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Corticosteroids for treatment of leptospirosis (Protocol)

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[Intervention Protocol]

Corticosteroids for treatment of leptospirosis

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ABSTRACT

Objectives

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

To assess the benefits and harms of corticosteroids for treatment of people with leptospirosis.

BACKGROUND

Description of the condition

Leptospirosis is a zoonotic and waterborne disease with a worldwide distribution caused by bacteria of the genus *Leptospira*. Animals such as cattle, pigs, horses, dogs, and rodents play the reservoir's role. Human infection occurs through contact with contaminated water, soil, or food by urine from infected animals. The *Leptospira* bacteria commonly enter the human body through mucous membranes or skin, especially abraded skin (Bharti 2003; Levett 2001).

Each year, more than one million cases of leptospirosis are reported worldwide, with an estimated 59,000 deaths. However, there are no reliable global incidence data for leptospirosis as they may be under-reported (Costa 2015). Leptospirosis is prevalent worldwide, particularly in tropical regions, and causes high mortality and morbidity during outbreaks in leptospirosis-endemic areas (Suneth 2011). The global burden is estimated to be significant, with approximately 2.90 million disability-adjusted life years (DALYs) lost each year, mainly in resource-limited tropical countries (Torgerson 2015).

There are no specific clinical symptoms for leptospirosis, which has a broad clinical picture mimicking several other tropical diseases. The severity of symptoms ranges from a mild, self-limiting febrile illness to a severe, life-threatening illness. The classic leptospirosis pattern has been defined as 'biphasic', with a one-week non-specific leptospirosis phase followed by a second-week immune phase with complications (Farrar 2014). The vast majority of patients have mild, self-limiting influenza-like symptoms and may not seek medical attention. A small percentage of patients have a sudden onset of febrile illness with non-specific symptoms such as headache, myalgias, back pain, abdominal pain, conjunctivitis, chills, diarrhoea, loss of appetite, transient rash, cough, and sore throat. Severe leptospirosis causes multi-organ dysfunction affecting the liver, kidneys, lungs, and brain, and in some cases, it 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).

Diagnosis of leptospirosis can be challenging, especially in under-resourced clinical settings. The clinical presentation is similar to other tropical infectious diseases, with non-specific symptoms. Diagnostic tests include polymerase chain reaction (PCR) platforms and serological assays, of which the macroscopic agglutination test (MAT) is the gold standard and most used (Budihal 2014). However, these tests are limited by availability and the costs of maintaining laboratory standards. In particular, MAT requires constant maintenance of bacterial cultures and is less sensitive in the acute phase of the disease. PCR tests, although more sensitive, are not widely available or used in regions of high endemicity. Laboratory diagnosis of leptospirosis requires a mixture of diagnostic procedures and samples appropriate to the stage of the disease and availability (Budihal 2014; Koizumi 2020).

Antibiotics, most commonly doxycycline, azithromycin, cephalosporins, or penicillin, are used to treat leptospirosis, though the benefit of antibiotic treatment remains unknown, particularly in severe diseases (Brett-Major 2012). Antibiotic treatment of spirochaetal infections such as leptospirosis can be complicated by the Jarisch-Herxheimer reaction, which is characterised by shaking chills, fever, worsening of skin rashes, and, in rare cases, multi-organ failure (Aronson 1976). In one review of 976 leptospirosis cases treated with antibiotics, the incidence of the Jarisch-Herxheimer reaction was 9% (Butler 2017). Due to the critical role that immune system mediators play in the pathophysiology of these manifestations, immunological therapeutics have been proposed in severe leptospirosis, particularly when lung and renal damage are present. As a result, corticosteroids and plasmapheresis were used (Rodrigo 2014).

Description of the intervention

Corticosteroids are hormones that are primarily produced by the adrenal gland. They play a role in a variety of physiological processes, including the immune response and inflammation regulation, the stress response, carbohydrate metabolism, protein catabolism, blood electrolyte regulation, vascular tone regulation, and endothelial integrity maintenance (Coutinho 2011; Kaufmann 2008). Corticosteroids are prescribed to treat infections, inflammatory diseases, allergies, and immunological and malignant disorders (Chen 2015). However, their beneficial effects are frequently accompanied by adverse effects such as immunosuppression, hypertension, wound repair inhibition, osteoporosis, psychosis, and metabolic disturbances (Rhen 2005).

How the intervention might work

The pathogenesis of leptospirosis is linked to immune activation, particularly cytokine production. In one study comparing 44 Thai people with definite or possible leptospirosis to healthy blood donors, De Fost and colleagues found that T-cell-mediated immunity is part of the early host response to leptospirosis (De Fost 2007). Profiling of antibody responses in people with severe or mild leptospirosis revealed that more than 74% of those in the severe group had a significant increase in immunoglobulin (Ig)G compared to those in the mild group (Aquino 2017). The study found the humoral immune response of people with severe leptospirosis was consistent with a demonstrated antibody profile typical of first exposure. Another study found that cytokine profiles distinguished between mild and severe leptospirosis cases, and that the cytokine storm is thought to be a major contributory factor in leptospirosis disease severity (Reis 2013).

Keeping this in mind, corticosteroids may be useful in modulating the immune response, particularly in people with severe leptospirosis. Corticosteroids may help maintain homeostasis and control immune dysregulation during critical illnesses. Corticosteroids may also work by reducing the frequency or severity of the Jarisch-Herxheimer reaction. However, studies on the efficacy of using corticosteroids before antibiotic administration to prevent or mitigate the severity of the reaction have not provided conclusive evidence (Butler 2017; Strominger 1994; Zifko 1994).

Why it is important to do this review

Corticosteroids such as methylprednisolone, prednisone, hydrocortisone, and dexamethasone have been used to treat leptospirosis (Khoo 2019; Tanaka 2017). However, the effectiveness of corticosteroids in treating leptospirosis is still debated. One 2014 systematic review identified five studies on high-dose corticosteroids in the treatment of severe leptospirosis, one of which was an open randomised clinical trial. Four studies showed

that corticosteroids were beneficial in the treatment of severe disease with pulmonary involvement. However, one trial found that using corticosteroids to treat severe leptospirosis was ineffective and may increase the risk of nosocomial infections (Rodrigo 2014).

More recently, several studies have revealed favourable benefits of corticosteroids in treating coronavirus disease 2019 (COVID-19) and similar severe acute respiratory diseases (Horby 2020; Ye 2020a; Ye 2020b). Given these developments and the possibility that trials evaluating corticosteroids for leptospirosis have been published since 2014, a thorough appraisal of the literature is required. This is important, given the worldwide prevalence and mortality potential of leptospirosis, and it will help clinicians navigate evidence related to the benefits and harms of corticosteroids in the treatment of people with leptospirosis.

OBJECTIVES

To assess the benefits and harms of corticosteroids for treatment of people with leptospirosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials studying corticosteroids for treatment of leptospirosis regardless of year, language, the form of publication, blinding or comparator, and outcomes reported. We will include cluster randomised trials and the first period of cross-over trials if found. We will evaluate the suitability of data from such trials for inclusion in the 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

People with leptospirosis, of any age and sex.

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. If the outcome results of the subset of eligible participants are not presented separately in the identified trial publications or could not 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

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

Control intervention

- Placebo.
- No intervention.
- Standard care (as defined by study authors).

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

Primary outcomes

- Proportion of people with all-cause mortality.
- Serious adverse events. Proportion of people with one or more serious adverse events. We will consider an event as a serious adverse event if it fulfilled the definition of serious adverse events of the International Council for Harmonisation (ICH) Guidelines, 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 that may have jeopardised the patient or requires intervention to prevent it (ICH-GCP 2016). A serious adverse reaction will be 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 (WHOQOL), 36-item Short Form (SF-36), 12-item Short Form (SF-12), Sickness Impact Profile, Nottingham Health Profile, EuroQol (EQ-5D), or Short-Form Six-Dimension (SF-6D) (Nemeth 2006; Pequeno 2020).
- Proportion of people with one or more adverse events considered as non-serious.
  - 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

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 (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid (Excerpta Medica Database), LILACS (Bireme), Science Citation Index Expanded, and Conference Proceedings Citation Index – Science. Science Citation Index Expanded and Conference Proceedings Citation Index – Science will be searched simultaneously through the Web of Science.

Appendix 1 provides the preliminary search strategies for the respective 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: the 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/). Search strategies are provided in Appendix 1. We will provide the date of search at the review stage.

We will also search the following conference abstracts and proceedings from as far back as possible when we can browse them to identify potentially eligible studies: 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 use its bibliography to search for further 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 even fatal flaws in included studies (Lefebvre 2022).

We will check the studies included in any reviews that are found in the searches, as these may be eligible.

We will search for relevant grey literature sources such as reports, dissertations, theses, and conference abstracts (e.g. 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 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 and perform meta-analyses (Review Manager Web 2020).

Selection of studies

Two review authors (NL, TZW) will independently review the entire list of candidate studies obtained by the searches. 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 2021). 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 these 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 use an online translation tool such as Google Translate and language skills of colleagues during screening. When non-English language articles meet the inclusion criteria, a member of our team with relevant language skills or an external translator will be involved during the review process, or we will use a premium translation tool. 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 2020 flow diagram for new systematic reviews, which includes searches of databases, registers, and other sources (Page 2021a; Page 2021b).

If we find observational studies (quasi-randomised studies, cohort studies, patient-reported) that report on adverse effects of corticosteroids during our search for randomised clinical trials that meet the inclusion criteria for our review, we will ensure to extract relevant data on harms and presented them 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 there is a benefit of the intervention (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 (NL, TZW) will independently extract the following study characteristics from included studies. Any disagreements will be resolved with a third review author (CS).

- 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
  - Total duration of 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 disease condition, comorbidity
  - Withdrawals and the reasons
- Interventions
  - Details of intervention
    - Type of corticosteroids
    - Route of admission
    - Dose
    - Timing of corticosteroid use
    - Duration of intervention
  - Definition of comparison, control groups
  - Concomitant treatment (antibiotic therapy)
- 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

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 (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; that is, we will use the intention-to-treat principle.

Two review authors (NL, TZW) will independently assess the risk of bias of the proportion of people with all-cause mortality, proportion of people with one or more serious adverse events, quality of life, and proportion of people with one or more adverse events considered as non-serious. 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: (1) Yes; (2) Probably yes; (3) Probably no; (4) No; and (5) 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 judgements 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 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 the review preparation, we will use 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 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). In summary of findings tables, we will present the outcomes that we consider most relevant for clinical practice. These outcomes are all-cause mortality; serious adverse events (hospitalisation and long-term disability); quality of life; and proportion of people with adverse events considered as non-serious. As we have one primary time point for analyses of the outcomes, we will present the results for the dichotomous and continuous outcomes at maximum follow-up.

Measures of treatment effect

We will enter the outcome data for each study 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 (RRs) 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. We will interpret the 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 that displays effect estimates and CIs for individual trials (Lewis 2001). We will undertake meta-analyses only when a group of trials is sufficiently homogeneous (Deeks 2022).

Unit of analysis issues

Unit of analysis is an individual participant for randomised clinical trials. If multiple trial arms are reported in a single trial, we will include only the treatment arms relevant to the review topic and comparison. We will list all treatment arms in the characteristics of included studies table, even if they are not used in the review. Although it is optimal that we can 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. corticosteroid A versus placebo and corticosteroid 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 2022d).

For cluster-randomised clinical trials, the cluster will be the unit of analysis, not the individual participants, so that we can avoid unit-of-analysis errors that may cause artificially narrow CIs and small P values, resulting in false-positive conclusions that the intervention had an effect (Higgins 2022c).

We do not anticipate finding many clinical trials of corticosteroids for treatment of leptospirosis using a cross-over design. In case there are trials using cross-over design, we will include the data from the first trial period to avoid residual effects from the treatment (Higgins 2022c). We will use participant trial data at the longest follow-up to avoid repeated observations of trial participants (Higgins 2022d).

Dealing with missing data

We will contact trial investigators to verify key study characteristics and obtain missing outcome data on the primary outcomes.

We will perform, as our primary analysis, an intention-to-treat analysis whenever possible, or we will perform a modified intention-to-treat analysis or available-case analysis, based on the study authors' data (Fergusson 2002). In case of studies with missing outcome data, we will then perform sensitivity analyses for binary outcomes to assess the effect of a possible attrition bias. We will include trial participants with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios.

- Extreme-case analysis favouring the experimental intervention ('best-worse' case scenario): none of the dropouts/participants lost from the experimental arm, but all the dropouts/participants lost from the control arm experienced the outcome, including all randomised participants in the denominator.
- Extreme-case analysis favouring the control intervention ('worst-best' case scenario): all dropouts/participants lost from the experimental arm, but none from the control arm experienced the outcome, including all randomised participants in the denominator.

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 would suggest a risk of attrition bias.

We will address the potential impact of all missing cases on our findings of the review in the discussion section (Deeks 2022).

Assessment of heterogeneity

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

We will visually inspect forest plots and describe the direction and magnitude of effects and the degree of overlap between CIs. We will assess statistical heterogeneity with the Chi^2 and I^2 statistics, using a cut-off point of P less than 0.10 to indicate statistical heterogeneity (Israel 2011). We will quantify heterogeneity using the I^2 statistic, with the following interpretation (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.

We will take into account interpretation of the value of the I^2 statistic with consideration of relation to the magnitude and direction of effects and strength of evidence for heterogeneity.

If we identify substantial heterogeneity, we will follow the strategies for addressing heterogeneity given by the *Cochrane Handbook for Systematic Reviews of Interventions* and explore possible causes based on the differences of population, intervention, comparison, and outcome and quality of research (Deeks 2022). We will aim to investigate possible reasons for heterogeneity via subgroup analyses where possible. We will use the random-effects model meta-analysis to account for the presence of between-study heterogeneity. If heterogeneity is considerable, we may decide not to do a meta-analysis, and instead, we will present the outcome result in a narrative way.

Assessment of reporting biases

If we identify 10 or more trials that can be included in a meta-analysis, per outcome, we will create and examine a funnel plot to analyse possible publication biases or bias in small-study effects. We will plot the RR on a logarithmic scale against its standard error (Egger 1997). Asymmetry in a funnel plot may be observed if study effect sizes are small, and may or may not be due to publication bias. If our searches identify any trial protocols, clinical trial registrations, or abstracts indicating the existence of unpublished studies, we will attempt to contact the investigators to determine the status of these unpublished studies.

Data synthesis

We will pool data and report summary statistics such as RRs and MDs with 95% CIs from trials that we determine to be clinically homogeneous. If more than one trial provides usable data in any single comparison, we will conduct a meta-analysis. However, if there is considerable heterogeneity, particularly if the direction of effects is inconsistent, we will not perform a meta-analysis regardless of the number of trials we find (Deeks 2022). We will apply both fixed-effect and random-effects meta-analysis. P values and 95% CIs will be calculated from both fixed-effect meta-analyses (DeMets 1987) and random-effects meta-analyses (DerSimonian 1986). We will use the fixed-effect meta-analysis as a sensitivity analysis.

We will perform a meta-analysis using Review Manager Web(Review Manager Web 2020).

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 conduct subgroup analyses for two reasons. First, we do not assume that there are many studies about corticosteroid use for leptospirosis. Second, subgroup analyses have a risk to overestimate positive intervention effects and underestimate negative effects because they are observational by nature and are not based on randomised comparisons (Lagakos 2006; Wang 2007).

However, if we detect substantial heterogeneity (I^2 greater than 50%) in the primary analyses and there are a sufficient number of trials for subgroup analyses (Deeks 2022), we will explore possible explanatory variables to assess whether the effect of corticosteroids was influenced by:

- disease severity (as defined by the study authors);
- intervention route;
- type of corticosteroids used;
- dose of corticosteroids;
- timing of corticosteroids administration; or
- duration corticosteroids administration.

We hypothesise that increased disease severity could be associated with increased effectiveness of the intervention and that the effectiveness of the intervention could vary by different corticosteroid type or formulations, doses, and duration of treatment. We plan to perform subgroup analysis on proportion of people with all-cause mortality and serious adverse events, that is the primary outcomes of our review. To assess the presence of a statistically significant subgroup difference, we will consider the P value from the Chi^2 test for subgroup differences.

Sensitivity analysis

We will perform sensitivity analyses to look at the impact of including trials for which missing statistics have been calculated, and the effect of risk of bias in the included studies as follows (Boutron 2022).

- Repeating the analysis excluding studies at an overall high risk of bias.
- Repeating the analysis using the fixed-effect method meta-analysis.
- Repeating the analysis excluding unpublished studies (if there are any).
- Extreme-case analyses favouring the experimental intervention as reported in Dealing with missing data.
- Extreme-case analysis favouring the control intervention (as reported in Dealing with missing data.

We will report the result of the sensitivity analyses by producing summary tables.

In addition, we plan to perform a Trial Sequential Analysis (see below) to assess imprecision of 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; i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect), and by one level if between 50% and 100% of the DARIS (Wetterslev 2009; Wetterslev 2017). 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; TSA 2017).

Trial Sequential Analysis

We will use Trial Sequential Analysis as a sensitivity analysis to assess imprecision for the two primary outcomes only (i.e. proportion of people with all-cause mortality and proportion of people with one or more 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 one 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 DARIS, that is, 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 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 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 create one or more summary of findings tables, depending on the number of comparisons. We will present outcome results for proportion of people with all-cause mortality, proportion of people with one or more serious adverse events, quality of life, and proportion of people with one or more adverse events considered as non-serious, all analysed at maximum follow-up. We will provide the mean or median, and their ranges of each outcome. We will provide comparative risks, relative risks, number of participants and studies, and certainty of the evidence for corticosteroid use versus placebo/no intervention/standard care comparisons. 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), using GRADEpro GDT (GRADEpro GDT). The GRADE approach uses five factors that reduce the certainty of evidence in randomised clinical trials (risk of bias, the inconsistency of results, indirectness of evidence, imprecision, and publication bias). Two review authors (NL, TZW) will independently assess these factors. We will resolve disagreements with a third review author (CS). The GRADE approach 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 draw conclusions about the certainty of the evidence presented in the review (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 we will add comments in the comment column to aid the reader's understanding of the review if necessary.

There are four GRADE Working Group grades of evidence.

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

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

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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 review stage	(corticosteroid* or corticoid* or glucocortico* or hydrocortison* or hydroxycorticosteroid* or prednisolon* or prednison* or betamethason* or dexamethason* or beclomethason* or methylprednisolon* or "adrenal cortex hormon*" or steroid* or hydroxypregnenolon* or tetrahydrocortisol* or cortodoxon* or cortison* or fludrocortison* or corticosteron* or paramethason* or cortisol* or triamcinolon*) 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: [Adrenal Cortex Hormones] explode all trees #2 MeSH descriptor: [Glucocorticoids] explode all trees #3 MeSH descriptor: [Steroids] explode all trees #4 (corticosteroid* or corticoid* or glucocortico* or hydrocortison* or hydroxycorticosteroid or prednisolon* or prednison* or betamethason* or dexamethason* or beclomethason* or methylprednisolon* or (adrenal next cortex next hormon*) or steroid* or hydroxypregnenolon* or tetrahydrocortisol* or cortodoxon* or cortison* or fludrocortison* or corticosteron* or paramethason* or cortisol* or triamcinolon*) #5 #1 or #2 or #3 or #4 #6 MeSH descriptor: [Leptospirosis] explode all trees #7 (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)) #8 #6 or #7 #9 #5 and #8
MEDLINE Ovid	1946 to the date of the search	1. exp Adrenal Cortex Hormones/ 2. exp Glucocorticoids/ 3. exp Steroids/ 4. (corticosteroid* or corticoid* or glucocortico* or hydrocortison* or hydroxycorticosteroid* or prednisolon* or prednison* or betamethason* or dexamethason* or beclomethason* or methylprednisolon* or adrenal cortex hormon* or steroid* or hydroxypregnenolon* or tetrahydrocortisol* or cortodoxon* or cortison* or fludrocortison* or corticosteron* or paramethason* or cortisol* or triamcinolon*).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] 5. 1 or 2 or 3 or 4 6. exp Leptospirosis/ 7. (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] 8. 6 or 7

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		9. 5 and 8
Embase Ovid	1974 to the date of the search	1. exp corticosteroid/ 2. exp steroid/ 3. (corticosteroid* or corticoid* or glucocortico* or hydrocortison* or hydroxycorticosteroid* or prednisolon* or prednison* or betamethason* or dexamethason* or beclomethason* or methylprednisolon* or adrenal cortex hormon* or steroid* or hydroxypregnenolon* or tetrahydrocortisol* or cortodoxon* or cortison* or fludrocortison* or corticosteron* or paramethason* or cortisol* or triamcinolon*).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] 4. 1 or 2 or 3 5. exp leptospirosis/ 6. (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] 7. 5 or 6 8. 4 and 7
LILACS (Bireme)	From 1982 to the date of the search	(corticosteroid$ or corticoid$ or glucocortico$ or hydrocortison$ or hydroxycorticosteroid$ or prednisolon$ or prednison$ or betamethason$ or dexamethason$ or beclomethason$ or methylprednisolon$ or adrenal cortex hormon$ or steroid$ or hydroxypregnenolon$ or tetrahydrocortisol$ or cortodoxon$ or cortison$ or fludrocortison$ or corticosteron$ or paramethason$ or cortisol$ or triamcinolone$ or beclometason$ or esteroid$ or hidrocortison$ or dexametason$ or metilpredonisolon$) [Words] and (leptospir$ 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 the date of the search	#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=(corticosteroid* or corticoid* or glucocortico* or hydrocortison* or hydroxycorticosteroid* or prednisolon* or prednison* or betamethason* or dexamethason* or beclomethason* or methylprednisolon* or “adrenal cortex hormon*” or steroid* or hydroxypregnenolon* or tetrahydrocortisol* or cortodoxon* or cortison* or fludrocortison* or corticosteron* or paramethason* or cortisol* or triamcinolon*)
Conference Proceedings Citation Index – Science (Web of Science)	1990 to the date of the search	#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))

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		#1 TS=(corticosteroid* or corticoid* or glucocortico* or hydrocortison* or hydroxycorticosteroid* or prednisolon* or prednison* or betamethason* or dexamethason* or beclomethason* or methylprednisolon* or "adrenal cortex hormon*" or steroid* or hydroxypregnenolon* or tetrahydrocortisol* or cortodoxon* or cortison* or fludrocortison* or corticosteron* or paramethason* or cortisol* or triamcinolon*)
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/	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 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, NL, PM, TZW, and TE specified the scope of the different components of the PICO (patient/population, intervention, comparison and outcomes) question.

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

KT, NL, PM, TZW, and CS reviewed the literature and drafted the background section.

CS, KT, TE, TZW, NL, and PM 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

TZW: none.

KT: none.

PM: none.

TE: none.

CS: none.

NL: none.

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- No funding sources to report, Other

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NOTES

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