

SHORT REPORT

A comparison of interview methods to ascertain fluoroquinolone exposure before tuberculosis diagnosis

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*Received 11 June 2014; Final revision 27 October 2014; Accepted 30 October 2014;
first published online 25 November 2014*

SUMMARY

Fluoroquinolone use before tuberculosis (TB) diagnosis delays the time to diagnosis and treatment, and increases the risk of fluoroquinolone-resistant TB and death. Ascertainment of fluoroquinolone exposure could identify such high-risk patients. We compared four methods of ascertaining fluoroquinolone exposure in the 6 months prior to TB diagnosis in culture-confirmed TB patients in Tennessee from January 2007 to December 2009. The four methods included a simple questionnaire administered to all TB suspects by health department personnel (FQ-Form), an in-home interview conducted by research staff, outpatient and inpatient medical record review, and TennCare pharmacy database review. Of 177 TB patients included, 72 (41%) received fluoroquinolones during the 6 months before TB diagnosis. Fluoroquinolone exposure determined by review of inpatient and outpatient medical records was considered the gold standard for comparison. The FQ-Form had 61% [95% confidence interval (CI) 48–73] sensitivity and 93% (95% CI 85–98) specificity (agreement 79%, kappa = 0.56) while the in-home interview had 28% (95% CI 18–40) sensitivity and 99% (94–100%) specificity (agreement 68%, kappa = 0.29). A simple questionnaire administered by health department personnel identified fluoroquinolone exposure before TB diagnosis with moderate reliability.

Key words: Infectious disease, tuberculosis (TB).

Fluoroquinolones are the most frequently prescribed class of antibiotics in the United States [1]. They are commonly used to treat a variety of bacterial infections and are often used empirically, including for respiratory infections. As a result, patients with

tuberculosis (TB) may inadvertently receive treatment with a fluoroquinolone prior to TB diagnosis. Up to 41% of TB patients have received a fluoroquinolone prior to diagnosis [2].

Patients who are treated with a fluoroquinolone before being diagnosed with TB have a higher risk of fluoroquinolone-resistant disease [3]. When tested, up to 3.6% of *Mycobacterium tuberculosis* isolates were resistant to fluoroquinolones [4]. In a study of culture-confirmed TB patients in Tennessee, we previously found that 7/54 (13%) patients with >10 days

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of fluoroquinolone exposure had fluoroquinolone-resistant TB [3]. Fluoroquinolone exposure before TB diagnosis has also been associated with delays in the diagnosis and initiation of appropriate treatment for TB [5], and an increased risk of death at the time of TB diagnosis or during TB treatment [6]. Since fluoroquinolones may be used in patients who do not tolerate first-line anti-TB medications and are under investigation for inclusion in first-line drug-susceptible TB treatment regimens, preserving fluoroquinolone susceptibility and optimizing conditions for successful treatment are essential [7, 8]. The development of a rapid, accurate method to assess the duration and timing of fluoroquinolone exposure prior to TB diagnosis could identify high-risk patients and have important implications for TB treatment. Specifically, if a drug-susceptible TB patient identified as having extensive fluoroquinolone exposure prior to TB diagnosis were to develop intolerance to first-line anti-TB medications, the provider might prioritize second-line drug susceptibility testing to better inform an alternate regimen.

Published studies reporting patient fluoroquinolone exposure data have used various methods, such as medical record review [9] and pharmacy databases linked to TB registries [2, 3, 10]. The validity of such sources of exposure data has not been determined.

In the current study we compared four methods of ascertaining fluoroquinolone exposure prior to diagnosis in TB patients in Tennessee.

Fluoroquinolone exposure data were gathered for a prospective study that evaluated the relationship between antecedent fluoroquinolone exposure and fluoroquinolone resistance in culture-confirmed TB patients reported to the Tennessee Department of Health from January 2007 to December 2009 [3]. For the current study, we sought to understand the potential clinical value of fluoroquinolone exposure assessment methods. In a clinical context, these methods would be implemented prior to identification of fluoroquinolone-resistant *M. tuberculosis*, and therefore fluoroquinolone resistance was not a requirement for inclusion. The Institutional Review Boards of Vanderbilt University, Tennessee Department of Health, and Davidson County Metro Public Health Department approved the study. The Bureau of TennCare also reviewed the study.

Fluoroquinolone exposure data were obtained in four different ways:

(1) *Fluoroquinolone assessment form* (FQ-Form, see Supplementary Appendix 1). The FQ-Form was

developed as a questionnaire to be administered to all TB suspects in Tennessee. Health department staff at all 11 regional public health TB clinics in Tennessee completed the form by interviewing patients during their initial visit to the clinic when possible (see further description in Supplementary Appendix 2).

(2) *In-home interview* (see Supplementary Appendix 3). All culture-confirmed TB patients in Tennessee were eligible to be interviewed at home. All eligible patients were asked to participate in the research study; patients who provided written consent were interviewed in their homes by research staff. Patients were excluded from the in-home interview if they were aged <18 years, did not speak English or Spanish, resided in a correctional facility or moved outside Tennessee during TB treatment, or if they were mentally impaired (see further description in Supplementary Appendix 2).

(3) *Medical records*. Participants who consented to the in-home interview were asked to sign an authorization to release their medical records for review. A study coordinator reviewed medical records from hospitals and physicians' offices in the 6 months prior to TB diagnosis.

(4) *Pharmacy records*. TB cases in TennCare recipients were linked to the TennCare pharmacy database to assess for outpatient fluoroquinolone use in the 6 months prior to TB diagnosis. TennCare is a managed healthcare programme that insures Tennessee residents eligible for Medicaid benefits. TennCare contains a pharmacy module with outpatient and emergency room prescription records, but it does not include prescriptions given during inpatient hospitalizations, prescriptions from non-TennCare pharmacy providers, or antibiotic samples given by physicians. During the study period, TennCare prescription insurance covered three generic and two non-generic medications per month. Additionally, patients aged ≥ 65 years received prescription coverage via Medicare rather than TennCare. Patients who had evidence of TennCare enrolment for at least 1 day in the 12 months before their TB diagnosis date were included. TennCare data were obtained through a contractual agreement between the State of Tennessee Bureau of TennCare and the Vanderbilt University School of Medicine.

Data collected using all four fluoroquinolone exposure ascertainment methods included the type of

fluoroquinolone received, duration of exposure, and date of exposure.

Demographic and clinical characteristics were compared using the Wilcoxon rank-sum test for continuous variables and Pearson's χ^2 test for categorical variables. Fluoroquinolone exposure was measured as a categorical and continuous variable. The timing of fluoroquinolone exposure was calculated for the earliest day of fluoroquinolone prescription captured, and the last day of fluoroquinolone prescription before TB diagnosis.

The study population was identified by starting with all culture-confirmed TB patients in Tennessee during the study period who consented to the in-home interview and medical record review. Then for each pairwise comparison of ascertainment methods, patients with unknown or missing exposure were removed from the analyses. Data were analysed using contingency tables.

We considered the overall medical record to be the gold standard for fluoroquinolone exposure and calculated the sensitivity and specificity of the remaining ascertainment methods [11]. The combination of clinic data and hospital discharge data constituted outpatient medical record exposure and hospital data constituted inpatient medical record exposure. Overall medical record exposure was determined by combining the inpatient and outpatient medical record exposures. Exposure as documented in the medical record was considered a categorical variable in each comparison. Fluoroquinolone exposure data from the FQ-Form and in-home interview were compared to the overall medical record exposure and then separately to outpatient medical record exposure alone. Since the TennCare pharmacy database did not capture inpatient prescription data, TennCare exposure data were only compared to outpatient medical record exposure. The TennCare exposure analysis also excluded patients aged ≥ 65 years since those patients did not receive prescription benefits through TennCare.

To assess the agreement between methods, we calculated the simple kappa coefficient. We interpreted the kappa values according to Landis & Koch [12]: values < 0 are indicative of poor agreement, 0.01–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 indicate almost perfect agreement. We also calculated positive and negative predictive values and likelihood ratios for the comparisons between the interview methods and the medical records.

SAS software v. 9.2 for Windows (SAS Institute Inc., USA) and Stata v. 12.1 (StataCorp LP, USA) were used for analyses. All *P* values were two-sided; *P* values < 0.05 were considered statistically significant.

A total of 493 culture-confirmed TB patients were reported to the Tennessee Department of Health during the study period. Of these, 177 (36%) consented to the in-home interview and signed a release of medical information form for medical record review. There were 128 (26%) patients who declined to participate, 23 (5%) who could not be reached, and 165 (33%) who did not meet eligibility criteria. The in-home interviews occurred a median of 70 days [interquartile range (IQR) 49–107] after TB diagnosis.

There were no statistically significant differences between patients who were enrolled and those not enrolled with regard to age, sex, race, ethnicity, birthplace, HIV status, prior TB, site of disease, and radiographic cavitary or miliary disease. The 177 enrolled participants were predominantly male (63%), not black (64%), not Hispanic or Latino (82%), born in the United States (77%), HIV negative (91%), and had pulmonary TB (89%).

According to the overall medical record exposure, of the 177 study patients, 72 (41%) received fluoroquinolones before TB diagnosis. The 72 exposed patients received a total of 122 courses of fluoroquinolones; most (58%) received a single prescription. Of the 72 patients exposed to fluoroquinolones, 30 (42%) received fluoroquinolones only as inpatients, 25 (35%) only as outpatients, and 17 (24%) in both inpatient and outpatient settings. The overall median duration of exposure was 7 days (IQR 2–13.5); 24 (33%) patients received > 10 days of fluoroquinolone exposure. The median outpatient exposure was longer than the median inpatient exposure (10 days, IQR 7–15 vs. 3 days, IQR 2–5). The median timing of the earliest fluoroquinolone exposure was 17.5 days (IQR 3.5–116.5) before TB diagnosis, and that of the last fluoroquinolone exposure was 7 days (IQR 2–35) before TB diagnosis. The clinical and demographic characteristics of the study population according to fluoroquinolone exposure obtained by the medical record review are displayed in Table 1.

When we compared the FQ-Form and in-home interview to the overall medical record exposure, the FQ-Form was more sensitive than the in-home interview, with sensitivities of 61% [95% confidence interval (CI) 48–73] and 28% (95% CI 18–40), respectively. The FQ-Form had lower specificity (93%, 95% CI 85–98) than the in-home interview

Table 1. Demographic and clinical characteristics of the 177 study patients according to fluoroquinolone exposure

Characteristic	FQ exposed* (N = 72) n (%)	FQ unexposed* (N = 105) n (%)	P value†
Age, yr, median (IQR)	45 (37–57)	48 (32–60)	0.91
Female sex	35 (49)	30 (29)	0.01
Black race	28 (39)	36 (34)	0.53
Hispanic or Latino ethnicity	11 (15)	21 (20)	0.42
Foreign-born	15 (21)	26 (25)	0.54
HIV positive	9 (13)	7 (7)	0.18
Pulmonary tuberculosis	63 (88)	94 (90)	0.68
Previous tuberculosis	4 (6)	5 (5)	0.81
FQ-resistant isolate	3 (4)	0 (0)	0.03

FQ, Fluoroquinolone; IQR, interquartile range.

* Fluoroquinolone exposure status determined by medical record review.

† Wilcoxon rank-sum test for continuous variables, Pearson's χ^2 test for categorical variables.

(99%, 95% CI 94–100), but better percent agreement (79% vs. 69%) and kappa value (0.56 vs. 0.29). The FQ-Form had 88% positive predictive value (PPV), 75% negative predictive value (NPV), a positive likelihood ratio (LR+) of 9.3, and a negative likelihood ratio (LR-) of 0.4. By comparison, the in-home interview had higher PPV (95%), lower NPV (64%), and higher likelihood ratios (LR+ 26.1, LR- 0.7). When we considered only the outpatient medical records and compared them to the FQ-Form, in-home interview, and TennCare pharmacy records, the FQ-Form had the highest sensitivity (71%, 95% CI 54–85), and the lowest specificity (84%, 95% CI 75–91). The in-home interview had the highest specificity (99%, 95% CI 96–100) for outpatient record review. The comparison of TennCare to outpatient records showed similar percent agreement and kappa values as the other comparisons, but the analyses had fewer patients ($n = 37$) since the comparison was limited to TennCare enrollees. Figure 1 and Supplementary Appendix 4 show the comparisons of all the exposure ascertainment methods to the medical record data.

This study investigated the ascertainment of fluoroquinolone exposure data obtained from patient interviews, pharmacy records, and medical records for a

sample of patients diagnosed with TB. This sample was of particular interest given the high rate (41%) of fluoroquinolone exposure before TB diagnosis.

All of the comparisons of the FQ-Form, in-home interview, and TennCare to medical record exposures, whether overall or outpatient only, showed relatively high specificities, indicating that when fluoroquinolone use was reported by any of these sources, there was usually medical record confirmation of such use. The low sensitivity of the in-home interview likely reflects the limits of patient recall, particularly since some of the in-home interviews were completed months after the fluoroquinolone exposure occurred. The lower agreement, sensitivity and specificity of the FQ-Form and in-home interview when compared to the overall medical record rather than the outpatient records alone suggest that patients may frequently be unaware of specific medications administered in the hospital. TennCare exposure data did not rely on patient recall, but only 37/177 (21%) study patients were included in the TennCare analysis. The lack of inpatient prescription data was a major factor preventing broader applicability of the TennCare database for capturing complete fluoroquinolone exposure data.

Our study has a number of limitations. First, we used the medical record as the 'gold standard,' and assumed that all reported prescriptions were written, filled, and taken, and thus may have overestimated fluoroquinolone exposure. In addition, we assumed that all prescriptions were reported in the medical record. Although patients could have provided incomplete lists of all healthcare providers for research staff to review, health department records were also available to help identify healthcare contacts for record review, which makes this assumption reasonable. Furthermore, fluoroquinolones require a prescription in the United States, making missed exposure from medical record review less likely than in settings where fluoroquinolones are available without a prescription. Second, our study population was limited to those who provided consent for the in-home interview and medical record review, and thus did not include all of the patients with culture-confirmed TB during the study period. Third, the TennCare comparison was limited to those enrolled in TennCare and aged <65 years. Fourth, the FQ-Form and the in-home interview methods were both subject to recall bias. Additionally, health department staff may have used available chart data to complete missing data on the FQ-Form during patient assessment at the

Overall medical records				Outpatient records					
	Exposed	Not exposed		Exposed	Not exposed		Exposed	Not exposed	
FQ-Form	Exposed	38	5	Exposed	27	16	Exposed	27	16
	Not exposed	24	71	Not exposed	11	84	Not exposed	11	84
	Sensitivity = 61% (95% CI 48-73)	Agreement = 79% (95% CI 71-86)		Sensitivity = 71% (95% CI 54-85)	Agreement = 80% (95% CI 73-87)		Sensitivity = 71% (95% CI 54-85)	Agreement = 80% (95% CI 73-87)	
	Specificity = 93% (95% CI 85-98)	$k = 0.56$ (95% CI 0.43-0.70)		Specificity = 84% (95% CI 75-91)	$k = 0.53$ (95% CI 0.37-0.68)		Specificity = 84% (95% CI 75-91)	$k = 0.53$ (95% CI 0.37-0.68)	
In-home Interview	Exposed	20	1	Exposed	20	1	Exposed	20	1
	Not exposed	52	93	Not exposed	22	123	Not exposed	22	123
	Sensitivity = 28% (95% CI 18-40)	Agreement = 68% (95% CI 60-75)		Sensitivity = 48% (95% CI 32-64)	Agreement = 86% (95% CI 80-91)		Sensitivity = 48% (95% CI 32-64)	Agreement = 86% (95% CI 80-91)	
	Specificity = 99% (95% CI 94-100)	$k = 0.29$ (95% CI 0.18-0.41)		Specificity = 99% (95% CI 96-100)	$k = 0.56$ (95% CI 0.41-0.71)		Specificity = 99% (95% CI 96-100)	$k = 0.56$ (95% CI 0.41-0.71)	
TennCare*				Exposed	4	1	Exposed	4	1
				Not exposed	7	25	Not exposed	7	25
				Sensitivity = 36% (95% CI 11-69)	Agreement = 76% (95% CI 62-90)		Sensitivity = 36% (95% CI 11-69)	Agreement = 76% (95% CI 62-90)	
				Specificity = 96% (95% CI 80-100)	$k = 0.36$ (95% CI 0.03-0.68)		Specificity = 96% (95% CI 80-100)	$k = 0.36$ (95% CI 0.03-0.68)	

Fig. 1. Sensitivity, specificity, agreement, and kappa values for pairwise comparisons of fluoroquinolone exposure ascertainment methods to exposure as determined by medical records. Outpatient record exposures were determined by review of clinic records and hospital discharge prescription records. Overall medical record exposures were determined by review of clinic records, hospital discharge prescription records, and hospital records. CI, Confidence interval; k , kappa coefficient. * TennCare pharmacy records included only outpatient prescriptions and were only available for patients aged <65 years.

health department. Finally, our data are from 2007 to 2009, but based on trends in antibiotic prescribing [1] and more recent reports [13], fluoroquinolone use remains high, similar to that of our study period.

Our study demonstrates high rates of fluoroquinolone use before TB diagnosis and suggests that tools such as the FQ-Form implemented at the start of TB care could alert providers to the possibility of fluoroquinolone exposure prior to diagnosis. Given the important role that fluoroquinolones play in the treatment of drug-susceptible and drug-resistant TB, identification of factors that could lead to fluoroquinolone resistance and ultimately jeopardize treatment success will be critical.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0950268814003136>.

ACKNOWLEDGEMENTS

The Tennessee Department of Health and the Tennessee Bureau of TennCare of the Department of Finance and Administration provided data used in this study. The authors thank Dr Marie Griffin for her contributions to this study.

This work was supported by the National Institute of Allergy and Infectious Diseases at the National

Institutes of Health (T.R.S., grant nos. R01 AI 063200, K24 AI65298), (Y.F.vd.H., grant no. T32 AI07474).

DECLARATION OF INTEREST

Vanderbilt has received research grant funding for Dr Timothy Sterling from Pfizer, Bristol-Myers Squibb and Virco for HIV observational studies. Dr Sterling has served as a consultant for Sanofi, and is a member of the data safety monitoring board for a study funded by Otsuka Pharmaceutical. All other authors declare no competing interests.

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