Increasing Outpatient Fluoroquinolone Exposure Before Tuberculosis Diagnosis and Impact on Culture-Negative Disease

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Background: Fluoroquinolones are widely used to treat routine bacterial infections, but they are also potential first-line antituberculosis agents. Empirical fluoroquinolone therapy can delay the diagnosis of tuberculosis and cause resistance in Mycobacterium tuberculosis. Rates of fluoroquinolone exposure before tuberculosis diagnosis and the impact of fluoroquinolones on culture-negative tuberculosis have not been previously reported.

Methods: All newly diagnosed tuberculosis cases reported to the Tennessee Department of Health between January 1, 2000, and December 31, 2004, were cross-matched with the TennCare (Medicaid) pharmacy database to assess for outpatient fluoroquinolone use in the 12 months before tuberculosis diagnosis.

Results: Of 1562 tuberculosis cases reported, 1055 occurred in TennCare participants; of these 1055 TennCare patients, 507 were enrolled in TennCare more than 300 days during the year before tuberculosis diagnosis. Of the 507 patients, 119 (23%) received a fluoroquinolone before tuberculosis diagnosis. The proportion of fluoroquinolone-exposed patients increased from 9% in 2000 to 41% in 2004 ($\chi^2$ test for trend $P < .001$). In multivariate logistic regression analysis, factors associated with fluoroquinolone exposure were older age (odds ratio [OR], 1.03 per year; 95% confidence interval [CI], 1.02-1.04) and year of diagnosis (OR, 1.64 per 1-year increase; 95% CI, 1.39-1.93); human immunodeficiency virus infection tended to be associated with increased exposure (OR, 1.94; 95% CI, 0.97-3.90). After controlling for age, sex, race, site of disease, human immunodeficiency virus, and year of diagnosis, prior fluoroquinolone exposure was not associated with culture-negative tuberculosis (OR, 0.81; 95% CI, 0.41-1.60).

Conclusions: Fluoroquinolone use before tuberculosis diagnosis increased significantly during the study period. However, fluoroquinolone exposure was not associated with an increased risk of culture-negative tuberculosis.

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quinoquinolone use over time, and assess the impact of fluoroquinolone exposure on rates of culture-negative tuberculosis.

**METHODS**

**STUDY POPULATION**

Persons in whom tuberculosis was reported to the Tennessee Department of Health between January 1, 2000, and December 31, 2004, and who had ever participated in TennCare were potential study participants. TennCare is a managed health care program that insures state residents who are eligible for federal Medicaid benefits and other selected low-income groups. Administrative data from TennCare are contained in several computerized databases, including an enrollment database that serves as the central registry and a pharmacy file that consists of all outpatient, nursing home, and emergency department prescription records. The Tennessee tuberculosis case registry was cross-matched with the TennCare enrollment database; matching criteria included name, date of birth, Social Security number, and address. Data on fluoroquinolone prescriptions filled in the 12 months before tuberculosis diagnosis were obtained from the TennCare pharmacy database. Because persons enrolled in TennCare for at least 300 days during the year before tuberculosis diagnosis had optimal characterization of fluoroquinolone use and nonuse, they composed the primary analysis group. For all analyses, if a patient had more than 1 episode of tuberculosis, only the first episode was included. The study was approved by the institutional review boards of Vanderbilt University and the Tennessee Department of Health.

**DEFINITIONS**

The date of tuberculosis diagnosis was defined as the date of antituberculosis therapy initiation. Culture-confirmed tuberculosis was defined as a case in which *M tuberculosis* was isolated from a clinical specimen. Culture-negative tuberculosis was defined as no cultures positive for *M tuberculosis* but (1) demonstration of *M tuberculosis* from a clinical specimen by nucleic acid amplification (eg, polymerase chain reaction [PCR]), (2) demonstration of acid-fast bacilli (AFB) in a clinical specimen, (3) meeting the clinical case definition, or (4) meeting criteria for physician-verified tuberculosis. The clinical case definition required all of the following: a positive tuberculin skin test result, signs and symptoms consistent with tuberculosis (eg, productive cough, night sweats, weight loss, and abnormal or unstable chest radiograph compatible with tuberculosis), treatment with 2 or more antituberculosis medications, and a diagnostic evaluation to rule out other diagnoses. The adequacy of the diagnostic evaluation to exclude other diagnoses was determined by the patient’s primary care physician and physicians at the Tennessee Department of Health. Physician-verified tuberculosis cases occurred when patients did not have laboratory-confirmed tuberculosis and did not fit the clinical case definition, but physicians at the Tennessee Department of Health thought there was sufficient evidence to consider them cases. All patients with culture-negative tuberculosis had to have demonstrated a clinical response to antituberculosis therapy.

Patients were considered to have pulmonary tuberculosis if specimens of sputum, bronchoalveolar lavage fluid, or pulmonary parenchyma were positive for *M tuberculosis* or if there was radiographic evidence of pulmonary disease. Extrapulmonary tuberculosis sites were defined as all sites outside the pulmonary parenchyma, including the pleura and pleural fluid.

Data extracted regarding fluoroquinolone use included type(s) of fluoroquinolone received, timing in relation to tuberculosis diagnosis, duration of therapy, and medical indication. The TennCare pharmacy database contained the name of the drug, date dispensed, dose, and days of supply. Each prescription for a fluoroquinolone was considered a course of therapy. The TennCare pharmacy database contained data only related to outpatient fluoroquinolone exposure, so it did not include exposure during hospitalizations.

**LABORATORY TECHNIQUES**

The AFB specimens were concentrated and stained with fluorescein isothiocyanate-acid-fast stain and were cultured for isolation and identification. Mycobacterial species were differentiated by high-performance liquid chromatography, DNA probe, and/or biochemical analysis. Initial mycobacterial cultures were inoculated on clinical media. Human immunodeficiency virus (HIV) infection was diagnosed by the patient’s local health department or primary care physician.

**STATISTICAL ANALYSIS**

Continuous variables were compared with the Wilcoxon rank sum test. Categorical variables were compared with the chi-square and Fisher exact tests. The chi-square test for trend assessed the proportion of patients with fluoroquinolone exposure and culture-negative tuberculosis over time. Case-control analyses were performed to assess for factors associated with fluoroquinolone exposure (cases indicate fluoroquinolone exposed; controls indicate fluoroquinolone unexposed) and culture-negative tuberculosis (cases indicate culture-negative disease; controls indicate culture-positive disease). Univariate logistic regression analyses determined predictors of fluoroquinolone exposure and culture-negative tuberculosis. All variables in the univariate analyses were considered clinically important and were therefore included in the multivariate logistic regression model. Fluoroquinolone exposure was measured as a categorical (ie, any vs no exposure), continuous (ie, number of days of exposure and number of courses of therapy), and dichotomous (ie, ≤10 vs >10 days of exposure) variable. The statistical package Stata, version 9 (StataCorp, College Station, Texas), was used for all analysis. All *P* values were 2 sided.

**RESULTS**

A total of 1562 patients with tuberculosis were reported to the Tennessee Department of Health during the study period. Of these, 1055 cross-matched with the TennCare database; of the 1055 patients, 507 were enrolled in TennCare for more than 300 days during the year before tuberculosis diagnosis. The clinical and demographic characteristics of all patients with tuberculosis are given in Table 1. Of the 1055 patients, 635 were HIV seronegative, 135 were HIV seropositive, and 285 had an unknown HIV status. For subsequent analyses, HIV-seronegative persons and those with an unknown HIV status were combined into 1 group.

During the study period, 136 TennCare enrollees received at least 1 course of fluoroquinolones before tuberculosis diagnosis. Forty-eight patients received more than 1 course, 27 received more than 2 courses, and 3 received 11 courses in the 12 months before diagnosis. The total number of prescriptions among the 136 pa-
patients was 263. The type and number of prescriptions according to fluoroquinolone were levofloxacin (137; 52% of total), ciprofloxacin (88; 33%), gatifloxacin (23; 9%), moxifloxacin (12; 5%), ofloxacin (2; 1%), and norfloxacin (1; 0.4%). Among the 507 persons in TennCare more than 300 days during the year before tuberculosis diagnosis, 119 (23%) received a fluoroquinolone. The proportion of patients with fluoroquinolone exposure before tuberculosis diagnosis increased more than 4-fold between 2000 and 2004 (P <.001; Table 2).

Of the 136 persons who received a fluoroquinolone, the medical indication for the prescription was respiratory (78; 57%), genitourinary (23; 17%), sinusitis or otitis media (1; 1%), osteomyelitis (1; 1%), and other (33; 24%). The median duration of fluoroquinolone exposure before tuberculosis diagnosis among the 136 exposed patients was 10 days (interquartile range [IQR], 7-19 days). The median duration of therapy was longer in patients who were not black (13 days; IQR, 7-25 days) than in black patients (10 days; IQR, 7-14 days) (P = .008), but duration did not differ by age, sex, HIV status, or tuberculosis culture status. The median period between receipt of fluoroquinolone and tuberculosis diagnosis was 80 days (IQR, 27-250 days).

Predictors of fluoroquinolone exposure are given in Table 3. In the univariate logistic regression analysis, older age and year of diagnosis were significantly associated with fluoroquinolone exposure; black race was associated with a decreased risk of fluoroquinolone exposure. In the multivariate logistic regression analysis, predictors of fluoroquinolone exposure were older age (P <.001), year of diagnosis (P <.001), and HIV infection (P = .06). The results did not differ when persons with an unknown HIV status were excluded from the analysis.

Of the 1055 TennCare enrollees, 220 (21%) had culture-negative tuberculosis. Of the 220 patients, AFB cultures were obtained in 176, of whom 137 met the clinical case definition (11 of whom also tested PCR positive for M tuberculosis or had a positive AFB smear) and 39 patients had physician-verified tuberculosis (13 of whom tested PCR positive for M tuberculosis or had a positive AFB smear). Of the 44 patients in whom cultures were not obtained, 3 had their conditions diagnosed based on a positive PCR or AFB smear result, 30 met the clinical case definition, and 11 had physician-verified tuberculosis.

Among persons enrolled in TennCare more than 300 days during the year before diagnosis, the proportion of patients with culture-negative disease increased from 15% in 2000 to 21% in 2004, but this trend was not statistically significant (P = .14; Table 4). Results were similar when 31 patients in whom cultures were not obtained were excluded (data not shown).

Predictors of culture-negative tuberculosis are given in Table 5. In the univariate logistic regression analysis, extrapulmonary tuberculosis was associated with an increased risk of culture-negative tuberculosis. Older age, HIV infection, and prior fluoroquinolone exposure were associated with a decreased risk of culture-negative disease. In the multivariate logistic regression analysis, extrapulmonary disease was associated with an increased risk of culture-negative disease (P = .008), but year of diagnosis was of only borderline statistical significance (P = .06).

Older age, black race, and HIV infection were associated with a decreased risk. Fluoroquinolone exposure was not associated with an increased risk of culture-negative disease; this also held true when persons with an unknown HIV status and the 31 patients in whom cultures were not obtained were excluded (data not shown).

The multivariate model in Table 5 used a categorical (yes/no) variable for fluoroquinolone exposure, but the results did not differ when fluoroquinolone exposure was treated as a continuous or dichotomous variable (data not shown). There was also no association between timing of fluoroquinolone exposure before tuberculosis diagnosis (treated as a continuous variable or <30 vs ≥30 days or <60 vs ≥60 days before diagnosis; data not shown) and culture-negative disease. The multivariate logistic regression analysis was then performed only for persons with pulmonary tuberculosis (Table 6). The results are similar to those of Table 5; fluoroquinolone exposure was associated with a decreased risk of culture-negative disease, although the trend did not reach statistical significance (P = .08).
Fluoroquinolone exposure was assessed in the 12 months before tuberculosis diagnosis among patients enrolled in TennCare for more than 300 days during the year before diagnosis. Reference groups were female sex, race other than black, no pulmonary disease, and HIV seronegative.

Trends over time were assessed among persons enrolled in TennCare for more than 300 days during the year before diagnosis. Reference groups were female sex, race other than black, no pulmonary disease, and HIV seronegative.

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prescribed and found that fluoroquinolone prescribing had increased in all age groups, but rates were highest in elderly patients. It is possible that HIV-infected persons may be more likely to receive antibiotics than HIV-uninfected persons owing to either their increased risk of infection or a lower threshold for prescribing antibiotics by physicians, but we are unaware of studies that have documented this.

Fluoroquinolone exposure before tuberculosis diagnosis was not associated with the diagnosis of culture-negative tuberculosis after controlling for age, sex, race, site of disease, HIV infection, and year of diagnosis. This relationship held whether fluoroquinolone exposure was measured as a categorical, continuous, or dichotomous variable.

Of note, in the multivariate analysis extrapulmonary disease was significantly associated with an increased risk of culture-negative disease. This is not surprising since most cases of extrapulmonary tuberculosis are paucibacillary, which decreases the sensitivity of diagnostic tests. Also, AFB smears and cultures are generally less sensitive in nonrespiratory samples. In addition, public health clinicians may not pursue culture confirmation of extrapulmonary tuberculosis because of delays and costs associated with referral to specialists in persons who are uninsured and have already started receiving antituberculosis therapy.

Levofloxacin and ciprofloxacin accounted for 85% of the fluoroquinolones prescribed in this study. However, moxifloxacin has more potent activity against Mycobacterium tuberculosis12 and therefore might be more likely to result in missing or incomplete data, tuberculosis is a reportable disease and therefore all tuberculosis cases were likely captured. We reviewed all reported cases of tuberculosis within Tennessee during a 5-year period. In addition, data on fluoroquinolone exposure were collected prospectively through the TennCare pharmacy database. Both of these factors minimized the extent of missing or incomplete data. Second, the assessment of fluoroquinolone exposure was limited to TennCare prescriptions obtained via outpatient medical encounters (eg, related to clinic or emergency department visits) and did not include medications prescribed during inpatient hospitalizations. Thus, there may have been underascertainment of fluoroquinolone exposure among the study population. However, for prescriptions in outpatient and emergency department settings, this automated database provides (1) uniform ascertainment for all patients, independent of the patient’s cognitive status and (2) specific information on drug, dose, and schedule of use, which allows for precise quantification of timing and duration of exposure. In addition, the TennCare pharmacy database includes

### Table 5. Predictors of Culture-Negative Tuberculosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>Age</td>
<td>0.95 (0.94-0.97)</td>
<td>0.95 (0.94-0.97)</td>
</tr>
<tr>
<td>Male sex</td>
<td>.75 (0.49-1.16)</td>
<td>0.95 (0.94-0.97)</td>
</tr>
<tr>
<td>Black race</td>
<td>1.13 (0.73-1.74)</td>
<td>0.95 (0.94-0.97)</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis</td>
<td>2.30 (1.47-3.62)</td>
<td>0.95 (0.94-0.97)</td>
</tr>
<tr>
<td>HIV seropositive</td>
<td>0.26 (0.10-0.67)</td>
<td>0.95 (0.94-0.97)</td>
</tr>
<tr>
<td>Fluoroquinolone exposure</td>
<td>0.48 (0.26-0.88)</td>
<td>0.95 (0.94-0.97)</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td>1.12 (0.96-1.31)</td>
<td>0.95 (0.94-0.97)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

a Multivariate logistic regression analysis was performed among persons enrolled in TennCare for more than 300 days during the year before diagnosis. Reference groups were female sex, race other than black, pulmonary disease only, HIV seronegative, and no fluoroquinolone exposure.

b Per 1-year increase.

c Per 1-year increase between 2000 and 2004.

### Table 6. Predictors of Culture-Negative Pulmonary Tuberculosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>0.95 (0.94-0.96)</td>
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<tr>
<td>Male sex</td>
<td>0.86 (0.47-1.58)</td>
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<tr>
<td>Black race</td>
<td>0.63 (0.33-1.21)</td>
<td>.16</td>
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<tr>
<td>HIV seropositive</td>
<td>0.24 (0.07-0.82)</td>
<td>.02</td>
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<tr>
<td>Fluoroquinolone exposure</td>
<td>1.18 (0.55-2.53)</td>
<td>.67</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td>1.18 (0.95-1.45)</td>
<td>.13</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

a Multivariate logistic regression analysis was performed among persons enrolled in TennCare for more than 300 days during the year before diagnosis. Reference groups were female sex, race other than black, HIV seronegative, and no fluoroquinolone exposure.

b Per 1-year increase.

c Per 1-year increase between 2000 and 2004.

This study has several limitations. First, it was a retrospective review of existing data. Although this approach can result in missing or incomplete data, tuberculosis is a reportable disease and therefore all tuberculosis cases were likely captured. We reviewed all reported cases of tuberculosis within Tennessee during a 5-year period. In addition, data on fluoroquinolone exposure were collected prospectively through the TennCare pharmacy database. Both of these factors minimized the extent of missing or incomplete data. Second, the assessment of fluoroquinolone exposure was limited to TennCare prescriptions obtained via outpatient medical encounters (eg, related to clinic or emergency department visits) and did not include medications prescribed during inpatient hospitalizations. Thus, there may have been underascertainment of fluoroquinolone exposure among the study population. However, for prescriptions in outpatient and emergency department settings, this automated database provides (1) uniform ascertainment for all patients, independent of the patient’s cognitive status and (2) specific information on drug, dose, and schedule of use, which allows for precise quantification of timing and duration of exposure. In addition, the TennCare pharmacy database includes
only prescriptions that were filled (not just those written by physicians), increasing the likelihood that patients took the medications.

With these noted, this study is valuable because it has characterized the extent of outpatient fluoroquinolone exposure before tuberculosis diagnosis in a large, representative population of patients with tuberculosis, assessed the clinical predictors of fluoroquinolone use in this population, documented an increase in outpatient fluoroquinolone use over time, and shown that fluoroquinolone exposure before the diagnosis of tuberculosis does not appear to increase the risk of culture-negative tuberculosis.

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Author Contributions: Drs Gaba and Sterling had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: Sterling. Acquisition of data: Haley, Griffin, Mitchel, Warkentin, Holt, and Baggett. Analysis and interpretation of data: Gaba, Griffin, and Sterling. Drafting of the manuscript: Gaba and Sterling. Critical revision of the manuscript for important intellectual content: Haley, Griffin, Mitchel, Warkentin, Holt, and Baggett. Analysis and interpretation of data: Gaba, Griffin, and Sterling. Study supervision: Sterling.

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Additional Contributions: The Tennessee Department of Health and the Tennessee Bureau of TennCare of the Department of Finance and Administration provided the data used in this study.

REFERENCES