Efficacy of Doxycycline for Mild-to-moderate Community-acquired Pneumonia in Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Key points: This study suggests that the efficacy of doxycycline is comparable to macrolides or fluoroquinolones in adult patients with mild-to-moderate community-acquired pneumonia (CAP). Larger trials are required to retain doxycycline as an option for CAP treatment.

ABSTRACT

Background. Doxycycline has been recommended as a treatment option for non-severe community-acquired pneumonia (CAP) in adults. We sought to review the evidence for the efficacy of doxycycline in adult patients with mild-to-moderate CAP.

Methods. We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) of doxycycline versus comparator to assess the clinical efficacy. The primary outcome was the clinical cure rate. Random effects model meta-analyses were used to generate pooled odds ratio (OR) and evaluate heterogeneity (I^2). Risk of bias (RoB) and quality of evidence (QoE) were evaluated using the Cochrane Risk of Bias 2.0 tool and GRADE methods, respectively.

Results. We included six RCTs with 834 clinically evaluable patients. The trials were performed between 1984 and 2004. Comparators were three macrolides (roxithromycin, spiramycin, and erythromycin) and three fluoroquinolones (ofloxacin, fleroxacin, and levofloxacin). Four trials had an overall high RoB. The clinical cure rate was similar between the doxycycline and comparator groups (87.2% [381/437] vs. 82.6% [328/397]; OR 1.29 [95% CI: 0.73-2.28]; I^2 = 30%; low QoE). Subgroup analysis of two studies with a low RoB showed significantly higher clinical cure rates in the doxycyline group (87.1% [196/225] vs. 77.8% [165/212]; OR 1.92 [95% CI: 1.15-3.21]; P = 0.01; I^2 = 0%). Adverse event rates were comparable between the doxycycline and comparator groups.

Conclusion. The efficacy of doxycycline was comparable to macrolides or fluoroquinolones in mild-to-moderate CAP and thus represents a viable treatment option. Considering the lack of recent trials, it warrants large-scale clinical trials.

INTRODUCTION

Community-acquired pneumonia (CAP) is a leading cause of morbidity and death among communicable diseases, representing a significant burden on the global healthcare system [1, 2]. Failure of initial empirical treatment is a well-known risk factor for worse outcomes in patients with CAP [3, 4]. This is further compounded by growing concerns about the resistance and safety of antimicrobial agents listed for CAP treatment.

Major guidelines recommend a β-lactam plus macrolide/doxycycline combination therapy or respiratory quinolone monotherapy for hospitalized patients with non-severe CAP or outpatient management in patients with comorbidities [5, 6]. Recommended options for outpatients without comorbidities include amoxicillin, doxycycline, or a macrolide. *Streptococcus pneumoniae* resistance to macrolides is now endemic in many parts of the world. Thus macrolide monotherapy is recommended only in areas with < 25% of pneumococcal resistance [6]. Macrolides and fluoroquinolones are also associated with an increased risk of cardiovascular adverse effects, such as QT interval prolongation, ventricular arrhythmias, and aortic aneurysms [7, 8].

Doxycycline is a long-acting tetracycline exhibiting wide-spectrum activity against most CAP pathogens, including intracellular organisms. It has almost complete oral bioavailability, excellent penetration into the lung tissue, low cost, and a favorable safety profile [9, 10]. However, doxycycline is not a preferred option in clinical practice or guideline recommendations. Current UK guidelines recommend doxycycline as an alternative, especially for those intolerant of β-lactam or macrolide (guideline statement grade: D) [5]. Although tetracyclines have long been used for respiratory tract infections, the efficacy of doxycycline has been less well studied than macrolides or fluoroquinolones. Therefore, we performed a systematic review and meta-analysis to assess the efficacy of doxycycline monotherapy in adult patients with mild-to-moderate CAP.

METHODS

PROSPERO Registration

This review was conducted in accordance with a prespecified protocol and registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42022320354). No changes were made to the protocol. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [11] (Supplementary data).

Eligibility Criteria

Inclusion and exclusion criteria were determined a priori, and only full-text articles were considered. All randomized controlled trials (RCTs) comparing clinical outcomes of patients with CAP treated with doxycycline and comparator antimicrobial agent were searched and considered for inclusion. Inclusion criteria included: (1) study design: RCTs; (2) population: patients diagnosed with CAP; (3) intervention: intravenous or peroral doxycycline; (4) comparison group: β-lactams or fluoroquinolones or macrolides; (5) outcome: at least one of clinical cure or success, mortality, microbiological eradication, length of hospital stay, or adverse events. Exclusion criteria included studies enrolling (1) pediatric patients (< 18 years of age), (2) critically ill patients admitted to an intensive care unit, (3) patients mechanically ventilated or in a shock state at enrollment, (4) the usage of two or more antimicrobial agents (combination therapy), and (5) comparison of doxycycline versus comparator in heterogeneous populations, with CAP only comprising a small subgroup of patients (< 10 patients).

Information Sources and Search Strategy

We performed electronic database searches of PubMed, Embase, Cochrane Library, and MedRxiv. Date and language were not restricted. The last search update was performed on 31 March 2022. The Boolean search strategy was performed as follows: ((Pneumonia OR Lower respiratory tract infection OR chest infection) AND (Doxycycline OR Tetracycline OR Minocycline OR Tigecycline) AND

(Clinical trial OR Randomized trial OR Randomised trial OR RCT)). Control group and outcomes were not defined in the search terms. We also hand-searched research articles and review articles for further relevant trials.

Study Selection

Two investigators (SC and AS) independently carried out the literature search and screened the titles and abstracts for further assessment. We then assessed the full texts of selected abstracts. A third investigator (TS) resolved discrepancies between the two investigators.

Data Extraction

Two investigators (SC and AC) independently extracted the following data: country of study, study design, study period, setting (hospitalized vs. non-hospitalized), number of participants, mean or median age, sex, dosage/route/duration of doxycycline and comparator antimicrobial agents, clinical cure rate, all-cause mortality, length of hospital stay, cost of the antimicrobial agents, microbiological eradication rate, and adverse events. Discrepancies were resolved through discussion with a third investigator (TS). Where intention-to-treat and per-protocol analyses were both reported, we used intention-to-treat data for analysis.

Primary and Secondary Outcomes

The primary outcome was the clinical cure rate, defined as the resolution of clinical signs and symptoms at the end of treatment or follow-up, without the new onset of symptoms, any complication, or need for further antimicrobial therapy. Secondary outcomes included all-cause mortality, length of hospital stay, cost of antimicrobial agents, microbiological eradication rate, and adverse events. Microbiological eradication was defined as presumed or documented eradication of pathogen(s) present at baseline.

Subgroup Analyses

Subgroup analyses were performed of the clinical cure rate by the comparator groups

(fluoroquinolone group vs. macrolide group) and setting (hospitalized patients versus outpatients). An additional subgroup analysis was performed to demonstrate whether the risk of bias (RoB) of the RCTs would affect the results.

Risk of Bias (RoB) Assessment

The methodological quality of the included RCTs was evaluated using the Revised Cochrane risk of bias tool in randomized trials (RoB 2) [12]. This tool assesses the following five bias domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. The RoB for each of the five domains and overall was categorized as low RoB, some concerns, or high RoB.

Grading Quality of Evidence (QoE)

The quality of each outcome measure was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [13]. We rated down the quality based on the following certainty assessment: RoB, inconsistency, indirectness, imprecision, and other considerations. Publication bias was assessed using a funnel plot and Egger's test [14]. The overall QoE was rated as very low, low, moderate, or high. We used the GRADEpro GDT software (version 2021) to create a summary of findings tables [15].

Statistical Analysis

A meta-analysis was undertaken using Review Manager (version 5.4, Cochrane Collaboration, Oxford, UK). A random-effects model with the generic Mantel-Haenszel method was used to evaluate the effect of doxycycline versus a comparator on outcomes. Effects of meta-analyses were reported as a pooled odds ratio (OR) for dichotomous outcomes and as a mean difference for continuous outcomes.

We planned a sensitivity analysis excluding RCTs in which comparators were not currently recommended for CAP therapy was planned for the clinical cure rate. An additional sensitivity analysis was performed using the fixed-effect model for the clinical cure rate. We also performed a

sensitivity analysis of the adverse events of all trials, including those that reported the adverse events of non-pneumonic- and pneumonic patients together.

Heterogeneity of effects among studies was assessed using the I^2 statistic. I^2 of 0%, 0% < I^2 < 30%, 30% ≤ I^2 < 50%, 50% ≤ I^2 <75%, and I^2 ≥75% indicated no, least, moderate, substantial, and considerable heterogeneity, respectively. All *P*-values were two-tailed, and $P < 0.05$ was considered significant.

Trial sequential analysis (TSA) was performed to reduce type I and type II errors in meta-analyses with small sample sizes. TSA quantifies the statistical reliability of cumulative meta-analysis data by combining both an information size calculation (cumulative sample sizes of all included trials) and adjustment of significance levels [16]. We quantified trial sequential monitoring boundaries and the required information size (RIS) with diversity-adjusted information size (D^2) and adjusted 95% confidence intervals. RIS was calculated using the relative risk reduction obtained from our actual meta-analysis of -5.5%. Two-sided *z*-score thresholds were adjusted using the O'Brien-Fleming α-spending function with a 2-sided 5% type I error and 80% power. All TSA analyses were performed using TSA software version 0.9.5.0 Beta, Copenhagen trial unit (www.ctu.dk/tsa).

RESULTS

Study Selection

Figure 1 shows the PRISMA flow diagram of the study selection process. The search strategy identified 2,131 results. After removing duplicates, 1,979 articles remained. Of these, 1,936 were excluded based on title or abstract. Forty-three full-text articles were reviewed, and 37 were excluded. The most common reasons were non-pneumonia studies (n=8) and non-randomized or non-comparative studies (n=6). Six RCTs were included in the final analysis [17-22].

Characteristics of RCTs

Table 1 summarizes the characteristics of the six RCTs. All trials were investigator-initiated with five conducted in Europe [17-21] and one in the United States [22]. Five trials were double-blinded [18-22], and five were multicenter [17-21]. The trials were conducted between 1984 and 2004. Three trials enrolled patients hospitalized in general wards [17, 19, 22], and two trials included only outpatients [18, 20]. One trial enrolled both in- and outpatients [21]. Four trials enrolled both pneumonic and non-pneumonic patients (acute exacerbation of chronic obstructive pulmonary disease or acute bronchitis) [17-20], and two trials only patients with CAP [21, 22]. The total number of participants with CAP was 921, with sample sizes ranging from 24 [20] to 414 [21]. Mean or median ages ranged from 32 [21] to 63 years [19]. The percentage of male patients ranged from 50.8% [22] to 68.6% [21]. Five trials used oral doxycycline [17-21], while one initially used intravenous doxycycline before converting to oral doxycycline [22]. Maintenance doxycycline regimens included 100 mg twice daily [17, 21, 22], 200 mg once daily [19], or 100 mg once daily [18, 20]. Comparators included three macrolides (erythromycin, spiramycin, and roxithromycin) [18-20] and three fluoroquinolones (ofloxacin, fleroxacin, and levofloxacin) [17, 21, 22]. The duration of an antimicrobial course ranged from 5 to 14 days.

Primary Outcome

A total of 834 clinically evaluable participants were included. Clinical cure rates were similar between the doxycycline and comparator groups (87.1% [381/437] vs. 82.6% [328/397]; OR: 1.29 [95% CI: 0.73-2.28]; P = 0.39; I^2 = 30%; low QoE). The cumulative Z curve crossed neither the conventional nor the TSA boundary for benefit or harm. The TSA-adjusted CI was 0.38-4.38. Table 2 and Figure 2 summarize the therapy outcomes and GRADE recommendations.

Secondary Outcomes

No mortality was reported in the six trials included. No studies reported a microbiological eradication rate. One trial reported length of hospital stay (doxycycline group; 4.0 ± 1.8 days vs. levofloxacin group; 5.7 ± 2.1 days, P < 0.001) and cost of the antimicrobial agent per patient (doxycycline group; USD 65.0 ± 24.4 vs. levofloxacin group; USD 122.1 ± 15.8, P < 0.001), which were significantly lower in patients receiving doxycycline compared to levofloxacin [22]. The meta-analysis, excluding three trials in which adverse events of pneumonia patients were reported alongside those of non-pneumonic patients, showed comparable adverse event rates between the doxycycline and comparator groups (27.6% [82/297] vs. 33.2% [94/283]; OR 0.78 [95% CI: 0.54-1.13]; P = 0.19; I^2 = 0%; very low QoE) (Figure 3).

Subgroup Analyses

In subgroup analyses assessing the class of comparator, clinical cure rates remained similar (fluoroquinolones; OR 1.14 [95% CI: 0.32-4.06]; P = 0.62; I^2 = 58%, macrolides; OR 1.19 [95% CI: 0.60-2.37]; P = 0.84; I^2 = 0%) (Table 2 and Figure 2). Enrollment setting was also not associated significant difference between the groups (hospitalized patients; OR 0.63 [95% CI: 0.27-1.48]; P = 0.36, I2 = 2%, outpatients; OR 1.76 [95% CI: 0.71-4.34]; P = 0.73, I2 = 0%) (Figure 4). Two studies with a low RoB [20, 21] showed a significantly higher clinical cure rate in the doxycyline group compared to comparator group (87.1% [196/225] vs. 77.8% [165/212]; OR 1.92 [95% CI: 1.15-3.21]; P = 0.01; I^2 = 0%) (Figure 5).

Sensitivity Analyses

A sensitivity analysis excluding two trials [17, 21] in which comparators are not currently recommended for CAP therapy (ofloxacin and fleroxacin) showed no significant difference between groups (88.2% [157/178] vs. 85.6% [131/153]; OR 1.25 [95% CI: 0.64-2.44]; P = 0.51; I^2= 0%) (Supplementary Figure 1). Using a fixed-effects model instead of a random-effects model, clinical success rates tended to be higher in the doxycycline group without reaching statistical significance (OR 1.42 [95% CI: 0.96-2.09]; P = 0.08; I^2 = 30%) (Supplementary Figure 2). Analyzing the adverse events of all trials, including those that reported events in both non-pneumonic- and pneumonic patients [17, 19, 20], the adverse events were 17.1% (122/713) and 17.7% (123/694) in the doxycycline and comparator groups, respectively (OR 1.03 [95% CI: 0.61-1.73]; P = 0.92; I^2 = 48%] (Supplementary Figure 3).

Risk of Bias (RoB) Assessment and GRADE recommendation

Supplementary Table 1 includes the detailed RoB assessment of each trial. Two RCTs had an overall low RoB [21, 22], and four had a high RoB [17-20]. Imprecision was judged to be serious because TSA showed a low percentage of RIS cases (Supplementary Table 2). The funnel plot was reasonably symmetric, and Egger's test did not suggest publication bias (P = 0.47) (Supplementary Figure 4). Overall QoE by GRADE assessment was 'low' for clinical cure rate and 'very low' for secondary outcomes, including adverse events (Table 2 and Supplementary Table 2).

DISCUSSION

In this comprehensive systematic review and meta-analysis, comprising six RCTs and 834 patients, there was no difference in clinical cure rate or adverse event rate between doxycycline and comparator groups used to treat mild-to-moderate CAP in adults. These results suggest that doxycycline is a viable option for treating non-severe CAP in adults.

As none of the included RCTs reported antimicrobial resistance data nor the microbiological eradication rate, our results should be interpreted with caution. Although tetracycline and doxycycline remain highly effective against *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumophila*, and *Staphylococcus aureus* [23-25], there is concern about pneumococcal resistance. Recent results from the SENTRY Antimicrobial Surveillance Program, collected in 2015-2017, found that 32.4% of pneumococcal isolates were resistant to azithromycin and 30.7% resistant to tetracycline [25]. Resistance rates were lower in Western Europe (azithromycin 23.8%, tetracycline 21.3%) and higher in the Asian-Pacific region (azithromycin 50.4%, tetracycline 40.2%). Since doxycycline is generally more active against *Streptococcus pneumoniae* than tetracycline [26], doxycycline can be at least as active as azithromycin. In a large Canadian surveillance study, resistance to clarithromycin and doxycycline was 23.3% and 9.6%, respectively [27]. Notably, pneumococcal resistance rates are much higher among penicillin-resistant isolates. One surveillance study from the United States and Europe showed that the doxycycline resistance rate was 6.2% in penicillin-susceptible isolates and 62.5% in penicillin-resistant isolates [28]. These findings suggest that doxycycline could be safely used as an empirical therapy option in areas with a low prevalence of penicillin resistance to *S. pneumoniae*. Therefore, monitoring local antimicrobial resistance profiles is essential. In highly resistant areas, doxycycline can be a definitive therapy option based on antimicrobial susceptibility results.

One excluded article in this review was from a hospital in Ohio, United States where an RCT was performed to evaluate the efficacy of doxycycline as empirical treatment in hospitalized adult patients

with mild to moderately severe CAP [29]. We excluded this study as the no comparator group antimicrobial agent was designated and the treating physician could choose the antimicrobial agents without restrictions. Doxycycline was as efficacious as the other regimens chosen for the CAP (clinical response rate 93.0% vs. 88.6%, $P = 0.48$). Median time to respond (2.0 vs. 3.0 days, $P = 0.001$), median length of hospitalization (3.0 vs. 5.0 days, $P = 0.04$), median cost of hospitalization (USD 5126.0 vs. USD 6528.1, $P < 0.001$), and median cost of antimicrobial agents (USD 33.0 vs. USD 170.9, $P < 0.001$) all favored doxycycline, which is in line with the results of our review.

Concerns have been voiced that the lack of new clinical trials could lead to the removal of doxycycline from CAP treatment guidelines. As doxycycline is generic, it is unlikely that an industry sponsor will initiate a clinical trial. Two decades ago, Dr. J.R. Johnson suggested support from the Infectious Diseases Society of America and the Centers for Disease Control and Prevention for unmet needs [30]. While this proposal has not been adopted, it remains relevant. Doxycycline deserves more consideration and should be retained as a CAP treatment option with confirmation by large-scale clinical trials, as it is inexpensive, convenient, and has activity against both typical and atypical respiratory bacterial pathogens. Notably, the latest RCTs that compared doxycycline to quinolones showed no significant difference [22] or favored doxycycline [21]. Doxycycline may also play a role in limiting antimicrobial resistance by sparing other antimicrobial agents.

We acknowledge some limitations to our analyses. First, the current research is limited in trial number, sample size, and varying quality of the trials included. The overall QoE was low for the primary outcome and very low for all secondary outcomes. Trials were also confined to European countries and the United States. Second, β-lactam agents and azithromycin were not used in any trials as comparators. Third, the most recent trial was conducted between 2001 and 2004 [22]. Resistance patterns have changed significantly since the source RCTs were completed. In addition, some comparator antimicrobial agents are not in current use, albeit sensitivity analyses excluding those trials showed similar results. Third, since none of the trials provided data regarding the microbiological eradication rate, the impacts of pathogens and antimicrobial resistance could not be

adequately evaluated. Finally, our analysis cannot be applied to the role of doxycycline in combination therapy.

In conclusion, our review showed that doxycycline is comparable to macrolides or fluoroquinolones for adult patients with mild-to-moderate CAP and remains a viable treatment option. Monitoring of local susceptibility patterns and larger RCTs are required.

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Conflicts of Interest: None declared.

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FIGURE LEGENDS

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of the study selection process.

Figure 2. Effect of doxycycline on clinical cure rate. **A.** Forest plot of clinical cure rate. The size of the squares for the odds ratio reflects the weight of the trial in the pooled analyses. Horizontal bars represent 95% confidence intervals. **B.** Trial sequential analysis (TSA) of the clinical cure rate. The uppermost and lowermost curves represent trial sequential monitoring boundary lines for benefit and harm. Horizontal red lines represent the traditional boundaries for statistical significance. Triangular lines represent the futility boundary. The cumulative Z-curve represents the trial data (blue line with black squares). The cumulative Z-curve crossed neither the conventional nor the TSA boundary for benefit or harm.

Figure 3. Forest plot of adverse events. Three trials in which adverse events of pneumonia patients were reported mixed with non-pneumonic patients were excluded. The size of the squares for the odds ratio reflects the weight of the trial in the pooled analyses. Horizontal bars represent 95% confidence intervals.

Figure 4. Forest plot of clinical cure rate according to the patient enrollment setting.

Figure 5. Forest plot of clinical cure rate according to the risk of bias.

Table 1. Characteristics and outcomes of randomized controlled trials included

Reference	Author, publication year, country	Study design	Study period	Setting/severity	Number of patients	Mean age, yr	Dosage, route, and duration		Evaluated outcomes
					Doxycycline /comparator	Doxycycline /comparator	Doxycycline	Comparator	
[17]	Harazim et al. 1987. Austria	Open-label, randomized, double-center study	Not stated	General ward/mild-to-moderate	69/62	Not presented	100 mg BD for 10 days	Ofloxacin 200 mg or 400 mg BD for 10 days	Clinical response, adverse event
[18]	Biermann et al., 1988. Norway	Double-blind, randomized, multicenter study	Not stated	Outpatients/mild	100/91	52/52	200 mg PO OD on day 1→ 100 mg PO OD for 8 days, total for 9 days	Spiramycin 1 g PO TID one day 1 → then 1 g PO BD for a further 4.5 days	Clinical response, adverse event
[19]	Charpin et al. 1988. France	Double-blind, randomized, multicenter study	1984-1985	General ward/mild-to-moderate	75/63	62.2/63.0	200 mg PO OD for at least 5 days	Roxithromycin 150 mg PO BD for at least 5 days	Clinical response, adverse event
[20]	Wiesner et al., 1993, Germany	Double-blind, randomized, multicenter study	Not stated	Outpatients/mild	13/11	41.7/44.1	100 mg PO OD for 7 to 14 days	Erythromycin 400 mg PO BD for 7 to 14 days	Clinical response, adverse event
[21]	Norrby et al., 1997, Denmark, Finland, Iceland, Sweden, Norway	Double-blind, randomized, multicenter study	1990-1993	Outpatients or general ward/mild-to-moderate	209/205	32/33 (median age)	100 mg PO BD for 10 days	Fleroxacin 400 mg PO OD for 10 days	Clinical response, adverse event
[22]	Mokabberi et al., 2010, USA	Double-blind, randomized, single-center study	2001-2004	General ward/mild-to-moderate	35/30	51.9/50.6	100 mg IV BD → 100 mg PO BD, total for 10 days	Levofloxacin 500 mg IV OD → 500 mg PO OD, total for 10 days	Clinical response, adverse event, cost of antimicrobial agent, length of hospital stay, readmission within 2 months

Abbreviation: CAP, community-acquired pneumonia; IV, intravenous; BD, twice daily; PO, per oral; OD, once daily; TID, thrice daily.

Table 2. Summary of the findings on the outcomes of doxycycline therapy and GRADE recommendation

Outcome	References	Doxycycline group	Comparator group	Conventional effect estimate (95% CI)	Overall effect	I^2 (%)	Quality of evidence
Clinical cure rate							
Total	[17-22]	381/437 (87.2%)	328/397 (82.6%)	1.29 (0.73-2.28)	Z=0.87, *P*=0.39	30	⊕⊕◯◯ Low
Comparator group							
vs. macrolides	[18-20]	123/143 (86.0%)	103/123 (83.7%)	1.19 (0.60-2.37)	Z=0.49, *P*=0.62	0	
vs. fluoroquinolones	[17, 21, 22]	258/294 (87.5%)	225/274 (82.2%)	1.14 (0.32-4.06)	Z=0.21, *P*=0.84	58	
Setting							
Hospitalized patients only	[17, 19, 22]	161/179 (89.9%)	145/155 (93.5%)	0.63 (0.27-1.48)	Z=1.05, *P*=0.36	2	
Outpatients only	[18, 20]	58/68 (85.3%)	46/60 (76.7%)	1.76 (0.71-4.34)	Z=1.23, *P*=0.73	0	
Hospitalized patients or outpatients	[21]	162/190 (85.3%)	137/182 (75.3%)	1.90 (1.13-3.21)	Z=2.40, *P*=0.02	-	
Risk of bias							
Low risk of bias	[21, 22]	196/225 (87.1%)	165/212 (77.8%)	1.92 (1.15-3.21)	Z=2.50, *P*=0.01	0	
High risk of bias	[17-20]	185/212 (87.3%)	163/185 (88.1%)	0.92 (0.41-2.06)	Z=0.20, *P*=0.84	30	
Adverse events[a]	[18, 21, 22]	82/297 (27.6%)	94/283 (33.2%)	0.78 (0.54-1.13)	Z=1.30, *P*=0.19	0	⊕◯◯◯ Very low
Length of hospital stay, days (mean ± SD)	[22]	4.0 ± 1.8[b]	5.7 ± 2.1[b]	-	-	-	⊕◯◯◯ Very low
Cost of antimicrobial agents/patient, USD (mean ± SD)	[22]	65.0 ± 24.4[c]	122.1 ± 15.8[c]	-	-	-	⊕◯◯◯ Very low

[a]excluding the trials in which adverse events in pneumonic patients were combined with those of non-pneumonic patients. [b]$P < 0.001$. [c]$P < 0.001$.

Figure 1

Click here to access/download;Figure (.tif and .eps files only);Figure 1.tiff

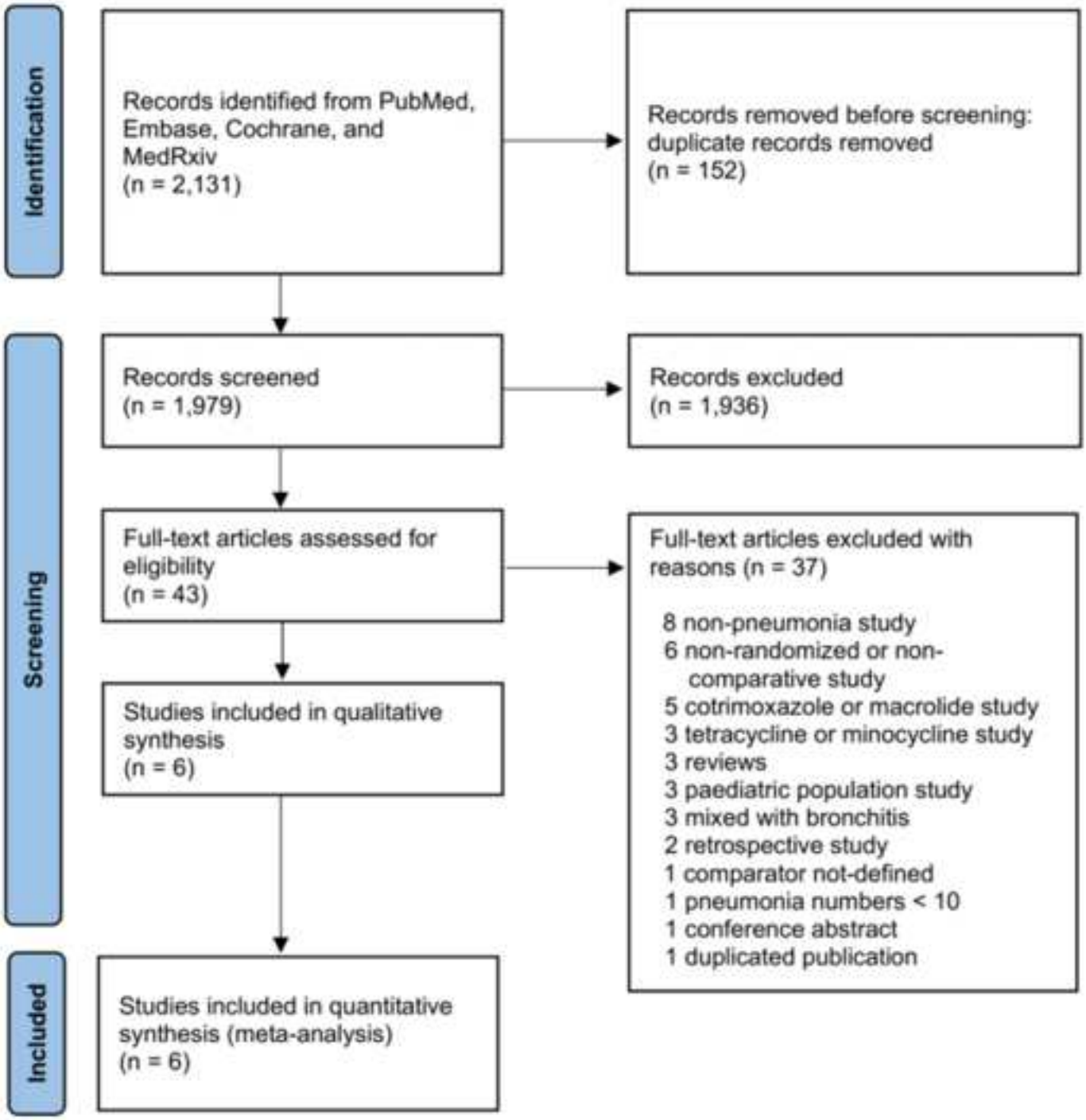
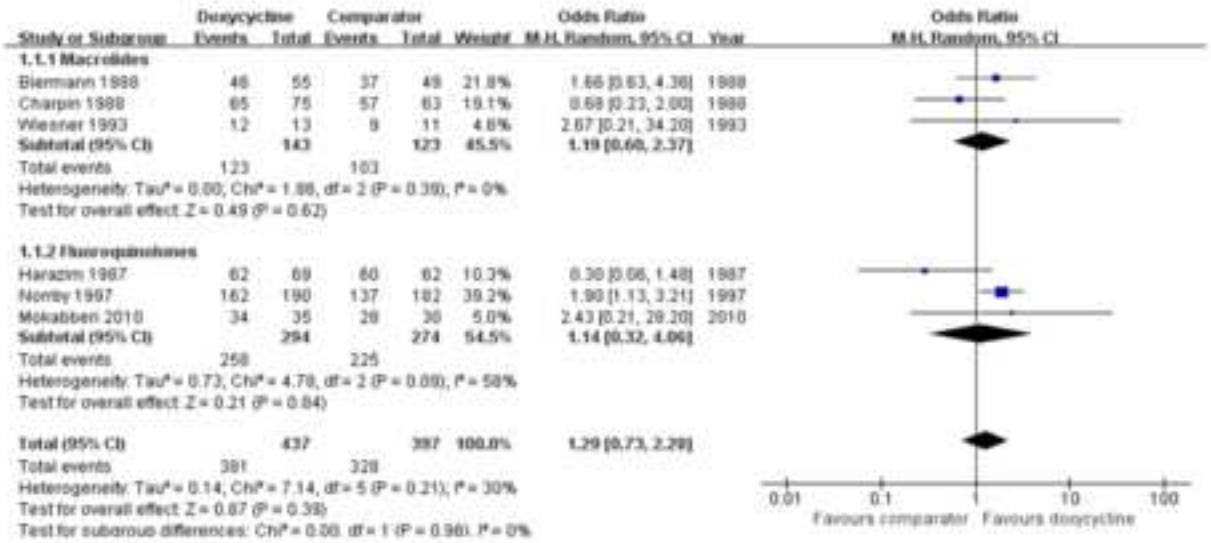


Figure (.tif and .eps files only)

Click here to access/download;Figure (.tif and .eps files only);Figure 2.tif

A



B

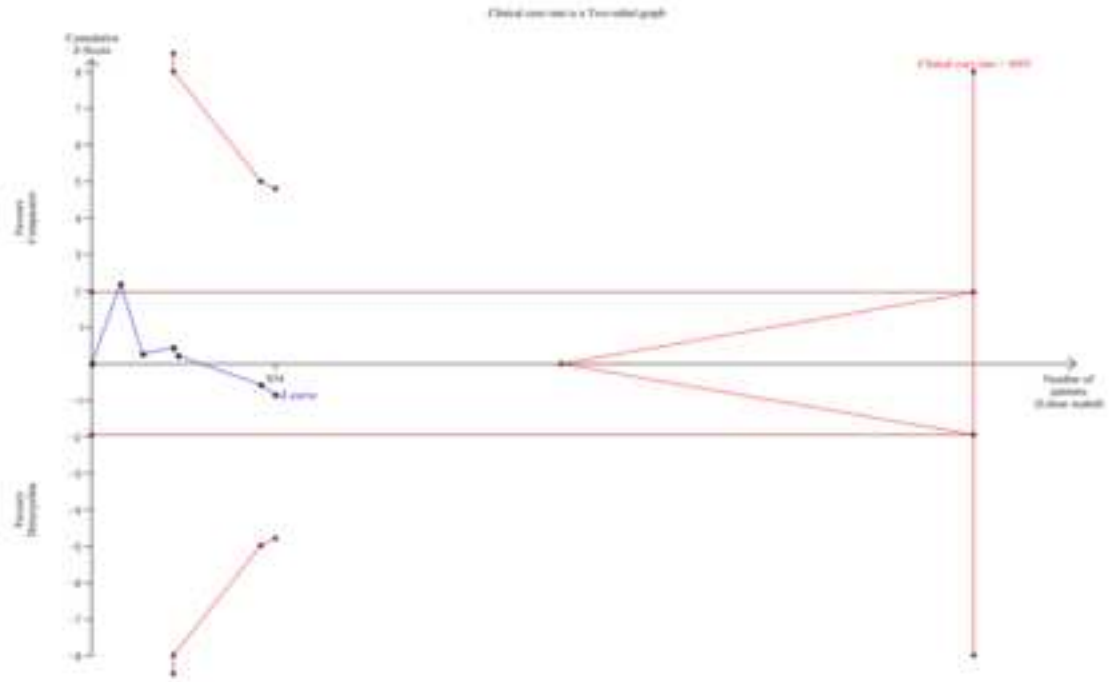
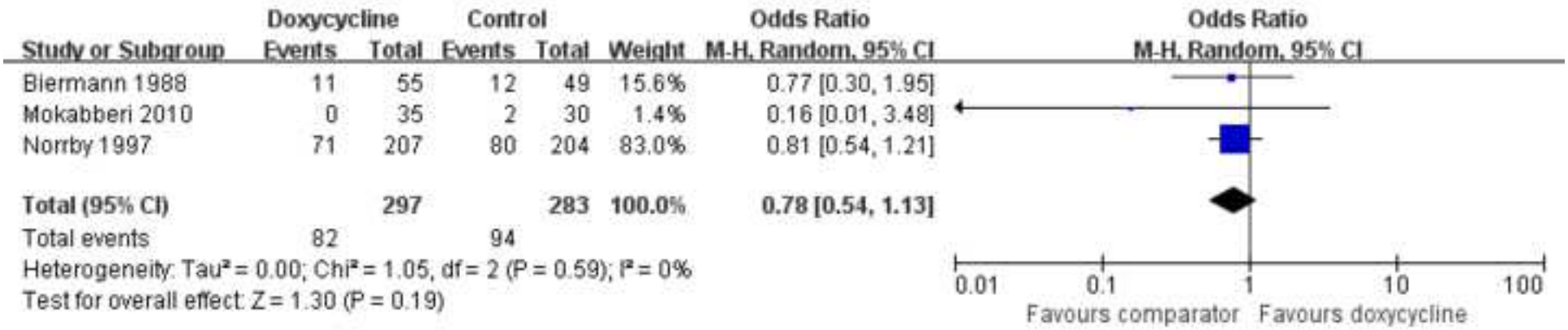
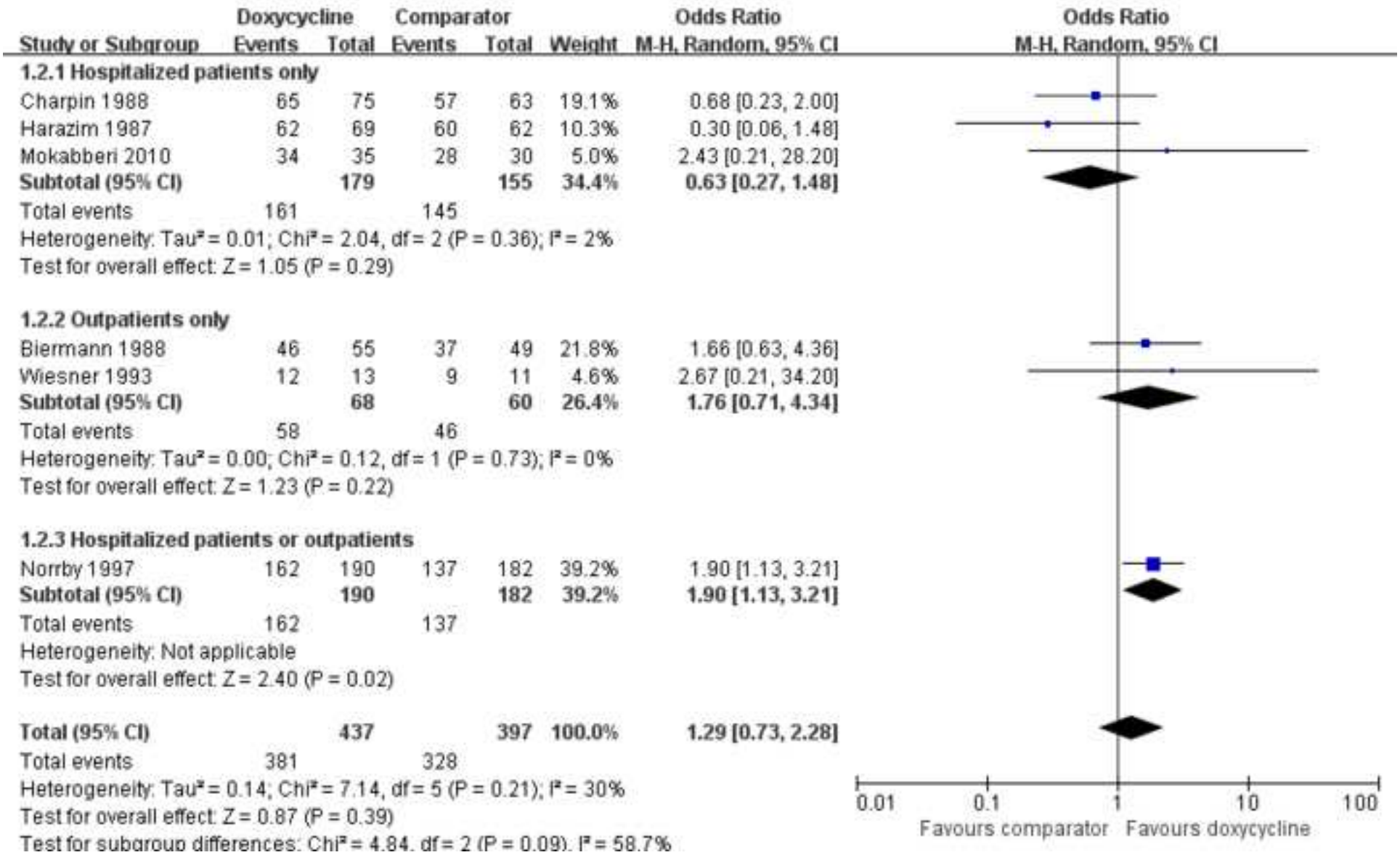
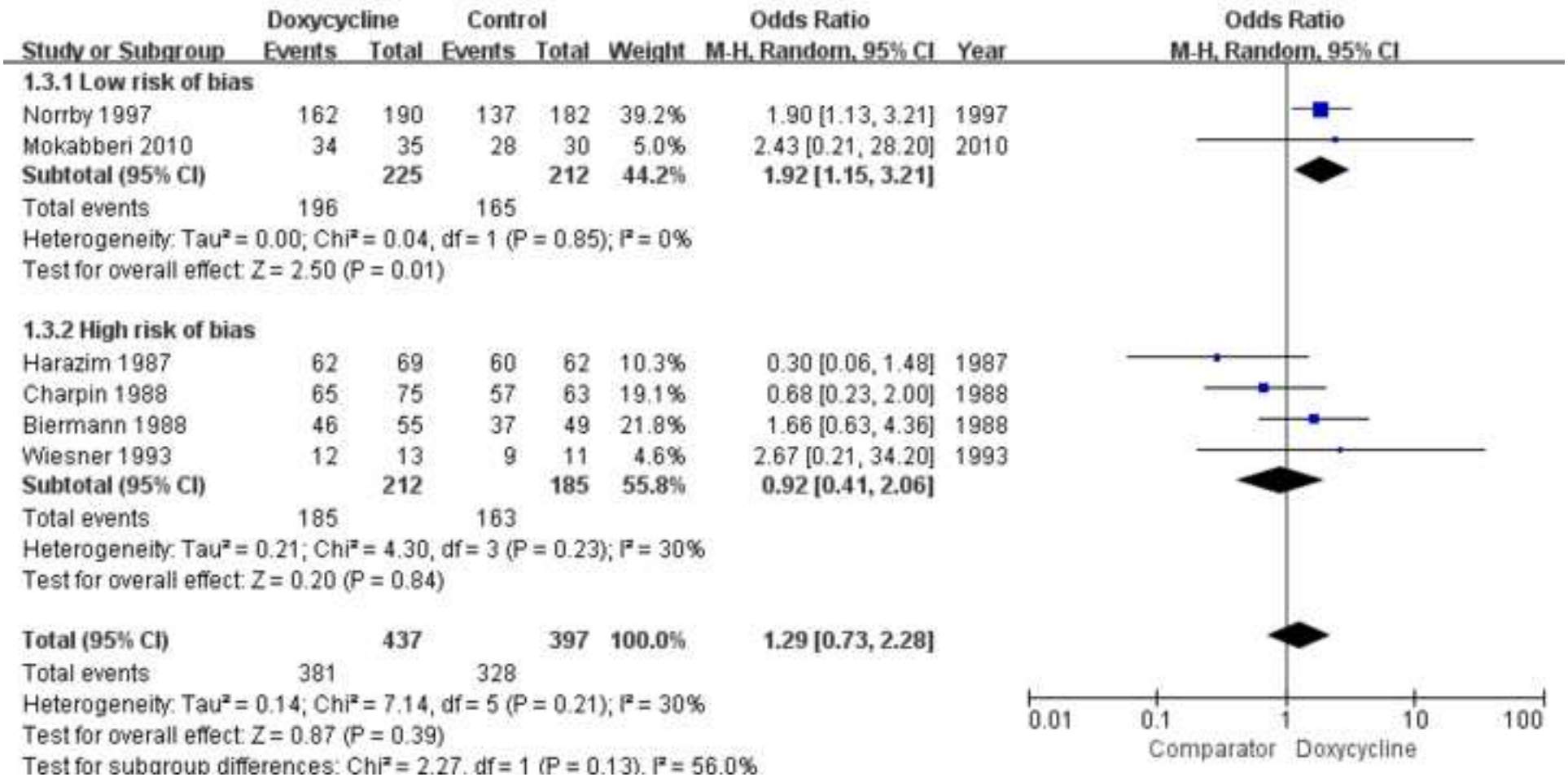


Figure 3







Supplementary Data

Efficacy of Doxycycline for Mild-to-moderate Community-acquired Pneumonia in Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Sang-Ho Choi et al.

Table of Contents

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			Page number
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	4-5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6-7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6-7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	8, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	10, Supplementary Table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	8-9. Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	10
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9-10, Table 2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9-10
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11

Section and Topic	Item #	Checklist item	Location where item is reported
	23b	Discuss any limitations of the evidence included in the review.	11
	23c	Discuss any limitations of the review processes used.	12-13
	23d	Discuss implications of the results for practice, policy, and future research.	12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	14
Competing interests	26	Declare any competing interests of review authors.	14
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	4, Supplementary data

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. doi: 10.1136/bmj. n71

Supplementary Table 1. Risk of Bias Assessment.

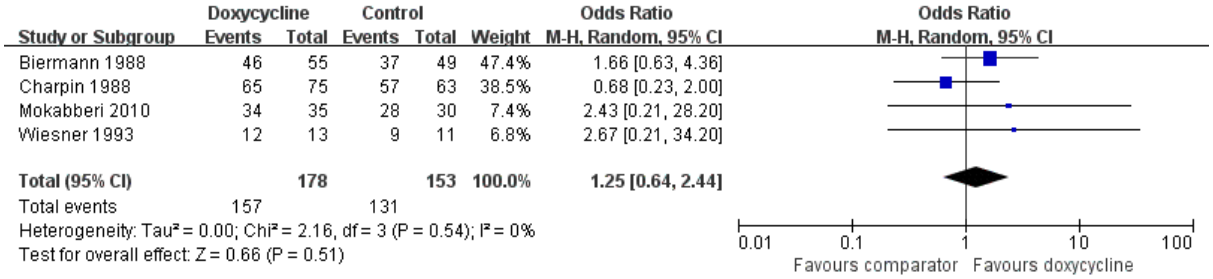
Author, year	Industry-sponsored	Randomization process		Assignment intervention		Missing outcome data		Measurement outcome		Selection of reported results		Overall bias	
Harazim et al., 1987	No	?	No detailed information	?	No detailed information	?	No information	?	No information	+		-	
Biermann et al., 1988	No	?	No detailed information but no baseline variable imbalance	+	Double-blinded placebo-controlled	+	Matched losses to follow-up	?	Detailed outcome definition not given	+		-	
Charpin et al. 1988	No	?	No detailed information but no baseline variable imbalance	+	Double-blinded placebo-controlled	+	Matched losses to follow-up	?	Detailed outcome definition not given	+		-	
Wiesner et al., 1993	No	?	Non-pneumonia patients randomized together	+	Double-blinded placebo-controlled	+	No losses	?	A detailed outcome definition was not given for the 'moderate' efficacy	+		-	
Norrby et al., 1997	No	+		+	Double-blinded placebo-controlled	+	Small, matched losses to follow-up	+		+		+	
Mokabberi et al., 2010	No	+		+	Double-blinded placebo-controlled	+	One patient in the levofloxacin group refused to study on 2nd day	+		+		+	

Supplementary Table 2. GRADE Recommendation.

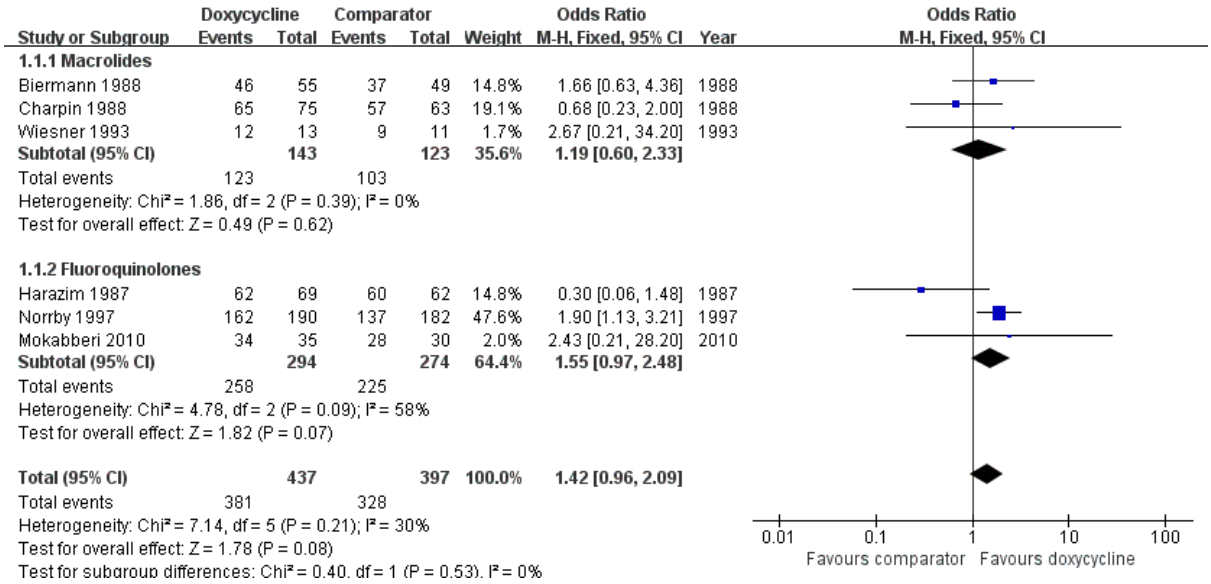
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Comparator	Relative (95% CI)	Absolute (95% CI)		
Clinical cure rate												
6	randomized trials	serious	not serious	not serious	serious	none	381/437 (87.2%)	328/397 (82.6%)	**OR 1.29** (0.72 to 2.28)	**34 more per 1,000** (from 52 fewer to 89 more)	⨁⨁◯◯ Low	IMPORTANT
Adverse event												
3	randomized trials	serious	not serious	serious	serious	none	82/297 (27.6%)	94/283 (33.2%)	**OR 0.78** (0.54 to 1.13)	**53 fewer per 1,000** (from 120 fewer to 28 more)	⨁◯◯◯ Very low	IMPORTANT
Cost of antimicrobial agent												
1	randomized trials	serious	serious	not serious	serious	none	64.98	122.07	-	**0** (0 to 0)	⨁◯◯◯ Very low	IMPORTANT
Length of hospital stay												
1	randomized trials	serious	serious	not serious	serious	none	5.7	4	-	**0** (0 to 0)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **OR:** odds ratio

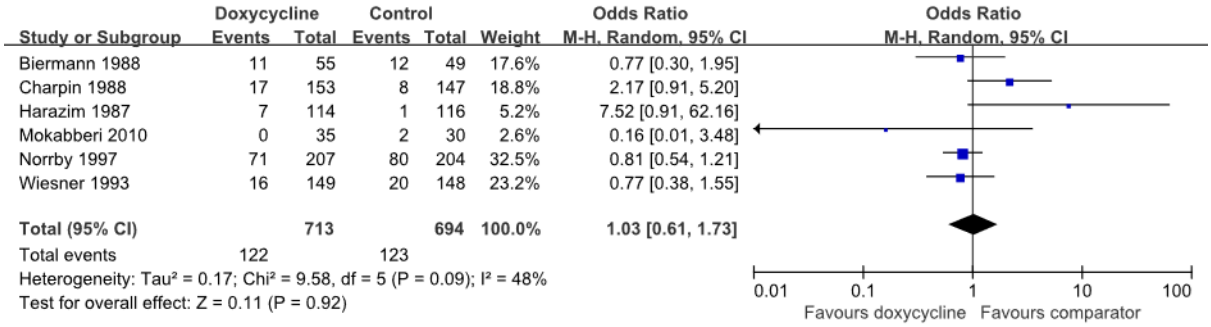
Supplementary Figure 1. Forest plot of clinical cure rate in trials in which comparators are not currently recommended for community-acquired pneumonia.



Supplementary Figure 2. Forest plot of clinical cure rate using a fixed-effect model.



Supplementary Figure 3. Forest plot of adverse events, including trials in which adverse events of pneumonic patients were mixed with those of non-pneumonic patients.



Supplementary Figure 4. Funnel plot of clinical cure rate for the publication bias.