

Recurrent Tuberculosis in the United States and Canada Relapse or Reinfection?

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Recurrence of active tuberculosis after treatment can be due to relapse of infection with the same strain or reinfection with a new strain of *Mycobacterium tuberculosis*. The proportion of recurrent tuberculosis cases caused by reinfection has varied widely in previous studies. We evaluated cases of recurrent tuberculosis in two prospective clinical trials: a randomized study of two regimens for the last 4 months of treatment (n = 1,075) and a study of a twice-weekly rifabutin-containing regimen for human immunodeficiency virus-infected tuberculosis (n = 169). Isolates at diagnosis and from positive cultures after treatment completion underwent genotyping using IS6110 (with secondary genotyping for isolates with less than six copies of IS6110). Of 85 patients having a positive culture after completing treatment, 6 (7.1%) were classified as false-positive cultures by a review committee blinded to treatment assignment. Of the remaining 75 cases with recurrent tuberculosis and genotyping data available, 72 (96%; 95% confidence interval, 88.8–99.2%) paired isolates had the same genotype; only 3 (4%; 95% confidence interval, 0.8–11.2%) had a different genotype and were categorized as reinfection. We conclude that recurrent tuberculosis in the United States and Canada, countries with low rates of tuberculosis, is rarely due to reinfection with a new strain of *M. tuberculosis*.

Keywords: DNA fingerprinting; pulmonary tuberculosis; reinfection; relapse

Active tuberculosis recurs in 2 to 7% of patients with drug-susceptible isolates treated with contemporary short-course chemotherapy (1–3). With DNA fingerprinting, cases of recurrent tuberculosis can be categorized as being due to relapse of the original infecting strain or reinfection with a new strain of *Mycobacterium tuberculosis*. Although reinfection clearly occurs (4), the proportion of recurrent cases caused by reinfection has varied widely in previous studies (5–11). Factors that appear to affect the rate of recurrence are the rate of exposure to new strains of *M. tuberculosis* (the prevalence of active tuberculosis in the community) and the presence of a condition that increases the likelihood of progression to active disease after exposure to new strains (most commonly, advanced human immunodeficiency virus [HIV] disease). However, the small number of cases evaluated in previous studies limits the strength of these tentative conclusions about the pathogenesis of recurrent tuberculosis.

False-positive cultures caused by laboratory cross-contamina-

tion can also be identified by genotyping and are indicated by a subsequent nonmatching genotype that matches that of another isolate processed in the laboratory during a similar period of time (12–14). Therefore, genotyping, in combination with a review of clinical and radiographic data, allows an estimation of the incidence of relapse, reinfection, and laboratory cross-contamination. The results of two clinical studies conducted by the Tuberculosis Trials Consortium (TBTC) provide a large number of cases of recurrent tuberculosis for such an evaluation. Some of the results of this study have been previously reported in abstract form (15).

METHODS

Studies Included

We included patients treated in two prospective clinical trials in which treatment was given under direct observation. The TBTC study 22 enrolled adults with drug-susceptible pulmonary tuberculosis who had completed 2 months of standard four-drug therapy (16–17). Participants were then randomly allocated to receive treatment with either rifampin and isoniazid once a week or rifampin and isoniazid twice per week to complete 6 months of therapy. Sputum cultures were obtained every 4 weeks during treatment and 3, 6, 9, 12, 18, and 24 months after treatment, as well as at the time of any symptoms of recurrent tuberculosis. Study 22 enrolled patients from 1995 to 1999, and the last follow-up for recurrent tuberculosis was completed in 2001. All patients in TBTC study 22 had HIV testing done, and 1,004 of 1,075 (93%) were HIV negative.

TBTC study 23 was a study of patients who were HIV infected with tuberculosis treated with isoniazid, rifabutin, ethambutol, and pyrazinamide for the first 2 months then with rifabutin and isoniazid twice weekly for at least 4 months (with 3 additional months for patients with a positive culture or a lack of a favorable clinical response after 2 months of treatment) (18). Sputum cultures were obtained monthly during treatment and 1.5, 3, 6, 12, 18, and 24 months after treatment completion and at the time of clinical evidence of recurrent tuberculosis. Patients in study 23 were enrolled between 1998 and 2002 and completed follow-up for recurrent tuberculosis in 2004.

Genotyping

Initial isolates of *M. tuberculosis* and from any cultures positive at or after 4 months of therapy underwent genotyping by IS6110-based restriction fragment length polymorphism analysis using the internationally standardized method (19). Isolates that had indistinguishable IS6110 restriction fragment length polymorphism patterns comprised of more than five hybridizing bands were considered as matched; those containing five or fewer hybridizing bands underwent secondary typing at the Veterans Administration Mycobacteriology Research Laboratory in Little Rock, Arkansas, using polymorphic guanine-cytosine-rich sequence-based restriction fragment length polymorphism analysis with the recombinant plasmid pTBN12. Isolates having fewer than five IS6110 bands were considered as matched if both the IS6110 and polymorphic guanine-cytosine-rich sequence genotypes were indistinguishable (20). Isolates from patients in TBTC study 23 underwent secondary genotyping using mycobacterial interspersed repeat units or spoligotyping (21).

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Definitions and Data Analysis

The primary analysis dealt with positive cultures after completion of tuberculosis treatment. Laboratory cross-contamination was defined as the occurrence of a single positive culture in a patient who had converted to culture negative, whose subsequent genotype did not match that of the original isolate and who lacked any clinical or radiographic evidence of recurrent tuberculosis. Relapse was defined as the occurrence of a positive culture after both documented culture conversion and treatment completion in a patient with symptoms of recurrent tuberculosis, whose original and subsequent isolates had matching genotypes. Reinfection was defined as the occurrence of nonmatching genotypes of original and subsequent isolates in patients with a clinical course consistent with failure or relapse.

We also evaluated positive cultures that occurred at or after the fourth month but before treatment completion. Treatment failure was defined as the occurrence of a positive culture for *M. tuberculosis* after at least 4 months of treatment, in which the original and subsequent isolates had matching genotypes and when symptoms/signs consistent with unresponsive or recrudescing tuberculosis were present.

All cases were reviewed and classified by a clinical events committee that had access to clinical information and the results of genotyping but were blind to treatment assignment.

We calculated rates of relapse and reinfection as the number of cases per 100 patient-years of follow-up. Calculation of patient-years began at treatment completion and ended at the first of the following: relapse date or date of censoring or 2 years. Patients were censored at either the date of death or date of last study evaluation before move/loss to follow-up.

RESULTS

The two studies enrolled a total of 1,244 patients (1,075 in study 22 and 169 in study 23) who had culture-positive tuberculosis. Eighty-six percent of patients were followed for at least 12 months after treatment, and 78% were followed for 24 months. The vast majority, 1,142 (91.8%) had negative follow-up cultures without clinical evidence of treatment failure or relapse (Figure 1). Ninety-four patients had a positive culture after at least 4 months of treatment or during follow-up, 13 of whom met the criteria for treatment failure. Clinical and demographic characteristics of these 94 patients are described in Table 1. Six patients had positive cultures caused by laboratory cross-contamination (Figure 1 and Table 2), and two had recurrent tuberculosis with cultures that were negative or not obtainable.

TABLE 1. CHARACTERISTICS OF THE 94 PATIENTS HAVING A POSITIVE CULTURE FOR *Mycobacterium tuberculosis* AFTER 4 MONTHS OF TREATMENT OR DURING FOLLOW-UP*

Characteristic	HIV Negative (n = 74)	HIV Infected (n = 20)
Demographic		
Age, mean yr ± SD	41.7 ± 13.6	38.4 ± 8.3
Men	62 (83.8)	17 (85)
Ethnic origin		
Non-Hispanic white	24 (32.4)	3 (15)
Non-Hispanic black	29 (39.2)	10 (50)
Hispanic	13 (17.6)	7 (35)
Asian/Pacific Islander	6 (8.1)	0 (0)
Native American	2 (3)	0 (0)
Birthplace		
United States or Canada	54 (73.0)	12 (60)
Mexico	8 (10.8)	5 (25)
Other	12 (16.2)	3 (15)
Sociologic features		
Homeless > 6 mo	12 (16.2)	4 (20)
Drug use in past 5 yr	24 (32.4)	7 (35)
Daily alcohol use in past 5 yr	40 (54.1)	5 (25)
> 1 mo in prison in past 5 yr	10 (13.5)	3 (15)
Clinical features		
Cavitation on chest radiograph	62 (83.8)	4 (20)
Bilateral disease on chest radiograph	56 (75.7)	9 (45)
Sputum positive by smear	20 (27.0)	0 (0)
CD-4 cell count, cells/μl	Not applicable	80 ± 139
On antiretrovirals in past 6 mo	Not applicable	8 (40)

Definition of abbreviation: HIV = human immunodeficiency virus.

* This does not include six patients who had a positive follow-up culture caused by laboratory cross-contamination or two patients who had recurrent tuberculosis with cultures negative or not obtainable.

The remaining 79 patients had a positive culture after treatment completion. Of these, 75 had paired isolates available for genotyping. Fourteen had less than six IS6110 bands and required secondary genotyping. Seventy-two (96.0%; 95% confidence interval, 88.2–99.2%) had identical genotypes in paired isolates and were classified as being due to relapse (Figure 1). Only three (4.0%; 95% confidence interval, 0.8–11.2%) had a

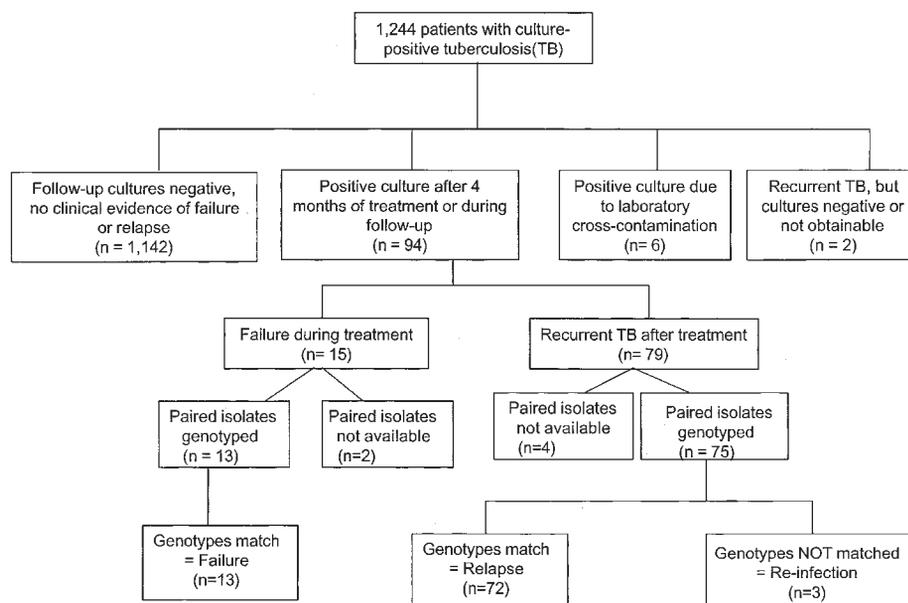


Figure 1. Genotypic classification of culture-positive events. The figure shows the classification of patients in the study. Ninety-four patients had a positive culture after 4 months of treatment or during follow-up that was not due to laboratory cross-contamination. Of these, 15 were due to treatment failure, and 79 occurred after treatment had ended. Of these 79, 72 were classified as relapses, and 3 were classified as reinfections (see text for details). TB = tuberculosis.

TABLE 2. CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS HAVING A POSITIVE FOLLOW-UP CULTURE OF *MYCOBACTERIUM TUBERCULOSIS* WITH A NONMATCHING GENOTYPE

Patient	Laboratory	Treatment	Description	Decision by Panel
1	A	Twice-weekly rifampin and isoniazid	The genotype of culture-positive isolate at 12 mo follow-up matched that of another patient whose specimen was processed on the same day. Baseline isolate and single follow-up culture had nonmatching genotypes. The patient had no symptoms. Multiple follow-up cultures were negative, and the patient completed 24 mo follow-up without recurrent disease.	Cross-contamination
2	A	Once-weekly rifapentine and isoniazid	The genotype of culture-positive isolate at 3 mo matched that of another patient whose specimen was processed on the same day. Baseline isolate and single follow-up culture had nonmatching genotypes. The patient had no symptoms. Multiple follow-up cultures were negative, and the patient completed 24 mo follow-up without recurrent disease.	Cross-contamination
3	A	Once-weekly rifapentine and isoniazid	The genotype of culture-positive isolate at 5 mo of treatment did not match that of the initial isolate. Treatment was extended by 9 mo because of a slow response to initial treatment and extensive disease on chest radiograph. Multiple specimens collected after 4, 5, and 6 mo of treatment and after 2, 3, 9, 18, and 24 mo of follow-up were culture negative. The patient completed 24 mo of follow-up without recurrent disease.	Cross-contamination
4	B	Twice-weekly rifampin and isoniazid	The genotype of culture-positive isolate 1 mo after completing treatment did not match that of the initial isolate. Treatment was extended by 6 mo after a single positive culture. Multiple specimens collected after 2, 3, 4, and 6 mo of treatment and after 2, 6, 9, 12, and 18 mo of follow-up were culture negative. The patient completed 18 mo of follow-up without recurrent disease.	Cross-contamination
5	C	Once-weekly rifapentine and isoniazid	The genotype of culture-positive isolate at 5 mo of treatment did not match that of the initial isolate. Treatment was extended by 1.5 mo before the laboratory confirmed nonmatching isolate, and the patient had no symptoms after initial treatment. Multiple specimens collected after 4 and 6 mo of treatment and after 3, 9, and 24 mo of follow-up were culture negative. The patient completed 24 mo of follow-up without recurrent disease.	Cross-contamination
6	D	Twice-weekly rifampin and isoniazid	The genotype of culture-positive isolate at 18 mo of follow-up did not match that of the initial isolate. The patient had no symptoms. The chest radiograph was unremarkable, and three consecutive sputa collected after single positive culture were all negative. Multiple specimens collected after 3, 4, 5, and 6 mo of treatment and after 19 and 24 mo of follow-up were culture negative. The patient completed 24 mo of follow-up without recurrent disease.	Cross-contamination
7	E	Once-weekly rifapentine and isoniazid	The genotype of culture-positive isolate 3 mo after completion of treatment did not match that of the initial isolate. Multiple cultures at this time were positive. The patient was HIV negative, had bilateral cavities on chest radiograph, and had symptoms of anorexia, chills, fever, cough, and weakness.	Reinfection
8	D	Once-weekly rifapentine and isoniazid	The genotype of a single, culture-positive isolate 21 mo after completion of treatment did not match that of the initial isolate. The patient was HIV negative and had been on chronic high-dose corticosteroid therapy for systemic lupus erythematosus. She had symptoms of sweats and nonpleuritic chest pain, and chest radiograph revealed noncavitary upper lobe infiltrates.	Reinfection
9	F	Twice-weekly rifampin and isoniazid	The genotype of a culture-positive isolate at 21 mo of follow-up (10/97) did not match that of the initial isolate (1/96) but did match the genotype of the initial isolate from her boyfriend (6/97), who was also a study subject. The patient had HIV infection and symptoms of cough and fever and was found to have pulmonary/extrapulmonary tuberculosis with a positive liver biopsy. The patient discontinued study therapy and was switched to isoniazid, rifampin, ethambutol, and pyrazinamide plus clarithromycin for coverage of <i>Mycobacterium avium-intracellulare</i> .	Reinfection

For definition of abbreviations see Table 1.

different genotype at the time of recurrence and were classified as being due to reinfection (Table 2). Genotypes of patients classified as having reinfection differed by at least two IS6110 bands between initial and follow-up isolates. Among all patients, the rate of relapse per 100 patient-years was 3.63, and the rate of reinfection was 0.15 per 100 patient-years (Table 3).

Among the 1,244 patients in this analysis, 240 (19.3%) had HIV infection and culture-positive tuberculosis and were enrolled in the two studies (71 in study 22 and 169 in study 23). Of these, three patients had a positive culture during the last 2 months of tuberculosis treatment and met the criteria for treatment failure. Fifteen patients had at least one positive culture after completing treatment and had paired isolates available for genotyping. Only 1 of these 15 patients (6.7%; 95% confidence interval, 1.7–31.9%) was classified as having recurrent tuberculosis caused by reinfection. Rates of relapse and reinfection were slightly higher among patients who were HIV positive (Table 3).

An analysis of recurrent tuberculosis by time of occurrence after conclusion of treatment showed that for patients who were HIV negative over two-thirds of relapses (69.0%) occurred within 6 months of the conclusion of treatment, and the vast majority (89.7%) occurred within 12 months (Figure 2). For patients who were HIV positive, 78.6% of relapses occurred within 6 months of the conclusion of treatment. The occurrence of reinfection in either patients who were HIV negative or HIV infected did not follow a predictable time course (Figure 2).

Rates per 100 patient-years were also determined among patients who were followed for at least 1 year after treatment. This analysis demonstrated that the rate of relapse in all patients per 100 patient-years was 6.46 at Year 1. Reinfection occurred at a rate of 0.15 per 100 patient-years.

DISCUSSION

In two tuberculosis treatment trials performed from 1995 to 2004 in the United States and Canada, nearly all cases of recurrent tuberculosis (96%) were due to relapse of the original infecting strain. The finding that nearly all recurrences were due to relapse was also true for the 240 patients who were HIV infected in the studies (93% of recurrences were relapse). To our knowledge, this is the largest study to date of recurrent tuberculosis, including 75 patients with paired isolates for which genotyping was performed. Another critical use of *M. tuberculosis* genotyping in clinical trials is to help detect false-positive cultures caused by laboratory cross-contamination. Without this tool, almost 6% of positive cultures after the completion of therapy in these studies might have been erroneously classified as recurrent tuberculosis.

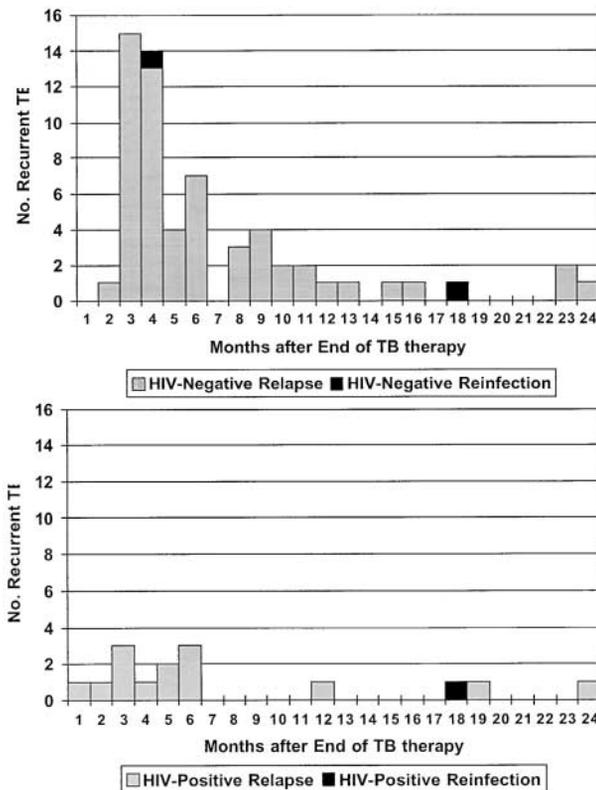


Figure 2. Occurrence of recurrent tuberculosis by time after conclusion of therapy. Each histogram displays the number of patients who had relapse or reinfection in relation to the number of months after the conclusion of therapy. The upper histogram shows results for patients without human immunodeficiency virus (HIV) infection. The bottom histogram shows results for HIV-infected patients. In both groups of patients, the vast majority of relapses occurred within 12 months after treatment had ended.

As previously reported, independent risk factors for treatment failure or relapse among the patients who were HIV negative in TBTC study 22 (assessing the role of rifapentine in the continuation phase of treatment of tuberculosis) were sputum culture positive at 2 months of treatment, cavitation on chest radiograph, bilateral pulmonary involvement on chest radiograph, being underweight, and being a non-Hispanic white person (16). Only one patient who was HIV negative had relapse with acquired resistance to rifampin. Relapse with acquired

TABLE 3. RATES OF RECURRENT TUBERCULOSIS CAUSED BY REINFECTION AND RELAPSE OVERALL AND BY PRESENCE OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Group	Analysis	Number of Events	Person-years of Follow-up	Rate per 100 Patient-years	95% CI
All patients	Recurrent TB	75	1,982.55	3.78	2.99–4.72
	Relapse	72		3.63	2.85–4.55
	Reinfection	3		0.15	0.03–0.44
HIV positive	Recurrent TB	15	367.12	4.09	2.31–6.65
	Relapse	14		3.81	2.10–6.32
	Reinfection	1		0.27	0.066–1.51
HIV negative	Recurrent TB	60	1,615.43	3.71	2.84–4.76
	Relapse	58		3.59	2.74–4.62
	Reinfection	2		0.12	0.015–0.44

Definition of abbreviations: CI = confidence interval; HIV = human immunodeficiency virus; TB = tuberculosis.

monoresistance to rifampin was increased in patients who were HIV negative in study 22 who received once-weekly rifapentine/isoniazid and in those who were younger, had a lower baseline CD-4 cell count, had extrapulmonary involvement, and received concomitant therapy with antifungal agents (17). For patients in TBTC study 23 (assessing the role of intermittent rifabutin in the treatment of tuberculosis in HIV-infected persons), low CD-4 cell count and use of twice weekly therapy during the first 2 months of tuberculosis treatment were independently associated with rifampin-resistant treatment failure or relapse (18).

Patients enrolled in TBTC clinical trials have demographic and clinical characteristics that are very similar to those of all reported cases of active tuberculosis in the United States (data not shown), suggesting that the results of our analysis should be representative of recurrent tuberculosis in the United States and Canada. Because the case rates of active tuberculosis in the United States and Canada are low (< 6 per 100,000 per year) (22–24), the probability of both coming into contact with another tuberculosis strain and developing disease with that strain (i.e., reinfection) must be much lower than the probability of treatment failure or relapse with the same strain of *M. tuberculosis*. The rate of recurrent tuberculosis caused by reinfection we found was relatively high, likely reflecting patient's epidemiologic characteristics, which place them at increased risk of repeat exposure to tuberculosis followed by progression to clinical disease. However, because the number of reinfection cases was low, confidence intervals of the estimated rates are quite wide.

Rates of relapse and reinfection were comparable among patients who were HIV positive and HIV negative in our study. Whether the duration of treatment for HIV-related tuberculosis should be longer than that for patients who are HIV negative remains controversial. One large randomized trial showed lower rates of recurrent tuberculosis among patients who were HIV negative receiving prolonged therapy (12 months) but did not distinguish between relapse and reinfection (25); a second smaller study showed similar results from 6 and 9 months of treatment for HIV-related tuberculosis (26). Several cohort studies in which patients were treated with a standard, directly observed 6-month regimen showed comparable results among patients who were HIV positive and HIV negative (27, 28). Other cohorts have shown somewhat higher rates of recurrent tuberculosis, particularly among patients with advanced HIV disease (29, 30). The one cohort study that was able to distinguish relapse from reinfection showed that the increased rate of recurrent tuberculosis among HIV-infected gold miners was entirely due to an increased risk of reinfection (7). Clearly, additional studies are necessary to determine the optimal duration of therapy for HIV-related tuberculosis.

Studies from other areas of the world have shown that reinfection becomes an increasingly common cause of recurrent tuberculosis as tuberculosis case rates increase. In low- to moderate-incidence countries (i.e., tuberculosis case rates < 50 per 100,000), studies have found the percentage of reinfection ranging from 10% in Switzerland to 16% in Italy and 33% in Spain (11, 31, 32). In studies of high-burden countries (i.e., > 200 cases per 100,000 persons per year), reinfection was common, ranging from 23% in Uganda to 60% in a township in Cape Town, South Africa, having a remarkably high rate of tuberculosis (> 1,000 per 100,000 persons per year) (5, 6). Results of these studies suggest that reinfection occurs more often in high-incidence countries because of more frequent exposure to *M. tuberculosis*.

The frequency of HIV infection, an illness that accelerates progression from initial infection with tuberculosis to disease, also increased the risk of reinfection among persons working in gold mines of South Africa (7). Rates of reinfection were not significantly higher among the HIV-infected persons in our stud-

ies, probably because of the very low risk of re-exposure to infectious tuberculosis. In addition, most patients (> 80%) in TBTC study 23 were treated with potent antiretroviral therapy, and the resultant improvement in immune function may have further decreased the risk of recurrent disease, if reinfected.

The rate of laboratory cross-contamination in our study is similar to the rates in previous studies of *M. tuberculosis* cultures and was roughly twice as frequent as reinfection. Most population-based studies have found rates of 0.9 to 3.5% (12–14, 33–35). However, almost all of the cross-contamination events in these studies have been detected in initial isolates rather than in follow-up isolates of patients known to have tuberculosis. In our study, because of the requirement that patients have a previously positive culture, all of the cross-contamination events occurred in follow-up specimens. Clinicians should be cognizant that not all subsequently positive cultures in a patient previously or currently on tuberculosis treatment indicate treatment failure or relapse, and appropriate evaluation, including radiographic and clinical examinations, collection of additional sputum specimens, and genotyping, should be considered to distinguish among treatment failure/relapse, laboratory cross-contamination, and reinfection.

Our study has several limitations. First, it is a study of patients enrolled into two clinical trials from multiple sites, not a cohort of patients from a specific geographic area. It is possible that selection biases associated with enrollment into a clinical trial affected the risk of relapse versus reinfection. The period of follow-up after treatment completion in the two studies was 2 years, and the proportion of cases caused by reinfection may be higher among the unusual cases of recurrent tuberculosis occurring more than 2 years after treatment completion. Because two of the treatment regimens used (once-weekly rifapentine plus isoniazid and twice-weekly rifabutin and isoniazid) are not standard, the somewhat decreased potency of these regimens may have resulted in a modest overestimation of the proportion of cases caused by relapse. Finally, we did not make any attempt to detect infection with more than one strain of *M. tuberculosis*, either at the time of initial diagnosis or at the time of recurrent disease. Mixed infection could result in misclassification that recurrent tuberculosis was due to reinfection if a strain not detected initially was then the dominant strain at the time of recurrence. However, given the very small number of nonmatching genotypes in subsequent isolates, this possibility would not affect the conclusion that reinfection is rare in the United States and Canada.

In summary, this study shows that in addition to clinical and radiographic exam genotyping is an extremely useful technique to distinguish treatment failure or relapse from reinfection or laboratory cross-contamination in patients with tuberculosis with recurrently positive cultures. In patients from low-incidence regions such as most parts of North America, the vast majority (96%) of such cultures are due to treatment failure or relapse rather than reinfection.

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