Fluoroquinolones *versus* B-Lactams Plus Macrolides for Community-Acquired Pneumonia in Adults: A Meta-Analysis of Randomised Controlled Trials

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ABSTRACT

Objective: Several randomized trials have been done to compare fluoroquinolones alone with the combination therapy of β-lactams plus macrolides for treating community-acquired pneumonia (CAP) in adults. However, the efficacy and safety between the two arms are still unclear.

Methods: We searched the PubMed, Embase, ScienceDirect and China National Knowledge Infrastructure (CNKI). Two reviewers independently extracted data and the mortality, treatment success and adverse events were compared between fluoroquinolones and β-lactams plus macrolides. RevMan 5.0 was used for statistical analysis.

Results: 11 randomized controlled trials were included in our meta-analysis. Mortality was not significantly different for fluoroquinolones vs. β-lactams plus macrolides (OR 1.29, 95% CI 0.73–2.27). Treatment success was higher with fluoroquinolones both in the intention-to-treat (ITT) population (OR 1.37, 95% CI 1.02–1.83) and the clinically evaluable population (OR 1.34, 95% CI 1.01–1.79). No difference was found between fluoroquinolones and β-lactams plus macrolides in microbiological treatment success (OR = 1.31, 95% CI 0.82-2.09).

Keywords: β-lactams, community-acquired, fluoroquinolones, macrolides, meta-analysis pneumonia,

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West Indian Med J **DOI: 10.7727/wimj.2015.011**

Regarding the happening of adverse events, serious adverse events and adverse events requiring discontinuation, there was no difference between the two therapies.

Conclusion: Our meta-analysis suggested that fluoroquinolones were more effective than β-lactams plus macrolides for the treatment of CAP and the safety of the two therapies were similar.

INTRODUCTION

Community-acquired pneumonia (CAP) is a remarkable cause of morbidity and mortality in adults (1). Estimated from some prospective population studies, the incidence of CAP per year is between 5 to 11 per 1000 adults in the community (2) and the incidence requiring hospitalisation reported to be 1.1 to 4‰ among the adult population (3). The mortality increased significantly from 1.2% to 31% in patients with different severity of CAP (3). Treatment failure appears in ~15% of all patients with CAP and usually leads to a longer time of hospital stay and increased costs (4).

For non-ICU hospitalized patients, combination therapy of β-lactams plus macrolides was advised to be used based on guideline recommendations (3, 5, 6). However, resistance to both antibiotics has remained in a high level (7). Recently, fluoroquinolones were introduced to be used in clinical application and their resistance rate was low especially to *Streptococcus pneumoniae* (7). And guidelines has recommended to use fluoroquinolones in the hospitalized patients (3, 5, 6). Several studies have been done to compare fluoroquinolones and β-lactams plus macrolides (8-18), but the results remained controversial.

In this meta-analysis, we compared fluoroquinolones alone with the combination therapy of

β-lactams plus macrolides, aiming to exam the efficacy and safety between the two therapies in treating CAP among the adult patients.

METHODS

Search methodology

We searched the PubMed, Embase, ScienceDirect and China National Knowledge Infrastructure (CNKI). 'Community-acquired pneumonia', 'fluoroquinolones', 'β-lactams' and 'macrolides' were used as search terms. The last search was done in June 2014. The languages were restricted to English and Chinese. The references were reviewed from the relevant articles.

Study selection

Two reviewers (XZ and ML) independently reviewed the articles and included the eligible ones. The article was considered to be eligible if it met the following inclusion criteria: (1) it was a RCT, (2) it compared fluoroquinolones with β-lactams plus macrolides about the efficacy and safety in treating adult patients with CAP.

Data extraction

The relevant data was extracted by two independent reviewers (XZ and ML). Any disagreement was resolved by discussion and reached a consensus. The Jadad scoring system was used to assess the quality of included studies (19). When the total is ≥3 points, the study is assessed as high quality (20).

Outcomes

Mortality in the population of intention-to-treat (ITT) and treatment success were the primary outcomes. The patients with a confirmed diagnosis of CAP and took ≥ 1 dose of study drug were included in the ITT. Either a cure or an improved condition was defined as treatment success. 'Cure' was defined as solving of clinical signs and symptoms and no further requirement for antimicrobial therapy of CAP. 'Improved' was defined as incomplete solving of symptoms or signs of infection. Secondary outcomes were microbiological treatment success which were extracted as defined in each studies, drug-related adverse outcome and drug-related serious adverse outcome.

Data analysis and statistical methods

The data from the eligible studies were pooled and the odds ratios (ORs) were calculated with 95% confidence intervals (CIs). $P < 0.05$ was considered to be statistically significant. The heterogeneity was assessed using the I^2 statistic. We initially conducted a fixed effects model unless high level of heterogeneity (>50%) existed between trials in which a random effects model was used. RevMan 5.0 was used for all statistical analysis.

RESULTS

In all, we searched 242 articles based on our searching strategy. After screening the titles and abstracts, 192 were excluded. After reviewing the remaining 50 articles' full texts, 11 articles were included in this meta-analysis (8-18) (Fig. 1). All trials included hospitalised adults with a diagnosis of CAP. The patients in the fluoroquinolones group were treated with levofloxacin or moxifloxacin, while in the β-lactams plus macrolides therapy group the drugs were

different between trials. Only one of the trials compared fluoroquinolone in high dose (18). Antibiotics were given intravenously initially in all but two trials, in which treatment were given orally (10, 15). Four trials (9, 10, 12, 13) also included β-lactams or macrolides alone in the comparator group, and we only got part of the data comparing fluoroquinolones with the combination group. The main characteristics are presented in Table.

All trials were RCTs except Torres et al. (10) who conducted the double-blinded study. The methods of randomization could be found in seven studies (8, 9, 11, 13, 15, 17, 18) and were unclear in the remaining four studies (10, 12, 14, 16). Most of the included studies were assessed to be good quality with a Jaded score ≥3.

Mortality

Four articles gave the data of mortality. In all, 28 (5.4%) of the 518 patients in the fluoroquinolones group and 23 (4.3%) of the 540 patients in β-lactams plus macrolides therapy group died during the studies. But none of the deaths were reported to be treatment related. No significant difference was found in mortality between study arms (1058 patients, OR 1.29, 95% CI 0.73–2.27, I^2= 0%) (Fig. 2). We did not make subgroup analysis due to lack of data.

Treatment success

Treatment success in the ITT population could be got in seven trials (8, 11, 14-18). In total, the clinical success rate was 82.0% in the fluoroquinolones group and 77.1% in the β-lactams plus macrolides group. Fluoroquinolones alone were more effective than the combination therapy of β-lactams plus macrolides by our meta-analysis (OR 1.37, 95% CI 1.02–1.83, P=0.03) (Fig. 3A). We also did analysis in the clinical evaluable population and found that

fluoroquinolones were also more effective (eleven RCTs, 1980 patients, OR 1.34, 95% CI 1.01–1.79) (Fig. 3B).

In the subgroup analysis, there was no significant difference in levofloxacin and moxifloxcin subgroups (levofloxacin subgroup, six RCTs, 684 patients, OR 1.29, 95% CI 0.79–2.12; moxifloxacin subgroup, five RCTs, 1296 patients, OR 1.37, 95% CI 0.96–1.95) (Fig. 3A). Rates of treatment success were similar in trials sponsored by pharmaceutical companies (OR 1.18; 95% CI 0.84–1.66, 8 trials). In addition, we analysis the articles whose scores were ≥ 3 and treatment success was significantly higher with fluoroquinolones (OR 1.44; 95% CI 1.06–1.96). Four trials added β-lactamase inhibitors in the β-lactams plus macrolides group. In this subgroup, the fluoroquinolones were also more effective than the combination therapy (OR 1.56, 95% CI 1.06–2.30). When we restricted the analysis to studies including moderate to severe CAP, no significant difference was found in the subgroup (OR 1.23, 95% CI 0.74–2.06).

The outcomes of microbiological treatment success were provided in seven trials. The overall outcome was 183 (82.1%) of the 223 patients in the fluoroquinolones group and 193 (78.1%) of the 247 patients in β-lactams plus macrolides group. And there was no significant difference between the two arms (470 patients, OR = 1.31, 95% CI 0.82–2.09). The rate was also similar in CAP caused by *S. pneumoniae* (OR 1.56, 95% CI 0.28–8.83).

Adverse outcomes

Adverse outcomes could be got in seven trials, of which six trials gave the drug-related adverse outcomes. Overall, 90 (19.9%) of the 452 patients in the fluoroquinolones group had at least one drug-related adverse event compared with 117 (25.1%) of the 467 patients in

β-lactams plus macrolides group. ORs were similar in the group of patients who had at least one drug-related adverse event (OR 0.73, 95% CI 0.53–1.02) (Fig. 4) and at least one serious drug-related adverse event (OR 0.68, 95% CI 0.41–1.11). Most adverse events were not severe. Gastrointestinal disorders were the most common. Five trials reported the adverse outcomes of diarrhea, the pooled analysis showed the happenings were similar between the two trials (OR 0.20, 95% CI 0.03–1.46). Because of the lack of data, we did not perform analysis of other adverse outcomes. Regarding the rate of patients withdrawn from the studies due to drug-related adverse outcomes, there was no significant difference between two arms (OR 0.59, 95% CI 0.34–1.01).

DISCUSSION

Our meta-analysis, which included 11 RCTs compared fluoroquinolones monotherapy with ß-lactams plus macrolides combination therapy for the treatment of CAP, indicated the fluoroquinolones monotherapy were more effective and safety between the two arms were similar. The pooled ORs in treatment success were higher in fluoroquinolones group, and the ORs were similar between two tials in mortality and adverse outcomes, respectively.

Vardakas et al (21) did a meta-analysis in which analyzed fluoroquinolones with comparator antibiotics including macrolides or β-lactams or both. Although they analyzed the treatment success between fluoroquinolones and combination therapy, they didn’t do any subgroup analysis between the two arms. In contrast to the previous meta-analysis, we only compared fluoroquinolones with ß-lactams plus macrolides combination therapy which is a

therapeutic strategy usually used in clinical, eliminating the interference of other therapies. In addition, we included a new study (18) in our meta-analysis.

In clinical practice, when choosing antibiotics physicians should consider several aspects such as the severity of the patients, the drug that the patients had before, the effectiveness of eliminating the pathogens, adverse effects and the costs. In our analysis, one of the trials used levofloxacin 750mg once daily. And most of the results remained the same when excluded or included this trial. Recently, the levofloxacin regimen of 750-mg for 5 days was shown to get comparable clinical and microbiological outcomes to those of 500-mg for 10 days (22). Whether 750-mg fluoroquinolones are more effective than combination group could be further studied. Four trials reported on all-cause mortality. But none of them focused on severe pneumonia. So we didn't make analysis of the effectiveness of treating severe CAP. The overall mortality was low in our meta-analysis and that maybe because most patients included were mild CAP. The mortality rates between two groups were similar. However, this results were analysed based on patients with mild to severe CAP. Although mortality is the most important outcome for severe CAP (23), few studies included in our meta-analysis compared the outcome in the population.

Recently, the rise in bacterial resistance of *S. pneumoniae* and other isolates of community-acquired pathogens affecting the respiratory tract were seen in several studies. However, the newer fluoroquinolones remained high activity (24). In our meta-analysis treatment success rate was similar between two arms in CAP caused by causative pathogen. However, the data was not much and more studies were needed to draw a conclusion of those. A recent review indicated that *S. Pneumoniae* was found to be the most frequent pathogen

among inpatiens both in the non-ICU and ICU (1). In addition, *S. pneumoniae* is rarely reported as resistant to respiratory fluoroquinolones (25, 26). However, reports in some countries have suggested that fluoroquinolone resistance in *S. pneumoniae* may be increasing (27). So it is important when and how to use fluoroquinolones to avoid the bacterial resistance increasing. Regarding the cost of therapy, Samsa et al (28) suggested direct medical costs of the combination group were less compared to the corresponding costs in the levofloxcin group, which should be considered by clinicians. With regards to the mortality of patients, the evidence is insufficient to make a conclusion any individual fluoroquinolone therapy is better than another (29). In our analysis, the results were the same between the levofloxacin and moxifloxacin subgroup. More studies comparing the outcomes between different fluoroquinolones may be conducted in the future. Adverse events are also one important factor when physicians choose antibiotics. Published reviews indicated fluoroquinolones were relatively well tolerated and associated with many rare adverse events which could be considered more clinically significant (29). In our analysis, regarding the rate of adverse events, fluoroquinolones were similar with the combination group.

These findings in our analysis should be viewed under the consideration of the limitations of this study. First the quality of the studies included in our analysis was not very high. So we made a analysis of the articles whose scores were ≥ 3 and the findings were the same with those of the primary analysis. What's more, most studies included in our meta-analysis were conducted a decade ago. But the level of ß-lactams and macrolides resistance remained steady over the past few years and the fluoroquinolones resistance was still low (7).

CONCLUSION

In conclusion, our meta-analysis indicated that fluoroquinolones monotherapy may be more effective than ß-lactams plus macrolides combination therapy for the treatment of CAP. Fluoroquinolones resulted in higher treatment success and were similar in mortality and advers outcomes. Fluoroquinolones monotherapy once daily may be an effective and safe choice for CAP compared to ß-lactams plus macrolides combination therapy. However, well-designed RCTs comparing the two therapies in patients with severe CAP are needed.

ACKNOWLEDGMENTS

This work was supported by grants 81230001 and 31171103 from the National Natural Science Foundation of China and grant 06-834 from the China Medical Board of New York to Dr. Fuqiang Wen. We are indebted to the authors of the primary studies included in this meta-analysis; without their contributions, this work would not have been possible.

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Table. Characteristics of the included studies.

Authors	Countries	Years	Included patients	NO. of patients (T/C)	Drugs used		Duration	Sponsors	Jadad score
					Fluoroquinolone	β-lactam plus macrolide			
Frank et al. (8)	US	1997-1999	Patients ≥18 years old with moderate-to-severe CAP at hospital	115/121	Oral or i.v. levofloxacin 500 mg q24h	Ordinal i.v. (for ≥ 2 days) and oral azithromycin 500mg q24h with ceftriaxone 1g q24h for 2 days	10 days	UNK	3
Finch et al. (9)	10 countries	NS	Patients ≥18 years old with CAP required initial parenteral therapy at hospital	258/168*	Ordinal i.v. and oral moxifloxacin 400mg q24h	Ordinal amoxicillin/clavulanate i.v. 1.2 g q8 h and oral 625 mg q8 h with i.v. or oral clarithromycin 500 mg q12 h	7-14days	UNK	3
Torres et al. (10)	13 coutries	NS	Patients ≥18 years old with CAP	215/143*	Oral moxifloxacin 400 mg q24 h	Oral amoxicillin 1 g q8 h and oral clarithromycin 500 mg q12 h	5-15 days	Industry	4
Fogarty et al. (11)	US	1997-2000	Patients ≥18 years old with CAP who met≥3 American Thoracic Society criteria at hospital	134/135	Ordinal i.v. and oral levofloxacin 500mg q24h	i.v. or i.m. ceftriaxone sodium 1–2 g q24h with i.v. erythromycin 500-1000 mg q6h followed by oral amoxicillin-clavulanate 875 mg	7-14 days	Industry	3

						plus clarithromycin 500 mg q12h			
Erard et al. (12)	Switzer- land	2000-2001	Patients ≥18 years old with CAP at hospital	79/20*	Oral levofloxacin 500 mg q12 h	i.v. ceftriaxone 2 g q24 h with i.v. or oral clarithromycin 500 mg q12 h	7-14 days	Industry	2
Katz et al. (13)	US	2001-2002	Patients ≥18 years old with CAP who required initial i.v. therapy at hospital	108/75*	Ordinal i.v. to oral moxifloxacin 400 mg q24h	i.v. ceftriaxone 2 g q24 h followed by oral cefuroxime 500 mg q12 h with i.v. or oral azithromycin 500 mg q24 h followed by oral 500/250 mg q24 h	7-14 days	Industry	3
Zervos et al. (14)	US, Canada, Europe	2001-2002	Patients ≥18 years old with CAP who got a PSI of ≥71 at hospital	107/112	Ordinal i.v. (for ≥ 2 days) and oral levofloxacin 500mg q24h	i.v. azithromycin 500mg and ceftriaxone 1g (for 2-5 days) once daily followed by oral azithromycin 500mg q24h	7-14 days	Industry	2
Portier et al. (15)	France	2001-2002	Patients ≥18 years old with CAP who was appropriate for oral therapy and had at least one risk factor at hospital	171/175	Oral moxifloxacin 400 mg q24h	Oral amoxicillin/clavulanic acid 1000/125 mg and roxithromycin 150 mg t.i.d.	10 days	Industry	3

Xu et al. (16)	China	NS	Patients ≥18 years old CAP requiring parenteral treatment initially	20/20	i.v. moxifloxacin 400 mg once daily	i.v. cefoperazone 2.0 g b.i.d. and i.v. azithromycin 0.5 g once daily	7-14 days	UNK	1
Lin et al. (17)	China	2004-2006	Patients ≥18 years old with CAP at hospital	26/24	Ordinal i.v. and oral levofloxacin 500 mg once daily	i.v. amoxicillin/clavulanate 500 mg/100 mg followed by oral 250 mg/125 mg q8h always with oral clarithromycin 500 mg q12h	7-14days	Industry	3
Lee et al. (18)	Korea	2010-2011	Adults with CAP at hospital	20/20	Ordinal i.v. and oral levofloxacin 750 mg once daily	i.v. ceftriaxone 2 g and oral azithromycin 500 mg for 3 consecutive days followed by oral cefpodoxime 200 mg per day	7-14days	Industry	3

Studies are classfied by the year of publication. NO.=number. T/C=treatment/control (in the intention-to-treat population,*in the clinically evaluable population). CAP=community-acquired pneumonia. UNK=unknown. PSI=Pneumonia Severity Index. Yeas indicates the time when the study was done.

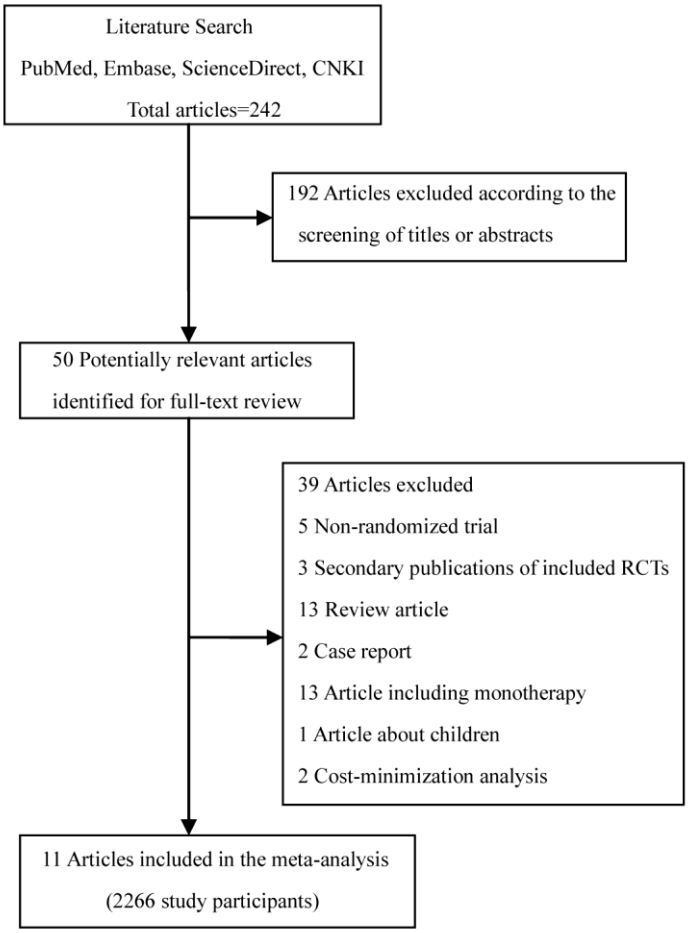


Figure 1. Literature search strategy. CNKI=China National Knowledge Infrastructure; RCT=randomised controlled trial.

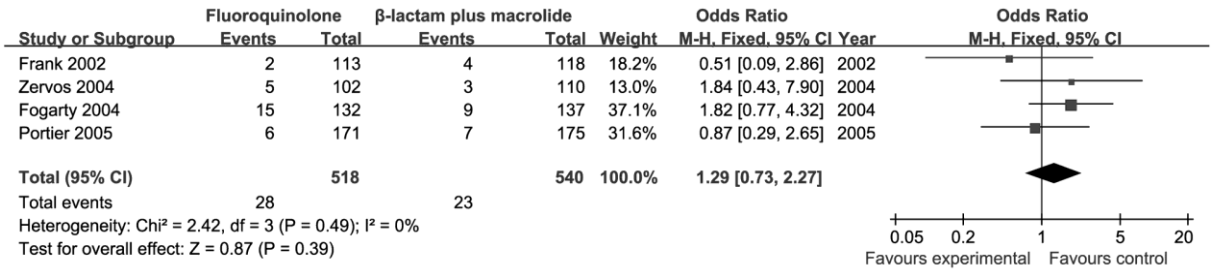
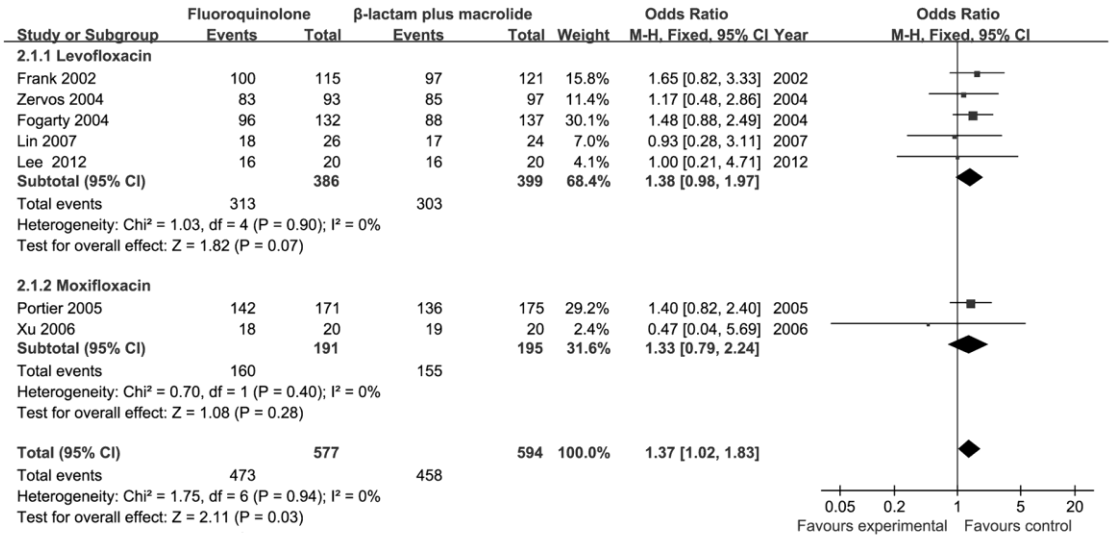


Figure 2. All cause mortality: meta-analysis of mortality comparing fluoroquinolones with β-lactams plus macrolides in patients with community-acquired pneumonia. CI=confidence interval.

A



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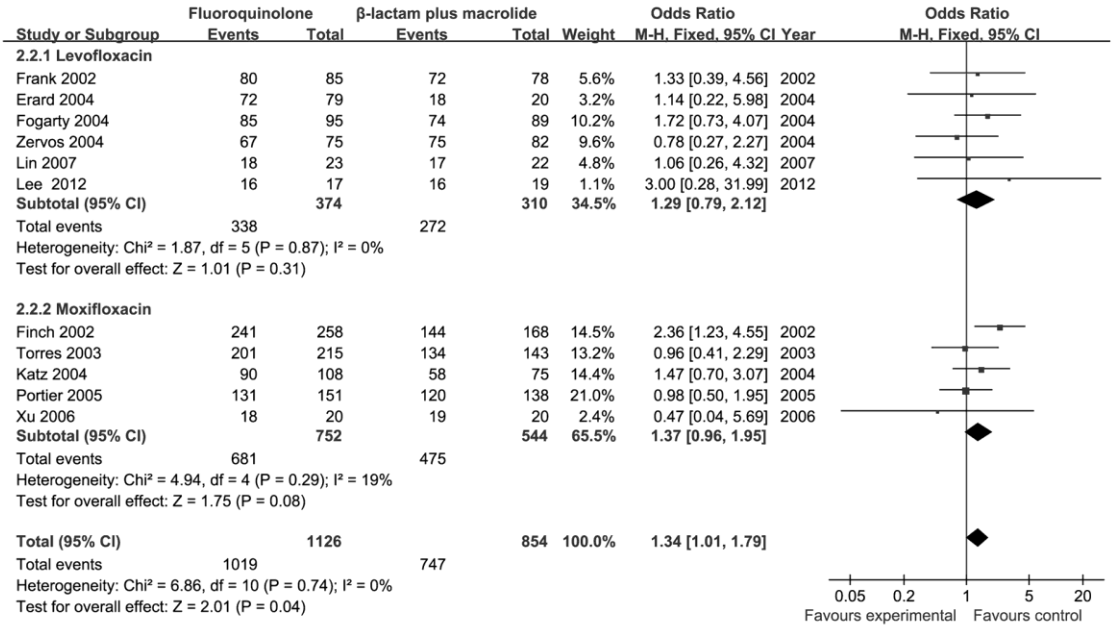

Figure 3. Treatment success: meta-analysis of treatment success comparing fluoroquinolones with β-lactams plus macrolides in patients with community-acquired pneumonia. (A) clinical treatment success analysis in the intention-to-treat population; (B) clinical treatment success analysis in the clinically evaluable population. CI = confidence interval.

Figure 4

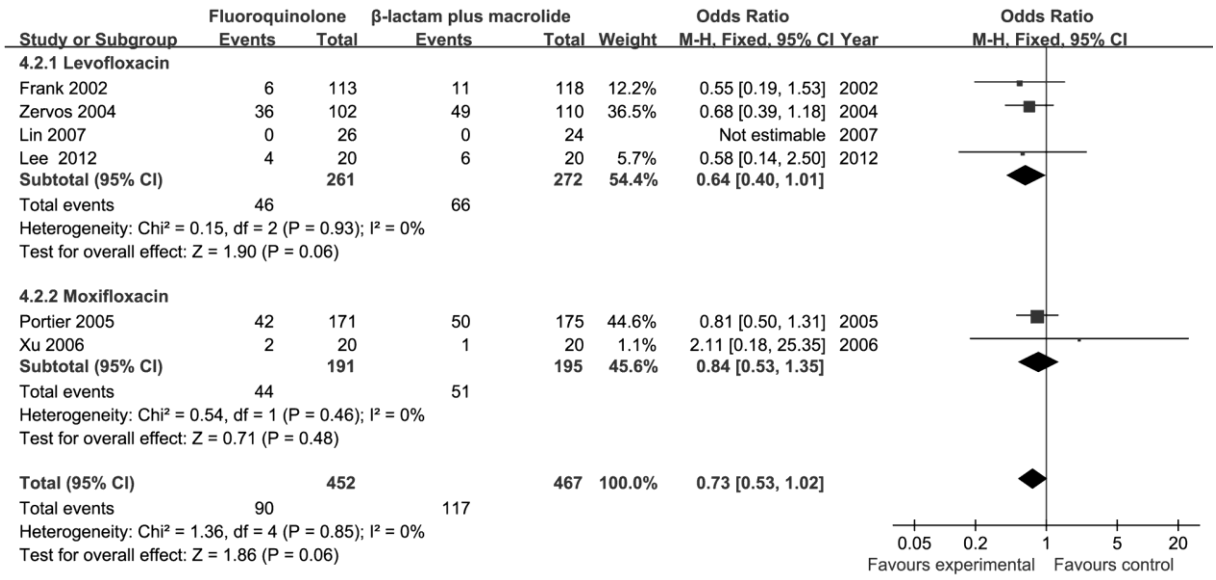

Figure 4. Adverse outcomes: meta-analysis of adverse outcomes comparing fluoroquinolones with β-lactams plus macrolides in patients with community-acquired pneumonia. CI = confidence interval.

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