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[Intervention Review]

Antibiotic prophylaxis for leptospirosis

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ABSTRACT

Background

Leptospirosis is a global zoonotic and waterborne disease caused by pathogenic *Leptospira* species. Antibiotics are used as a strategy for prevention of leptospirosis, in particular in travellers and high-risk groups. However, the clinical benefits are unknown, especially when considering possible treatment-associated adverse effects. This review assesses the use of antibiotic prophylaxis in leptospirosis and is an update of a previously published review in the Cochrane Library (2009, Issue 3).

Objectives

To evaluate the benefits and harms of antibiotic prophylaxis for human leptospirosis.

Search methods

We identified randomised clinical trials through electronic searches of the Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, LILACS, Science Citation Index Expanded, and other resources. We searched online clinical trial registries to identify unpublished or ongoing trials. We checked reference lists of the retrieved studies for further trials. The last date of search was 17 April 2023.

Selection criteria

We included randomised clinical trials of any trial design, assessing antibiotics for prevention of leptospirosis, and with no restrictions on age, sex, occupation, or comorbidity of trial participants. We looked for trials assessing antibiotics irrespective of route of administration, dosage, and schedule versus placebo or no intervention. We also included trials assessing antibiotics versus other antibiotics using these criteria, or the same antibiotic but with another dose or schedule.

Data collection and analysis

We followed Cochrane methodology. The primary outcomes were all-cause mortality, laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome (inclusive of asymptomatic cases), clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation, clinical diagnosis of leptospirosis confirmed by laboratory diagnosis (exclusive of asymptomatic cases), and serious adverse events. The secondary outcomes were quality of life and the proportion of people with non-serious adverse events. We

assessed the risk of bias of the included trials using the RoB 2 tool and the certainty of evidence using GRADE. We presented dichotomous outcomes as risk ratios (RR) and continuous outcomes as mean difference (MD), with their 95% confidence intervals (CI). We used a random-effects model for our main analyses and the fixed-effect model for sensitivity analyses. Our primary outcome analyses included trial data at the longest follow-up.

Main results

We identified five randomised clinical trials comprising 2593 participants that compared antibiotics (doxycycline, azithromycin, or penicillin) with placebo, or one antibiotic compared with another. Four trials assessed doxycycline with different durations, one trial assessed azithromycin, and one trial assessed penicillin. One trial had three intervention groups: doxycycline, azithromycin, and placebo. Three trials assessed pre-exposure prophylaxis, one trial assessed postexposure prophylaxis, and one did not report this clearly. Four trials recruited residents in endemic areas, and one trial recruited soldiers who experienced limited time exposure. The participants' ages in the included trials were 10 to 80 years. Follow-up ranged from one to three months.

Antibiotics versus placebo

Doxycycline compared with placebo may result in little to no difference in all-cause mortality (RR 0.15, 95% CI 0.01 to 2.83; 1 trial, 782 participants; low-certainty evidence). Prophylactic antibiotics may have little to no effect on laboratory-confirmed leptospirosis, but the evidence is very uncertain (RR 0.56, 95% CI 0.25 to 1.26; 5 trials, 2593 participants; very low-certainty evidence). Antibiotics may result in little to no difference in the clinical diagnosis of leptospirosis regardless of laboratory confirmation (RR 0.76, 95% CI 0.53 to 1.08; 4 trials, 1653 participants; low-certainty evidence) and the clinical diagnosis of leptospirosis with laboratory confirmation (RR 0.57, 95% CI 0.26 to 1.26; 4 trials, 1653 participants; low-certainty evidence). Antibiotics compared with placebo may increase non-serious adverse events, but the evidence is very uncertain (RR 10.13, 95% CI 2.40 to 42.71; 3 trials, 1909 participants; very low-certainty evidence).

One antibiotic versus another antibiotic

One trial assessed doxycycline versus azithromycin but did not report mortality. Compared to azithromycin, doxycycline may have little to no effect on laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome (RR 1.49, 95% CI 0.51 to 4.32; 1 trial, 137 participants), on the clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation (RR 4.18, 95% CI 0.94 to 18.66; 1 trial, 137 participants), on the clinical diagnosis of leptospirosis confirmed by laboratory diagnosis (RR 4.18, 95% CI 0.94 to 18.66; 1 trial, 137 participants), and on non-serious adverse events (RR 1.12, 95% CI 0.36 to 3.48; 1 trial, 137 participants), but the evidence is very uncertain. The certainty of evidence for all the outcomes was very low.

None of the five included trials reported serious adverse events or assessed quality of life.

One study is awaiting classification.

Funding

Four of the five trials included statements disclosing their funding/supporting sources, and the remaining trial did not include this. Three of the four trials that disclosed their supporting sources received the supply of trial drugs directly from the same pharmaceutical company, and the remaining trial received financial support from a governmental source.

Authors' conclusions

We do not know if antibiotics versus placebo or another antibiotic has little or have no effect on all-cause mortality or leptospirosis infection because the certainty of evidence is low or very low. We do not know if antibiotics versus placebo may increase the overall risk of non-serious adverse events because of very low-certainty evidence.

We lack definitive rigorous data from randomised trials to support the use of antibiotics for the prophylaxis of leptospirosis infection. We lack trials reporting data on clinically relevant outcomes.

PLAIN LANGUAGE SUMMARY

Does the use of antibiotics prevent leptospirosis?

Key message

– Antibiotics probably do not reduce the chance of developing leptospirosis infection and may cause non-serious adverse events. The evidence is very limited, so our findings may change if there are more quality trials published.

What is leptospirosis?

Leptospirosis is a zoonotic (that is,infection that can be transmitted naturally from animals with a backbone to humans or from humans to animals with a backbone)and waterborne disease that occurs worldwide. Humans are infected when they come into contact with water, soil, or food contaminated with the urine of infected animals. Most infected people experience mild, self-limiting flu-like symptoms, and

do not seek medical attention. Some people infected with leptospirosis develop severe disease, which can cause multiple organs to stop functioning properly and death.

What did we want to find out?

We wanted to find out if antibiotics can be an effective prophylaxis for leptospirosis (that is, prevent leptospirosis) and if they have unwanted side effects?

What did we do?

We searched medical databases for studies that assessed the use of antibiotics for the prophylaxis of leptospirosis. The studies could have compared antibiotics versus placebo (a pretend treatment) or no treatment, and antibiotics versus another antibiotic, or another dose or schedule of the same antibiotic.

What did we find?

We found five studies with 2593 participants, which took place in Brazil, Sri Lanka, India, Panama, and Iran. Participants mostly resided in these areas.

Main results

Three studies compared doxycycline versus either placebo or no treatment. One trial compared doxycycline versus azithromycin versus placebo. Only one trial compared penicillin versus placebo.

Antibiotics may not reduce the chance of developing leptospirosis infection and may lead to some non-serious side effects (for example, diarrhoea (loose stools), nausea (feeling sick), and vomiting (being sick)), particularly if doxycycline is used.

None of the studies reported serious side effects or assessed quality of life.

What are the limitations of the evidence?

We have low or very low confidence in the results. This was based on a few studies that had a wide range of results, problems in how the studies selected participants, a low number of participants, a high amount of missing information, and considerable differences between groups of participants.

Funding

Four studies included statements disclosing their funding/supporting sources, and one study did not include this. Three of the four studies that disclosed their supporting sources received the supply of study medicine directly from the same pharmaceutical company, and the remaining trial received financial support from a governmental source.

How up to date is this evidence?

This review updates the previous Cochrane review. The evidence is up to date to 17 April 2023.

Summary of findings 1. Summary of findings table - Antibiotics compared to placebo or no intervention for prophylaxis for leptospirosis

Antibiotics compared to placebo or no intervention for prophylaxis for leptospirosis

Patient or population: farmworkers, soldiers, and people in endemic areas
Setting: different endemic areas
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 follow-up: 12 weeks	8 per 1000	**1 per 1000** (0 to 21)	**RR 0.15** (0.01 to 2.83)	782 (1 RCT)	⊕⊕⊖⊖ Low[a]	0 participants in the antibiotics group died in this trial.
Laboratory-confirmed leptospirosis follow-up: mean 7.8 weeks	116 per 1000	**65 per 1000** (29 to 146)	**RR 0.56** (0.25 to 1.26)	2593 (5 RCTs)	⊕⊖⊖⊖ Very low[b]	1 trial diagnosed 0 participants with leptospirosis in the antibiotics group. Some trials used the microscopic agglutination test and some used enzyme-linked immunosorbent assay to diagnose participants and confirm leptospirosis.
Clinical diagnosis of infection regardless of laboratory confirmed follow-up: mean 8.5 weeks	80 per 1000	**61 per 1000** (43 to 87)	**RR 0.76** (0.53 to 1.08)	1653 (4 RCTs)	⊕⊕⊖⊖ Low[c]	The definition for the clinical diagnosis of infection varied between trials.
Clinical diagnosis confirmed by laboratory diagnosis follow-up: mean 8.5 weeks	46 per 1000	**26 per 1000** (12 to 58)	**RR 0.57** (0.26 to 1.26)	1653 (4 RCTs)	⊕⊕⊖⊖ Low[d]	In 1 trial, 0 participants in the antibiotics group developed a clinical diagnosis confirmed by laboratory diagnostics.
Serious adverse events - not reported	-	-	-	-	-	Except for mortality reported in 1 of the 5 trials, there were no other serious adverse events reported. Therefore, we did not duplicate the data.

Quality of life - not reported	-	-	-	-	-	No trials reported this outcome.
Non-serious adverse events follow-up: mean 9.7 weeks	1 per 1000	**11 per 1000** (3 to 47)	**RR 10.13** (2.40 to 42.71)	1909 (3 RCTs)	⊕⊝⊝⊝ Very low[e]	The definition of non-serious adverse events differed between trials. 0 participants in the placebo groups of 2 trials developed non-serious adverse events. 1 trial provided most data on this outcome.

*__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_439581531852831820.

[a] Downgraded one level for risk of bias (no information on randomisation, allocation concealment, missing outcome data, and selection of reported result) and one level for imprecision (the optimal information size (OIS) criterion was not met, i.e. sample size fewer than the OIS of 54,558 participants, wide CIs in the result, and 95% CI included both benefits and harms).
[b] Downgraded one level for risk of bias (no information on randomisation, allocation concealment, missing outcome data, and selection of reported result); one level for inconsistency (there was considerable heterogeneity with an I^2 value of 79% (five RCTs contributed to the analysis: two trials favoured the intervention, three trials found no difference)), and one level for imprecision (the OIS criterion was not met, i.e. sample size fewer than the OIS of 3276 participants, and 95% CI included both benefits and harms).
[c] Downgraded one level for risk of bias (no information on randomisation, allocation concealment, missing outcome data, and selection of reported result) and one level for imprecision (the OIS criterion was not met, i.e. sample size fewer than the OIS of 5108 participants, and 95% CI included both benefits and harms).
[d] Downgraded one level for risk of bias (no information on randomisation, allocation concealment, missing outcome data, and selection of reported result) and one level for imprecision (the optimal information size criterion was not met, i.e. sample size fewer than the optimal information size (OIS) of 13,490 participants, and 95% CI included both benefits and harms).
[e] Downgraded two levels for risk of bias (no information on randomisation, allocation concealment, missing outcome data, and selection of reported result) and three levels for imprecision (very wide CIs in the result).

Summary of findings 2. Summary of findings table - Antibiotics compared to other antibiotics for prophylaxis of leptospirosis

Antibiotics compared to other antibiotics for prophylaxis of leptospirosis

Patient or population: farmworkers
Setting: endemic area

Intervention: doxycycline
Comparison: azithromycin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with azithromycin	Risk with doxycycline				
All-cause mortality - not reported	-	-	-	-	-	The trial did not report this outcome.
Laboratory-confirmed leptospirosis follow-up: 12 weeks	76 per 1000	**116 per 1000** (40 to 337)	**RR 1.53** (0.53 to 4.45)	137 (1 RCT)	⊕⊖⊖⊖ Very low[a]	Trial had 3 interventions, i.e. azithromycin, doxycycline, and placebo. Used an enzyme-linked immunosorbent assay to confirm the diagnosis of leptospirosis.
Clinical diagnosis of leptospirosis regardless of laboratory confirmation follow-up: 12 weeks	30 per 1000	**127 per 1000** (28 to 565)	**RR 4.18** (0.94 to 18.66)	137 (1 RCT)	⊕⊖⊖⊖ Very low[b]	Trial used a questionnaire to confirm clinical diagnosis.
Clinical diagnosis of leptospirosis confirmed by laboratory diagnosis follow-up: 12 weeks	30 per 1000	**127 per 1000** (28 to 565)	**RR 4.18** (0.94 to 18.66)	137 (1 RCT)	⊕⊖⊖⊖ Very low[b]	This outcome was established both clinically and by laboratory confirmation.
Serious adverse events - not reported	-	-	-	-	-	The trial did not report this outcome.
Quality of life - not reported	-	-	-	-	-	The trial did not report this outcome.
Non-serious adverse events follow-up: 12 weeks	76 per 1000	**85 per 1000** (27 to 264)	**RR 1.12** (0.36 to 3.48)	137 (1 RCT)	⊕⊖⊖⊖ Very low[c]	Trial used a questionnaire to confirm non-serious adverse events.

*__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_439581559468129395.

[a] Downgraded one level for risk of bias (no information on randomisation, allocation concealment, missing outcome data, 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 5398 participants, wide CIs in the result, and 95% CI included both benefits and harms).

[b] Downgraded one level for risk of bias (no information on randomisation, allocation concealment, missing outcome data, and selection of reported result) and three levels for imprecision (the OIS criterion was not met, i.e. sample size fewer than the OIS of 16,528 participants, very wide CIs in the result, and 95% CI included both benefits and harms).

[c] Downgraded one level for risk of bias (no information on randomisation, allocation concealment, missing outcome data, and selection of reported result) and two levels for imprecision (wide CIs in the result, and 95% CI included both benefits and harms).

BACKGROUND

Description of the condition

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

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

Leptospirosis has a broad range of symptoms that overlap with those of several other diseases. It can have a 'biphasic' pattern, with a non-specific phase lasting one week and a complicating immune phase lasting the second week (Chierakul 2014). Most people experience mild and self-limiting influenza-like symptoms for which they do not seek medical attention. Symptoms include headache, myalgia, backache, abdominal pain, conjunctival suffusion, chills, diarrhoea, anorexia, transient rash, cough, and a sore throat. Severe leptospirosis causes multi-organ dysfunction in the liver, kidneys, and brain, and is occasionally associated with pulmonary haemorrhage. Weil's disease, which was first described in 1886 and is characterised by jaundice and renal failure, is still one of the most clinically recognised severe forms of leptospirosis (Haake 2015). According to one systematic study of leptospirosis outbreaks worldwide from 1970 to 2012, the overall case fatality rate was 5% (Munoz-Zanzi 2020). According to the US Center for Disease Control and Prevention (CDC), the case fatality rate is about 5% to 15% amongst severely affected people and more than 50% amongst people with severe pulmonary haemorrhagic syndrome (CDC 2018). Most deaths occur between the 10th and 15th days of sickness, but can happen as early as the fifth day (Kobayashi 2001).

Leptospirosis can be difficult to diagnose in clinical practice because non-specific clinical signs can mimic those of other tropical infectious diseases. The diagnosis of leptospirosis is based on laboratory tests that vary depending on the disease's stage of evolution. Molecular methods (polymerase chain reaction (PCR) amplification and bacterial genome sequencing) can be used to make a laboratory diagnosis during the first week of illness after fever onset, or serological methods (enzyme-linked immunosorbent assay, lateral flow tests, immunohistochemistry, or microagglutination test) can be used at the beginning of the second week of illness. In some people, laboratory diagnosis of leptospirosis may require a combination of diagnostic methods using appropriate specimens, depending on the stage of illness (Budihal 2014; Koizumi 2020).

Leptospirosis is a treatable and preventable disease. Most leptospirosis infections are self-limiting; however, complications do occur in some people. Severe illness may necessitate admission to a hospital for treatment. To reduce the risk of complications, medical resuscitation and early antibiotic administration are used. Although the efficacy of antibiotic treatment for severe forms of leptospirosis has not been proven, the most commonly used antibiotics are doxycycline, azithromycin, cephalosporins, or penicillin. Immunological therapies have been proposed in severe forms of leptospirosis, particularly with pulmonary and renal involvement, because immune system mediators play a critical role in the pathophysiology of these manifestations. As a result, corticosteroids and plasmapheresis have been employed. However, there is currently insufficient evidence to support the use of corticosteroids in severe leptospirosis, and the literature on the subject is limited (Rodrigo 2014; Soler 2021).

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

Description of the intervention

Early diagnosis and treatment are recommended for leptospirosis in order to improve prognosis and reduce fatalities (Levett 2001). The disease is often associated with heavy rains or flooding, which, when they occur, may impact civil infrastructure and damage healthcare infrastructure, making access to healthcare difficult or impossible (WHO 2020). The World Health Organization (WHO) guidelines recommend antibiotic prophylaxis for leptospirosis as a possible preventive intervention, particularly for travellers and high-risk groups (Galloway 2020; WHO 2003). Prophylaxis for leptospirosis is an approach in which an individual takes an antibiotic to reduce the likelihood of infection either before or after potential exposure (Bhardwaj 2010).Prophylaxis may be given once or more than once, depending on local protocols and choice of antibiotic. A population-based mass prophylaxis has been used before or after floods, whereas a more targeted strategy is often used for occupational or recreational activities where there is a risk

of exposure (Bhardwaj 2010). Doxycycline is the most commonly used prophylactic antibiotic in the literature, but other antibiotic classes have been used (Bharti 2003; Chierakul 2014; Illangasekera 2008). However, the use of antibiotic prophylaxis for leptospirosis must be carefully considered because of the potential for adverse effects and the unclear benefit of prophylaxis. One systematic review concluded that weekly use of oral doxycycline 200 mg significantly increases the incidence of adverse effects such as nausea and vomiting, while the benefits in terms of reducing *Leptospira* seroconversion and clinical sequelae of infection are unclear (Brett-Major 2009).

How the intervention might work

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

Why it is important to do this review

Leptospirosis is a potentially preventable and treatable condition with a significant global mortality and morbidity burden. Factors such as recent flooding, dense urban populations, and occupational or recreational exposures continue to pose a predictably high risk for leptospirosis. Antibiotic prophylaxis has been proposed as a method of preventing leptospirosis in humans. Mass antibiotic prophylaxis can provide protection by reducing the overall number of leptospirosis-infected people following high-risk exposure, decreasing the incidence and prevalence of the disease, and preventing morbidity and mortality (Aklil 2018; Goarant 2016). One 2009 Cochrane review examined the evidence for antibiotic prophylaxis with oral doxycycline against leptospirosis (Brett-Major 2009). The review identified three trials conducted in Brazil, Panama, and the northern Andaman Islands (Gonsalez 1998; Sehgal 2000; Takafuji 1984). It concluded that taking 200 mg of doxycycline once a week increased the risk of nausea and vomiting but did not seem to have an effect on the incidence of leptospirosis. Although the use of antibiotics for leptospirosis prophylaxis is generally recommended, data on its effectiveness are limited. The results of this present systematic review may provide a sound basis for policymakers and public health authorities in formulating guidelines for the prevention and control of leptospirosis.

OBJECTIVES

To evaluate the benefits and harms of antibiotic prophylaxis for human leptospirosis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials studying antibiotic prophylaxis for leptospirosis regardless of year, language, and form of publication; blinding; comparator; and outcomes. We considered cluster-randomised trials and cross-over trials also eligible for inclusion due to the likelihood of limited published trial data forleptospirosis.

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

Types of participants

We included participants with no restriction on age, sex, occupation, or comorbidity. People at high risk of contracting leptospirosis included:

- agricultural workers in endemic regions and veterinarians;
- people with other high-risk occupations due to contact with water or animals;
- high-risk activity travellers, such as troops and ecotourists;
- people experiencing emergencies resulting in potential exposure to contaminated water such as floods, heavy rains, or tsunamis.

As published trial data for leptospirosis were likely to be limited, we also decided we would include any trial that only had a subset of eligible participants while remaining faithful to the objectives of the review and Cochrane guidelines. We consulted regularly with the advisory group and documented difficult decisions in the review. We planned to apply sensitivity analyses to assess the impact of these decisions on the review's findings (McKenzie 2022a).

Types of interventions

Experimental intervention

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

Control interventions

- Placebo or no intervention
- Another antibiotic, or another dose or schedule of the same antibiotic

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

Types of outcome measures

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

Primary outcomes

- All-cause mortality

- Proportion of people with laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome (inclusive of asymptomatic cases)
- Proportion of people with clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation
- Proportion of people with clinical diagnosis of leptospirosis confirmed by laboratory diagnosis (exclusive of asymptomatic cases)
- Proportion of people with serious adverse events (excluding mortality, which is reported under 'All-cause mortality')

We considered a serious adverse event using the definition of the International Council for Harmonisation's (ICH) guidelines (ICH-GCP 2016). This included: any event that led to death; was life-threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability, congenital birth defect, or anomaly; and any important medical event which may have jeopardised the participant or required intervention to prevent permanent damage. A serious adverse reaction would be a serious adverse event where the study authors clearly stated a suspicion or confirmation that the event was due to an experimental or control intervention.

Secondary outcomes

- Quality of life assessed using a validated questionnaire such asthe World Health Organization Quality of Life (WHOQOL), 36-item Short Form (SF-36), 12-item Short Form (SF-12), Sickness Impact Profile, Nottingham Health Profile, EuroQol (EQ-5D), or Short Form 6-Dimensions (SF-6D) (Nemeth 2006; Pequeno 2020)
- Proportion of people with non-serious adverse events
  - Gastrointestinal symptoms such as abdominal cramps, nausea, vomiting, diarrhoea; or as defined by study authors
  - Other non-serious adverse events as defined by study authors (e.g. discolouration of teeth, photosensitivity, or transient hearing loss)

We considered including trials regardless of whether they reported these outcomes.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group (CHBG) Controlled Trials Register which was searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web on 17 April 2023. We also searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2023; Issue 4) in the Cochrane Library, MEDLINE Ovid (1946 to 17 April 2023), Embase Ovid (1974 to 17 April 2023), Latin American and Caribbean Health Science Literature (LILACS, VHL Regional Portal; 1982 to 17April 2023), Science Citation Index Expanded (Web of Science; 1900 to 17 April 2023), and Conference Proceedings Citation Index-Science (Web of Science; 1990 to 17 April 2023). Appendix 1 presents the search strategies with the actual date range of the electronic searches.

Searching other resources

We searched the following clinical trials registries for ongoing clinical trials: WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp), 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 actual date of the searches.

We searched for potentially eligible studies from the following proceedings and conference abstracts: American Society of Tropical Medicine and Hygiene (ASTMH; 2005 to 17 April 2023), Infectious Diseases Society of America (IDSA; 2003 to 17 April 2023), and the International Society of Travel Medicine (ISTM; 2011 to 17 April 2023).

Once we decided to include a study, we screened its bibliography to seek other potential candidate studies. We also searched for postpublication amendments and examined the included studies for any relevant retraction statements, and errata which could reveal important limitations or even fatal flaws (Lefebvre 2022).

Data collection and analysis

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

Selection of studies

Two review authors (PM and TZW) independently reviewed titles and abstracts of publications obtained by electronic searches to determine if they met the inclusion criteria of our systematic review after removing duplicates. We obtained full-text papers of all studies that appeared eligible and reviewed them to identify the studies that met the eligibility criteria. We recorded the reasons for exclusions of studies that did not match the inclusion criteria. We resolved disagreements through discussion with a third review author (CS). We did not impose any language restrictions. For screening of non-English language publications, we used Google Translate (translate.google.com) to assist in eligibility assessment. If needed, we planned to seek translators, through the CHBG Editorial Team office, to assist with assessing the eligibility of studies and, if eligible, to assist with data extraction.

We used Covidence software for study screening (Covidence). We recorded the selection process in sufficient detail to complete a PRISMA-S flow diagram (Page 2021a; Page 2021b).

During the selection of randomised clinical trials, we noted and extracted data on adverse effects from controlled and observational studies such as quasi-randomised studies, cohort studies, or patient reports. We did not run a separate search for observational studies. We recognise that by not conducting a separate systematic search for controlled and observational studies, we would limit the data that we otherwise would be able to collect on adverse events. A systematic review of harms based on observational studies would be required if the benefit of antibiotic prophylaxis is found in such studies (Storebø 2018).

Data extraction and management

Two review authors (PM and TZW) independently extracted the following characteristics from the included studies. Due to the small number of trials, it was irrelevant to pilot a data extraction form.

- **Study and publication identifiers:** study ID, 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, study centre locations, funding source for trial, and notable conflicts of interest of trial authors
- **Study methods:** study design, number of trial groups, randomisation and group allocations, description of interventions and control procedures, how blinding and concealment was accomplished, type of analysis, start date, end date, total duration of the study, duration of follow-up, 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 (including details on diagnostic laboratory assays employed) and adverse effects, outcomes measurements, outcome data, time points for follow-up reported, and notes

We resolved any disagreements through discussion with a third review author (CS).

Assessment of risk of bias in included studies

Two review authors (PM and TZW) independently assessed the risk of bias of the outcomes using the Cochrane RoB 2 tool (Higgins 2022b; Sterne 2019). We assessed the effect of the assignment on the intervention using the intention-to-treat principle, which includes all randomised participants, irrespective of the interventions that participants received. We resolved disagreements through discussion with a third review author (CS). We assessed the risk of bias 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 intervention 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 randomised, if there was any evidence that the result was not biased by missing outcome data, and if the absence of the outcome was likely to depend on its true value.
- Bias in measurement of the outcome: we evaluated if the method of measuring the outcome was inappropriate, if the assessors of the outcome were aware of the intervention each study participant received, if the measurement of the outcome could have differed between intervention groups, and 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, and if the assessed numerical result was likely to have been selected from either multiple outcome measurements within the outcome domain or from the 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 were: yes, probably yes, probably no, no, and no information. Elaborations on these signalling questions can be found in Higgins 2022c. Once these questions had been answered, the tool's algorithm reached a risk of bias judgement and assigned one of the following three levels to each domain (Higgins 2022b).

- Low risk of bias: all the domains were at low risk of bias.
- Some concerns: the trial raised some concerns in at least one of the domains, 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 in multiple domains in a way that substantially lowered confidence in the result.

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

For cluster-randomised trials, we were to consider an additional domain that specifically applies to the design of the cluster-randomised trial: RoB 2 Domain 1b 'bias arising from the timing of identification and recruitment of individual participants within clusters in relation to timing of randomisation'. We planned to consider 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 2021; Higgins 2020; Higgins 2022c). At the time of review preparation, we planned to use the most recent recommendations for assessing the risk of bias in cluster-randomised trials.

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

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.10796245).

The risk of bias assessment feeds into the risk of bias domain of the GRADE approach for assessing certainty of a body of evidence (Schünemann 2013). In the summary of findings tables, we presented the outcomes which we considered most relevant for clinical practice. These outcomes were all-cause mortality, proportion of people with leptospirosis, serious adverse events (excluding mortality, which is reported under 'All-cause mortality'), quality of life, and non-serious adverse events.

Measures of treatment effect

We collected and uploaded the outcome data for each trial onto the data tables on Review Manager so that we could calculate the treatment effects (RevMan 2023). We planned to analyse dichotomous outcome data as risk ratios (RR) with 95% CIs, and continuous data as mean differences (MD) with 95% CIs or

standardised mean differences (SMD) with 95% CIs when studies used different scales to measure the same outcome. We planned to present the median and interquartile ranges in a narrative format for skewed continuous data. We planned to present a forest plot that displays effect estimates and CIs for individual trials (Lewis 2001). We planned to conduct meta-analyses if the trials were sufficiently homogeneous (Deeks 2022).

We focussed on a hybrid approach (including both a prespecified set of adverse events and any other adverse events identified during the conduct of the review) in order to maximise the inclusion of available safety data. We applied the same eligibility criteria for intended (benefit) and unintended effects (harm). Before comparing or synthesising adverse effects data across studies, we planned to evaluate the consistency and similarity of case definitions and methods of ascertainment for harms outcomes from the included trials. We considered coding adverse events carefully to avoid having categories that have not been reported in the primary studies or to avoid unnecessary splitting of categories, or both (Peryer 2022).

We planned to analyse participants in the intervention groups to which they were randomised regardless of the intervention they actually received, and we included all randomised participants in the outcome analyses (i.e. intention-to-treat).

Unit of analysis issues

The unit of analysis for randomised clinical trials is the individual participant. If multiple arms were reported in a single trial, we planned to include only the arms relevant to the review subject and comparison. In order to include multiple groups from one trial, we followed the guidance in Sections 6.2 and 23.3.4 of *the Cochrane Handbook for Systematic Reviews of Interventions* to avoid arbitrary omission of relevant groups and double-counting of participants (Higgins 2022c; Higgins 2022d). We combined the relevant groups to create a single pair-wise comparison.

For cluster-randomised clinical trials, the cluster would be the unit of analysis and not the individual participant. This would avoid potential unit-of-analysis error which may cause artificially narrow CIs and small P values, resulting in false-positive conclusions that the intervention had an effect (Higgins 2022c).

If we identified trials with a cross-over design, we would have included the data from the first trial period in order to avoid residual effects from the treatment (Higgins 2022c). We considered using participant trial data at the longest follow-up to avoid repeated observations on trial participants (Higgins 2022d).

Dealing with missing data

We contacted authors to try to verify study design and key study characteristics, and obtain missing numerical outcome data on the primary outcomes, but we were not successful. We planned to calculate numerical outcome data that were missing, such as standard deviations or correlation coefficients, from other available statistics such as P values according to the methods described inthe *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022). If these calculations were not possible, we were to assess the risk of bias due to missing outcome data using the RoB 2 tool, and undertake sensitivity analyses to explore the impact of including these trials in the overall assessment of results (Page 2022). We performed an intention-to-treat analysis as a primary analysis approach whenever possible, or used the available-case analysis or modified intention-to-treat approach when not possible (Fergusson 2002). An intention-to-treat approach assumed that missing data were missing at random. We conducted sensitivity analyses for binary outcomes assuming 1. a worst-case scenario (missing data are assumed to be a 'negative' outcome) and 2. a best-case scenario (missing data are assumed to be a 'positive' outcome), using the random-effects model (Mavridis 2014). These two sensitivity analysis approaches could indicate the extent of uncertainty due to attrition bias. If the CIs and P value of the results of the primary meta-analysis and the results of the sensitivity analysis are similar, the validity of the results increases (Jakobsen 2014). However, if they differ substantially, this suggests a risk of attrition bias. For continuous data, we planned to impute the mean value for 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 explicitly described assumptions that we made in sensitivity analyses.

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

Assessment of heterogeneity

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

Based on the visual assessment of the forest plot, we described the direction and magnitude of the effect and the degree of overlap of the CIs. We assessed statistical heterogeneity using the Chi^2 and I^2 statistics, using $P < 0.10$ as a cut-off point for statistical heterogeneity (Israel 2011). We also quantified the heterogeneity using the I^2 statistic and interpreted it as follows (Deeks 2022).

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

Had we identified substantial heterogeneity, we planned to follow the strategies described inthe *Cochrane Handbook for Systematic Reviews of Interventions* for dealing with heterogeneity and explore possible causes for differences in population, intervention, comparison, outcome, and the quality of the research (Deeks 2022). If heterogeneity was to be judged likely, we planned to explore this in subgroup analyses or sensitivity analyses, or both. If heterogeneity was present, we planned to conduct a random-effects meta-analysis to account for between-study heterogeneity.

Assessment of reporting biases

We planned to report biases (e.g. publication, time lag, or multiple publications) at all points of data analysis and interpretation. We attempted to contact investigators to determine the status of unpublished studies when we identified any trial protocols, clinical trial registrations, or abstracts indicating the existence of unpublished studies.

To examine small-study effects, we applied Mantel-Haenszel weighting rather than inverse-weighting, conducting both random-

effects and fixed-effect regression (Deeks 2022). We could not explore tests of funnel plot asymmetry since the total number of included trials in the review meta-analysis was fewer than 10 (Page 2022).

Data synthesis

We included as much data as possible due to a limited number of trials meeting the eligibility criteria. We pooled data, such as RRs and MDs with 95% CIs, from trials we determined to be clinically homogeneous. We used Review Manager software and performed the meta-analyses with the random-effects model as our primary analysis and the fixed-effect model as sensitivity analysis (RevMan 2023).

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 circumstances (McKenzie 2022b).

Subgroup analysis and investigation of heterogeneity

We considered performing subgroup analyses in the case of substantial heterogeneity (I^2 > 50%) and a sufficient number of trials (Deeks 2022).

The planned subgroups of interest were:

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

However, we did not perform subgroup analyses for two reasons. First, there was an insufficient number of trials assessing prophylactic antibiotics against leptospirosis. Second, conducting subgroup analysis with only a few trials would not provide meaningful results due to insufficient power in the subgroups.

Sensitivity analysis

To assess the robustness of the results, we planned to perform the following sensitivity analyses of the impact of heterogeneity of the included trials and the risk of bias (Boutron 2022).

- Repeat the analysis excluding trials at an overall high risk of bias
- Repeat the analysis excluding unpublished trials (if any)

As there were no trials at an overall low risk of bias, we could not perform the planned sensitivity analysis. Instead, we conducted the following sensitivity analyses.

- Repeat the analysis excluding trials of postexposure
- Repeat the analysis excluding trials of pre-exposure
- Repeat the analysis including only the trials that were implemented amongst the endemic population

In addition, we planned to perform a Trial Sequential Analysis to assess imprecision of primary outcome results (see below). Then, we planned to compare our evaluation of imprecision based on GRADE with our choice of plausible relative risk reduction (RRR) and multiplicity correction to Trial Sequential Analysis, using similar choices of a plausible RRR and multiplicity correction.

Trial Sequential Analysis

We planned to use Trial Sequential Analysis as a sensitivity analysis to assess imprecision for the five primary outcomes (i.e. all-cause mortality, laboratory-confirmed leptospirosis, clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation, clinical diagnosis of leptospirosis confirmed by laboratory diagnosis, serious adverse events (excluding mortality, which is reported under 'all-cause mortality') (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 five primary outcomes (all dichotomous), we based the DARIS on the event proportion in the control group, assuming a plausible relative risk reduction for all-cause mortality, laboratory-confirmed leptospirosis, clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation, clinical diagnosis of leptospirosis confirmed by laboratory diagnosis, serious adverse events of 10%; a risk of type I error of 1.67% due to five 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 program 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). A summary of the findings table provides information on comparative risk, relative risk, number of participants, number of trials, and certainty of the evidence for the outcomes in the review comparisons. We created two summary of findings tables: one on the comparison of antibiotic prophylaxis versus placebo or no intervention; and one on antibiotic prophylaxis versus another antibiotic. We presented our assessment of the proportion of people with all-cause mortality, leptospirosis, serious adverse events (hospitalisation and long-term disability), quality of life, and non-serious adverse events. 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 2022), and theGRADE Handbook (Schünemann 2013). We provided the maximum follow-up and the range of follow-up for each outcomes. One review author (TZW) graded the evidence of these outcomes and other review authors agreed with the assessment.

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

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

Through this approach, we assessed the certainty of the evidence presented in the review and drew conclusions (GRADEpro GDT). To inform the GRADE assessment, we used the overall judgement of risk of bias (see Assessment of risk of bias in included studies). We have justified all decisions to downgrade the certainty of evidence using footnotes and, where appropriate, we added a comment to aid the reader's understanding.

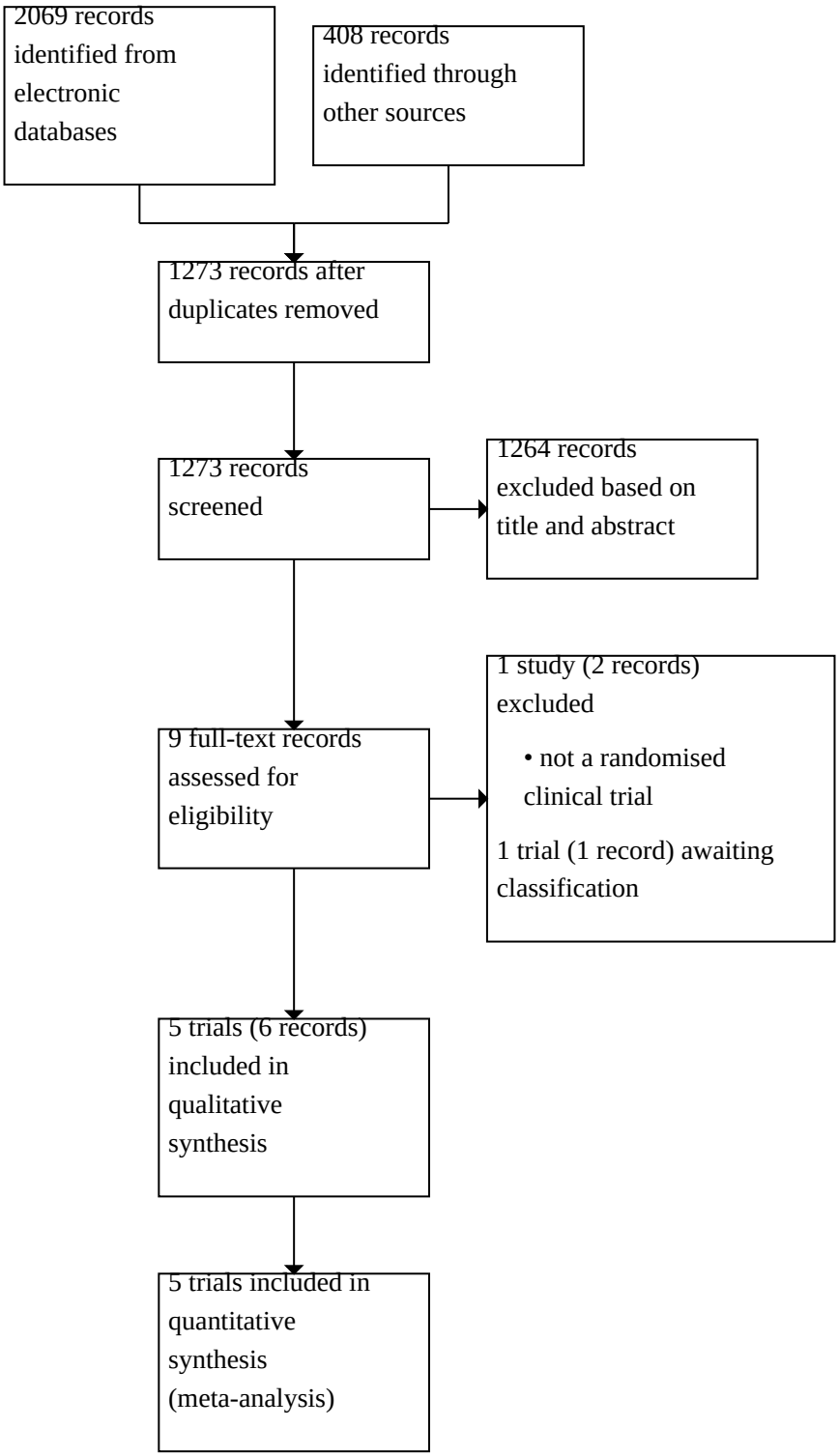
RESULTS

Description of studies

Results of the search

The systematic literature searches returned 2477 records on 17 April 2023. We screened the titles and abstracts of 1273 records, following removal of duplicates, and excluded a further 1264 records (Figure 1). We performed full-text assessment of the remaining nine records.

Figure 1. PRISMA flow diagram.



We excluded one non-randomised study at the full-text stage (two records; see Characteristics of excluded studies table). However, we included the reported data on adverse events from this trial as prespecified in our protocol (Tabei 2022). One trial did not report outcomes clearly and was included as a study awaiting classification (one record; see Characteristics of studies awaiting classification table). We identified no ongoing studies.

We included five trials in quantitative synthesis (six records; see Characteristics of included studies table). Amongst these, three were included in the previous systematic review (Brett-Major 2009).

Included studies

Trial characteristics

The five randomised clinical trials were published in peer-reviewed journals (Alikhani 2018; Gonsalez 1998; Illangasekera 2008; Sehgal 2000; Takafuji 1984). All trial settings were in areas endemic with leptospirosis. The trials were conducted in India (Sehgal 2000), Iran (Alikhani 2018), Brazil (Gonsalez 1998), Panama (Takafuji 1984), and Sri Lanka (Illangasekera 2008).

The review included 2593 participants, and the sample size of the individual trials ranged from 82 to 1047. Further details are provided in the Characteristics of included studies table.

Participant characteristics

The age range of the participants across the five trials was 10 years to 80 years. Two trials recruited farmworkers (Alikhani 2018; Illangasekera 2008), one trial recruited participants at high risk of leptospirosis following a flood (Gonsalez 1998), one recruited participants from an island population with high rainfall (Sehgal 2000), and one trial recruited soldiers who were stationed in an endemic region (Takafuji 1984).

Intervention characteristics (comparisons)

Three trials assessed pre-exposure prophylaxis with doxycycline (Alikhani 2018; Sehgal 2000; Takafuji 1984). One trial assessed pre-exposure prophylaxis with azithromycin (Alikhani 2018). Alikhani 2018 started the intervention one week before exposure to the paddy field. Takafuji 1984 started the intervention at the time of enrolment in the trial. Sehgal 2000 started the intervention in the second week of September, before the post-monsoon season, when leptospirosis outbreaks are common. One trial assessed postexposure prophylaxis with doxycycline (Gonsalez 1998). Gonsalez 1998 started the intervention during the 48 hours of exposure to an area potentially contaminated with water from a flood. One trial evaluated penicillin; however, it was unclear whether it was administered as pre- or postexposure (Illangasekera 2008).

The duration of doxycycline prophylaxis was different amongst trials. Gonsalez 1998 used doxycycline 200 mg as a one-off dose, while three other trials advocated for continuous administration for three weeks (Takafuji 1984), 11 weeks (Alikhani 2018), and 12 weeks (Sehgal 2000). Illangasekera 2008 used penicillin 250 mg in two tablets twice a day for one month.

Outcomes and follow-up

Four trials evaluated diagnosis of leptospirosis, as confirmed through both clinical and laboratory assessments, as their primary outcome (Alikhani 2018; Gonsalez 1998; Illangasekera 2008; Sehgal 2000). Takafuji 1984 used only laboratory-confirmed diagnosis of leptospirosis as the primary outcome. Sehgal 2000 assessed the outcomes of mortality (including disease severity such as pulmonary complications) and adverse effects.

Alongside differing lengths of intervention period, the follow-up of the outcomes also varied. Takafuji 1984 reported that laboratory testing was performed one week and four weeks to six weeks after the exposure period. Gonsalez 1998 conducted laboratory testing 45 days after an initial baseline test, at the beginning of the trial period. Illangasekera 2008 reported a one-month follow-up time-point. Both Sehgal 2000 and Alikhani 2018 had a follow-up of 12 weeks, conducting laboratory testing at baseline, 6 weeks, and 12 weeks.

Dropouts

Gonsalez 1998 reported 106 participants were enrolled, but only 82 participants were eligible for analysis. The reason for the missing participants was not specified. Sehgal 2000 reported that 127 participants from the doxycycline group and 116 participants from the placebo group were withdrawn due to non-compliance with instructions, medication use for other illnesses, adverse effects, or relocation outside the study area, which made them untraceable. Takafuji 1984 wrote that 107 soldiers were withdrawn from the trial before it was completed, primarily because they received other antibiotics for unrelated medical problems during training. Illangasekera 2008 mentioned data were not available from 198 participants and the reason for their absence was not provided. In Alikhani 2018, two participants from the azithromycin group and 11 participants from the placebo group were lost to follow-up because they left the study area.

Funding

Four of the five trials included statements disclosing their funding/supporting sources, and the remaining trial did not include this (Illangasekera 2008). Three of the four trials that disclosed their supporting sources received supplies of trial drugs directly from the same pharmaceutical company (Gonsalez 1998; Sehgal 2000; Takafuji 1984), and the remaining study received financial support from a governmental source (i.e. was financially supported by the Vice Chancellor Research and Technology of Mazandaran University of Medical Sciences) (Alikhani 2018).

Excluded studies

We excluded one study (two references) that was a non-randomised study (Chusri 2014; Characteristics of excluded studies table).

Studies awaiting classification

One study is awaiting classification while we attempt to contact the corresponding author (Shivaraj 2012).

Ongoing studies

We identified no ongoing studies.

Risk of bias in included studies

We assessed risk of bias for the five trials (Alikhani 2018; Gonsalez 1998; Illangasekera 2008; Sehgal 2000; Takafuji 1984). We evaluated the risk of bias for all-cause mortality, laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome, clinical diagnosis of leptospirosis regardless

of the presence of laboratory confirmation, and non-serious adverse events. Only one trial reported all-cause mortality (Sehgal 2000), all five trials reported laboratory-confirmed leptospirosis outcome (Alikhani 2018; Gonsalez 1998; Illangasekera 2008; Sehgal 2000; Takafuji 1984), four trials reported the clinical diagnosis of leptospirosis (Alikhani 2018; Gonsalez 1998; Illangasekera 2008; Sehgal 2000), and three trials reported non-serious adverse events (Alikhani 2018; Sehgal 2000; Takafuji 1984).

For all-cause mortality, Sehgal 2000 was at high risk of bias overall. Regarding the laboratory-confirmed leptospirosis, four of the five trials were at high risk of bias overall (Gonsalez 1998; Illangasekera 2008; Sehgal 2000; Takafuji 1984). For clinical diagnosis of leptospirosis, three of the four trials were at high risk of bias overall (Gonsalez 1998; Illangasekera 2008; Sehgal 2000). For the non-serious adverse events, two of the three trials were at high risk of bias overall (Sehgal 2000; Takafuji 1984). No trials were at low risk of bias overall for any of the outcomes in this review.

Bias arising from the randomisation process

One trial reported that randomisation was performed by allowing participants to choose between identical white containers that included penicillin and placebo and were labelled independently, and had the randomisation sequence blinded (Illangasekera 2008). One trial reported that the randomisation was by computer-generated coding (Takafuji 1984). The remaining three trials reported that the interventions were 'randomly' allocated but did not detail information on the randomisation process (Alikhani 2018; Gonsalez 1998; Sehgal 2000). Only Illangasekera 2008 mentioned allocation sequence concealment. Of the four remaining trials, there were some concerns for bias arising from the randomisation process (one of one trial for all-cause mortality; four of five trials for laboratory-confirmed leptospirosis; three of four trials for the clinical diagnosis of leptospirosis, and three of three trials for non-serious adverse events).

Bias due to deviations from the intended intervention

We judged most trials (three of five trials for laboratory-confirmed; two of four trials for clinical diagnosis of leptospirosis, and two of three trials for non-serious adverse events) to be at low risk of bias for deviations from the intended intervention. Gonsalez 1998 was considered to have high risk and Sehgal 2000 as some concerns for risk of bias due to deviations from the intended intervention.

The participants were blinded at assignment in all included trials (Alikhani 2018; Gonsalez 1998; Illangasekera 2008; Sehgal 2000; Takafuji 1984). However, two trials did not provide detailed information on the awareness of the assignment by carers and people delivering the interventions, and there was no information to assess any deviations from the intended intervention that arose because of the experimental context (Gonsalez 1998; Sehgal 2000).

Bias due to missing outcome data

For all outcomes, the included trials were predominantly at high risk of bias except for Alikhani 2018, which was at low risk of bias. In Sehgal 2000, 243/1025 participants were withdrawn because of non-compliance with instructions, medication for other illnesses, adverse effects, or because they moved out of the area and could not be traced. The dropout rates were 24.8% in the doxycycline group and 22.7% in the control group. The other trials also had a high proportion of missing data: 10.2% in Takafuji 1984, 25% in Illangasekera 2008, and 12% in Alikhani 2018.

Bias in measurement of the outcome

For all-cause mortality and laboratory-confirmed diagnosis, we judged all the trials at low risk of bias. Regarding clinical diagnosis, Gonsalez 1998 and Sehgal 2000 did not report any information on the awareness of the intervention by the outcome assessors, and information to determine whether outcome assessment could be influenced by knowledge of the intervention. We judged the risk of bias in these two trials with some concerns. For non-serious adverse events, we judged Alikhani 2018 to be at low risk of bias, Takafuji 1984 to be at some concerns of risk of bias due to the absence of information about the method of measuring the outcome and ascertainment of the outcome, and Sehgal 2000 at high risk of bias due to the absence of information about the method of measuring the outcome, ascertainment of the outcome, and awareness of the intervention by the outcome assessors.

Bias in selection of the reported result

Regarding laboratory-confirmed diagnosis, clinical diagnosis, and non-serious adverse events, most of the included trials did not provide a predetermined statistical analysis plan (except Alikhani 2018). There was insufficient detailed information to assess whether the trials were analysed in various ways and if the results were reported in a selective manner. Therefore, we determined all trials to have some concerns of bias in selection of the reported result. We determined Sehgal 2000 at low risk of bias for all-cause mortality since the data analysis of any outcome measurements may not have an impact on the mortality outcome.

Effects of interventions

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

Antibiotics versus placebo or no intervention

Five trials compared antibiotics versus placebo or no intervention (Alikhani 2018; Gonsalez 1998; Illangasekera 2008; Sehgal 2000; Takafuji 1984).

Primary outcomes

All-cause mortality

One trial reported all-cause mortality (Sehgal 2000); 0/386 (0%) participants in the doxycycline and 3/396 (0.8%) participants in the placebo group died. Doxycycline results in little to no difference in all-cause mortality compared with placebo (RR 0.15, 95% CI 0.01 to 2.83; 1 trial, 782 participants; low-certainty evidence; Analysis 1.1; Summary of findings 1). We downgraded the certainty of evidence one level for risk of bias and one level for imprecision.

Subgroup analysis and investigation of heterogeneity

We could not perform the prespecified subgroup analyses on all-cause mortality because there was only one trial.

Sensitivity analysis

We could not conduct the sensitivity analysis on all-cause mortality due to lack of or few data.

Proportion of people with laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome

Five trials with 2593 participants reported data on laboratory-confirmed leptospirosis (Alikhani 2018; Gonsalez 1998; Illangasekera 2008; Sehgal 2000; Takafuji 1984). The five trials compared doxycycline, penicillin, or azithromycin administered as pre- or postexposure prophylaxis versus placebo.

The true effect of antibiotics compared with placebo on laboratory-confirmed leptospirosis is likely different from the effect estimate of no difference (RR 0.56, 95% CI 0.25 to 1.26; I^2 = 79%; 5 trials, 2593 participants; very low-certainty evidence; Analysis 1.2; Summary of findings 1). We downgraded the certainty of evidence one level for risk of bias, one level for inconsistency, and one level for imprecision.

Subgroup analysis and investigation of heterogeneity

Due to the limited number of trials (fewer than 10 trials), we could not perform subgroup analysis.

Sensitivity analysis

In the prespecified sensitivity analysis of best- and worst-case scenarios for the outcome of laboratory-confirmed leptospirosis, the best-case analysis produced a stronger effect in the direction of benefit than the primary analysis (RR 0.40, 95% CI 0.20 to 0.82; I^2 = 78%; 5 trials, 2849 participants; Analysis 1.3); and the worst-case analysis showed a similar result to the primary analysis (RR 0.65, 95% CI 0.23 to 1.84; I^2 = 89%; 5 trials, 2849 participants; Analysis 1.4).

There was no evidence of either pre- or postexposure prophylactic effect of antibiotics compared with placebo (pre-exposure: RR 0.88, 95% CI 0.72 to 1.09; I^2 = 88%; 3 trials, 1909 participants; Analysis 1.5; postexposure: RR 0.98, 95% CI 0.52 to 1.86; 2 trials, 684 participants; Analysis 1.6).

Restricting the pooled analysis to data from four published trials of endemic community study populations yielded an RR closer to the null effect (RR 1.02, 95% CI 0.83 to 1.25; I^2 = 69%; 4 trials, 1653 participants; Analysis 1.7).

Proportion of people with clinical diagnosis of leptospirosis regardless of laboratory confirmation

Antibiotics (doxycycline, azithromycin, or penicillin) may have little to no effect on clinical diagnosis regardless of laboratory confirmation compared with placebo (RR 0.76, 95% CI 0.53 to 1.08; I^2 = 0%; 4 trials, 1653 participants; low-certainty evidence; Analysis 1.8; Summary of findings 1). We downgraded the certainty of the evidence one level for risk of bias and one level for imprecision.

Subgroup analysis and investigation of heterogeneity

There was no heterogeneity, so we did not perform subgroup analysis by grouping the trials by risk of bias.

Sensitivity analysis

The prespecified best-case scenario analysis of the four trials showed a better effect in the direction of benefit than the primary analysis (RR 0.36, 95% CI 0.17 to 0.76; I^2 = 72%; 4 trials, 1909 participants; Analysis 1.9); and the worst-case scenario analysis showed a similar result to the primary analysis of no effect (RR 1.51, 95% CI 0.54 to 4.23, I^2 = 78%; 4 trials, 1909 participants; Analysis 1.10).

Proportion of people with clinical diagnosis of leptospirosis confirmed by laboratory diagnosis

Antibiotics (doxycycline, azithromycin, or penicillin) may have little to no effect on laboratory-confirmed clinical diagnosis compared with placebo (RR 0.57, 95% CI 0.26 to 1.26; I^2 = 27%; 4 trials, 1653 participants; low-certainty evidence; Analysis 1.11; Summary of findings 1). We downgraded the certainty of the evidence one level for risk of bias and one level for imprecision.

Subgroup analysis and investigation of heterogeneity

Due to the limited number of trials, and low heterogeneity, we did not perform subgroup analysis by grouping the trials by risk of bias.

Sensitivity analysis

In the sensitivity analyses of clinical diagnosis with laboratory confirmation to account for missing data, the pooled best-case analysis showed a better effect in the direction of benefit than the primary analysis (RR 0.21, 95% CI 0.07 to 0.62; I^2 = 76%; 4 trials, 1909 participants; Analysis 1.12) and the worst-case RR showed a similar result to the primary analysis of no effect (RR 1.41, 95% CI 0.31 to 6.36; I^2 = 80%; 4 trials, 1909 participants; Analysis 1.13).

Serious adverse events

Except for mortality reported in one of the five trials (see 'All-cause mortality' above), no other serious adverse events were documented, and we could not find any further published data.

Secondary outcomes

Quality of life

No trials reported quality of life.

Proportion of people with non-serious adverse events

Antibiotics (doxycycline, azithromycin, and penicillin) compared with placebo may increase non-serious adverse events, but the evidence is very uncertain (RR 10.13, 95% CI 2.40 to 42.71; I^2 = 0; 3 trials, 1909 participants; very low-certainty evidence; Analysis 1.14; Summary of findings 1). This result was primarily due to data from Takafuji 1984 (940 participants), which found evidence of a difference between the trial groups. The other two trials individually found no evidence of a difference. We downgraded the certainty of the evidence two levels for risk of bias and three levels for imprecision.

Subgroup analysis and investigation of heterogeneity

Due to the limited number of trials, and low heterogeneity, we did not perform subgroup analysis by grouping the trials by risk of bias.

Sensitivity analysis

The prespecified sensitivity analyses of the best-case analysis provided an uncertain result for non-serious adverse effects (RR 0.47, 95% CI 0.03 to 8.26; I^2 = 94%; 3 trials, 2165 participants; Analysis 1.15), whereas the worst-case analysis led to a stronger

effect for increased non-serious adverse events for antibiotics (doxycycline, azithromycin, and penicillin) versus placebo (RR 31.90, 95% CI 3.22 to 316.21; I^2 = 60%; 3 trials, 2165 participants; Analysis 1.16).

Antibiotic prophylaxis versus another antibiotic, or another dose or schedule of the same antibiotic

One trial compared antibiotic prophylaxis versus another antibiotic (Alikhani 2018).

Primary outcomes

All-cause mortality

The trial did not report all-cause mortality.

Proportion of people with laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome

Doxycycline may have little to no effect on laboratory-confirmed leptospirosis compared with azithromycin (RR 1.49, 95% CI 0.51 to 4.32; 1 trial, 137 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.

Subgroup analysis and investigation of heterogeneity

Due to the limited number of trials, we did not perform subgroup analysis by grouping the trials by risk of bias.

Sensitivity analysis

We could not conduct the sensitivity analysis on laboratory-confirmed leptospirosis because there was only one trial.

Clinical diagnosis of infection with or without laboratory confirmation

Doxycycline may have little to no effect on clinical diagnosis with or without laboratory confirmation compared with azithromycin (RR 4.18, 95% CI 0.94 to 18.66; 1 trial, 137 participants; very low-certainty evidence; Analysis 2.2; Analysis 2.3; Summary of findings 2). We downgraded the certainty of the evidence one level for risk of bias and three levels for imprecision.

Subgroup analysis and investigation of heterogeneity

Due to the limited number of trials, we did not perform subgroup analysis by grouping the trials by risk of bias.

Sensitivity analysis

We could not conduct the sensitivity analysis on clinical diagnosis of infection regardless of laboratory-confirmed leptospirosis because there was only one trial.

Serious adverse events

The trial did not report the proportion of people with serious adverse events.

Secondary outcomes

Quality of life

The trial did not report quality of life.

Proportion of people with non-serious adverse events

Doxycycline may have little to no effect on non-serious adverse events compared with azithromycin (RR 1.12, 95% CI 0.36 to 3.48; 1 trial, 137 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.

Subgroup analysis and investigation of heterogeneity

Due to the limited number of trials, we did not perform subgroup analysis by grouping the trials by risk of bias.

Sensitivity analysis

We could not conduct the sensitivity analysis on non-serious adverse events because there was only one trial.

Adverse events reported in non-randomised studies retrieved through the searches for randomised trials

One non-randomised prospective study reported 13 people experienced adverse effects due to antibiotics (i.e. gastrointestinal symptoms and skin rash) (Chusri 2014; Table 1).

DISCUSSION

Summary of main results

This review updates the current body of evidence on the use of prophylactic antimicrobials in the management of leptospirosis. The original review, Brett-Major 2009, included three trials (Gonsalez 1998; Sehgal 2000; Takafuji 1984). We added two new trials to this updated analysis (Alikhani 2018; Illangasekera 2008). Pooled data included antibiotics versus placebo or no intervention, and one antibiotic versus another antibiotic, or another dose or schedule of the same antibiotic. Three trials assessed pre-exposure prophylaxis, one trial measured postexposure prophylaxis, and one trial was unclear and assumed as postexposure.

This review could not prove or disprove benefit for either laboratory-confirmed or clinically suspected leptospirosis with the use of antibiotic prophylaxis. In the pooled comparison of antibiotic prophylaxis versus the control group irrespective of laboratory-confirmed or clinically diagnosed disease, the certainty of evidence for an effect of antibiotic prophylaxis was very low to low. There was uncertain evidence for the effect of prophylactic antibiotics on either laboratory-confirmed or clinically suspected leptospirosis disease compared to the control group. This is in contrast to results for clinical diagnosis with laboratory confirmation in the previous review of Brett-Major 2009, which included only one trial (Sehgal 2000). Data from this single trial suggested evidence of an effect of antibiotic prophylaxis, whereas pooled data from three trials did not. There was very low-certainty evidence for the effect of prophylactic antibiotics on increased occurrence of non-serious adverse events compared to the control group.

Only one trial compared one antibiotic versus another antibiotic for prophylaxis purposes, which was doxycycline versus azithromycin (Alikhani 2018). However, we are uncertain about the effect of the two treatments on the outcome of laboratory-confirmed disease, clinical disease with or without laboratory confirmation, or non-serious adverse events.

None of the trials reported serious adverse events (other than mortality in Sehgal 2000) and quality of life.

Overall completeness and applicability of evidence

There continues to be insufficient evidence to support the use of antibiotic prophylaxis against leptospirosis disease despite the addition of two additional trials since the last review. Disparity in outcome measures remains a key factor preventing meaningful contributory data for pooled analysis. As previously highlighted, limiting outcome measures of interest to laboratory confirmation is not the main purpose for antimicrobial prophylactic strategies (Brett-Major 2009). More work is required to identify meaningful and acceptable study outcomes that can be standardised for the benefit of future studies.

There remains a disparity in the applicability of study results amongst the various included populations. For example, although there was evidence of benefit from pre-exposure doxycycline versus placebo in one military study population in Panama in a publication that could have a high risk of bias (Takafuji 1984), this was not replicated in a resident community population in Iran with less risk of bias (Alikhani 2018).

Although a wider number of antimicrobials were included in this updated review, the main prophylactic antimicrobial of choice continues to be doxycycline. The Iranian community trial suggested some benefits for azithromycin over doxycycline compared with placebo, but results did not reach significance. We were unable to obtain additional confirmatory information regarding the trial employing doxycycline that was conducted in southern India.

The choice of an antimicrobial is of great importance due to the finding of adverse events impacting treatment. Non-serious adverse events were reported more frequently in antibiotic groups, particularly events such as vomiting and nausea, and the incidence was very similar for the trial including two antibiotic treatment groups of doxycycline and azithromycin. Therefore, further work is required to explore different antimicrobial choices.

Quality of the evidence

Antibiotics compared with placebo or no intervention for prophylaxis of leptospirosis

We included data from five trials assessing the efficacy of antibiotics in the prophylaxis of leptospirosis compared with placebo. We rated the certainty of evidence for leptospirosis infection as low to very low (see Summary of findings 1). We downgraded the certainty of evidence due to the risk of bias arising from the randomisation process, deviation from the intended intervention, missing outcome data, and selection of reported results.

In all included trials except Alikhani 2018, a high number of participants were withdrawn. Almost all trials did not clearly mention allocation randomisation and sequence concealment. One trial did not explain the reason for excluding 24 participants, and it was difficult to determine whether the intended intervention was followed. A prespecified analysis plan was available for only one trial, and there was no information for other trials about whether they reported results selectively.

We further downgraded the certainty of evidence one level due to serious inconsistency where trial heterogeneity was 50% to 90% and serious imprecision where the optimal information size was not met, and CIs crossed the clinical decision threshold. We downgraded the certainty of evidence for non-serious adverse events to very low due to risk of bias (arising from the randomisation process, deviation from the intended intervention, missing outcome data, and selection of reported results) and serious imprecision (very wide CIs).

Antibiotics compared to other antibiotics for prophylaxis of leptospirosis

We included data from one trial assessing the efficacy of doxycycline in the prophylaxis of leptospirosis compared to azithromycin. We rated the certainty of evidence for leptospirosis infection and non-serious adverse events as very low due to high risk of bias from the randomisation process, deviation from intended intervention, missing outcome data, and selection of reported results; and imprecision where the optimal information size was not met, very wide CIs, and the CIs crossing the clinical decision threshold (see Summary of findings 2).

Potential biases in the review process

Funnel plot analysis to further assess publication bias as described in the protocol was not conducted due to a limited number of trials. We made all attempts to contact the authors for additional information about missing data, but we received no responses.

Due to the limited number of trials, we could not perform subgroup analysis, and we could not make any conclusion about the prophylactic effect of antibiotics for leptospirosis. However, we are confident that we have identified all relevant trials. Only one trial reported a mortality outcome, and we graded the certainty of evidence as low. Although nearly all trials were at high risk of bias, we decided to perform meta-analyses.

There was also a risk of bias regarding the definition of outcomes, especially for non-serious adverse events. Included trials reported different non-serious adverse events, and we synthesised them in our meta-analysis.

Agreements and disagreements with other studies or reviews

Three systematic reviews (Aklil 2018; Brett-Major 2009; Guidugli 2000), one literature review (Schneider 2017), and one meta-analysis (Perez 2021), evaluating the benefits of antibiotic prophylaxis for leptospirosis, have been published.

Aklil 2018 included eight studies involving 3319 participants. Four studies were randomised clinical trials, one a non-randomised trial, one a retrospective cohort study, one a case-control study, and one a case series study. Aklil 2018 concluded that antibiotic prophylaxis was effective in preventing leptospirosis disease in high-risk groups, with minimal adverse effects. The inclusion of both randomised and non-randomised studies in the same meta-analysis could have impacted the results of the study.

Brett-Major 2009 included three randomised clinical trials involving 1804 participants. The authors concluded that regular use of oral doxycycline increased the likelihood of nausea and vomiting, but its benefit in reducing leptospiral infection was unclear.

Guidugli 2000 included two randomised clinical trials involving 1022 participants. This review concluded that doxycycline might be effective as leptospirosis prophylaxis amongst soldiers training in leptospirosis-endemic areas.

Perez 2021 included eight studies involving 4905 participants. One study was a non-randomised trial, whilst the other seven studies were randomised clinical trials. The author of the review concluded that there were no significant differences amongst different types of antibiotics in preventing leptospirosis-symptomatic infection, and well-designed clinical trials were recommended.

Brett-Major 2009 and Guidugli 2000 are the original versions of the current review. We identified two additional trials from our search which we added to the three trials included in the 2009 review (Brett-Major 2009). Similar to the prior review, trials were conducted in five countries, in both low- and middle-income resource settings. In an update to the previous review, trial data were sufficient in order to apply a 'best-case' and 'worst-case' analysis to missing data. Additionally, the inclusion of trials with different antimicrobials allowed for the comparative analysis considering antimicrobial choice. However, these updates did not alter the major conclusions of our analysis.

AUTHORS' CONCLUSIONS

Implications for practice

This review found insufficient evidence to support or refute the use of antibiotic prophylaxis for the prevention of leptospirosis. The optimal choice and dosage of prophylactic antimicrobial agents also remain unclear. We do not know whether doxycycline prophylaxis is effective in reducing mortality compared with placebo based on the low-certainty evidence obtained from the single included trial. The effects of antibiotic prophylaxis on leptospirosis infection compared with placebo or to other antibiotics are also very uncertain. Meta-analysed data from three trials revealed an increased risk of non-serious adverse events (such as epigastric pain, vomiting, and heart burn) with antibiotics, with very low-certainty evidence. However, these findings should be interpreted with caution as they are based on a limited number of trials and mostly very low- or low-certainty evidence. Therefore, we do not know what the effects of antibiotic prophylaxis against human leptospirosis are.

Implications for research

We were unable to draw robust conclusions regarding the prophylaxis effect of antibiotics on leptospirosis. This review is limited by the quality of identified trials due to flaws in randomisation, allocation concealment, and inappropriate sample sizes. Trials need to be adequately powered for clearly defined and objectively measured outcomes. We would suggest future trials carefully documenting the methodology such as randomisation, allocation, and concealment. A prespecified analysis plan should be published to avoid the possibility of selection of the reported results. Results from single-centre trials are also difficult to generalise, and multi-site international studies should be considered. There would be benefits to standardising clinical outcomes to ensure reporting of meaningful and clinically relevant outcomes, reduce inter-trial heterogeneity, and allow for more meaningful pooling. Identification of adverse events must also be prioritised.

In the intervening period following the last review, trials exploring prophylactic antimicrobial strategies have focused on a pre-exposure dose administration strategy. As proposed by Brett-Major 2009, determining the optimum time for prophylactic treatment has useful public health implications. There have also been further studies exploring different types of antimicrobials. It will be vital to continue exploring different antimicrobial options given our conclusions regarding non-serious adverse effects of the antibiotics used in the known studies.

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Editorial and peer-reviewer contributions

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- Sign-off Editor (final editorial decision): Christian Gluud, Co-ordinating Editor, CHBG, Denmark
- Contact Editor (provided editorial decision): Goran Poropat, Croatia
- Managing Editor (selected peer reviewers and editors, provided editorial guidance to authors, edited the review): Dimitrinka Nikolova, Denmark
- Information Specialist (design and running the searches): Sarah Klingenberg, Denmark
- Peer-reviewers (provided clinical and content review comments): Cristina Torres Vargas, Spain; Benjie M Clemente, The Philippines; Juan Carlos Gabaldón Figueira, Spain; (checked Trial Sequential Analysis text and figures); Mark Aninakwah Asante, Denmark; (provided comments on RoB 2): Rachel Richardson, UK
- Evidence Synthesis Development Editor (screening comments): Leslie Choi, Evidence Production and Methods Department, Cochrane, UK
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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Alikhani 2018

Study characteristics	
Methods	Randomised double-blind placebo-controlled trial **Location:** Iran (single centre) **Date:** June to September 2016 No detailed information on analysis method. **Number of people randomised:** 200 **Trial aim:** pre-exposure prophylaxis 3 trial groups (2 experimental and 1 control) **Trial protocol:** there is no published trial protocol, but trial registry information can be obtained from trial registration number IRCT2015052322383N1.
Participants	**Male:** 66.5%

Alikhani 2018 *(Continued)*

	Mean age: 47.5 (standard deviation 10.6) years **Inclusion criteria:** people aged 18–65 years, residing in endemic area (Sari, Ghaemshahr, and Jouybar in Mazandaran province, Iran), and who were supposed to work in the paddy field after giving consent **Exclusion criteria:** history of hypersensitivity to azithromycin and doxycycline, positive first screening test for leptospirosis, pregnant women, history of any severe adverse reaction to doxycycline and azithromycin
Interventions	Pre-exposure prophylaxis with azithromycin, doxycycline, or placebo **Experimental group 1** (68 participants): azithromycin 500 mg weekly **Experimental group 2** (71 participants): doxycycline 200 mg weekly Antibiotic prophylaxis was administered 1 week before exposure to paddy field, during exposure to paddy field (took around 6 weeks), and to 4 weeks after exposure to paddy field **Control group** (61 participants): placebo **Co-interventions:** none **Dropouts:** 2.9% in experimental group 1, 0% in experimental group 2, and 18% in control group **Intention-to-treat analysis:** no **Follow-up:** 12 weeks
Outcomes	**Primary outcomes:** fever, body pain, red eye, calf pain, icter Time point: 0, 6, 12 weeks for immunoglobulin G and 2nd week after developing disease for immunoglobulin M **Secondary outcomes:** nausea, vomiting, oesophagitis, photosensitivity Time point: drug consumption periods
Notes	Contacted trial author to request additional data on 14 June 2022, but received no reply. **Funding:** trial received financial support from the Vice Chancellor Research and Technology of Mazandaran University of Medical Sciences.

Gonsalez 1998

Study characteristics	
Methods	Randomised clinical trial **Location:** Brazil **Date:** 29 March 1992 until 45 days later No detailed information on analysis method **Number of people randomised:** 82 **Trial aim:** postexposure prophylaxis 2 trial groups (1 experimental and 1 control) **Trial protocol:** there was no published trial protocol

Gonsalez 1998 *(Continued)*

Participants	**Age range:** 18–74 years **Male:** 41.4% **Inclusion criteria:** residents in an area at high risk for flooding, Cabucu District, Sao Paulo region **Exclusion criteria:** allergy to tetracycline or a high-exposure risk to leptospirosis in the last 6 months
Interventions	Postexposure prophylaxis with a single 200 mg dose of doxycycline or placebo **Experimental group** (40 participants): doxycycline 200 mg once at first bleeding **Control group** (42 participants): placebo **Co-interventions:** no **Dropouts:** 22.6% **Intention-to-treat analysis:** no **Follow-up:** 45 days
Outcomes	**Laboratory-confirmed leptospirosis** Time point: 0 and 45 days for immunoglobulin M measured by enzyme immunoassay **Clinical case:** fever, chills, myalgia, nausea, vomiting, abdominal pain, conjunctivitis, and headache accompanied by neck stiffness Time point: period immediately after exposure to flooding
Notes	Contacted trial author requesting additional data on 14 June 2022, but received no reply. **Funding:** trial received doxycycline and placebo from Pfizer of Brazil.

Illangasekera 2008

Study characteristics	
Methods	Randomised clinical trial **Location:** Sri Lanka (2 centres) **Date:** October 2005 No detailed information on analysis method **Number of people randomised:** 800 **Trial aim:** postexposure prophylaxis 2 trial groups (1 experimental and 1 control) **Trial protocol:** there was no published trial protocol
Participants	**Age:** 20–80 years **Male:** 100% **Inclusion criteria:** residents in high transmission area in the Medical Officer of Health division of Yatinuwara and Udunuwara in the Central Province, Sri Lanka

Illangasekera 2008 *(Continued)*

	Exclusion criteria: allergy to penicillin or who were taking other antibiotics at the time of the study
Interventions	Pre- or postexposure prophylaxis with penicillin or placebo **Experimental group** (292 participants): penicillin 250 mg in 2 tablets twice a day for 1 month **Control group** (310 participants): placebo **Co-interventions:** no **Dropouts:** 24.75% **Intention-to-treat analysis:** no **Follow-up:** 4 weeks
Outcomes	**Clinical case of leptospirosis** Time point: during and after the study period using checklist of symptoms of leptospirosis **Laboratory-confirmed case** Time point: paired blood samples taken 10 days apart for *Leptospira* serology by microagglutination test
Notes	Contacted trials author requesting additional data on 14 June 2022, but received no reply **Funding:** not reported

Sehgal 2000

Study characteristics	
Methods	Randomised clinical trial **Location:** India **Date:** second week of September until first week of December, year not reported. No detailed information on analysis method **Number of people randomised:** 1025 **Trial aim:** pre-exposure prophylaxis 2 trial groups (1 experimental and 1 control) **Trial protocol:** there was no published trial protocol
Participants	**Age:** 10–40 years and above **Male:** not reported **Inclusion criteria:** residents lived in high endemic area around Diglipur, Andaman Islands, India **Exclusion criteria:** people with chronic diseases or on medication, pregnant women and lactating mothers
Interventions	Pre-exposure prophylaxis with weekly administration of 2 doses of 100 mg doxycycline for 12 weeks **Experimental group** (513 participants): doxycycline 100 mg in 2 doses

Sehgal 2000 *(Continued)*

	Control group (512 participants): placebo (vitamin B complex) **Co-interventions:** no **Dropouts:** 24.8% in experimental group; 22.7% in control group **Intention-to-treat analysis:** no **Follow-up:** 12 weeks
Outcomes	**Leptospirosis case** Time point: day 0, after 6 weeks, after 12 weeks using the microagglutination test. Isolation of leptospirosis was performed for all participants who had febrile illness during the trial. **Mortality, febrile illness, and adverse events** Time point: during the trial period
Notes	Contacted trial author requesting additional data on 14 June 2022, but received no reply **Funding:** trial received doxycycline tablets free of cost from Pfizer Ltd, India.

Takafuji 1984

Study characteristics	
Methods	Randomised clinical trial **Location:** Panama **Date:** 1982 No detailed information on analysis method **Number of people randomised:** 940 **Trial aim:** pre-exposure prophylaxis 2 trial groups (1 experimental and 1 control) **Trial protocol:** there was no published trial protocol
Participants	**Age:** not reported **Male:** not reported **Inclusion criteria:** volunteer soldiers present at the Jungle Operations Training Center at Fort Sherman, a military installation on the Atlantic side of the Panama Canal region **Exclusion criteria:** history of allergy to tetracyclines or receiving other antibiotics at the beginning of the trial
Interventions	Pre-exposure prophylaxis with weekly administration of a single dose of doxycycline or placebo **Experimental group** (469 participants): doxycycline 200 mg at the time of enrolment in the trial. The same dose was taken at the beginning of each subsequent week of training and at the completion of the exercise immediately before departure from Panama **Control group** (471 participants): placebo **Co-interventions:** no

Takafuji 1984 *(Continued)*

	Dropouts: 10% **Intention-to-treat analysis:** no **Follow-up:** 11 weeks
Outcomes	**Laboratory-confirmed case** Time point: 1 week before travel to Panama, within 1 week after their return to the US, and approximately 4–6 weeks later for leptospiral antibody by microagglutination test and culture **Specific symptoms:** fever, chills, headache, neck stiffness, dizziness, back pain, muscle aches, joint pain, tiredness, nausea, vomiting, abdominal pain, diarrhoea, eye redness or pain, photophobia, rash, cough, and nasal congestion Time point: at the end of each week's training for 3 weeks
Notes	Contacted trial author via research gate requesting additional data on 14 June 2022, but received no reply. **Funding:** trial received doxycycline and placebo from Pfizer.

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

Study	Reason for exclusion
Chusri 2014	Non-randomised study TCTR20131106001 is the co-publication of Chusri 2014.

Characteristics of studies awaiting classification *[ordered by study ID]*

Shivaraj 2012

Methods	Randomised clinical trial Poster presentation **Location:** India **Date:** 1 October to 30 December 2011 No detailed information on analysis method
Participants	**Inclusion criteria:** paddy field farmers working and residing in the study area following their consent **Exclusion criteria:** not reported
Interventions	**Experimental group** (732 participants): doxycycline 200 mg once per week for 5 weeks **Control group** (639 participants): no treatment
Outcomes	Laboratory-confirmed case was measured by enzyme-linked immunosorbent assay Clinical case was measured by clinical examination

Shivaraj 2012 *(Continued)*

Notes	Contacted the Administrative Editor of *International Journal of Infectious Diseases* to request contact information of trial author on 20 September 2022. Received reply on 20 September 2022 mentioning that private information of author could not be provided.

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**
Sehgal 2000	~	~	✗	✓	✓	✗

Risk of bias for analysis 1.2 Proportion of people with laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome (inclusive of asymptomatic cases)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~
Gonsalez 1998	~	✗	✗	✓	~	✗
Illangasekera 2008	✓	✓	✗	✓	~	✗
Sehgal 2000	~	~	✗	✓	~	✗
Takafuji 1984	~	✓	✗	✓	~	✗

Risk of bias for analysis 1.3 Sensitivity analysis: laboratory-confirmed leptospirosis (best-case scenario)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~
Gonsalez 1998	~	~	✗	✓	~	✗
Illangasekera 2008	✓	✓	✗	✓	~	✗
Sehgal 2000	~	~	✗	✓	~	✗
Takafuji 1984	~	✓	✗	✓	~	✗

Risk of bias for analysis 1.4 Sensitivity analysis: laboratory-confirmed leptospirosis (worst-case scenario)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~
Gonsalez 1998	~	~	✗	✓	~	✗
Illangasekera 2008	✓	✓	✗	✓	~	✗
Sehgal 2000	~	~	✗	✓	~	✗
Takafuji 1984	~	✓	✗	✓	~	✗

Risk of bias for analysis 1.5 Sensitivity analysis: laboratory-confirmed leptospirosis (only pre-exposure prophylaxis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sehgal 2000	~	~	✗	✓	~	✗
Takafuji 1984	~	✓	✗	✓	~	✗

Risk of bias for analysis 1.6 Sensitivity analysis: laboratory-confirmed leptospirosis (only postexposure prophylaxis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gonsalez 1998	~	~	✗	✓	~	✗
Illangasekera 2008	✓	✓	✗	✓	~	✗

Risk of bias for analysis 1.7 Sensitivity analysis: laboratory-confirmed leptospirosis (including only endemic community)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~
Gonsalez 1998	~	~	✗	✓	~	✗
Illangasekera 2008	✓	✓	✗	✓	~	✗
Sehgal 2000	~	~	✗	✓	~	✗

Risk of bias for analysis 1.8 Proportion of people with clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~
Gonsalez 1998	~	✗	✗	~	~	✗
Illangasekera 2008	✓	✓	✗	✓	~	✗
Sehgal 2000	~	~	✗	~	~	✗

Risk of bias for analysis 1.9 Sensitivity analysis: clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation (best-case scenario)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	✓	~
Gonsalez 1998	~	✗	✗	~	~	✗
Illangasekera 2008	✓	✓	✗	✓	~	✗
Sehgal 2000	~	~	✗	~	~	✗

Risk of bias for analysis 1.10 Sensitivity analysis: clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation (worst-case scenario)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gonsalez 1998	~	✗	✗	~	~	✗
Illangasekera 2008	✓	✓	✗	✓	~	✗
Sehgal 2000	~	~	✗	~	~	✗

Risk of bias for analysis 1.11 Proportion of people with clinical diagnosis of leptospirosis confirmed by laboratory diagnosis (exclusive of asymptomatic cases)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~
Gonsalez 1998	~	~	✗	✓	~	✗
Illangasekera 2008	✓	✓	✗	✓	~	✗
Sehgal 2000	~	~	✗	✓	~	✗

Risk of bias for analysis 1.12 Sensitivity analysis: clinical diagnosis confirmed by laboratory diagnosis (best-case scenario)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	✓	~
Gonsalez 1998	~	~	✗	✓	~	✗
Illangasekera 2008	✓	✓	✗	✓	~	✗
Sehgal 2000	~	~	✗	✓	~	✗

Risk of bias for analysis 1.14 Proportion of people with non-serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~
Sehgal 2000	~	~	✗	✗	~	✗
Takafuji 1984	~	✓	✗	~	~	✗

Risk of bias for analysis 1.15 Sensitivity analysis: non-serious adverse events (best-case scenario)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	✓	~
Sehgal 2000	~	~	✗	✗	~	✗
Takafuji 1984	~	✓	✗	~	~	✗

Risk of bias for analysis 2.1 Proportion of people with laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome (inclusive of asymptomatic cases)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~

Risk of bias for analysis 2.2 Proportion of people with clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~

Risk of bias for analysis 2.3 Proportion of people with clinical diagnosis of leptospirosis confirmed by laboratory diagnosis (exclusive of asymptomatic cases)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~

Risk of bias for analysis 2.4 Proportion of people with non-serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Alikhani 2018	~	✓	✓	✓	~	~

DATA AND ANALYSES

Comparison 1. Antibiotics versus placebo or no intervention

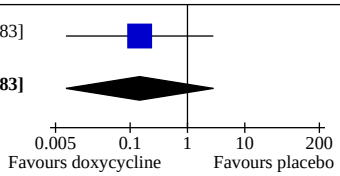
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	1	782	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.83]
1.2 Proportion of people with laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome (inclusive of asymptomatic cases)	5	2593	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.25, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Sensitivity analysis: laboratory-confirmed leptospirosis (best-case scenario)	5	2849	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.20, 0.82]
1.4 Sensitivity analysis: laboratory-confirmed leptospirosis (worst-case scenario)	5	2849	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.23, 1.84]
1.5 Sensitivity analysis: laboratory-confirmed leptospirosis (only pre-exposure prophylaxis)	3	1909	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.72, 1.09]
1.6 Sensitivity analysis: laboratory-confirmed leptospirosis (only postexposure prophylaxis)	2	684	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.52, 1.86]
1.7 Sensitivity analysis: laboratory-confirmed leptospirosis (including only endemic community)	4	1653	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.83, 1.25]
1.8 Proportion of people with clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation	4	1653	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.53, 1.08]
1.9 Sensitivity analysis: clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation (best-case scenario)	4	1909	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.17, 0.76]
1.10 Sensitivity analysis: clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation (worst-case scenario)	4	1909	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.54, 4.23]
1.11 Proportion of people with clinical diagnosis of leptospirosis confirmed by laboratory diagnosis (exclusive of asymptomatic cases)	4	1653	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.26, 1.26]
1.12 Sensitivity analysis: clinical diagnosis confirmed by laboratory diagnosis (best-case scenario)	4	1909	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.07, 0.62]
1.13 Sensitivity analysis: clinical diagnosis confirmed by laboratory diagnosis (worst-case scenario)	4	1909	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.31, 6.36]
1.14 Proportion of people with non-serious adverse events	3	1909	Risk Ratio (M-H, Random, 95% CI)	10.13 [2.40, 42.71]
1.15 Sensitivity analysis: non-serious adverse events (best-case scenario)	3	2165	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.03, 8.26]
1.16 Sensitivity analysis: non-serious adverse events (worst-case scenario)	3	2165	Risk Ratio (M-H, Random, 95% CI)	31.90 [3.22, 316.21]

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

Study or Subgroup	Doxycycline Events	Doxycycline Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Sehgal 2000	0	386	3	396	100.0%	0.15 [0.01 , 2.83]	? ? − + + −
Total (95% CI)		**386**		**396**	**100.0%**	**0.15 [0.01 , 2.83]**	
Total events:	0		3				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable

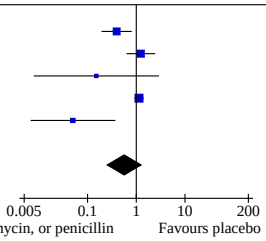


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 2: Proportion of people with laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome (inclusive of asymptomatic cases)

Study or Subgroup	Doxycycline, azithromycin, or penicillin Events	Doxycycline, azithromycin, or penicillin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alikhani 2018	13	137	12	50	25.7%	0.40 [0.19 , 0.81]	? + + + ? ?
Gonsalez 1998	13	40	11	42	26.2%	1.24 [0.63 , 2.44]	? − − + ? −
Illangasekera 2008	0	292	3	310	6.0%	0.15 [0.01 , 2.92]	+ + − + ? −
Sehgal 2000	112	386	101	396	31.4%	1.14 [0.90 , 1.43]	? ? − + ? −
Takafuji 1984	1	469	20	471	10.7%	0.05 [0.01 , 0.37]	? + − + ? −
Total (95% CI)		**1324**		**1269**	**100.0%**	**0.56 [0.25 , 1.26]**	
Total events:	139		147				

Heterogeneity: Tau² = 0.52; Chi² = 19.47, df = 4 (P = 0.0006); I² = 79%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable

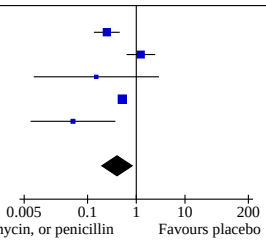


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 3: Sensitivity analysis: laboratory-confirmed leptospirosis (best-case scenario)

Study or Subgroup	Doxycycline, azithromycin, or penicillin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alikhani 2018	13	139	23	61	27.0%	0.25 [0.13 , 0.46]	? + + + ? ?
Gonsalez 1998	13	40	11	42	25.9%	1.24 [0.63 , 2.44]	? ? − + ? −
Illangasekera 2008	0	292	3	310	5.0%	0.15 [0.01 , 2.92]	+ + − + ? −
Sehgal 2000	112	513	217	512	32.8%	0.52 [0.42 , 0.62]	? ? − + ? −
Takafuji 1984	1	469	20	471	9.3%	0.05 [0.01 , 0.37]	? + − + ? −
Total (95% CI)		**1453**		**1396**	**100.0%**	**0.40 [0.20 , 0.82]**	
Total events:	139		274				

Heterogeneity: Tau² = 0.40; Chi² = 18.18, df = 4 (P = 0.001); I² = 78%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Not applicable

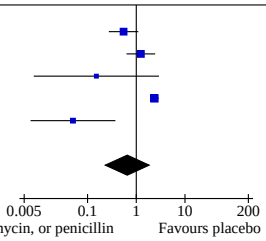


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 4: Sensitivity analysis: laboratory-confirmed leptospirosis (worst-case scenario)

Study or Subgroup	Doxycycline, azithromycin, or penicillin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alikhani 2018	15	139	12	61	24.9%	0.55 [0.27 , 1.10]	? + + + ? ?
Gonsalez 1998	13	40	11	42	25.1%	1.24 [0.63 , 2.44]	? ? − + ? −
Illangasekera 2008	0	292	3	310	8.5%	0.15 [0.01 , 2.92]	+ + − + ? −
Sehgal 2000	239	513	101	512	27.8%	2.36 [1.94 , 2.88]	? ? − + ? −
Takafuji 1984	1	469	20	471	13.7%	0.05 [0.01 , 0.37]	? + − + ? −
Total (95% CI)		**1453**		**1396**	**100.0%**	**0.65 [0.23 , 1.84]**	
Total events:	268		147				

Heterogeneity: Tau² = 1.00; Chi² = 35.46, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable

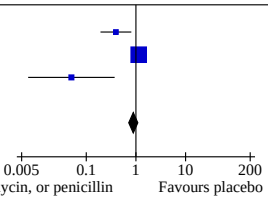


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 5: Sensitivity analysis: laboratory-confirmed leptospirosis (only pre-exposure prophylaxis)

Study or Subgroup	Doxycycline, azithromycin, or penicillin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Alikhani 2018	13	137	12	50	12.8%	0.40 [0.19 , 0.81]	? + + + ? ?
Sehgal 2000	112	386	101	396	72.6%	1.14 [0.90 , 1.43]	? ? − + ? −
Takafuji 1984	1	469	20	471	14.5%	0.05 [0.01 , 0.37]	? + − + ? −
Total (95% CI)		**992**		**917**	**100.0%**	**0.88 [0.72 , 1.09]**	
Total events:	126		133				

Heterogeneity: Chi² = 17.37, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable

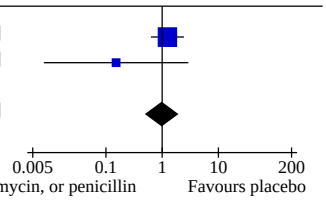


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 6: Sensitivity analysis: laboratory-confirmed leptospirosis (only postexposure prophylaxis)

Study or Subgroup	Doxycycline, azithromycin, or penicillin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gonsalez 1998	13	40	11	42	76.0%	1.24 [0.63 , 2.44]
Illangasekera 2008	0	292	3	310	24.0%	0.15 [0.01 , 2.92]
Total (95% CI)		**332**		**352**	**100.0%**	**0.98 [0.52 , 1.86]**
Total events:	13		14			

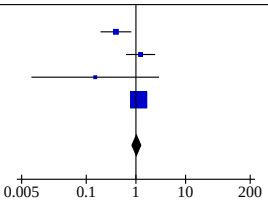
Heterogeneity: Chi² = 2.00, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 0.06 (P = 0.95)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 7: Sensitivity analysis: laboratory-confirmed leptospirosis (including only endemic community)

Study or Subgroup	Doxycycline, azithromycin, or penicillin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Alikhani 2018	13	137	12	50	13.4%	0.40 [0.19 , 0.81]	? + + + ? ?
Gonsalez 1998	13	40	11	42	8.2%	1.24 [0.63 , 2.44]	? ? − + ? −
Illangasekera 2008	0	292	3	310	2.6%	0.15 [0.01 , 2.92]	+ + − + ? −
Sehgal 2000	112	386	101	396	75.9%	1.14 [0.90 , 1.43]	? ? − + ? −
Total (95% CI)		**855**		**798**	**100.0%**	**1.02 [0.83 , 1.25]**	
Total events:	138		127				

Heterogeneity: Chi² = 9.54, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable

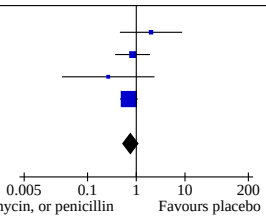


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.8. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 8: Proportion of people with clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation

Study or Subgroup	Doxycycline, azithromycin, or penicillin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alikhani 2018	11	137	2	50	5.9%	2.01 [0.46 , 8.74]	? + + + ? ?
Gonsalez 1998	8	40	10	42	18.9%	0.84 [0.37 , 1.91]	? - - ? ? -
Illangasekera 2008	1	292	4	310	2.7%	0.27 [0.03 , 2.36]	+ + - + ? -
Sehgal 2000	33	386	48	396	72.5%	0.71 [0.46 , 1.07]	? ? - ? ? -
Total (95% CI)		**855**		**798**	**100.0%**	**0.76 [0.53 , 1.08]**	
Total events:	53		64				

Heterogeneity: Tau² = 0.00; Chi² = 2.74, df = 3 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)
Test for subgroup differences: Not applicable

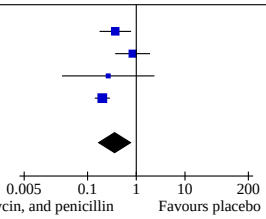


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.9. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 9: Sensitivity analysis: clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation (best-case scenario)

Study or Subgroup	Doxycycline, azithromycin, or penicillin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alikhani 2018	11	139	13	61	28.3%	0.37 [0.18 , 0.78]	? + + + + ?
Gonsalez 1998	8	40	10	42	26.6%	0.84 [0.37 , 1.91]	? - - ? ? -
Illangasekera 2008	1	292	4	310	9.1%	0.27 [0.03 , 2.36]	+ + - + ? -
Sehgal 2000	33	513	164	512	36.0%	0.20 [0.14 , 0.29]	? ? - ? ? -
Total (95% CI)		**984**		**925**	**100.0%**	**0.36 [0.17 , 0.76]**	
Total events:	53		191				

Heterogeneity: Tau² = 0.38; Chi² = 10.91, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 2.67 (P = 0.008)
Test for subgroup differences: Not applicable

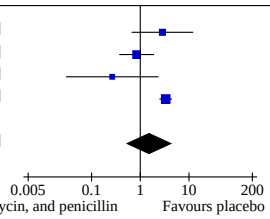


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.10. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 10: Sensitivity analysis: clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation (worst-case scenario)

Study or Subgroup	Doxycycline, azithromycin, or penicillin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alikhani 2018	13	139	2	61	21.1%	2.85 [0.66 , 12.26]	? + + + + ?
Gonsalez 1998	8	40	10	42	29.6%	0.84 [0.37 , 1.91]	? − − ? ? −
Illangasekera 2008	1	292	4	310	13.8%	0.27 [0.03 , 2.36]	+ + − + ? −
Sehgal 2000	160	513	48	512	35.5%	3.33 [2.47 , 4.48]	? ? − ? ? −
Total (95% CI)		**984**		**925**	**100.0%**	**1.51 [0.54 , 4.23]**	
Total events:	182		64				

Heterogeneity: Tau² = 0.75; Chi² = 13.95, df = 3 (P = 0.003); I² = 78%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable

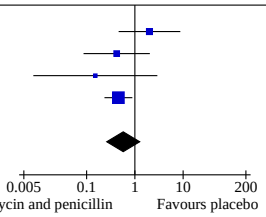


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.11. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 11: Proportion of people with clinical diagnosis of leptospirosis confirmed by laboratory diagnosis (exclusive of asymptomatic cases)

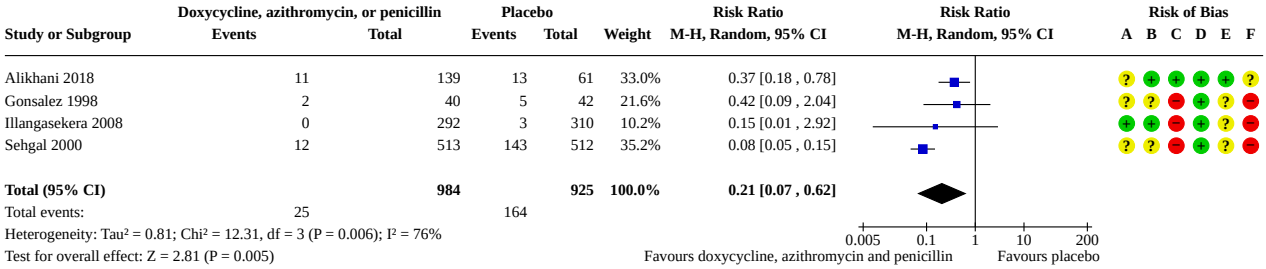
Study or Subgroup	Doxycycline, azithromycin, and penicillin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Alikhani 2018	11	137	2	50	21.4%	2.01 [0.46 , 8.74]	? + + + ? ?
Gonsalez 1998	2	40	5	42	19.2%	0.42 [0.09 , 2.04]	? ? − + ? −
Illangasekera 2008	0	292	3	310	6.5%	0.15 [0.01 , 2.92]	+ + − + ? −
Sehgal 2000	12	386	27	396	52.9%	0.46 [0.23 , 0.89]	? ? − + ? −
Total (95% CI)		**855**		**798**	**100.0%**	**0.57 [0.26 , 1.26]**	
Total events:	25		37				

Heterogeneity: Tau² = 0.19; Chi² = 4.11, df = 3 (P = 0.25); I² = 27%
Test for overall effect: Z = 1.39 (P = 0.17)
Test for subgroup differences: Not applicable



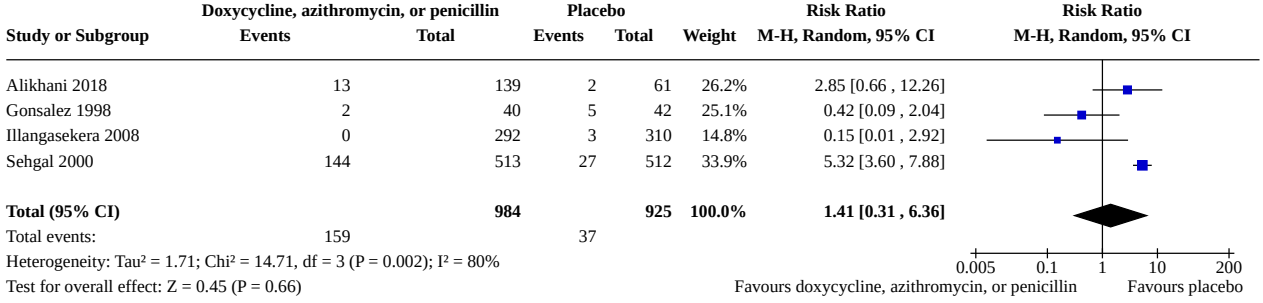
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.12. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 12: Sensitivity analysis: clinical diagnosis confirmed by laboratory diagnosis (best-case scenario)

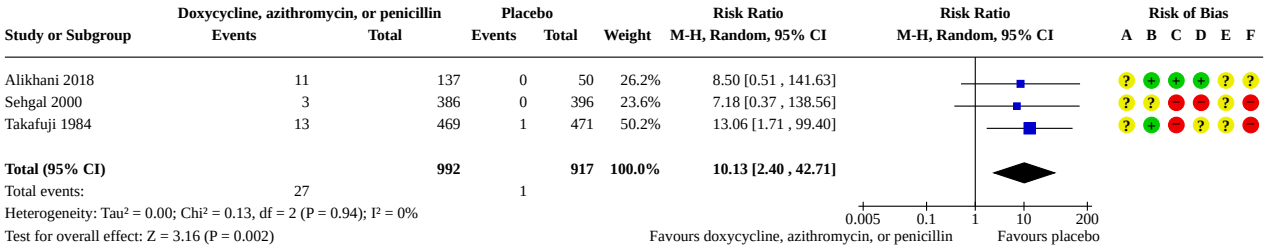


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.13. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 13: Sensitivity analysis: clinical diagnosis confirmed by laboratory diagnosis (worst-case scenario)

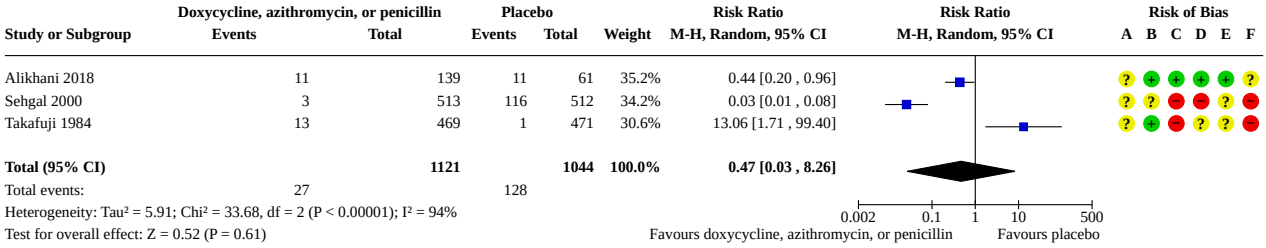


Analysis 1.14. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 14: Proportion of people with non-serious adverse events



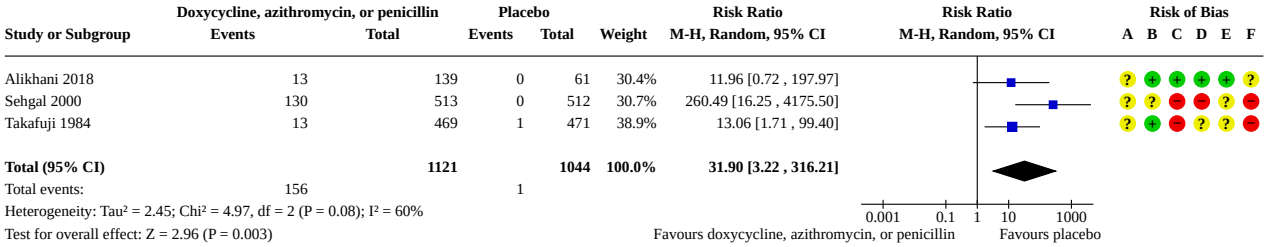
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.15. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 15: Sensitivity analysis: non-serious adverse events (best-case scenario)



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 1.16. Comparison 1: Antibiotics versus placebo or no intervention, Outcome 16: Sensitivity analysis: non-serious adverse events (worst-case scenario)



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. Antibiotic prophylaxis versus another antibiotic, or another dose, or schedule of the same antibiotic

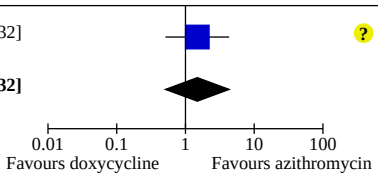
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Proportion of people with laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome (inclusive of asymptomatic cases)	1	137	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.51, 4.32]
2.2 Proportion of people with clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation	1	137	Risk Ratio (M-H, Fixed, 95% CI)	4.18 [0.94, 18.66]
2.3 Proportion of people with clinical diagnosis of leptospirosis confirmed by laboratory diagnosis (exclusive of asymptomatic cases)	1	137	Risk Ratio (M-H, Fixed, 95% CI)	4.18 [0.94, 18.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Proportion of people with non-serious adverse events	1	137	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.36, 3.48]

Analysis 2.1. Comparison 2: Antibiotic prophylaxis versus another antibiotic, or another dose, or schedule of the same antibiotic, Outcome 1: Proportion of people with laboratory-confirmed leptospirosis regardless of the presence of an identified clinical syndrome (inclusive of asymptomatic cases)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Azithromycin Events	Azithromycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Alikhani 2018	8	71	5	66	100.0%	1.49 [0.51 , 4.32]	?	+	+	+	?	?
Total (95% CI)		**71**		**66**	**100.0%**	**1.49 [0.51 , 4.32]**						
Total events:	8		5									

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable

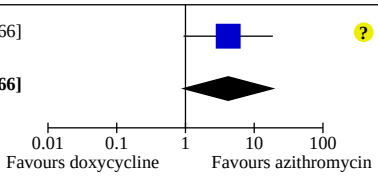


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Antibiotic prophylaxis versus another antibiotic, or another dose, or schedule of the same antibiotic, Outcome 2: Proportion of people with clinical diagnosis of leptospirosis regardless of the presence of laboratory confirmation

Study or Subgroup	Doxycycline Events	Doxycycline Total	Azithromycin Events	Azithromycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Alikhani 2018	9	71	2	66	100.0%	4.18 [0.94 , 18.66]	?	+	+	+	?	?
Total (95% CI)		**71**		**66**	**100.0%**	**4.18 [0.94 , 18.66]**						
Total events:	9		2									

Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)
Test for subgroup differences: Not applicable

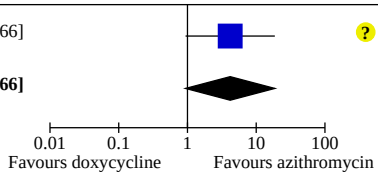


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Antibiotic prophylaxis versus another antibiotic, or another dose, or schedule of the same antibiotic, Outcome 3: Proportion of people with clinical diagnosis of leptospirosis confirmed by laboratory diagnosis (exclusive of asymptomatic cases)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Azithromycin Events	Azithromycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alikhani 2018	9	71	2	66	100.0%	4.18 [0.94 , 18.66]
Total (95% CI)		**71**		**66**	**100.0%**	**4.18 [0.94 , 18.66]**
Total events:	9		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)
Test for subgroup differences: Not applicable

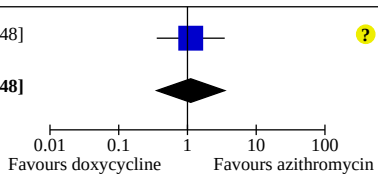


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Antibiotic prophylaxis versus another antibiotic, or another dose, or schedule of the same antibiotic, Outcome 4: Proportion of people with non-serious adverse events

Study or Subgroup	Doxycycline Events	Doxycycline Total	Azithromycin Events	Azithromycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alikhani 2018	6	71	5	66	100.0%	1.12 [0.36 , 3.48]
Total (95% CI)		**71**		**66**	**100.0%**	**1.12 [0.36 , 3.48]**
Total events:	6		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)
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

ADDITIONAL TABLES

Table 1. Adverse events (non-randomised study)

Study	Doxycycline		No intervention		Risk ratio
	Events	Total	Events	Total	M-H, Fixed, 95% CI
Chusri 2014	13	600	0	41	1.89 (0.11 to 31.19)

CI: confidence interval; M-H: Mantel-Haenszel.

APPENDICES

Appendix 1. Search strategies

Database	Timespan	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register (via the Cochrane Register of Studies Web)	17 April 2023	(prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*) 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 4	#1 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees #2 prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos* #3 #1 or #2 #4 MeSH descriptor: [Leptospirosis] explode all trees #5 (leptospir* or ((weil* or Swineherd*) and disease*) or (Stuttgart next disease*) or (hemorrhagic next jaundice) or (spirochetal next jaundice) or (((cane next cutter) or canicola or icterohemorrhagic or mud or (rice next field) or swamp) and fever)) #6 #4 or #5 #7 #3 and #6
MEDLINE Ovid	1946 to 17 April 2023	1. exp Antibiotic Prophylaxis/ 2. (prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 3. 1 or 2 4. exp Leptospirosis/ 5. (leptospir* or ((weil* or Swineherd*) and disease*) or Stuttgart disease* or hemorrhagic jaundice or spirochetal jaundice or ((cane cutter or canicola or icterohemorrhagic or mud or rice field or swamp) and fever)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 6. 4 or 5 7. 3 and 6 8. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. 9. clinical trials as topic.sh. 10. (random* or placebo*).ab. or trial.ti. 11. 8 or 9 or 10

(Continued)

		12. exp animals/ not humans.sh. 13. 11 not 12 14. 7 and 13
Embase Ovid	1974 to 17 April 2023	1. exp antibiotic prophylaxis/ 2. (prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword 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.

(Continued)

		22. (nonrandom$ not random$).ti,ab. 23. 'Random field$'.ti,ab. 24. (random cluster adj3 sampl$).ti,ab. 25. (review.ab. and review.pt.) not trial.ti. 26. 'we searched'.ab. and (review.ti. or review.pt.) 27. 'update review'.ab. 28. (databases adj4 searched).ab. 29. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 30. Animal experiment/ not (human experiment/ or human/) 31. or/18-30 32. 17 not 31 33. 7 and 32
LILACS (VHL Regional Portal)	1982 to 17 April 2023	((prophyla* OR prevent* OR protec* OR premedical* OR chemoprophyla* OR expos*)) 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 17 April 2023	#5 #3 AND #4 #4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=(leptospir* or ((weil* or Swineherd*) and disease*) or “Stuttgart disease*” or “hemorrhagic jaundice” or “spirochetal jaundice” or ((“cane cutter” or canicola or icterohemorrhagic or mud or “rice field” or swamp) and fever)) #1 TS=(prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*)
Conference Proceedings Citation Index – Science (Web of Science)	1990 to 17 April 2023	#5 #3 AND #4 #4 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #3 #2 AND #1 #2 TS=(leptospir* or ((weil* or Swineherd*) and disease*) or “Stuttgart disease*” or “hemorrhagic jaundice” or “spirochetal jaundice” or ((“cane cutter” or canicola or icterohemorrhagic or mud or “rice field” or swamp) and fever)) #1 TS=(prophyla* or prevent* or protec* or premedic* or chemoprophyla* or expos*)
World Health Organization International Clinical Trials Registry	April 2023	leptospirosis OR leptospira OR leptospir*

(Continued)

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

HISTORY

Protocol first published: Issue 2, 2022

CONTRIBUTIONS OF AUTHORS

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

TP: screening, writing of the review, and taking responsibility of reading and checking the review before submission.

PM: screening and data extraction.

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

TE: methodological expertise and advice, meta-analysis and writing of the review.

SMH: writing of risk of bias assessment and result.

HTM: risk of bias assessment.

DMB: clinical and methodological expertise and advice.

NL: writing of the review, and taking responsibility of reading and checking the review before submission.

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

DECLARATIONS OF INTEREST

TZW: none.

TP: none.

PM: none.

CS: none.

TE: none.

SMH: none.

HTM: none.

DMB: none.

NL: none.

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Internal sources

- Source of support, Japan

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

External sources

- Cochrane Hepato-Biliary, Denmark

  Provided help with the review preparation until publication, including the peer review process.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

Objective: we wrote the objective in a clearer way, from "To assess the beneficial and harmful effects of antibiotics for the prevention of leptospirosis" into "To evaluate the benefits and harms of antibiotic prophylaxis for human leptospirosis."

Measure of treatment effect: we planned to only conduct meta-analysis when the study group was sufficiently homogeneous. However, due to the limited number of included trials, we performed meta-analysis, although the study group was substantially heterogeneous. The included trials did not clearly report case definitions and methods of ascertainment for harm outcomes; therefore, we could not evaluate the consistency.

Sensitivity analysis: we prespecified sensitivity analysis by risk of bias and unpublished studies. However, the limited number of included trials did not favour performing the intended analysis. We applied sensitivity analyses by including only the trials of pre-exposure, the trials of postexposure, and the trials that were implemented amongst the endemic population.

Certainty of evidence: we planned that two review authors would grade the certainty of evidence, but due to the limited features in GRADEpro GDT, it was completed by only one review author. Other review authors agreed with the assessment.

Summary of findings table: we planned not to include non-serious adverse events in the summary of findings table. But we decided to include it since it is clinically important.

INDEX TERMS

Medical Subject Headings (MeSH)

*Anti-Bacterial Agents [adverse effects] [therapeutic use]; *Antibiotic Prophylaxis [adverse effects]; Bias; Doxycycline [adverse effects] [therapeutic use]; *Leptospirosis [prevention & control]; *Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans