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Fluoroquinolones are associated with delayed treatment and resistance in tuberculosis: a systematic review and meta-analysis

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SUMMARY

Background: Current guidelines for treating community-acquired pneumonia recommend the use of fluoroquinolones for high-risk patients. Previous studies have reported controversial results as to whether fluoroquinolones are associated with delayed diagnosis and treatment of pulmonary tuberculosis (TB) and the development of fluoroquinolone-resistant *Mycobacterium tuberculosis*. We performed a systematic review and meta-analysis to clarify these issues.

Methods: The following databases were searched through September 30, 2010: PubMed, EMBASE, CINAHL, Cochrane Library, Web of Science, BIOSIS Previews, and the ACP Journal Club. We considered studies that addressed the issues of delay in diagnosis and treatment of TB and the development of resistance.

Results: Nine eligible studies (four for delays and five for resistance issues) were included in the meta-analysis from the 770 articles originally identified in the database search. The mean duration of delayed diagnosis and treatment of pulmonary TB in the fluoroquinolone prescription group was 19.03 days, significantly longer than that in the non-fluoroquinolone group (95% confidence interval (CI) 10.87 to 27.18, $p < 0.001$). The pooled odds ratio of developing a fluoroquinolone-resistant *M. tuberculosis* strain was 2.70 (95% CI 1.30 to 5.60, $p = 0.008$). No significant heterogeneity was found among studies in the meta-analysis.

Conclusions: Empirical fluoroquinolone prescriptions for pneumonia are associated with longer delays in diagnosis and treatment of pulmonary TB and a higher risk of developing fluoroquinolone-resistant *M. tuberculosis*.

1. Introduction

The Infectious Diseases Society of America and the American Thoracic Society (IDSA/ATS) have recommended the use of respiratory fluoroquinolones for the treatment of adult community-acquired pneumonia in the presence of co-morbidities or risk factors for drug-resistant *Streptococcus pneumoniae*.[1] Empirical treatment of community-acquired pneumonia with fluoroquinolones raises great concerns about delayed diagnosis and treatment of pulmonary tuberculosis (TB) and the development of fluoroquinolone-resistant *Mycobacterium tuberculosis*.[2] Several case reports have demonstrated that the administration of fluoroquinolones may delay the diagnosis of pulmonary TB and lead to the emergence of fluoroquinolone-resistant *M. tuberculosis*;[3–8] in particular, Singh indicated that the use of fluoroquinolones in endemic areas would increase the potential for masking active TB and the emergence of an epidemic of widespread drug-resistant *M. tuberculosis*.[9] To determine whether fluoroquinolone prescriptions are associated with delayed diagnosis and treatment of pulmonary TB and the development of fluoroquinolone-resistant *M. tuberculosis*, we performed a systematic review and meta-analysis for these two issues.

2. Materials and methods

2.1. Search strategy and study selection

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to conduct this systematic review.[10] We used the Medical Subject Heading (MeSH) terms of 'fluoroquinolones/quinolones' (also including all fluoroquinolones approved by the US Food and Drug Administration, such as ciprofloxacin, ofloxacin, norfloxacin, levofloxacin, moxifloxacin, and gemifloxacin) and 'tuberculosis', combined with 'delay' or 'resistant/ce', to search the databases of

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PubMed, EMBASE, CINAHL, Cochrane Library, Web of Science, BIOSIS Previews, and ACP Journal Club through September 30, 2010. The articles were selected with no language restriction. We included prospective and retrospective cohort studies, case–control studies, and randomized control trials that addressed the two issues: (1) Whether fluoroquinolone prescriptions are associated with delayed diagnosis and treatment of pulmonary TB or (2) whether fluoroquinolone prescriptions are associated with the development of fluoroquinolone-resistant *M. tuberculosis*. The duration of delays and resistance rates for fluoroquinolones after the use of fluoroquinolones before the diagnosis of TB were criteria for inclusion in the meta-analysis. Case reports were excluded.

2.2. Data extraction

The data were abstracted by two independent reviewers (T.-C. Chen and C.-Y. Lin) using a standardized protocol and definitions. Disagreement on specific studies between the two reviewers was resolved through discussion. The reviewers abstracted the duration of delays and resistance rates for fluoroquinolones after using fluoroquinolones before a diagnosis of TB was made. The duration of delayed diagnosis and treatment for pulmonary TB was defined as the time interval from presenting to the hospital system (health care delays) or the initiation of antibiotics (antibiotic delays) to the initiation of anti-TB medications. Because the presentations of delays are different, one study used mean and standard deviations (SDs) and the others used median and range or interquartile range (IQR). In our analysis, we assumed the median to be equal to the mean, the IQR to be $1.35 \times$ SD, and the range to be $4 \times$ SD, according to the instructions in the statistical software used. A fluoroquinolone prescription-associated fluoroquinolone-resistant TB included any isolate from a patient who had any kind of fluoroquinolone prescribed within 12 months before the fluoroquinolone-resistant TB culture was obtained.

2.3. Statistical analysis

Data were combined using a random-effects model, which assumes that individual studies are estimating different treatment effects, rather than the fixed-effects model, which is based on the mathematical assumption that a single common effect underlies every study in the meta-analysis. Statistical heterogeneity was evaluated using the Cochran Q test (a Chi-square test for heterogeneity) and the I^2 statistic. 'I^2' denotes the percentage of total variation across the studies that is the result of heterogeneity rather than chance. We assessed for the presence of publication bias using a funnel plot. The meta-analysis was performed using Review Manager Version 5.0.24 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). A p-value of <0.05 was considered statistically significant.

3. Results

Initially, 770 abstracts were identified from the database search and then 33 relevant articles were selected for critical evaluation. Nine eligible studies (four for delays and five for resistance issues)[11–19] were included in the final meta-analysis (Figure 1 and Table 1).

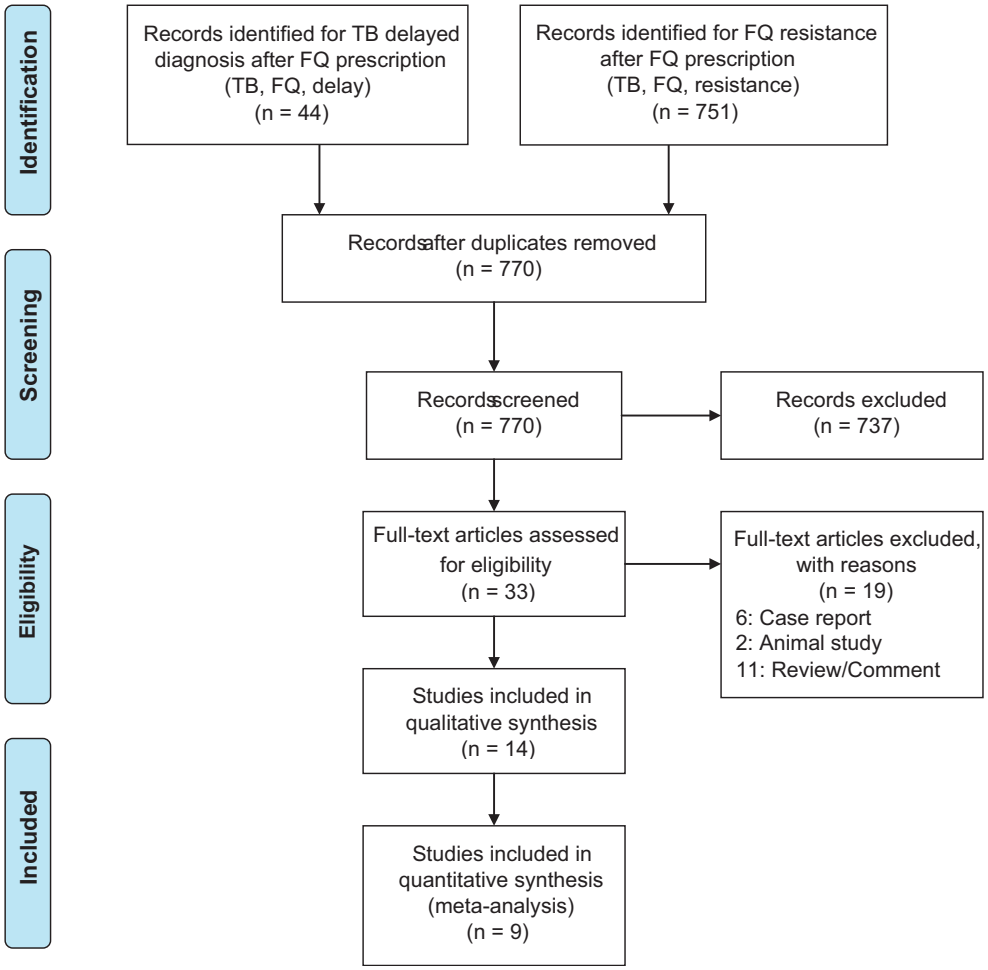

Figure 1. Selection of the studies included in the meta-analyses.

Table 1
Summary of the nine studies eligible for the meta-analysis

Author, publication year [Ref.]	Country	Years	Study design and population characteristics	Sample size	Median or mean FQ exposure/FQ prescriptions (No.)	Effects
Whether fluoroquinolone prescriptions are associated with delayed diagnosis and treatment of pulmonary TB						
Dooley, 2002 [11]	USA	1998– 2001	Retrospective, all newly diagnosed, culture-positive, age ≥18 years, pulmonary TB cases Excluded: no respiratory symptoms and no use of antibiotics	FQ: 16 Non-FQ: 17	NA/Levo (11), Gati (1), Trova (2), Cipro (1), Cipro→Trova (1)	Health care delays: FQ: 21 days (IQR 5–32) Non-FQ: 5 days (IQR 1–16)
Yoon, 2005 [14]	Korea	2000– 2004	Retrospective, all newly diagnosed, culture-positive, FQ or other antibiotic treatment >5 days, pulmonary TB cases Excluded: coexisting bacterial infection	FQ: 9 Non-FQ: 19	14.2 ± 8.3 days/Levo (7), Cipro (2)	Antibiotic delays: FQ: 43.1 ± 40.0 days Non-FQ: 18.7 ± 16.9 days
Golub, 2005 [13]	USA	2000– 2001	Prospective, all newly diagnosed, culture-positive, pulmonary TB cases	FQ: 45 Non-FQ: 40	NA/NA	Antibiotic delays: FQ: 29 days Non-FQ: 31 days
Wang, 2006 [15]	Taiwan	2002– 2003	Retrospective, all newly diagnosed, culture-positive, age ≥14 years, pulmonary and extrapulmonary TB cases	FQ: 79 Non-FQ: 218	9.5 ± 6.0 days/Cipro (42), Levo (21), Moxi (16)	Health care delays: FQ: 41 days (range 6–233 days) Non-FQ: 16 days (range 0–198 days)
Whether fluoroquinolone prescriptions are associated with development of fluoroquinolone-resistant *Mycobacterium tuberculosis*						
Ginsberg, 2003 [12]	USA	1998– 2002	Retrospective, all newly diagnosed, culture-positive, age ≥18 y, pulmonary TB (29), extrapulmonary TB (19), and both (7)	FQ: 19 Non-FQ: 36	4 days/NA	FQ: 1.5% FQ resistance Non-FQ: 0% FQ resistance
Wang, 2007 [16]	Taiwan	2004– 2005	Retrospective, pulmonary TB (380), extrapulmonary TB (23), and both (17)	FQ: 108 Non-FQ: 312	7 days/NA	FQ: 4.6% FQ resistance Non-FQ: 2.9% FQ resistance
Park, 2007 [17]	Korea	1997– 2005	Retrospective, culture-positive, pulmonary and extrapulmonary TB	FQ: 39 Non-FQ: 2749	7 days/Cipro (23), Levo (11), Moxi (3), Tosu (2)	FQ: 2.6% FQ resistance Non-FQ: 3.4% resistance
Devasia, 2009 [18]	USA	2002– 2006	Retrospective, all newly diagnosed, culture-positive, pulmonary TB (500), extrapulmonary TB (77), and both (63)	FQ: 116 (264 courses) Non-FQ: 524	FQ-resistant 30.5 days; FQ-susceptible 10 days/Levo (147), Cipro (78), Moxi (20)	FQ: 6.9% FQ resistance Non-FQ: 1.7% FQ resistance
Long, 2009 [19]	Canada	1996– 2003	Retrospective, all newly diagnosed, culture-positive, age ≥14 y, pulmonary TB cases	FQ: 74 Non-FQ: 74	Multiple FQ prescription: 16 days; single FQ prescription: 7 days/NA	FQ: 4.1% FQ resistance Non-FQ: 0% FQ resistance

TB, tuberculosis; FQ, fluoroquinolone; NA, data not available; IQR, interquartile range; Levo, levofloxacin; Cipro, ciprofloxacin; Moxi, moxifloxacin; Gati, gatifloxacin; Trova, trovafloxacin; Tosu, tosufloxacin; NA, data not available.

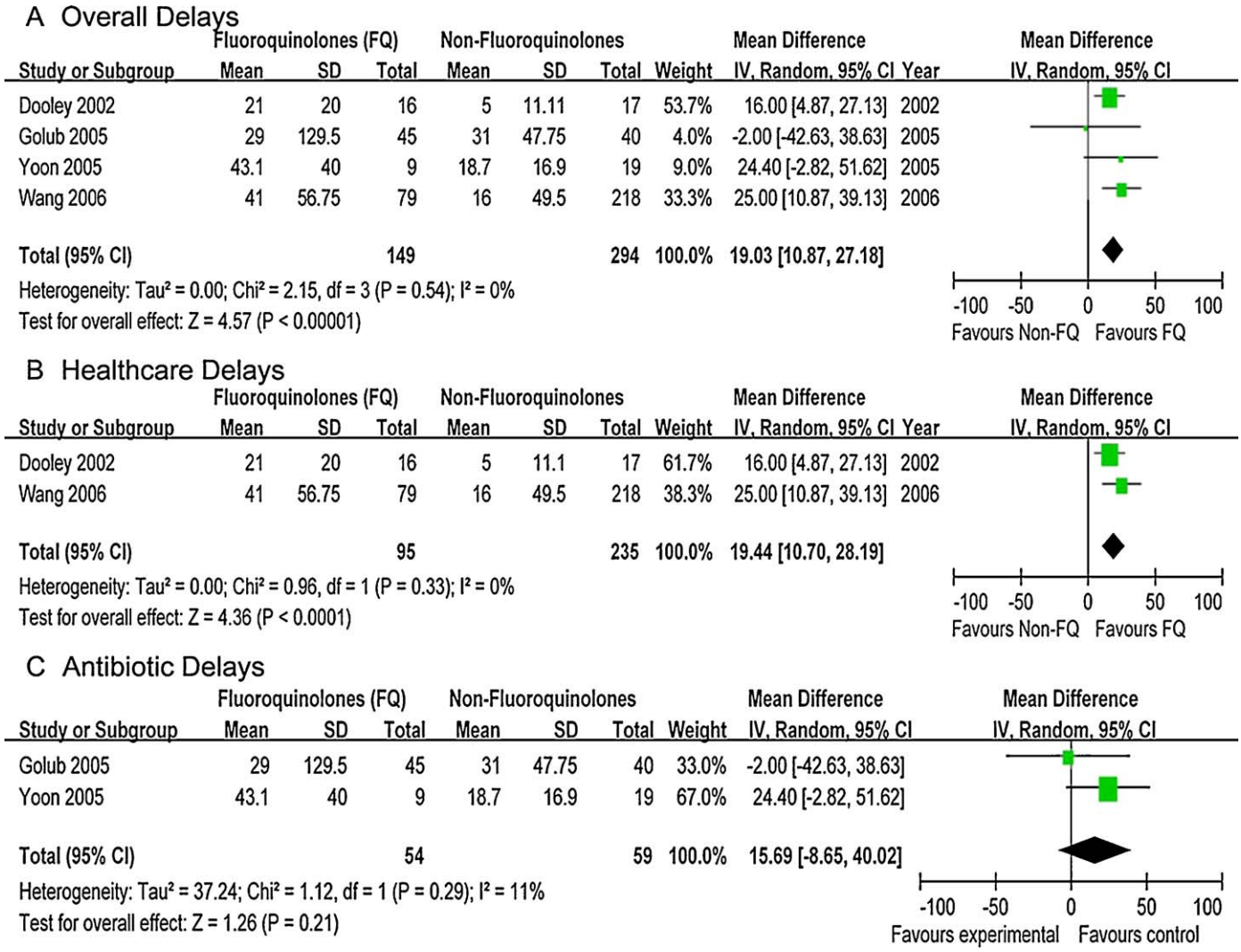

Figure 2. Forest plots of the studies showing the association between fluoroquinolone prescription and the duration of delayed diagnosis and treatment of pulmonary TB (A), and health care delays (B) and antibiotic delays (C) in the management of pulmonary TB.

Funnel plot analysis did not suggest significant publication bias for these meta-analyses. The mean duration of delayed diagnosis and treatment of pulmonary TB (pooled health care and antibiotic delays) in the fluoroquinolone prescription group was 19.03 days, significantly longer than in the non-fluoroquinolone group (95% confidence interval (CI) 10.87 to 27.18, $p < 0.001$). No statistically significant heterogeneity was found among the studies ($I^2 = 0\%$, $p = 0.54$; Figure 2A). The mean duration of health care delay in the fluoroquinolone group was 19.44 days, significantly longer than in the non-fluoroquinolone group (95% CI 10.70 to 28.19, $p < 0.001$; Figure 2B), but the mean difference of antibiotic delay was not significant (15.69 days, 95% CI −8.65 to 40.02, $p = 0.29$; Figure 2C). The pooled odds ratio of developing a fluoroquinolone-resistant TB strain was 2.70 (95% CI 1.30 to 5.60, $p = 0.008$). No statistically significant heterogeneity was found among these studies ($I^2 = 10\%$, $p = 0.35$; Figure 3).

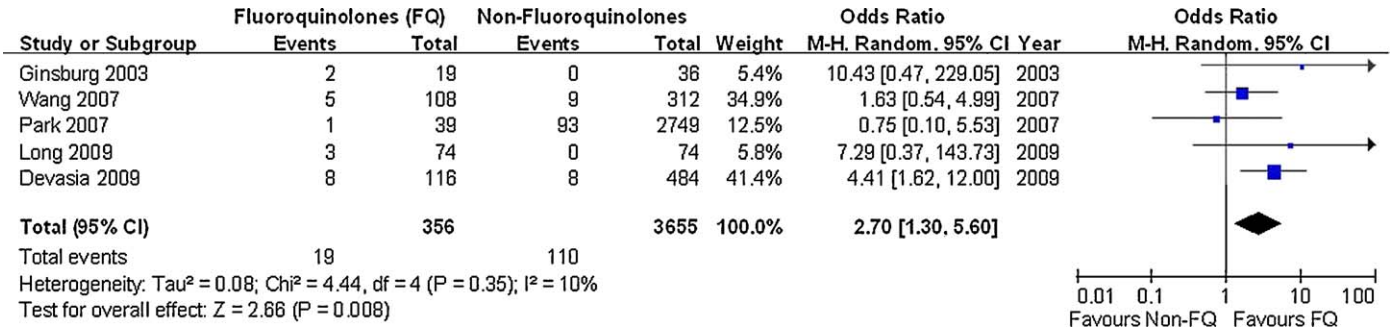

Figure 3. Forest plot of the five studies showing the association between fluoroquinolone prescription and the risk of developing fluoroquinolone-resistant *Mycobacterium tuberculosis*.

4. Discussion

Both the IDSA/ATS and the European guidelines[20] for the management of community-acquired pneumonia recommend respiratory fluoroquinolones as the drugs of choice or alternative choices for treating community-acquired pneumonia. However, the British[21] and Australian guidelines[22] for managing community-acquired pneumonia do not include the fluoroquinolones as first-line agents for treatment. The reasons for the differences in these guidelines are based on the rates of penicillin-resistant pneumococci, which are lower in Australia and the UK than in the USA, and concerns regarding fluoroquinolone resistance.[21,22]

Our meta-analysis showed a 19-day delay in the diagnosis and treatment of pulmonary TB with the prescription of fluoroquinolones, longer than that with the prescription of non-fluoroquinolone antibiotics, and a 2.7-fold higher risk of developing fluoroquinolone-resistant TB strains. Fluoroquinolones were found to be effective for *M. tuberculosis*, and respiratory symptoms and results seen on chest radiography usually improved under fluoroquinolone monotherapy.[11,13–15] However, such therapy will mask and delay the diagnosis of TB. Two studies also showed that inappropriate prescribing patterns for antibiotics in treating respiratory tract infections can delay the diagnosis of pulmonary TB and play a role in the development of drug-resistant *M. tuberculosis*.[23,24] Two animal studies demonstrated that fluoroquinolone monotherapy will cause the emergence of fluoroquinolone-resistant *M. tuberculosis*, which is not due to poor microbial kill but to rapid emergence of resistance.[25,26] Another interesting question is the relationship between the duration of fluoroquinolone use and the development of resistance to the fluoroquinolone. Previous reports showed short-term exposure to fluoroquinolones not to be associated with the development of fluoroquinolone resistance. In recent studies, however, multiple fluoroquinolone prescriptions[19] and the use of a fluoroquinolone for >10 days[18] have been linked to fluoroquinolone-resistant tuberculosis. In addition, Chang et al.[27] also indicated that the duration of exposure to moxifloxacin had a dose–response relationship to masking TB in a TB endemic area. Levofloxacin and ciprofloxacin were the most prescribed fluoroquinolones, but this meta-analysis could not address the effects of the different fluoroquinolones on delays or resistance. Older fluoroquinolones, such as ciprofloxacin, had higher minimal inhibitory concentrations against *M. tuberculosis* and were ineffective in treating TB, with higher failure rates clinically.[28] Ciprofloxacin was not recommended for treating TB and may create a higher risk of developing resistance.

Factors associated with TB diagnostic delays included infection with HIV, coexistence of chronic cough or other lung diseases, negative sputum smear, extrapulmonary TB, rural residence, low access to health care/facilities, older age, female sex, alcoholism or substance abuse, stigma of being a person with TB infection, and low psychosocial status.[29] In this meta-analysis, being elderly,[15,19] having extrapulmonary TB,[12,18] and carrying an HIV infection[11] were associated with delayed diagnosis or fluoroquinolone resistance. Another report from our hospital also showed exposure to fluoroquinolones in addition to negative sputum smear, non-cavitary lung lesions, admission to non-chest medicine/infectious diseases wards, and age >65 years as independent risk factors for in-hospital delay of diagnosis of pulmonary TB.[30]

However, this analysis has some limitations. First, the issue of most concern was the use of fluoroquinolones in patients with community-acquired pneumonia. However, the enrolled populations in the meta-analysis varied. Four studies included patients with extrapulmonary TB in addition to pulmonary TB[15–17] and only one study was prospective.[13] The prescriptions of fluoroquinolones were not only for respiratory tract infections, but also for urinary tract infections, wound infections, etc. A recent retrospective study of extrapulmonary TB demonstrated that fluoroquinolone monotherapy of unsuspected renal TB may delay diagnosis and lead to fluoroquinolone resistance.[31] Therefore, delayed diagnosis and fluoroquinolone resistance should also be considered and lead to caution in the use of fluoroquinolone treatment for urinary tract infections. Second, the definitions of delay differed. Two studies assessed health care delays[11,15] rather than antibiotic delays. In our study, the pooled health care and antibiotic delay and health care delay only were of longer duration in the fluoroquinolone prescription group than in the non-fluoroquinolone prescription group, but not for antibiotic delay only. Thus, further prospective studies with larger populations are necessary to validate the results.

In conclusion, this meta-analysis suggests that empirical prescriptions of fluoroquinolones for pneumonia are associated with longer delays in the diagnosis and treatment of pulmonary TB and a higher risk of developing fluoroquinolone-resistant TB. In patients with pneumonia, the possibility of pulmonary TB should be considered before a fluoroquinolone is prescribed to avoid the consequences of delayed management of TB and the development of fluoroquinolone-resistant TB.

Conflict of interest: No conflict of interest to declare.

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