# Revisiting Rates of Reactivation Tuberculosis
## A Population-based Approach

C. Robert Horsburgh, Jr.[1,2], Max O'Donnell[2], Sandra Chamblee[3], Janet L. Moreland[4], Johnny Johnson[3†], Bryan J. Marsh[5], Masahiro Narita[6], Linda Scoles Johnson[7], and C. Fordham von Reyn[5]

[1]Boston University School of Public Health, Boston, Massachusetts; [2]Boston University School of Medicine, Boston, Massachusetts; [3]Glades Health Initiative, Inc., Belle Glade, Florida; [4]C.L. Brumback Health Center, Belle Glade, Florida; [5]Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; [6]Public Health, Seattle and King County and University of Washington School of Medicine, Seattle, Washington; and [7]Science Applications International Corporation, Atlanta Georgia

*Rationale*: **Reactivation tuberculosis (TB) occurs as a result of reactivation of latent TB infection (LTBI), and was reported to occur in the United States at a rate of 0.10 to 0.16 cases per 100 person-years in the 1950s; it has not been measured since.**

*Objectives*: **To calculate the rate of reactivation TB in a U.S. community.**

*Methods*: **A population-based tuberculin skin test survey for LTBI was performed in western Palm Beach County, Florida, from 1998 to 2000 along with a cluster analysis of TB case isolates in the same area from 1997 to 2001. Reactivation (unclustered) TB was presumed to have arisen from the population with LTBI.**

*Measurements and Main Results*: **The rate of reactivation TB among persons with LTBI without HIV infection was 0.040 cases per 100 person-years (95% confidence interval [CI], 0.024–0.067) using the n method and 0.058 cases per 100 person-years (95% CI, 0.038–0.089) using the n-1 method. HIV infection was the strongest risk factor for reactivation (rate ratio [RR], 57; 95% CI, 27–120; $P < 0.001$). Among persons without HIV infection, reactivation was increased among those older than 50 years (RR, 3.8; 95% CI, 1.3–11) and among those born in the United States (RR, 3.2; 95% CI, 1.1–9.3).**

*Conclusions*: **Rates of reactivation TB in this area have declined substantially since the 1950s. The greatest part of this decline may be attributed to the disappearance of old, healed TB in the population. If similar declines are seen in other areas of the United States, the cost-effectiveness of screening and treatment of LTBI may be substantially less than previously estimated.**

**Keywords:** tuberculosis; tuberculin test; *Mycobacterium tuberculosis*; Southeastern United States; HIV infections

### AT A GLANCE COMMENTARY

#### Scientific Knowledge on the Subject

The rate of tuberculosis (TB) occurring among persons with a positive tuberculin skin test in the United States is generally assumed to be 0.10 to 0.16 cases per 100 person-years.

#### What This Study Adds to the Field

This study measured the rate of TB occurring among persons with a positive tuberculin skin test in a southeastern United States population. The rate, 0.040 to 0.058 per 100 person-years, was substantially lower than rates measured during the 1950s and 1960s. This decrease is likely due to the disappearance of old, healed but untreated TB in the U.S. population. If these lower rates are representative of other areas of the United States, treatment of latent TB infection may not be as cost-effective as previously reported.

The incidence of tuberculosis disease (TB) has been declining in the United States since 1993, but more than 10,000 cases continue to occur each year (1). Moreover, the rate of this decline has slowed in the past decade (1). TB disease can occur as a result of recent transmission (primary TB) or by reactivation of latent infection (reactivation TB) (2, 3). These two types of TB are clinically indistinguishable, but entail different prevention strategies: primary TB is prevented by prompt and diligent contact tracing with treatment of infected contacts, whereas prevention of reactivation TB is accomplished by screening for and treatment of latent TB infection (LTBI) (4).

Molecular studies have shown that the decline in TB cases in the United States over the past decade has been associated with an increased proportion of cases occurring from reactivation of LTBI (5–7). Therefore, prevention of reactivation TB by treatment of LTBI is a major goal of the national strategy for TB elimination in the United States (8–10). Direct measurement of the rate of reactivation TB among persons with LTBI in the United States was last performed in the 1950s. These studies prospectively followed cohorts of persons with LTBI and showed that the rate of occurrence of TB was 0.10 to 0.16 cases per 100 person-years (11–14).

Several important changes have occurred in the United States since the period when reactivation rates were last measured that suggest that rates may be substantially different today than they were in the past. First, HIV infection, which was not present before 1970, has been shown to significantly increase the rate of reactivation among persons with LTBI (15, 16). Second, TB now occurs largely among the foreign-born population, whereas in the 1950s it occurred largely among the U.S.-born. Foreign-born persons may have increased reactivation as a result of recent exposure in a high-prevalence setting, because reactivation is higher in the first few years after infection (17). Third, the median age of TB cases has increased steadily since 1950, and older persons may have higher rates of reactivation because of declining immunity with age (18). Last, isonicotinic acid hydrazide (INH) treatment of LTBI was first recommended in the 1970s; to the extent that it has been

(*Received in original form September 8, 2009; accepted in final form April 14, 2010*)

† Deceased.

Supported by Centers for Disease Control and Prevention cooperative agreement U64 CCU118611 and by National Institute of Allergy and Infectious Diseases grant T32 AI52074 (M.O'D.).

Correspondence and requests for reprints should be addressed to C. Robert Horsburgh, Jr., M.D., M.U.S., Department of Epidemiology, Boston University School of Public Health, 715 Albany Street, Boston, Massachusetts 02118. E-mail: rhorsbu@bu.edu

**Am J Respir Crit Care Med Vol 182. pp 420–425, 2010**
**Originally Published in Press as DOI: 10.1164/rccm.200909-1355OC on April 15, 2010**
**Internet address: www.atsjournals.org**

prescribed and a course of treatment completed, rates of reactivation TB among persons with a positive tuberculin skin test (TST) may have been reduced (19).

Cohort studies of reactivation are not practical today in the United States, because TB occurs infrequently and because INH would need to be given to persons with LTBI, thus preventing observation of reactivation TB disease. However, the advent of molecular typing of *Mycobacterium tuberculosis* isolates allows rates of reactivation TB to be measured by performing a molecular clustering study of *M. tuberculosis* isolates concurrent with a population-based TST survey. Cases of reactivation TB are unclustered cases, and can be assumed to have arisen from the *M. tuberculosis*-infected (TST-positive) population. Therefore, to determine if rates of reactivation TB have changed since the 1950s and to identify risk factors for reactivation among persons with LTBI, a population-based TST survey and cluster analysis of TB cases was performed in western Palm Beach County, Florida, a geographically circumscribed community, between 1997 and 2001. Some of the results of these studies have been previously reported in the form of an abstract (20).

## METHODS

### Community Survey

Detailed descriptions of the survey methods have been previously reported (21–23). Between January 1998 and October 2000, a randomized population-based tuberculin skin test survey was performed in a rural area of western Palm Beach County, Florida. Informed consent was obtained from each participant. The survey design was approved by human subjects committees of the Florida Department of Health, Emory University, Boston University, Dartmouth Medical School, and the Centers for Disease Control and Prevention.

To identify survey households, a computer program randomly selected 800 addresses using study area water meter records (due to the high water table and brackish groundwater, all houses are served by piped water). To reduce bias, addresses were visited at least six times, including at least twice in the evening and/or weekends, before being classified as unoccupied. One participant from each occupied, selected household was then chosen using a random selection table. Children younger than 1 year of age were excluded from the study, as were persons with a history of a blistering reaction to a previous tuberculin skin test. To enhance precision for the proportions of specific risk factors in the HIV-infected population, self-identified HIV-infected community residents were also surveyed and skin tested (but not included in the population-based results).

A trained interviewer administered a standardized questionnaire to each participant in English, Spanish, or Haitian Creole. Demographic characteristics and bacillus Calmette-Guérin status were determined by patient self-report. Each participant received a TST with purified protein derivative (5 tuberculin units; Connaught Laboratories, Swiftwater, PA) injected intradermally. A single nurse trained in TST planting and reading administered and read all TSTs in the survey. LTBI was defined as a positive TST according to standard definitions, namely induration of greater than 10 mm when read at 48 to 72 hours, except for HIV-infected persons, for whom induration of greater than 5 mm was used. Subjects were tested for antibody to HIV using ELISA and confirmed by Western blot (22).

### Surveillance for TB

Cases of active TB in the survey area were identified through active and passive case finding by the Palm Beach County Health Department. For patients with TB occurring between January 1, 1997 and December 31, 2001, in the survey area, demographic and risk factor data were collected using a standardized questionnaire. For patients with *M. tuberculosis* isolates, IS6110 restriction-fragment–length polymorphism (RFLP) analysis was performed using standardized methods (24). *M. tuberculosis* strains with fingerprints of five or fewer bands on RFLP were further analyzed using spoligotyping. These isolates were assigned to clusters only if their spoligotypes were identical and specific to the IS6110 fingerprint. Cases of TB that were clinically diagnosed or cases whose isolates were lost had cluster status assigned in proportion to those from the same population group that had isolates available for RFLP analysis.

### Calculation of Rates of Reactivation TB

Rates of reactivation TB (in person-years of follow-up) were calculated by dividing the number of unclustered cases of TB in the group of interest by the number of TST-positive persons in that group, multiplied by 5 years. Subgroup population sizes were obtained from census data or were calculated by multiplying subgroup prevalence in the population-based survey by the overall population size. Confidence intervals were calculated according to Wilson's method using SISA (http://home.clara.net/sisa/). Rate ratios were calculated using EpiSheet (http://www.epidemiolog.net/studymat/). The population with a positive TST at risk for reactivation TB was calculated by multiplying the number of persons with a positive TST times the fraction of those in the population-based survey who had not received and completed a course of INH. Reactivation rates were calculated both by the "n" method, in which all unclustered cases of TB are used in the numerator, and the "n-1" method, in which the first chronologic case in each cluster is also assumed to be a case of reactivation and is added to the unclustered cases to use as the numerator.

## RESULTS

### Skin Test Survey

Of the 800 addresses selected for the survey, 191 addresses could not be used to select participants because they were businesses, vacant lots, or unoccupied. For randomly selected residents at the 609 remaining addresses, 447 (73%) were enrolled and analyzed in the cross-sectional study. Sixty-nine (11%) completed only the questionnaire, 92 (15%) declined to participate, and 1 (0.2%) was ineligible because of a history of a blistering reaction on prior TST. Of the 447 randomly selected community participants, 135 (30%) had LTBI as determined by TST; of these, 45 (33%) had previously been found to have a positive TST and had begun a course of INH. Fifteen of the 45 persons beginning INH reported that they had completed at least 6 months of treatment.

### Cases of TB

Between 1997 and 2001, 80 cases of TB were diagnosed in the survey area. *M. tuberculosis* isolates were obtained in 72 cases, whereas in 8 cases the diagnosis of TB was made on clinical grounds (without microbiologic confirmation). This translates to an incidence rate of 46 cases per 100,000 inhabitants per year. Of the 72 culture-confirmed cases of TB disease, 48 (67%) had isolates available for analysis (24 isolates were unable to be recovered from storage). Cases with missing isolates were similar to cases with available isolates in terms of demographic characteristics and risk factor variables. The 48 isolates showed 25 different IS*6110* band patterns. Thirty-two isolates (67%) were found to have seven cluster patterns, whereas 16 isolates (33%) were found in one patient each (unique pattern isolates). Four of the seven clusters had their first isolate in 1997, whereas the other three had the first isolate in 1998. Thus, for the n method of analysis there were 16 unclustered isolates, whereas for the n-1 analysis there were 23 unclustered isolates.

### Rates of Reactivation TB

The overall rate of reactivation TB among persons with LTBI using the n method was 0.070 cases per 100 person-years (95% CI, 0.048–0.10), whereas the rate among persons without HIV

**TABLE 1. RATES OF REACTIVATION TUBERCULOSIS BY POPULATION GROUP**

| Characteristic | Number of Cases Not Clustered* | Positive Skin Test Rate in Population† | No. of Persons in Population | No. of Persons With LTBI | Person-Years of Observation‡ | Reactivation TB Rate (Per 100 Person-Years) | Relative Risk (95% CI) | *P* Value |
|---|---|---|---|---|---|---|---|---|
| Male | 24 | 0.293 (0.242–0.345) | 18,418 | 4,906 | 24,529 | 0.098 (0.066–0.15) | 4.4 (1.3–15) | 0.016 |
| Female | 3 | 0.181 (0.145–0.222) | 16,341 | 2,689 | 13,444 | 0.022 (0.008–0.066) | | |
| Black | 24 | 0.288 (0.244–0.336) | 20,821 | 5,451 | 27,257 | 0.088 (0.059–0.13) | 3.4 (1.0–11) | 0.049 |
| Non-Black | 3 | 0.180 (0.136–0.232) | 13,938 | 2,281 | 11,404 | 0.026 (0.009–0.077) | | |
| Age >50 yr | 16 | 0.412 (0.332–0.498) | 7,162 | 2,684 | 13,422 | 0.12 (0.073–0.19) | 2.7 (1.3–5.9) | 0.01 |
| Age ⩽50 yr | 11 | 0.202 (0.166–0.242) | 27,597 | 5,063 | 25,314 | 0.043 (0.024–0.078) | | |
| U.S.-born | 13 | 0.137 (0.107–0.173) | 24,081 | 2,999 | 14,995 | 0.087 (0.051–0.15) | 1.5 (0.70–3.1) | 0.33 |
| Foreign-born | 14 | 0.490 (0.415–0.565) | 10,678 | 4,756 | 23,783 | 0.059 (0.035–0.099) | | |
| HIV-infected | 12 | 0.250 (0.176–0.341) | 466 | 106 | 530 | 2.3 (1.3–3.9) | 57 (27–120) | <0.001 |
| HIV-uninfected | 15 | 0.242 (0.209–0.277) | 34,293 | 7,544 | 37,722 | 0.040 (0.023–0.066) | | |
| Total | 27 | 0.245 (0.212–0.281) | 34,759 | 7,742 | 38,709 | 0.070 (0.048–0.10) | | |

*Definition of abbreviations*: CI = confidence interval; LTBI = latent TB infection; TB = tuberculosis.

Rates were calculated by dividing the number of nonclustered TB cases among persons in each group by the number of person-years of follow-up of persons with a positive tuberculin skin test in that group.

* Observed plus imputed, as described in METHODS.

† Adjusted for age and birthplace.

‡ Number of persons with LTBI times 0.89 (adjustment for previous LTBI treatment) times 5 yr.

infection was 0.040 cases per 100 person-years (95% CI, 0.023–0.066). Using the n-1 method, the corresponding rates were 0.099 cases per 100 person-years (95% CI, 0.072–0.14) and 0.058 cases per 100 person-years (95% CI, 0.038–0.089).

Using the n method, HIV infection was the strongest risk factor for reactivation (rate ratio [RR], 57; 95% CI, 26–120; $P < 0.001$; Table 1). This RR was only minimally changed when calculated using the n-1 method (data not shown). Significantly increased rates of reactivation were also seen among male compared with female subjects and among those older than 50 years of age compared with those less than or equal to 50 years of age. Because HIV is a strong promoter of reactivation TB among persons with LTBI and confounding by HIV could have explained the differences seen by race and age in the analysis in Table 1, we stratified the analysis of rates of reactivation TB by HIV status. The results in the HIV-uninfected strata (again using the n method) are shown in Table 2. These results show significantly increased rates of reactivation among persons older than 50 years of age compared with persons less than or equal to 50 years old (RR, 3.8; 95% CI, 1.3–11; $P = 0.015$) and among U.S.-born persons when compared with foreign-born persons (RR, 3.2; 95% CI, 1.1–9.3; $P = 0.035$). RRs were also elevated among men compared with women and among Blacks compared with whites, but these differences were not statistically significant.

## DISCUSSION

This study indicates that reactivation TB disease occurs substantially less frequently in this area among persons with LTBI without HIV than it did in the United States in the decade leading up to 1960. In four cohort studies, all performed before 1960, reactivation TB was observed to occur among persons with LTBI at rates of 0.10 to 0.16 per 100 person-years (11–14). In contrast, our results show that the overall rate of reactivation TB among similarly HIV-uninfected persons with LTBI was 0.040 to 0.058 cases per 100 person-years. Because four of our seven clusters had their first case in 1997, the initial year of our surveillance, it is likely that some of these cases were not the initial case in the cluster, and therefore the true rate of reactivation likely lies between the rates of 0.040 and 0.058.

Although some of this decrease could be attributed to misclassification of reinfection in the earlier studies (when molecular typing was not available), we believe that the most likely explanation is the decreased prevalence of old, untreated but spontaneously healed TB in the population of the United States now compared with the period 1950 to 1960. Old, healed TB increases the risk of reactivation by more than fivefold (11, 17), so that increased prevalence of this risk factor would result in increased overall rates of reactivation TB. Because effective chemotherapy for TB became available only in 1948 and TB

**TABLE 2. RATES OF REACTIVATION TUBERCULOSIS, BY POPULATION GROUP, AMONG HIV-UNINFECTED PERSONS ONLY**

| Characteristic | Number of Cases Not Clustered* | Positive Skin Test Rate in Population† | No. of Persons in Population | No. of Persons with LTBI | Person-Years of Observation‡ | Reactivation TB Rate (Per 100 Person-Years) | Relative Risk (95% CI) | *P* Value |
|---|---|---|---|---|---|---|---|---|
| Male | 13 | 0.293 (0.242–0.345) | 18,190 | 4,841 | 24,209 | 0.054 (0.031–0.092) | 3.6 (0.80–16) | 0.095 |
| Female | 2 | 0.181 (0.145–0.222) | 16,103 | 2,647 | 13,236 | 0.011 (0.004–0.055) | | |
| Black | 13 | 0.288 (0.244–0.336) | 20,403 | 5,352 | 26,759 | 0.049 (0.028–0.083) | 2.7 (0.62–12) | 0.18 |
| Non-Black | 2 | 0.180 (0.136–0.232) | 13,890 | 2,274 | 11,268 | 0.018 (0.005–0.065) | | |
| Age >50 | 10 | 0.412 (0.332–0.498) | 7,031 | 2,644 | 13,218 | 0.076 (0.041–0.14) | 3.8 (1.3–11) | 0.015 |
| Age ⩽50 | 5 | 0.202 (0.166–0.242) | 27,262 | 5,000 | 25,000 | 0.020 (0.009–0.047) | | |
| U.S.-born | 10 | 0.137 (0.107–0.173) | 23,735 | 2,952 | 14,759 | 0.068 (0.037–0.13) | 3.2 (1.1–9.3) | 0.035 |
| Foreign-born | 5 | 0.490 (0.415–0.565) | 10,557 | 4,697 | 23,486 | 0.021 (0.009–0.050) | | |

For definition of abbreviations, *see* Table 1.

Rates were calculated by dividing the number of nonclustered TB cases among persons in each group by the number of person-years of follow-up of persons with a positive tuberculin skin test in that group.

* Observed plus imputed, as described in Methods.

† Adjusted for age and birthplace.

‡ Number of persons with LTBI times 0.89 (adjustment for previous LTBI treatment) times 5 yr.

disease can self-cure in 30 to 80% of cases (25, 26), there were many cases of old healed TB in the TST-positive population that was studied between 1950 and 1960 (13). In contrast, the present study was performed after a period of 50 years of effective TB chemotherapy. Thus, it is likely that there were few persons in the current study sample of persons with LTBI who had old healed but untreated TB; a recent national survey showed that only 1.4% of persons with LTBI in the United States and Canada have old healed TB (27). Although molecular tools to accurately differentiate primary from reactivation TB were not available in 1964, Grzybowski and Allen noted that among cases of presumed reactivation TB in their study, 46% were seen in persons known to have previously had old, healed, but untreated disease (13). If such persons are indeed no longer in the population of persons with LTBI today, the rate of reactivation TB might be expected to have declined by 46%, a decline consistent with our findings.

Indeed, Gryzbowski and Allen provided an estimate of the rate of reactivation TB among persons without old untreated disease, and calculated it to be 675 cases of TB among 1,180,000 persons with a positive TST but no old healed disease, a rate of 0.057 per 100 person-years (95% CI, 0.053–0.062) (13). Similarly, a 1950 to 1970 study of the rate of reactivation TB in the placebo arm of a bacillus Calmette-Guérin vaccine trial that excluded persons with untreated, healed TB disease revealed a rate of 0.066 per 100 person-years (95% CI, 0.055–0.080) (28), whereas in a 1949 to 1969 study, reactivation TB among children with LTBI (who rarely have old healed disease) was found to occur at a rate of 0.067 per 100 person-years (95% CI, 0.056–0.081) (29).

The results of the current study also confirm the increased risk for reactivation TB disease among HIV-infected persons. Previous studies of reactivation TB among HIV-infected persons with LTBI have reported relative risks of 9.5 and 9.9 (3). In contrast, this study identified a relative risk of 57. Although the CIs around this estimate are large, it is still substantially greater than those previously reported. One possible explanation for this difference could be the degree of immunosuppression among the HIV-infected persons in the current study. CD4 counts were not reported for subjects in the previous studies, but the median CD4 count of HIV-infected persons in this study was 290, indicating that the HIV-infected population had moderately advanced HIV disease. This may explain the higher relative risk.

After stratification to control for the effect of HIV, increased rates of reactivation TB were also seen among persons older than 50 years of age. Increased rates of reactivation TB among older persons have been suggested by decreased rates of clustering among older persons (5, 6), but such results lack denominators and could be the result of increased primary transmission among younger persons, rather than increased rates of reactivation among older persons. Cohort studies in nursing homes have also suggested increased rates of reactivation TB among older persons with LTBI, but lack a comparison group of younger persons with LTBI (30, 31). In contrast, our study clearly demonstrates an increase in reactivation among older persons with LTBI compared with younger persons with LTBI. Waning immunity with age has been suggested as a potential biologic mechanism for such an increase (18), but studies seeking to demonstrate direct evidence of waning of antituberculosis immunity with age have been unable to do so (32, 33).

Additionally, decreased rates of reactivation TB were seen among persons with LTBI born outside the United States when compared with persons born in the United States. These results confirm the observation that foreign-born persons with LTBI do not have increased rates of reactivation TB compared with U.S.-born persons with LTBI (34), and support the conclusion that persons born outside the United States have increased overall risk for reactivation TB only because LTBI is more common in such persons, and not because they have a higher rate of reactivation, given infection. Moreover, we conclude that neither recent infection with isolates from outside the study area nor old, untreated disease were common among the foreign-born persons in the current survey, as these would have increased the rate of (apparent or real) reactivation compared with U.S.-born persons. Last, the rate of reactivation was substantially greater among men than among women. This difference was not statistically significant, but the power to detect a difference was small. This finding may partially explain the higher rates in TB seen among men compared with women (2), but no previous studies have examined rates of reactivation in men with LTBI compared with women with LTBI.

This study has several limitations. First, although case finding was actively pursued during the study period and few cases of TB were likely to have been missed, the number of TB cases in many of the subgroups is small. Thus the estimates of rates and rate ratios are imprecise. Second, the cluster analysis lacked one-third of the cases. Although this introduces a degree of uncertainty into our conclusions, incomplete cluster analysis would be expected to lead to failure to identify some clusters, and thus underestimation, rather than overestimation, of clusters. Thus, the rates of reactivation that were obtained may be overestimates (35, 36). Similarly, if the clinical cases were not TB but some other condition, the TB rates would also be overestimates. Third, in- or out-migration could have led to misclassification of recently acquired infection as reactivation. We believe this is unlikely because the community studied is geographically isolated and has not experienced substantial in- or out-migration; 72% of the foreign-born persons in the study population had been in the United States longer than 5 years. Moreover, such misclassification would also have resulted in overestimation, rather than underestimation, of the reactivation rate. Fourth, some small clusters could represent simultaneous reactivation, and thus cases could have been misclassified as having been the result of recent transmission. However, we believe that such an occurrence was rare. Finally, failure to participate in the population-based study could have introduced bias. However, the participation rate that was achieved (85%) is relatively high and comparable to that achieved in population-based surveys of other uncommon infections (37, 38).

The community in which these rates were observed differs from other parts of the United States with regard to some characteristics that limit the generalizability of these results, such as the prevalence of HIV infection and incidence of TB disease. However, stratification by HIV status removes some of the effect of these two factors. Another difference is the historically higher prevalence of skin test reactivity to nontuberculous mycobacteria in the southeastern United States. Such reactivity could have led to overestimation of the prevalence of LTBI when persons with a positive nontuberculous reaction that cross-reacted with the TST were misclassified as having LTBI. We measured this misclassification and found it to be less than 15% (39). To the extent that this occurred, our rates are underestimates. We have not corrected our calculations for such misclassification because earlier studies also did not correct for this, and many were performed largely or exclusively in the Southeast (11, 28, 29).

We conclude that the rates of reactivation TB today in the HIV-uninfected population in this area are significantly lower than U.S. rates measured 50 years ago, but similar to the older

rates when the effect of old healed disease is removed. This similarity suggests that the rate of reactivation TB among persons with LTBI is largely a function of the immune status of the host. Therefore, the rates of reactivation TB among persons with LTBI observed in this study may be applicable to the population of the United States as a whole. It is important to determine if this is the case, because cost-effectiveness studies using the older rates have indicated that LTBI treatment is generally beneficial in all persons with LTBI (40–43). A lower rate of reactivation among persons with LTBI would call into question the cost-effectiveness of LTBI treatment among persons with LTBI who do not have risk factors for increased rates of reactivation, such as HIV infection, old healed disease, or exogenous immunosuppression.

***Author Disclosure:*** C.R.H. received $1,001–$5,000 from Otsuka Pharmaceuticals for serving on an advisory board and up to $1,000 from the American Society for Microbiology in royalties. M.O.D. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.L.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.J. is deceased and is unable to provide a financial disclosure statement. B.J.M. received $1,001–$5,000 from Merck, $1,001–$5,000 from GlaxoSmithKline, $1,001–$5,000 from Tibotec, and $1,001–$5,000 from Gilead in advisory board fees. M.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. L.S.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.F.V.R. received $10,001–$50,000 from Oxford Immunotec in industry-sponsored grants.

***Acknowledgment***: The authors thank the members of the Glades Health Initiative staff, Mr. Denny Abbott, Dr. Tedd Ellerbrock, Dr. Robert Trenschel, and Dr. Vikas Virkud for assistance with and support for the survey, and Maria Pedrosa for molecular analysis of isolates.

## References

1. Pratt R, Robison V, Navin T. Trends in Tuberculosis – United States, 2006. *MMWR Morb Mortal Wkly Rep* 2007;56:245–250.
2. Horsburgh CR, Moore M, Castro KG. Epidemiology of tuberculosis in the United States. In: Rom WN, Garay SM, editors. Tuberculosis, 2nd ed. Philadelphia PA: Lippincott Williams and Wilkins; 2004. pp. 31–45.
3. Horsburgh CR. Prioritizing treatment of latent tuberculosis infection in the United States. *N Engl J Med* 2004;350:260–267.
4. American Thoracic Society, Centers for Disease Control and Prevention, Infectious Disease Society of America. Controlling tuberculosis in the United States. *Am J Respir Crit Care Med* 2005;172:1169–1227.
5. Small PM, Hopewell PC, Singh SP, Paz A, Parsonnet J, Ruston DC, Schecter GF, Daley CL, Schoolnik GK. The epidemiology of tuberculosis in San Francisco. A population-based study using conventional and molecular methods. *N Engl J Med* 1994;330:1703–1709.
6. Geng E, Kreiswirth B, Driver C, Li J, Burzynski J, DellaLatta P, LaPaz A, Schluger NW. Changes in the transmission of tuberculosis in New York City from 1990 to 1999. *N Engl J Med* 2002;346:1453–1458.
7. Sharnprapai S, Miller AC, Suruki R, Corkren E, Etkind S, Driscoll J, McGarry M, Nardell E. Genotyping analyses of tuberculosis cases in US- and foreign-born Massachusetts residents. *Emerg Infect Dis* 2002; 8:1239–1245.
8. US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Prevention Services, Division of Tuberculosis Control. A strategic plan for the elimination of tuberculosis in the United States. *MMWR Morb Mortal Wkly Rep* 1989;38:269–272.
9. US Department of Health and Human Services, Centers for Disease Control and Prevention. Tuberculosis elimination revisited: obstacles, opportunities, and a renewed commitment. Advisory Council for the Elimination of Tuberculosis (ACET). *MMWR Recomm Rep* 1999;48: 1–13.
10. Institute of Medicine. Ending neglect: the elimination of tuberculosis in the United States. Geiter L, editor. Washington DC: National Academy Press; 2000.
11. Ferebee SH, Mount FW, Murray FJ, Livesay VT. A controlled trial of isoniazid prophylaxis in mental institutions. *Am Rev Respir Dis* 1963; 88:161–175.
12. Palmer CE, Jablon S, Edwards PQ. Tuberculosis morbidity of young men in relation to tuberculin sensitivity and body build. *Am Rev Tuberc* 1957;76:517–539.
13. Grzybowski S, Allen EA. The challenge of tuberculosis in decline. *Am Rev Respir Dis* 1964;90:707–720.
14. Edwards LB, Livesay VT, Acquaviva FA, Palmer CE. Height, weight, tuberculous infection, and tuberculous disease. *Arch Environ Health* 1971;22:106–112.
15. Moss AR, Hahn JA, Tulsky JP, Daley CL, Small PM, Hopewell PC. Tuberculosis in the homeless. A prospective study. *Am J Respir Crit Care Med* 2000;162:460–464.
16. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, Walker AT, Friedland GH. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med* 1989;320:545–550.
17. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc* 1970;26:28–106.
18. Stead WW, Lofgren JP. Does the risk of tuberculosis increase in old age? *J Infect Dis* 1983;147:951–955.
19. Sterling TR, Bethel J, Goldberg S, Weinfurter P, Yun L, Horsburgh CR. TBESC. The scope and impact of treatment of latent tuberculosis infection in the United States and Canada. *Am J Respir Crit Care Med* 2006;173:927–931.
20. Horsburgh R, O'Donnell M, Chamblee S, Moreland JL, Johnson J, Marsh B, Narita M, Pedrosa M, Johnson LS, von Reyn CF. Population-based assessment of the rate of reactivation tuberculosis in a Southeastern US community [abstract]. *Am J Respir Crit Care Med* 2009;179:A2200.
21. Stratford D, Chamblee S, Ellerbrock TV, Johnson RJ, Abbott D, Reyn CF, Horsburgh CR. Integration of a participatory research strategy into a rural health survey. *J Gen Intern Med* 2003;18:586–588.
22. Ellerbrock TV, Chamblee S, Bush TJ, Johnson JW, Marsh BJ, Lowell P, Trenschel RJ, Von Reyn CF, Johnson LS, Horsburgh CR Jr. Human immunodeficiency virus infection in a rural community in the United States. *Am J Epidemiol* 2004;160:582–588.
23. Reed C, von Reyn CF, Chamblee S, Ellerbrock TV, Johnson JW, Marsh BJ, Johnson LS, Trenschel RJ, Horsburgh CR Jr. Environmental risk factors for infection with Mycobacterium avium complex. *Am J Epidemiol* 2006;164:32–40.
24. Van Soolingen D. Molecular epidemiology of tuberculosis and other mycobacterial infections: main methodologies and achievements. *J Intern Med* 2001;249:1–26.
25. Mitchell RM. Mortality and relapse of uncomplicated advanced pulmonary tuberculosis before chemotherapy: 1,504 consecutive admissions followed for fifteen to twenty-five years. *Am Rev Tuberc* 1955;72:487–501.
26. Alling DW, Bosworth EB. The after-history of pulmonary tuberculosis. VI. The first fifteen years following diagnosis. *Am Rev Respir Dis* 1960;81:839–849.
27. Horsburgh CR, Goldberg S, Bethel J, Chen S, Colson PW, Hirsch-Moverman Y, Hughes S, Shrestha-Kuwahara R, Sterling TR, Wall K, Weinfurter P; Tuberculosis Epidemiologic Studies Consortium. Latent tuberculosis infection treatment acceptance and completion in 2002 in the United States and Canada. *Chest* 2010;137:401–409.
28. Comstock GW, Woolpert SF, Livesay VT. Tuberculosis studies in Muscogee County, Georgia. Twenty year evalution of a community trial of BCG vaccination. *Public Health Rep* 1976;91:276–280.
29. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 1974;99:131–138.
30. Stead WW, Lofgren JP, Warren E, Thomas C. Tuberculosis as an endemic and nosocomial infection among the elderly in nursing homes. *N Engl J Med* 1985;312:1483–1487.
31. Stead WW, To T. The significance of the tuberculin skin test in elderly persons. *Ann Intern Med* 1987;107:837–842.
32. Battershill JH. Cutaneous testing in the elderly patient with tuberculosis. *Chest* 1980;77:188–189.
33. Palitz LS, Aronsohn MH. Tuberculin sensitivity in the aged. *Am Rev Respir Dis* 1957;75:461–468.
34. Patel S, Parsyan AE, Gunn J, Barry MA, Reed C, Sharnprapai S, Horsburgh CR Jr. Risk of progression to active tuberculosis among foreign-born persons with latent tuberculosis. *Chest* 2007;131:1811–1816.
35. Murray M. Sampling bias in the molecular epidemiology of tuberculosis. *Emerg Infect Dis* 2002;8:363–369.

36. Glynn JR, Bauer J, de Boer AS, Borgdorff MW, Fine PEM, Godfrey-Faussett P, Vynnycky E. Interpreting DNA fingerprint clusters of *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis* 1999;3:1055–1060.
37. McQuillan GM, Ezzati-Rice TM, Siller AB, Visscher W, Hurley P. Risk behavior and correlates of risk for HIV infection in the Dallas County Household HIV survey. *Am J Public Health* 1994;84: 747–753.
38. McQuillan GM, Khare M, Karon JM, Schable CA, Vlahov D. Update on the seroepidemiology of human immunodeficiency virus in the United States household population: NHANES III, 1988–1994. *J Acquir Immune Defic Syndr* 1997;14:355–360.
39. Horsburgh CR, Chamblee S, Ellerbrock TE, Johnson JW, Marsh B, Johnson LS, von Reyn CF. Dual skin testing to assess misclassification of latent tuberculosis infection among foreign-born persons in the United States (abstract). *Proc Am Thorac Soc* 2006;3:A505.
40. Rose DN, Schecter CB, Fahs MC, Sulver AL. Tuberculosis prevention: cost-effectiveness of isoniazid chemoprophylaxis. *Am J Prev Med* 1988;4:102–109.
41. Salpeter SR, Sanders GD, Salpeter EE, Owens DK. Monitored isoniazid prophylaxis for low-risk tuberculin reactors older than 35 years of age: a risk-benefit and cost-effectiveness analysis. *Ann Intern Med* 1997; 127:1051–1061.
42. Taylor Z. The cost-effectiveness of screening for latent tuberculosis infection. *Int J Tuberc Lung Dis* 2000;4:S127–S133.
43. Rose DN. Benefits of screening for latent *Mycobacterium tuberculosis* infection. *Arch Intern Med* 2000;160:1513–1521.