomes from the various studies. We will code adverse events carefully to avoid having categories that have not been reported in the primary studies and to avoid splitting unnecessarily (Peryer 2021).

Unit of analysis issues

The unit of analysis for randomised clinical trials is an individual participant. If multiple trial arms are reported in a single trial, we will include only the treatment arms relevant to the review topic and comparison. Although it is optimal to create a single pair-wise comparison, if two comparisons are combined in the same study with the same placebo participants 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 arbitrary omission of relevant groups and double-counting of participants (Higgins 2021d).

For cluster-randomised clinical trials, the cluster will be the unit of analysis, not the individual participant, so that we can avoid unit-of-analysis error which may cause artificially narrow CIs and small P values, resulting in false-positive conclusions that the intervention had an effect (Higgins 2021c).

We do not anticipate finding many clinical trials of antibiotic prophylaxis for leptospirosis using a cross-over design. If we identify trials with a cross-over design, we will include the data from the first trial period in order to avoid residual effects from the treatment (Higgins 2021c). We will use participant trial data at the longest follow-up to avoid repeated observations on trial participants (Higgins 2021d).

Dealing with missing data

We will contact authors to try to verify study design and key study characteristics, and obtain missing numerical outcome data on the primary outcomes. If this is not successful, 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 according to the methods described in *the Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). If these calculations are not possible, we will assess the risk of bias due to missing outcome data by using the RoB 2, undertake sensitivity analyses, and explore the impact of including these studies in the overall assessment of results (Page 2021). We will perform an intention-to-treat analysis as a primary analysis approach (available case analysis or modified intention-to-treat approach), whenever possible (Fergusson 2002). Intention-to-treat approach assumes that missing data are missing at random. We will conduct sensitivity analyses for binary outcomes, assuming i) a worst-case scenario (missing data are assumed to be a “negative” outcome) and ii) 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 for 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 discuss the potential impact of all missing cases on our findings of the review in the Discussion section.

Assessment of heterogeneity

We will consider the clinical and methodological diversity of the evidence in the review text based on the characteristics of the study, including study design, population characteristics, and details of the intervention.

Based on the visual assessment of the forest plot, we will describe the direction and magnitude of the effect and the degree of overlap between the CIs. We will assess statistical heterogeneity by performing Chi^2 and I^2 statistics, using $P < 0.10$ as a cut-off point for statistical heterogeneity (Israel 2011). We will also quantify the heterogeneity using the I^2 statistic and interpret it as follows (Deeks 2021).

- 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

If we identify substantial heterogeneity, we will follow the strategies for dealing with heterogeneity described in *the Cochrane Handbook for Systematic Reviews of Interventions* and explore possible causes for differences in population, intervention, comparison, and outcome and the quality of the research (Deeks 2021). If heterogeneity is judged to be likely, we will consider subgroup analyses and/or sensitivity tests. If heterogeneity is present, we will conduct a random-effects meta-analysis to account for between-study heterogeneity.

Assessment of reporting biases

We will report biases (e.g. publication, time lag or multiple publications) at all points of data analysis and interpretation. If we are able to identify 10 or more trials that can be included in a meta-analysis, we will create and examine a funnel plot to analyse possible publication bias (Page 2021). If we identify any trial protocols, clinical trial registrations, or abstracts indicating the existence of unpublished studies, we will attempt to contact the investigators in order to determine the status of these unpublished studies.

Sensitivity analyses to examine small-study effects will include: applying Mantel-Haenszel weighting rather than inverse-weighting; conducting both random-effects and fixed-effect regression (Deeks 2021); and inspection and tests of funnel plot asymmetry, when there are at least 10 studies to be included in the meta-analysis (Page 2021).

Data synthesis

We will pool data, such as RRs and MDs with 95% CIs, from studies we determine to be clinically homogeneous. If there is more than one study providing usable data in any single comparison, we will conduct a meta-analysis (Ryan 2016). However, if we find considerable heterogeneity, particularly in the direction of the effect, we will not perform a meta-analysis, regardless of the number of trials found (Deeks 2021). We will apply both fixed-effect and random-effects meta-analysis. We will report P values and 95% CIs from both methods. If these analyses show different results, we will choose as the main result the analysis with the highest P value (Jakobsen 2014).

We will use Review Manager Web software to perform meta-analysis (RevMan Web 2020).

Given the likelihood that there will be a limited number of studies meeting eligibility criteria, we will aim to include as much data as possible. We will perform a sensitivity analysis including only studies at low risk of bias in the meta-analysis if possible.

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 2021).

Subgroup analysis and investigation of heterogeneity

We do not think that we will perform subgroup analysis for two reasons. First, we do not expect that many studies have been conducted on the use of prophylactic antibiotics for leptospirosis, and power for a subgroup analysis would be extremely limited. Second, because of the nature of subgroup analyses, which are not based on randomised comparisons unless the randomisation was stratified by the subgroup of interest, subgroup analyses may overestimate positive intervention effects or underestimate negative effects (Lagakos 2006; Wang 2007).

However, if we detect substantial heterogeneity ($I^2 > 50\%$) and there are a sufficient number of trials (Deeks 2021), there is potential to explore possible explanatory variables in subgroup analyses.

Subgroups of interest could include:

- Vested interests compared to no vested interests (Lundh 2017);
- Type of intervention such as type of antibiotic (doxycycline, penicillin, etc);
- Type of administration such as route, dose, timing (pre- or post-exposure), and duration; and
- Population such as troops or travellers compared to endemic populations.

Should we consider it appropriate, outcomes in any subgroup analyses will be our three primary outcomes which we will analyse using interaction tests available within RevMan Web (RevMan Web 2020), reporting the results in forest plots with the Chi^2 statistic, P value, and I^2 value of the interaction test.

Sensitivity analysis

For the purpose of assessing the robustness of the results, we plan to perform the following sensitivity analyses of the impact of heterogeneity of the included studies and the risk of bias (Boutron 2021).

- Repeat the analysis excluding studies at an overall high risk of bias.
- Repeat the analysis excluding unpublished studies (if there are any).

We will prepare a table summarising the results of the sensitivity analysis.

In addition, we plan to perform a Trial Sequential Analysis to assess imprecision of primary outcome results. We will then compare our evaluation of imprecision based on GRADE 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.

Trial Sequential Analysis

We will use Trial Sequential Analysis as a sensitivity analysis to assess imprecision for the three primary outcomes, i.e. all-cause mortality; people with leptospirosis; and serious adverse events (hospitalisation and long-term disability; Jakobsen 2014; Castellini 2018; Gartlehner 2019). 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 diversity-adjusted required information size (DARIS), i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect (Brok 2008; Wetterslev 2008; Brok 2009; Wetterslev 2009; Thorlund 2010; Wetterslev 2017). On the basis of the DARIS, we will construct the trial sequential monitoring boundaries for benefit, harm, and futility (Wetterslev 2008; Wetterslev 2009; Thorlund 2017; 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 trials may be superfluous. However, if the boundaries for benefit or harm are not crossed, it is most probably necessary to continue conducting trials in order 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 three primary outcomes (all dichotomous), we will base the DARIS on the event proportion in the control group; assuming a plausible relative risk reduction for all-cause mortality, leptospirosis, and serious adverse events of 10%; a risk of type I error of 2.5% due to three 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). 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 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).

Summary of findings and assessment of the certainty of the evidence

We will use GRADEpro software (GRADEpro GDT) to create summary of findings tables. Summary of findings tables provide information on comparative risk, relative risk, number of participants, number of studies, and certainty of the evidence for the outcomes in the review comparisons. We will create two summary of findings tables: one on the comparison of antibiotic prophylaxis versus placebo or no intervention; and another on antibiotic prophylaxis versus another antibiotic, dose, or schedule. We will present our assessment of proportion of people with all-cause mortality, leptospirosis, serious adverse events (hospitalisation and long-term disability), and quality of life. We will use methods and recommendations described in Section 8.5 and Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b; Schünemann 2021), and the GRADE Handbook (Schünemann 2013). We will provide the maximum follow-up and the range of follow-up for each of the afore listed outcomes. Two review authors (PM and TZW) will grade the evidence of these outcomes independently of each other; we will resolve disagreements through discussion, with arbitration from CS if necessary.

In the GRADE approach, there are five factors that reduce the certainty of evidence in randomised clinical trials: risk of bias, inconsistency of results, indirectness of evidence, imprecision, and publication bias. The GRADE approach classifies the certainty of evidence into four levels:

- **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.

Through this approach, we will assess the certainty of the evidence presented in the review and draw conclusions (GRADEpro GDT). To inform the GRADE assessment, we will use the overall judgement of risk of bias (see Assessment of risk of bias in included studies). We will justify all decisions to downgrade the certainty of evidence using footnotes and, where appropriate, a comment section to aid the reader's understanding.

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APPENDICES

Appendix 1. Search strategies

Database	Timespan	Search strategy
Cochrane Hepato Biliary Group Controlled Trials Register (via the Cochrane Register of Studies Web)	Date of search will be given at the review stage.	(leptospir* or (weil* disease)) AND (prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*)
Cochrane Central Register of Controlled Trials in the Cochrane Library	Latest issue	#1 MeSH descriptor: [Leptospirosis] explode all trees #2 (leptospir* or (weil* disease)) #3 #1 or #2 #4 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees #5 (prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*) #6 #4 or #5 #7 #3 and #6
MEDLINE Ovid	1946 to the date of the search	1. exp Leptospirosis/ 2. (leptospir* or (weil* disease)).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 Antibiotic Prophylaxis/ 5. (prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*).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

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		8. (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or trial.ti. 9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 10. 7 and (8 or 9)
EMBASE Ovid	1974 to the date of the search	1. exp leptospirosis/ 2. (leptospir* or (weil* disease)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 3. 1 or 2 4. exp antibiotic prophylaxis/ 5. (prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*).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] 6. 4 or 5 7. 3 and 6 8. Randomized controlled trial/ or Controlled clinic trial/ or trial.ti. 9. (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] 10. 7 and (8 or 9)
LILACS (Bireme)	1982 to the date of the search	(leptospir$ or weil$ disease) [Words] and (prophyla$ or prevent$ or protec$ or premedic$ or chemoprophyla$ or expos$) [Words]
Science Citation Index Expanded (Web of Science)	1900 to the date of the search	#5 #4 AND #3 #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=(prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*) #1 TS=(leptospir* or (weil* disease))
Conference Proceedings Citation Index – Science (Web of Science)	1990 to the date of the search	#5 #4 AND #3 #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=(prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*)

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		#1 TS=(leptospir* or (weil* disease))
World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/ictrp)	Date of search will be given at the review stage.	leptospirosis OR leptospira OR leptospir*
ClinicalTrial.gov (clinicaltrials.gov/)	Date of search will be given at the review stage.	Condition: leptospirosis OR leptospira OR leptospir* OR leptospira infection
Clinical trials for steroid, EU Clinical Trials Register, European Medicines Agency (www.clinicaltrialsregister.eu/ctr-search/search)	Date of search will be given at the 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 the review stage.	leptospirosis OR leptospira
American Society of Tropical Medicine and Hygiene (ASTMH) (www.astmh.org/)	Presented abstract programs, national meetings from 2005 to the date of the 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 programs, national meetings from 2003 to the date of the search	PDF search “leptospir*"
International Society of Travel Medicine (ISTM) (www.istm.org/)	Presented abstract programs, international meetings from 2011 to the date of the search	Abstract search engine with "leptospir*" and use the search box with "leptospir", dependent upon year of meeting

CONTRIBUTIONS OF AUTHORS

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

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

KT, DMB, TZW, PM, and CS drafted the background section.

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

KT and CS designed the search strategy.

CS critically revised the protocol.

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

DECLARATIONS OF INTEREST

CS: none known

KT: none known

DMB: none known

TZW: none known

PM: none known

TE: none known

EK: none known

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Internal sources

- No funding sources to report, Other

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External sources

- No funding sources to report, Other

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