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Original Article

Antibiotics in the treatment of scrub typhus: A network meta-analysis and cost-effectiveness analysis

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Abstract

Introduction: A pharmacoeconomic analysis model was developed to evaluate the cost-effectiveness of antibiotics from a societal perspective in Korea and China. A network meta-analysis was conducted to evaluate the efficacy of antibiotics.

Methodology: We conducted a systematic search for randomized controlled trials or quasi-randomized controlled trials on antibiotics employed as therapy in scrub typhus management. We performed a network meta-analysis to obtain their relative efficacy. The outcome measures for efficacy were cure rate and non-relapse rate. To evaluate their relative cost-effectiveness in Korea and China, a decision analytic model simulating a cohort of scrub typhus patients using antibiotics as therapy was constructed from a societal perspective over 8 weeks. The number of cure cases per 1000 patients and the incremental cost-effectiveness ratio (ICER) was calculated.

Results: We identified 11 relevant articles for network meta-analysis. Of the seven comparisons (azithromycin, chloramphenicol, doxycycline, high-dose rifampin, low-dose rifampin, telithromycin, tetracycline) included in the network meta-analysis, tetracycline was the most effective drug for the treatment of scrub typhus, but the difference is not significant. In the cost-effectiveness analysis, all the treatments were dominated by tetracycline in Korea and China.

Conclusions: Tetracycline is the most economic drug for the treatment of scrub typhus. Hence, tetracycline is recommended as the first choice for the treatment of scrub typhus without contraindications in China and Korea.

Key words: Scrub typhus; network meta-analysis; cost-effectiveness analysis; decision analytic model; antibiotics.

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Introduction

Scrub typhus is a life-threatening zoonosis caused by *Orientia tsutsugamushi*, which has a wide geographical distribution [1]. *Orientia tsutsugamushi* is an obligately intracytosolic bacterium that is transmitted by the larval stage of mites (“chiggers”) in the family Trombiculid [2,3]. In the past, it mainly occurred in the Asia-Pacific region, including China, Korea, Vietnam, India, and other countries (the "tsutsugamushi triangle"). The “tsutsugamushi triangle” lives in about half of the world's population [4], and it is estimated that 1 million people living with scrub typhus each year and approximately 1 billion people at risk [5-7]. Recent studies have shown that scrub typhus is no longer limited to the "tsutsugamushi triangle" [8]. Cases of scrub typhus have also been reported in Africa, South America, the Middle East, and other regions [9]. The clinical manifestations of scrub typhus vary from fever and eschar to pneumonia, meningoencephalitis, shock, renal failure, and even death [10]. The median mortality of untreated scrub typhus is 6% (range 0~70%) [11]. Kim *et al.* [12] evaluated the value of a scrub typhus prevention program that estimated $6.6 million per year were salvaged. As it is, scrub typhus caused $6.6 million in economic losses per year in Korea at least. Therefore, we should keep a watchful eye on scrub typhus due to limited health resources. Conventional antibiotics are ineffective in the treatment of scrub typhus, and the main therapeutic drugs are azithromycin, chloramphenicol, tetracycline, doxycycline and quinolone [6]. There are a few systematic reviews to compare the efficacy and safety of antibiotics in the treatment of scrub typhus by a pairwise meta-analysis [6,13-15] or a network meta-analysis [16-18], but there are no studies to evaluate economy. Therefore, the primary aim of this research is to evaluate the economy of antibiotics in the treatment of scrub typhus by a decision analytical model. The secondary purpose is to make a network meta-analysis to obtain the relative efficacy (the cure rate and the relapse rate) of antibiotics.

Methodology

Search Strategy

A systematic search of PubMed, Embase, Web of science and the Cochrane Library were conducted up to November 9, 2023. The highly sensitive search strategy was employed to identify randomized controlled trials, using a combination of medical subject headings (MeSH) and text words related to the term "scrub typhus" and "treatment" (Supplementary Table 1).

Inclusion criteria: 1. The study participants had to be diagnosed as scrub typhus. 2. Randomized controlled trial (RCT) or quasi-randomized controlled trial (QRCT) was included. A quasi-randomized controlled trial is a clinical controlled trial assigned by the method of quasi-randomization, that is, according to number odd and even hospital numbers to group.

Exclusion criteria: 1. Non-randomized controlled trials. 2. Retrospective analysis, case reports, reviews, conference articles, etc. 3. Combination therapy. 4. Ongoing randomized controlled trials or \unable to access the records.

Data Extraction and Quality Assessment

Two authors independently evaluated all eligible articles. These articles were scrutinized, and the data regarding "country", "design", "age", "comparisons", "dose" and "outcomes" from the selected studies were extracted. The data we extracted used for analyzed is presented in Supplementary Table 2 and 3. The Cochrane 'Risk of bias' tool was used to evaluate the quality of all eligible articles. We resolved discrepancies through discussion and reached an agreement.

Data Synthesis

Statistical Selection

The primary outcome measure of efficacy was cure rate defined as defervescence (body temperature < 37.3 ℃) after antibiotic treatment and persist for more than 48 hours. Special precautions usually need to be taken in the case of the occasional trial with a zero cell count when we perform a frequentist network meta-analysis. Some popular frequentist approaches for log odds ratios or log relative risks have to add an arbitrary constant, usually 0.5, to cells to obtain non-infinite estimates of treatment effects and non-infinite variance, but in so doing they generate biased estimates of effect size [19]. So, our secondary outcome measure of efficacy was "non-relapse rate" (1-"relapse rate", not "relapse rate" (some trials with zero count). Relapse defined in most trials as the recurrence of fever or clinical symptoms recurrence within 30 days after the patient is determined to be completely cured [20].

Pairwise Meta-analysis

We conducted a random-effects meta-analysis of all direct comparisons, allowing for heterogeneity in treatment effects between studies. All pairwise analysis was conducted using the "*meta*" package in R version 4.1.2. I^2 statistic was used to estimate statistical heterogeneity. The values of 25%, 50%, 75% denoted little, medium and severe level of heterogeneity, respectively [21].

Network Meta-analysis

A frequentist network meta-analysis was performed in Stata version 14.0 using the "*mvmeta*" and "*network*" package. We assumed network consistency and a common heterogenity parameter across all treatment contrasts [22]. The summary treatment effect estimates for all treatment comparisons were presented in league tables with relative risk ratios (RRs) and 95% confidence intervals (CIs). We also computed ranking probabilities for all outcomes to obtain the treatment hierarchies.

We used χ^2 statistics and p values to determine whether to use the consistency model or the inconsistency model. If $p > 0.05$, it is suggested that there was no inconsistency, the consistency model was used. We also estimated absolute differences between direct and indirect evidence by computed inconsistency factors (IFs) and 95% CIs for each closed triangular loop within treatment networks. To measure the small-study effect, we drew the funnel plots. The commands used in R and Stata are presented in Supplementary Table 4.

Cost-Effectiveness Analysis

Model Structure

A decision analytic model was developed to simulate the clinical management of patients with scrub typhus over a time horizon of 8 weeks (Figure 1), using TreeAge Pro Version 2020. The target population was patients with scrub typhus. We adopted a societal perspective to identify and measure costs. Major clinical events covered in the model were recovery, relapse, and prolong the course of treatment (Prolong Course). The 8-week time horizon was considered sufficient to capture important clinical events that would determine the effectiveness of an antibiotic.

Model Assumptions

Our model assumed that the treatment doses were the most commonly used doses in eligible articles, and the course of treatment of all antibiotics was 7 days. We assumed the patients who treated failure and relapsed after recovery underwent a "Prolong Course" therapy (Original treatment protocols were extended for 3 days) [23]. Our model also assumed that adverse reactions did not affect the therapeutic effect of drugs, which ignored the possibility of therapeutic change due to adverse reactions.

Model Inputs

Cost included direct medical costs (such as drug costs, laboratory investigations and other direct medical costs), indirect costs associated with the productivity loss and intangible costs (Table 1). In Korea, drug costs are derived from Health Insurance Review and Assessment Service (HIRA*)*. Other direct medical costs, direct non-medical costs, and indirect costs (productivity loss) in the treatment of scrub typhus derived from a cost-effective study of Korea [12]. The above costs were discounted to November 2023 at an annual rate of 5%.

In China, drug costs are derived from local hospitals in Fujian Province. Other direct medical costs in the treatment of scrub typhus derived from the real-world cases of the third-class A hospitals in Fujian Province (Fujian Medical University Union Hospital, Longyan First Hospital, and Nanping First Hospital). By screening the patients with scrub typhus in these hospitals, we obtained the average of direct medical costs. We screened the cases from January 2014 to July 2019, we included a total of 346 cases of scrub typhus. Indirect costs and intangible costs derived from a cost-effective study of China [24]. All costs were discounted to November 2023 at an annual rate of 5%.

The failure rate (1-"cure rate") and the relapse rate (1-"non-relapse rate") of the antibiotics were derived from our network meta-analysis, which represented the comparative clinical effectiveness of all treatment comparisons (Table 1). The same dataset was used to represent the clinical effectiveness of "Prolong Course" therapy.

There was no study has previously reported the utility of scrub typhus. Scrub typhus and dengue fever have so many similarities in duration, high-risk population, signs and symptoms, pathogenesis and prognosis [25] that utility of dengue fever (0.66) [26] was referred in the research of scrub typhus.

Model Outcome

We estimated the total expected cost and quality-adjusted life years (QALY) for all antibiotics over 8 weeks. The incremental cost-effectiveness ratio (ICER) per QALY gained and the number of cure cases per 1000 patients were calculated. The willingness-to-pay (WTP) threshold was set at 38160.6 US dollars (USD) per QALY gained in China and 96763.8 US dollars (USD) per QALY gained in Korea (3 × domestic GDP per capita in 2022).

Sensitivity Analysis

The uncertainties of key parameters were analyzed using one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA). For drug costs, direct medical costs, direct non-medical costs, indirect costs and intangible costs, one-way sensitivity analysis was performed across a wide range (± 20%) to capture all possible scenarios. For all key parameters, PSA was applied to reflect the impact of their stochastic characteristics on the results.

Figure 1. Schematic representation of model structure. A decision-tree analysis assessed six antibiotics as monotherapy management of scrub typhus over a time horizon of 8 weeks.

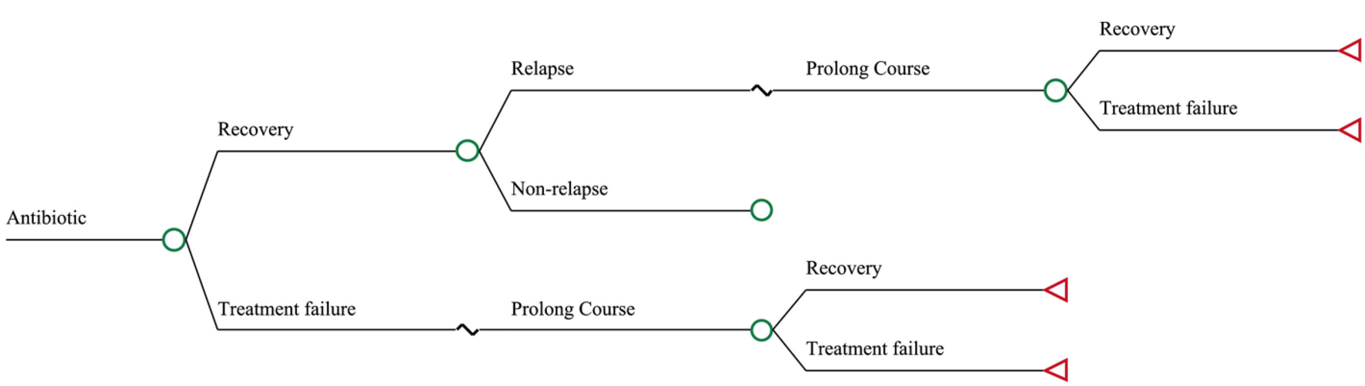


Table 1. Model inputs.

Parameters	Base case / $	Uncertainty (distribution/range)	Source
Korean Costs			
Drug costs			***HIRA*** [19]
Azithromycin	0.792/250mg	Gamma (0.634-0.950)	
Chloramphenicol	0.245/50mg	Gamma (0.196-0.294)	
Doxycycline	0.115/100mg	Gamma (0.092-0.138)	
Rifampicin	0.066/150mg	Gamma (0.053-0.079)	
Tetracycline	0.051/250mg	Gamma (0.041-0.061)	
Direct medical costs§	149.1/day	Gamma (119.3-178.9)	***Kim Jinhyun*** [9]
Direct non-medical costs§	11.80/day	Gamma (9.440-14.16)	
Indirect costs§			
Productivity loss	217.3/day	Gamma (173.8-260.8)	
Chinese Costs			
Drug costs			***Local hospital***
Azithromycin	0.788/250mg	Gamma (0.630-0.946)	
Chloramphenicol	0.024/250mg	Gamma (0.019-0.029)	
Doxycycline	0.024/100mg	Gamma (0.019-0.029)	
Rifampicin	0.041/150mg	Gamma (0.033-0.049)	
Tetracycline	0.011/250mg	Gamma (0.009-0.013)	
Other direct medical costs			***Local hospital***
Hospitalization	46.66/day	Gamma (37.33-55.99)	
Other drug costs	39.25/day	Gamma (31.40-47.10)	
Laboratory	111.0/day	Gamma (88.80-133.2)	
Direct non-medical costs§			***Da-fei Ren*** [20]
Transportation	9.89/day	Gamma (7.912-11.87)	
Indirect costs§			
Productivity loss	56.24/day	Gamma (44.99-67.49)	
Intangible costs§	84.68/day	Gamma (67.75-101.6)	
Failure rate			***Network meta-analysis***
Azithromycin	8.03%	Beta (0.86-15.20%)	
Chloramphenicol	5.97%	Beta (0.00-13.57%)	
Doxycycline	9.83%	Beta (3.72-15.94%)	
High-dose Rifampicin	10.07%	Beta (1.28-18.86%)	
Low-dose Rifampicin	9.90%	Beta (3.41-16.39%)	
Tetracycline	5.77%	Beta (0.00-14.05%)	
Relapse rate			***Network meta-analysis***
Azithromycin	8.11%	Beta (4.32-11.91%)	
Chloramphenicol	10.18%	Beta (2.28-16.89%)	
Doxycycline	8.06%	Beta (5.26-10.87%)	
High-dose Rifampicin	6.88%	Beta (0.00-14.39%)	
Low-dose Rifampicin	7.87%	Beta (4.29-11.45%)	
Tetracycline	8.09%	Beta (0.67-15.52%)	
Relapse interval time	4	Gamma (3-14)	
Utility of scrub typhus	0.66	Gamma (0.53-0.79)	***Bach Xuan Tran*** [22]

§ We calculated the daily mean costs based on the assumption that the average hospitalization days was 7 days.

Results

Search Results

Study Selection and Study Characteristics

The process of record screening and inclusion is shown in Figure 2. We eventually included 11 articles [20,27-36] (9 RCTs and 2 QRCTs), with a total of 880 participants, including seven comparisons (six antibiotics) (Supplementary Table 5). The geographical locations where these studies were conducted is shown in Supplementary Figure 1. A majority of the studies were conducted in Korea and Thailand. Apart from Chanta and Phloenchaiwanit [34] who compared three antibiotics, other trials were compared antibiotics in pairs. The efficacy of azithromycin versus doxycycline or chloramphenicol in the treatment of scrub typhus was compared in the study by Chanta and Phloenchaiwanit [34], therefore, we assumed that doxycycline and chloramphenicol had the same cure rate their study.

Articles Quality Assessment

We used Cochrane 'Risk of bias' tool to evaluate the quality of all eligible articles. We made a subjective judgement for each domain as having "high, low, or unclear" risk of bias. We included all assessments in a "Risk of bias" graph (Supplementary Figure 2). In addition to the studies by Kim *et al.* [20] and Kim *et al.* [32], a quasi-randomized distribution method was used, and most of the eligible articles were randomized. All eligible articles were not double-blind, and most of the studies were of low risk for other biases.

Network Meta-Analysis

Network plot

The network plot of eligible comparisons for efficacy (cure rate) and non-relapse rate in the network meta-analysis is shown in Figure 3.

Pairwise Meta-Analysis

The results of pairwise meta-analysis and heterogeneity estimates are presented in Supplementary Table 6. The forest plots are presented in Supplementary Figure 3. We found that there were no differences between all treatment comparisons neither cure rate nor non-relapse rate. The heterogeneity between trials about doxycycline compared with tetracycline was severe (I^2 = 59.1%), and others were little or medium.

Figure 3. The Network Plot of Eligible Comparisons for the Analysis.

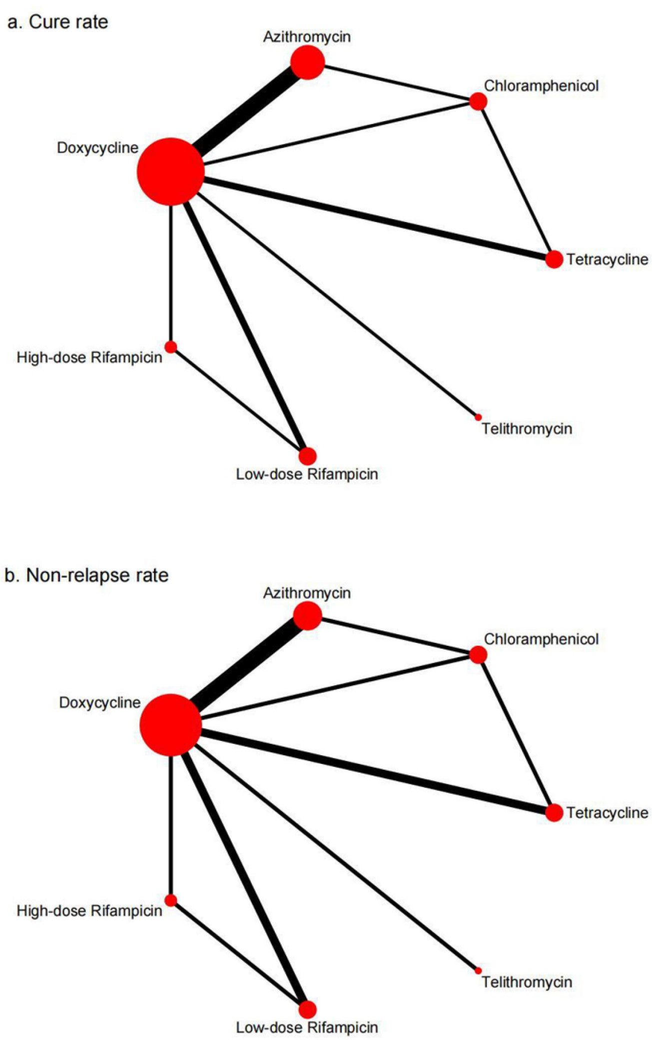
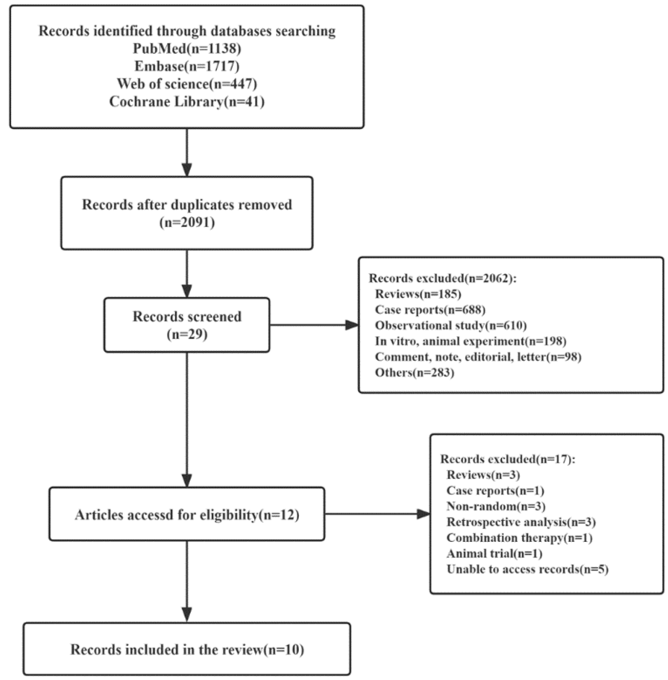


Figure 2. Study screening and inclusion flow diagram.



Network Meta-Analysis

A consistency model was used to make network meta-analysis for the cure rate (χ^2 = 0.80, p = 0.848) and non-relapse rate (χ^2 = 2.58, p = 0.462). The league tables of network meta-analysis were shown in Figure 4. And the forest plots are presented in Supplementary Figure 4. No significant difference among them was observed. We present the inconsistency plots for each outcome in Supplementary Figure 5. There was no evidence of inconsistency for all outcomes. And the small-study effects are presented in funnel plots (Supplementary Figure 6).

The cumulative ranking plots and the Surface Under the Cumulative RAnking curve (SUCRA) values are presented in Supplementary Figure 7.

Probability of Antibiotics

According to the efficacy result of network meta-analysis, we obtained the relative failure rate and relapse rate of seven comparisons by calculation (Table 1).

Cost-Effectiveness Analysis

Table 2 shows the costs and effectiveness of comparisons in the base-case analysis for Korea and China. All comparisons were dominated by Tetracycline in China and Korea. Sensitivity analysis shows that the results are robust (Supplementary Figures 8-10).

Figure 4. Results derived from network meta-analysis. Results are the relative risks (RRs) with 95% confidence intervals (CIs) in the former column-defining treatments compared with the latter column-defining treatments.

Efficacy (Cure rate) | Comparison | Non-Relapse rate

Azithromycin	1.023 (0.947,1.099)	0.999 (0.971,1.028)	0.987 (0.906,1.067)	0.997 (0.960,1.035)	0.977 (0.917,1.046)	1.000 (0.958,1.041)
0.978 (0.868,1.089)	**Chloramphenicol**	0.977 (0.907,1.059)	0.965 (0.873,1.079)	0.975 (0.902,1.060)	0.956 (0.873,1.056)	0.977 (0.904,1.063)
1.019 (0.978,1.061)	1.043 (0.940,1.170)	**Doxycycline**	0.987 (0.919,1.067)	0.998 (0.974,1.023)	0.978 (0.923,1.039)	1.000 (0.970,1.031)
1.022 (0.943,1.101)	1.045 (0.926,1.201)	1.003 (0.939,1.075)	**High-dose Rifampicin**	1.011 (0.938,1.084)	0.990 (0.904,1.095)	1.013 (0.931,1.095)
1.020 (0.972,1.067)	1.043 (0.939,1.174)	1.001 (0.978,1.025)	0.998 (0.931,1.066)	**Low-dose Rifampicin**	0.980 (0.921,1.047)	1.002 (0.963,1.041)
0.997 (0.929,1.075)	1.019 (0.907,1.161)	0.978 (0.923,1.039)	0.975 (0.896,1.070)	0.977 (0.919,1.043)	**Telithromycin**	1.023 (0.955,1.091)
0.976 (0.900,1.052)	0.998 (0.917,1.094)	0.957 (0.892,1.022)	0.954 (0.861,1.048)	0.956 (0.887,1.025)	0.980 (0.891,1.068)	**Tetracycline**

Discussion

In the network meta-analysis, the most efficacious antibiotic was tetracycline, followed by chloramphenicol, telithromycin, azithromycin high-dose rifampin, doxycycline, low-dose rifampicin, but there is no significant difference in efficacy among those comparisons. Telithromycin had the lowest relapse rate, followed by high-dose rifampin, low-dose rifampicin, tetracycline, doxycycline, azithromycin, and chloramphenicol, there are also no significant differences in efficacy among those comparisons. In other words, there are no antibiotics showed a significant advantage or disadvantage in the treatment of scrub typhus. This is similar to the conclusions of two recently published network meta-analysis [17,18]. The difference is that the order of cure rate. Their studies included more research which were excluded in our network meta-analysis because they were not considered as randomized controlled trials in our view.

In the cost-effectiveness analysis, a decision analytic model was developed to simulate the clinical management of patients with scrub typhus over a time horizon of 8 weeks. In the base analysis, the patients with scrub typhus received tetracycline produced the lowest costs ($2802.38 in Korea and $2574.40 in China) and highest benefits (0.14629 QALYs in Korea and China). Therefore, the most economic antibiotic was tetracycline in Korea and China. The results of the sensitivity analysis supported the conclusion.

It seems most appropriate to use tetracycline for the treatment of scrub typhus. Rifampicin is a common anti-tuberculosis drug, which is used as a monotherapy for scrub typhus may increase the possibility of occurrence of drug-resistant *Mycobacterium tuberculosis*, so should be used with caution [37]. Chloramphenicol was shown to cause serious and fatal aplastic anemia and is now used rarely and reserved for severe, life-threatening infections for which other antibiotics are not available [37]. Currently, the drug of choice is doxycycline, but doxycycline is contraindicated in pregnant women and young children due to its potential fetotoxicity [38,39]. Azithromycin is classified in category B by the US Food and Drug Administration (US FDA) Pregnancy Category and is recommended as an alternative drug in these patients [40]. Hence, in China and Korea, we recommend tetracycline as the first choice for the treatment of scrub typhus without contraindications and azithromycin as

Table 2. Cost and health outcomes over 8 weeks in Korea and China.

Treatment	Cost (USD)	Incremental cost	Effectiveness (QALY)	Incremental QALY	ICER per QALY gained	Effectiveness (Cure cases per 1000 patients)
Korea						
Tetracycline	2802.38	-	0.14629	-	-	992.3
High-dose Rifampicin	2834.82	32.44	0.14583	-0.00046	Dominated	983.6
Azithromycin	2834.96	32.58	0.14603	-0.00026	Dominated	987.6
Low-dose Rifampicin	2842.16	39.78	0.14580	-0.00049	Dominated	983.2
Doxycycline	2843.12	40.74	0.14580	-0.00049	Dominated	983.2
Chloramphenicol	2933.50	131.12	0.14619	-0.00010	Dominated	990.7
China						
Tetracycline	2574.40	-	0.14629	-	-	992.3
Chloramphenicol	2598.32	23.92	0.14619	-0.00010	Dominated	990.7
High-dose Rifampicin	2605.47	31.07	0.14583	-0.00046	Dominated	983.6
Azithromycin	2607.38	32.97	0.14603	-0.00026	Dominated	987.6
Low-dose Rifampicin	2612.51	38.11	0.14580	-0.00049	Dominated	983.2
Doxycycline	2613.48	39.07	0.14580	-0.00049	Dominated	983.2

an alternative treatment in pregnant women and young children.

Our study has several advantages. Firstly, our study was the first one to estimate the efficacy and economy for antibiotics in the treatment of scrub typhus by a frequentist network meta-analysis and a decision analytical model. Secondly, our Chinese medical costs were derived from real-world data, that is, from the costs of real clinical cases in local hospitals, so it was more in line with real-world study.

Meanwhile, our study also has some limitations. First, there were only ten original randomized controlled trials, the result may be affected when there are more studies in the future. Second, we used the utility of dengue fever instead of the utility of scrub typhus in the cost-effectiveness analysis due to the lack of the utility of scrub typhus. Although scrub typhus and dengue fever have so many similarities in duration, high-risk population, signs and symptoms, pathogenesis and prognosis, there may be some minor discrepancy scenarios, so we performed the uncertainty analysis to capture all possible scenarios.

Conclusions

In this study, we evaluated the efficacy and economy of various classes of antibiotics for scrub typhus in a network meta-analysis and cost-effectiveness analysis. No antibiotics showed a significant advantage or disadvantage in the treatment of scrub typhus. But we found that tetracycline showed a significant advantage with regard to economy. In the Korean and Chinese health systems, tetracycline may be recommended as the drug of choice for the treatment of scrub typhus without contraindications, and azithromycin as an alternative treatment in pregnant women and young children.

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Authors' contributions

CCX, CTT, XD, LMB and ZB contributed to the conception and design of the study; CCX and CTT contributed to the acquisition and analysis of data; CCX, CTT and ZB contributed to drafting the text or preparing the figures.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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Conflict of interests

No conflict of interests is declared.

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Annex – Supplementary Items

Supplementary Table 1. Literature search strategy.

Electronic Databases	Literature Search Strategy
PubMed	((((((((((((((Scrub typhus) OR (Tsutsugamushi Fever)) OR (Fever, Tsutsugamushi)) OR (Fevers, Tsutsugamushi)) OR (Tsutsugamushi Fevers)) OR (Tsutsugamushi Disease)) OR (Disease, Tsutsugamushi)) OR (Diseases, Tsutsugamushi)) OR (Tsutsugamushi Diseases)) OR (Orientia tsutsugamushi Infection)) OR (Infection, Orientia tsutsugamushi)) OR (Infections, Orientia tsutsugamushi)) OR (Orientia tsutsugamushi Infections)) OR (Typhus, Scrub)) AND (((((((Therapeutics) OR (Therapeutic)) OR (Therapy)) OR (Therapies)) OR (Treatment)) OR (Treatments)) OR (Treat))
Embase	#1 'therapy'/exp OR treatment OR treat #2 'scrub typhus'/exp #3 #1 and #2
Web of Science	((((((((((((((ALL = (scrub typhus)) OR ALL = (Infection, Orientia tsutsugamushi)) OR ALL = (Typhus, Scrub)) OR ALL = (Infections, Orientia tsutsugamushi)) OR ALL = (Tsutsugamushi Fever)) OR ALL = (Orientia tsutsugamushi Infection)) OR ALL = (Fever, Tsutsugamushi)) OR ALL = (Diseases, Tsutsugamushi)) OR ALL = (Fevers, Tsutsugamushi)) OR ALL = (Orientia tsutsugamushi Infections)) OR ALL = (Tsutsugamushi Diseases)) OR ALL = (Tsutsugamushi Fevers)) OR ALL = (Disease, Tsutsugamushi)) OR ALL = (Tsutsugamushi Disease)) AND (((((((ALL = (Therapeutics)) OR ALL = (Therapeutic)) OR ALL = (Therapy)) OR ALL = (Therapies)) OR ALL = (Treatment)) OR ALL = (Treatments)) OR ALL = (Treat))
Cochrane Library	*scrub typhus in Title Abstract Keyword*

Supplementary Table 2. Data used for analyzing cure rate of drugs.

Study	Intervene1 (Age)			Intervene2			Intervene3		
	Drug	Cure case	Sample size	Drug	Cure case	Sample size	Drug	Cure case	Sample size
Thomas W. Sheehy, 1973	Chl	29	30	Tet	29	30	N/A	N/A	N/A
G. W. Brown, 1978	Dox	28	31	Tet	19	24	N/A	N/A	N/A
Jae-Hoon Song, 1995	Dox	62	66	Tet	50	50	N/A	N/A	N/A
George Watt, 2000	Dox	28	28	Lrif	26	26	Hrif	24	24
Yeon-Sook Kim, 2004	Dox	43	46	Azi	47	47	Azi	47	47
Dong-Min Kim, 2007	Dox	44	45	Tel	47	47	N/A	N/A	N/A
Kriangsak Phimda, 2007	Dox	27	27	Azi	29	30	N/A	N/A	N/A
Chulapong Chanta, 2015	Azi	23	29	Dox	8	9	Chl	16	19
Yun Sung Kim, 2018	Dox	83	83	Lrif	75	75	N/A	N/A	N/A
Karthika I. Kabir, 2022	Azi	55	56	Dox	56	58	N/A	N/A	N/A
Anjali Sharma, 2023	Azi	33	36	Dox	34	39	N/A	N/A	N/A

Chl: Chloramphenicol; Tet:Tetracycline; Dox: Doxycycline; Lrif: Low-dose Rifampicin; Hrif: High-dose Rifampicin; Azi: Azithromycin; Tel: Telithromycin; N/A: Not applicable.

Supplementary Table 3. Data used for analyzing non-relapse rate of drugs.

Study	Intervene1 (Age)			Intervene2			Intervene3		
	Drug	Non-relapse case	Sample size	Drug	Non-relapse case	Sample size	Drug	Non-relapse case	Sample size
Thomas W. Sheehy, 1973	Chl	25	30	Tet	28	30	N/A	N/A	N/A
G. W. Brown, 1978	Dox	31	31	Tet	24	24	N/A	N/A	N/A
Jae-Hoon Song, 1995	Dox	66	66	Tet	50	50	N/A	N/A	N/A
George Watt, 2000	Dox	26	28	Lrif	26	26	Hrif	24	24
Yeon-Sook Kim, 2004	Dox	46	46	Azi	47	47	N/A	N/A	N/A
Dong-Min Kim, 2007	Dox	44	45	Tel	47	47	N/A	N/A	N/A
Kriangsak Phimda, 2007	Dox	27	27	Azi	30	30	N/A	N/A	N/A
Chulapong Chanta, 2015	Azi	29	29	Dox	9	9	Chl	19	19
Yun Sung Kim, 2018	Dox	83	83	Lrif	75	75	N/A	N/A	N/A
Karthika I. Kabir, 2022	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Anjali Sharma, 2023	Azi	36	36	Dox	39	39	N/A	N/A	N/A

Chl: Chloramphenicol; Tet: Tetracycline; Dox: Doxycycline; Lrif: Low-dose Rifampicin; Hrif: High-dose Rifampicin; Azi: Azithromycin; Tel: Telithromycin; N/A: Not applicable.

Supplementary Table 4. The commands used in R and Stata.

Software	Package	Commands
R	meta	data < -read.table("flie.txt",header = T) meta < -metabin(r1,n1,r2,n2,data = AB,sm = "RR",studlab = sort) summary(meta)
Stata	mvmeta/network	insheet using file.txt,clear network setup r n, studyvar(id) trtvar(t) format(augment)rr network map,improve network meta i network meta c netleague, lab (Chl Tet Dox Lrif Hrif Azi Tel) eform network forest, eform network sidesplit all, tau network rank max, all zero reps(5000) gen(prob) sucra prob*, lab (Chl Tet Dox Lrif Hrif Azi Tel) intervalplot, null(1) pred lab(Chl Tet Dox Lrif Hrif Azi Tel) eform network convert pairs netfunnel _y _stderr _t1 _t2, random bycomp add (lfit _stderr _ES_CEN) noalpha ifplot _y _stderr _t1 _t2 id, tau2 (loop) netweight _y _stderr _t1 _t2

Supplementary Table 5. Studies included in the network meta-analysis and study characteristics.

Study	Country	Design	Age	Comparisons	Dose	Outcomes
Thomas W. Sheehy, 1973 [1]	Vietnam	RCT	Unclear	Chl vs. Tet	Chl: 3 g once daily, at least 3d; Tet: 2g, at least 3d	Cure rate, Non-relapse rate
G. W. Brown, 1978 [2]	Malaysia	RCT	18~67 years	Dox vs. Tet	Dox: 200 mg, single dose; Tet: 500 mg six hourly, 7d	Cure rate, Non-relapse rate
Jae-Hoon Song, 1995 [3]	South Korea	RCT	19-82 years	Dox vs. Tet	Dox: 100 mg twelve hourly, 3d; Tet: 500 mg six hourly, 7d	Cure rate, Non-relapse rate
George Watt, 2000 [4]	Thailand	RCT	18~65 years	Dox vs. Lrif vs. Hrif	Dox: 200 mg followed by 100 mg twice daily, 7d; Rif: 300mg or 450mg twice daily, 7d	Cure rate, Non-relapse rate
Yeon-Sook Kim, 2004 [5]	South Korea	RCT	≥ 18 years	Azi vs. Dox	Azi: 500 mg, single dose; Dox: 200 mg once daily, 7d	Cure rate, Non-relapse rate
Dong-Min Kim, 2007 [6]	South Korea	QRCT	≥ 18 years	Dox vs. Tel	Dox: 200 mg once daily, 5d; Tel: 800 mg once daily, 5d	Cure rate, Non-relapse rate
Kriangsak Phimda, 2007 [7]	Thailand	RCT	15~88 years	Dox vs. Azi	Dox: 200 mg followed by 100 mg twice daily, 7d; Azi: 1g followed by 500 mg once daily, 3d	Cure rate, Non-relapse rate
Chulapong Chanta, 2015 [8]	Thailand	RCT	≤ 15 years	Azi vs. Dox vs. Chl	Azi: 20 mg/kg followed 10 mg/kg once daily, 2d; Dox: 2.2 mg/kg twice daily followed once daily, 5d; Chl: 100 mg/kg divided six hourly, 5d	Cure rate, Non-relapse rate
Yun Sung Kim, 2018 [9]	South Korea	QRCT	52~72 years	Dox vs. Lrif	Dox: 100 mg twice daily, 5d; Lrif: 600 mg once daily, 5d	Cure rate, Non-relapse rate
Karthika I. Kabir, 2022 [10]	India	RCT	1~14 years	Azi vs. Dox	Azi: 10 mg/kg once daily, 5d; Dox: 4.5 mg/kg divided 12 Hourly, 5d	Cure rate
Anjali Sharma, 2023 [11]	India	RCT	1~14 years	Azi vs. Dox	Azi: 10 mg/kg once daily, 5d; Dox: 2.2 mg/kg twice daily for children < 40 kg and 100mg twice daily in children weighing > 40 kg, 5d	Cure rate, Non-relapse rate

RCT: Randomized Controlled Trial; QRCT: Quasi-Randomized Controlled Trial; Chl: Chloramphenicol; Tet: Tetracycline; Dox: Doxycycline; Lrif: Low-dose Rifampicin; Hrif: High-dose Rifampicin; Azi: Azithromycin; Tel: Telithromycin.

[1] Sheehy TW, Hazlett D, Turk RE (1973) Scrub typhus. A comparison of chloramphenicol and tetracycline in its treatment. Archives of Internal Medicine. 132: 77.
[2] Brown GW, Saunders JP, Singh S, Huxsoll DL, Shirai A (1978) Single dose doxycycline therapy for scrub typhus. Transactions of the Royal Society of Tropical Medicine and Hygiene. 72: 412.
[3] Song J, Lee C, Chang WH, Choi SW, Choi JE, Kim YS, Cho SR, Ryu J, Pai CH (1995) Short-Course Doxycycline Treatment Versus Conventional Tetracycline Therapy for Scrub Typhus: A Multicenter Randomized Trial. Clinical infectious diseases. 21: 506.
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[6] Kim D, Yu KD, Lee JH, Kim HK, Lee S (2007) Controlled Trial of a 5-Day Course of Telithromycin versus Doxycycline for Treatment of Mild to Moderate Scrub Typhus. Antimicrobial Agents and Chemotherapy. 51: 2011.
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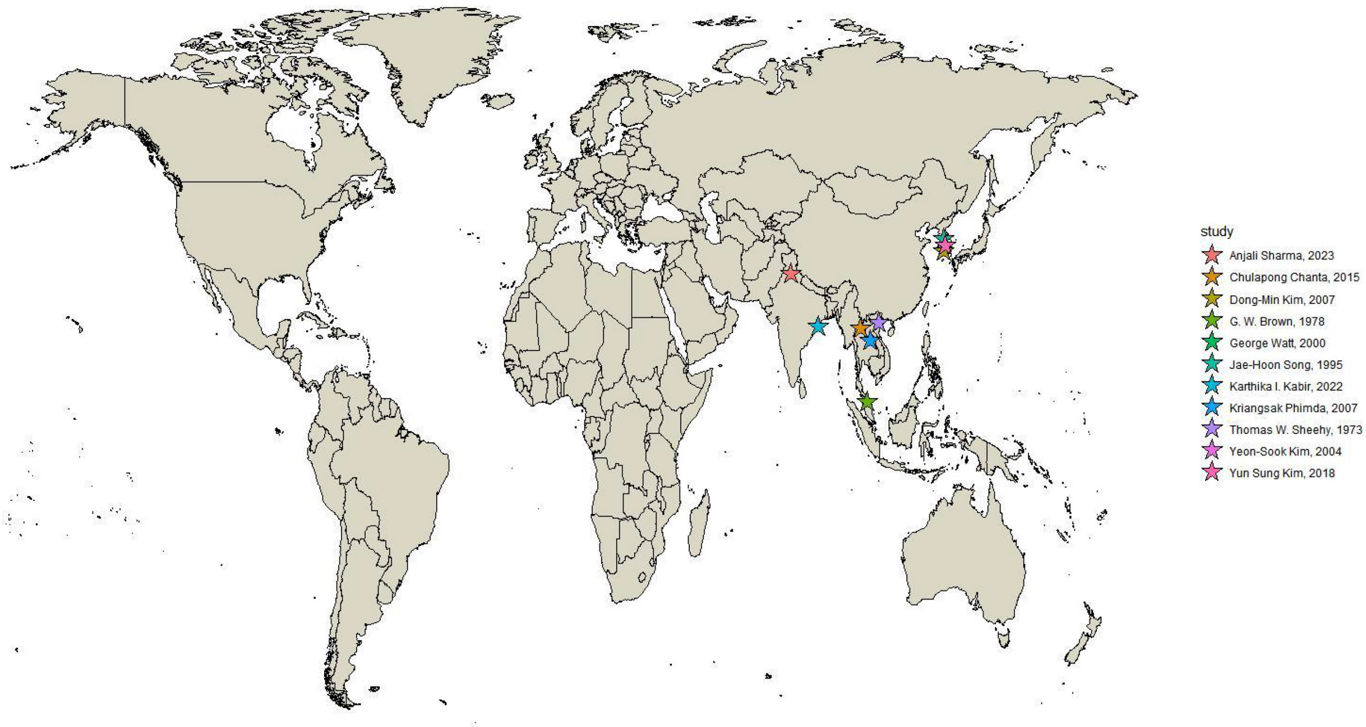
[8] Chanta C, Phloenchaiwanit P (2015) Randomized Controlled Trial of Azithromycin versus Doxycycline or Chloramphenicol for Treatment of Uncomplicated Pediatric Scrub Typhus. Journal of the Medical Association of Thailand. 98: 756.
[9] Kim YS, Kim D, Yoon N, Jang M, Kim C (2018) Effects of Rifampin and Doxycycline Treatments in Patients With Uncomplicated Scrub Typhus: An Open-Label, Randomized, Controlled Trial. Clinical Infectious Diseases. 67: 600.
[10] Kabir KI, John J, Satapathy AK, Sahu S, Behera B, Padhy BM (2022) Oral Azithromycin Versus Doxycycline in the Treatment of Children With Uncomplicated Scrub Typhus. Pediatric Infectious Disease Journal. 41: 224.
[11] Sharma A, Mahajan V, Guglani V, Singla N, Saini SS (2023) Open-labeled Randomized Controlled Trial on Efficacy of Azithromycin Versus Doxycycline in Pediatric Scrub Typhus. Pediatric Infectious Disease Journal. 42: 1067.

Supplementary Table 6. Pairwise meta-analysis of cure rate and non-relapse rate.

Comparison	Study	Cure rate				Non-relapse rate			
		RR[§]	95% CI		τ^2	RR[§]	95% CI		τ^2
Chl vs. Tet	Thomas W. Sheehy, 1973	1.000	0.910	1.099	-	0.893	0.741	1.076	-
	Summary effect	1.000	0.910	1.099	-	0.893	0.741	1.076	-
	Heterogeneity (I^2)	-	-	-	-	-	-	-	-
Dox vs. Chl	Chulapong Chanta, 2015	1.056	0.780	1.428	-	0.974	0.832	1.142	-
	Summary effect	1.056	0.780	1.428	-	0.974	0.832	1.142	-
	Heterogeneity (I^2)	-	-	-	-	-	-	-	-
Dox vs. Tet	G. W. Brown, 1978	1.141	0.902	1.444	-	1.000	0.930	1.075	-
	Jae-Hoon Song, 1995	0.940	0.884	0.999	-	1.000	0.966	1.035	-
	Summary effect	1.000	0.838	1.194	-	1.000	0.969	1.032	-
	Heterogeneity (I^2)	59.1%	0.0%	90.4%	0.011	0.0%	-	-	0.000
Dox vs. Lrif	George Watt, 2000	1.000	0.931	1.075	-	0.930	0.841	1.029	-
	Yun Sung Kim, 2018	1.000	0.976	1.025	-	1.000	0.976	1.025	-
	Summary effect	1.000	0.977	1.024	-	0.981	0.921	1.045	-
	Heterogeneity (I^2)	0.0%	-	-	0.000	46.9%	-	-	0.001
Dox vs. Hrif	George Watt, 2000	1.003	0.931	1.080	-	0.932	0.823	1.057	-
	Summary effect	1.003	0.931	1.080	-	0.932	0.823	1.057	-
	Heterogeneity (I^2)	-	-	-	-	-	-	-	-
Dox vs. Tel	Dong-Min Kim, 2007	0.978	0.920	1.039	-	0.978	0.920	1.039	-
	Summary effect	0.978	0.920	1.039	-	0.978	0.920	1.039	-
	Heterogeneity (I^2)	-	-	-	-	-	-	-	-
Lrif vs. Hrif	George Watt, 2000	1.002	0.928	1.081	-	1.002	0.928	1.081	-
	Summary effect	1.002	0.928	1.081	-	1.002	0.928	1.081	-
	Heterogeneity (I^2)	-	-	-	-	-	-	-	-
Azi vs. Chl	Chulapong Chanta, 2015	0.942	0.720	1.233	-	1.009	0.927	1.097	-
	Summary effect	0.942	0.720	1.233	-	1.009	0.927	1.097	-
	Heterogeneity (I^2)	-	-	-	-	-	-	-	-
Azi vs. Dox	Yeon-Sook Kim, 2004	1.069	0.991	1.153	-	1.000	0.959	1.043	-
	Kriangsak Phimda, 2007	0.967	0.906	1.033	-	1.000	0.934	1.071	-
	Chulapong Chanta, 2015	0.892	0.663	1.200	-	1.000	0.855	1.170	-
	Karthika I. Kabir, 2022	1.017	0.958	1.080	-	-	-	-	-
	Anjali Sharma, 2023	1.052	0.900	1.228	-	1.000	0.949	1.053	-
	Summary effect	1.014	0.968	1.062	-	1.000	0.971	1.029	-
	Heterogeneity (I^2)	17.0%	0.0%	82.7%	0.001	0.0%	0.0%	84.7%	0.000

Summary effect sizes estimated using random-effects meta-analysis. RR: Relative Risks; Chl: Chloramphenicol; Tet: Tetracycline; Dox: Doxycycline; Lrif: Low-dose Rifampicin; Hrif: High-dose Rifampicin; Azi: Azithromycin; Tel: Telithromycin. [§] Except for rows labelled "Heterogeneity (I^2).

Supplementary Figure 1. The Geographical Map of Studies Included in the Network Meta-Analysis.

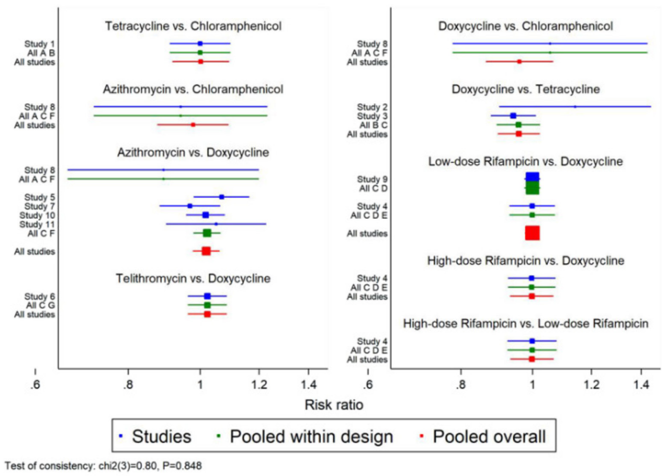


Supplementary Figure 2. Cochrane Risk of Bias Tool.

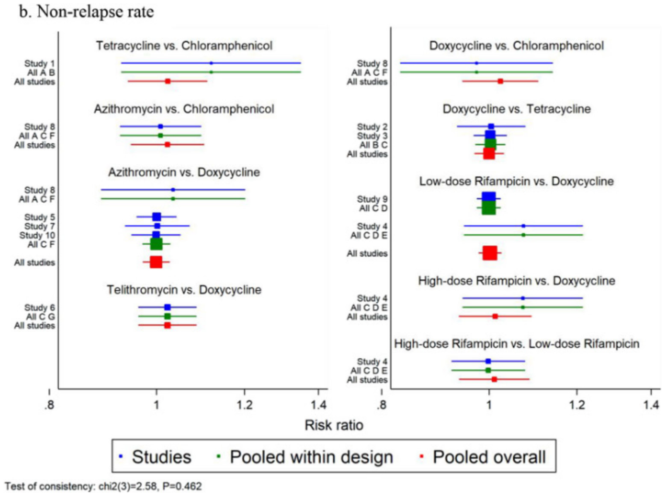
	Thomas W. Sheehy, 1973	G. W. Brown, 1978	Jae-Hoon Song, 1995	George Watt, 2000	Yeon-Sook Kim, 2004	Dong-Min Kim, 2007	Kriangsak Phimda, 2007	Chulapong Chanta, 2015	Yun Sung Kim, 2018	Karthika I. Kabir, 2022	Anjali Sharma, 2023
Random sequence generation (selection bias)	?	?	+	?	+	–	+	+	–	+	+
Allocation concealment (selection bias)	–	+	+	?	+	–	+	+	–	+	+
Blinding of participants and personnel (performance bias)	–	?	–	?	–	–	–	–	–	–	–
Blinding of outcome accessment (detection bias)	?	?	?	?	?	?	?	?	?	?	?
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+	+	+	+
Other bias	+	+	+	–	+	+	+	–	+	+	+

Summary of the assessment of the risk of bias of RCTs. + low risk of bias, – high risk of bias; ? unclear risk of bias.

Supplementary Figure 3. Forest Plots of Pairwise Meta-Analysis.

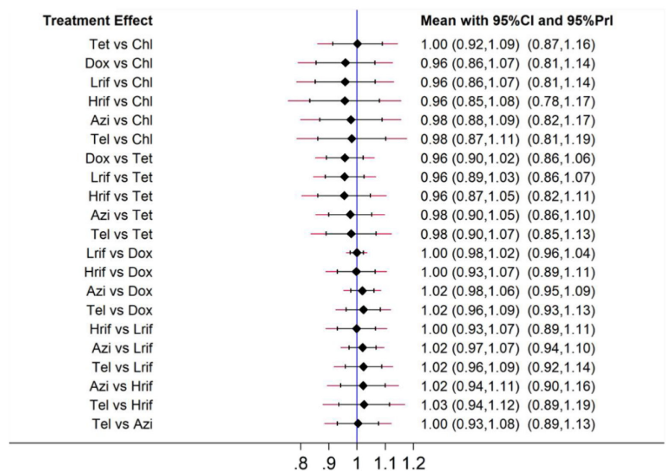


b. Non-relapse rate

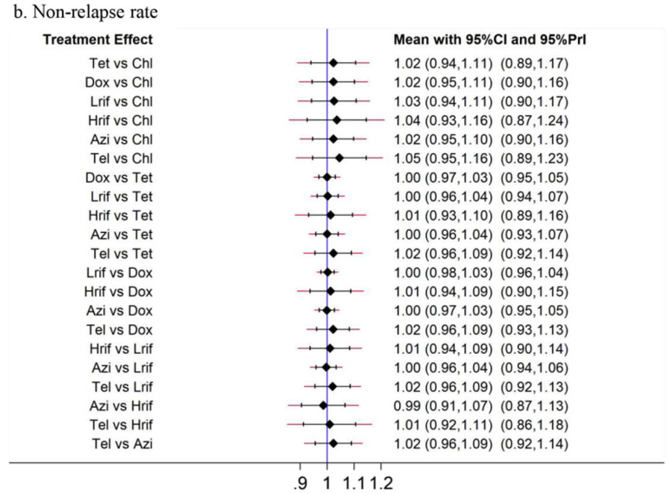


Supplementary Figure 4. Forest Plots of Network Meta-Analysis.

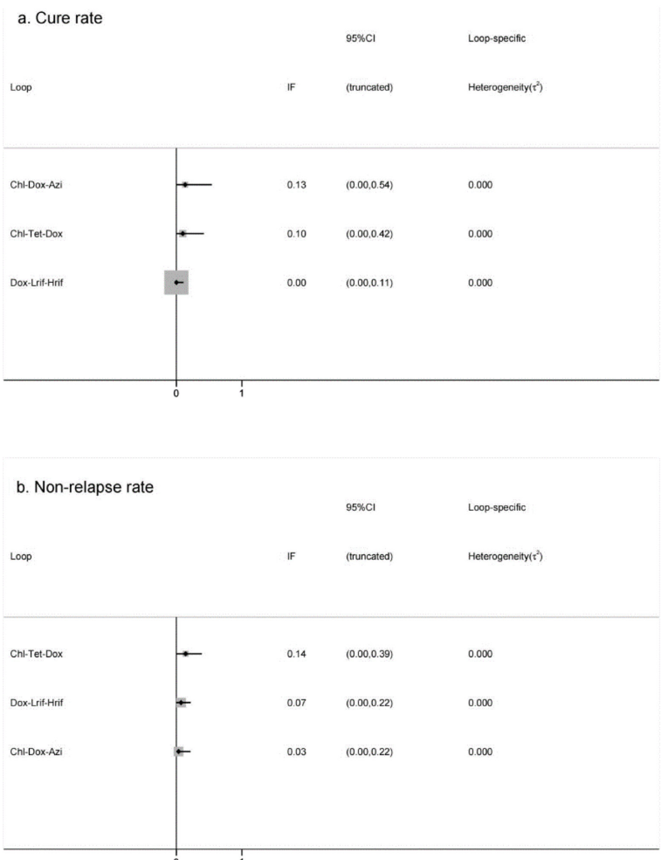
a. Cure rate



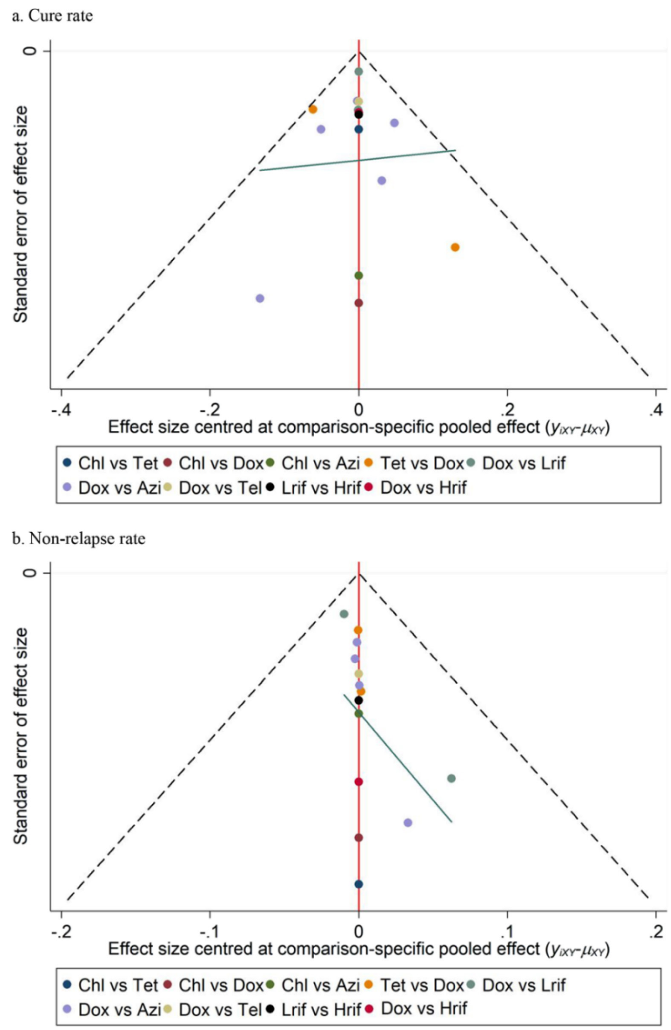
b. Non-relapse rate



Supplementary Figure 5. Inconsistency Plots.

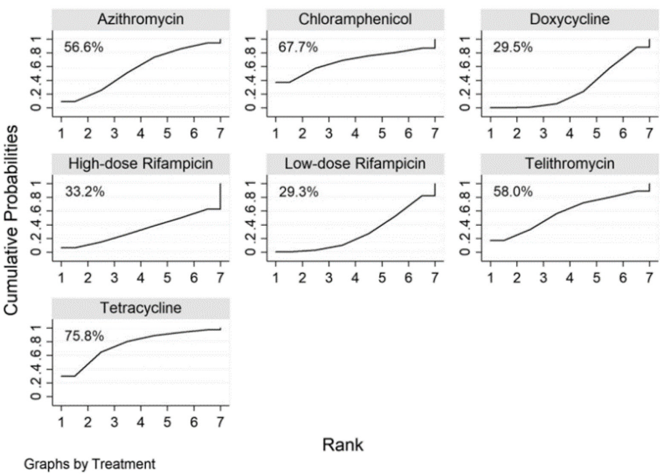


Supplementary Figure 6. Small-Study Effects (Funnel Plots).

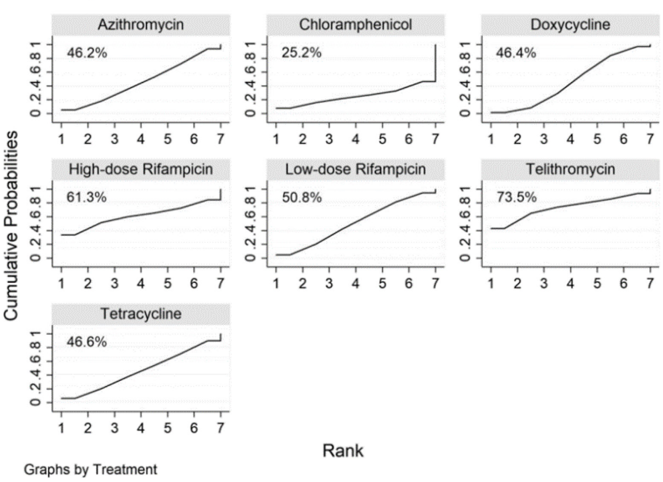


Supplementary Figure 7. The Cumulative Ranking Plots.

a. Cure rate

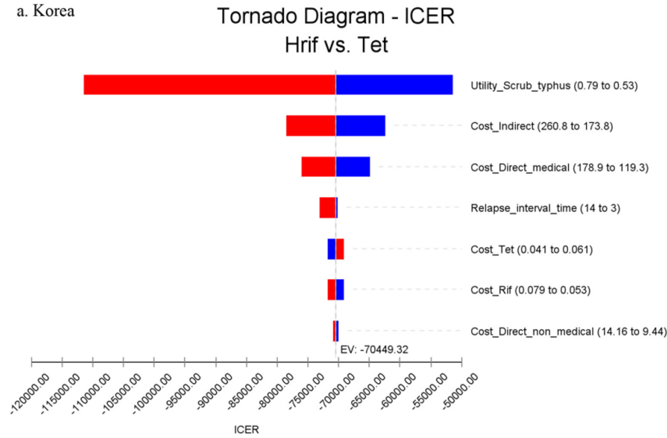


b. Non-relapse rate

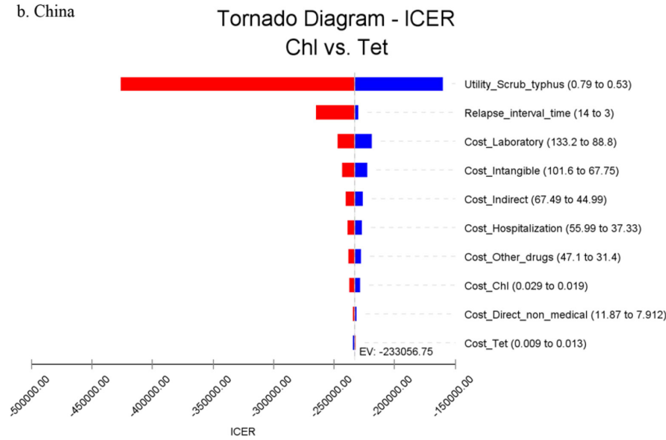


Supplementary Figure 8. Tornado Charts (ICER).

a. Korea

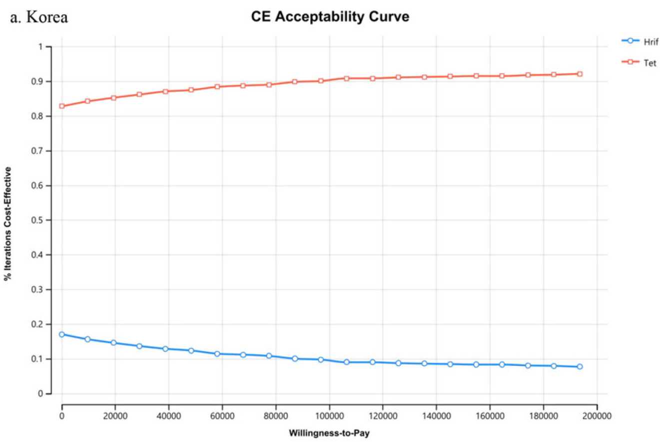


b. China

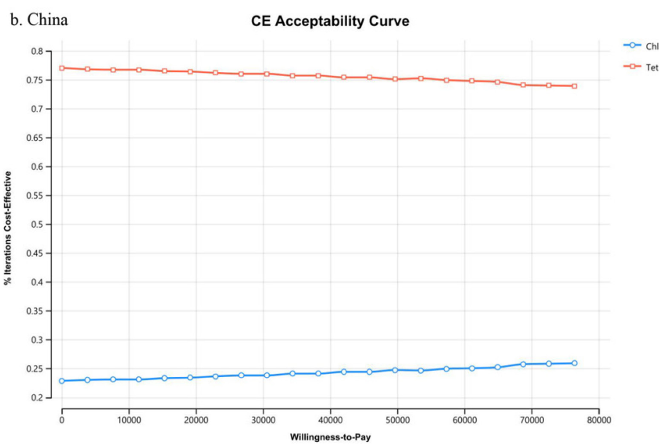


Supplementary Figure 9. Acceptability Curves.

a. Korea

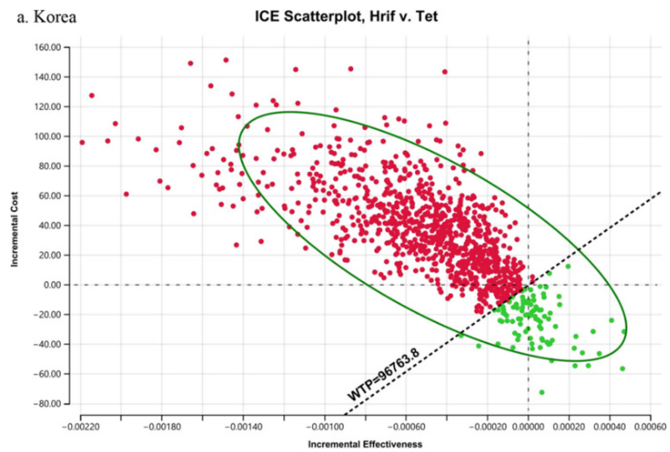


b. China



Supplementary Figure 10. Scatter Plots.

a. Korea



b. China