Antibiotics for treating scrub typhus (Review)

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[Intervention Review]

Antibiotics for treating scrub typhus

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A B S T R A C T

Background

Scrub typhus, an important cause of acute fever in Asia, is caused by *Orientia tsutsugamushi,* an obligate intracellular bacterium. Antibiotics currently used to treat scrub typhus include tetracyclines, chloramphenicol, macrolides, and rifampicin.

Objectives

To assess and compare the effects of different antibiotic regimens for treatment of scrub typhus.

Search methods

We searched the following databases up to 8 January 2018: the Cochrane Infectious Diseases Group specialized trials register; CENTRAL, in the Cochrane Library (2018, Issue 1); MEDLINE; Embase; LILACS; and the *meta*Register of Controlled Trials (*m*RCT). We checked references and contacted study authors for additional data. We applied no language or date restrictions.

Selection criteria

Randomized controlled trials (RCTs) or quasi-RCTs comparing antibiotic regimens in people with the diagnosis of scrub typhus based on clinical symptoms and compatible laboratory tests (excluding the Weil-Felix test).

Data collection and analysis

For this update, two review authors re-extracted all data and assessed the certainty of evidence. We meta-analysed data to calculate risk ratios (RRs) for dichotomous outcomes when appropriate, and elsewhere tabulated data to facilitate narrative analysis.

Main results

We included six RCTs and one quasi-RCT with 548 participants; they took place in the Asia-Pacific region: Korea (three trials), Malaysia (one trial), and Thailand (three trials). Only one trial included children younger than 15 years (N = 57). We judged five trials to be at high risk of performance and detection bias owing to inadequate blinding. Trials were heterogenous in terms of dosing of interventions and outcome measures. Across trials, treatment failure rates were low.

Two trials compared doxycycline to tetracycline. For treatment failure, the difference between doxycycline and tetracycline is uncertain (very low-certainty evidence). Doxycycline compared to tetracycline may make little or no difference in resolution of fever within 48 hours (risk ratio (RR) 1.14, 95% confidence interval (CI) 0.90 to 1.44, 55 participants; one trial; low-certainty evidence) and in time to defervescence (116 participants; one trial; low-certainty evidence). We were unable to extract data for other outcomes.

Three trials compared doxycycline versus macrolides. For most outcomes, including treatment failure, resolution of fever within 48 hours, time to defervescence, and serious adverse events, we are uncertain whether study results show a difference between doxycycline and macrolides (very low-certainty evidence). Macrolides compared to doxycycline may make little or no difference in the proportion of patients with resolution of fever within five days (RR 1.05, 95% CI 0.99 to 1.10; 185 participants; two trials; low-certainty evidence). Another trial compared azithromycin versus doxycycline or chloramphenicol in children, but we were not able to disaggregate date for the doxycycline/chloramphenicol group.

One trial compared doxycycline versus rifampicin. For all outcomes, we are uncertain whether study results show a difference between doxycycline and rifampicin (very low-certainty evidence). Of note, this trial deviated from the protocol after three out of eight patients who had received doxycycline and rifampicin combination therapy experienced treatment failure.

Across trials, mild gastrointestinal side effects appeared to be more common with doxycycline than with comparator drugs.

Authors' conclusions

Tetracycline, doxycycline, azithromycin, and rifampicin are effective treatment options for scrub typhus and have resulted in few treatment failures. Chloramphenicol also remains a treatment option, but we could not include this among direct comparisons in this review.

Most available evidence is of low or very low certainty. For specific outcomes, some low-certainty evidence suggests there may be little or no difference between tetracycline, doxycycline, and azithromycin as treatment options. Given very low-certainty evidence for rifampicin and the risk of inducing resistance in undiagnosed tuberculosis, clinicians should not regard this as a first-line treatment option. Clinicians could consider rifampicin as a second-line treatment option after exclusion of active tuberculosis.

Further research should consist of additional adequately powered trials of doxycycline versus azithromycin or other macrolides, trials of other candidate antibiotics including rifampicin, and trials of treatments for severe scrub typhus. Researchers should standardize diagnostic techniques and reporting of clinical outcomes to allow robust comparisons.

11 April 2019

Up to date

All studies incorporated from most recent search

All eligible published studies found in the last search (8 Jan, 2018) were included and four ongoing studies have been identified (see 'Characteristics of ongoing studies' section)

PLAIN LANGUAGE SUMMARY

Antibiotics for treating scrub typhus

What is the aim of this review?

The aim of this Cochrane Review is to find out whether certain antibiotics are more effective in treating scrub typhus. We collected and analysed all relevant studies to answer this question and included seven studies.

Key messages

Tetracycline, doxycycline, azithromycin, and rifampicin are effective antibiotics for scrub typhus treatment that have led to few treatment failures. For specific outcomes, some low-certainty evidence suggests there may be little or no difference between tetracycline, doxycycline, and azithromycin. Healthcare workers should not use rifampicin as a first-line treatment. Researchers should standardize the way they diagnose and assess scrub typhus.

What was studied in the review?

Scrub typhus is an important cause of fever in Asia. We studied people with scrub typhus diagnosed by health professionals and confirmed by laboratory tests. We compared different antibiotic treatments. We looked at whether choice of antibiotic made a difference in the number of people who experienced failed treatment, and we determined the proportions who had resolution of fever at 48 hours.

What are the main results of the review?

We found seven relevant studies. Only one study included children younger than 15 years.

We are uncertain whether doxycycline compared to tetracycline affects treatment failure, as the certainty of the evidence is very low. Studies looked at resolution of fever within five days. Doxycycline compared to tetracycline may make little or no difference in the proportion of patients with resolution of fever within 48 hours and in time to defervescence. Studies did not formally report serious adverse events.

We are uncertain whether macrolides compared to doxycycline affect treatment failure, resolution of fever within five days, time to defervescence, or serious adverse events, as the certainty of the evidence is very low. Macrolides compared to doxycycline may make little or no difference in the proportion of patients with resolution of fever within five days.

We are uncertain whether rifampicin compared to doxycycline affects treatment failure, proportion of patients with resolution of fever within 48 hours, or time to defervescence, as the certainty of evidence is very low. The single study that performed this comparison did not look at resolution of fever within five days and did not formally report serious adverse events.

How up-to-date is this review?

We searched for studies that had been published up to 8 January 2018.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.   Doxycycline compared to tetracycline for treating scrub typhus

Doxycycline compared to tetracycline for treating scrub typhus

Patient or population: adults with scrub typhus

Settings: hospitals in endemic areas

Intervention: doxycycline 200 mg single oral dose (Brown 1978), doxycycline oral 100 mg 12-hourly for 3 days (Song 1995)

Comparison: tetracycline 500 mg 6-hourly for 7 days (Brown 1978), tetracycline oral 500 mg 12-hourly for 7 days (Song 1995)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with tetracycline	**Risk with doxycycline**				
Treatment failure	0 events in 50 participants	4 events in 66 participants	RR 6.85 (0.38 to 124.38)	116 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b] Due to risk of bias and imprecision	We are uncertain whether doxycycline compared to tetracycline affects treatment failure, as the certainty of the evidence is very low.
Resolution of fever within 48 hours	792 per 1000	902 per 1000 (713 to 1000)	RR 1.14 (0.90 to 1.44)	55 (1 RCT)	⊕⊕⊖⊖ LOW[c,d] Due to risk of bias and imprecision	Doxycycline compared to tetracycline may make little or no difference in the proportions of patients with resolution of fever within 48 hours.
Resolution of fever within 5 days	Not reported					Neither of the studies looked at resolution of fever within 5 days.
Time to defervescence	Mean 37 hours, SD 26.6 hours	Mean 34 hours, SD 26.5 hours	-	116 (1 RCT)	⊕⊕⊖⊖ LOW[a,e] Due to risk of bias and imprecision	Doxycycline compared to tetracycline may make little or no difference in time to defervescence.
Serious adverse events	Not formally reported					

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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; SD: standard deviation.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

[a]Downgraded by 1 due to serious risk of bias. Song 1995 had unclear allocation concealment and was not blinded.
[b]Downgraded by 2 due to very serious imprecision. Sample size and number of events were small and did not meet optimal information size.
[c]Downgraded by 1 due to serious risk of bias. Brown 1978 had high risk of attrition bias, although this was not likely to differentially affect treatment groups, and unclear risk of bias from sequence generation, allocation concealment, and blinding.
[d]Downgraded by 1 due to serious imprecision. The 95% CI overlaps no effect (that is, CI includes RR of 1.0), and the CI fails to exclude appreciable benefit.
[e]Downgraded by 1 for serious imprecision: Song 1995 was underpowered to detect this effect.

Summary of findings 2.   Macrolides compared to doxycycline for treating scrub typhus

Macrolides compared to doxycycline for treating scrub typhus

Patient or population: adults and adolescents with scrub typhus

Settings: hospitals in endemic areas

Intervention: doxycycline 200 mg per day for 7 days (Kim 2004; Phimda 2007); doxycycline 200 mg per day for 5 days (Kim 2007)
Comparison: azithromycin 500 mg single oral dose (Kim 2004); telithromycin 800 mg daily for 5 days (Kim 2007); azithromycin 1 g daily for 3 days, followed by 500 mg daily for 2 days (Phimda 2007)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with doxycycline	**Risk with macrolides**				
Treatment failure	Assumed risk: 19 per 1000[a]	51 per 1000 (2 to 1000)	RR 2.71 (0.12 to 63.84)	242 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[b,c] Due to risk of bias and imprecision	We are uncertain whether macrolides compared to doxycycline affect treatment failure, as the certainty of the evidence is very low.

Resolution of fever within 48 hours	671 per 1000	544 per 1000 (215 to 1000)	RR 0.81 (0.32 to 2.03)	150 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[b,d] Due to risk of bias, imprecision, and inconsistency	We are uncertain whether macrolides compared to doxycycline affects the proportion of patients with resolution of fever within 48 hours.
Resolution of fever within 5 days	956 per 1000	1000 per 1000 (946 to 1000)	RR 1.05 (0.99 to 1.10)	185 (2 RCTs)	⊕⊕⊖⊖ LOW[b,e] Due to risk of bias and inconsistency	Macrolides compared to doxycycline may make little or no difference in the proportion of patients with resolution of fever within 5 days.
Time to defervescence	Each included study detected no significant difference between groups.			242 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[b,d] Due to risk of bias and inconsistency	We are uncertain whether macrolides compared to doxycycline affect time to defervescence, as the certainty of the evidence is very low.
Serious adverse events	No included trial reported serious adverse events.			242 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[b,c] Due to risk of bias and imprecision	We are uncertain whether macrolides compared to doxycycline affects serious adverse events, as the certainty of the evidence is very low.

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RCT: randomized controlled trial; 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

[a]Derived from risk across all included trials in patients treated with doxycycline (four events in 212 patients).
[b]Downgraded by 1 due to serious risk of bias: all three included trials were open-label; Kim 2007 was quasi-randomized.
[c]Downgraded by 2 due to very serious imprecision: sample size and number of events were small, and confidence intervals cross the line of no effect. Two trials reported no events in either treatment arm, so they do not contribute to the risk ratio.
[d]Downgraded by 2 due to very serious inconsistency: data show quantitative and qualitative inconsistency between trials.
[e]Downgraded by 1 due to serious inconsistency: Kim 2004 gave azithromycin as a single oral dose; Kim 2007 gave telithromycin for five days.

Summary of findings 3.   Rifampicin compared to doxycycline for treating scrub typhus

Rifampicin compared to doxycycline for treating scrub typhus

Patient or population: adults with scrub typhus

Settings: hospitals in endemic areas

Intervention: rifampicin

Comparison: doxycycline

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	doxycycline	**rifampicin**				
Treatment failure	The included reported no treatment failures.		-	78 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b] Due to risk of bias and imprecision	We are uncertain whether rifampicin compared to doxycycline affects treatment failure, as the certainty of the evidence is very low.
Resolution of fever within 48 hours	464 per 1000	780 per 1000 (510 to 1000)	RR 1.68 (1.10 to 2.57)	78 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,c] Due to risk of bias and imprecision	We are uncertain whether rifampicin compared to doxycycline affects the proportion of patients with resolution of fever within 48 hours, as the certainty of the evidence is very low.
Resolution of fever within 5 days	Not reported					The study did not look at resolution of fever within 5 days.
Time to defervescence	Study authors report that time to defervescence was less with rifampicin.		-	78 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,c] Due to risk of bias and imprecision	We are uncertain whether rifampicin compared to doxycycline affects time to defervescence, as the certainty of the evidence is very low.
Serious adverse events	Not formally reported					

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

[a]Downgraded by 2 due to very serious risk of bias. In Watt 2000, sequence generation, allocation concealment, and blinding were unclear; risk of attrition bias with incomplete follow-up was high (67.8%), as was risk of other bias due to deviation from the trial protocol.
[b]Downgraded by 2 due to very serious imprecision. Number of events is very small and does not meet optimum information size (< 300 events), and the sample size is small.
[c]Downgraded by 1 due to serious imprecision. The sample size is small.

BACKGROUND

Description of the condition

Scrub typhus is an important cause of acute fever in Asia. It is caused by *Orientia tsutsugamushi* (formerly *Rickettsia tsutsugamushi)*, an obligate intracellular bacterium in the order Rickettsia. This bacterium is transmitted in the bite of larvae of the *Leptotrombidium* mite, commonly called chiggers, which form the reservoir. Clinical features are non-specific and include fever, headache, and myalgia (Watt 2003). An eschar, an ulcerated lesion with a black crust, may develop at the site of the bite. The frequency of eschar formation varies across populations from 7% to 80%. Scrub typhus may lead to pneumonia, shock, meningoencephalitis, renal failure, or myocarditis (Griffith 2014). Disease severity appears to be related to the virulence of the *O tsutsugamushi* strain, patient age, patient genetic factors, and previous infections, but literature regarding prognostic factors is limited (Rajapakse 2012). For untreated scrub typhus, median mortality is 6% (range 0 to 70%) (Taylor 2015). With treatment, median mortality is 1.4% (range 0 to 33.3%) (Bonell 2017).

As *O tsutsugamushi* is intracellular, it cannot be isolated via standard bacterial culture but instead requires cell culture. Therefore, the main modalities for diagnosis of scrub typhus are nucleic acid amplification tests (for example, polymerase chain reaction (PCR)) and serology (including immunofluorescence assays (IFAs), rapid diagnostic tests (RDTs), and enzyme-linked immunosorbent assay (ELISA)). The historical mainstay of diagnosis has been indirect immunofluorescence assay, but this is limited by subjectivity and a requirement for paired acute and convalescent sera. Increasingly, ELISA tests are replacing IFAs, as they are more sensitive, specific, and reproducible. Real-time PCR on blood or eschar biopsy is helpful in diagnosing early-stage infection (Paris 2016). In some resource-limited settings, the only serological test available is the Weil-Felix test, a non-specific antibody agglutination test that cannot distinguish *O tsutsugamushi* from other Rickettsial infections (Koralur 2018).

Scrub typhus is endemic to Asia-Pacific. Most cases occur in a region traditionally known as the 'tsutsugamushi triangle', which extends from Japan to India, and to Northern Australia. Incidence varies across the region, ranging from 1.2 to 17.7 per 100,000 per year. Seroprevalence similarly varies, ranging from 9.3% to 27.9% (Bonell 2017). In the Mekong region, scrub typhus represents the second most common cause of non-malarial febrile illness after dengue (Acestor 2012). Infection classically occurs when humans encroach upon 'mite islands' - discrete areas where infected chiggers are found. For this reason, cases often occur in association with land clearing, logging, or military operations; in rice fields; and during outdoor travel activities (Watt 2003).

Description of the intervention

Antibiotics currently recommended to treat scrub typhus include the following (CDC 2017).

- Tetracyclines: doxycycline 100 mg twice per day for one week. In clinical practice, this is favoured over tetracycline owing to convenience of the dosing schedule.
- Chloramphenicol.
- Macrolides: azithromycin.
- Rifampicin.

A previous version of this review also identified fluoroquinolones as a possible alternative treatment (Liu 2002).

How the intervention might work

Doxycycline historically has been the mainstay of treatment across the rickettsial diseases, including scrub typhus. Given the difficulties associated with cell culture, there is a relative paucity of in vitro susceptibility data needed to provide a theoretical basis for its use. Chloramphenicol is the traditional second-line treatment and was one of the first drugs found to be effective (Smadel 1950).

Several reports have indicated suspected doxycycline resistance inferred by treatment failures in cohort studies such as Thipmontree 2016, or due to acquisition of scrub typhus during doxycycline malaria prophylaxis (Corwin 1999). However, few studies have correlated clinical evidence suggesting drug resistance with in vitro data, possibly because of the difficulty involved in culturing *O tsutsugamushi*. Watt 1996 studied 19 patients with scrub typhus and through mouse fibroblast cell culture identified one isolate as doxycycline-resistant and another isolate as showing partial resistance; these findings correlated with attenuated therapeutic response. Whole-genome sequencing has indicated the presence of putative resistance genes, but evaluating their potential to mediate resistance is challenging (Kelly 2017). Overall, we found uncertain evidence to support the existence or clinical significance of doxycycline resistance in *O tsutsugamushi,* and this remains a public health concern.

Fluoroquinolones such as ciprofloxacin have been used; however, one in vitro study indicates that *O tsutsugamushi* may be intrinsically resistant to these antibiotics (Tantibhedhyangkul 2010).

Why it is important to do this review

This is an update of a Cochrane Review first published in 2000 (Panpanich 2000), and later updated (Liu 2002), which identified seven small trials and presented several limited conclusions.

The review authors concluded that rifampicin seemed to be more effective than doxycycline in areas where scrub typhus responds poorly to standard drugs; they based these conclusions on data from one study (Watt 2000). A recent non-Cochrane systematic review performed an analysis of the same study and reached a different conclusion (Wee 2017), cautioning against interpreting the results in favour of rifampicin. The disagreement marked an important reason to update this review. Since the last update in 2002, the review process has become more sophisticated. This updated review is improved by GRADE methods and 'Summary of findings' tables, which enable more conclusions and provide clear indications to the reader regarding the certainty of evidence presented. Wee 2017 did not use GRADE methods.

Scrub typhus remains an important cause of morbidity in endemic areas, and choice of antibiotic remains a topical clinical question.

OBJECTIVES

To assess and compare the effects of different antibiotic regimens for treatment of scrub typhus.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We searched for all relevant randomized controlled trials (RCTs) and quasi-RCTs. We define quasi-RCTs as those using an allocation method that is not truly random (for example, based on date of birth).

Types of participants

Trials had to include people with a diagnosis of scrub typhus based on clinical symptoms and compatible laboratory tests, including the following.

- Serology (IFA, ELISA, RDT).
- Nucleic acid amplification (PCR).
- Isolation (cell culture).

Given the poor specificity of the Weil-Felix test, we excluded studies that used this as the sole measure to confirm the diagnosis.

Types of interventions

Interventions

Anti-rickettsial antibiotics, irrespective of route of administration, dose, dose frequency, or course duration.

Controls

Other anti-rickettsial antibiotics. We excluded studies comparing interventions versus placebo or no drug as it is clear antibiotics are effective. We planned to include trials that provided additional interventions to all treatment arms, but we did not encounter such trials.

Types of outcome measures

Primary outcomes

- Treatment failure, defined as persistence of symptoms at the end of the treatment course.
- Resolution of fever within 48 hours.

Secondary outcomes

- Resolution of fever within five days.
- Time to defervescence
  * Defined as the time interval between administration of the first dose of antibiotic and the first time at which temperature was less than 37.5°C and was thereafter maintained for > 48 hours.
- Serious adverse events.
- Frequency and types of reported adverse events.

Search methods for identification of studies

We performed a comprehensive search to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and ongoing) up to 8 January 2018.

Electronic searches

We searched the following databases using the search terms and strategy detailed in Table 1.

- Cochrane Infectious Diseases Group Specialized Register.
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library (2018, Issue 1).
- MEDLINE (1966 to January 2018).
- Embase (1980 to January 2018).
- Latin American Caribbean Health Sciences Literature (LILACS) (1982 to January 2018).

We searched the *meta*Register of Controlled Trials (*m*RCT) using ''scrub typhus'' OR ''orientia tsutsugamushi'', "antibiotics" OR ''antimicrobial therapy'' as search terms. The search strategy remains unchanged since the previous version of the protocol was prepared.

Searching other resources

Reference lists

To identify additional published, unpublished, and ongoing studies, we checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

For this update, two review authors (IES and IW) independently screened search results to identify potentially relevant trials and obtained the full-text reports of these trials. For English language studies, IES and IW then used a standard eligibility form to assess newly identified studies and to re-assess previously included studies against inclusion and exclusion criteria. For Chinese language studies, IW and QL followed the same process. We resolved disagreements by discussion with a third review author (PH). We documented reasons for excluding trials in the Characteristics of excluded studies table. We scrutinized each trial report to ensure that we did not include multiple publications from the same trial.

Data extraction and management

Three review authors (IES, QL, and IW) independently extracted data onto a data extraction form (modified from previous versions of this review). We extracted information on study design, setting, population, diagnostic criteria, antibiotic regimen (dose, route, duration, timing, and frequency), total numbers randomized, number of participants in each group, numbers lost to follow-up, duration of follow-up, dates of the study, funding source, and withdrawals from each group. We encountered no disagreements.

For dichotomous data, we extracted the number of participants who experienced the event of interest and the number of participants randomized and analysed in each group.

For continuous outcomes, we extracted mean values, standard deviations, and number of participants in each group for whom the outcome was assessed. When medians were reported, we extracted ranges or interquartile ranges. When data were incomplete, we contacted trial authors to request additional data.

Assessment of risk of bias in included studies

Three review authors (IES, QL, and IW) independently assessed potential biases of included studies using a prepared form and the Cochrane 'Risk of bias' tool (Higgins 2011). For each domain,

we described what trial authors reported and made a subjective judgement for each domain as having 'high, low, or unclear' risk of bias. We resolved discrepancies by discussion and reached agreement. We included all assessments in a 'Risk of bias' graph and a 'Risk of bias' summary figure. We provided in the Results section a narrative description of our risk of bias conclusions for each domain of all included studies.

We assessed the following domains for each study: sequence generation, allocation concealment, blinding or masking, incomplete outcome data, selective outcome reporting, and other sources of bias.

Sequence generation

We described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We considered trials as having low risk of bias if the investigator described a random component of sequence generation (for example, a random number table, a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing lots, minimization); high risk of bias if sequence generation was non-random (for example, sequence generated by odd or even date of birth, some rule based on date (or day) of admission, some rule based on hospital or clinic record number); or unclear risk of bias if the randomization process was not clearly described.

Allocation concealment

We assessed whether participants and investigators enrolling participants could foresee assignment. We judged this domain as having low risk of bias if the investigator used central allocation (including telephone-based, web-based, and pharmacy-controlled randomization), sequentially numbered drug containers of identical appearance, or sequentially numbered opaque, sealed envelopes to conceal allocation; high risk of bias if the allocation process was not concealed (for example, open randomization, unsealed or non-opaque envelopes); or unclear risk of bias if study authors did not describe the process of concealing allocation sufficiently to permit a judgement.

Blinding of participants or personnel

We described whether blinding was done and who was blinded. We regarded a trial as having low risk of performance bias if blinding was done; high risk of bias if blinding was not done and this was likely to affect the results; or unclear risk of bias if study authors did not clearly describe blinding.

Blinding of outcome assessment

We described knowledge of allocated interventions by outcome assessors. All primary and secondary outcomes in our review are subjective. So, we judged trials as having low risk of detection bias if blinding of outcome assessment was ensured and it was unlikely that the blinding could have been broken; high risk of detection bias if no blinding of outcome assessment was performed; or unclear risk of detection bias if study authors did not adequately describe this domain to allow a judgement of 'low risk' or 'high risk'.

Incomplete outcome data

We assessed the proportions of missing outcome data between different groups. We judged trials as having a low level of attrition

bias if the proportion of participants lost to follow-up was < 10%, or if missing outcome data were balanced in numbers across intervention groups, with similar reasons provided for missing data across groups. We regarded trials as having high risk of attrition bias if the proportion of participants lost to follow-up was > 10%, or if reasons for missing outcome data were likely to be related to true outcomes, with imbalance in numbers or reasons for missing data across intervention groups. We judged trials as having unclear risk of attrition bias if study authors did not adequately describe this domain to permit a judgement of 'low risk' or 'high risk'.

Selective outcome reporting

We determined that if published reports included all expected outcomes, including those prespecified in the Methods section, then those trials had low risk of bias. We considered trials to have high risk of bias if not all of the study's prespecified primary outcomes were reported; if one or more primary outcomes were reported through measurement or analysis methods that were not prespecified; or if one or more reported primary outcomes were not prespecified.

Other sources of bias

We assessed other potential sources of bias related to the specific study design used, baseline imbalance, and deviation from the trial protocol.

Measures of treatment effect

We calculated the risk ratio (RR) for dichotomous outcomes. We presented all measures with corresponding 95% confidence intervals (CIs). When we assessed the data, we regarded time to defervescence as a time-to-event outcome, as we were not certain whether all participants experienced this outcome. We therefore decided it was inappropriate to analyse time to defervescence using methods for continuous outcomes. We were unable to extract the log hazard ratio and its standard error from Cox proportional hazards models; therefore we did not combine this outcome in the meta-analysis but instead presented a narrative analysis.

Unit of analysis issues

We did not encounter unit of analysis issues.

Dealing with missing data

We extracted data to allow an intention-to-treat analysis in which all randomized participants were analysed in the groups to which they were originally assigned, outcome data were provided on all participants, and all randomized participants were included in the analysis. For three included studies (Brown 1978; Song 1995; Watt 2000), we tried to contact the study authors to request missing data. We emailed the corresponding author for one study (Watt 2000), but we did not receive a reply. We did not find email addresses for corresponding authors for two included studies (Brown 1978; Song 1995). We then conducted a complete-case analysis and included in the analysis only participants with a recorded outcome.

Assessment of heterogeneity

We visually inspected forest plots that displayed overlapping confidence intervals for two or more studies as an indicator of clinical heterogeneity. We assessed statistical heterogeneity using Chi² and I² tests. We considered a Chi² test P value < 0.1 and an I² statistic value > 75% as indicating substantial heterogeneity.

Assessment of reporting biases

We planned to investigate potential publication bias by using a funnel plot if at least 10 studies met the inclusion criteria of the review.

Data synthesis

We analysed the data using Review Manager 5 (RevMan 5) (RevMan 2014). We used a fixed-effect model and Mantel-Haenszel methods if we noted no heterogeneity. Otherwise, we used a random-effects model and Mantel-Haenszel methods for significant heterogeneity.

Certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach (Schünemann 2013). We appraised the certainty of evidence in relation to the following criteria.

- Study design.
- Risk of bias.
- Inconsistency.
- Indirectness.
- Imprecision.
- Other considerations (including publication bias).

We used GRADEpro GDT software to create 'Summary of findings' tables for comparisons included in the review (GRADEpro 2015). We included our primary outcomes and used these tables to guide our conclusions.

Subgroup analysis and investigation of heterogeneity

We planned to investigate heterogeneity by conducting prespecified subgroup analyses for primary outcomes, according to the following potential sources.

- Geographical setting, which may influence antibiotic susceptibility.

- Date of the study (before or after antibiotic resistance was first reported).
- Participant age (children versus adults).
- Dose, frequency, and duration of treatment.

However, the number of included studies for each comparison was not sufficient to permit subgroup analysis.

Sensitivity analysis

We planned to assess the robustness of summary estimates by restricting analysis to studies with low risk of bias, especially in terms of allocation concealment and low incomplete follow-up (< 10%), but the number of included studies was not sufficient.

R E S U L T S

Description of studies

Results of the search

The previous version of this review included seven studies. We re-screened these according to our eligibility criteria and excluded one previously included study, as those researchers used only the Weil-Felix test for laboratory diagnosis (Sheehy 1973).

Through the updated literature search on 8 January 2018, we identified 128 references. We excluded 36 duplicate records and excluded 81 of the remaining 92 references after title and abstract screening. We assessed 12 full-text articles for eligibility, from which we excluded 10 articles (see Characteristics of excluded studies). One new study - Chanta 2015 - met the inclusion criteria, in addition to six previously included studies (see Characteristics of included studies), and two new ongoing trials met these criteria (see Characteristics of ongoing studies). In total, seven studies (in seven publications) met the inclusion criteria of this review (Figure 1).

Figure 1. PRISMA flow diagram.
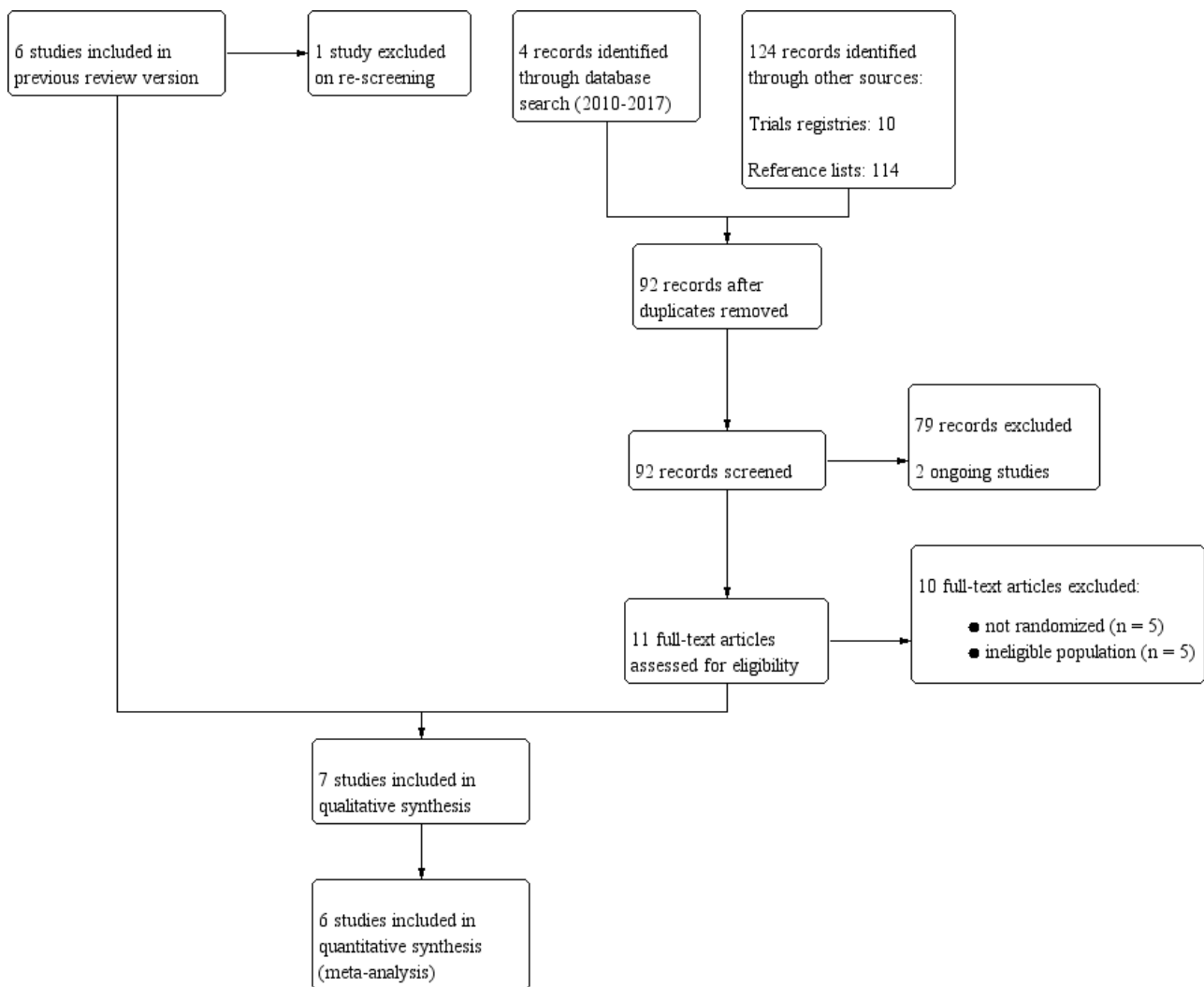
Included studies

Seven studies met our inclusion criteria (see Characteristics of included studies).

Six were RCTs (Brown 1978; Chanta 2015; Kim 2004; Phimda 2007; Song 1995; Watt 2000), and one was a quasi-RCT (Kim 2007). These studies contributed 548 participants to this review.

All studies took place within hospital settings, located in Korea (three trials), Malaysia (one trial), and Thailand (three trials).

The point at which participants were randomized varied between studies.

- One study randomized patients with acute undifferentiated fever (Phimda 2007).
- Four studies randomized patients with clinically suspected scrub typhus (Brown 1978; Kim 2004; Kim 2007; Song 1995).
- Two studies randomized patients after a positive RDT (Chanta 2015; Watt 2000).

The number of randomized participants ranged from 57 in Chanta 2015, to 296 in Phimda 2007. Five studies recruited adults only (n =

434); one study recruited people aged 14 and over (n = 57; Phimda 2007); and one study recruited children under the age of 15 (n = 57; Chanta 2015). All studies recruited males and females.

Four studies confirmed diagnosis using IFA only (Kim 2004; Kim 2007; Phimda 2007; Song 1995); one study confirmed diagnosis using IFA, agglutination testing, or isolation (Brown 1978); one study used only screening RDT for laboratory confirmation (Chanta 2015); and another study used screening RDT followed by confirmatory indirect immunoperoxidase (Watt 2000).

Two trials compared doxycycline and tetracycline (Brown 1978; Song 1995); and four trials compared doxycycline versus a macrolide (Chanta 2015; Kim 2004; Kim 2007; Phimda 2007). Chanta 2015 investigated children and used chloramphenicol in place of doxycycline for children under the age of eight but did not report results for chloramphenicol and doxycycline separately. One trial compared doxycycline alone, rifampicin alone at low and high doses, and doxycycline and rifampicin in combination (Watt 2000).

Included studies reported a variety of outcome measures and used different terminology to incorporate similar categories. With respect to our primary outcomes:

- treatment failure: six studies provided data (Chanta 2015; Kim 2004; Kim 2007; Phimda 2007; Song 1995; Watt 2000). Definitions of treatment failure varied according to the persistence of fever and/or symptoms at time points including 48 hours, 72 hours, and after treatment completion; and

- resolution of fever within 48 hours: two studies provided data (Brown 1978; Watt 2000).

With respect to our secondary outcomes:

- resolution of fever within five days: three studies provided data (Kim 2004; Kim 2007; Phimda 2007);

- time to defervescence: six studies provided data (Chanta 2015; Kim 2004; Kim 2007; Phimda 2007; Song 1995; Watt 2000); and

- adverse events: all studies provided data.

Excluded studies

We excluded 13 studies (see Characteristics of excluded studies) for the following reasons: five studies were retrospective and confirmed laboratory diagnosis via the Weil-Felix test only; four studies had an unclear study design and confirmed laboratory diagnosis via the Weil-Felix test only; two studies assessed antibiotics for preventing rather than treating scrub typhus; and two studies confirmed laboratory diagnosis via the Weil-Felix test only, one of which was included in the previous version of this review (Sheehy 1973).

Risk of bias in included studies

See Figure 2 for a summary of the 'Risk of bias' assessments. Further details are available in the Characteristics of included studies table.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

We judged four studies to have low risk of selection bias because they adequately described generation of allocation sequences (Chanta 2015; Kim 2004; Phimda 2007; Song 1995). We judged one study as having high risk of selection bias because researchers randomized participants according to the last digit of a registration number (Kim 2007). We judged two studies to have unclear risk of selection bias as study authors did not provide sufficient information (Brown 1978; Watt 2000).

Allocation concealment was unclear in all trials except one, which used an opaque and numbered envelope for allocation concealment (Phimda 2007).

Blinding

Five studies were open-label and provided inadequate blinding of participants and providers. We judged these studies as having high risk of performance and detection bias (Chanta 2015; Kim 2004; Kim 2007; Phimda 2007; Song 1995). Description of blinding was unclear in Brown 1978 and Watt 2000.

Incomplete outcome data

We assessed five trials to be at low risk of attrition bias (Chanta 2015; Kim 2004; Kim 2007; Phimda 2007; Song 1995). Chanta 2015 and Kim 2007 had no missing data; in Phimda 2007, missing data

were balanced between different groups; and in Kim 2004 and Song 1995, small percentages of participants were lost to follow-up.

We considered two trials as having high risk of attrition bias because large numbers of participants from both intervention and control arms were lost to follow-up (> 10%) (Brown 1978; Watt 2000).

Selective reporting

We judged all trials as having low risk of reporting bias. These trials adequately reported all prespecified primary and secondary outcomes.

Other potential sources of bias

All trials reported comparable baseline characteristics between groups of participants. We judged one trial to have high risk of bias owing to deviation from the protocol (Watt 2000); in one arm, participants were initially randomized to receive combined doxycycline and rifampicin therapy; and treatment failure occurred in three of eight participants receiving combination therapy.

Effects of interventions

See: **Summary of findings for the main comparison** Doxycycline compared to tetracycline for treating scrub typhus; **Summary of findings 2** Macrolides compared to doxycycline for treating scrub typhus; **Summary of findings 3** Rifampicin compared to doxycycline for treating scrub typhus

Comparison 1: doxycycline versus tetracycline

Two trials compared doxycycline with tetracycline (Brown 1978; Song 1995).

One trial reported treatment failure (Song 1995); results show no significant differences between doxycycline and tetracycline (116 participants, 1 trial; Analysis 1.1).

One trial reported the proportion of participants with resolution of fever within 48 hours (Brown 1978); data show little or no difference between doxycycline and tetracycline (risk ratio (RR) 1.14, 95% confidence interval (CI) 0.90 to 1.44; 55 participants, 1 trial; Analysis 1.2).

Neither trial reported proportions of participants with resolution of fever within five days.

One trial reported mean time to defervescence (Song 1995). Results show a mean of 37 hours (standard deviation (SD) ± 26.6 hours) for the tetracycline group and a mean of 34 hours (SD ± 26.5 hours) for the doxycycline group. Study authors reported that the difference was non-significant via the log-rank test.

Both trials discussed adverse events but did not formally report the presence or absence of serious adverse events. Gastrointestinal symptoms occurred more frequently with doxycycline than with tetracycline in both trials (not meta-analysed; Table 2).

Comparison 2: macrolides versus doxycycline

Three trials compared macrolide antibiotics with doxycycline (Kim 2004; Kim 2007; Phimda 2007).

All three trials reported treatment failure; meta-analysis of this outcome revealed no significant differences between macrolides and doxycycline (242 participants, 3 RCTs; Analysis 2.1). In two of these trials (Kim 2004; Kim 2007), data show no treatment failures in either arm, and these data did not contribute to the risk ratio in meta-analysis.

Two trials reported the proportion of participants with resolution of fever within 48 hours (Kim 2007; Phimda 2007). Meta-analysis revealed no differences between macrolides and doxycycline but showed quantitative and qualitative heterogeneity between trials (150 participants, 2 RCTs; Analysis 2.2).

Two trials reported the proportion of participants with resolution of fever within five days (Kim 2004; Kim 2007); results show little or no difference between groups (RR 1.05, 95% CI 0.99 to 1.10; 185 participants, 2 RCTs; Analysis 2.3; Figure 3).

Figure 3.   Forest plot of comparison: 2 Macrolides versus doxycycline, outcome: 2.3 Resolution of fever within five days.
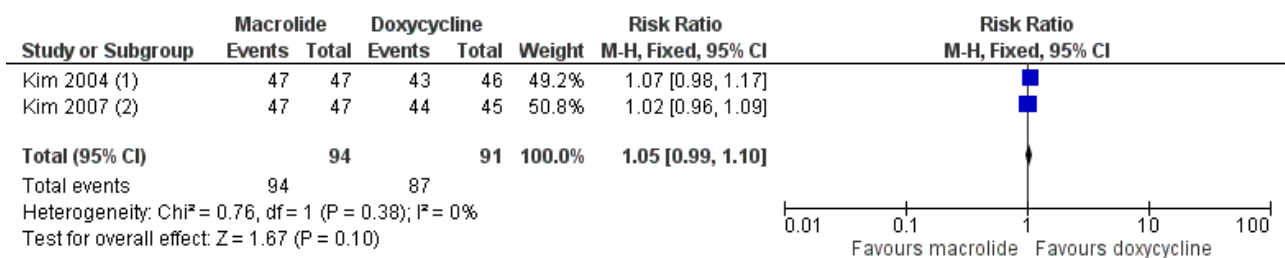
Footnotes
(1) Azithromycin 500mg one dose versus Doxycycline 200mg once daily for 7 days.
(2) Telithromycin 800mg once daily for 5 days versus Doxycycline 200mg once daily for 5 days.

All three trials reported time to defervescence as median times with ranges, which we have presented in Table 3. Between studies, median times ranged from 18 to 45 hours; within studies, ranges were also wide. The included studies detected no statistically significant differences between groups.

All three trials reported that no serious adverse events occurred across treatment arms (242 participants, 3 RCTs; Analysis 2.4). Gastrointestinal symptoms occurred more frequently with doxycycline than with macrolides in all three trials (not meta-analysed; Table 2).

Subgroup analysis restricted to macrolide subtypes (azithromycin, telithromycin) did not indicate significant differences between findings (Analysis 5.1 to Analysis 6.3).

Comparison 2a: macrolides versus doxycycline/chloramphenicol

In addition to the three trials comparing macrolide antibiotics with doxycycline, one trial compared azithromycin with doxycycline or chloramphenicol (Chanta 2015). We were unable to include this trial in the meta-analysis as study authors included doxycycline or chloramphenicol as a single arm within the trial and did not report disaggregated data.

For treatment failure, trial authors reported one case in the azithromycin group and zero cases in the doxycycline or chloramphenicol group. We were unable to extract data for resolution of fever at five days or at 48 hours. The median time to defervescence was 36 hours (interquartile range (IQR) 20 to 68 hours) in the azithromycin group and 30 hours (IQR 21 to 48 hours) in the doxycycline/chloramphenicol group. Study authors determined that the difference was non-significant via the log-rank test. Adverse event reporting was unclear in this trial.

Comparison 3: rifampicin versus doxycycline

One trial compared rifampicin with doxycycline (Watt 2000). For this analysis, we combined standard- and high-dose rifampicin arms into one group.

Researchers detected no treatment failure in either group (78 participants, 1 trial; Analysis 3.1).

For resolution of fever within 48 hours, a higher proportion of participants had resolved fever with rifampicin compared to doxycycline (RR 1.68, 95% CI 1.10 to 2.57; 78 participants, 1 trial; Analysis 3.2).

Trial authors did not report the proportions of participants with resolution of fever within five days.

Results show time to defervescence as median times with ranges: 52 hours (range 4 to 108 hours) with doxycycline, 27.5 hours (range 4 to 84 hours) with 600 mg rifampicin, and 22.5 hours (range 3 to 76 hours) with 900 mg rifampicin. Study authors used the Kruskal-Wallis test to determine that the difference between the doxycycline group and the other two groups was significant.

Researchers did not formally report the presence or absence of serious adverse events, instead stating that there were no "serious complications". The trial excluded two participants from the doxycycline arm owing to gastrointestinal side effects. "Mild" gastrointestinal side effects occurred more commonly with doxycycline than with rifampicin. Rash and eosinophilia occurred more commonly with rifampicin than with doxycycline (Table 2).

As previously discussed, this trial deviated from the protocol after three of eight patients receiving doxycycline and rifampicin combination therapy experienced treatment failure.

Comparison 4: high-dose rifampicin versus standard-dose rifampicin

One trial compared 900 mg rifampicin versus 600 mg rifampicin, implementing a change to the original protocol (Watt 2000). Data show no treatment failure in either rifampicin arm (50 participants,

1 trial; Analysis 4.1). For proportions of participants with resolution of fever within 48 hours, results show little or no difference between high-dose and standard-dose rifampicin (RR 1.03, 95% CI 0.77 to 1.38; 50 participants, 1 trial; Analysis 4.2). Researchers did not report the proportions of participants with resolution of fever within five days. We were unable to compare time to defervescence using available data. Trial authors did not formally report the presence or absence of serious adverse events.

DISCUSSION

See Summary of findings for the main comparison, Summary of findings 2, and Summary of findings 3.

Summary of main results

Across the trials included in this review, treatment failure rates were low.

Two trials compared doxycycline versus tetracycline (Summary of findings for the main comparison). For treatment failure, the difference between doxycycline and tetracycline is uncertain (very low-certainty evidence). Doxycycline compared to tetracycline may make little or no difference in resolution of fever within 48 hours (low-certainty evidence) or in time to defervescence (low-certainty evidence). We were unable to extract data for other outcomes.

Three trials compared doxycycline versus macrolides (azithromycin and telithromycin; Summary of findings 2). For most outcomes, including treatment failure, resolution of fever within 48 hours, time to defervescence, and serious adverse events, we are uncertain whether results show a difference between doxycycline and macrolides (very low-certainty evidence). Macrolides compared to doxycycline may make little or no difference in the proportion of patients with resolution of fever within five days (low-certainty evidence). Another trial compared azithromycin to doxycycline or chloramphenicol in children, but we were unable to disaggregate data for the doxycycline/chloramphenicol group.

One trial compared doxycycline to rifampicin (Summary of findings 3). For all outcomes, we are uncertain whether results show a difference between doxycycline and rifampicin (very low-certainty evidence). Of note, this trial deviated from the protocol after three out of eight patients who received doxycycline and rifampicin combination therapy experienced treatment failure.

Across trials, mild gastrointestinal side effects appeared to be more common with doxycycline than with comparator drugs; this finding does not derive from meta-analysis but from narrative analysis of Table 2. When reported, serious adverse events were few.

Overall completeness and applicability of evidence

All included studies were reported from Malaysia, Thailand, and Korea; we excluded several studies from China because they were not RCTs. Given that there may be geographical variation in antibiotic susceptibility across the 'tsutsugamushi triangle', applicability of findings may be limited.

Factors specific to the antibiotics included in this review may influence the applicability of evidence. In general, doxycycline is preferred over tetracycline because of its more convenient dosing schedule. Production of the macrolide antibiotic telithromycin

was discontinued by the manufacturer in 2016, and before this, safety warnings had been issued; therefore this agent no longer represents a viable treatment option. In tuberculosis endemic areas, rifampicin monotherapy carries the risk of inducing rifampicin resistance in undiagnosed tuberculosis. The dose schedules of included antibiotics varied across trials.

Findings with respect to rifampicin have emerged from only one trial (Watt 2000), which provided low-certainty evidence of very limited applicability. Of concern, doxycycline and rifampicin combination therapy resulted in a high rate of treatment failures, but the reasons for this are unclear and are not discussed further by the study author team. Although study authors suggest that rifampicin should be considered in cases where *Orientia tsutsugamushi* is resistant to doxycycline, it is unclear epidemiologically whether such resistance is clinically significant.

The included trials employed a variety of diagnostic techniques and recruited patients at different points within the diagnostic pathway. Some of the participants included in this review may represent misdiagnoses, which also may limit the applicability of findings.

Certainty of the evidence

We have included in this update seven trials, which represented 548 participants, with dates ranging from 1978 to 2015. Most trials were open-label and did not report clear allocation concealment or randomization techniques. Results were imprecise owing to the small numbers of participants included for each comparison. Therefore, the body of evidence in relation to treatment of scrub typhus is of low or very low certainty.

Potential biases in the review process

We attempted to minimize bias in the review process by conducting a comprehensive search of all published and non-published literature with no language restrictions. Two review authors assessed the eligibility of studies, extracted data, and independently judged risk of bias. We resolved disagreements by consensus and by consultation with the fourth review author. We altered our inclusion criteria for this updated review. In particular, we excluded studies that used the Weil-Felix test as the sole measure of laboratory confirmation, given poor specificity. As a result, we excluded one trial that had been included in the previous review (Sheehy 1973).

Agreements and disagreements with other studies or reviews

Our findings are in agreement with those of a recently published meta-analysis (Wee 2017), which concluded that evidence is insufficient to support recommending one drug over the others examined here. However, authors of the meta-analysis included trials that employed the Weil-Felix test as the sole diagnostic tool, and the poor specificity associated with this test may raise the level of heterogeneity amongst pooled participants.

AUTHORS' CONCLUSIONS

Implications for practice

Tetracycline, doxycycline, azithromycin, and rifampicin are effective treatment options for scrub typhus that have been associated with few treatment failures. Chloramphenicol remains a treatment option, but we could not include this agent in direct comparisons for this review.

For specific outcomes, low-certainty evidence suggests there may be little or no difference between tetracycline, doxycycline, and azithromycin as treatment options. In the light of very low-certainty evidence for rifampicin and the risk of inducing resistance in undiagnosed tuberculosis, clinicians should not regard this agent as a first-line treatment option but should consider it as a second-line treatment option after exclusion of active tuberculosis.

Implications for research

Further research should include adequately powered trials of doxycycline versus azithromycin or other macrolides, trials of other candidate antibiotics including rifampicin, and trials of treatment of severe scrub typhus. Researchers should standardize diagnostic techniques and reporting of clinical outcomes to allow robust comparisons.

ACKNOWLEDGEMENTS

REFERENCES

References to studies included in this review

Brown 1978 *{published data only}*

Brown GW, Saunders JP, Singh SL, Haxsoll DL, Shirai A. Single dose doxycycline therapy for scrub typhus. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1978;**72**(4):412-6.

Chanta 2015 *{published data only}*

Chanta C, Phloenchaiwanit P. Randomized controlled trial of azithromycin versus doxycycline or chloramphenicol for treatment of uncomplicated pediatric scrub typhus. *Journal of the Medical Association of Thailand* 2015;**98**(8):756-60.

Kim 2004 *{published data only}*

Kim YS, Yun HJ, Shim SK, Koo SH, Kim SY, Kim S. A comparative trial of a single dose of azithromycin versus doxycycline for the treatment of mild scrub typhus. *Clinical Infectious Diseases* 2004;**39**(9):1329-35.

Kim 2007 *{published data only}*

Kim DM, Yu KD, Lee JH, Kim HK, Lee SH. Controlled trial of a 5-day course of telithromycin versus doxycycline for treatment of mild to moderate scrub typhus. *Antimicrobial Agents and Chemotherapy* 2007;**51**(6):2011-5.

Phimda 2007 *{published data only}*

Phimda K, Hoontrakul S, Suttinont C, Chareonwat S, Losuwanaluk K, Chueasuwanchai S, et al. Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus. *Antimicrobial Agents and Chemotherapy* 2007;**51**(9):3259-63.

Song 1995 *{published data only}*

Song JH, Lee C, Chang LW, Choi SW, Choi JE, Kim YS, et al. Short-course doxycycline treatment versus conventional tetracycline therapy for scrub typhus: a multiple randomized trial. *Clinical Infectious Diseases* 1995;**21**(3):506-10.

Watt 2000 *{published data only}*

Watt G, Kantipong P, Jongsakul K, Watcharapichat P, Phulsuksombati D, Strickman D. Doxycycline and rifampicin for mild scrub typhus infections in northern Thailand: a randomised trial. *Lancet* 2000;**356**(9235):1057-61.

References to studies excluded from this review

Chen 2007 *{published data only}*

Chen SX, Lin XM, Shen HF, Zhang LJ, Sun ZM. Treatment of scrub typhus with macrolide antibiotic. *Journal of Tropical Medicine* 2007;**7**:783-84.

Chen 2008 *{published data only}*

Chen SX, Shen HF, Zhang LJ, Xu CX, Sun ZM. Effect of antibiotics in the treatment of scrub typhus in South China Sea area. *Journal of Preventive Medicine of Chinese People's Liberation Army* 2008;**26**:59.

Feng 2009 *{published data only}*

Feng X. Treatment of scrub typhus with several antibiotics. *Journal of Practical Medicine* 2009;**25**:526.

Li 2004 *{published data only}*

Li Y. Macrolide antibiotic to cure child scrub typhus. *Journal of Pediatric Pharmacy* 2004;**10**:36.

Li 2007 *{published data only}*

Li RC, Pang L, Lu XH. Effect of antibiotics in the treatment of scrub typhus. *Modernizing Medicine's Healthcare* 2007;**23**:1936-7.

Olson 1980 *{published data only}*

Olson JG, Bourgeois AL, Fang RCY, Coolbaugh JC, Dennes DT. Prevention of scrub typhus: prophylactic administration of doxycycline in a randomized double blind trial. *Journal of Tropical Medicine and Hygiene* 1980;**29**(5):989-97.

Quan 2002 *{published data only}*

Quan B. The third generation of quinolone therapy for scrub typhus. *Journal of Tropical Medicine* 2002;**2**:163-4.

Sheehy 1973 *{published data only}*

Sheehy TW, Hazlett D, Turk RE. Scrub typhus. A comparison of chloramphenicol and tetracycline in its treatment. *Archives of Internal Medicine* 1973;**132**:77-80.

Twartz 1982 *{published data only}*

Twartz JC, Selvarju SG, Saunders JP, Huxsoll DL, Groves MG. Doxycycline prophylaxis for human scrub typhus. *Journal of Infectious Diseases* 1982;**146**(6):811-8.

Wei 2004 *{published data only}*

Wei MX, Lin SJ, Yan R, Guo WZ. A comparison of azithromycin versus chloramphenicol for treatment of pediatric scrub typhus. *Journal of Applied Clinical Pediatrics* 2004;**19**:66.

Wu 2006 *{published data only}*

Wu X, Xiao H, Zhu DJ. Therapeutic effect of azithromycin on children with tsutsugamushi disease. *Chinese Journal of Pediatrics* 2006;**24**:769-70.

Yang 2005 *{published data only}*

Yang YF, Li B, Liu XM, Zhang LP. Effect of roxithromycin in the treatment of scrub typhus. *Journal of Pediatric Pharmacy* 2005;**11**:32.

Zhong 1996 *{published data only}*

Zhong ZY, Zhang WY, Wu YX. Scrub typhus. A comparison of doxycycline and chloramphenicol in its treatment. *Journal of Guangdong Medical College* 1996;**14**:354-5.

References to ongoing studies

ISRCTN47812566 *{published data only}*

ISRCTN47812566. Oral doxycycline versus oral azithromycin in the treatment of scrub and murine typhus in Laos. isrctn.com/ISRCTN47812566 (date applied 7 December 2005).

NCT00351182 *{published data only}*

NCT00351182. 5-day course of telithromycin versus doxycycline for the treatment of mild to moderate scrub typhus. ClinicalTrials.gov/show/NCT00351182 (first posted 12 July 2006).

NCT00568711 *{published data only}*

NCT00568711. Controlled trial: 5-day course of rifampin versus doxycycline for the treatment of mild to moderate scrub typhus. clinicaltrials.gov/ct2/show/NCT00568711 (first posted 6 December 2007).

NCT03083197 *{unpublished data only}*

NCT03083197. Scrub typhus antibiotic resistance trial (START). clinicaltrials.gov/show/NCT03083197 (first posted 17 March 2017).

Additional references

Acestor 2012

Acestor N, Cooksey R, Newton PN, Ménard D, Guerin PJ, Nakagawa J, et al. Mapping the aetiology of non-malarial febrile illness in Southeast Asia through a systematic review - terra incognita impairing treatment policies. *PLoS One* 2012;**7**(9):e44269.

Bonell 2017

Bonell A, Lubell Y, Newton PN, Crump JA, Paris DH. Estimating the burden of scrub typhus: a systematic review. *PLoS Neglected Tropical Diseases* 2017;**11**(9):e0005838.

CDC 2017

Centers for Disease Control and Prevention. Scrub typhus. www.cdc.gov/typhus/healthcare-providers/index.html (accessed 13 March 2018).

Corwin 1999

Corwin A, Soderquist R, Suwanabun N, Sattabongkot J, Martin L, Kelly D, et al. Scrub typhus and military operations in Indochina. *Clinical Infectious Diseases* 1999;**29**(4):940-1.

GRADEpro 2015 [Computer program]

GRADEpro GDT. GRADEpro Guideline Development Tool. Hamilton (ON): McMaster University (developed by Evidence Prime, Inc.), 2015.

Griffith 2014

Griffith M, Peter JV, Karthik G, Ramakrishna K, Prakash JA, Kalki RC, et al. Profile of organ dysfunction and predictors of mortality in severe scrub typhus infection requiring intensive care admission. *Indian Journal of Critical Care Medicine* 2014;**18**(8):497-502.

Higgins 2011

Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Kelly 2017

Kelly D, Fuerst P, Richards A. The historical case for and the future study of antibiotic-resistant scrub typhus. *Tropical Medicine and Infectious Disease* 2017;**2**(4):63.

Koralur 2018

Koralur M, Singh R, Varma M, Shenoy S, Acharya V, Kamath A, et al. Scrub typhus diagnosis on acute specimens using serological and molecular assays - a three-year prospective study. *Diagnostic Microbiology and Infectious Disease* 2018;**91**(2):112-7. [DOI: 10.1016/j.diagmicrobio.2018.01.018]

Paris 2016

Paris DH, Dumler JS. State of the art of diagnosis of rickettsial diseases: the use of blood specimens for diagnosis of scrub typhus, spotted fever group rickettsiosis, and murine typhus. *Current Opinion in Infectious Diseases* 2016;**29**(5):433-9.

Rajapakse 2012

Rajapakse S, Rodrigo C, Fernando D. Scrub typhus: pathophysiology, clinical manifestations and prognosis. *Asian Pacific Journal of Tropical Medicine* 2012;**5**(4):261-4.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editors. Introduction to GRADE HandbookHandbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. http://gdt.guidelinedevelopment.org/app/handbook/handbook.html (accessed 18 April 2018).

Smadel 1950

Smadel JE, Traub R, Frick LP, Dierck FH, Bailey CA. Chloramphenicol (chloromycetin) in the chemoprophylaxis of scrub typhus (Tsutsugamushi disease). *American Journal of Hygiene* 1950;**51**:216-28.

Tantibhedhyangkul 2010

Tantibhedhyangkul W, Angelakis E, Tongyoo N, Newton PN, Moore CE, Phetsouvanh R, et al. Intrinsic fluoroquinolone resistance in Orientia tsutsugamushi. *International Journal of Antimicrobial Agents* 2010;**35**(4):338-41.

Taylor 2015

Taylor AJ, Paris DH, Newton PN. A systematic review of mortality from untreated scrub typhus (Orientia tsutsugamushi). *PLoS Neglected Tropical Diseases* 2015;**9**(8):e0003971.

Thipmontree 2016

Thipmontree W, Tantibhedhyangkul W, Silpasakorn S, Wongsawat E, Waywa D, Suputtamongkol Y. Scrub typhus in Northeastern Thailand: eschar distribution, abnormal electrocardiographic findings, and predictors of fatal outcome. *American Journal of Tropical Medicine and Hygiene* 2016;**95**(4):769-73.

Watt 1996

Watt G, Chouriyagune C, Ruangweerayud T, Watcharapichat P, Phulsuksombati D, Jongasakul K, et al. Scrub typhus infections poorly responsive to antibiotics in northern Thailand. *Lancet* 1996;**348**:86-9.

Watt 2003

Watt G, Parola P. Scrub typhus and tropical rickettsioses. *Current Opinion in Infectious Disease* 2003;**16**(5):429-36.

Wee 2017

Wee I, Lo A, Rodrigo C. Drug treatment of scrub typhus: a systematic review and meta-analysis of controlled clinical trials. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2017;**111**(8):336-44.

References to other published versions of this review

Liu 2002

Liu Q, Panpanich R. Antibiotics for treating scrub typhus. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD002150]

Panpanich 2000

Panpanich R, Garner P. Antibiotics for treating scrub typhus. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD002150]

CHARACTERISTICS OF STUDIES

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

Brown 1978

Methods	RCT
	Duration: 11 months (September 1976 to July 1977)
	Adverse event monitoring: patient report
Participants	Adults with suspected scrub typhus (randomized before confirmed diagnosis)
	Number randomized: 149
	Inclusion criteria: adults ≥ 18 years with febrile illness
	Exclusion criteria: previous tetracycline and chloramphenicol; history of allergy to tetracycline; jaundice; pregnancy; clinical and laboratory evidence of non-rickettsial disease
	Diagnosis: isolation of *Rickettsia tsutsugamushi;* OR a 4-fold or greater rise in IFA titre to at least 1:200 or in static titre of 1:800 or more; OR a 4-fold or greater rise in Proteus OXK agglutination test titre to at least 1:200
Interventions	• Doxycycline 200 mg single oral dose*
	• Tetracycline 500 mg 6-hourly for 7 days*
	*Clinicians gave additional treatment at their discretion if no improvement within 48 hours, or if clinical and laboratory evidence of alternative diagnosis
Outcomes	• Resolution of fever within 48 hours
	• Disappearance of symptoms
	• Relapse
	• Side effects
Notes	Country: Malaysia
	Setting: district hospital
	Date: September 1976 to July 1977
	Funding: US Army Medical Research and Development Command, Washington, DC, and Ministry of Health, Malaysia
	Follow-up: 14 days

Brown 1978 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Volunteers were randomly assigned"; no further details
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details reported
Incomplete outcome data (attrition bias) All outcomes	High risk	149 randomized before confirmed diagnosis. 65 with confirmed diagnosis of scrub typhus. 10 excluded (mixed infection). 55 included in final analysis (84.6% of participants with a confirmed diagnosis)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes adequately reported
Other bias	Low risk	No obvious other sources of bias

Chanta 2015

Methods	RCT
	Duration: 2 years, 11 months (June 2010 to May 2013)
	Adverse event monitoring: patient report
Participants	Children with positive scrub typhus RDT
	Number randomized: 57
	Inclusion criteria: hospitalized children ≤ 15 years of age; clinical manifestations compatible with scrub typhus; confirmatory laboratory tests
	Exclusion criteria: allergy to study drug; severe clinical complications (hypotension, coma, respiratory failure, acute renal failure with renal replacement therapy); anti-microbial therapy < 7 days pre-admission
	Laboratory diagnosis: dipstick RDT (SD Bioline Tsutsugamushi test)
Interventions	• Azithromycin: oral sachets 20 mg/kg/dose initially, maximum 1000 mg first day followed by 10 mg/kg/dose, maximum 500 mg for 2 days (n = 29)[*]
	• Chloramphenicol: intravenous 100 mg/kg/d 6-hourly (n = 9; patients aged < 8 years)[†]
	• Doxycycline: oral 2.2 mg/kg/dose (maximum 100 mg/dose) 12-hourly day 1; same dose once daily for at least 5 days or until defervescence (3 days; n = 19)[†]
	*Changed to "standard treatment" if clinical failure
	†Children under 8 received chloramphenicol; children 8 and older received doxycycline
Outcomes	• Cure, defined as defervescence* within 72 hours
	• Failure, defined as persistence of fever > 72 hours or complications
	• Time to defervescence*

Chanta 2015 *(Continued)*

- Relapse (within 30 days)
- Adverse events

*Temperature < 37.3°C maintained for > 48 hours

Notes	Country: Thailand
	Setting: tertiary hospital, paediatrics unit
	Funding: Chiangrai Prachanukroh Hospital fund
	Follow-up: 1 month after discharge

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization; no further details
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	High risk	"Open-label"; no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	57 randomized after RDT positive diagnosis. No missing data (57/57)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes adequately reported. Adverse events defined as those "related to the administration of the antibiotic"
Other bias	Low risk	No obvious other sources of bias

Kim 2004

Methods	RCT
	Duration: 1 year, 2 months (September 2002 to November 2003)
	Adverse event monitoring: patient report
Participants	Adults with suspected scrub typhus (randomized before confirmed diagnosis)
	Number randomized: 99
	Inclusion criteria: fever (oral temperature ≥ 38°C); eschar or a maculopapular skin rash with 2 of: headache, generalized weakness, myalgia, abdominal discomfort, coughing, or nausea
	Exclusion criteria: hypersensitivity to study drugs; pregnancy; severe complications (shock requiring vasopressor therapy for > 1 hour, disturbed consciousness level, respiratory failure, and renal failure with immediate dialysis); antibiotics with potential anti-rickettsial activity within previous 2 days
	Laboratory diagnosis: IFA with specific IgM ≥ 1:10; OR> 4-fold increased titres in paired serum specimens
Interventions	• Azithromycin 500 mg single oral dose (n = 47)

Kim 2004 *(Continued)*

	• Doxycycline 200 mg once daily for 7 days (n = 46)
Outcomes	• Time to defervescence* • Resolution of fever within 5 days ("cure") • Treatment failure, defined as persistence of fever • Relapse (within 30 days) • Adverse events *Temperature < 37.3°C maintained for > 48 hours
Notes	Country: Republic of Korea Setting: tertiary hospital Funding: Chungnam National University Hospital (Daejeon, South Korea) Follow-up: 1 month after discharge

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequences
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	High risk	"Open-label"; no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	99 randomized before confirmed diagnosis. 6 excluded after randomization (combined infection, vomiting, medication error). 93 completed treatment and included in final analysis. 75 with laboratory-confirmed diagnosis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes adequately reported
Other bias	Low risk	No obvious other sources of bias

Kim 2007

Methods	Quasi-RCT Duration: 4 months (September to December 2005) Adverse event monitoring: patient report
Participants	Adults with suspected scrub typhus (randomized before confirmed diagnosis) Number randomized: 92 Inclusion criteria: fever > 37.5°C; eschar or a maculopapular skin rash with 2 of: headache, malaise, myalgia, coughing, nausea, or abdominal discomfort Exclusion criteria: unable to take oral medications; pregnancy; hypersensitivity to trial drugs, antibiotics with potential anti-rickettsial activity within previous 2 days; severe scrub typhus (shock requiring

vasopressor therapy for longer than 1 hour, a stuporous or comatose level of consciousness, respiratory failure requiring mechanical ventilation, or renal failure requiring immediate dialysis); mixed infection

Laboratory diagnosis: IFA with specific IgM > 1:80; OR > 4-fold increased titres in paired serum specimens

Interventions	• Telithromycin: 800 mg daily for 5 days (n = 47) • Doxycycline: 200 mg daily for 5 days (n = 45)
Outcomes	• Time to defervescence* ("fever clearance time") • Resolution of fever within 5 days ("cure") • Treatment failure, defined as persistence of fever • Relapse (within 30 days) • Adverse events
Notes	Country: Republic of Korea Setting: university hospital and 2 community hospitals Funding: Sanofi-Aventis Korea Co., Ltd.; The Clinical Medicine Research Institute at Chosun University Hospital Follow-up: 4 weeks after discharge

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomized by last digit of resident registration number (odd numbers assigned to doxycycline, even numbers assigned to telithromycin)
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	High risk	"Open-label"; no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	92 randomized before confirmed diagnosis. 92 patients included in final analysis. 76 with laboratory-confirmed diagnosis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes adequately reported
Other bias	Low risk	No obvious other sources of bias

Phimda 2007

Methods	RCT Duration: 1 year, 6 months (July 2003 to January 2005) Adverse event monitoring: patient report

Participants	Adults and adolescents with acute undifferentiated fever (subsequent diagnoses included leptospirosis, scrub typhus, murine typhus, mixed infections)
	Number randomized: 296 (57 patients with subsequent diagnosis of scrub typhus)
	Inclusion criteria: age > 14 years; oral temperature ≥ 38°C for < 15 days; no obvious focus of infection
	Exclusion criteria: inability to take oral medications; pregnancy/breastfeeding; allergy to study drugs; concurrent infection; anti-rickettsial drugs < 48 hours before enrolment
	Laboratory diagnosis: IFA (microimmunofluorescence) with specific IgM and/or IgG > 1:400; OR > 4-fold increased titres in paired serum specimens
Interventions	• Azithromycin 1 g daily for 3 days, followed by 500 mg daily for 2 days (n = 30) • Doxycycline 200 mg day 0, then 100 mg 12-hourly for 7 days (n = 27)
Outcomes	• Resolution of fever within 5 days ("cure") • Treatment failure, defined as persistence of fever or development of complications after 48 hours of treatment • Time to defervescence* • Adverse events *Temperature < 37.5°C maintained for > 2 measurements without anti-pyretics
Notes	Country: Thailand
	Setting: 4 hospitals
	Funding: Thailand Research Fund, Ministry of Public Health, Thailand, and the Welcome Trust of Great Britain
	Follow-up: 15 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent, computer-generated, simple random allocation sequences
Allocation concealment (selection bias)	Low risk	Central randomization; sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label. Outcome assessment "independent". Statistician blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	296 randomized. 43 excluded after randomization owing to prior antibiotics. 89 lost to follow-up (uncertain diagnosis). 296 included in final analysis; of these 57 participants had confirmed scrub typhus. Missing data balanced between final diagnosis groups
Selective reporting (reporting bias)	Low risk	All prespecified outcomes adequately reported
Other bias	Low risk	No obvious other sources of bias

Song 1995

Methods	RCT
	Duration: 1 year, 1 month (October 1991 to November 1992)
	Adverse event monitoring: patient report.
Participants	Adults with positive scrub typhus IFA
	Number randomized: 129
	Inclusion criteria: age ≥ 18 years; acute febrile illness with high fever, rash, and eschar
	Exclusion criteria: subsequent unconfirmed diagnosis; allergy to study drugs; received study drugs within last 72 hours; raised serum creatinine; pregnancy or lactation
	Laboratory diagnosis: IFA with specific IgG > 1:80; OR > 4-fold increased titres in paired serum specimens
Interventions	• Doxycycline oral 100 mg 12-hourly for 3 days (n = 66)
	• Tetracycline oral 500 mg 12-hourly for 7 days (n = 50)
Outcomes	• Cure (resolution of fever, signs, and symptoms by end of course)
	• Treatment failure (persistence of fever/signs and symptoms by end of course)
	• Time to defervescence*
	• Relapse (4 weeks)
	• Time to resolution of symptoms
	• Adverse events
	*Temperature < 37.3°C maintained for > 48 hours
Notes	Country: Korea.
	Setting: 8 branch hospitals
	Funding: Asian Institute for Life Science
	Follow-up: 4 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally computer-generated random orders
Allocation concealment (selection bias)	Unclear risk	''Central randomisation''; no further details
Blinding (performance bias and detection bias) All outcomes	High risk	Non-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	129 randomized. 13 excluded owing to negative or indeterminate diagnosis. 116 included in final analysis (90% of those randomized)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes adequately reported

Song 1995 *(Continued)*

Other bias	Low risk	No obvious other sources of bias

Watt 2000

Methods	RCT
	Duration: no details
	Adverse event monitoring: patient report

Participants	Adults with positive scrub typhus RDT
	Number: 126
	Inclusion criteria: adults; ambulatory mild scrub typhus; ability to take oral medication
	Exclusion criteria: severe disease (hypotension, shock, impaired consciousness, or pulmonary dysfunction); coinfection or other febrile illness; vomiting; serum bilirubin > 25.7 μmol/L; serum ALT > 100 U/L; anti-rickettsial drugs < 48 hours before enrolment
	Laboratory diagnosis: screened with dot-blot ELISA rapid test. Confirmed with indirect immunoperoxidase test: IgM > 1:400, IgG > 1:1600

Interventions	- Doxycycline monotherapy oral 200 mg day 0, then 100 mg 12-hourly for 7 days (n = 28) - Rifampicin 300 mg 12-hourly for 7 days (n = 26) - Combined doxycycline 100 mg 12-hourly and rifampicin 300 mg 12-hourly for 7 days (n = 11)* - Rifampicin 450 mg 12-hourly for 7 days (n = 24)*
	*In a change to the protocol, arm 4 (450 mg rifampicin) replaced arm 3 (combined therapy) after 1 year owing to protracted fever.

Outcomes	- Time to defervescence* ("fever clearance time") - Treatment failure (remaining pyretic after therapy) - Relapse (1 month) - Resolution of fever within 48 hours - Adverse events
	*Temperature < 37.3°C maintained for > 48 hours without anti-pyretics

Notes	Country: Thailand
	Setting: tertiary hospital
	Funding source: US Army Research and Material Command and the Royal Thai Army
	Follow-up: 1 month during first year of study; 2 weeks in following years

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned"; no further details
Allocation concealment (selection bias)	Unclear risk	No details reported

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Watt 2000 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Describes efforts to "mask" investigators from evidence of drug allocation in the form of red discolouration of body fluids but provides limited details
Incomplete outcome data (attrition bias) All outcomes	High risk	357 of 2090 with positive RDT; 231 excluded before randomization as "ineligible"; 126 seropositive and randomized. 32 excluded after randomization; 5 excluded as diagnosis not confirmed. 78 completed protocol and were analysed (67.8% of those randomized)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes adequately reported
Other bias	High risk	Deviation from the study protocol. Participants initially randomized to receive combined doxycycline and rifampicin therapy; 3 of 8 participants receiving combination therapy experienced failed treatment. Combined therapy arm changed to high-dose rifampicin arm

Abbreviations: ALT: alanine aminotransferase; ELISA: enzyme-linked immunosorbent assay; IFA: immunofluorescence assay; IgG: immunoglobulin G; IgM: immunoglobulin M; RCT: randomized controlled trial; RDT: rapid diagnostic test.

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

Study	Reason for exclusion
Chen 2007	A retrospective analysis, not an RCT. Diagnosis based only on Weil-Felix reaction
Chen 2008	A retrospective analysis, not an RCT. Diagnosis based only on Weil-Felix reaction
Feng 2009	A retrospective analysis, not an RCT. Diagnosis based only on Weil-Felix reaction
Li 2004	A retrospective analysis, not an RCT. Diagnosis based only on Weil-Felix reaction
Li 2007	Diagnosis based only on Weil-Felix reaction Unclear study design. Participants were randomly allocated to 5 treatment groups, but study authors did not describe the randomization process.
Olson 1980	Assessed efficacy for prevention rather than for treatment
Quan 2002	Diagnosis based only on Weil-Felix reaction Unclear study design. Participants were randomly allocated to 2 treatment groups, but study authors did not describe detailed randomization methods. Whether it is a real RCT needs clarification.
Sheehy 1973	Diagnosis based only on Weil-Felix reaction
Twartz 1982	Assessed efficacy for prevention rather than for treatment
Wei 2004	Diagnosis based only on Weil-Felix reaction Unclear study design. Participants were randomly allocated to 2 treatment groups, but study authors did not describe detailed randomization methods. Whether it is a real RCT needs clarification.
Wu 2006	Diagnosis based only on Weil-Felix reaction

Study	Reason for exclusion
	Unclear study design. Participants were randomly allocated to 2 treatment groups, but study authors did not describe detailed randomization methods.
Yang 2005	Diagnosis based only on Weil-Felix reaction
	A retrospective analysis, not an RCT
Zhong 1996	Diagnosis based only on Weil-Felix reaction

Abbreviations: RCT: randomized controlled trial.

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

ISRCTN47812566

Trial name or title	Oral Doxycycline Versus Oral Azithromycin in the Treatment of Scrub and Murine Typhus in Laos
Methods	Randomized controlled trial (RCT)
Participants	**Inclusion criteria** • Adult (> 15 years) non-pregnant patients with suspected typhus. Suspected typhus will be defined as undifferentiated fever (aural temperature > 37.5°C), with or without an eschar, with a positive scrub typhus lateral flow IgM result or a murine typhus IgM Dip-Sticks result • Written informed consent to participate in the study • Ability to stay in hospital for duration of treatment (up to 7 days) and high likelihood of completing at least 4 weeks of follow-up • Ability to take oral medication • Negative urinary pregnancy test for all women of child-bearing age • None of the exclusion criteria **Exclusion criteria** • Known hypersensitivity to tetracycline, doxycycline, or azithromycin • Administration of chloramphenicol, doxycycline, tetracycline, fluoroquinolones, or azithromycin during the preceding week • Pregnancy or breast-feeding • Contraindications to doxycycline: severe hepatic impairment, known systemic lupus erythematosus (SLE) • Contraindications to azithromycin: severe hepatic impairment • Severe typhus defined as: * Reduced level of consciousness * Clinical jaundice * Shock (blood pressure (BP) systolic < 80 mmHg) * Vomiting sufficient to disallow the use of oral medication * Clinical or radiological evidence of lung involvement * Clinical evidence of meningitis/encephalitis or the need for a lumbar puncture (LP) * Any other syndrome that in the opinion of the admitting doctor constitutes severe typhus (reason must be stated)
Interventions	• Oral doxycycline 100 mg every 12 hours for 7 days (after a 200-mg loading dose) • Doxycycline 100 mg every 12 hours for 3 days (after a 200-mg loading dose) • Oral azithromycin 500 mg on day 1, then 250 mg every 24 hours for 2 more days
Outcomes	• Fever clearance time

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ISRCTN47812566 *(Continued)*

- Frequencies of treatment failure
- Frequencies of relapse
- Treatment failure frequency
- Relapse frequency

Starting date	4 August 2003
	End of follow-up: 31 December 2009
Contact information	Dr. Paul Newton
	paul@tropmedres.ac; Ministry of Health, Mahosot Hospital, Mahosot Road, Vientiane, Laos
Notes	Location: Mahosot Hospital, Vientiane, Laos
	Registration number: ISRCTN47812566
	Source of funding: The Wellcome Trust (UK) (grant ref: 066828)

NCT00351182

Trial name or title	Controlled Trial: 5-Day Course of Telithromycin Versus Doxycycline for the Treatment of Mild to Moderate Scrub Typhus
Methods	Multi-centre randomized open-label clinical trial
Participants	**Inclusion criteria**
	Adult patients aged 18 years and older presenting with fever ≥ 37.5°C, eschar, or maculopapular rash and with at least 2 of the following: headache, malaise, myalgia, coughing, nausea, and abdominal discomfort
	Exclusion criteria
	- Inability to take oral medications
	- Pregnancy
	- Hypersensitivity to trial drugs
	- Previous drug therapy with potential anti-rickettsial activity within 48 hours before admission
	- Severe scrub typhus (shock requiring vasopressor therapy for > 1 hour, comatose level of consciousness, respiratory failure requiring mechanical ventilation, or renal failure requiring immediate dialysis)
Interventions	5-day course of telithromycin versus doxycycline
Outcomes	Fever clearance time
Starting date	September 2005
	Last update posted: 12 July 2006
Contact information	Prof. Dong-Min Kim
	drongkim@chosun.ac.kr; Chosun University Hospital, Republic of Korea
Notes	Location: Chosun University Hospital, Republic of Korea
	Registration number: Telit_L_00276

NCT00351182 *(Continued)*

Sources of funding: Chosun University Hospital

NCT00568711

Trial name or title	Controlled Trial: 5-Day Course of Rifampin Versus Doxycycline for the Treatment of Mild to Moderate Scrub Typhus
Methods	RCT
Participants	**Inclusion criteria** • Adults 18 years of age or older • Fever higher than 37.5˚C • Concurrent presence of eschar or a maculopapular skin rash; and clear presence of more than 2 symptoms such as headache, malaise, myalgia, coughing, nausea, and abdominal discomfort • Patients hospitalized between 2006 and 2009 at Chosun University Hospital in Gwangju, South Korea, or at one of its 2 community-based affiliated hospitals, all of which are located in southwestern Korea **Exclusion criteria** • Inability to take oral medications • Pregnancy • Hypersensitivity to trial drugs • Previous drug therapy with potential anti-rickettsial activity (for example, rifampicin, chloramphenicol, macrolides, fluoroquinolones, tetracyclines) within 48 hours before admission • Severe scrub typhus (shock requiring vasopressor therapy for longer than 1 hour) • Stuporous or comatose level of consciousness • Respiratory failure requiring mechanical ventilation or renal failure requiring immediate dialysis • For the differential diagnosis of scrub typhus from other diseases with similar symptoms (for example, murine typhus, leptospirosis, haemorrhagic fever with renal syndrome, systemic lupus erythematosus), patients underwent diagnostic tests. We thus excluded patients with concurrent infections at risk for causing different outcomes
Interventions	• 5-day rifampin therapy • 5-day doxycycline therapy
Outcomes	• Fever clearance time • Cure • Failure • Relapse
Starting date	September 2006 Expected completion: December 2009 Unknown recruitment status
Contact information	Prof. Dong-Min Kim drongkim@chosun.ac.kr; Chosun University Hospital, Kwangju, Jeollanamdo, South Korea
Notes	Location: Chosun University Hospital, or one of its 2 community-based affiliated hospitals, all of which are located in southwestern Korea Study ID number: NCT00568711

NCT03083197

Trial name or title	Scrub Typhus Antibiotic Resistance Trial (START)
Methods	Prospective, open-label, RCT
Participants	**Inclusion criteria** • Age ≥ 15 years • Hospitalization with acute fever > 37.5°C for ≤ 14 days or admission with a history of fever ≤ 14 days and developing fever within 24 hours after hospitalization • Clinically suspected scrub typhus: acute undifferentiated fever with no clear focus of infection (negative malaria blood smear and/or negative malaria RDT). Patients may have 1 or a combination of symptoms and signs such as eschar, rash, lymphadenopathy, headache, myalgia, cough, nausea, and abdominal discomfort. • Positive scrub typhus RDT (Scrub Typhus Detect IgM RDT, InBios International, Seattle, Washington, USA) and/or positive PCR-based detection of *Orientia tsutsugamushi* DNA from the admission blood sample • Written informed consent • Ability to take oral medication **Exclusion criteria** • Hypersensitivity to trial drugs • Administration of anti-microbial therapy within 7 days before the trial • Pregnancy or breast-feeding • Established infection (for example, acute malaria, dengue, leptospirosis, typhoid, Japanese encephalitis) • Confirmed TB or TB treatment in ≤ 6 months • Severe disease for which the clinical team thinks that current treatment is not enough (for example, IV chloramphenicol and/or PO/NG rifampicin) • Long-term use of immunosuppressants (for example, steroids, chemotherapy, TNF-inhibitors) and use of HAART for HIV patients • Systemic lupus erythematosus and myasthenia gravis
Interventions	• Doxycycline 100 mg PO every 12 hours for 7 days (after loading dose, 200 mg PO) • Doxycycline 100 mg PO every 12 hours for 3 days (after loading dose, 200 mg PO) • Azithromycin 500 mg PO every 24 hours on days 2 and 3 (after loading dose, 1000 mg PO on day 1)
Outcomes	**Primary** • Fever clearance time **Secondary** • Resolution of bacteraemia in relation to drug plasma level • Occurrence of severe disease or treatment failure/relapse • Presence of in vitro anti-microbial resistance • Genotyping of clinical *Orientia tsutsugamushi* isolates • Antigen-specific positive cellular and humoral immune responses
Starting date	17 March 2017. Last update posted: 14 December 2017 Expected completion time: October 2019
Contact information	Assoc. Prof. Daniel Paris

NCT03083197 *(Continued)*

	parigi@tropmedres.ac; Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand
Notes	Location: Shoklo Malaria Research Unit (SMRU), Chiangrai Prachanukroh Hospital, Thailand
	Study ID number: START
	Source of funding: University of Oxford, Shoklo Malaria Research Unit and Chiangrai Prachanukroh Hospital

Abbreviations: BP: blood pressure; HAART: highly active anti-retroviral therapy; HIV: human immunodeficiency virus; IgM: immunoglobulin M; LP: lumbar puncture; PCR: polymerase chain reaction; RDT: rapid diagnostic test; SLE: systemic lupus erythematosus; TB: tuberculosis; TNF: tumour necrosis factor.

DATA AND ANALYSES

Comparison 1. Doxycycline versus tetracycline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1	116	Risk Ratio (M-H, Fixed, 95% CI)	6.85 [0.38, 124.38]
2 Resolution of fever within 48 hours	1	55	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.90, 1.44]

Analysis 1.1. Comparison 1 Doxycycline versus tetracycline, Outcome 1 Treatment failure.

Study or subgroup	Doxycycline n/N	Tetracycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Song 1995	4/66	0/50		100%	6.85[0.38,124.38]
Total (95% CI)	**66**	**50**		**100%**	**6.85[0.38,124.38]**

Total events: 4 (Doxycycline), 0 (Tetracycline)
Heterogeneity: Not applicable
Test for overall effect: Z=1.3(P=0.19)

Favours doxycycline 0.005 0.1 1 10 200 Favours tetracycline
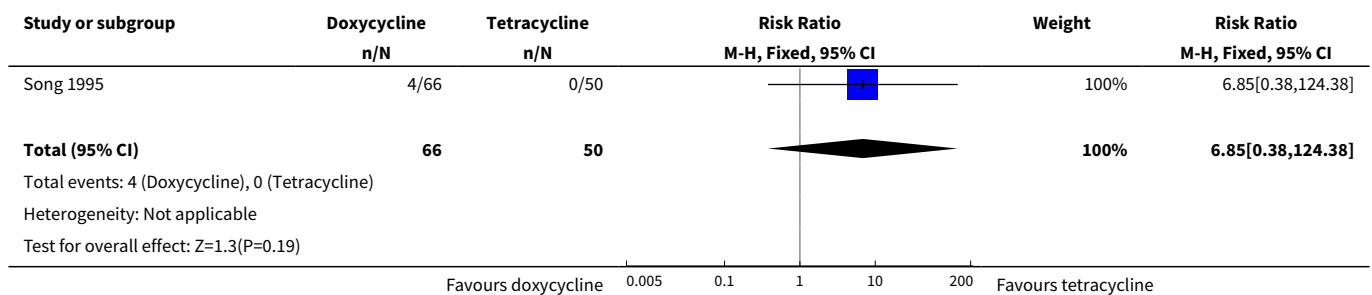
Analysis 1.2. Comparison 1 Doxycycline versus tetracycline, Outcome 2 Resolution of fever within 48 hours.
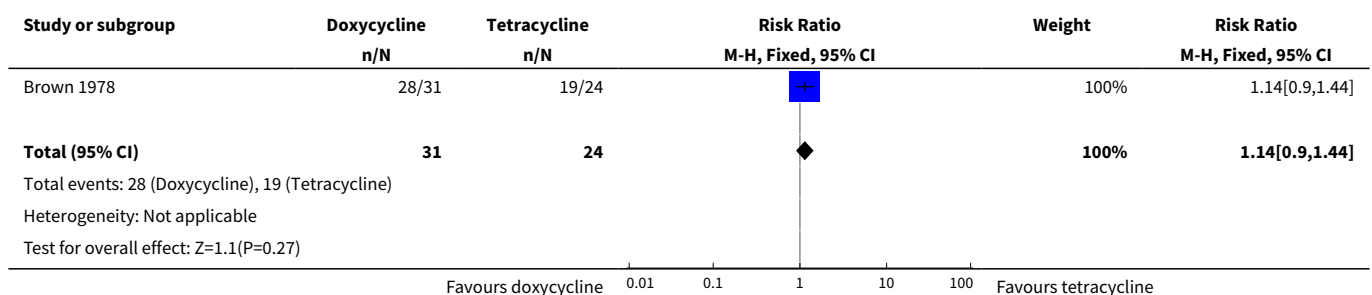
Study or subgroup	Doxycycline n/N	Tetracycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Brown 1978	28/31	19/24		100%	1.14[0.9,1.44]
Total (95% CI)	**31**	**24**		**100%**	**1.14[0.9,1.44]**

Total events: 28 (Doxycycline), 19 (Tetracycline)
Heterogeneity: Not applicable
Test for overall effect: Z=1.1(P=0.27)

Favours doxycycline 0.01 0.1 1 10 100 Favours tetracycline

Comparison 2. Macrolides versus doxycycline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	3	242	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.12, 63.84]
2 Resolution of fever within 48 hours	2	150	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.32, 2.03]
3 Resolution of fever within 5 days	2	185	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.99, 1.10]
4 Serious adverse events	3	242	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Macrolides versus doxycycline, Outcome 1 Treatment failure.

Study or subgroup	Macrolide n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2004	0/47	0/46			Not estimable
Kim 2007	0/47	0/45			Not estimable
Phimda 2007	1/30	0/27		100%	2.71[0.12,63.84]
Total (95% CI)	**124**	**118**		**100%**	**2.71[0.12,63.84]**
Total events: 1 (Macrolide), 0 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.62(P=0.54)					

Favours macrolide   0.01   0.1   1   10   100   Favours doxycycline
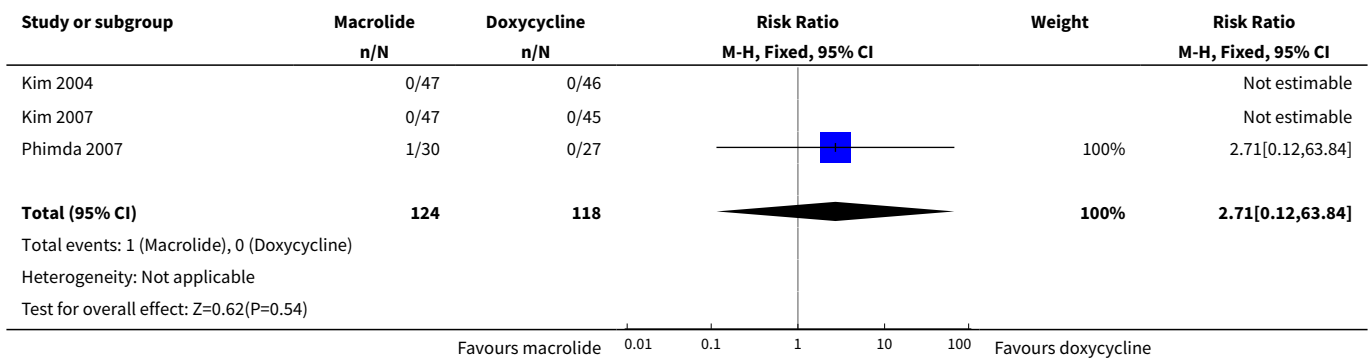
Analysis 2.2. Comparison 2 Macrolides versus doxycycline, Outcome 2 Resolution of fever within 48 hours.

Study or subgroup	Macrolide n/N	Doxycycline n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kim 2004	40/47	33/46		55.14%	1.19[0.95,1.47]
Phimda 2007	9/30	16/27		44.86%	0.51[0.27,0.95]
Total (95% CI)	**77**	**73**		**100%**	**0.81[0.32,2.03]**
Total events: 49 (Macrolide), 49 (Doxycycline)					
Heterogeneity: Tau²=0.38; Chi²=7.66, df=1(P=0.01); I²=86.94%					
Test for overall effect: Z=0.45(P=0.65)					

Favours macrolide   0.5   0.7   1   1.5   2   Favours doxycycline
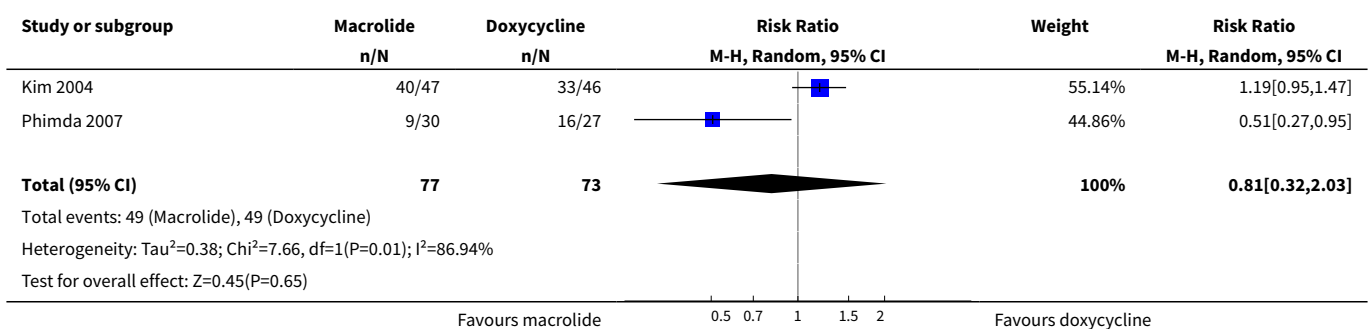
Analysis 2.3. Comparison 2 Macrolides versus doxycycline, Outcome 3 Resolution of fever within 5 days.

Study or subgroup	Macrolide n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2004	47/47	43/46		49.17%	1.07[0.98,1.17]
Kim 2007	47/47	44/45		50.83%	1.02[0.96,1.09]
Total (95% CI)	**94**	**91**		**100%**	**1.05[0.99,1.1]**
Total events: 94 (Macrolide), 87 (Doxycycline)					
Heterogeneity: Tau²=0; Chi²=0.76, df=1(P=0.38); I²=0%					
Test for overall effect: Z=1.67(P=0.1)					

Favours macrolide 0.01 0.1 1 10 100 Favours doxycycline
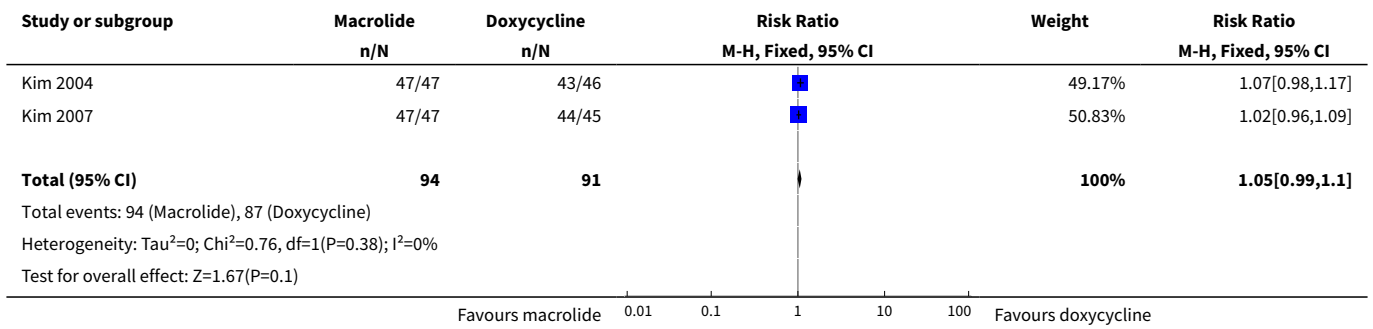
Analysis 2.4. Comparison 2 Macrolides versus doxycycline, Outcome 4 Serious adverse events.
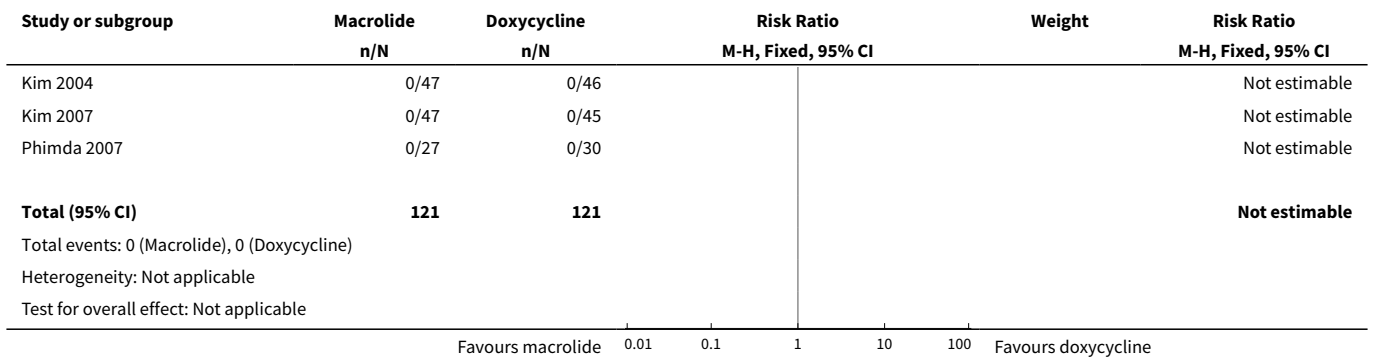
Study or subgroup	Macrolide n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2004	0/47	0/46			Not estimable
Kim 2007	0/47	0/45			Not estimable
Phimda 2007	0/27	0/30			Not estimable
Total (95% CI)	**121**	**121**			**Not estimable**
Total events: 0 (Macrolide), 0 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours macrolide 0.01 0.1 1 10 100 Favours doxycycline

Comparison 3. Rifampicin versus doxycycline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Resolution of fever within 48 hours	1	78	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [1.10, 2.57]
3 Serious adverse events	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Rifampicin versus doxycycline, Outcome 1 Treatment failure.

Study or subgroup	Rifampicin n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Watt 2000	0/50	0/28			Not estimable
Total (95% CI)	**50**	**28**			**Not estimable**
Total events: 0 (Rifampicin), 0 (Doxycycline)					

Favours rifampicin 0.01 0.1 1 10 100 Favours doxycyline

Study or subgroup	Rifampicin n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours rifampicin 0.01 0.1 1 10 100 Favours doxycyline

Analysis 3.2. Comparison 3 Rifampicin versus doxycycline, Outcome 2 Resolution of fever within 48 hours.

Study or subgroup	Rifampicin n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Watt 2000	39/50	13/28		100%	1.68[1.1,2.57]
Total (95% CI)	**50**	**28**		**100%**	**1.68[1.1,2.57]**
Total events: 39 (Rifampicin), 13 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.4(P=0.02)					

Favours doxycycline 0.01 0.1 1 10 100 Favours rifampicin
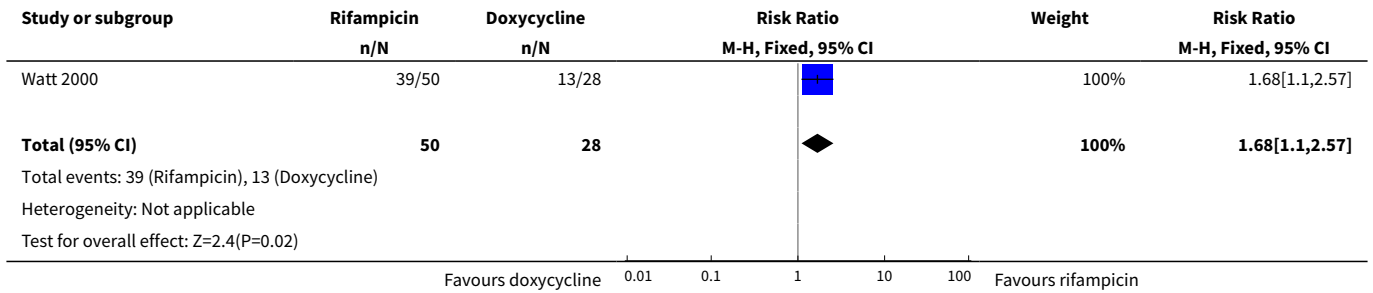
Analysis 3.3. Comparison 3 Rifampicin versus doxycycline, Outcome 3 Serious adverse events.

Study or subgroup	Rifampicin n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Watt 2000	0/50	0/28			Not estimable
Total (95% CI)	**50**	**28**			**Not estimable**
Total events: 0 (Rifampicin), 0 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours rifampicin 0.01 0.1 1 10 100 Favours doxycycline
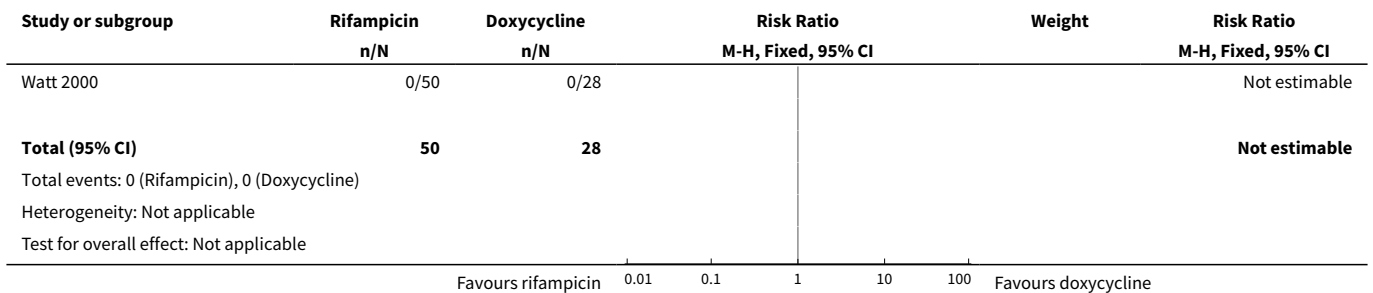
Comparison 4. High rifampicin dose versus standard rifampicin dose

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Failure	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Resolution of fever within 48 hours	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.77, 1.38]
3 Serious adverse events	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 High rifampicin dose versus standard rifampicin dose, Outcome 1 Failure.

Study or subgroup	High rifampicin	Standard rifampicin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Watt 2000	0/24	0/26			Not estimable
Total (95% CI)	**24**	**26**			**Not estimable**
Total events: 0 (High rifampicin), 0 (Standard rifampicin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours high dose 0.01 0.1 1 10 100 Favours standard dose
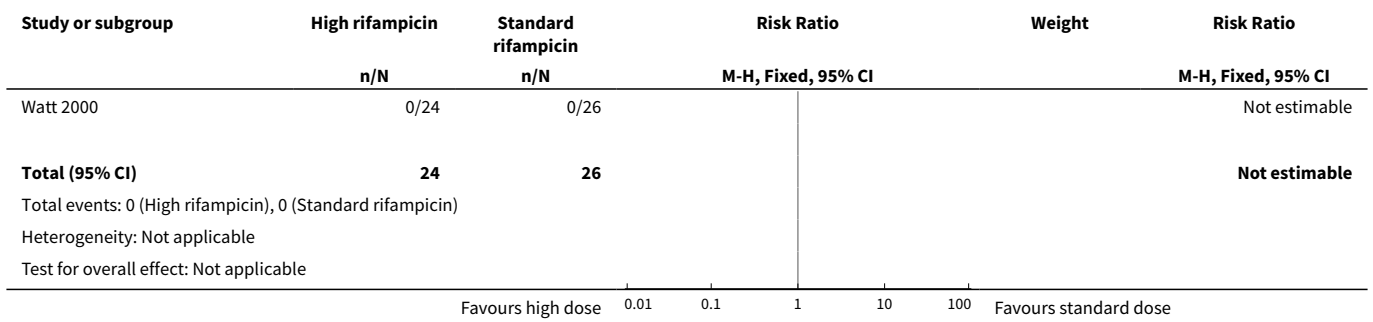
Analysis 4.2. Comparison 4 High rifampicin dose versus standard rifampicin dose, Outcome 2 Resolution of fever within 48 hours.

Study or subgroup	High rifampicin dose	Standard rifampicin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Watt 2000	19/24	20/26		100%	1.03[0.77,1.38]
Total (95% CI)	**24**	**26**		**100%**	**1.03[0.77,1.38]**
Total events: 19 (High rifampicin dose), 20 (Standard rifampicin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					

Favours standard dose 0.01 0.1 1 10 100 Favours high dose
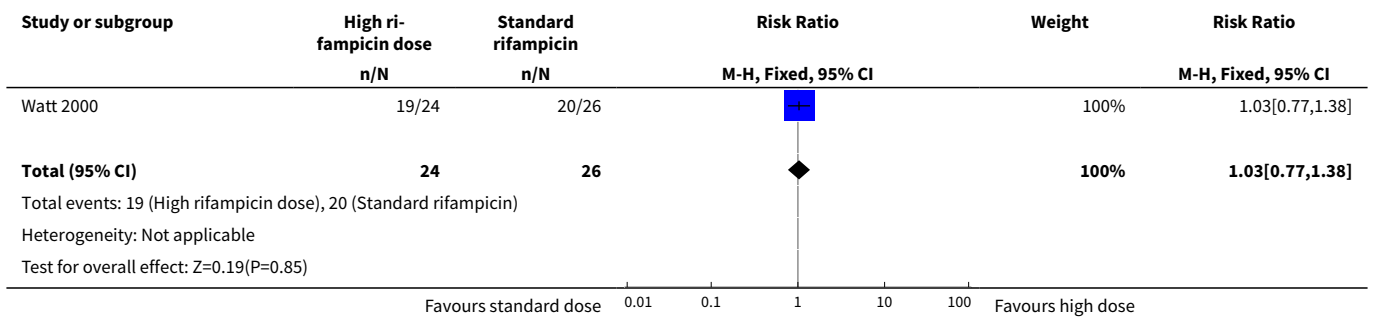
Analysis 4.3. Comparison 4 High rifampicin dose versus standard rifampicin dose, Outcome 3 Serious adverse events.
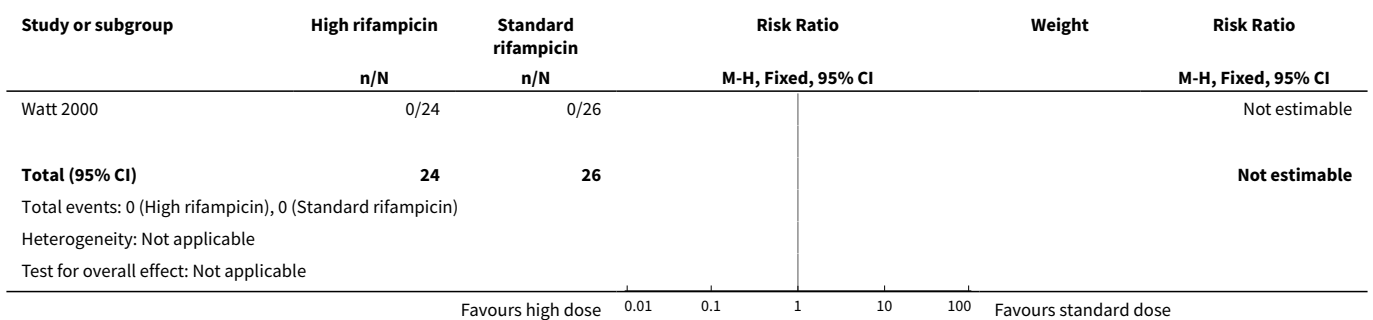
Study or subgroup	High rifampicin	Standard rifampicin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Watt 2000	0/24	0/26			Not estimable
Total (95% CI)	**24**	**26**			**Not estimable**
Total events: 0 (High rifampicin), 0 (Standard rifampicin)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours high dose 0.01 0.1 1 10 100 Favours standard dose

Comparison 5. Macrolide subgroup: azithromycin versus doxycycline

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Treatment failure	2	150	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.12, 63.84]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Resolution of fever within 48 hours	2	150	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.32, 2.03]
3 Resolution of fever within 5 days	1	93	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.98, 1.17]
4 Serious adverse events	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Macrolide subgroup: azithromycin versus doxycycline, Outcome 1 Treatment failure.

Study or subgroup	Azithromycin n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2004	0/47	0/46			Not estimable
Phimda 2007	1/30	0/27		100%	2.71[0.12,63.84]
Total (95% CI)	77	73		100%	2.71[0.12,63.84]
Total events: 1 (Azithromycin), 0 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.62(P=0.54)					

Favours azithromycin 0.01 0.1 1 10 100 Favours doxycycline

Analysis 5.2. Comparison 5 Macrolide subgroup: azithromycin versus doxycycline, Outcome 2 Resolution of fever within 48 hours.

Study or subgroup	Azithromycin n/N	Doxycycline n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kim 2004	40/47	33/46		55.14%	1.19[0.95,1.47]
Phimda 2007	9/30	16/27		44.86%	0.51[0.27,0.95]
Total (95% CI)	77	73		100%	0.81[0.32,2.03]
Total events: 49 (Azithromycin), 49 (Doxycycline)					
Heterogeneity: Tau²=0.38; Chi²=7.66, df=1(P=0.01); I²=86.94%					
Test for overall effect: Z=0.45(P=0.65)					

Favours doxycycline 0.5 0.7 1 1.5 2 Favours azithromycin
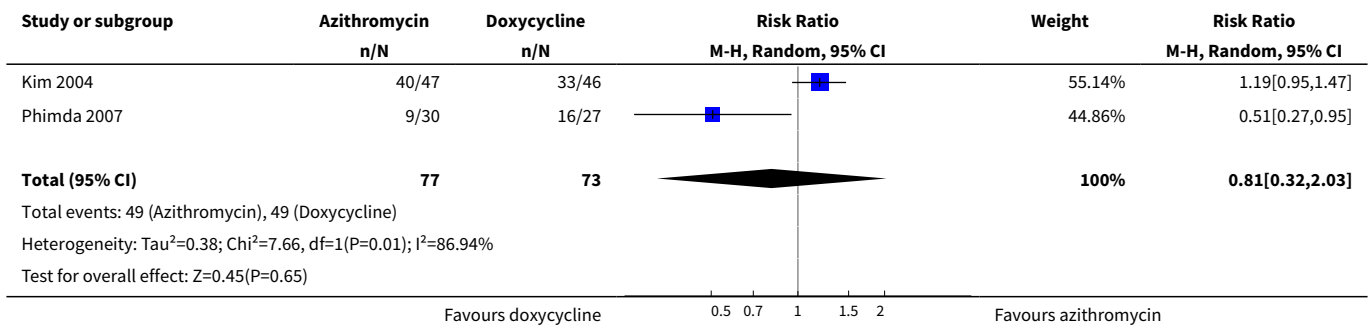
Analysis 5.3. Comparison 5 Macrolide subgroup: azithromycin versus doxycycline, Outcome 3 Resolution of fever within 5 days.

Study or subgroup	Azithromycin n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2004	47/47	43/46		100%	1.07[0.98,1.17]
Total (95% CI)	47	46		100%	1.07[0.98,1.17]
Total events: 47 (Azithromycin), 43 (Doxycycline)					

Favours doxycycline 0.01 0.1 1 10 100 Favours azithromycin

Study or subgroup	Azithromycin	Doxycycline	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=1.52(P=0.13)					

Favours doxycycline   0.01   0.1   1   10   100   Favours azithromycin

Analysis 5.4. Comparison 5 Macrolide subgroup: azithromycin versus doxycycline, Outcome 4 Serious adverse events.

Study or subgroup	Azithromycin	Doxycycline	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Kim 2004	0/47	0/46			Not estimable
Phimda 2007	0/27	0/30			Not estimable
Total (95% CI)	74	76			Not estimable
Total events: 0 (Azithromycin), 0 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

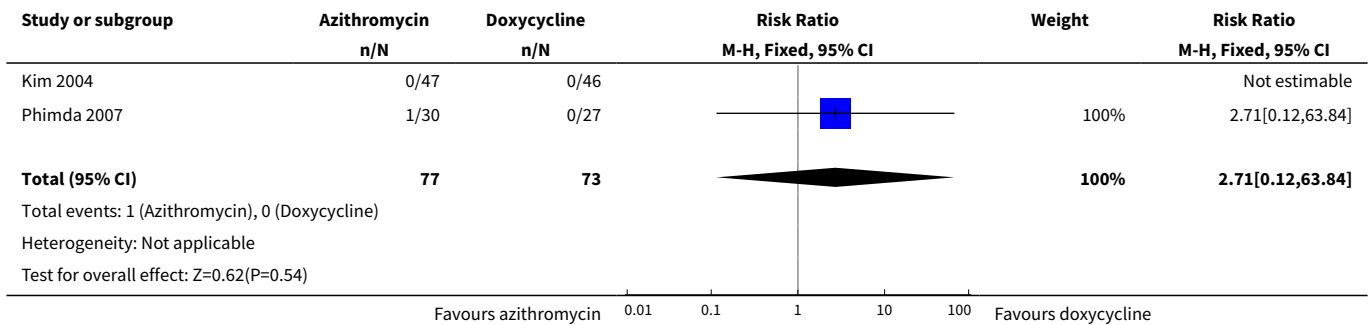Favours azithomycin   0.01   0.1   1   10   100   Favours doxycycline

Comparison 6. Macrolide subgroup: telithromycin versus doxycycline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Resolution of fever within 5 days	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.96, 1.09]
3 Serious adverse events	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

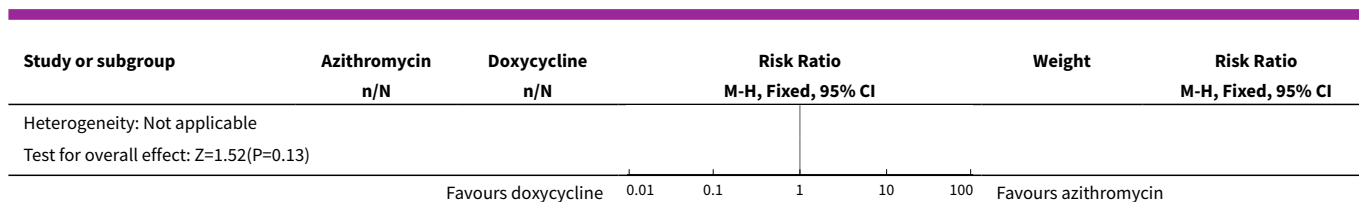### Analysis 6.1. Comparison 6 Macrolide subgroup: telithromycin versus doxycycline, Outcome 1 Treatment failure.

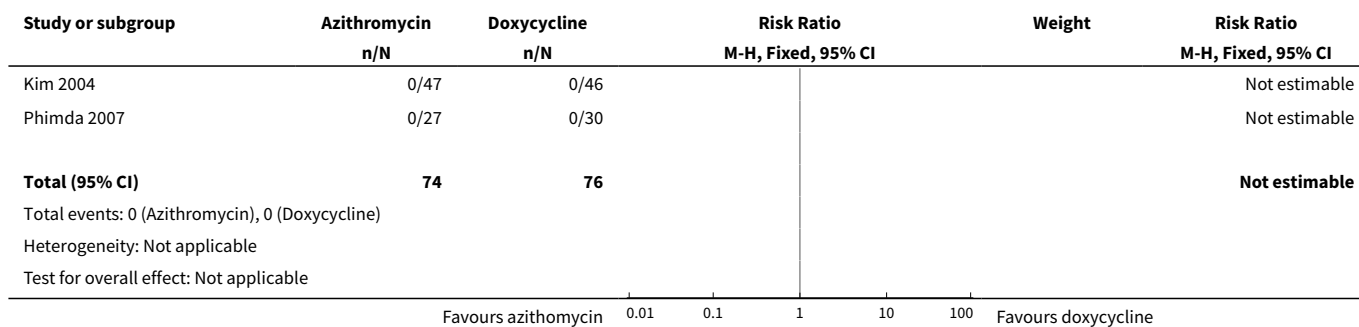| Study or subgroup	Telithromycin	Doxycycline	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Kim 2007	0/47	0/45			Not estimable
Total (95% CI)	47	45			Not estimable
Total events: 0 (Telithromycin), 0 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours telithromycin   0.01   0.1   1   10   100   Favours doxycycline

Analysis 6.2. Comparison 6 Macrolide subgroup: telithromycin versus doxycycline, Outcome 2 Resolution of fever within 5 days.

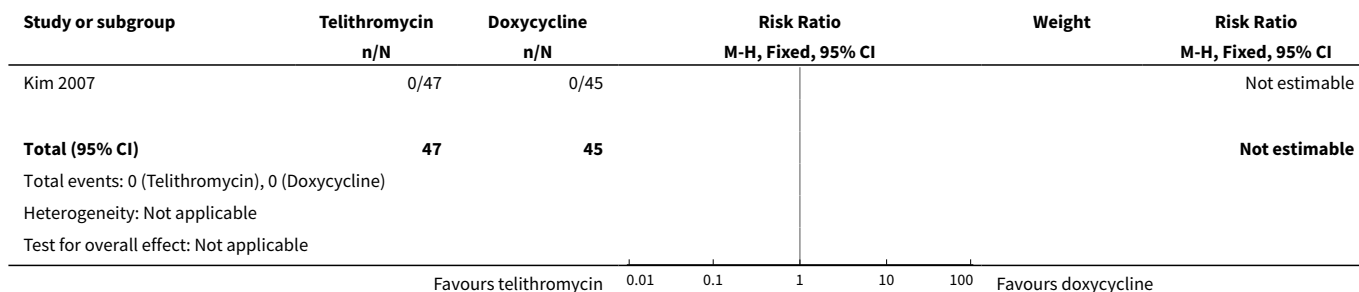| Study or subgroup	Telithromycin n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2007	47/47	44/45		100%	1.02[0.96,1.09]
Total (95% CI)	**47**	**45**		**100%**	**1.02[0.96,1.09]**

Total events: 47 (Telithromycin), 44 (Doxycycline)

Heterogeneity: Not applicable

Test for overall effect: Z=0.74(P=0.46)

Favours telithromycin 0.01 0.1 1 10 100 Favours doxycycline

Analysis 6.3. Comparison 6 Macrolide subgroup: telithromycin versus doxycycline, Outcome 3 Serious adverse events.

Study or subgroup	Telithromycin n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kim 2007	0/47	0/45			Not estimable
Total (95% CI)	**47**	**45**			**Not estimable**

Total events: 0 (Telithromycin), 0 (Doxycycline)

Heterogeneity: Not applicable

Test for overall effect: Not applicable

Favours telithromycin 0.01 0.1 1 10 100 Favours doxycycline

ADDITIONAL TABLES

Table 1. Detailed search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	Embase[b]	LILACS[b]
1	Scrub typhus	SCRUB TYPHUS	SCRUB TYPHUS	SCRUB TYPHUS	Scrub typhus
2	*Rickettsia tsutsugamushi*	Scrub typhus [ti, ab]	Scrub typhus [ti, ab]	Scrub typhus [ti, ab]	*Rickettsia tsutsugamushi*
3	*Orientia tsutsugamushi*	*Orientia tsutsugamushi* [ti, ab]	*Orientia tsutsugamushi* [ti, ab]	*Orientia tsutsugamushi* [ti, ab]	*Orientia tsutsugamushi*
4	1 or 2 or 3	*Rickettsia tsutsugamushi* [ti, ab]	*Rickettsia tsutsugamushi* [ti, ab]	*Rickettsia tsutsugamushi* [ti, ab]	1 or 2 or 3
5	¬	*ORIENTIA TSUTSUGAMUSHI*	*ORIENTIA TSUTSUGAMUSHI*	*ORIENTIA TSUTSUGAMUSHI*	¬
6	¬	1 or 2 or 3 or 4 or 5	1 or 2 or 3 or 4 or 5	1 or 2 or 3 or 4 or 5	¬
7	¬	¬	Limit 6 to humans	Limit 6 to humans	¬

*a*Cochrane Infectious Diseases Group Specialized Register.

[b]Search terms used in combination with the search strategy for retrieving trials developed by Cochrane; upper case: MeSH or EMTREE heading; lower case: free text term.

Table 2. Adverse events (non-severe)

Study	Intervention	Comparison
	Doxycycline	**Tetracycline**
[Brown 1978](#)	Vomiting (8/35)	None reported
	Rash (1/35)	
[Song 1995](#)	Gastrointestinal reactions (33/66)	Gastrointestinal reactions (10/50)
Study	**Doxycycline**	**Macrolides**
[Kim 2004](#)	Nausea (4/47)	*(Azithromycin)*
	Diarrhoea (2/47)	Nausea (6/46)
	Abdominal discomfort (1/47)	Vomiting (3/46)
	Raised ALT (5/47)	Raised ALT (4/46)
	Thrombocytopaenia (1/47)	
[Kim 2007](#)	Nausea (2/45)	*(Telithromycin)*
	Vomiting (1/45)	Abdominal discomfort (3/47)
	Diarrhoea (1/45)	Elevated ALT (4/47)
	Abdominal discomfort (2/45)	
	Elevated ALT (2/45)	
	Skin rash (2/45)	
	Oesophageal candidiasis (1/45)	
[Phimda 2007](#)	Nausea (3/145)	*(Azithromycin)*
	Vomiting (22/145)	Nausea (1/151)
	Nausea and vomiting (10/145)	Vomiting (10/151)
	Diarrhoea (1/145)	Nausea and vomiting (1/151)
	Abdominal pain (1/145)	Diarrhoea (1/151)
	Rash (1/145)	Rash (3/151)
	Dizziness (1/145)	
Study	**Doxycycline**	**Rifampicin**
[Watt 2000](#)	Rash and eosinophilia (1/28)	Rash and eosinophilia (7/50)
	"Severe gastrointestinal (GI) side effects" (2/28)	"Mild GI side effects" (18/50)
	"Mild GI side effects" (14/28)	Red-orange discolouration of urine (50/50)

Abbreviations: ALT: alanine aminotransferase; GI: gastrointestinal.

Table 3. Time to defervescence: macrolides versus doxycycline

Study	Doxycycline		Macrolide	
	Median	**Range**	**Median**	**Range**
Kim 2004	29 hours	4 to 176 hours	21 hours	1 to 120 hours
Kim 2007	18 hours	4 to 105 hours	18 hours	4 to 176 hours
Phimda 2007	45 hours	8 to 118 hours	40 hours	8 to 136 hours

A P P E N D I C E S

Appendix 1. Prespecified changes for review update 2018

Protocol section	Refreshed protocol
Background and research question	• We have updated information in the background to follow the advised Cochrane/MECIR subheading structure • We have included further information on diagnostics and have elaborated on antibiotics and antibiotic resistance • The main review question remains relevant
	• The existing PICO remains relevant. We have added clarification to the diagnostic criteria used to define cases of scrub typhus • We have identified new concerns in relation to the use of quinolone antibiotics that were not covered by the original review • We have not identified changes in core standards or in standardized core outcome sets • We are aware of no patient-reported outcomes • We do not think that any changes to studies may warrant stricter inclusion criteria
Methods	• We have updated the description of the risk of bias tool • We have added a plan to summarize the evidence using the GRADE approach

This table was approved by the CIDG editorial team on 16 March 2018.

W H A T ' S   N E W

Date	Event	Description
20 September 2018	New citation required and conclusions have changed	We updated the literature search to 8 January 2018, included one new trial (Chanta 2015), and excluded one previously included trial (Sheehy 1973). The conclusions changed to reflect certainty of evidence and to present more guarded conclusions about rifampicin.

Date	Event	Description
20 September 2018	New search has been performed	The review author team changed. The review author team revised the protocol, which was approved by the CIDG editorial team on 16 March 2018 (see Appendix 1). We reworded the objectives: "To assess and compare the effects of different antibiotic regimens for treatment of scrub typhus", replaces "To evaluate antibiotic regimens for treating scrub typhus". We assessed the certainty of the evidence using the GRADE approach.

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 2, 2000

Date	Event	Description
27 May 2010	New search has been performed	New search performed and new studies added. Primary outcomes amended
8 June 2009	Amended	Review converted to new review format
3 January 2007	New citation required and conclusions have changed	Substantive amendments made

CONTRIBUTIONS OF AUTHORS

Iman El Sayed: prepared initial drafts of background and methods; selected studies; extracted data; synthesized data in RevMan 2014; and prepared initial drafts of results and 'Summary of findings' tables.

Qin Liu: selected studies and extracted data; assessed risk of bias; contributed to 'Summary of findings' tables; and contributed to the discussion.

Ian Wee: selected studies and extracted data; assessed risk of bias; and contributed to results and discussion sections.

Paul Hine: completed drafts of background, methods, results, 'Summary of findings' tables, discussion, and conclusions.

DECLARATIONS OF INTEREST

IES has no known conflicts of interest.
QL has no known conflicts of interest.
IW has no known conflicts of interest.
PH has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review author team revised the protocol, which was approved by the CIDG editorial team on 16 March 2018 (see Appendix 1). Owing to small numbers of trials per each comparison, we did not perform subgroup analysis according to geographical setting (which may influence antibiotic susceptibility), dates of the study (before or after antibiotic resistance was first reported), participant age (children versus adults), or dose, frequency, and duration of treatment. We also did not perform sensitivity analysis to assess robustness of our results after restricting analysis to studies with low risk of bias. Otherwise, we fulfilled all proposed changes as shown in Appendix 1.

Upon receiving editorial feedback on the first draft of this review, we changed 'resolution of fever within five days' from a primary to a secondary outcome.

NOTES

REVIEW HISTORY (started 4 March 2002).
4 March 2002: updated review received by editorial base: included a new trial (Watt 2000); responded to comments received from Assistant Editor and statistician: (1) made slight change to the objective; (2) changed adverse outcomes from "Number and seriousness of side effects" to "Number of adverse events"; and (3) used risk ratio for binary outcomes (previously Peto odds ratio).

June 2010: updated review received by editorial base: (1) amended primary outcomes so no longer include "death" as a primary outcome; and (2) added new trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Azithromycin [therapeutic use]; Chloramphenicol [therapeutic use]; Doxycycline [therapeutic use]; Macrolides [therapeutic use]; Randomized Controlled Trials as Topic; Rifampin [therapeutic use]; Scrub Typhus [*drug therapy]; Tetracycline [therapeutic use]

MeSH check words

Adult; Child, Preschool; Humans