

Meta-analysis Evaluating Respiratory Fluoroquinolones for Community-Acquired Pneumonia



From left to right

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In a recently published meta-analysis (CMAJ 2008; 179: 1269–77.) we sought to examine whether respiratory fluoroquinolones were

associated with better clinical outcomes in adult patients with pneumonia. We searched PubMed, Current Contents, Scopus, EMBASE, ClinicalTrials.gov and Cochrane for published trials comparing fluoroquinolones (levofloxacin, moxifloxacin and gemifloxacin) with macrolides and/or β -lactams and extracted data regarding effectiveness and toxicity. A meta-analysis including 23 trials was performed. Mortality was not different between the compared antibiotics (odds ratio [OR]: 0.85; 95% confidence interval [CI]: 0.65–1.12). Fluoroquinolones were more effective for the treatment of pneumonia than comparator antibiotics in the intention-to-treat (OR: 1.17; 95% CI: 1.00–1.36), clinically evaluable (OR: 1.26; 95% CI: 1.06–1.50) and microbiologically assessed (OR: 1.67; 95% CI: 1.28–2.20) populations. Fluoroquinolones were also more effective than β -lactam/macrolide combinations (OR: 1.39; 95% CI: 1.02–1.90), for patients with severe pneumonia (OR: 1.84; 95% CI: 1.02–3.29), for hospitalized patients (OR: 1.30; 95% CI: 1.04–1.61) and for patients requiring intravenous therapy (OR: 1.44; 15% CI: 1.13–1.85). Fluoroquinolones were more effective in open label (OR: 1.35; 95% CI: 1.08–1.69) but not in blinded trials (OR: 1.13; 95% CI: 0.85–1.50). In conclusion, fluoroquinolones were associated with higher treatment success for severe forms of pneumonia, but a benefit in mortality is not evident. A well-designed randomized controlled trial that includes patients with severe pneumonia with or without bacteremia is needed to further clarify this important clinical question.

Introduction

Community-acquired pneumonia (CAP) is among the leading reasons for hospitalization, resource consumption and the intensive care unit admission (1–4). The β -lactam/macrolide combination was used for several years for its treatment (5). More recently, fluoroquinolones with enhanced activity against *Streptococcus pneumoniae* (*S. pneumoniae*) and favorable pharmacokinetic profiles were introduced in clinical practice. In the latest guidelines of the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (6), levofloxacin, gemifloxacin and moxifloxacin were proposed as the preferred, equally effective to the β -lactam/macrolide combination treatment option for patients with pneumonia.

Since the trials that compared fluoroquinolones with other antibiotic regimens for the treatment of patients with pneumonia were designed on the basis of non-inferiority, we used the methodology of meta-analysis to examine whether the use of fluoroquinolones is associated with more advantages or disadvantages than treatment with macrolides and/or β -lactams in terms of effectiveness and safety.

Methods

A search of PubMed, Current Contents, Scopus, EMBASE, ClinicalTrials.gov and the Cochrane Central Register of randomized controlled trials was performed to identify relevant published trials for our meta-analysis. Search terms included “flu-

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oroquinolones”, “levofloxacin”, “moxifloxacin”, “gemifloxacin”, “macrolides”, “ β -lactams”, all in combination with the term “community-acquired pneumonia”. References from relevant articles, including review papers were also reviewed.

Two reviewers independently searched the literature and examined the identified relevant trials for data on effectiveness and toxicity. A trial was eligible for inclusion in the meta-analysis if it compared a fluoroquinolone with enhanced activity against *S. pneumoniae* as proposed in the IDSA 2007 guidelines (levofloxacin, gemifloxacin and moxifloxacin) with the macrolide/ β -lactam combination therapy or monotherapy (e.g. macrolides, ketolides or β -lactams alone) for the treatment of patients with pneumonia. Trials that studied other fluoroquinolones than the proposed ones were excluded. No restriction in language was set.

Two reviewers independently extracted the relevant data. Any disagreement between the reviewers was resolved by consensus in meetings with all authors. When data was missing the corresponding authors of the original trials were contacted. Each trial was subject to a quality review that included details of randomization, generation of random numbers, double-blinding, information on withdrawals, and concealment of allocation. When each criterion was met, one point was awarded; the maximum score for a study was 5. A minimum of 3 points was necessary for a high-quality trial, while low-quality trials scored 2 or fewer points (7).

The primary end-point of the meta-analysis was all-cause mortality in an intention-to-treat (ITT) analysis during the study period (e.g. during the treatment and follow-up period). Patients receiving at least one dose of the study medication comprised the ITT population. Treatment success (*cure* defined as resolution of all symptoms and signs of infections, or *improvement* defined as resolution of two or more of the baseline symptoms or signs of infections), and adverse effects probably or possibly related to study regimens were considered as secondary outcome measures. We performed sensitivity analyses to assess the robustness of the findings according to 2 different aspects of the trials methodology: high modified Jadad score (>2) and double blinding.

Statistical analyses were done using the Review Manager 4.2 software (RevMan version 4.2, Cochrane Collaboration, 2006). The heterogeneity between trials was assessed by using a chi-squared and I^2 test; a p value lower than 0.10 was defined to note statistical significance in the analysis of heterogeneity. Publication bias was assessed by the funnel plot method using Egger’s test (8).

Pooled odds ratios (OR) and 95% confidence intervals (CI) for all primary and secondary outcomes were calculated using both the Mantel-Haenszel fixed effects (9) and the DerSimonian-Laird random effects models (10). For all analyses, results from the fixed effects model are presented only when there was no heterogeneity between trials; otherwise results from the random effects model are presented.

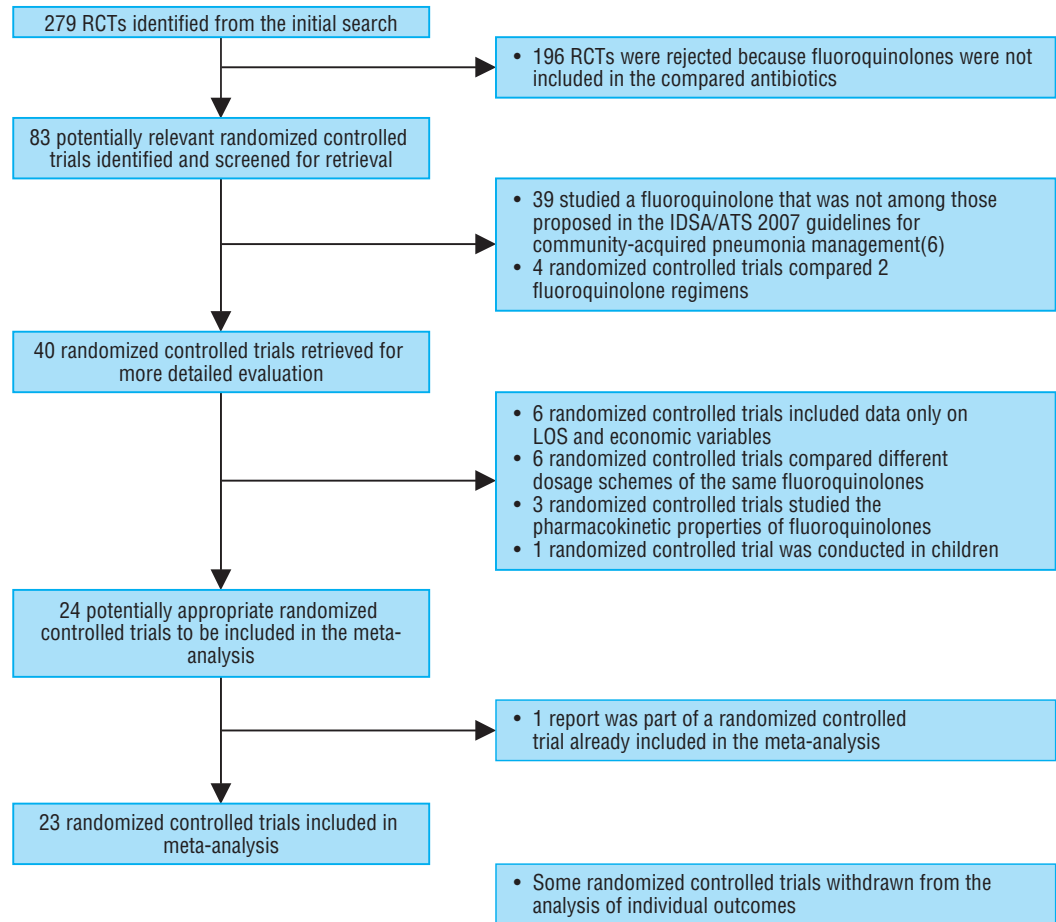
Results

Figure 1 shows the process for the selection of the 23 trials (studying 7,885 patients) that were included in the meta-analysis (11–33). The two reviewers had initial agreement on 943/1,058 (89%) entries regarding trials methodology and outcomes [k statistic = 0.78 (substantial agreement)]. The main characteristics of the analyzed trials are shown in the internet appendices of the Canadian Medical Association Journal, in which the original article was published [Appendix 2 (available at www.cmaj.ca/cgi/content/full/179/12/1269/DC2) and Appendix 3 (available at www.cmaj.ca/cgi/content/full/179/12/1269/DC2)].

Mortality was not different between the two groups of patients (Figure 2A, OR: 0.85; 95% CI: 0.65–1.12). Data regarding mortality of patients with severe or bacteremic pneumonia were not available. Mortality was not different in inpatients (Figure 2B, OR: 0.92; 95% CI: 0.68–1.24).

Fifteen trials reported data on treatment success in the ITT population. Fluoroquinolones were statistically significantly more effective than the comparator antibiotics (Figure 3A, OR: 1.17; 95% CI: 1.00–1.36). All trials provided data regarding treatment success in clinically evaluable populations. Overall, treatment success for patients with pneumonia was significantly higher in the fluoroquinolone group (Figure 3B; OR: 1.26; 95% CI: 1.06–1.50). Fluoroquinolones were also more effective than combination therapy (Figure 3C; OR: 1.39; 95% CI: 1.02–1.90). No difference was found when fluoroquinolones were compared with β -lactam or macrolide monotherapy (Figure 3D; OR: 1.19; 95% CI: 0.93–1.50). Interestingly, when data from non-industry trials were pooled, fluoroquinolones were more effective than comparator antibiotics (Figure 3E, OR: 1.86; 95% CI: 1.26–2.75); the analysis of industry-funded trials did not show statistically significant differences between the compared groups (OR: 1.13; 95% CI: 0.93–1.38).

Fluoroquinolones were more effective than comparator antibiotics for patients with severe pneumonia (Figure 4A; OR: 1.84; 95% CI: 1.02–3.29). Data was also available to analyze fluoro-

Figure 1. Flow diagram of reviewed randomized controlled trials (RCTs)

quinolones versus comparator antibiotics for patients with mild to moderate (Figure 4B, OR: 1.22; 95% CI: 0.98–1.51) and moderate to severe (Figure 4C, OR: 1.34; 95% CI: 0.97–1.85) pneumonia.

When fluoroquinolones were administered orally, they were not more effective than comparator antibiotics (Figure 5A, OR: 1.10; 95% CI: 0.85–1.41). However, fluoroquinolones were associated with higher effectiveness when initial intravenous treatment for either antibiotic regimen was employed (Figure 5B, OR: 1.44, 95% CI: 1.13–1.85). In addition, although no benefit was seen when fluoroquinolones were prescribed to outpatients (Figure 5C, OR: 1.06; 95% CI: 0.75–1.50), we noticed a statistically significant higher treatment success in hospitalized patients receiving fluoroquinolones (Figure 5D, OR: 1.30; 95% CI: 1.04–1.61). No difference was found for levofloxacin (Figure 6A, OR: 1.28; 95% CI: 0.97–1.67) or moxifloxacin (Figure 6B, OR: 1.22; 95% CI: 0.95–1.55) versus comparator antibiotics.

Overall, fluoroquinolones were more effective than comparator antibiotics in the microbiologically evaluable population (Figure 7A, OR:

1.67; 95% CI: 1.28–2.20). For patients with pneumonia due to *S. pneumoniae* no differences were seen (Figure 7B, OR: 0.72; 95% CI: 0.39–1.33). Finally, there was no difference in effectiveness among patients with bacteremic pneumonia (Figure 7C; OR: 0.84; 95% CI: 0.37–1.89) or bacteremic pneumonia due to *S. pneumoniae* (Figure 7D, OR: 1.30; 95% CI: 0.43–3.95).

The mean quality score of the included trials was 2.6 (range 1–5). The quality of 11 trials was high, while the quality of the remaining 12 was low. Fluoroquinolones were associated with a statistically significant better treatment success when data from low quality trials were pooled (Figure 8B, OR: 1.30; 95% CI: 1.01–1.67), but no differences between the compared regimens were found in high quality trials (Figure 8A, OR: 1.22; 95% CI: 0.95–1.57). Sensitivity analysis including only double-blinded trials showed no difference between antibiotic regimens (Figure 8C, OR: 1.13; 95% CI: 0.85–1.50) whereas a statistically significant difference in favor of fluoroquinolones was noticed for open label trials (Figure 8D, OR: 1.35; 95% CI: 1.08–1.69).

All trials reported data on drug-related ad-

verse effects – the majority related to mild to moderately severe disturbances of the gastrointestinal tract. Fluoroquinolones were associated with statistically significant fewer adverse effects (Figure 9A, OR: 0.86, 95% CI: 0.78–0.96), but withdrawals due to drug-related adverse effects were not different (Figure 9B, OR: 0.85; 95% CI: 0.69–1.06). Finally, no differences were observed between the compared antibiotic groups regarding recurrent infections (Figure 9C, OR: 0.98; 95% CI: 0.59–1.63).

Discussion

In this meta-analysis, the reported mortality was similar for fluoroquinolones when compared with β -lactam/macrolide combination or monotherapy for the treatment of patients with community-acquired pneumonia. However in both ITT and clinically evaluable populations treatment success was significantly higher in patients receiving fluoroquinolones. In addition, treatment success was higher in patients with severe pneumonia and those requiring hospitalization or initial intravenous therapy. The findings are also enhanced by a significantly higher treatment success in non-industry funded trials in patients treated with fluoroquinolones. Fluoroquinolones were also associated with fewer adverse effects.

However, we must acknowledge that these findings are based mainly on open label and low quality trials. The sensitivity analysis that included only high quality or double-blinded trials showed that fluoroquinolones were not more effective than comparator antibiotics for the treatment of pneumonia. Patients with milder forms of pneu-

monia were enrolled in these high quality trials. Another limitation was the inclusion of trials studying the fluoroquinolones proposed in the IDSA 2007 guidelines (6). Finally, data on adjunctive therapies that may improve outcomes in patients with severe pneumonia (like hydrocortisone, statins, inhibitors of angiotensin converting enzyme etc) were not collected (34).

In addition, most of the trials did not provide data on mortality and, when they did mortality was relatively low and data on mortality for patients with severe and bacteremic pneumonia were not reported, thus limiting our ability to draw conclusions about the most severely ill patients. Two non-randomized reports reached conflicting conclusions one favoring levofloxacin and one favoring the β -lactam/macrolide combination (35,36).

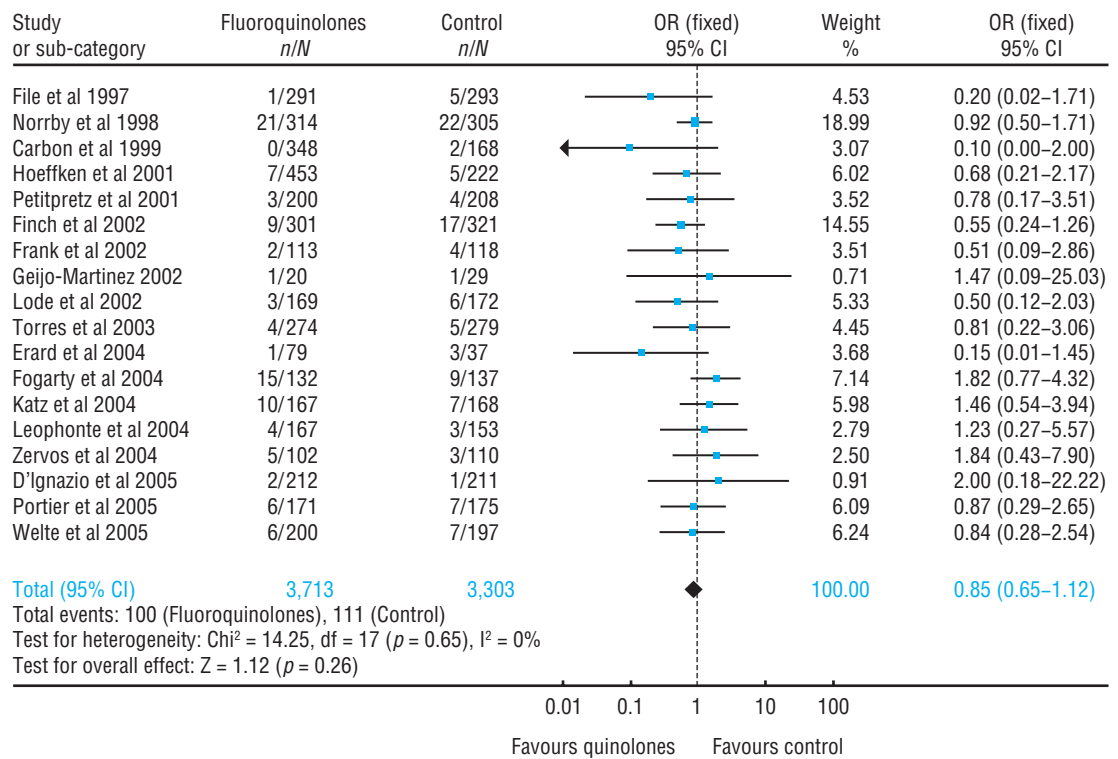
In conclusion, this meta-analysis suggests that no differences in mortality between antibiotic regimens were observed. Fluoroquinolones should be considered mainly for the treatment of patients with moderate to severe pneumonia as well as for patients requiring hospitalization and initial intravenous treatment. A well designed randomized controlled trial that will include mainly patients with severe community-acquired pneumonia with or without bacteremia is needed.

Acknowledgements

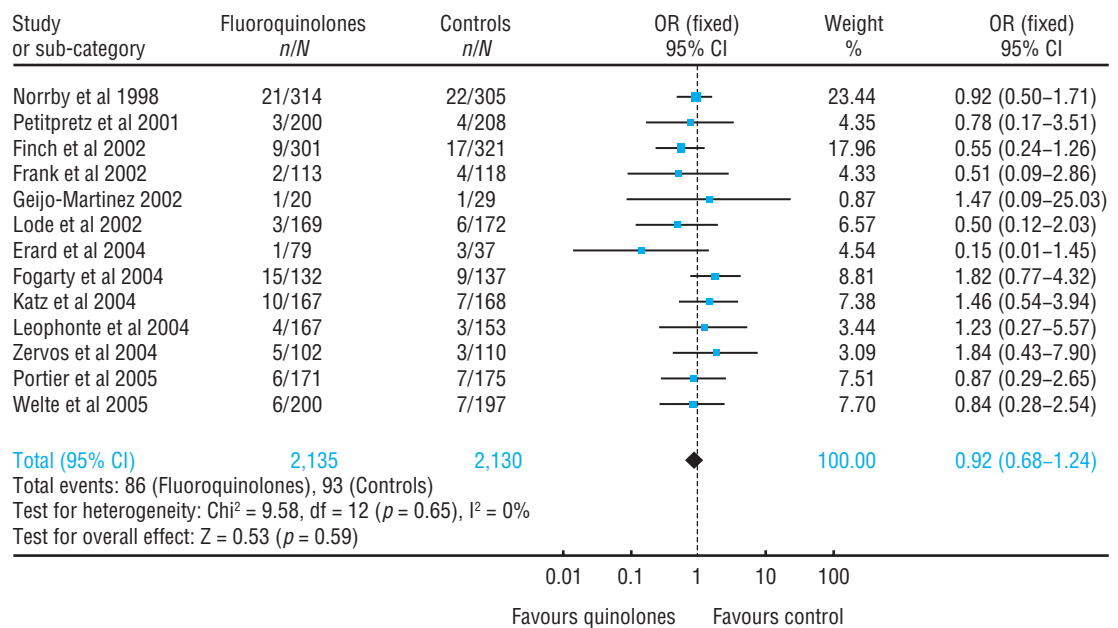
The present article is based on a previous article of ours published in the Canadian Medical Association Journal [CMAJ 2008; 179(12): 1269–77].

Figure 2. Odds ratios of mortality for the intention-to-treat (ITT) population**Figure 2A: Total mortality**

Review: Fluoroquinolones in CAP
 Comparison: O2 Mortality
 Outcome: O1 Mortality total ITT

**Figure 2B: Mortality in inpatients**

Review: Fluoroquinolones in CAP
 Comparison: O2 Mortality
 Outcome: O2 Mortality inpatients ITT



Vertical line = "no difference" point between the two regimens. Square = odds ratio; Diamond = pooled odds ratio for all randomized controlled trials. Horizontal lines = 95% CI.

Abbreviations: CAP = community-acquired pneumonia, ITT = intention-to-treat, OR = odds ratio, CI = confidence interval.

Figure 3. Odds ratios of treatment success for the intention-to-treat (ITT) and clinically evaluable (CE) patients

Figure 3A: ITT patients

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 02 ITT population

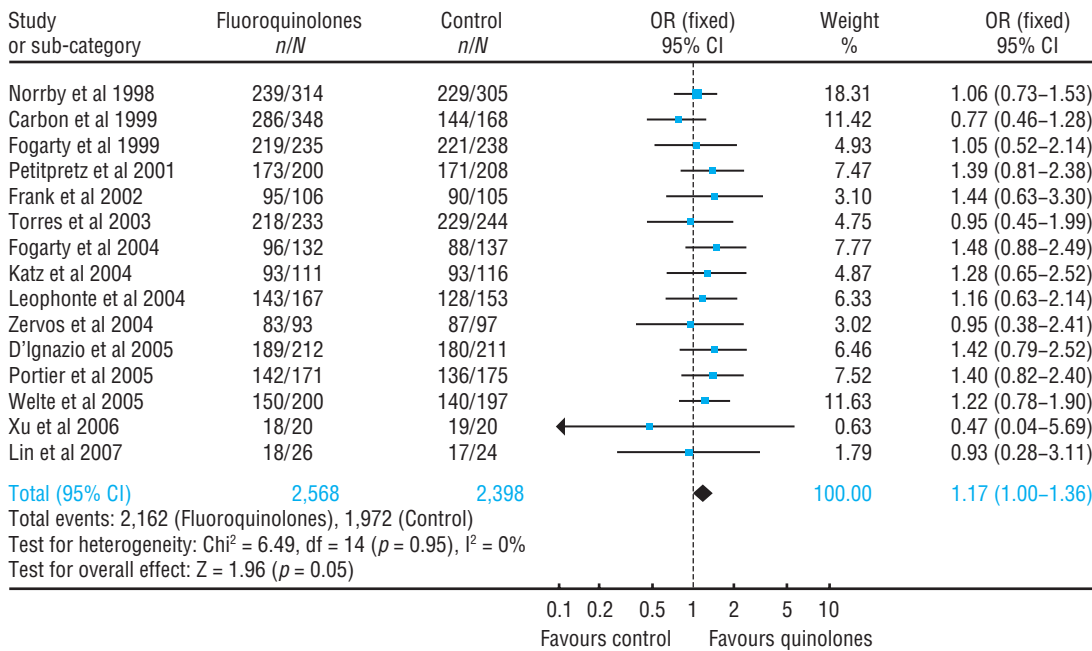


Figure 3B: All CE patients

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 01 CE population

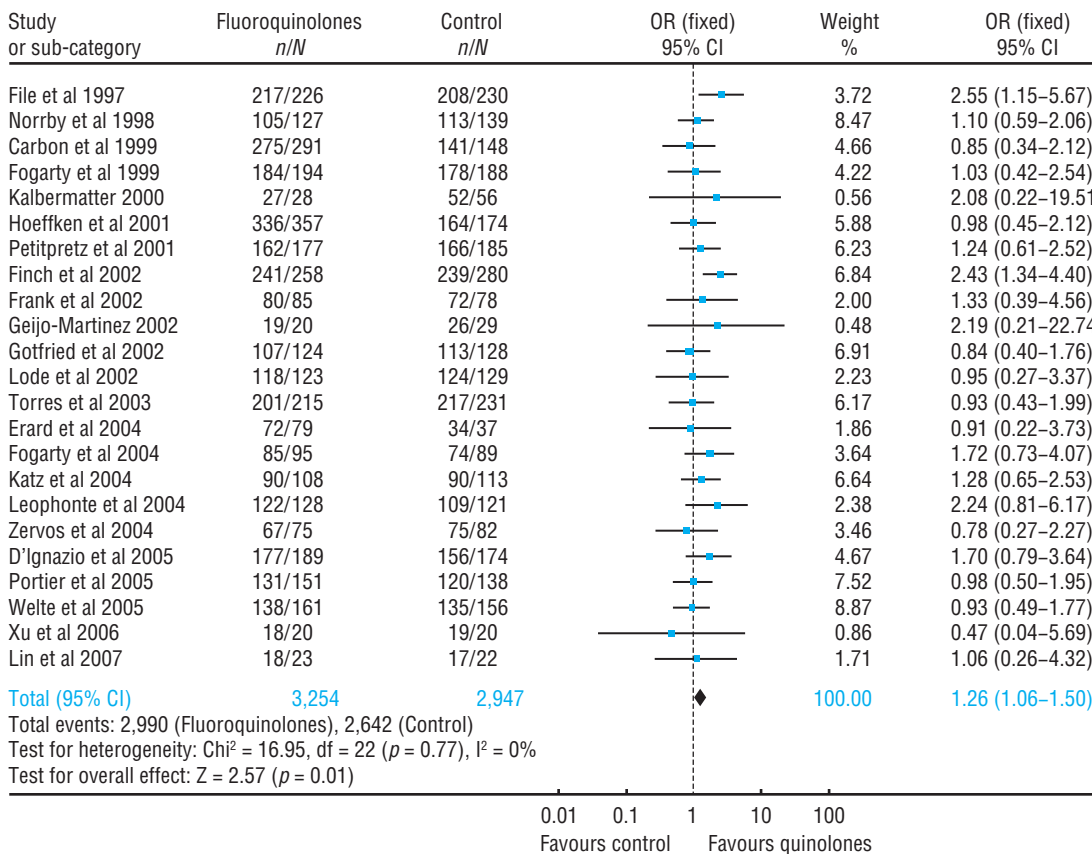
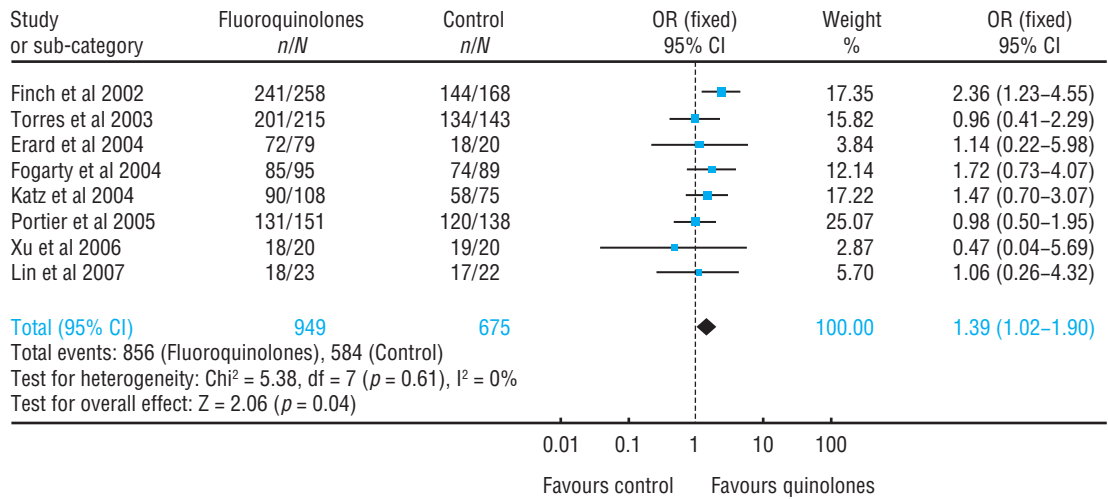


Figure 3C: Fluoroquinolones versus combination therapy

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 04 Combination therapy CE

**Figure 3D: Fluoroquinolones versus monotherapy**

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 03 Monotherapy CE

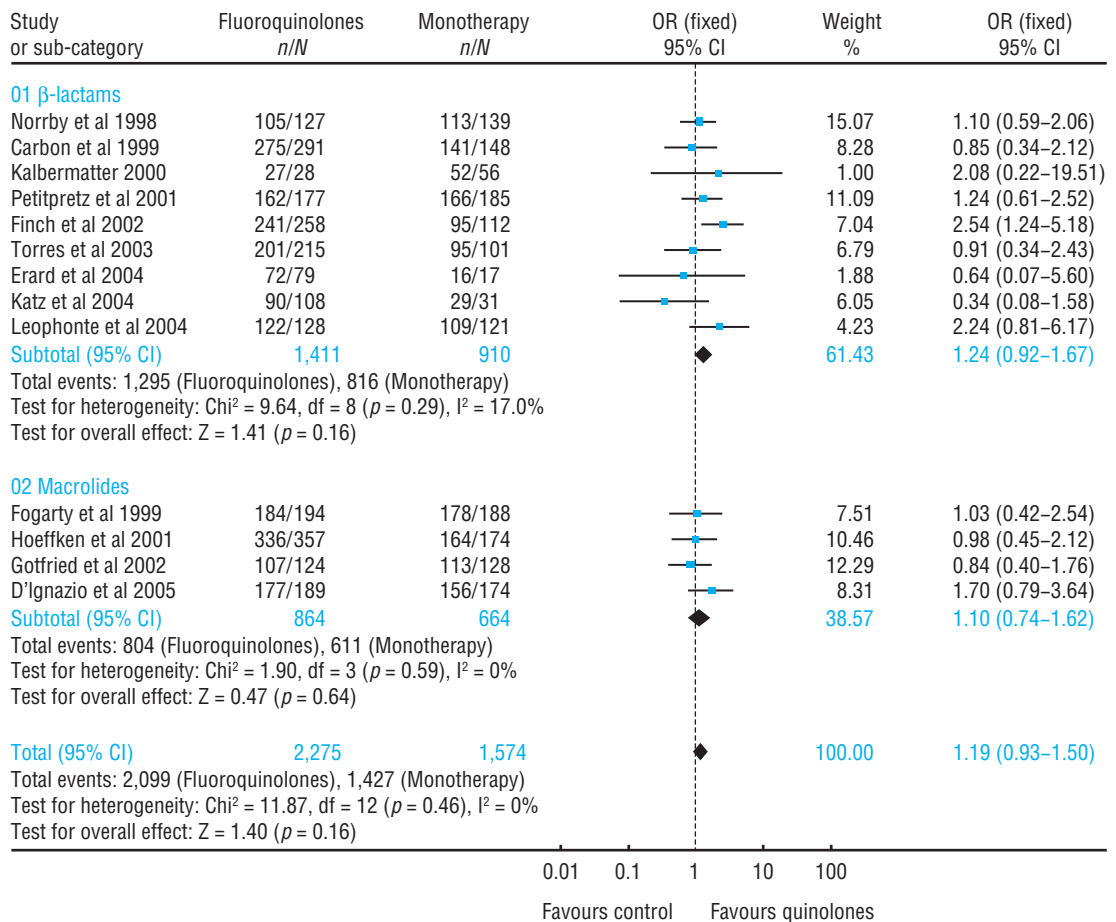
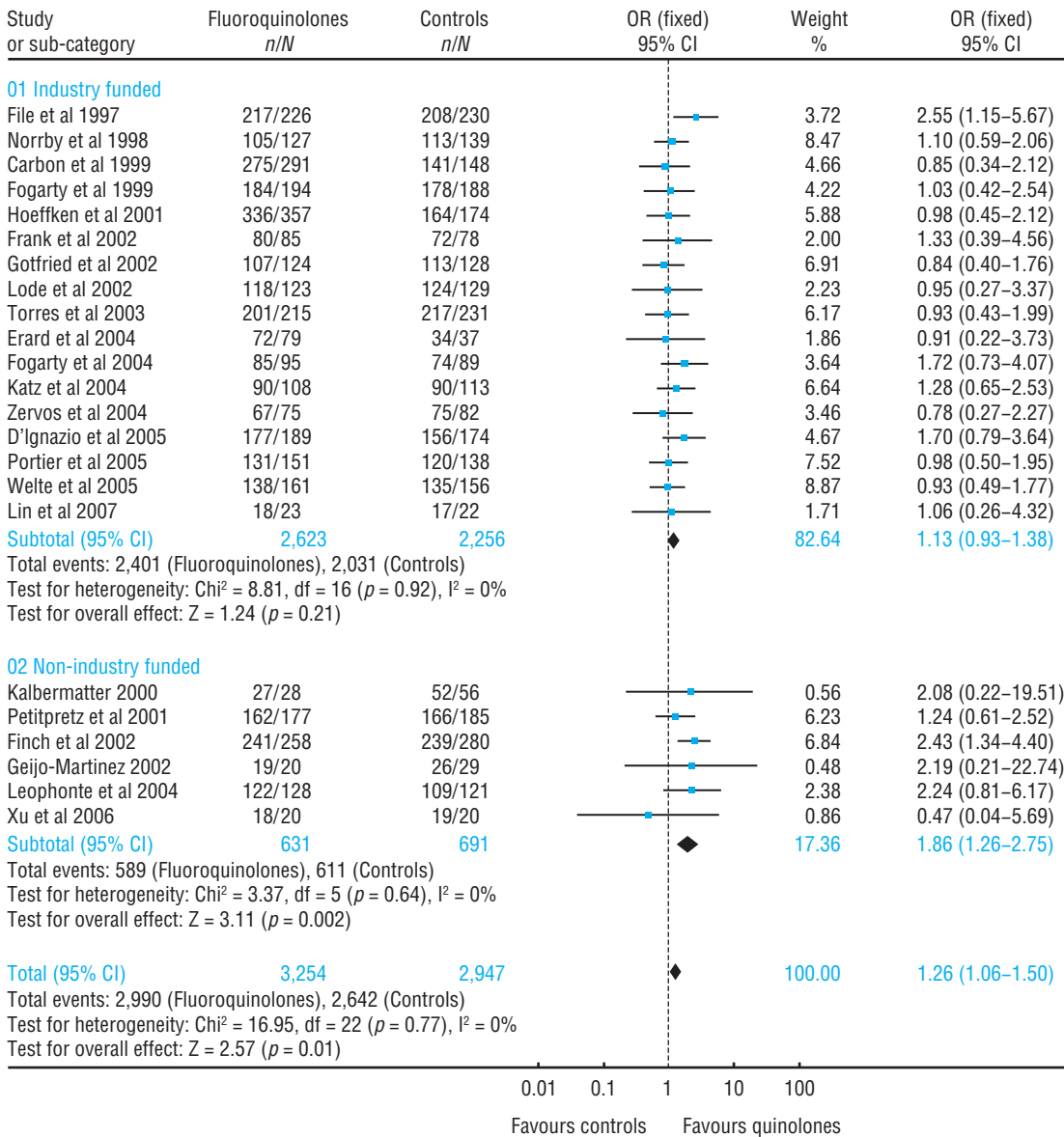


Figure 3E: Funding of the study

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 24 Funding of the study CE

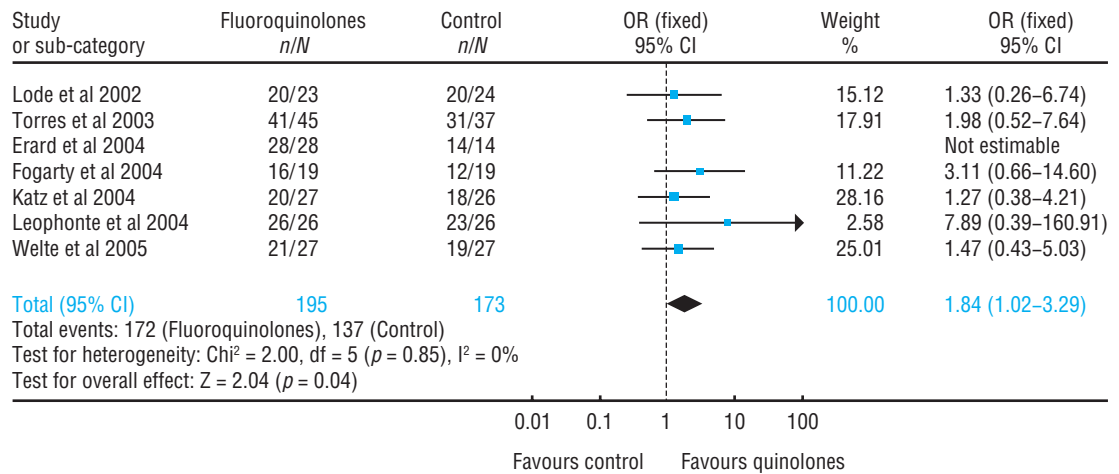


Vertical line = “no difference” point between the two regimens. Square = odds ratio; Diamond = pooled odds ratio for all randomized controlled trials. Horizontal lines = 95% CI.

Abbreviations: CAP = community-acquired pneumonia, ITT = intention-to-treat, OR=odds ratio, CI = confidence interval, CE = clinically evaluable.

Figure 4. Odds ratios of treatment success according to severity of pneumonia for the clinically evaluable (CE) patients**Figure 4A: Patients with severe pneumonia**

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 05 Severe pneumonia CE

**Figure 4B: Patients with mild to moderately severe pneumonia**

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 12 Mild to moderate pneumonia CE

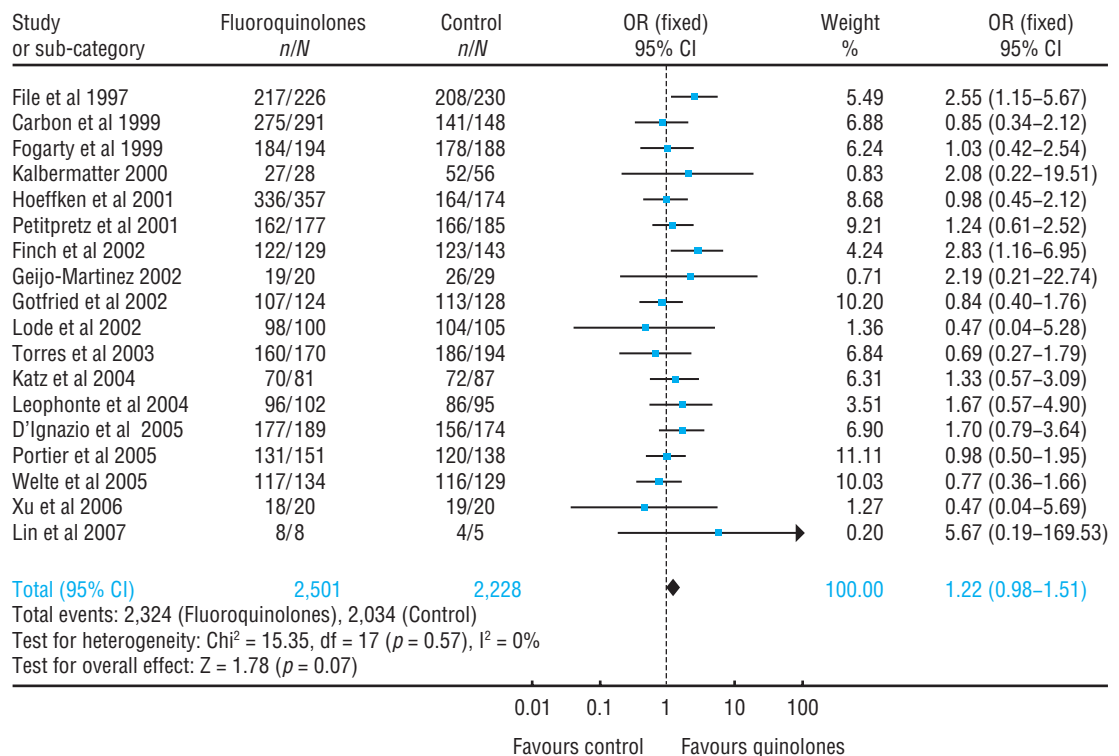
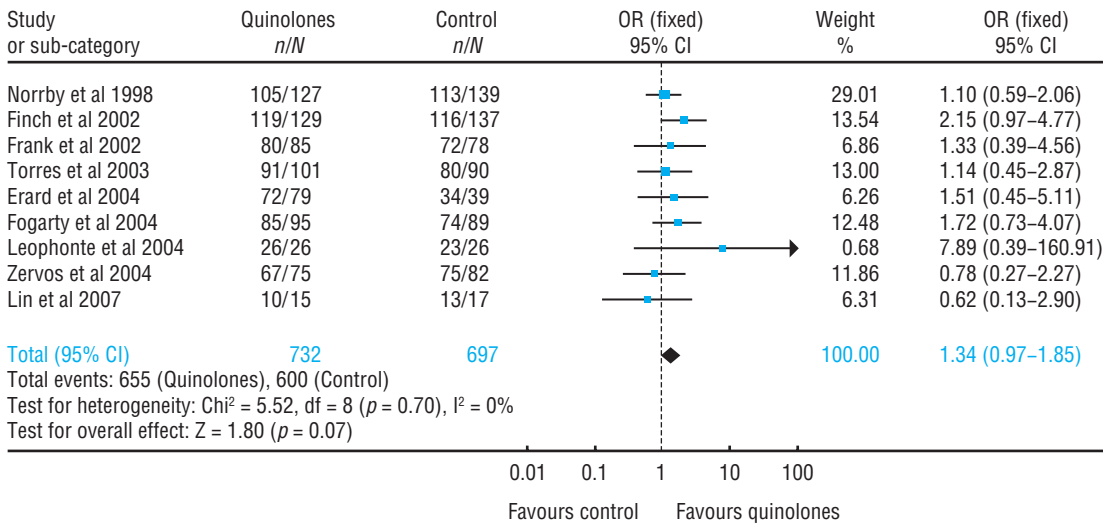


Figure 4C: Patients with moderate to severe pneumonia

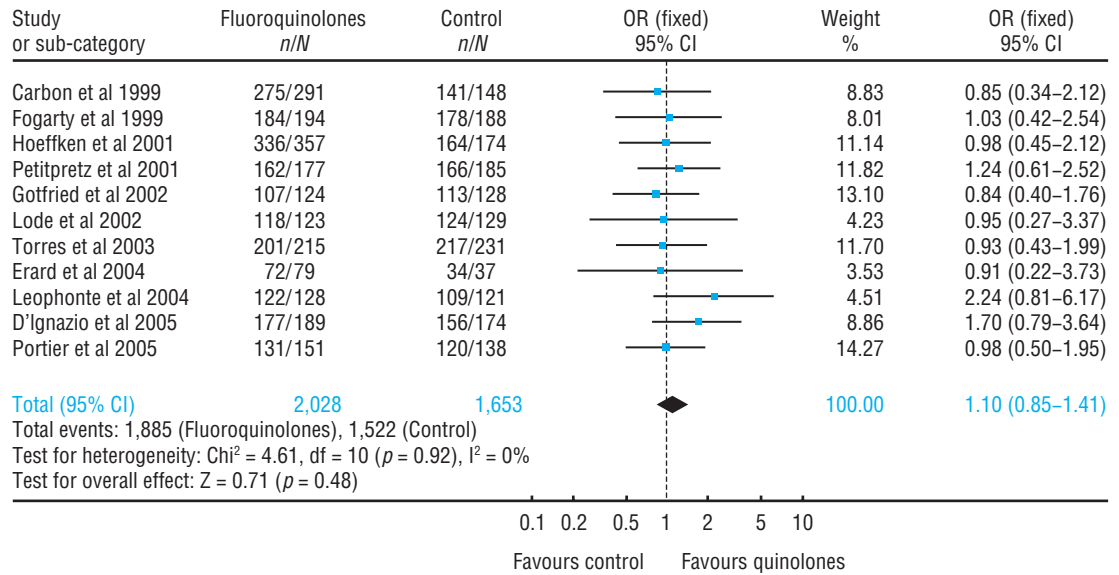
Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 11 Moderate to severe pneumonia CE



Vertical line = “no difference” point between the two regimens. Square = odds ratio; Diamond = pooled odds ratio for all randomized controlled trials. Horizontal lines = 95% CI.
 Abbreviations: CAP = community-acquired pneumonia, OR = odds ratio, CI = confidence interval, CE = clinically evaluable.

Figure 5. Odds ratios of treatment success according to the route of antibiotic administration and hospitalization for the clinically evaluable (CE) patients**Figure 5A: Oral administration**

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 18 Oral administration CE

**Figure 5B: Intravenous administration**

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 19 Intravenous administration CE

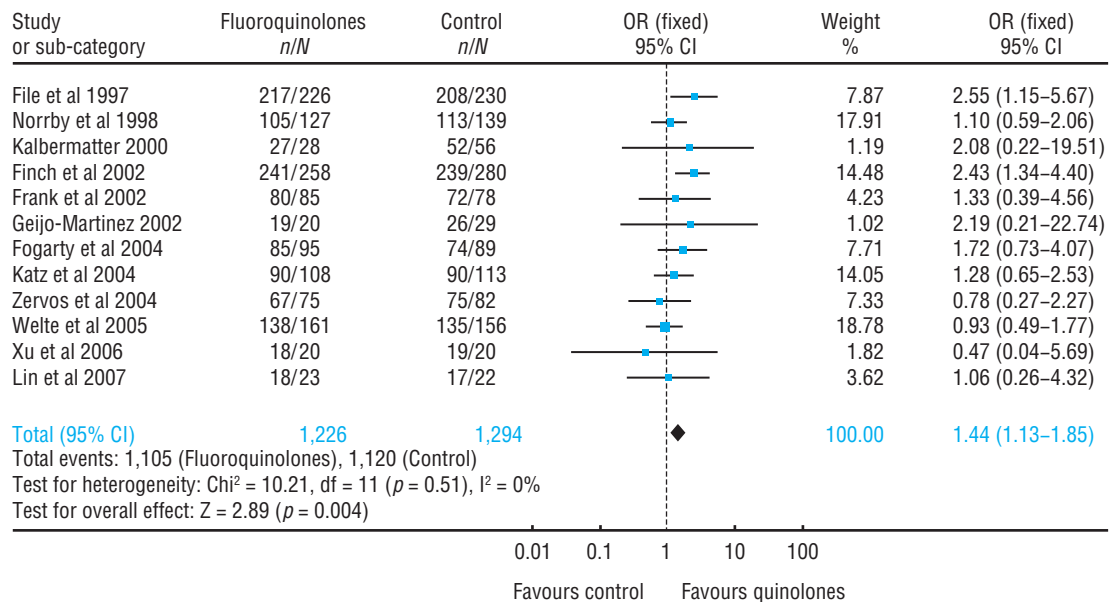


Figure 5C: Outpatients

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 17 Outpatients CE

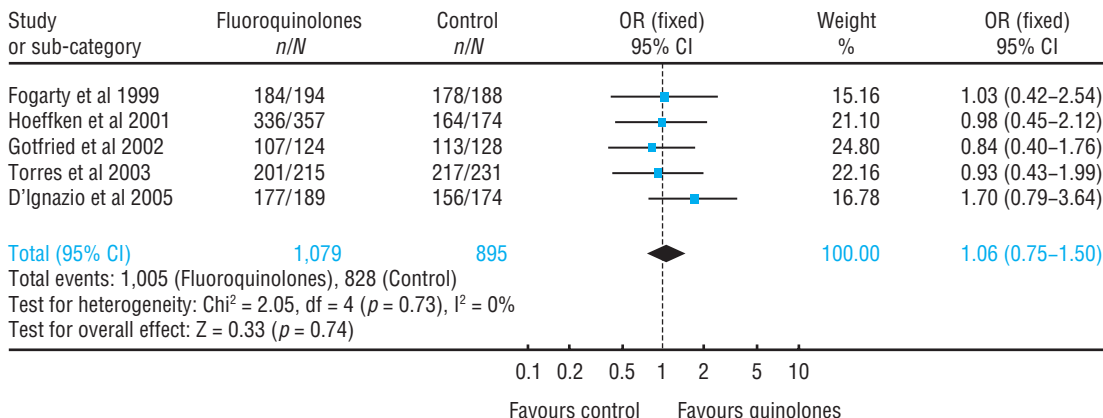
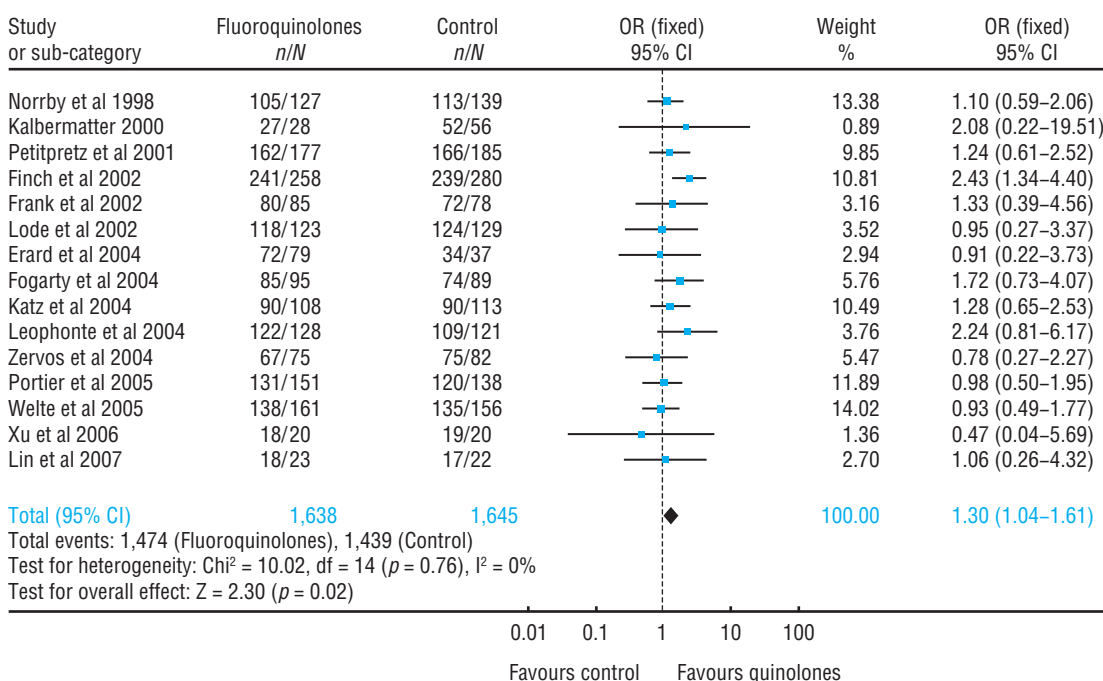


Figure 5D: Inpatients

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 16 Inpatients CE

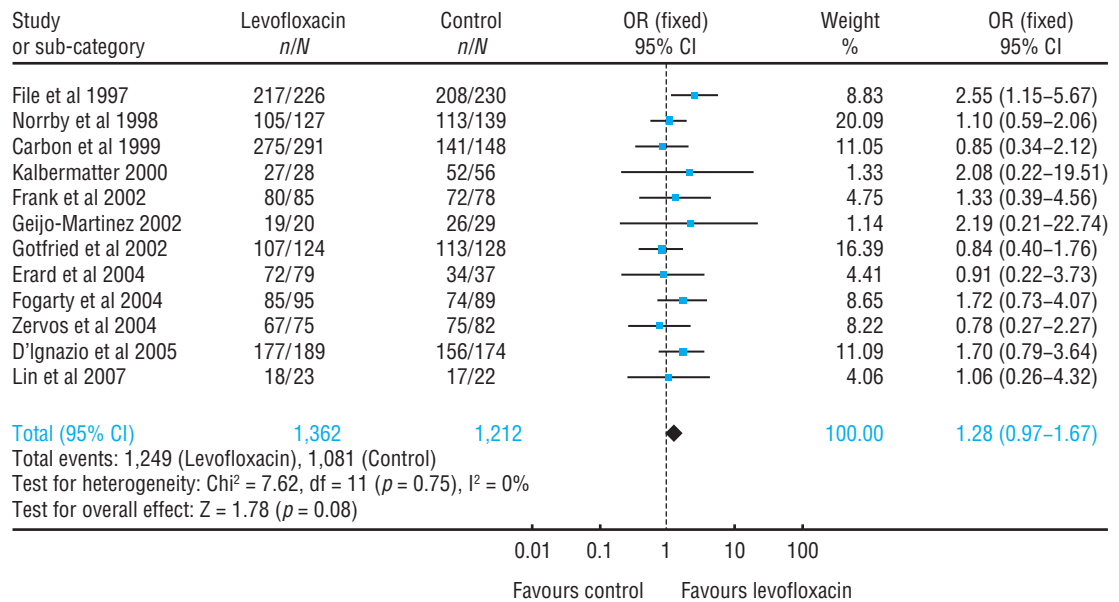


Vertical line = “no difference” point between the two regimens. Square = odds ratio; Diamond = pooled odds ratio for all randomized controlled trials. Horizontal lines = 95% CI.

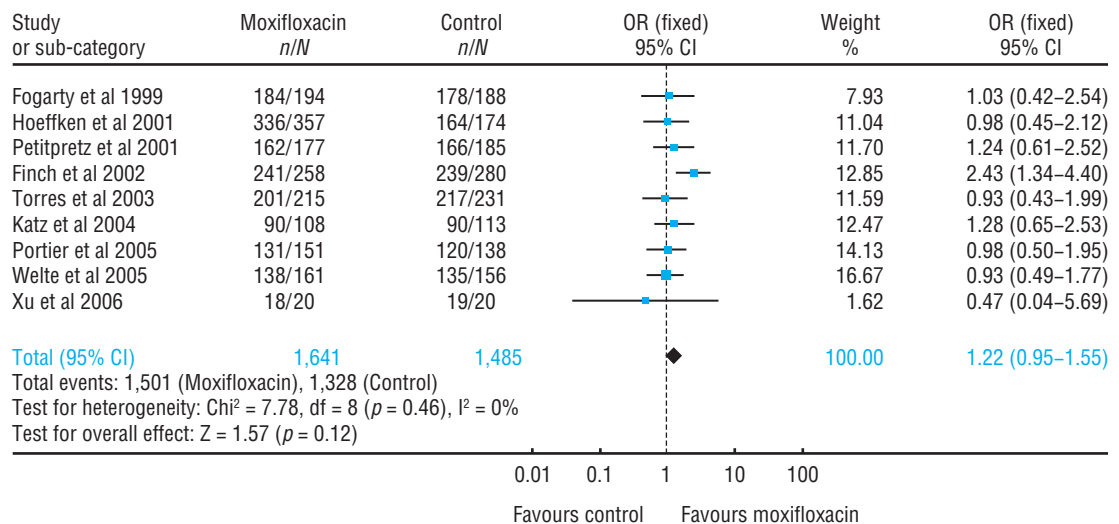
Abbreviations: CAP = community-acquired pneumonia, OR = odds ratio, CI = confidence interval, CE = clinically evaluable.

Figure 6. Odds ratios of treatment success according to the studied fluoroquinolone for the clinically evaluable (CE) patients**Figure 6A: Levofloxacin**

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 22 Levofloxacin trials CE

**Figure 6B: Moxifloxacin**

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 23 Moxifloxacin trials CE



Vertical line = "no difference" point between the two regimens. Square = odds ratio; Diamond = pooled odds ratio for all randomized controlled trials. Horizontal lines = 95% CI.

Abbreviations: CAP = community-acquired pneumonia, OR = odds ratio, CI = confidence interval, CE = clinically evaluable.

Figure 7. Odds ratios of treatment success for the microbiologically evaluable (ME) patients

Figure 7A: All patients

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 09 ME population

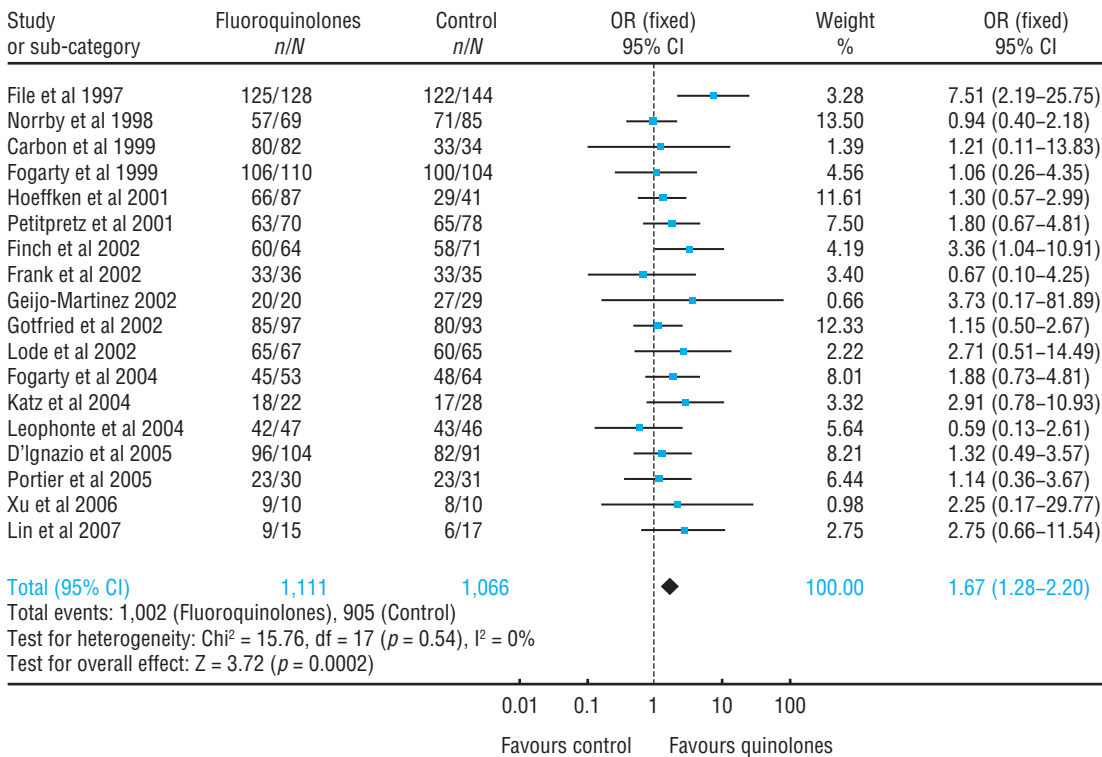


Figure 7B: Patients with *Streptococcus pneumoniae*

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 10 *Streptococcus pneumoniae* ME

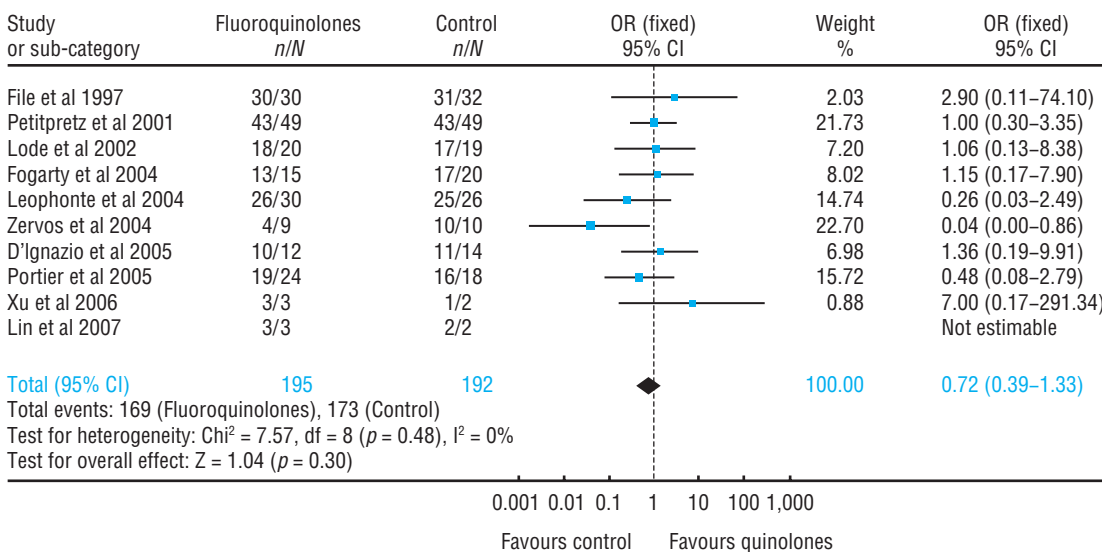
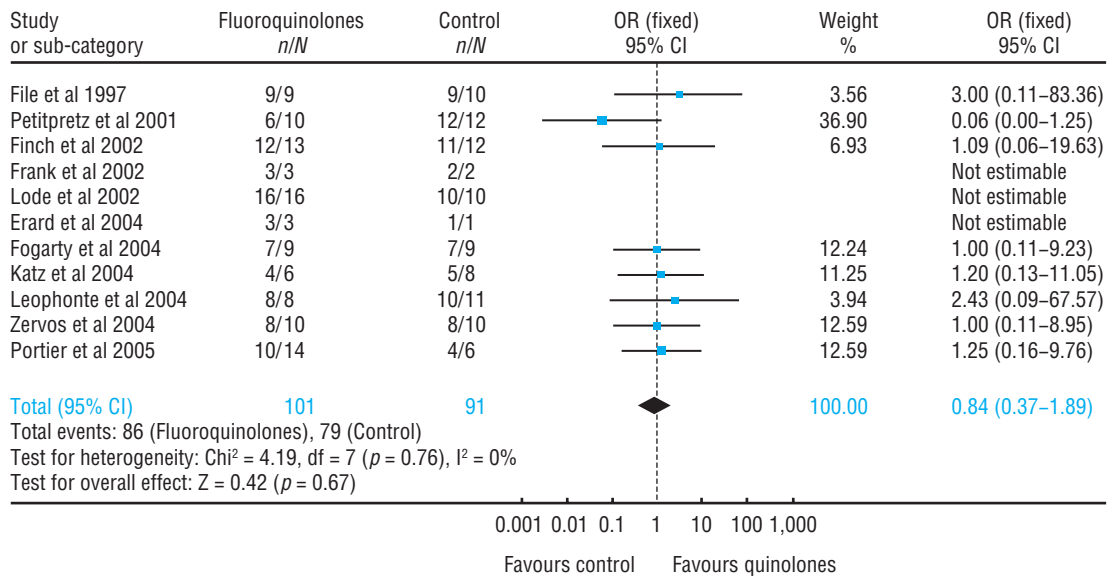
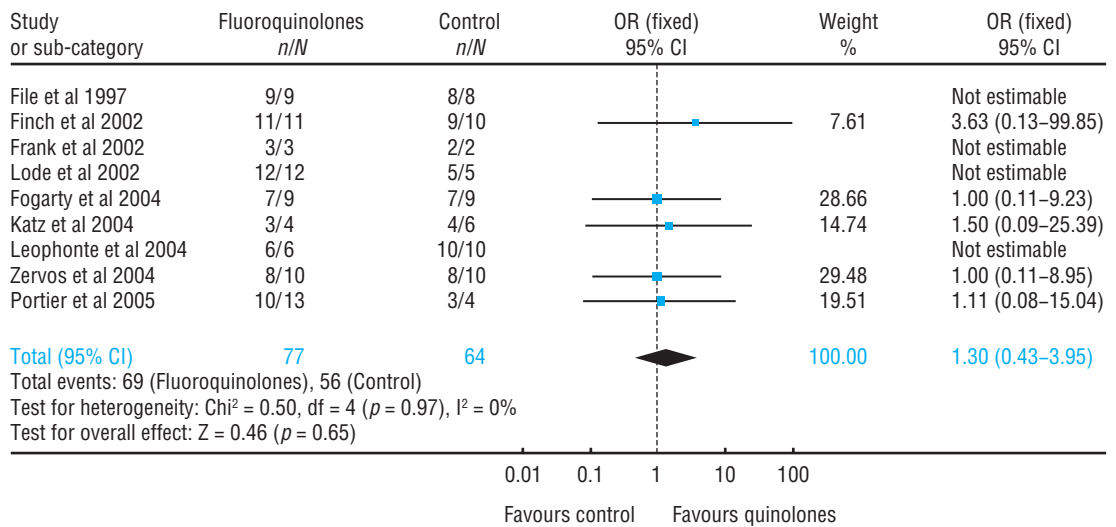


Figure 7C: Bacteremic pneumonia

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 08 Bacteremic pneumonia ME

**Figure 7D: Bacteremic pneumonia due to *Streptococcus pneumoniae***

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 13 Bacteremic pneumonia due to *Streptococcus pneumoniae* ME



Vertical line = "no difference" point between the two regimens. Square = odds ratio; Diamond = pooled odds ratio for all randomized controlled trials. Horizontal lines = 95% CI.

Abbreviations: CAP = community-acquired pneumonia, OR = odds ratio, CI = confidence interval, ME = microbiologically evaluable.

Figure 8. Odds ratios of treatment success according to the quality of trials for the clinically evaluable (CE) patients

Figure 8A: High quality trials

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 14 High quality trials CE

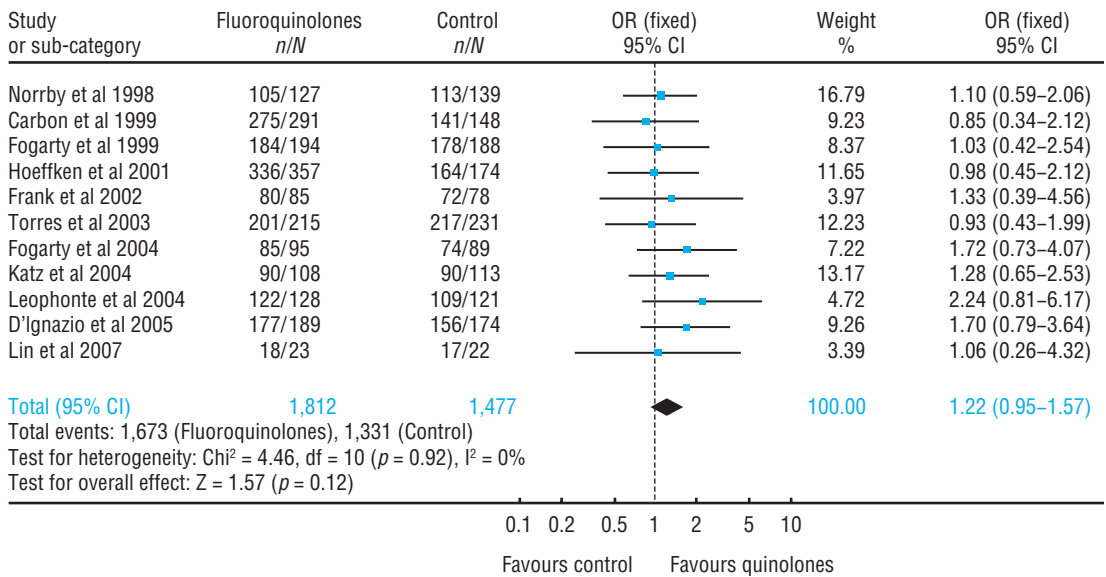


Figure 8B: Low quality trials

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 15 Low quality trials CE

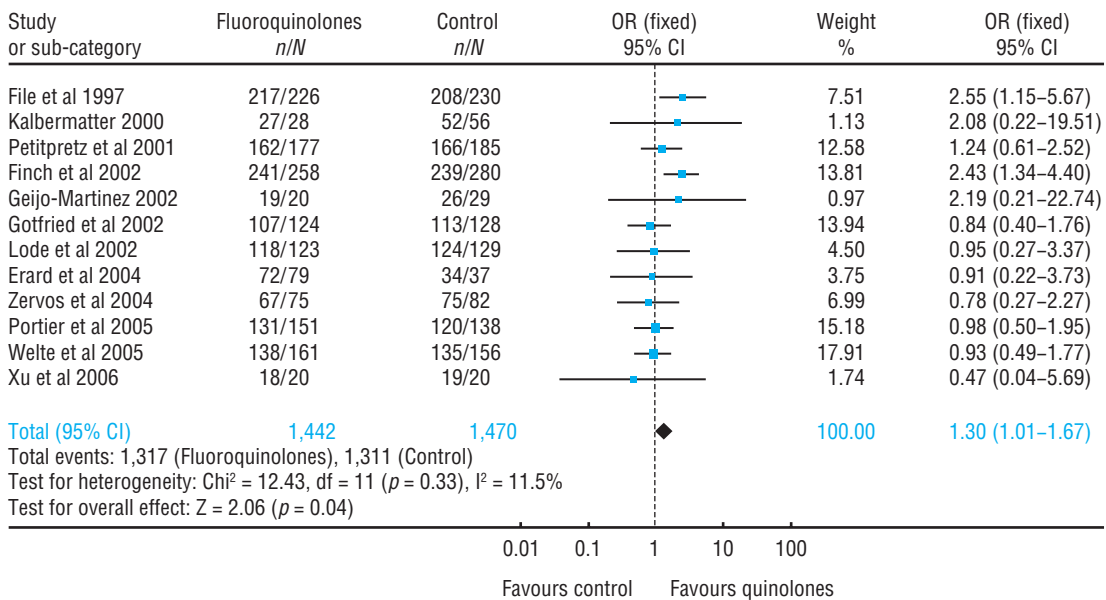
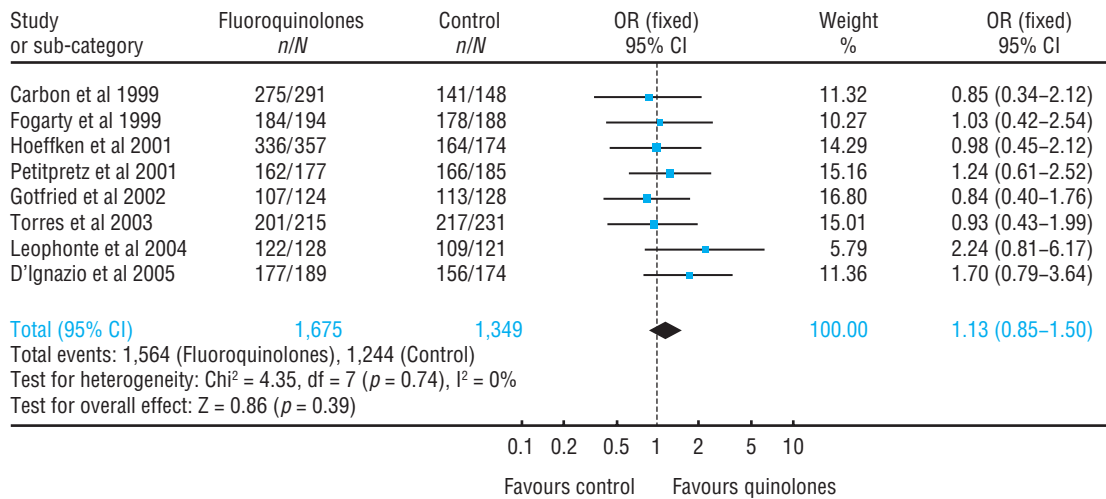
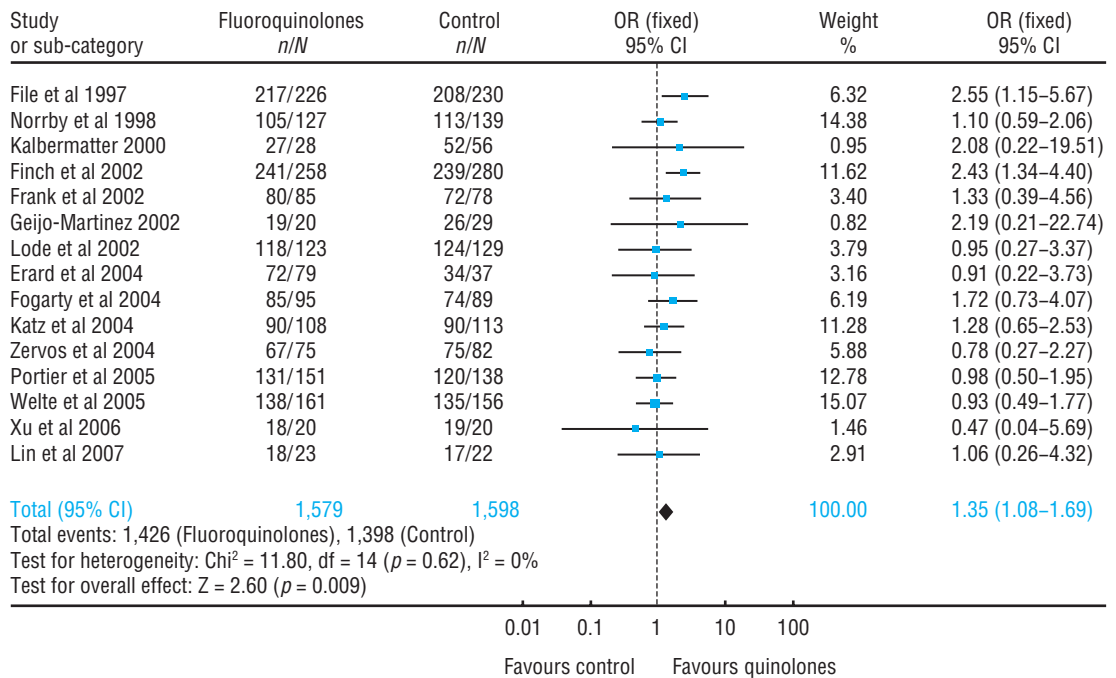


Figure 8C: Double blind trials

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 20 Double blind trials CE

**Figure 8D: Open label trials**

Review: Fluoroquinolones in CAP
 Comparison: 01 Clinical success
 Outcome: 21 Open label trials CE



Vertical line = "no difference" point between the two regimens. Square = odds ratio; Diamond = pooled odds ratio for all randomized controlled trials. Horizontal lines = 95% CI.

Abbreviations: CAP = community-acquired pneumonia, OR = odds ratio, CI = confidence interval, CE = clinically evaluable.

Figure 9. Odds ratios of adverse effects for the ITT patients

Figure 9A: All adverse effects

Review: Fluoroquinolones in CAP
 Comparison: 03 Adverse effects
 Outcome: 01 Total adverse effects

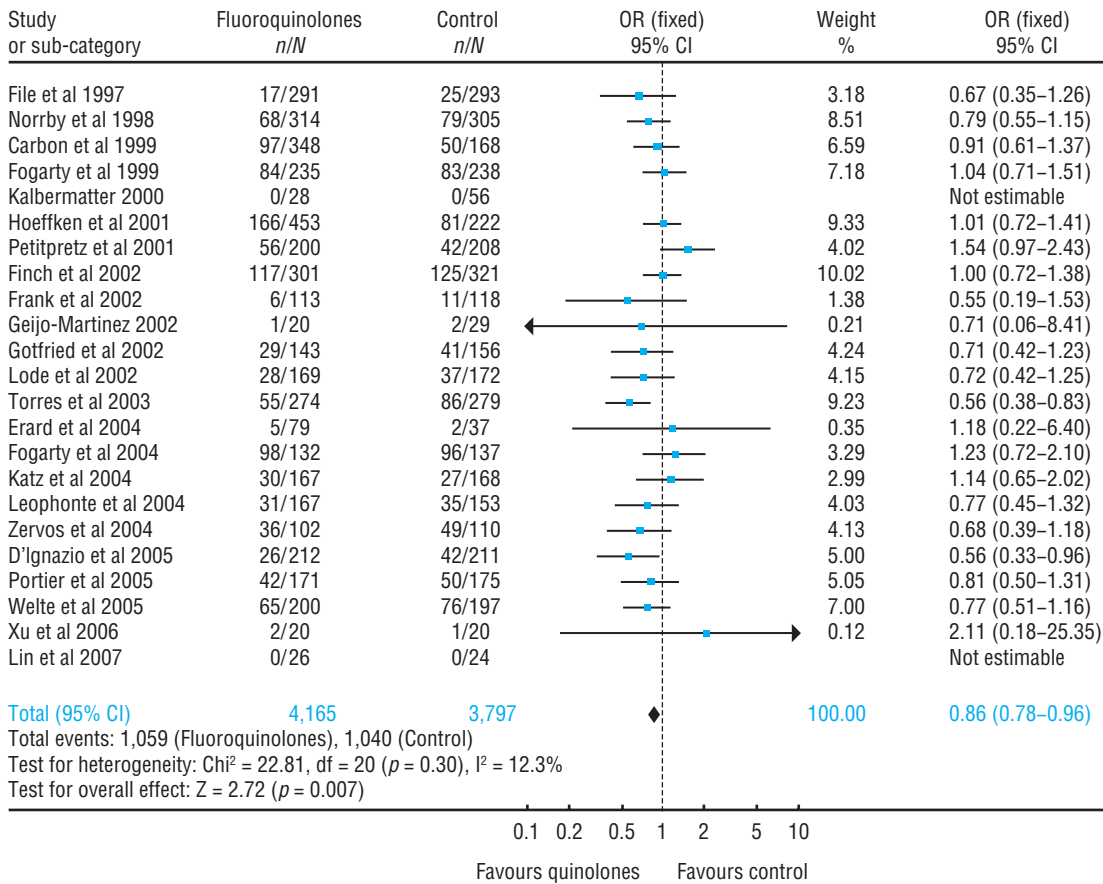
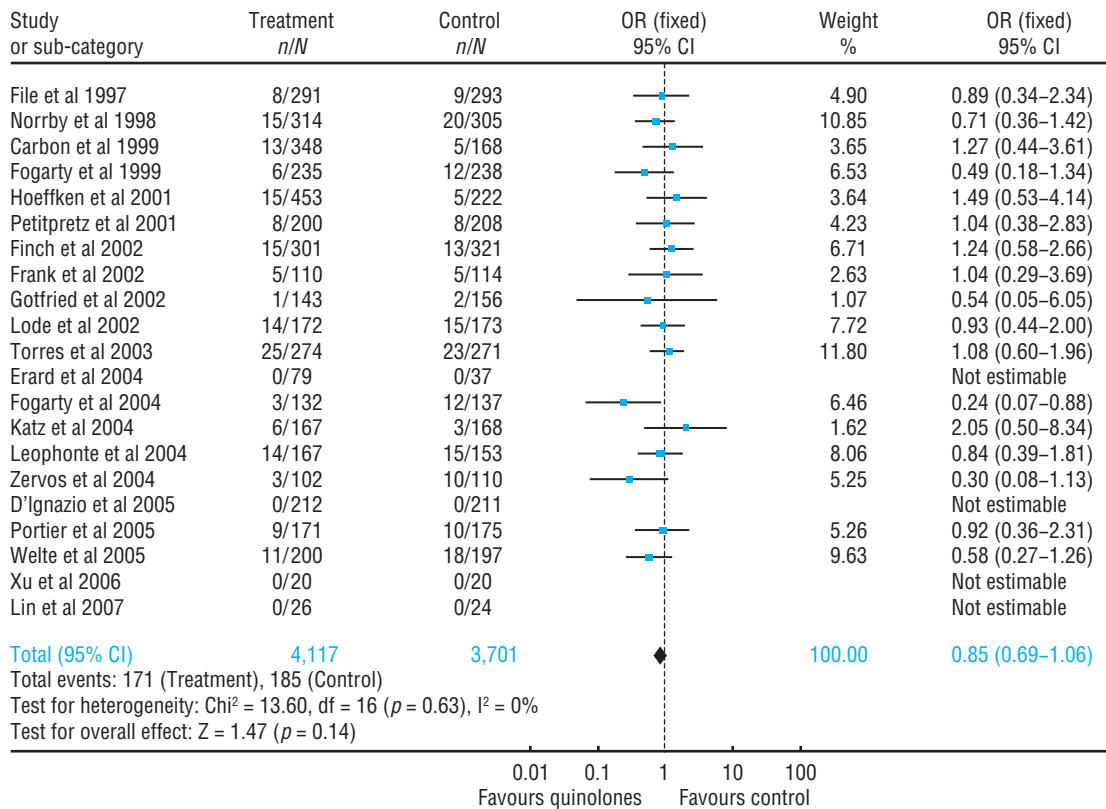
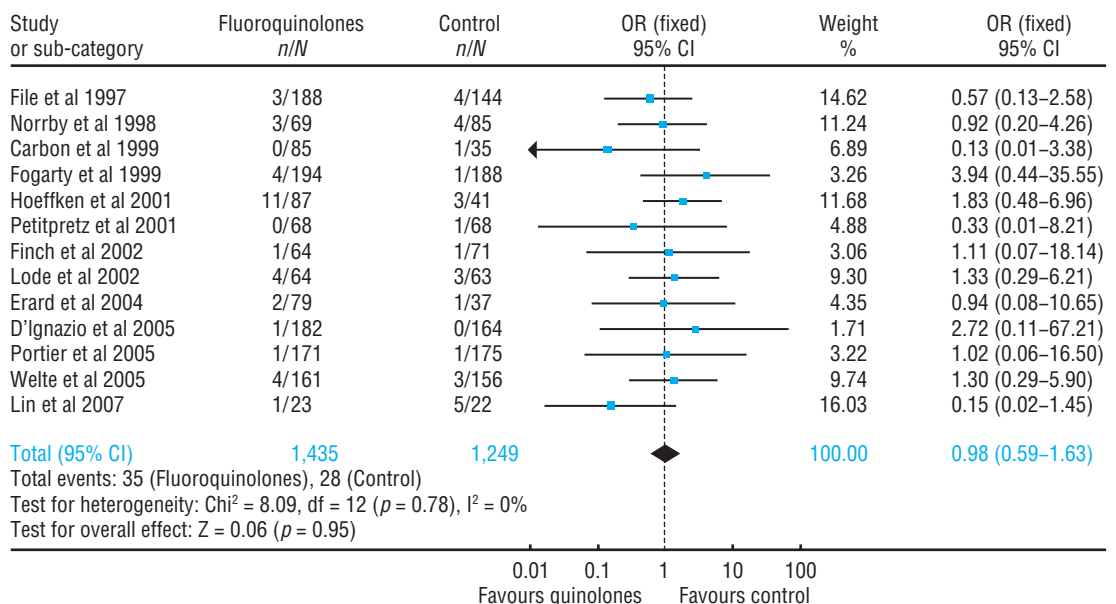


Figure 9B: Withdraw due to adverse effects

Review: Fluoroquinolones in CAP
 Comparison: 03 Adverse effects
 Outcome: 02 Withdraw due to adverse effects

**Figure 9C: Recurrent infections (CE patients)**

Review: Fluoroquinolones in CAP
 Comparison: 03 Adverse effects
 Outcome: 09 Recurrent infections



Vertical line = "no difference" point between the two regimens. Square = odds ratio; Diamond = pooled odds ratio for all randomized controlled trials. Horizontal lines = 95% CI.

Abbreviations: CAP = community-acquired pneumonia, ITT = intention-to-treat, OR = odds ratio, CI = confidence interval, CE = clinically evaluable.

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