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# Antibiotics for treatment of leptospirosis (Review)

Win TZ, Han SM, Edwards T, Maung HT, Brett-Major DM, Smith C, Lee N

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[Intervention Review]

# Antibiotics for treatment of leptospirosis

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## ABSTRACT

### Background

Leptospirosis is a disease transmitted from animals to humans through water, soil, or food contaminated with the urine of infected animals, caused by pathogenic *Leptospira* species. Antibiotics are commonly prescribed for the management of leptospirosis. Despite the widespread use of antibiotic treatment for leptospirosis, there seems to be insufficient evidence to determine its effectiveness or to recommend antibiotic use as a standard practice. This updated systematic review evaluated the available evidence regarding the use of antibiotics in treating leptospirosis, building upon a previously published Cochrane review.

### Objectives

To evaluate the benefits and harms of antibiotics versus placebo, no intervention, or another antibiotic for the treatment of people with leptospirosis.

### Search methods

We identified randomised clinical trials following standard Cochrane procedures. The date of the last search was 27 March 2023.

### Selection criteria

We searched for randomised clinical trials of various designs that examined the use of antibiotics for treating leptospirosis. We did not impose any restrictions based on the age, sex, occupation, or comorbidities of the participants involved in the trials. Our search encompassed trials that evaluated antibiotics, regardless of the method of administration, dosage, and schedule, and compared them with placebo or no intervention, or compared different antibiotics. We included trials regardless of the outcomes reported.

### Data collection and analysis

During the preparation of this review, we adhered to the Cochrane methodology and used Review Manager. The primary outcomes were all-cause mortality and serious adverse events (nosocomial infection). Our secondary outcomes were quality of life, proportion of people with adverse events considered non-serious, and days of hospitalisation. To assess the risk of bias of the included trials, we used the RoB 2 tool, and for evaluating the certainty of evidence we used GRADEpro GDT software. We presented dichotomous outcomes as risk ratios (RR) and continuous outcomes as mean differences (MD), both accompanied by their corresponding 95% confidence intervals (CI). We used the random-effects model for all our main analyses and the fixed-effect model for sensitivity analyses. For our primary outcome analyses, we included trial data from the longest follow-up period.

**Main results**

We identified nine randomised clinical trials comprising 1019 participants. Seven trials compared two intervention groups and two trials compared three intervention groups. Amongst the trials comparing antibiotics versus placebos, four trials assessed penicillin and one trial assessed doxycycline. In the trials comparing different antibiotics, one trial evaluated doxycycline versus azithromycin, one trial assessed penicillin versus doxycycline versus cefotaxime, and one trial evaluated ceftriaxone versus penicillin. One trial assessed penicillin with chloramphenicol and no intervention. Apart from two trials that recruited military personnel stationed in endemic areas or military personnel returning from training courses in endemic areas, the remaining trials recruited people from the general population presenting to the hospital with fever in an endemic area. The participants' ages in the included trials was 13 to 92 years. The treatment duration was seven days for penicillin, doxycycline, and cephalosporins; five days for chloramphenicol; and three days for azithromycin. The follow-up durations varied across trials, with three trials not specifying their follow-up periods. Three trials were excluded from quantitative synthesis; one reported zero events for a prespecified outcome, and two did not provide data for any prespecified outcomes.

**Antibiotics versus placebo or no intervention**

The evidence is very uncertain about the effect of penicillin versus placebo on all-cause mortality (RR 1.57, 95% CI 0.65 to 3.79; $I^2$ = 8%; 3 trials, 367 participants; very low-certainty evidence).

The evidence is very uncertain about the effect of penicillin or chloramphenicol versus placebo on adverse events considered non-serious (RR 1.05, 95% CI 0.35 to 3.17; $I^2$ = 0%; 2 trials, 162 participants; very low-certainty evidence).

None of the included trials assessed serious adverse events.

**Antibiotics versus another antibiotic**

The evidence is very uncertain about the effect of penicillin versus cephalosporin on all-cause mortality (RR 1.38, 95% CI 0.47 to 4.04; $I^2$ = 0%; 2 trials, 348 participants; very low-certainty evidence), or versus doxycycline (RR 0.93, 95% CI 0.13 to 6.46; 1 trial, 168 participants; very low-certainty evidence). The evidence is very uncertain about the effect of cefotaxime versus doxycycline on all-cause mortality (RR 0.18, 95% CI 0.01 to 3.78; 1 trial, 169 participants; very low-certainty evidence).

The evidence is very uncertain about the effect of penicillin versus doxycycline on serious adverse events (nosocomial infection) (RR 0.62, 95% CI 0.11 to 3.62; 1 trial, 168 participants; very low-certainty evidence) or versus cefotaxime (RR 1.01, 95% CI 0.15 to 7.02; 1 trial, 175 participants; very low-certainty evidence). The evidence is very uncertain about the effect of doxycycline versus cefotaxime on serious adverse events (nosocomial infection) (RR 1.01, 95% CI 0.15 to 7.02; 1 trial, 175 participants; very low-certainty evidence).

The evidence is very uncertain about the effect of penicillin versus cefotaxime (RR 3.03, 95% CI 0.13 to 73.47; 1 trial, 175 participants; very low-certainty evidence), versus doxycycline (RR 2.80, 95% CI 0.12 to 67.66; 1 trial, 175 participants; very low-certainty evidence), or versus chloramphenicol on adverse events considered non-serious (RR 0.74, 95% CI 0.15 to 3.67; 1 trial, 52 participants; very low-certainty evidence).

**Funding**
Six of the nine trials included statements disclosing their funding/supporting sources and three trials did not mention funding source. Four of the six trials mentioning sources received funds from public or governmental sources or from international charitable sources, and the remaining two, in addition to public or governmental sources, received support in the form of trial drug supply directly from pharmaceutical companies.

**Authors' conclusions**

As the certainty of evidence is very low, we do not know if antibiotics provide little to no effect on all-cause mortality, serious adverse events, or adverse events considered non-serious.

There is a lack of definitive rigorous data from randomised trials to support the use of antibiotics for treating leptospirosis infection, and the absence of trials reporting data on clinically relevant outcomes further adds to this limitation.

## PLAIN LANGUAGE SUMMARY

### Is the use of antibiotics beneficial for treating leptospirosis?

**Key message**

– Antibiotics (for example, penicillin, doxycycline, azithromycin, cefotaxime, and chloramphenicol) may have no effect on mortality (death) and side effects associated with leptospirosis infection. However, due to the limited evidence, these findings may change if more trials of high quality are conducted.

**What is leptospirosis?**

Leptospirosis is a global disease transmitted from animals (cattle, pigs, horses, dogs, and rodents) to humans (called zoonotic) through contaminated water sources, soil, or food contaminated with the urine of infected animals. Leptospirosis is a treatable and preventable disease. While most people experience mild flu-like symptoms that resolve on their own and do not require medical attention, some people develop severe forms of the disease, leading to multiple organ dysfunction (organs stop functioning properly) and even death.

**What did we want to find out?**

We wanted to find out if antibiotics are an effective treatment for leptospirosis and if they have any unwanted side effects.

**What did we do?**

We searched medical databases for trials that assessed the use of antibiotics for treatment of leptospirosis.

Trials could have compared antibiotics versus placebo (a pretend treatment) or no intervention; or versus another antibiotic.

**What did we find?**

We found nine trials with 1019 participants, which took place in Barbados, Brazil, Malaysia, Panama, the Philippines, and Thailand. The participants were aged 13 to 92 years.

Participants resided in these areas except two trials which recruited military personnel.

**Main results**

Four trials compared penicillin versus either placebo or no intervention. One trial compared penicillin versus doxycycline versus cefotaxime. One trial compared penicillin versus ceftriaxone. One trial compared penicillin versus chloramphenicol versus no intervention. One trial compared doxycycline versus azithromycin. One trial compared doxycycline versus placebo. We combined results from six trials.

***Antibiotics versus placebo***

– May not reduce deaths (3 trials, 367 participants)

– May not reduce minor side effects (for example, diarrhoea (loose stools), nausea (feeling sick), and vomiting (being sick); 2 trials, 162 participants)

None of the included trials reported serious side effects.

***Antibiotics versus other antibiotics***

– May not decrease deaths (penicillin versus cephalosporin: 2 trials, 348 participants; penicillin versus doxycycline: 1 trial, 168 participants; cefotaxime versus doxycycline: 1 trial, 169 participants)

– May not affect the occurrence of serious side effects (penicillin versus doxycycline: 1 trial, 168 participants; penicillin versus cefotaxime: 1 trial, 175 participants; doxycycline versus cefotaxime: 1 trial, 175 participants)

– May not affect the occurrence of side effects considered non-serious (penicillin versus cefotaxime: 1 trial, 175 participants; penicillin versus doxycycline: 1 trial, 168 participants; penicillin versus chloramphenicol: 1 trial, 52 participants)

**What are the limitations of the evidence?**

We have low confidence in our results for death and side effects because of the small number of trials with widely varying results.

**Funding**

Six trials included statements disclosing their funding/supporting sources and three trials did not mention funding sources. Four of the six trials mentioning funding sources received monies from public or governmental sources or from international charitable sources, and the remaining two trials, in addition to public or governmental sources, also received support in the form of trial medicines directly from pharmaceutical companies.

**How up to date is this evidence?**

This review updates the previous Cochrane review. The evidence is up to date to 27 March 2023.

## SUMMARY OF FINDINGS

### Summary of findings 1. Summary of findings table - Antibiotics compared with placebo or no intervention for treatment of leptospirosis

**Antibiotics compared with placebo or no intervention for treatment of leptospirosis**

**Patient or population:** people with leptospirosis
**Setting:** inpatient
**Intervention:** antibiotics
**Comparison:** placebo or no intervention

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo or no intervention | Risk with antibiotics | | | | |
| All-cause mortality<br>follow-up: 1 year | 59 per 1000 | **92 per 1000**<br>(38 to 222) | **RR 1.57**<br>(0.65 to 3.79) | 367<br>(3 RCTs) | ⊕⊖⊖⊖<br>Very low[a] | 2 trials favoured placebo or no intervention. 2 trials did not provide follow-up period. |
| Serious adverse event - not reported | - | - | - | - | - | No trials reported this outcome. |
| Adverse events considered non-serious<br>follow-up: 1 year | 56 per 1000 | **58 per 1000**<br>(19 to 176) | **RR 1.05**<br>(0.35 to 3.17) | 162<br>(2 RCTs) | ⊕⊖⊖⊖<br>Very low[b] | There were differences in the definition of non-serious adverse events between these trials. 1 trial favoured placebo and 1 trial showed no difference between the intervention and placebo. 1 trial did not provide follow-up period. |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **RR:** risk ratio

**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.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_441797335238052247.

[a] Downgraded one level for risk of bias (no information on randomisation and allocation concealment) and two levels for imprecision (the optimal information size criterion (OIS) was not met, i.e. sample size fewer than the OIS of 6940 participants, wide CIs, and 95% CI included both benefits and harms).
[b] Downgraded two levels for risk of bias (no information on randomisation, allocation concealment, measurement of the outcome, and selection of reported result) and two levels for imprecision (the OIS criterion was not met, i.e. sample size fewer than the OIS of 6940 participants, wide CIs, and 95% CI included both benefits and harms).

**Summary of findings 2. Summary of findings table - Antibiotics compared with other antibiotics for people with leptospirosis**

**Antibiotics compared with other antibiotics for people with leptospirosis**

**Patient or population:** people with leptospirosis
**Setting:** inpatient
**Intervention:** antibiotics
**Comparison:** other antibiotics

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with other antibiotics | Risk with antibiotics | | | | |
| All-cause mortality (penicillin versus a cephalosporin (cefotaxime or ceftriaxone))<br>follow-up: mean 2.5 weeks | 29 per 1000 | **39 per 1000**<br>(13 to 115) | **RR 1.38**<br>(0.47 to 4.04) | 348<br>(2 RCTs) | ⊕⊖⊖⊖<br>Very low[a] | 0 deaths in the cephalosporin group in 1 trial. |
| All-cause mortality (penicillin versus doxycycline)<br>follow-up: 4 weeks | 25 per 1000 | **23 per 1000**<br>(3 to 160) | **RR 0.93**<br>(0.13 to 6.46) | 168<br>(1 RCT) | ⊕⊖⊖⊖<br>Very low[b] | Numbers of events were equal in both arms. |
| All-cause mortality (a cephalosporin (cefotaxime) versus doxycycline)<br>follow-up: 4 weeks | 25 per 1000 | **4 per 1000**<br>(0 to 93) | **RR 0.18**<br>(0.01 to 3.78) | 169<br>(1 RCT) | ⊕⊖⊖⊖<br>Very low[b] | 0 deaths in the cephalosporin group in this trial. |
| Serious adverse events (nosocomial infection) (penicillin versus cefotaxime)<br>follow-up: 4 weeks | 23 per 1000 | **23 per 1000**<br>(3 to 160) | **RR 1.01**<br>(0.15 to 7.02) | 175<br>(1 RCT) | ⊕⊖⊖⊖<br>Very low[c] | It was not reported how the outcome was measured. Numbers of events were equal in both arms. |
| Serious adverse events (nosocomial infection) (penicillin versus doxycycline)<br>follow-up: 4 weeks | 37 per 1000 | **23 per 1000**<br>(4 to 134) | **RR 0.62**<br>(0.11 to 3.62) | 168<br>(1 RCT) | ⊕⊖⊖⊖<br>Very low[d] | It was not reported how the outcome was measured. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Serious adverse events (nosocomial infection) (doxycycline versus cefotaxime)<br>follow-up: 4 weeks | 23 per 1000 | **23 per 1000**<br>(3 to 160) | **RR 1.01**<br>(0.15 to 7.02) | 175<br>(1 RCT) | ⊕⊖⊖⊖<br>Very low[c] | It was not reported how the outcome was measured. Numbers of events were equal in both arms. |
| Adverse events considered non-serious (penicillin versus cefotaxime)<br>follow-up: 4 weeks | 0 per 1000 | **0 per 1000**<br>(0 to 0) | **RR 3.03**<br>(0.13 to 73.47) | 175<br>(1 RCT) | ⊕⊖⊖⊖<br>Very low[e] | 0 participants in the cephalosporin group developed adverse events considered non-serious in this trial. |
| Adverse events considered non-serious (penicillin versus doxycycline)<br>follow-up: 4 weeks | 0 per 1000 | **0 per 1000**<br>(0 to 0) | **RR 2.80**<br>(0.12 to 67.66) | 168<br>(1 RCT) | ⊕⊖⊖⊖<br>Very low[e] | 0 participants in the doxycycline group developed adverse events considered non-serious in this trial. |
| Adverse events considered non-serious (penicillin versus chloramphenicol)<br>follow-up: 4 weeks | 129 per 1000 | **95 per 1000**<br>(19 to 474) | **RR 0.74**<br>(0.15 to 3.67) | 52<br>(1 RCT) | ⊕⊖⊖⊖<br>Very low[f] | There were 3 interventions (penicillin, chloramphenicol, and no antibiotics) in this trial. We did not include the data for no antibiotics in this analysis. |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

**CI:** confidence interval; **RR:** risk ratio

**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.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_441797404707785184.

[a] Downgraded one level for risk of bias (no information on deviations from intended intervention and selection of reported result) and two levels for imprecision (the optimal information size (OIS) criterion was not met, i.e. sample size fewer than the OIS of 14,266 participants, wide CIs, and 95% CI included both benefits and harms).
[b] Downgraded one level for risk of bias (no information on deviations from intended intervention) and two levels for imprecision (the OIS criterion was not met, i.e. sample size fewer than the OIS of 7652 participants, wide CIs, and 95% CI included both benefits and harms).
[c] Downgraded one level for risk of bias (no information on deviations from intended intervention, measurement of the outcome and selection of the reported result) and two levels for imprecision (the OIS criterion was not met, i.e. sample size fewer than the OIS of 17,092 participants, wide CIs, and 95% CI included both benefits and harms).
[d] Downgraded one level for risk of bias (no information on deviations from intended intervention, measurement of the outcome and selection of the reported result) and two levels for imprecision (the OIS criterion was not met, i.e. sample size fewer than the OIS of 12,184 participants, wide CIs, and 95% CI included both benefits and harms).

[e] Downgraded one level for risk of bias (no information on measurement of the outcome and selection of the reported result) and three levels for imprecision (the OIS criterion was not met, i.e. sample size fewer than the OIS of 72,484 participants, very wide CIs, and 95% CI included both benefits and harms).
[f] Downgraded one level for risk of bias (no information on measurement of the outcome and selection of the reported result) and two levels for imprecision (the OIS criterion was not met, i.e. sample size fewer than the OIS of 3072 participants, wide CIs, and 95% CI included both benefits and harms).

# BACKGROUND

## Description of the condition

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

It is estimated that approximately 59,000 people die each year from leptospirosis and more than one million people are infected with it worldwide. However, there are no reliable global incidence data for leptospirosis as it may be under-reported (Costa 2015). Leptospirosis is widespread worldwide, especially in the tropics, where outbreaks following heavy rainfall and flooding cause considerable mortality and mobility (Suneth 2011). The global burden of leptospirosis is substantial. In 2015, leptospirosis was reported to have caused an estimated 2.9 million disability-adjusted life years, with most instances occurring in low- and middle-income tropical countries (Torgerson 2015). The incidence of leptospirosis was highest in Oceania, South-East Asia, the Caribbean, and East Sub-Saharan Africa (Costa 2015).

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

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

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

## Description of the intervention

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

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

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

## How the intervention might work

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

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

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

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

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

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

### Why it is important to do this review

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

## OBJECTIVES

To evaluate the benefits and harms of antibiotics versus placebo, no intervention, or another antibiotic for the treatment of people with leptospirosis.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included randomised clinical trials studying antibiotic treatment for leptospirosis regardless of year, language, form of publication (including unpublished data), blinding or comparator, and outcomes reported. We considered any cluster-randomised trials and cross-over trials also eligible for inclusion due to the likelihood of limited published trial data for leptospirosis. We excluded pseudo-randomised studies (i.e. quasi-randomised studies) as the method of allocation to the study groups is not truly random, that is, alternation, date of birth, or case record number were used, as well as observational studies.

#### Types of participants

People with suspected or confirmed leptospirosis infection by molecular (polymerase chain reaction amplification or sequencing of the bacterial genome) or serological methods (enzyme-linked immunosorbent assay, ImmunoDOT (i.e. visually interpreted, rapid-test, dipstick enzyme-linked immunosorbent assay), lateral flow tests, immunohistochemistry, microagglutination test) irrespective of clinical presentation (mild or severe cases), origin, sex, or age.

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

#### Types of interventions

##### *Experimental intervention*

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

##### *Control interventions*

- Placebo or no intervention
- Another antibiotic intervention

We allowed any co-interventions if they were administered equally to the trial participants in the experimental and control groups.

#### Types of outcome measures

We aimed to assess the following dichotomous and continuous outcomes at maximum follow-up.

##### *Primary outcomes*

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

##### *Secondary outcomes*

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

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

We included trials regardless of whether they reported these outcomes.

## Search methods for identification of studies

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

### Electronic searches

The Cochrane Hepato-Biliary Group Information Specialist searched the Cochrane Hepato-Biliary Group Controlled Trials Register internally via the Cochrane Register of Studies Web on 27 March 2023. We also searched the Cochrane Central Register of Controlled Trials (2023; Issue 3) in the Cochrane Library, MEDLINE ALL Ovid (1946 to 27 March 2023), Embase Ovid (1974 to 27 March 2023), Latin American and Caribbean Health Science Literature (LILACS, VHL Regional Portal; 1982 to 27 March 2023), Science Citation Index Expanded (1900 to 27 March 2023), and Conference Proceedings Citation Index–Science (1990 to 27 March 2023). The latter two were searched simultaneously through Web of Science.

Appendix 1 provides the final search strategies for the databases with the date range of the searches.

### Searching other resources

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

We also searched conference abstracts and proceedings such as American Society of Tropical Medicine and Hygiene (ASTMH; 2005 to 27March 2023), Infectious Diseases Society of America (IDSA; 2003 to 27 March 2023), and the International Society of Travel Medicine (ISTM; 2011 to 27 March 2023).

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

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

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

We used items from the PRISMA-S checklist that are relevant to our review to ensure that we reported and documented our searches as advised (PRISMA-S Checklist; Rethlefsen 2021).

## Data collection and analysis

We followed the instructions inthe *Cochrane Handbook for Systematic Reviews of Interventions* for data collection and analysis (Higgins 2022a). We used Review Manager software to perform the meta-analyses (RevMan 2023).

### Selection of studies

Two review authors (TZW, HTM) independently reviewed the list of all candidate studies obtained by the search. We planned to identify and exclude duplicates, and collate multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We used Covidence software for study selection (Covidence). After screening titles and abstracts according to the inclusion criteria of our systematic review, we obtained and reviewed full-text papers of potentially eligible studies to identify whether they met the eligibility criteria. We contacted authors of the selected publications by email to request any missing information that could help us determine the eligibility of a study. We recorded the reasons for exclusion of studies not fulfilling the inclusion criteria in the Characteristics of excluded studies table. We resolved any disagreements with a third review author (CS). We imposed no language restrictions. We included trials no matter if they reported our outcomes of interest or not. We recorded the selection process in sufficient detail to complete a PRISMA-S flow diagram (Page 2021a; Page 2021b).

For screening of non-English language publications, we, in the first instance, used Google Translate to assist in eligibility assessment (translate.google.com). If needed, we considered seeking translators, through the Cochrane Hepato-Biliary Group Editorial Team office, to assist with assessing the eligibility of studies and, if eligible, assist with data extraction.

We planned to extract and present relevant data on harms in a narrative or tabular way from observational studies (quasi-randomised studies, cohort studies, patient reports) that reported on adverse effects of antibiotics identified during our search for randomised clinical trials. This was considered to be done regardless of the number of randomised clinical trials that were found to report on adverse events, as we did not expect to identify numerous randomised clinical trials.

We recognised that not conducting separate systematic searches 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 was a benefit of the intervention (Storebø 2018).

### Data extraction and management

Two review authors (TZW, HTM) independently extracted the following study characteristics from included studies and completed the Characteristics of included studies table. Any disagreements were resolved in discussion with a third review author (CS). Because the number of trials was limited, piloting a data extraction form was not relevant.

- **Study and publication identifiers:** study ID, ethics committee approval, database index number, first author, corresponding author, journal, year of publication, language, country in which the study was conducted, location (country, prefecture/district), type and number of study centres and locations, funding source for trial, and notable conflicts of interest of trial authors
- **Study methods:** study design, number of groups, randomisation and how randomised participants were allocated to groups, description of experimental and control interventions, how blinded methods were conducted and how concealment was accomplished, type of analysis, start date, end date, the total duration of the study, duration participants were followed, and details of any 'run-in' period
- **Participants:** inclusion and exclusion criteria, total number of participants and the number of participants in each group, demographics characteristics, severity of condition, comorbidities, and withdrawals and the reasons for withdrawal
- **Interventions:** details of intervention (type of antibacterial agent, route of admission, dose, timing of administration, duration of intervention), definition of comparison and control groups, and concomitant treatment
- **Outcomes:** definition of primary and secondary outcomes, outcomes measurements, outcome data, time points for follow-up reported, and notes

We planned to record whether a trial measured adverse events as the number of participants with an adverse event or measured multiple adverse events in the same participant.

### Assessment of risk of bias in included studies

We assessed the effect of assignment to the intervention using the Cochrane RoB 2 tool, which is a revised tool to assess the risk of bias in randomised trials (Higgins 2022b; Sterne 2019). In our bias risk assessments, we used the intention-to-treat principle, which includes all randomised participants, irrespective of the interventions that participants actually received.

Two review authors (TZW, HTM) independently assessed the risk of bias for all the outcomes at maximum follow-up. We resolved disagreements with a third review author (CS). We assessed the risk of bias in the included randomised parallel-group trials, based on the following domains (Higgins 2022b; Higgins 2022c; Lasserson 2022; Sterne 2019).

- Bias arising from the randomisation process: we assessed whether the allocation sequence was random and adequately concealed. We also assessed if the baseline differences between intervention groups suggested an issue with the randomisation process.
- Bias due to deviations from intended interventions: we evaluated 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 interventions during the trial.
- Bias due to missing outcome data: we analysed if the data for the studied outcome were available for all, or nearly all participants who were randomised, if there was any evidence that the result was not biassed 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 evaluated if the method of measuring the outcome was inappropriate. We also evaluated if the assessors of the outcome were aware of the intervention each study participant received, and if the measurement of the outcome could have differed between intervention groups. We also assessed, 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 addressed whether the trial analysis was made in accordance with a predetermined plan before unblinded outcome data were available for analysis. We also evaluated if the assessed numerical result is likely to have been selected from either multiple outcome measurements within the outcome domain or from multiple analyses of the data.

We answered signalling questions for each domain, using the algorithm proposed by the RoB 2 tool. The response options for the signalling questions are: yes, probably yes, probably no, no, and no information. Elaborations on these signalling questions can be found in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022c). Once these questions have been answered, the tool's algorithm reaches a risk of bias judgement and assigns one of the following three levels to each domain.

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

We provided a justification for our judgements in the risk of bias tables, including reasons against the algorithm.

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

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

For cluster-randomised clinical trials, we planned to 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 the timing of randomisation'. We planned to 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).

For cross-over trials, we planned to use the data only from the period before cross-over, and therefore, we considered using the standard version of RoB 2 (Sterne 2019). However, we did not identify any cross-over trials.

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 used the RoB 2 Excel tool (available at www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2). We stored our RoB 2 data in Microsoft Excel files saved in online repository (doi.org/10.5281/zenodo.10796226).

The risk of bias assessments feeds into the risk of bias domain of the GRADE approach for assessing the certainty of a body of evidence (Schünemann 2013; Schünemann 2022a). We presented the outcomes that we considered most relevant for clinical practice in summary of findings tables. These outcomes were all-cause mortality, serious adverse events (nosocomial infection), and proportion of people with adverse events considered non-serious.

### Measures of treatment effect

We entered the outcome data for each trial into the data tables in Review Manager to calculate the treatment effects (RevMan 2023). We planned to analyse dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs). We planned to measure continuous outcomes, such as quality of life, using the mean difference (MD) with 95% CI if trials used the same tool. We planned to use the standardised mean difference (SMD) with 95% CI to analyse quality of life if trials used different scales to measure it. The SMD expresses the size of the intervention effect when the MD between groups is divided by the standard deviation amongst participants (Higgins 2022b). We considered interpreting SMDs 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 planned to present median and interquartile ranges for continuous data that were not normally distributed (skewed data), in a narrative format. We presented a forest plot to display effect estimates and CIs for individual trials (Lewis 2001). We considered conducting meta-analyses only when the study group was sufficiently homogeneous (Deeks 2022).

### Unit of analysis issues

We considered the individual participant as the unit of analysis for randomised clinical trials. Where a trial reported multiple trial arms, we planned to include only the treatment arms relevant to the review topic but list all treatment arms in the Characteristics of included studies table, even if they were not used in the review. Our optimal approach was to create a single pair-wise comparison. However, if there were trials with more than two arms, for example with the same participants in the placebo arm in both comparisons (e.g. antibiotic A versus placebo and antibiotic B versus placebo), we divided the placebo group into two if data of participants in the placebo group were to be used within the same comparison. In this way, we avoid double-counting of participants and arbitrary omission of relevant groups (Higgins 2022d).

If we had found cluster-randomised clinical trials, we planned to consider the clusters as the unit of analysis, and not the individual participant. This is to avoid unit-of-analysis errors, which may cause artificially narrow CIs and small P values, resulting in a false-positive result that leads to conclusions that the intervention had an effect (Higgins 2022c).

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

To avoid repeated observations of study participants, our main analyses included trial data for the participants at the longest follow-up (Higgins 2022d).

If we identified trials that had also included participants with diseases other than leptospirosis, then we planned to contact trial authors to obtain individual participant data. However, this was not a likely scenario and was not the case.

### Dealing with missing data

We planned to contact investigators to verify key study characteristics and obtain missing numerical outcome data on the primary outcomes. If we were not successful, then we planned to calculate numerical outcome data that were still missing, such as standard deviations or correlation coefficients, from other available statistics such as P values, following the method described inthe *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). If these calculations were not possible, we planned to assess the risk of bias due to missing outcome data as defined by the RoB 2 domain, undertaking sensitivity analyses, and exploring the impact of including these trials in the overall assessment of results (Page 2022). We planned to use the intention-to-treat analysis as a primary analysis, as far as possible, and available-case analysis or modified intention-to-treat approach if data for the intention-to-treat analysis were lacking (Fergusson 2002). A modified intention-to-treat approach assumes that missing data are missing at random.

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

We considered addressing the potential impact of all missing data on our findings of the review in the Discussion.

### Assessment of heterogeneity

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

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

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

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

If we identified substantial heterogeneity, we planned to follow the strategies for handling heterogeneity given inthe *Cochrane Handbook for Systematic Review of Interventions* to explore possible causes based on differences in population, intervention, comparison, and outcome, and difference in the quality of research (Deeks 2022). We planned to investigate possible reasons for heterogeneity via subgroup analyses where possible. If heterogeneity was considerable, we would have conducted a random-effects meta-analysis to account for between-study heterogeneity.

### Assessment of reporting biases

We planned to record biases (e.g. publication, time lag, multiple publications) at all points of data analysis and interpretation. If we identified 10 or more trials that could be included in a meta-analysis, we would have created a funnel plot to analyse possible publication biases. If our search identified any trial protocols, abstracts, or clinical trial registrations that indicated the existence of unpublished studies, we would have tried to contact the investigators to determine the status of these unpublished studies.

### Data synthesis

We pooled data, such as RRs and MDs with 95% CIs, from trials that were judged clinically homogeneous. If we found multiple trials that provided usable data in any single comparison, we considered performing a meta-analysis. However, if there was considerable heterogeneity, especially if the direction of effect was not consistent, we considered not performing a meta-analysis, regardless of the number of trials found. We planned to present the results in a narrative or a table format or both.

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

We considered including all trials in the primary analysis and exploring the effect of bias in a sensitivity analysis in which we would exclude small studies if there were systematic differences.

We used Review Manager software to perform our meta-analyses (RevMan 2023).

Given the likely limited number of trials meeting the eligibility criteria, we included as much data as possible. We planned to perform a sensitivity analysis excluding trials at high risk of bias or with some concerns of bias from the meta-analyses.

If statistical pooling was not appropriate due to incomplete reported data in the primary trials, we considered applying 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 did not expect to perform subgroup analyses for two reasons. First, we did not consider there would be many trials on the use of antibiotics for the treatment of leptospirosis and second, because of the observational nature of subgroup analyses. Subgroup analyses are not based on randomised comparisons, and therefore, there is a risk of overestimating positive intervention effects and underestimating negative effects (Lagakos 2006; Wang 2007).

Potential subgroup differences in effectiveness of an intervention for leptospirosis might be hypothesised to occur if the same drug is given according to a different regimen in terms of route, dosing, or duration. Differences by age might be observed if, for example, drug dosing is according to weight and the dose is suboptimal for younger participants with lower weight. Therefore, we considered exploring if subgroup analyses were possible, for all outcomes, to assess potential differences in effectiveness of the intervention where there was information available about intervention route, dosing, duration, and age. If considered appropriate, outcomes in any subgroup analyses would have been our two primary outcomes.

Where possible, we would have assessed subgroup differences by interaction tests available within Review Manager (RevMan 2023). We planned to report the results of subgroup analyses using stratified forest plots, quoting the $Chi^2$ statistic, P value, and interaction test $I^2$ value.

### Sensitivity analysis

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

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

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

In addition, we planned to perform a Trial Sequential Analysis to assess the imprecision of our primary outcome results. Then, we planned to compare our evaluation of imprecision with Trial Sequential Analysis with that based on GRADE.

### Trial Sequential Analysis

We planned to use Trial Sequential Analysis as a sensitivity analysis to assess imprecision for the two primary outcomes (i.e. all-cause mortality and serious adverse events) (Castellini 2018; Gartlehner 2019; Jakobsen 2014). The underlying assumption of Trial Sequential Analysis is that testing for statistical significance might be performed each time a new trial is added to the meta-analysis. We add the trials according to the year of publication, and, if more than one trial is published in a year, the trials are added alphabetically according to the last name of the first author. For the random-effects meta-analyses, we consider the calculation 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) (Brok 2008; Brok 2009; Thorlund 2010; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). On the basis of the DARIS, we aim to construct trial sequential monitoring boundaries for benefit, harm, and futility (Thorlund 2017; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). These boundaries determine the statistical inference one might draw regarding the cumulative meta-analysis that had not reached the DARIS; if the trial sequential monitoring boundary for benefit or harm is crossed before the DARIS is reached, firm evidence might be established, and further trials might be superfluous. However, if the boundaries for benefit or harm are not crossed, it is likely 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 would be needed.

In our Trial Sequential Analysis of the two primary outcomes (both dichotomous), we based the DARIS on the event proportion in the control group, assuming a plausible relative risk reduction 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 2021). We used the random-effects model. We also considered calculating the Trial Sequential Analysis-adjusted CIs (Thorlund 2017; Wetterslev 2017). In Trial Sequential Analysis, we would downgrade our assessment of imprecision by two levels if the accrued number of participants was below 50% of the DARIS, and by one level if between 50% and 100% of the DARIS. We would not downgrade if futility or DARIS was reached. A more detailed description of Trial Sequential Analysis and the software programme can be found at www.ctu.dk/tsa/ (Thorlund 2017).

We attempted to conduct trial sequential analyses as planned, but due to little information, informative Trial Sequential Analysis graphs could not be constructed (not shown).

### Summary of findings and assessment of the certainty of the evidence

We used GRADEpro GDT software to create summary of findings tables (GRADEpro GDT). Summary of findings tables provide information on comparative risk, relative risk, number of participants, number of trials, and certainty of the evidence for antibiotics use for the treatment of leptospirosis versus no intervention, placebo, or another antibiotic. We planned to create three summary of findings tables comparing: antibiotic treatment versus no intervention; antibiotic treatment versus placebo; and one antibiotic treatment versus another antibiotic treatment. However, we created only two tables by combining placebo and no intervention group due to the limited number of trials. We planned to present outcome results for all-cause mortality, serious adverse events, quality of life, and proportion of people with adverse events considered non-serious. We used 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 theGRADE Handbook(Schünemann 2013). We provided the maximum follow-up and the mean or median, and their ranges of each outcome. One review author (TZW) graded the evidence of these outcomes and the remaining authors checked the assessments. We solved disagreements by discussion.

The assessment of GRADE approach is based on 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). It specifies four levels of the certainty of evidence (i.e. high, moderate, low, and very low; see definitions below). Through this approach, we evaluated and formed conclusions about the certainty of the evidence shown in the review (GRADEpro GDT).

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

The four GRADE Working Group grades of evidence are:

- **high certainty:** we were very confident that the true effect lays close to that of the estimate of the effect;
- **moderate certainty:** we were moderately confident in the effect estimate: the true effect was likely to be close to the estimate of the effect, but there was a possibility that it was substantially different;
- **low certainty:** our confidence in the effect estimate was limited: the true effect might be substantially different from the estimate of the effect;
- **very low certainty:** we had very little confidence in the effect estimate: the true effect was likely to be substantially different from the estimate of effect.

We conducted the review according to the published protocol (Mukadi 2022), and reported any deviations from it in the Differences between protocol and review section.

## RESULTS

### Description of studies

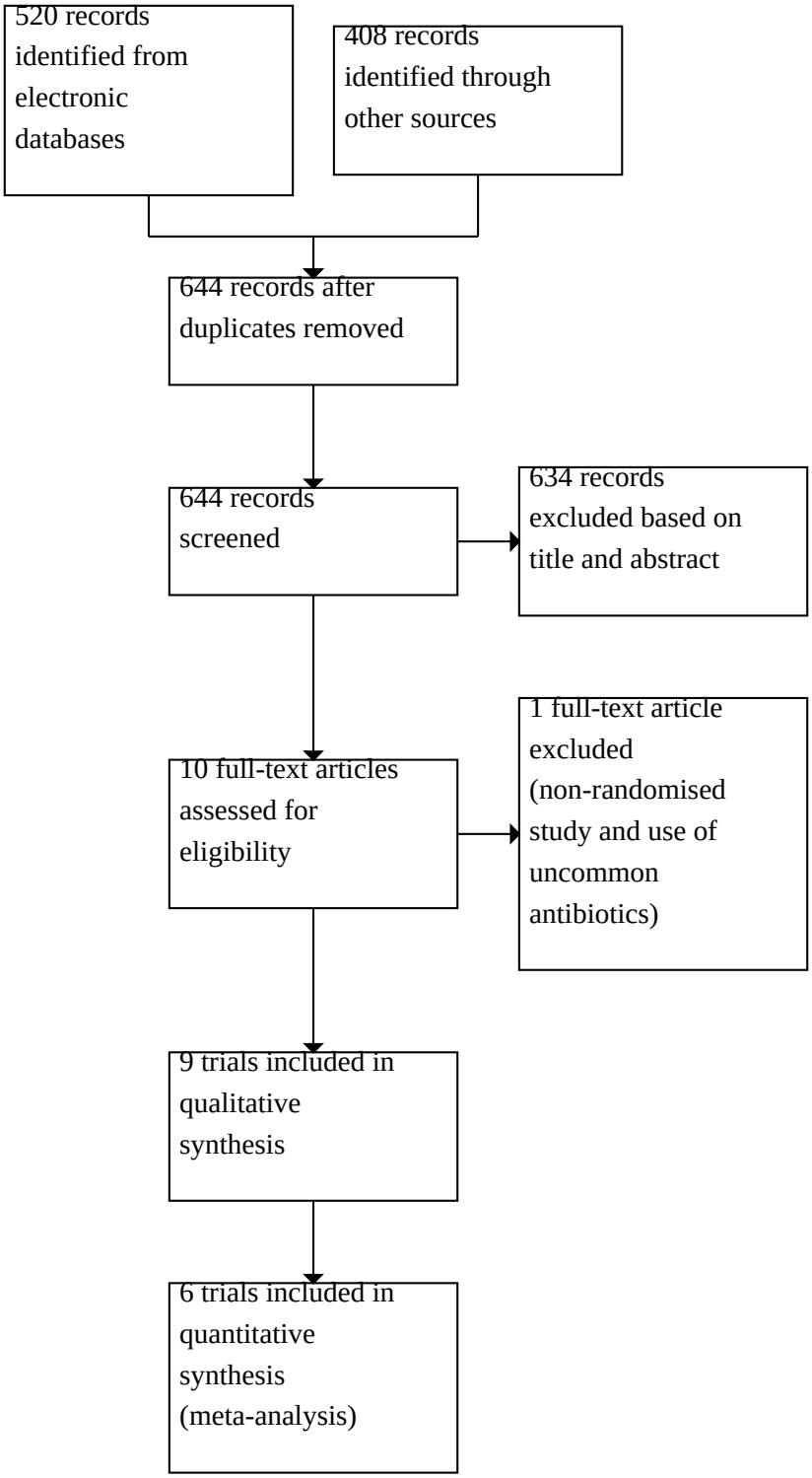
See Included studies and Excluded studies.

### Results of the search

The search of the literature identified 928 records. After removal of 284 duplicates, we excluded 634 titles based on the title and abstract (Figure 1). We retrieved 10 records for full-text review. Nine trials were suitable for inclusion, and all were randomised clinical trials. All trials were included in qualitative synthesis and six trials were included in quantitative synthesis. Seven of the included trials

were featured in the previous systematic review. We excluded one record.

**Figure 1. PRISMA flow diagram. Date of search 27 March 2023**



### Included studies

We included nine randomised clinical trials (Characteristics of included studies table).

#### *Trial characteristics*

The nine trials were randomised clinical trials published in peer-reviewed journals. Trials were conducted in areas where leptospirosis was endemic. These included Barbados (Edwards 1988), Brazil (Costa 2003; Daher 2000), Malaysia (Fairburn 1956), Panama (McClain 1984), the Philippines (Watt 1988), and Thailand (Panaphut 2003; Phimda 2007; Suputtamongkol 2004). The studies included 1019 participants, with sample sizes in individual trials ranging from 29 to 256. Seven trials compared two intervention groups as either antibiotics versus placebo or no intervention (Costa 2003; Daher 2000; Edwards 1988; McClain 1984; Watt 1988) or one antibiotic versus another antibiotic (Panaphut 2003; Phimda 2007). Two trials compared three intervention groups as either one antibiotic versus another antibiotic versus no intervention (Fairburn 1956) or one antibiotic versus another antibiotic versus another antibiotic (Suputtamongkol 2004).

#### *Participants*

The age range of all participants was 13 to 92 years. One trial recruited military personnel stationed in an endemic area (Fairburn 1956), and one trial recruited military personnel returning from training courses in endemic areas (McClain 1984). The remaining seven trials recruited people presenting to the hospital with a fever in an endemic area. Sex and occupation were not reliably reported across all trials.

#### *Intervention (comparisons)*

The interventions were delivered in hospitals, but most authors did not mention the person responsible for delivering them. In trials evaluating antibiotics versus placebos or no intervention, four trials assessed penicillin (Costa 2003; Daher 2000; Edwards 1988; Watt 1988), and one trial assessed doxycycline (McClain 1984). In trials evaluating different antibiotics, one trial assessed doxycycline versus azithromycin (Phimda 2007), one trial assessed penicillin versus doxycycline versus cefotaxime (Suputtamongkol 2004), and one trial assessed ceftriaxone versus penicillin (Panaphut 2003). One trial compared penicillin versus chloramphenicol versus no intervention (Fairburn 1956).

In the trials using penicillin, formulations and doses varied or were not reported fully; three trials reported the use of sodium penicillin G dosed at 1.5 million units every six hours (Panaphut 2003; Suputtamongkol 2004; Watt 1988); two trials specified the use of crystalline penicillin with different doses: six million units per day in Daher 2000 and two million units every six hours in Edwards 1988. Two trials only stated penicillin at a dose of 600,000 units every six hours (Fairburn 1956) and at a dose of 1 million unit every four hours (Costa 2003). In one trial, intravenous sodium penicillin G was switched to the oral semisynthetic penicillin amoxicillin at a dose of 2 g per day once the participant was afebrile or sufficiently well (Suputtamongkol 2004). The total duration of penicillin treatment for trials using this intervention was seven days, except in one trial which reported a five-day total duration (Edwards 1988), in one trial which reported a minimum duration of five days but a mean duration of six days (Fairburn 1956), and in one trial which reported a total duration of eight days (Daher 2000).

One trial initially gave doxycycline as an intravenous infusion loading dose at 200 mg once followed by 100 mg intravenous infusion twice daily (Suputtamongkol 2004). The intravenous formulation was then switched to an oral formulation when clinically appropriate. The remaining trials used only oral doxycycline, and the dose varied by study. One trial reported using an initial 200 mg loading dose followed by 100 mg twice daily (Phimda 2007), and one trial reported using doxycycline 100 mg twice daily without a loading dose (McClain 1984). The total duration of treatment was seven days for all trials using doxycycline.

Two trials reported the use of cephalosporins. One trial assessed the intravenous third-generation cephalosporin, ceftriaxone, dosed at 1 g once daily for a total duration of seven days (Panaphut 2003). One trial reported the use of the intravenous third-generation cephalosporin, cefotaxime, dosed at 1 g every six hours, which was switched to oral amoxicillin for a total duration of treatment of seven days (Suputtamongkol 2004).

One trial reported the use of chloramphenicol 0.5 g every six hours for a minimum of five days, but with a reported mean antibiotic duration of 6.2 days (Fairburn 1956). One trial reported the use of oral azithromycin 1 g once followed by 500 mg once daily for a total duration of three days (Phimda 2007).

#### *Outcomes*

Five trials evaluated all-cause mortality as the primary outcome (Costa 2003; Daher 2000; Panaphut 2003; Suputtamongkol 2004; Watt 1988). However, Watt and colleagues reported zero events of all-cause mortality outcome in both arms, so it was excluded from the analysis (Watt 1988).

One trial reported serious adverse events (nosocomial infection) (Suputtamongkol 2004).

Three trials reported adverse events considered non-serious, such as skin rash (Suputtamongkol 2004), rising blood urea (Fairburn 1956), and a Jarisch-Herxheimer-type reaction (Edwards 1988).

No trials reported quality of life.

Two trials reported days of hospitalisation (Costa 2003; Daher 2000).

Two trials did not report any of our prespecified outcomes (McClain 1984; Phimda 2007).

#### *Follow-up*

The duration of follow-up differed between trials. Three trials did not specify their follow-up periods (Costa 2003; Daher 2000; Fairburn 1956). One trial followed up for eight days for the ceftriaxone group and seven days for the penicillin group (Panaphut 2003). One trial followed up for one to two weeks (Phimda 2007), one trial at one week and one month (Watt 1988), one trial for two to four weeks (Suputtamongkol 2004), one trial for three-month periods up to one year (Edwards 1988), and one trial for three weeks after hospital discharge (McClain 1984).

#### *Funding*

Six of the nine trials included statements disclosing their funding/supporting sources (Costa 2003; Daher 2000; Panaphut 2003;

Phimda 2007; Suputtamongkol 2004; Watt 1988), and the remaining three trials did not mention funding sources (Edwards 1988; Fairburn 1956; McClain 1984). Four of the six trials mentioning sources received funds from public or governmental sources or from international charitable sources, and the remaining two, in addition to public or governmental sources, received support in the form of trial drug supply directly from pharmaceutical companies (Panaphut 2003; Suputtamongkol 2004).

### Excluded studies

We excluded one non-randomised study that used oxytetracycline, which was not in common practice at that time (Russell 1958; Characteristics of excluded studies table).

### Studies awaiting classification

No studies are awaiting classification.

### Ongoing studies

We found no ongoing studies.

## Risk of bias in included studies

We assessed risk of bias in the six published trials contributing to the meta-analyses (Costa 2003; Daher 2000; Edwards 1988; Fairburn 1956; Panaphut 2003; Suputtamongkol 2004). We evaluated the risk of bias for the outcomes: all-cause mortality, serious adverse events (nosocomial infection), adverse events considered non-serious, and days of hospitalisation.

For all-cause mortality, four of the five trials were judged to have some concerns of bias overall (Costa 2003; Daher 2000; Edwards 1988; Suputtamongkol 2004). For nosocomial infection, one trial was at high risk overall (Suputtamongkol 2004). For adverse events considered non-serious, two of the three trials were at high risk of bias overall (Fairburn 1956; Suputtamongkol 2004). For the days of hospitalisation, both trials were at high risk of bias overall (Costa 2003; Daher 2000).

We considered no trial to be at overall low risk of bias for any of the outcomes in this review.

### Bias arising from the randomisation process

One trial reported using stratified block randomisation by a computer-generating technique (a random code via a block of four), and each label was enclosed in a sealed and opaque envelope (Panaphut 2003). One trial reported that the randomisation was performed by an independent computer-generated method and the sequences were sealed in numbered opaque envelopes (Suputtamongkol 2004). Two trials did not report on the randomisation and allocation sequence (Costa 2003; Daher 2000). One trial did not report clearly on the use of randomisation in assigning the participants into each group (Fairburn 1956). Similarly, one trial reported that participants were assigned by random numbers, but detailed information on randomisation methods was not mentioned (Edwards 1988). We judged these trials to have some concerns for bias arising from the randomisation process (3/5 for all-cause mortality; 2/3 for adverse events considered non-serious; and 2/2 for days of hospitalisation).

### Bias due to deviations from the intended intervention

We judged most trials (4/5 for all-cause mortality, 3/3 for adverse events considered non-serious, and 2/2 for days of hospitalisation) to be at low risk of bias for deviations from the intended intervention (Costa 2003; Daher 2000; Edwards 1988; Fairburn 1956; Panaphut 2003). One trial had some concerns for risk of bias due to deviations from the intended intervention (Suputtamongkol 2004). Three trials did not comment on blinding methods (Daher 2000; Fairburn 1956; Suputtamongkol 2004). Two trials reported that, respectively, nurses assessing resolution of fever or pulmonologist assessing the participants were blinded, but blinding of participants and people delivering the intervention was not mentioned (Costa 2003; Panaphut 2003). One trial reported that a member of the investigation team examined all participants on admission, but this did not influence their management (Edwards 1988). However, there was no other information about whether they blinded the participants.

### Bias due to missing outcome data

In all outcomes of interest, all included trials were predominantly at low risk of bias.

### Bias in measurement of the outcome

For all-cause mortality, we judged all trials at low risk of bias. Regarding nosocomial infection, we judged one trial at high risk of bias due to the absence of information in the measurement of outcome (Suputtamongkol 2004). For days of hospitalisation, we judged two trials at high risk of bias due to the absence of information in the measurement of outcome, information on the awareness of the intervention by the outcome assessors, and information to determine whether outcome assessment could have been influenced by knowledge of intervention (Costa 2003; Daher 2000). For adverse events considered non-serious, we judged two trials at high risk of bias due to the absence of information on the awareness of the intervention by the outcome assessors, and information to determine whether outcome assessment could have been influenced by knowledge of the intervention (Fairburn 1956; Suputtamongkol 2004).

### Bias in selection of the reported result

For all outcomes, we judged one trial at high risk of bias because it was mentioned that both a per-protocol and intention-to-treat analysis were applied, but only the result of the intention-to-treat analysis was reported (Panaphut 2003). We determined other trials to be at low risk of bias for all-cause mortality since the data analysis of the any-outcome measurements may not have had an impact on the mortality outcome (Costa 2003; Daher 2000; Edwards 1988; Suputtamongkol 2004).For nosocomial infection, adverse events considered non-serious, and days of hospitalisation, we judged all trials except Panaphut 2003 to have some concerns of risk of bias as these trials did not provide a prespecified analysis plan.

## Effects of interventions

See: **Summary of findings 1** Summary of findings table - Antibiotics compared with placebo or no intervention for treatment of leptospirosis; **Summary of findings 2** Summary of findings table - Antibiotics compared with other antibiotics for people with leptospirosis

### Antibiotics versus placebo or no intervention

#### *Primary outcomes*

##### All-cause mortality

The evidence is very uncertain about the effect of penicillin on all-cause mortality compared with placebo or no intervention (RR 1.57, 95% CI 0.65 to 3.79; $I^2$ = 8%; 3 trials, 367 participants; very low-certainty evidence; Analysis 1.1; Summary of findings 1). We downgraded the certainty of evidence one level for risk of bias and two levels for imprecision.

##### Serious adverse events

None of the included trials reported the proportion of people with serious adverse events.

#### *Secondary outcomes*

##### Quality of life

None of the included trials planned to assess quality of life.

##### Adverse events considered non-serious

The evidence is very uncertain about the effect of any antibiotic (penicillin or chloramphenicol) on adverse events considered as non-serious compared with placebo or no intervention (RR 1.05, 95% CI 0.35 to 3.17; $I^2$ = 0%; 2 trials, 162 participants; very low-certainty evidence; Analysis 1.2; Summary of findings 1). We downgraded the certainty of evidence two levels for risk of bias and two levels for imprecision.

##### Days of hospitalisation

There was no suggestion of any difference in days of hospitalisation between trial arms (MD 0.15 days, 95% CI −0.74 to 1.05; $I^2$ = 0%; 2 trials, 288 participants; Analysis 1.3).

### Antibiotic treatment versus another antibiotic

#### *Primary outcomes*

##### All-cause mortality

###### Penicillin versus a cephalosporin

The evidence is very uncertain about the effect of penicillin on all-cause mortality compared with a cephalosporin (cefotaxime or ceftriaxone) (RR 1.38, 95% CI 0.47 to 4.04; $I^2$ = 0%; 2 trials, 348 participants; very low-certainty evidence; Analysis 2.1; Summary of findings 2). We downgraded the certainty of the evidence one level for risk of bias and two levels for imprecision.

###### Penicillin versus doxycycline

The evidence is very uncertain about the effect of penicillin on all-cause mortality compared with doxycycline (RR 0.93, 95% CI 0.13 to 6.46; 1 trial, 168 participants; very low-certainty evidence; Analysis 2.2; Summary of findings 2). We downgraded the certainty of the evidence one level for risk of bias and two levels for imprecision.

###### Cefotaxime versus doxycycline

The evidence is very uncertain about the effect of cefotaxime on all-cause mortality compared with doxycycline (RR 0.18, 95% CI 0.01 to 3.78; 1 trial, 169 participants; very low-certainty evidence; Analysis 2.3; Summary of findings 2). We downgraded the certainty of the evidence one level for risk of bias and two levels for imprecision.

##### Serious adverse events (nosocomial infection)

###### Penicillin versus cefotaxime

The evidence is very uncertain about the effect of penicillin on serious adverse events (nosocomial infection) compared with cefotaxime (RR 1.01, 95% CI 0.15 to 7.02; 1 trial, 175 participants; very low-certainty evidence; Analysis 2.4; Summary of findings 2). We downgraded the certainty of the evidence one level for risk of bias and two levels for imprecision.

###### Penicillin versus doxycycline

The evidence is very uncertain about the effect of penicillin on serious adverse events (nosocomial infection) compared with doxycycline (RR 0.62, 95% CI 0.11 to 3.62; 1 trial, 168 participants; very low-certainty evidence; Analysis 2.5; Summary of findings 2). We downgraded the certainty of the evidence one level for risk of bias and two levels for imprecision.

###### Doxycycline versus cefotaxime

The evidence is very uncertain about the effect of doxycycline on serious adverse events (nosocomial infection) compared with cefotaxime (RR 1.01, 95% CI 0.15 to 7.02; 1 trial, 175 participants; very low-certainty evidence; Analysis 2.6; Summary of findings 2). We downgraded the certainty of the evidence one level for risk of bias and two levels for imprecision.

#### *Secondary outcomes*

##### Quality of life

None of the included trials planned to assess this outcome.

##### Adverse events considered non-serious

###### Penicillin versus cefotaxime

The evidence is very uncertain about the effect of penicillin on adverse events considered non-serious compared with cefotaxime (RR 3.03, 95% CI 0.13 to 73.47; 1 trial, 175 participants; very low-certainty evidence; Analysis 2.7; Summary of findings 2). We downgraded the certainty of the evidence one level for risk of bias and three levels for imprecision.

###### Penicillin versus doxycycline

The evidence is very uncertain about the effect of penicillin on adverse events considered non-serious compared with doxycycline (RR 2.80, 95% CI 0.12 to 67.66; 1 trial, 168 participants; very low-certainty evidence; Analysis 2.8; Summary of findings 2). We downgraded the certainty of the evidence one level for risk of bias and three levels for imprecision.

###### Penicillin versus chloramphenicol

The evidence is very uncertain about the effect of penicillin on adverse events considered non-serious compared with chloramphenicol (RR 0.74, 95% CI 0.15 to 3.67; 1 trial, 52 participants; very low-certainty evidence; Analysis 2.9; Summary of findings 2). We downgraded the certainty of the evidence one level for risk of bias and two levels for imprecision.

##### Days of hospitalisation

None of the included trials reported days of hospitalisation.

# DISCUSSION

## Summary of main results

This review updates the current body of evidence on the use of antibiotics in the treatment of leptospirosis. The current review included nine trials, six of which could be pooled in the quantitative synthesis. Amongst the pooled data, three trials assessed penicillin versus placebo and one trial assessed penicillin versus chloramphenicol and versus no intervention. Therefore, it was included in both comparisons. One trial assessed penicillin versus doxycycline and versus cefotaxime. One trial assessed ceftriaxone versus penicillin.

In the pooled comparison of antibiotic treatment versus placebo or no intervention, the certainty of evidence for an effect of antibiotic treatment was very low. There was very uncertain evidence for the effect of antibiotic treatment on either all-cause mortality or adverse events considered non-serious compared with the placebo or no intervention. This updates the results reported from a previous version of this review by Guidugli and colleagues, which included three trials and concluded that the benefits of administration of penicillin or doxycycline may outweigh the harms (Guidugli 2000). The findings from this updated Cochrane review agree with previous published systematic reviews in that there is no evidence for the effectiveness of antibiotics for treatment of leptospirosis (Charan 2013; Perez 2021).

In the summary of trials comparing antibiotics, the certainty of evidence for an effect was very low. There was very uncertain evidence for the effect of antibiotic treatment compared with another antibiotics on mortality, serious adverse events (nosocomial infection), or adverse events considered non-serious.

## Overall completeness and applicability of evidence

There continues to be insufficient evidence to support the use of antibiotic treatment against leptospirosis disease despite the additional two trials since the previous version of this review. A lack of harmonisation of inclusion criteria and treatment outcome measures continues to contribute to the disparity of results and overall uncertainty of evidence.

The inclusion criteria and their definitions varied by study. Daher and colleagues required epidemiological, clinical, and laboratory diagnosis of leptospirosis, and the definition of disease severity was acute renal failure (defined as plasma creatinine more than 1.5 mg/dL) and jaundice at admission (Daher 2000). Panaphut and colleagues specified the age limits (16 years or older), had received no parenteral or oral antibiotics for less than one day, no allergy to trial antibiotics, never had cardiopulmonary resuscitation prior to admission, not neurologically obtunded, and severity criteria were fulfilled only if there was the presence of jaundice, a serum creatinine greater than 180 µmol/L, or a mean arterial pressure less than 70 mmHg after fluid resuscitation (Panaphut 2003). McClain and colleagues included all febrile people returning from jungle military training exercises but excluded those with severe disease with no definition provided (McClain 1984).

There were no significant differences between penicillin and other antibiotics in terms of mortality and adverse events.

## Quality of the evidence

### Antibiotics compared with placebo or no intervention for treatment of leptospirosis

We included data from four trials assessing the efficacy of antibiotics in the treatment of leptospirosis compared with placebo or no intervention. One of the four trials compared two antibiotics and no intervention. Therefore, it was also included in the comparison of antibiotics versus other antibiotics. We rated the certainty of evidence for mortality and adverse events considered non-serious as very low (see Summary of findings 1). We downgraded the certainty of evidence due to the risk of bias arising from the randomisation process, allocation concealment, measurement of the outcome, and selection of reported result. All trials did not explicitly specify allocation randomisation, sequence concealment, and prespecified analysis plan. Fairburn and colleagues did not clearly mention if outcome assessors were aware of the intervention received by study participants (Fairburn 1956). We further downgraded the certainty of evidence due to serious imprecision where the optimal information size was not met, CIs were wide, and CIs crossed the clinical decision threshold.

### Antibiotics compared with other antibiotics for treatment of leptospirosis

We included data from three trials assessing the efficacy of antibiotics in the treatment of leptospirosis compared with other antibiotics. We rated the certainty of evidence for mortality, serious adverse events (nosocomial infection), and adverse events considered non-serious as very low due to the risk of bias from deviation from intended interventions, measurement of the outcome and selection of reported results, and serious imprecision where the optimal information size was not met, CIs were very wide, and the CIs crossed the clinical decision threshold (see Summary of findings 2).

## Potential biases in the review process

Due to the insufficient number of trials, we were unable to conduct funnel plot analysis to further assess publication bias and subgroup analysis, as described in the protocol (Mukadi 2022). However, we are certain that we identified all relevant trials. We chose to undertake a meta-analysis even though nearly all the trials had a high risk of bias. In addition, included trials reported different adverse events considered non-serious, and we synthesised them in our meta-analysis.

## Agreements and disagreements with other studies or reviews

We identified three systematic reviews (Brett-Major 2012; Charan 2013; Guidugli 2000) and one meta-analysis (Perez 2021) evaluating the benefits of antibiotics for treatment of leptospirosis. Two of the reviews were previous versions of this present review (Brett-Major 2012; Guidugli 2000).

Guidugli and colleagues included three randomised clinical trials involving 150 participants (Guidugli 2000). This review concluded that, although methodological constraints made defining the indication for antibiotics difficult, the benefits of using penicillin or doxycycline may outweigh the harms (Guidugli 2000).

Brett-Major and colleagues included seven randomised clinical trials involving 909 participants (Brett-Major 2012). The authors

concluded that use of antibiotics for leptospirosis may have decreased the duration of clinical illness by two to four days, but overall, did not find a compelling use for antibiotics (Brett-Major 2012).

Charan and colleagues included 10 clinical trials in the qualitative analysis, but only five were included in a meta-analysis involving 492 participants (Charan 2013). They concluded that the use of antibiotics was unclear for the treatment of leptospirosis and more trials with better methodologies were recommended (Charan 2013).

Perez and colleagues included 10 trials involving 1071 participants (Perez 2021). The authors concluded that there is a lack of good-quality studies on the efficacy of antibiotics at various stages of the disease and detected no treatment effects (Perez 2021).

We identified two additional trials from our search that were added to the seven trials included in the 2012 review (Brett-Major 2012). The trial characteristics of the included trials were like the prior review as trials were conducted in six countries from both low- and middle-income resource settings.

## AUTHORS' CONCLUSIONS

### Implications for practice

This review found insufficient evidence to support the use of antibiotics as leptospirosis treatment. Antibiotic choice, timing of administration, route of administration, and dosage of antimicrobial agents also remain undetermined.

We do not know if antibiotics are effective in reducing mortality or have favourable adverse events (either serious or adverse events considered non-serious) because of the very low-certainty evidence found from the data analysis.

### Implications for research

The current review found a lack of evidence to draw definitive conclusions about the effectiveness of antibiotics in treating leptospirosis. Further high-quality randomised clinical trials with clear and clinically relevant inclusion criteria are required to provide a more comprehensive insight into the effects of antibiotics for treating leptospirosis. Future trials should develop and adhere to standardised inclusion criteria and treatment outcomes to enhance the internal validity of the individual trials and to make it easier for meaningful comparisons across the trials. More head-to-head antimicrobial studies are required to compare the effectiveness of antimicrobials in the treatment of leptospirosis disease. Recommendations for SPIRIT interventional trials statement on design (SPIRIT 2013a; SPIRIT 2013b) and for the CONSORT reporting guidelines (Moher 2010; www.consort-statement.org/) ought to be followed.

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# CHARACTERISTICS OF STUDIES

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

### Costa 2003

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised clinical trial<br>**Location:** Salvador, Brazil (single centre)<br>**Date:** August 1997 to July 1999<br>**Number of participants randomised:** 253 |

**Costa 2003** *(Continued)*

| | |
|---|---|
| | **Number of trial groups:** 1 experimental and 1 control<br><br>**Trial protocol:** no published trial protocol |
| Participants | **Mean age:** experimental group: 35.8 (SD 13.9) years; control group: 35.1 (SD 13.1) years<br><br>**Males:** 89.7%<br><br>**Inclusion criteria:** people with > 4 days of symptoms (i.e. late stage) and reach ≥ 26 points in the WHO probability score for leptospirosis which includes 6 clinical findings (headache, fever, conjunctival suffusion in both eyes, meningeal signs, myalgia, and jaundice), azotaemia, and evidence of exposure to sources of *Leptospira* (i.e. rats or contaminated water)<br><br>**Exclusion criteria:** aged < 15 years, allergy to penicillin, immunodeficiency, history of nephropathy or cardiomyopathy, diabetes mellitus, and pregnancy |
| Interventions | **Experimental group** (125 participants): penicillin 1 million units every 4 hours for 7 days<br><br>**Control group** (128 participants): no treatment<br><br>**Co-intervention:** not reported<br><br>**Dropouts:** no<br><br>**Intention-to-treat analysis:** yes<br><br>**Follow-up:** not reported |
| Outcomes | **Mortality**<br><br>**Days of hospitalisation**<br><br>Time point: during the trial period |
| Notes | Contacted trial author for additional data 1 December 2022, received no reply.<br><br>**Funding source:** trial received partial support from the Conselho Nacional de Ciencia e Tecnologia, CNPq, grant 520823/97-4. |

**Daher 2000**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Randomised clinical trial<br><br>**Location:** Brazil (single centre)<br><br>**Dates:** May 1996 to June 1998<br><br>**Number of participants randomised:** 35<br><br>**Number of trial groups:** 1 experimental and 1 control<br><br>**Trial protocol:** no published trial protocol |
| Participants | **Mean age:** experimental group: 37 (SD 10) years; control group: 32 (SD 9) years<br><br>**Males:** 85.7%<br><br>**Inclusion criteria:** had acute renal failure, defined as plasma creatinine (polymerase chain reaction) > 1.5 mg/dL and jaundice on admission |

**Daher 2000** *(Continued)*

| | |
|---|---|
| | **Exclusion criteria:** aged > 60 years, had renal lithiasis, no diagnosis of leptospirosis confirmed by serology, died within the first 48 hours of admission, receiving penicillin therapy, with massive haemoptysis and acute respiratory distress syndrome |
| Interventions | **Experimental group** (16 participants): crystalline penicillin 6 million units per day for 8 days<br>**Control group** (19 participants): no treatment<br>**Co-intervention:** furosemide for participants with oliguria, hydration with crystalloids, and potassium replacement depending on the need of participants<br>**Dropout:** not reported<br>**Intention-to-treat analysis:** not reported<br>**Follow-up:** not reported |
| Outcomes | **Mortality**<br>**Time of hospitalisation**<br>Time point: during the trial period |
| Notes | Contacted trial author for additional data 1 December 2022, but email address provided was no longer in operation.<br>**Funding source:** trial received part grant support from CAPES (a Brazilian federal government agency under the Ministry of Education). |

**Edwards 1988**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised clinical trial<br>**Location:** Barbados (single centre)<br>**Dates:** 1 October 1983 to 31 December 1986<br>**Number of participants randomised:** 79<br>**Number of trial groups:** 1 experimental and 1 control<br>**Trial protocol:** no published trial protocol |
| Participants | **Mean age:** experimental group: 39 years; control group: 40 years<br>**Males:** 82.3%<br>**Inclusion criteria:** admitted to Queen Elizabeth Hospital from 1 October 1983 to 31 December 1986 with a history and physical findings compatible with leptospirosis<br>**Exclusion criteria:** without sustainable leptospirosis diagnosis |
| Interventions | **Experimental group** (38 participants): crystalline penicillin 2 million units every 6 hours for 5 days<br>**Control group** (41 participants): intravenous fluids<br>**Co-intervention:** not reported<br>**Dropouts:** no |

**Edwards 1988** *(Continued)*

| | |
|---|---|
| | **Intention-to-treat analysis:** not reported |
| | **Follow-up:** 1 year |
| Outcomes | **Mortality** |
| | **Non-serious adverse events** (Jarisch Herxheimer-type reaction) |
| | Time point: during the trial period |
| Notes | Contact address of trial author was not provided. |
| | **Funding source:** not reported |

**Fairburn 1956**

| | |
|---|---|
| ***Study characteristics*** | |
| Methods | Randomised clinical trial |
| | **Location:** Malaysia (2 centres) |
| | **Date:** not reported |
| | **Number of participants randomised:** 83 |
| | **Number of trial groups:** 2 experimental and 1 control |
| | **Trial protocol:** no published trial protocol |
| Participants | **Mean age:** 21 (range 18–35) years |
| | **Males:** 100% |
| | **Inclusion criteria:** British troops engaged in Malaya and those admitted to 1 of 2 military hospitals |
| | **Exclusion criteria:** associated attack of malaria or unconfirmed diagnosis |
| Interventions | **Experimental group 1** (21 participants): penicillin 600,000 units every 6 hours for 5 days |
| | **Experimental group 2** (31 participants): chloramphenicol 0.5 g every 6 hours for 5 days |
| | **Control group** (31 participants): no treatment |
| | **Co-intervention:** fluid replacement and analgesics |
| | **Dropout:** not reported |
| | **Intention-to-treat analysis:** not reported |
| | **Follow-up:** not reported |
| Outcomes | **Adverse events** (rising blood urea) |
| | Time point: during the trial period |
| Notes | Contact address of trial author was not provided. |
| | **Funding source:** not reported |

### McClain 1984

| *Study characteristics* | |
|---|---|
| Methods | Randomised, double-blind trial<br>**Location:** Panama (single centre)<br>**Dates:** not reported<br>**Number of participants randomised:** 29<br>**Number of trial groups:** 1 experimental and 1 control<br>**Trial protocol:** no published trial protocol |
| Participants | **Age:** not reported<br>**Males:** not reported<br>**Inclusion criteria:** febrile people returning from the jungle training school<br>**Exclusion criteria:** concurrent use of antibiotics, presence of another cause of fever, history of recent hepatitis, pregnancy, body temperature < 38 °C orally, allergy to tetracycline, or illness severe enough to threaten life |
| Interventions | **Experimental group** (14 participants): doxycycline 100 mg orally twice a day for 7 days<br>**Control group** (15 participants): placebo<br>**Co-intervention:** not reported<br>**Dropouts:** no<br>**Intention-to-treat analysis:** not reported<br>**Follow-up:** 3 weeks |
| Outcomes | None of the prespecified outcomes were reported. We included this trial only for qualitative synthesis. |
| Notes | Contact address of trial author was not provided.<br>**Funding source:** not reported |

### Panaphut 2003

| *Study characteristics* | |
|---|---|
| Methods | Large-scale randomised clinical trial<br>**Location:** Thailand (single centre)<br>**Dates:** July 2000 to December 2001<br>**Number of participants randomised:** 173<br>**Number of trial groups:** 2 experimental<br>**Trial protocol:** no published trial protocol |

**Panaphut 2003** *(Continued)*

| | |
|---|---|
| Participants | **Median age:** experimental group 1: 42 (interquartile range 31–53) years; experimental group 2: 41 (interquartile range 31–52) years<br><br>**Males:** 91.9%<br><br>**Inclusion criteria:** aged ≥ 16 years, had severe leptospirosis, had received no parenteral or oral antibiotics for < 1 day, no history of allergy to penicillin or cephalosporin, experienced no cardiopulmonary resuscitation before admission; and not stuporous or comatose<br><br>**Exclusion criteria:** concurrent infection with other organisms at hospital admission; presented with haemoconcentration (haematocrit > 45%) in first 48 hours after hospital admission; atypical lymphocytes were noted on peripheral blood smear |
| Interventions | **Experimental group 1** (87 participants): ceftriaxone 1 g intravenously once per day for 7 days<br><br>**Experimental group 2** (86 participants);sodium penicillin G 1.5 million units intravenously every 6 hours for 7 days<br><br>**Co-intervention:** gentamicin was also administered for participants in group 2 for whom septicaemia due to gram-negative pathogens could not be initially excluded.<br><br>**Dropouts:** 5 participants from experimental group 1 and 2 participants from experimental group 2 withdrew as fever subsided and discharged from hospital.<br><br>**Intention-to-treat analysis:** yes<br><br>**Follow-up:** 8 days for experimental group 1 and 7 days for experimental group 2 |
| Outcomes | **Mortality**<br><br>Time point: during the trial period |
| Notes | Contacted trial author for additional data 1 December 2022, but email address provided was no longer in operation.<br><br>**Funding source:** trial received financial support from National Centre for Genetic Engineering and Biotechnology (Bangkok, Thailand), the Khon Kaen Hospital Research Fund (Khon Kaen, Thailand), and ceftriaxone support from Siam Pharmaceutical (Bangkok). |

**Phimda 2007**

| ***Study characteristics*** | |
|---|---|
| Methods | Multicentre, open, randomised clinical trial<br><br>**Location:** Thailand (3 centres)<br><br>**Dates:** July 2003 to January 2005<br><br>**Number of participants randomised:** 69<br><br>**Number of trial groups:** 2 experimental<br><br>**Trial protocol:** no published trial protocol |
| Participants | **Age:** not reported<br><br>**Males:** not reported<br><br>**Inclusion criteria:** aged > 14 years, suspected leptospirosis or scrub typhus as described by acute fever without clear source of infection, able to tolerate oral antibiotic therapy |

**Phimda 2007** *(Continued)*

| | |
|---|---|
| | **Exclusion criteria:** unable to take oral medications, pregnant or breastfeeding, allergy to macrolides or tetracyclines, positive malarial blood smear, clinical dengue virus infection, severe leptospirosis or scrub typhus-related complication, taken treatment for leptospirosis or scrub typhus for > 48 hours before enrolment |
| Interventions | **Experimental group 1** (34 participants): oral doxycycline 200 mg in the first dose, followed by 100 mg every 12 hours for 7 days<br><br>**Experimental group 2** (35 participants):azithromycin 1 g initially, followed by 500 mg once daily for 2 days<br><br>**Co-intervention:** not reported<br><br>**Dropout:** not reported<br><br>**Intention-to-treat analysis:** yes<br><br>**Follow-up:** 2 weeks |
| Outcomes | None of the prespecified outcomes were reported. We included this trial only for qualitative synthesis. |
| Notes | Contacted trial author for additional data 1 December 2022, but received no reply.<br><br>**Funding source:** the trial received funding support from the Thailand Research Fund, the Ministry of Public Health, Thailand, and the Wellcome Trust of Great Britain. |

**Suputtamongkol 2004**

| ***Study characteristics*** | |
|---|---|
| Methods | Open, randomised clinical trial<br><br>**Location:** Thailand (4 centres)<br><br>**Dates:** July 2001 to December 2002<br><br>**Number of participants randomised:** 256<br><br>**Number of trial groups:** 3 experimental<br><br>**Trial protocol:** no published trial protocol |
| Participants | **Median age:** experimental group 1: 35 (13–70) years; experimental group 2: 33 (15–61) years; experimental group 3: 35 (16–70) years<br><br>**Males:** 87.5%<br><br>**Inclusion criteria:** adults with suspected severe leptospirosis, i.e. presented with acute fever (duration < 15 days) in absence of an obvious focus of infection<br><br>**Exclusion criteria:** pregnancy or lactation, diabetes, known allergy to any of the study medications, history of receipt of treatment active against leptospirosis for > 48 hours |
| Interventions | **Experimental group 1** (87 participants): sodium penicillin G 1.5 million units intravenously every 6 hours for 7 days<br><br>**Experimental group 2** (81 participants): doxycycline 200 mg infused for 30 minutes, followed by infusion of 100 mg every 12 hours for 7 days<br><br>**Experimental group 3** (88 participants): cefotaxime 1 g intravenously every 6 hours for 7 days |

**Suputtamongkol 2004** *(Continued)*

| | |
|---|---|
| | **Co-intervention:** gentamicin was given in cases where the possibility of gram-negative sepsis could not be ruled out as a differential diagnosis. Parenteral treatment was switched to oral therapy (amoxicillin for experimental group 1 and 3; and oral doxycycline for group 2).<br><br>**Dropout:** not reported<br><br>**Intention-to-treat analysis:** yes<br><br>**Follow-up:** 2–4 weeks |
| Outcomes | **Mortality**<br><br>**Adverse events** (skin rash, nosocomial infection)<br><br>Time point: during the trial period |
| Notes | Contacted trial authors for additional data 1 December 2022, but received no reply.<br><br>**Funding source:** trial received financial support from Thailand Research Fund, Ministry of Public Health Thailand, and was also part of the Wellcome Trust-Mahidol University Oxford Tropical Medicine Research Programme funded by the Wellcome Trust of Great Britain. The trial received parenteral doxycycline from Dr Charles Knirsch (Pfizer International). |

**Watt 1988**

| ***Study characteristics*** | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled trial<br><br>**Location:** Philippines (single centre)<br><br>**Date:** September 1985 to October 1986<br><br>**Number of participants randomised:** 42<br><br>**Number of trial groups:** 1 experimental and 1 control<br><br>**Trial protocol:** no published trial protocol |
| Participants | **Mean age:** experimental group 1: 31 (19–52) years; control group: 31 (16–58) years<br><br>**Males:** 80%<br><br>**Inclusion criteria:** aged > 16 years, received < 6 doses of parenteral antibiotics or had completed < 3 days of an oral antibiotic regimen, screening test indicated a high likelihood of leptospirosis<br><br>**Exclusion criteria:** people with anuria on admission; presence of a second illness; and confusion, stupor, or coma |
| Interventions | **Experimental group** (23 participants): sodium penicillin G 1.5 million units intravenously every 6 hours for 7 days<br><br>**Control group** (19 participants): equal volumes of normal saline<br><br>**Co-intervention:** not reported<br><br>**Dropouts:** no<br><br>**Intention-to-treat analysis:** not reported<br><br>**Follow-up:** 1 week and 1 month |

**Watt 1988** *(Continued)*

| | |
|---|---|
| Outcomes | **Mortality**<br>Time point: during the trial period<br>We included this trial only for qualitative synthesis, since the author reported 0 events of mortality outcome in both arms. |
| Notes | Contact address of trial author was not provided.<br>**Funding source:** trial received funding support from the Naval Medical Research and Development Command, Navy Department for Work Unit 3M162770870 AN 315, and from the Philippine Department of Health. |

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

| Study | Reason for exclusion |
|---|---|
| Russell 1958 | Non-randomised study and use of uncommon antibiotics |

## RISK OF BIAS

**Legend:** ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

**Risk of bias for analysis 1.1 All-cause mortality**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Costa 2003 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Daher 2000 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |
| Edwards 1988 | ~ | ✓ | ✓ | ✓ | ✓ | ~ |

**Risk of bias for analysis 2.4 Serious adverse event (nosocomial infection) (penicillin versus cefotaxime)**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Suputtamongkol 2004 | ✓ | ~ | ✓ | ✗ | ~ | ✗ |

**Risk of bias for analysis 2.5 Serious adverse event (nosocomial infection) (penicillin versus doxycycline)**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Suputtamongkol 2004 | ✓ | ~ | ✓ | ✗ | ~ | ✗ |

**Risk of bias for analysis 2.6 Serious adverse event (nosocomial infection) (doxycycline versus cefotaxime)**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Suputtamongkol 2004 | ✓ | ~ | ✓ | ✗ | ~ | ✗ |

**Risk of bias for analysis 2.7 Proportion of people with adverse events considered non-serious (penicillin versus cefotaxime)**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Suputtamongkol 2004 | ✓ | ✓ | ✓ | ✗ | ~ | ✗ |

**Risk of bias for analysis 2.8 Proportion of people with adverse events considered non-serious (penicillin versus doxycycline)**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Suputtamongkol 2004 | ✓ | ✓ | ✓ | ✗ | ~ | ✗ |

**Risk of bias for analysis 2.9 Proportion of people with adverse events considered non-serious (penicillin versus chloramphenicol)**

| | Bias | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported results** | **Overall** |
| Fairburn 1956 | ~ | ✓ | ✓ | ✗ | ~ | ✗ |

## DATA AND ANALYSES

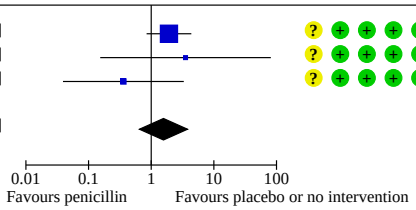
### Comparison 1. Antibiotics versus placebo or no intervention

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 All-cause mortality | 3 | 367 | Risk Ratio (M-H, Random, 95% CI) | 1.57 [0.65, 3.79] |
| 1.2 Proportion of people with adverse events considered non-serious | 2 | 162 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.35, 3.17] |
| 1.3 Days of hospitalisation | 2 | 288 | Mean Difference (IV, Random, 95% CI) | 0.15 [-0.74, 1.05] |

## Analysis 1.1. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 1: All-cause mortality

| Study or Subgroup | Penicillin Events | Penicillin Total | Placebo or no intervention Events | Placebo or no intervention Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Costa 2003 | 15 | 125 | 8 | 128 | 77.5% | 1.92 [0.84 , 4.37] |
| Daher 2000 | 1 | 16 | 0 | 19 | 7.7% | 3.53 [0.15 , 81.11] |
| Edwards 1988 | 1 | 38 | 3 | 41 | 14.8% | 0.36 [0.04 , 3.31] |
| **Total (95% CI)** | | **179** | | **188** | **100.0%** | **1.57 [0.65 , 3.79]** |
| Total events: | 17 | | 11 | | | |

Heterogeneity: Tau² = 0.09; Chi² = 2.17, df = 2 (P = 0.34); I² = 8%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable





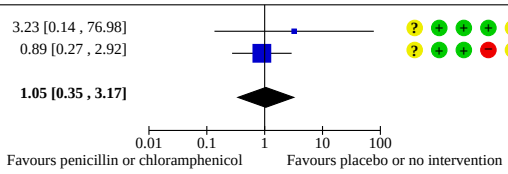


**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 1.2. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 2: Proportion of people with adverse events considered non-serious

| Study or Subgroup | Penicillin or chloramphenicol Events | Penicillin or chloramphenicol Total | Placebo or no intervention Events | Placebo or no intervention Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Edwards 1988 | 1 | 38 | 0 | 41 | 12.2% | 3.23 [0.14 , 76.98] |
| Fairburn 1956 | 6 | 52 | 4 | 31 | 87.8% | 0.89 [0.27 , 2.92] |
| **Total (95% CI)** | | **90** | | **72** | **100.0%** | **1.05 [0.35 , 3.17]** |
| Total events: | 7 | | 4 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable



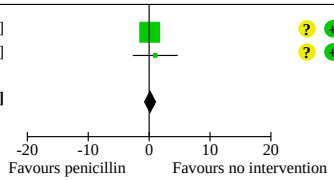


**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 1.3. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 3: Days of hospitalisation

| Study or Subgroup | Penicillin Mean | Penicillin SD | Penicillin Total | No intervention Mean | No intervention SD | No intervention Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Costa 2003 | 8.9 | 3.9 | 125 | 8.8 | 3.6 | 128 | 94.1% | 0.10 [-0.83 , 1.03] |
| Daher 2000 | 12 | 6 | 16 | 11 | 5 | 19 | 5.9% | 1.00 [-2.70 , 4.70] |
| **Total (95% CI)** | | | **141** | | | **147** | **100.0%** | **0.15 [-0.74 , 1.05]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable





**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

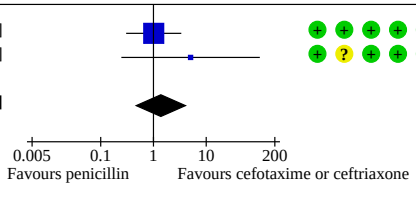
## Comparison 2. Antibiotics versus another antibiotic

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 All-cause mortality (penicillin versus cefotaxime or ceftriaxone) | 2 | 348 | Risk Ratio (M-H, Fixed, 95% CI) | 1.38 [0.47, 4.04] |
| 2.2 All-cause mortality (penicillin versus doxycycline) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.3 All-cause mortality (cefotaxime versus doxycycline) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.4 Serious adverse event (nosocomial infection) (penicillin versus cefotaxime) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.5 Serious adverse event (nosocomial infection) (penicillin versus doxycycline) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.6 Serious adverse event (nosocomial infection) (doxycycline versus cefotaxime) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.7 Proportion of people with adverse events considered non-serious (penicillin versus cefotaxime) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.8 Proportion of people with adverse events considered non-serious (penicillin versus doxycycline) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 2.9 Proportion of people with adverse events considered non-serious (penicillin versus chloramphenicol) | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Totals not selected |

## Analysis 2.1. Comparison 2: Antibiotics versus another antibiotic, Outcome 1: All-cause mortality (penicillin versus cefotaxime or ceftriaxone)

| Study or Subgroup | Penicillin Events | Penicillin Total | Cefotaxime or ceftriaxone Events | Cefotaxime or ceftriaxone Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Panaphut 2003 | 5 | 86 | 5 | 87 | 90.9% | 1.01 [0.30 , 3.37] |
| Suputtamongkol 2004 | 2 | 87 | 0 | 88 | 9.1% | 5.06 [0.25 , 103.83] |
| **Total (95% CI)** | | **173** | | **175** | **100.0%** | **1.38 [0.47 , 4.04]** |
| Total events: | 7 | | 5 | | | |

Heterogeneity: Chi² = 0.97, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable



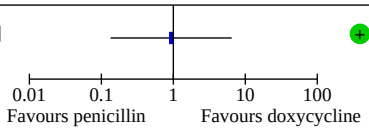




**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 2.2. Comparison 2: Antibiotics versus another antibiotic, Outcome 2: All-cause mortality (penicillin versus doxycycline)

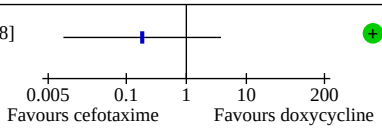
| Study or Subgroup | Penicillin Events | Penicillin Total | Doxycycline Events | Doxycycline Total | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A | B | C | D | E | F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suputtamongkol 2004 | 2 | 87 | 2 | 81 | 0.93 [0.13 , 6.46] | | + | ? | + | + | + | ? |




**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 2.3. Comparison 2: Antibiotics versus another antibiotic, Outcome 3: All-cause mortality (cefotaxime versus doxycycline)

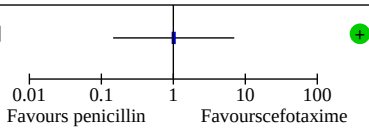
| Study or Subgroup | Cefotaxime Events | Cefotaxime Total | Doxycycline Events | Doxycycline Total | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A | B | C | D | E | F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suputtamongkol 2004 | 0 | 88 | 2 | 81 | 0.18 [0.01 , 3.78] | | + | ? | + | + | + | ? |




**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 2.4. Comparison 2: Antibiotics versus another antibiotic, Outcome 4: Serious adverse event (nosocomial infection) (penicillin versus cefotaxime)

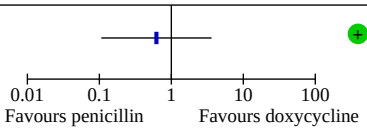
| Study or Subgroup | Penicillin Events | Penicillin Total | Cefotaxime Events | Cefotaxime Total | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A | B | C | D | E | F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suputtamongkol 2004 | 2 | 87 | 2 | 88 | 1.01 [0.15 , 7.02] | | + | ? | + | − | ? | − |




**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 2.5. Comparison 2: Antibiotics versus another antibiotic, Outcome 5: Serious adverse event (nosocomial infection) (penicillin versus doxycycline)

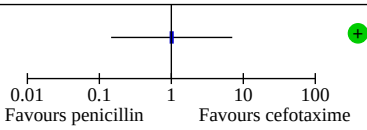
| Study or Subgroup | Penicillin Events | Penicillin Total | Doxycycline Events | Doxycycline Total | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A | B | C | D | E | F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suputtamongkol 2004 | 2 | 87 | 3 | 81 | 0.62 [0.11 , 3.62] | | + | ? | + | − | ? | − |




**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 2.6. Comparison 2: Antibiotics versus another antibiotic, Outcome 6: Serious adverse event (nosocomial infection) (doxycycline versus cefotaxime)

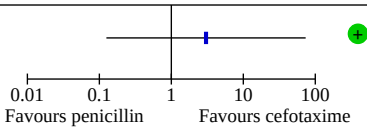
| Study or Subgroup | Doxycycline Events | Doxycycline Total | Cefotaxime Events | Cefotaxime Total | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A | B | C | D | E | F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suputtamongkol 2004 | 2 | 87 | 2 | 88 | 1.01 [0.15 , 7.02] | | + | ? | + | − | ? | − |




**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## Analysis 2.7. Comparison 2: Antibiotics versus another antibiotic, Outcome 7: Proportion of people with adverse events considered non-serious (penicillin versus cefotaxime)

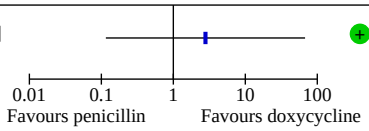
| Study or Subgroup | Penicillin Events | Penicillin Total | Cefotaxime Events | Cefotaxime Total | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A | B | C | D | E | F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suputtamongkol 2004 | 1 | 87 | 0 | 88 | 3.03 [0.13 , 73.47] | | + | + | + | − | ? | − |




**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

### Analysis 2.8. Comparison 2: Antibiotics versus another antibiotic, Outcome 8: Proportion of people with adverse events considered non-serious (penicillin versus doxycycline)

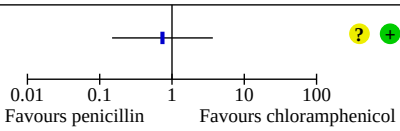
| Study or Subgroup | Penicillin Events | Penicillin Total | Doxycycline Events | Doxycycline Total | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A | B | C | D | E | F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suputtamongkol 2004 | 1 | 87 | 0 | 81 | 2.80 [0.12 , 67.66] | | + | + | + | − | ? | − |




**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

### Analysis 2.9. Comparison 2: Antibiotics versus another antibiotic, Outcome 9: Proportion of people with adverse events considered non-serious (penicillin versus chloramphenicol)

| Study or Subgroup | Penicillin Events | Penicillin Total | Chloramphenicol Events | Chloramphenicol Total | Risk Ratio M-H, Fixed, 95% CI | Risk Ratio M-H, Fixed, 95% CI | Risk of Bias A | B | C | D | E | F |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fairburn 1956 | 2 | 21 | 4 | 31 | 0.74 [0.15 , 3.67] | | ? | + | + | − | ? | − |




**Risk of bias legend**
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

## APPENDICES

### Appendix 1. Search strategies

| Database | Timespan | Search strategy |
|---|---|---|
| Cochrane Hepato-Biliary Group Controlled Trials Register (via the Cochrane Register of Studies Web) | 27 March 2023 | (antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*) 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 in the Cochrane Library | 2023; Issue 3 | #1 MeSH descriptor: [Anti-Bacterial Agents] explode all trees<br><br>#2 (antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*) |

*(Continued)*

| | | |
|---|---|---|
| | | #3 #1 or #2<br><br>#4 MeSH descriptor: [Leptospirosis] explode all trees<br><br>#5 (leptospir* or ((weil* or Swineherd*) and disease*) or (Stuttgart next disease*) or (hemorrhagic next jaundice) or (spirochetal next jaundice) or (((cane next cutter) or canicola or icterohemorrhagic or mud or (rice next field) or swamp) and fever))<br><br>#6 #4 or #5<br><br>#7 #3 and #4 |
| MEDLINE ALL Ovid | 1946 to 27 March 2023 | 1. exp Anti-Bacterial Agents/<br><br>2. (antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]<br><br>3. 1 or 2<br><br>4. exp Leptospirosis/<br><br>5. (leptospir* or ((weil* or Swineherd*) and disease*) or Stuttgart disease* or hemorrhagic jaundice or spirochetal jaundice or ((cane cutter or canicola or icterohemorrhagic or mud or rice field or swamp) and fever)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]<br><br>6. 4 or 5<br><br>7. 3 and 6<br><br>8. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt.<br><br>9. clinical trials as topic.sh.<br><br>10. (random* or placebo*).ab. or trial.ti.<br><br>11. 8 or 9 or 10<br><br>12. exp animals/ not humans.sh.<br><br>13. 11 not 12<br><br>14. 7 and 13 |
| Embase Ovid | 1974 to 27 March 2023 | 1. exp antibiotic agent/<br><br>2. (antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, |

(Continued)

drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

3. 1 or 2

4. exp leptospirosis/

5. (leptospir* or ((weil* or Swineherd*) and disease*) or Stuttgart disease* or hemorrhagic jaundice or spirochetal jaundice or ((cane cutter or canicola or icterohemorrhagic or mud or rice field or swamp) and fever)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

6. 4 or 5

7. 3 and 6

8. Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or retracted article/

9. (random$ or placebo or parallel group$1 or crossover or cross over or assigned or allocated or volunteer or volunteers).ti,ab.

10. (compare or compared or comparison or trial).ti.

11. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.

12. (open adj label).ti,ab.

13. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.

15. (controlled adj7 (study or design or trial)).ti,ab.

16. (erratum or tombstone).pt. or yes.ne.

17. or/8-16

18. (random$ adj sampl$ adj7 ('cross section$' or questionnaire$ or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)

19. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)

20. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.

21. (Systematic review not (trial or study)).ti.

22. (nonrandom$ not random$).ti,ab.

23. 'Random field$'.ti,ab.

24. (random cluster adj3 sampl$).ti,ab.

25. (review.ab. and review.pt.) not trial.ti.

26. 'we searched'.ab. and (review.ti. or review.pt.)

*(Continued)*

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| | | 27. 'update review'.ab.<br><br>28. (databases adj4 searched).ab.<br><br>29. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/<br><br>30. Animal experiment/ not (human experiment/ or human/)<br><br>31. or/18-30<br><br>32. 17 not 31<br><br>33. 7 and 32 |
| LILACS (VHL Regional Portal) | 1982 to 27 March 2023 | ((antibiotic* OR anti-biotic* OR antimicrobial* OR anti-microbial* OR antibacterial* OR anti-bacterial* OR antimycobacterial* OR anti-mycobacterial* OR bacteriocid* OR chloramphenicol* OR penicillin* OR benzylpenicillin* OR doxycyclin* OR cefotaxim* OR ceftriaxon* OR azithromycin* OR oxytetracyclin* OR cephalosporin* OR amoxycillin* OR cefotaxim* OR quinolone*)) 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))) AND ( db:("LILACS")) |
| Science Citation Index Expanded (Web of Science) | 1900 to 27 March 2023 | #5 #3 AND #4<br><br>#4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*)<br><br>#3 #2 AND #1<br><br>#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))<br><br>#1 TS=(antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*) |
| Conference Proceedings Citation Index – Science (Web of Science) | 1990 to 27 March 2023 | #5 #3 AND #4<br><br>#4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*)<br><br>#3 #2 AND #1<br><br>#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))<br><br>#1 TS=(antibiotic* or anti-biotic* or antimicrobial* or anti-microbial* or antibacterial* or anti-bacterial* or antimycobacterial* or anti-mycobacterial* or bacteriocid* or Chloramphenicol* or Penicillin* or Benzylpenicillin* or Doxycyclin* or Cefotaxim* or Ceftriaxon* or Azithromycin* or Oxytetracyclin* or Cephalosporin* or Amoxycillin* or Cefotaxim* or quinolone*) |
| World Health Organization International | 27 March 2023 | leptospirosis OR leptospira OR leptospir* |

(Continued)

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|---|---|---|
| Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp) | | |
| ClinicalTrial.gov (clinicaltrials.gov/) | 27 March 2023 | Condition: leptospirosis OR leptospira OR leptospir* OR leptospira infection |
| EU Clinical Trials Register, European Medicines Agency (www.clinicaltrialsregister.eu/ctr-search/) | 27 March 2023 | leptospirosis OR leptospira OR leptospir* |
| International Standard Randomised Controlled Trial Number Registry (ISRCTN) (www.isrctn.com/) | 27 March 2023 | leptospirosis OR leptospira |
| American Society of Tropical Medicine and Hygiene (ASTMH) (www.astmh.org/) | Presented abstract programmes, national meetings from 2005 to 27 March 2023 | Abstract search engine and PDF search, dependent upon year of meeting, with “leptospir” |
| Infectious Diseases Society of America (IDSA) (idsa.confex.com/idsa/) | Presented abstract programmes, national meetings from 2003 to 27 March 2023 | PDF search “leptospir*" |
| International Society of Travel Medicine (ISTM) (www.istm.org/) | Presented abstract programmes, international meetings from 2011 to 27 March 2023 | Abstract search engine with "leptospir*" and use the search box with "leptospir", dependent upon year of meeting |

## HISTORY

Protocol first published: Issue 5, 2022

## CONTRIBUTIONS OF AUTHORS

TZW: screening, data extraction, risk of bias and certainty of evidence assessment, meta-analysis, drafting of the review, taking responsibility for reading and checking the review before submission

SMH: writing the review, and taking responsibility for reading and checking the review before submission

TE: methodological expertise and advice

HTM: screening, data extraction, and risk of bias assessment

DMB: clinical and methodological expertise and advice

CS: clinical and methodological expertise and advice, conception and writing of the review, taking responsibility for reading and checking the review before submission

NL: clinical and methodological expertise and advice, meta-analysis, writing of the review, and taking responsibility for reading and checking the review before submission

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

## DECLARATIONS OF INTEREST

TZW: none.

SMH: none.

TE: none.

HTM: none.

DMB: none.

CS: none.

NL: none.

## SOURCES OF SUPPORT

### Internal sources

- Internal sources of support, Japan

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

### External sources

- Hepato-Biliary Group, the Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital — Rigshospitalet, Denmark

  Help with literature searches and preparation of the review, including editorial processes

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes from the protocol (Mukadi 2022).

**Additional outcome:** we reported the outcomes specified during the protocol stage. Additionally, we included days of hospitalisation as a secondary outcome, which encompassed the outcomes of 'days of clinical illness' and 'days of fever' that we aimed to include.

**Summary of finding tables:** we planned to create three summary of finding tables. However, we created only two tables by combining placebo and no intervention group due to the limited number of trials.

**Measure of treatment effect:** we only intended to perform meta-analysis where the study group was sufficiently homogeneous. Although the study group is highly heterogeneous, we nonetheless performed a meta-analysis because there were so few included trials.

**Certainty of evidence:** due to the limited functionality of GRADEpro GDT, only one review author was able to grade the certainty of the evidence, as opposed to the two review authors we had originally anticipated. The remaining authors checked the assessments.

## NOTES

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

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Anti-Bacterial Agents [therapeutic use]; *Bias; Ceftriaxone [therapeutic use]; Doxycycline [therapeutic use]; *Leptospirosis [drug therapy]; Placebos [therapeutic use]; Quality of Life; *Randomized Controlled Trials as Topic

### MeSH check words

Humans