In doing so, findings from this study contribute important information for clinical and public health action to improve TB control in the UK and in other low incidence countries with a comparable TB epidemiology moving towards the elimination phase [5, 6]. As the epidemic in many low incidence countries changes from one affecting particular risk groups, misdiagnosis will become an increasingly important issue. Further progress towards the ambitious goals of the End TB Strategy and the elimination of TB [7] will also require more effective TB prevention among vulnerable and TB high-risk groups [8], and addressing the social and structural determinants of TB [9].

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The changing epidemiology of TB in low incidence settings has implications for TB diagnosis and therefore elimination http://ow.ly/KN6Vq

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Fluoroquinolone use delays tuberculosis treatment despite immediate mycobacteriology study

To the Editor:

Despite its excellent activity against *Mycobacterium tuberculosis* [1], empirical fluoroquinolone (FQ) therapy has been associated with delayed initiation of appropriate treatment [2–4] and acquired resistance [5, 6] in tuberculosis (TB) patients presenting as community-acquired pneumonia (CAP). A previous study conducted in intensive care unit revealed immediate mycobacteriology study may possibly prevent the delay in anti-TB treatment [7]. However, this hypothesis has not been confirmed.

With a longitudinal follow-up of >99% of the residents of Taiwan (>22 million subjects) since 1996 [8], the National Health Insurance Research Database (NHIRD) provided very suitable research material for this study to investigate factors associated with delayed anti-TB treatment in patients with pulmonary TB initially presenting as pneumonia. The impact of empirical use of FQ and prescription of mycobacteriology studies on the first consultation for pneumonia was particularly emphasised.

From the NHIRD, a total of 81 081 adult patients (age ⩾20 years) with pulmonary TB in the period 2004–2009 were identified. Among them, 16 683 (20.6%) had pneumonia within 6 months prior to anti-TB treatment [9] and were followed-up until December 31, 2010 or until lost to follow-up (cancelled health insurance prior to December 31, 2010). A pneumonia episode was considered if all of the following three elements were present: 1) compatible diagnosis (International Classification of Diseases, ninth revision, clinical modification: code 480–486 or 507); 2) prescription of antibiotics; and 3) chest radiography performed.

The 16 683 pulmonary TB patients had a mean±SD age of 67.4±18.1 years (range 20.0–105.5 years). Among them, 69.7% were male and 72.9% lived in an urban area (population density >1500 persons per km^2). Mycobacterial culture and *M. tuberculosis* nucleic acid amplification test (MTB-NAA) became more frequently prescribed on the first consultation for pneumonia, from 48.3% and 0.2%, respectively, in 2004, to 56.8% and 4.9%, respectively, in 2009. Delays in anti-TB treatment from the first consultation for pneumonia gradually shortened, from 53.3 days in 2004 to 48.5 days in 2009.

Of the 16 683 patients, 2051 (12.3%) received a prescription of FQ for ⩾7 days on the first consultation for pneumonia (FQ group) while the rest formed the non-FQ group. The prescribed FQ was levofloxacin in 908 (44.3%) patients, moxifloxacin in 716 (34.9%), ciprofloxacin in 402 (19.6%) and ofloxacin in 25 (1.2%). The clinical characteristics, including age, sex, severity of pneumonia (requiring emergency room visit or hospitalisation, intensive care, and mechanical ventilation), presence of comorbidity (as previously defined [10]), and income status, of the FQ and non-FQ groups were similar. However, in the FQ group, the first consultation for pneumonia was less likely to be at a local hospital (including local clinics and community hospitals) (34.5% *versus* 45.3%, p<0.001), more likely to be in an urban area (75.8% *versus* 72.5%, p=0.002), and had a higher frequency of mycobacterial culture (67.6% *versus* 50.3%, p<0.001) and MTB-NAA (4.0% *versus* 3.0%, p=0.008) prescribed on the first consultation. Delays in anti-TB treatment was significantly longer in the FQ group (63.0±47.1 *versus*. 49.4±47.6 days, p<0.001).

In multivariate linear regression analysis (table 1), prescribing FQ for ⩾7 days on the first consultation for pneumonia was associated with a delay of 16.50 days (95% CI 14.39–18.61 days) in anti-TB treatment. Age, underlying comorbidities, low income, first consultation for pneumonia in an urban area and pneumonia requiring an emergency department visit or hospitalisation were also associated with delayed treatment. Immediate mycobacteriology study, including mycobacterial culture (−15.78 days, 95% CI −17.20–−14.35 days) and/or MTB-NAA (−13.78 days, 95% CI −17.81–−9.74 days) on the first consultation for pneumonia and later TB diagnosis year (−0.65 days, 95% CI −1.06–−0.23 days; per year increment) were associated with shorter delay.

TABLE 1 Independent factors on the delay in anti-tuberculosis (TB) treatment for patients initially diagnosed as having pneumonia (n=16 683), by linear regression analysis

	p-value	β (95% CI)
Age ⩾65 years	<0.001	11.30 (9.79–12.81)
Diabetes mellitus	0.024	1.71 (0.22–3.20)
Chronic obstructive pulmonary disease	<0.001	12.17 (10.12–14.23)
End-stage renal disease	<0.001	18.77 (14.53–23.01)
Malignancy	<0.001	8.39 (6.17–10.62)
Low income	<0.001	12.71 (9.31–16.11)
First visit for pneumonia in urban area	<0.001	2.82 (1.26–4.38)
Prescribed mycobacterial culture at first visit for pneumonia	<0.001	−15.78 (−17.20–−14.35)
Prescribed MTB-NAA at first visit for pneumonia	<0.001	−13.78 (−17.81–−9.74)
Prescribe FQ for ⩾7 days at first visit for pneumonia	<0.001	16.50 (14.39–18.61)
Pneumonia requiring ED visit or hospitalisation	<0.001	15.06 (13.45–16.67)
Later TB diagnosis year per year increment	0.002	−0.65 (−1.06–−0.23)

MTB-NAA: *Mycobacterium tuberculosis* nucleic acid amplification test; FQ: fluoroquinolone; ED: emergency department.

Sensitivity analyses revealed that prescription of FQ for ⩾7 days on the first consultation for pneumonia was associated with delayed anti-TB treatment among six subpopulations: 1) the 8780 cases with immediate mycobacteriology study (14.70 days, 95% CI 12.43–16.96 days); 2) the 7903 cases without immediate mycobacteriology study (19.54 days, 95% CI 15.47–23.61 days); 3) the 2730 outpatient cases (requiring neither an emergency department visit nor hospitalisation) without underlying comorbidity (7.69 days, 95% CI 3.14–12.23 days); 4) the 1227 outpatient cases without underlying comorbidity and with immediate mycobacteriology study (7.58 days, 95% CI 2.75–12.40 days); 5) the 6590 cases who had bacterial culture performed and had no bacterial pathogen isolated during pneumonia event (11.52 days, 95% CI 8.41–14.62 days); and 6) the 4092 cases with a duration of pneumonia >21 days (25.48 days, 95% CI 21.54–29.41 days). In sensitivity analysis (5), prescription of susceptibility test was used as a surrogate for the presence of a bacterial pathogen, as bacterial isolates that could possibly be responsible for pneumonia are routinely tested for susceptibility in clinical practice in Taiwan.

Using the NHIRD, a powerful tool to investigate the influence and interactions between diseases and treatments, we found that despite the fact that immediate mycobacteriology study, including mycobacterial culture and MTB-NAA, might significantly reduce delays in anti-TB treatment [7, 11], empirical FQ use still delays treatment in patients with immediate mycobacteriology study.

In patients presenting with pneumonia requiring hospitalisation, FQs have been recommended as first-line empirical antibiotic therapy due to their broad-spectrum microbial coverage and their proven effect of reducing the length of hospital stay, thus being more cost-effective compared to the combination therapy of β-lactams plus macrolides [12]. The major concern of empirical FQ use for pneumonia is the masking of TB, resulting in delayed diagnosis and treatment [2–4], and further dissemination of the disease. Thus, the best management for pneumonia patients may be the use of FQs under the premise that TB is still being considered and all possible intentions have been made for timely diagnosis.

The results of the present study support the hypothesis that immediate mycobacteriology study reduces the impact of TB masking due to empirical FQ use. However, the benefit is marginal, with only a 1.8-day reduction. Because only 38.4% of TB patients in Taiwan are smear-positive cases [13], for the majority of TB patients, the smear-negative cases, a clinical response after FQ use still significantly delays the initiation of anti-TB treatment until the results of mycobacterial culture become available. Furthermore, the time interval from inoculation of the respiratory specimen for mycobacterial culture to notification of a positive culture may be lengthened after FQ use because its anti-mycobacterial effect may compromise the culture efficiency.

As shown in the analysis, immediate mycobacterial culture and MTB-NAA are the only two factors that can possibly shorten the delay in anti-TB treatment by ∼2 weeks. Further studies are warranted to confirm these findings and to optimise the use of mycobacterial culture and MTB-NAA for the early detection of TB in patients initially presenting as pneumonia. This is especially true in TB-endemic areas, where *M. tuberculosis* maybe the causal microorganism of ⩾10% of pneumonia cases [14].

This study has some limitations. First, results of laboratory and radiological studies are unavailable in the NHIRD. As such, the diagnosis of TB and pneumonia may not be 100% accurate. Second, patients may receive other antibiotics during follow-up consultations, resulting in misclassification and biasing the result toward the null hypothesis, causing underestimation of the impact of FQ use [15]. Third, the protective effect of immediate mycobacteriology study may be confounded by the indication, resulting in an overestimation of its benefits.

In conclusion, empirical FQ use for ⩾7 days delays anti-TB treatment despite immediate mycobacteriology study.

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Empirical fluoroquinolone use for ⩾7 days delays antituberculosis treatment despite immediate mycobacteriology study http://ow.ly/L8fIm

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Antipyretic effect of dexamethasone in community-acquired pneumonia

To the Editor:

The cornerstones of treatment for community-acquired pneumonia (CAP) are early diagnosis and initiation of appropriate antibiotic therapy [1]. Despite prevention with vaccination, and optimal antibiotic treatment, CAP is associated with high mortality and morbidity and significant healthcare costs [2, 3]. Adjunctive therapy for CAP could help to reduce disease severity and, indeed, the addition of dexamethasone to antibiotic treatment in patients hospitalised with CAP has shown to reduce the length of hospital stay by 1 day [4]. Recent trials showed similar results [5, 6]. One of the comments raised to our previous study was that the antipyretic effect of dexamethasone might be the major underlying explanation for this result [7]. In patients, hospitalised with CAP, body temperature measurement is part of the standard care. Stable defervescence is one of the criteria used to define clinical stability [8]. Other clinical markers used in the decision to discharge a patient are respiratory and haemodynamic stability, the ability to maintain oral intake and a normal mental status [9–11]. Besides white cell count, C-reactive protein can be a useful marker of treatment response [10, 11].

In a *post hoc* analysis, we assessed the effect of dexamethasone on body temperature in our previously conducted trial [4] and studied whether its antipyretic properties may have influenced the length of stay in hospital.