Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Lisa Sharling Date

RIFAMYCIN-RESISTANT TUBERCULOSIS IN THE UNITED STATES, 1998–2008; an Analysis of the National Tuberculosis Surveillance System

By

Lisa Sharling

Master of Public Health

Global Epidemiology

_____

Michael Goodman, MD, MPH

Committee Chair

_____

Sundari Mase, MD, MPH

Committee Member

RIFAMYCIN-RESISTANT TUBERCULOSIS IN THE UNITED STATES, 1998–2008; an Analysis of the National Tuberculosis Surveillance System

By

Lisa Sharling

MBiochem., Bath University, 2000

PhD, Edinburgh University, 2005

Thesis Committee Chair: Michael Goodman, MD, MPH

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Global Epidemiology

2011

Abstract

RIFAMYCIN-RESISTANT TUBERCULOSIS IN THE UNITED STATES, 1998–2008; an Analysis of the National Tuberculosis Surveillance System

By Lisa Sharling

Background: Tuberculosis (TB) incidence rates in the United States have declined since 1993; however drug resistance and HIV co-infection have slowed this decline over the past decade. *Mycobacterium tuberculosis* bacteria resistant to the first line rifamycin (RIF) drugs pose significant challenges to TB control. RIF resistance results in fewer and more expensive treatment options, prolonged duration of treatment and poor treatment outcomes. Through analysis of the National TB Surveillance System (NTSS) this study examines the demographic and clinical characteristics associated with RIF-resistant TB.

Methods: Two definitions of RIF resistance were considered; (1) cases reported at the initial drug susceptibility test to be infected with rifampin (RMP)-monoresistant (RMR) *M. tuberculosis* and (2) possible acquired RIF resistance. Polytomomous logistic regression was used to examine the associations between RIF resistance and a number of social, clinical and treatment outcome variables with particular focus on the two main exposures of interest - HIV co-infection and prior TB diagnosis. Confounding and interactions were assessed using multiple logistic regression. The proportions of drug-resistant cases before and after the year 2002 were compared using a two-sample t-test. The time until culture conversion from a positive to a negative culture was compared for RIF-resistant TB cases and drug-susceptible controls using a Wilcoxon test.

Results: All forms of RIF resistance examined were positively associated with HIV co-infection and this association was strongest for possible acquired RIF-monoresistance (prevalence odds ratio [POR], 31.82; 95% confidence interval [CI], 14.76-68.69). RMR cases were more likely to have HIV infection (POR, 3.46; CI, 2.65-4.52) or a prior diagnosis of TB (POR, 3.50; CI, 2.61-4.71). Among RMR-TB cases with a previous TB diagnosis the magnitude of the association with HIV co-infection was larger (POR, 6.88; CI, 3.50, 13.52). Patients with RIF resistance took longer to culture convert and were more likely to die during TB treatment.

Conclusions: This is the first report of the epidemiology of RIF-resistant TB on the national level for the United States. Our findings should aid in supporting recommendations for the case management of HIV co-infected patients. This study highlights the significant burden of RIF resistance on the patient and on local TB control programs.

RIFAMYCIN-RESISTANT TUBERCULOSIS IN THE UNITED STATES, 1998–2008; an Analysis of the National Tuberculosis Surveillance System

By

Lisa Sharling

MBiochem, Bath University, 2000

PhD, Edinburgh University, 2005

Thesis Committee Chair: Michael Goodman, MD, MPH

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Global Epidemiology

2011

ACKNOWLEDGEMENT

I would like to thank Dr Sundari Mase at the CDC's Division of Tuberculosis Elimination for giving me the opportunity to become part of her research team and delve into the field of tuberculosis epidemiology. Despite spending a relatively short period of time with her research group, due to Dr Mase's encouragement and support to attend national and international conferences I have also gained exposure to national, state and local tuberculosis control programs. Furthermore, I feel lucky to have had the opportunity to learn from Dr Mase's example of successfully juggling many responsibilities and roles while motivating and managing a diverse range of research.

In addition I would like to thanks all the staff within the Division of Tuberculosis Elimination for sharing their collective experience and wealth of knowledge during the challenging process of selecting the most appropriate case definitions.

Finally, I thank my academic advisor Dr Michael Goodman for always being available with a cool, calm disposition and the appropriate, concisely delivered advice that was necessary and sufficient to keep me focused and on track during the preparation of this thesis.

CONTENTS

INTRODUCTION

Tuberculosis (TB) remains a major infectious cause of death globally. In 2008 there were an estimated 9.4 million new cases of TB disease and 1.8 million deaths due to TB [1]. Although there are indications that the global incidence rate of TB may be reaching a plateau the human immunodeficiency virus (HIV) epidemic has fuelled explosive increases in TB incidence in many parts of the world [2]. Drug-resistant TB also poses significant challenges to TB control programs both in terms of clinical management and infection control [3-7]. The HIV epidemic, drug resistant-TB and particularly their convergence threaten TB control globally [8].

In 2008 the United States reported 12,898 incident cases of TB, the lowest rate (4.2 cases per 100, 000) since national reporting began in 1953 [9]. TB incidence rates have continued to decrease in the United States since 1993, however this decline has slowed over the past decade. Drug resistance and HIV co-infection, acquired both within the United States and through immigration, pose significant barriers to the Centers' for Disease Control and Prevention (CDC) goal of TB elimination [10, 11].

The drugs rifampin (RMP) and izoniazid (INH) are critical first line drugs for treating TB [12]. Treatment of TB disease generally requires the four drugs RMP, INH, pyrazinamide (PZA), and ethambutol (EMB) be taken for two months, followed by an additional four months of INH and RMP. However, the joint American Thoracic Society (ATS), CDC and Infectious Diseases Society of America (IDSA) TB treatment guidelines recommend a number of alternative treatment regimens depending on the presence of certain additional factors such as HIV co-infection and drug resistance [13].

RMP is exceptionally effective against *Mycobacterium tuberculosis* with valuable bactericidal activity against the dormant stage of infection and is the principal rifamycin (RIF) used worldwide [12]. The inclusion of RMP along with PZA in multi-drug treatment regimens has allowed for a significant reduction in the duration of therapy from 18 months to 6 months. The consequences of RIF resistance are significant and include fewer and more expensive treatment options, prolonged duration of treatment and poor treatment outcomes [7].

Several studies have reported relatively low rates of RIF-resistant TB (in the absence of INH resistance) with a range of 0.3%-0.4% in the United States [14-16]. Interestingly RIF resistance is less common than the concomitant resistance to both RIF and INH (multi-drug-resistant TB (MDR-TB)), which was estimated to be 1.0% [17]. Despite the low rate of RIF-resistant TB it is characterized by having a disproportionate burden among patients co-infected with HIV [18-20]. Previous studies have estimated the rate to be about seven times higher among persons co-infected with HIV compared to HIV negative TB cases [21].

This study is part of the CDC's Tuberculosis Epidemiologic Studies Consortium (TBESC) Task Order 21 entitled "Acquired Rifamycin Resistance in Tuberculosis in the United States." The three broad primary objectives of Task Order 21 are 1) to describe the epidemiology of RIF-resistant TB, 2) to ascertain whether treatment recommendations pertaining to acquired RIF-resistant TB among HIV co-infected patients released by the CDC in 2002 [18, 22] are implemented by medical practitioners, and 3) to identify risk factors for RIF-resistant TB.

The epidemiology of RIF-resistant TB using the National TB Surveillance System (NTSS) has not been studied previously. Given the low rate of RIF-resistant TB this national dataset is of particular value because it provides a large and representative sample. The NTSS captures demographic and clinical patient information such as drug susceptibility testing for an estimated 98% of TB cases (50 states and the District of Columbia).

The first objective of this study is to compare the rate of RIF-resistant TB for the 5 years before and after the release of the CDC treatment guidelines for HIV co-infected patients [22] to ascertain whether there was a reduction in the rate of RIF resistance following the release of the guideline. Previous studies have used the NTSS dataset to examine the demographic and clinical characteristics associated with different drug resistance profiles, such INH monoresistance [23] and primary and acquired extensively drug-resistant TB [24]. Interestingly, the study of INH-monoresistant TB trends in the United States (1993-2003) highlighted that, despite national downward trends in both total TB cases and MDR-TB cases, the number of INH-monoresistant TB cases remained relatively constant [23]. It is not known whether the overall rate of RIF-resistant TB has mirrored that of INH-monoresistance or that of MDR-TB.

The second objective of this study is to determine which demographic and clinical characteristics are associated with RIF-resistant TB. Several studies published since the late 1990s, and summarized in Table 1, have examined factors associated with acquired-RIF resistance and concurrent treatment failure and relapse (primarily among patients co-infected with HIV). Highly intermittent RIF-based treatment regimens and a low CD4 count (defined as $<100/mm^3$) have been consistently associated with acquired-RIF

resistance [18-20, 25-32]. There is also some evidence to suggest that HIV infection may contribute to the prevalence of multidrug-resistant TB (MDR-TB) [33]. For this reason, HIV infection will be the primary exposure of interest in the current analysis of the NTSS dataset.

METHODS

Study population

The study population included all TB cases reported through the Report of Verified Case of Tuberculosis (RVCT) form (Appendix A) to the CDC between 1998 and 2008 by the 50 states and the District of Columbia. The NTSS dataset analyzed in this study was finalized in May 2009. All analyses were performed using SAS V9.2 for Windows (SAS Institute, Inc., Cary, NC) statistical software. This study of the NTSS dataset was reviewed by the CDC and approved as a public health surveillance activity, which is exempt from human subjects review and does not require informed consent. An IRB exemption letter from Emory University is included as Appendix B. An Assurance of Confidentiality for non-CDC employees was signed prior to accessing the NTSS (Appendix C).

Univariate Analysis of RIF-monoresistance at Initial Drug Susceptibility Testing

Eligible cases were culture positive, reported to have had an initial drug susceptibility test (DST) performed on their isolate and had an initial DST result for RMP, INH and EMB. Only the drug susceptibility pattern at the initial DST report was considered in defining the initial drug resistance status. 76% of cases reported via the RVCT form were eligible (Figure 2).

A RMR-TB case was defined as a person for whom an initial DST result was reported as resistant to RMP, susceptible to INH and EMB, with no resistance to PZA. No documented resistance to PZA as opposed to documented susceptibility was used in the definition of RMR-TB as 70 (19%) of eligible RMR-TB cases lacked an initial DST

result for PZA. We identified 91 cases that were resistant to the rifamycin rifabutin but susceptible to RMP. We choose to exclude rifabutin-resistant, RMP-susceptible cases due to suspected lab errors. Resistance to one of these members of the RIF class of drugs usually confers resistance to the other and no reports of rifabutin resistance and concurrent RMP susceptibility were found in the literature [34-38].

Previous studies have taken varied approaches to defining monoresistance to a particular drug. Studies have differed with respect to the inclusion criteria for documented resistance to other TB drugs [15, 19, 31, 39], in their definitions of MDR-TB by treating rifabutin and RPM as a class and also have including follow-up DST results [24]. To ensure that the findings of this study are not influenced by differences in case definition, we analyzed the relation of the same sociodemographic or clinical factors to IMR-TB and to MDR-TB. For a given association with RMR-TB knowing the strength and direction of the equivalent association for IMR-TB and MDR-TB was anticipated to aid in determining whether the association is similar to other forms of acquired drug resistance or is particular to RMR-TB.

An IMR-TB case was defined by resistance to INH, susceptibility to RMP and EMB, with no reported resistance to PZA. A MDR-TB case was defined by reported resistance to at least INH and RMP. A drug-susceptible TB case was defined as a person in whom the initial DST result was reported as susceptible to INH, RMP, and EMB, with no reported resistance to PZA. Cases with any other alternative drug resistance pattern were combined into a separate category.

Polytomous logistic regression was used to calculate prevalence odds ratios (PORs) and 95% confidence intervals (CIs) for the comparisons of RMR-TB, IMR-TB

and MDR-TB to drug-susceptible TB for a number of social, clinical and treatment outcome variables. A one-sided two-sample t-test was used to compare the proportion of drug-resistant cases before and after 2002. A one-sided Wilcoxon two-sample test was used to compare the time until culture conversion.

Multivariate Analysis for RMR-TB

The factors associated with RMR-TB were examined using multiple logistic regression models. Since the State of California does not report the HIV status of TB patients and HIV status at diagnosis was the primary exposure of interest, multivariate analyses excluded cases from California. A prior TB diagnosis and receipt of directly observed therapy (DOT) were considered as two additional exposure variables. HIV status was coded as a three-level categorical variable: HIV positive, unknown HIV status and HIV negative (referent category). A prior TB diagnosis was binary (yes versus no). Receipt of DOT was categorized as either totally self-administered, both DOT and self administered or totally DOT (referent category).

Age at TB diagnosis, gender and ethnicity were considered as control variables. Age was defined as $\leq$24 years old, 25-44 years old, 45-64 years old and $\geq$ 65 years (referent category). Ethnicity was defined as American Indian (non-Hispanic), Native Hawaiian (non-Hispanic), multiple ethnicities ((non-Hispanic) or unknown ethnicity), Hispanic, Asian (non-Hispanic), black (non-Hispanic), and white (referent category).

The initial model included all possible two-way interaction terms involving at least one of the three exposure variables (HIV status, prior TB diagnosis and receipt of DOT). Collinearity was assessed using the SAS collin macro which was developed by

the CDC and latter modified by Emory University's School of Public Health [40]. A condition index (CNI) of ≥20 with two or more variance decomposition proportions (VDPs) of approximately 0.5 (±0.05) was used to diagnose collinearity.

The interaction term involving the variables associated with the highest CNI above the cut-off were excluded and the resulting model reassessed using the SAS collin macro until all CNI values were <20. Three interaction terms involving DOT with ethnicity, DOT with age and HIV with age were excluded from the initial model during the assessment of collinearity. An interaction assessment for the resulting model, which included three exposure variables (HIV, previous TB diagnosis and DOT), three control variables (age, ethnicity and gender), and the nine remaining two-way interaction terms was performed. An initial likelihood ratio test comparing the model after collinearity assessment to a reduced model containing only the exposure and control variables was not significant, however each of the interaction terms was then assessed sequentially using a likelihood ratio test. The interaction term between HIV status at diagnosis and a prior diagnosis of TB was significant.

During confounding assessment for the three potential control variables (age, ethnicity and gender) gender was excluded from the model due to minimal confounding of the point estimates and having little impact on precision. The final logistic model included the variables HIV, previous TB diagnosis, the interaction term between HIV and previous TB diagnosis, DOT, age and ethnicity. The final model used 260 RMR-TB and 82494 drug-susceptible observations.

Univariate Analysis of Cases with Possible Acquired RIF-Resistant TB

Eligible cases were culture positive and reported to have had a DST performed on their initial and a follow-up isolate (Figure 3). A case of possible acquired RIF-resistant (ARR) TB was defined by an initial DST indicating RMP susceptibility and a final DST result reporting RMP resistance. Since the NTSS did not routinely collect *M. tuberculosis* genotyping information during the period covered by this study it is not possible to confirm whether a change from reported RMP susceptibility at initial DST to RMP resistance at final DST is the result of re-infection with a RMP-resistant TB strain following an initial infection with a drug susceptible TB strain (primary resistance) or the consequence of the *M. tuberculosis* strain 'acquiring' RMP resistance.

The incidence rates of TB and RIF resistance in the United States are very low and the likelihood of re-infection with a RIF-resistant TB strain following initial infection with a RIF-susceptible strain is also unlikely, however it cannot be ruled out. For this reason, cases of acquired RIF resistance are considered 'possible' to recognize the limitations of utilizing surveillance data to capture acquired drug-resistance. Furthermore, since there is increasing evidence that some of the risk factors for acquired RIF monoresistance (in the absence of INH resistance at initial DST) are distinct from those associated with acquired multi-drug resistance cases, cases of possible ARR-TB were further sub-classified according to presence of INH resistance at initial and final DST.

Figure 1 is a schematic that depicts the three classes of possible acquired RIF resistance with respect to INH resistance at initial and final DST. Polytomous logistic regression was used to calculate PORs and 95% CIs for the comparisons of possible

ARR-TB cases (and each of the 3 sub-classes) to cases that were RIF and INH susceptible at both initial and final DSTs. A number of the social, clinical and outcome variables captured by the NTSS were analyzed.

For the definition of RMR-TB the DST result at follow-up was not considered in order to ensure that RMR-TB cases were mutually exclusive from those captured by the definition of possible acquired RIF-resistant TB.

RESULTS

RIF-monoresistant TB at Initial Drug Susceptibility Testing

A total of 126,578 (76%) of 166,241 TB cases reported via the RVCT to the NTSS between 1998 and 2008 had sufficient initial drug susceptibility results to be eligible for inclusion (Figure 2). 365 (0.29%) of eligible cases were reported to be RMR at initial DST. The prevalence of RMR-TB was significantly lower than that of concomitant RMP and INH resistance (MDR-TB), which among eligible cases for this study was 1.2% (1476 cases). The proportion of all RMR-resistant cases that were not INH-resistant was 19.8% (excluding RMP-resistant cases captured by the alternative drug resistance category from the denominator). The prevalence of IMR-TB was 6.1% (7693 cases). The prevalence of cases infected with a *M. tuberculosis* strain with an alternative drug resistance pattern not captured by the RMR, IMR, MDR or drug-susceptible case definitions was 2.3% (2,939 cases). The remaining 114,167 (90.1%) cases were drug susceptible.

Figures 4-6 show the temporal trends in RMR-TB, IMR-TB and MDR-TB between 1998 and 2008. The proportion of RMR-TB cases fluctuated between 0.24%-

0.40% from 1998 to 2005, but it appears the proportion may have remained slightly lower between 2006 and 2008 (0.22%-0.24%) (Figure 4). There was not however a significant decrease in the prevalence of RMR-TB when the six years (2003-2008) after the release of the CDC treatment guidelines were compared to the previous five years (1998-2002) (p=0.68; Table 2).

Univariate analysis of RIF-monoresistant TB at initial DST

As shown in Table 3, RMR-TB cases were more likely to be of Hispanic ethnicity (POR, 1.66; 95% CI, 1.24-2.24) and less likely to be ≥64 years old (POR, 0.37; CI, 0.26-0.53). A positive association with Hispanic ethnicity and other non-Hispanic non-white ethnicities (compared to non-Hispanic whites) was apparent for IMR-TB and MDR-TB. An inverse association with older age, specifically with the age group ≥64 years at TB diagnosis, was also apparent for both IMR-TB (POR, 0.52; CI, 0.49-0.56) and MDR-TB (POR, 0.27; CI, 0.22-0.33).

Table 4 compares the clinical characteristics of drug-resistant TB cases to those of patients with drug-susceptible disease. Cases of RMR-TB (POR, 3.50; CI, 2.61-4.71), IMR-TB (POR, 1.45; 95% CI 1.32-1.59), and MDR-TB (POR, 4.43; 95% CI, 3.86-5.08) were all more likely to have had a prior diagnosis of TB. RMR-TB cases were also more likely to have been HIV positive (POR, 3.46; CI, 2.65-4.52); this association was less pronounced for MDR-TB cases (POR= 1.41; 95% CI, 1.19-1.67), whereas for IMR-TB cases no difference in HIV status was observed (POR =0.94; 95% CI, 0.86-1.03).

A comparison of treatment outcomes and DOT characteristics for drug-resistant TB cases versus patients with drug-susceptible disease is shown in Table 5. Although the

proportion of RMR-TB cases with reported culture conversion was not different from that of drug-susceptible TB cases (POR, 0.99; 95% CI, 0.71-1.37) there was a significant delay in culture conversion (from a *M. tuberculosis* positive culture to a negative culture; p<0.001). For RMR-TB cases, the median time until culture conversion was 63 days (interquartile range (IQR), 35-114 days) and for drug-susceptible cases 51 days (IQR, 28-81 days). The time until culture conversion was also significantly longer for MDR-TB cases (median, 79 days; IQR, 42-127 days; p<0.001), but was similar for IMR-TB cases (median, 50 days; IQR, 27-82 days; p=0.202). Compared to their counterparts with drug-susceptible disease RMR-TB patients were more likely to die during treatment (13% v 9%; POR, 1.66; CI, 1.19, 2.32) and this association was similar in magnitude to that of MDR-TB cases (11% v 9%; POR, 1.48; CI, 1.24, 2.77). Conversely, mortality during treatment was significantly lower among IMR-TB cases (7% v 9%; POR, 0.73; CI, 0.66, 0.80). RMR-TB cases were significantly more likely to have received partial DOT (POR, 1.38; 95% CI, 1.08-1.76)**.**

Multivariate Analysis of RIF-monoresistant TB at Initial Drug Susceptibility Testing

The multiple logistic model evaluated the association between RMR-TB and the main exposure variables (HIV status at TB diagnosis and a prior TB diagnosis) while controlling for ethnicity and age. During model selection the two-way interaction term involving HIV and a prior TB diagnosis was found to be significant and was included in the final model. Although DOT was initially considered a potential exposure variable, the variable was associated with a small effect size and so to facilitate interpretation of

the interaction model was included as a control variable in the final model. Table 6 summarizes the model fit statistics.

The summary POR estimates for the exposure variables while controlling for DOT, ethnicity and age are shown in Table 7. Among cases with no previous TB diagnosis RMR-TB cases were more likely to be HIV positive (POR, 3.09; CI, 2.26, 4.24). The magnitude of the association with HIV co-infection was larger among cases with a previous TB diagnosis (POR, 6.88; CI, 3.50, 13.52). The estimated PRs for the control variables DOT, ethnicity and age are summarized in Table 8.

Possible Acquired RIF-Resistant TB

Prevalence of Possible Acquired RIF-Resistant TB

Of the 166,241 TB cases reported to the NTSS between 1998 and 2008 10,503 (6.3%) had sufficient initial and final drug susceptibility results to be eligible (Figure 3). Of eligible cases 160 (1.5%) were possible ARR-TB cases. For the sub-classes of possible ARR-TB that were defined based on INH resistance at initial and final DST 58 (0.55%) were INH-susceptible at both initial and final DST (Aqrd-RIF INH-S), 58 (0.55%) were INH-resistant at initial DST (Aqrd-RIF INH-R) and 44 (0.42%) were INH-susceptible at initial DST, but INH-resistant at final DST (Aqrd MDR). Of eligible cases 8,752 (83.33%) were susceptible to both INH and RMP at final DST and 1,531 (14.58%) cases had an alternative drug resistance pattern (Figure 3).

Univariate Analysis of Possible Acquired RIF-Resistant TB

Table 9 compares the sociodemographic factors of possible ARR-TB cases to those of patients with TB susceptible to both RIF and INH. Categories of race/ethnicity, age, being foreign born, residence in a correctional facility at time of TB diagnosis and homelessness in the past year were associated with possible ARR-TB**.** Possible ARR-TB cases were more likely to be either Hispanic (POR, 1.62; CI, 1.01-2.62), Asian (POR, 1.80; CI, 1.04-3.12), or non-Hispanic Black (POR, 1.78; CI, 1.12-2.85), however the association with different race/ethnicity varied depending on the sub-class of possible ARR-TB. For all subclasses of possible ARR-TB there was a negative association with older age groups. Although possible ARR-TB cases were more likely to reside in a correctional facility at the time of TB diagnosis (POR, 2.31; CI, 1.32-4.04) the association was evident only for the Aqrd-RIF INH-R (POR, 2.78; CI, 1.19-6.51) and Aqrd-MDR (POR, 3.80; CI, 1.60-9.06) sub-classes. The Aqrd-RIF INH-R subclass patients were more likely to be foreign born (POR, 3.55; CI, 1.99-6.32) and those in the Aqrd RIF INH-S subclass were more likely to have been homeless in the past year (POR, 2.23; CI, 1.18-4.23).

A comparison of the clinical characteristics of possible ARR-TB cases to those of patients with TB susceptible to both RIF and INH is shown in Table 10. HIV status, location of TB disease and cavitary disease were all associated with possible ARR-TB. Of the 133 possible ARR-TB patients with HIV status reported, 65 (49%) were positive (POR, 9.13; 95% CI, 6.25-13.33). Although all three subclasses of possible ARR-TB were more likely to be HIV positive the strength of the association varied considerably. Of the 47 Aqrd-RIF INH-S patients with HIV status reported 37 (79%) were HIV positive, with the highest POR (31.82; 95% CI, 14.76-68.69) among all three subclasses.

Possible ARR-TB cases were more likely to have concurrent pulmonary and extrapulmonary disease (POR, 4.21; 95% CI, 1.98-8.94), however this association was evident only for the Aqrd-RIF INH-S subclass (POR, 5.48; 95% CI, 3.13-9.61)**.** Only the Aqrd-RIF INH-S subclass was less likely to have an abnormal chest x-ray (POR, 0.36; 95% CI, 0.16-0.80). Both the Aqrd-RIF INH-S (POR, 0.42; 95% CI, 0.22-0.82) and Aqrd MDR (POR, 0.48; 95% CI, 0.25-0.94) subclasses were less likely to have cavitary disease.

Table 11 compares the treatment outcomes of possible ARR-TB cases to those of patients with TB susceptible to both RIF and INH. Possible ARR-TB cases were more likely to have died (due to any cause) during treatment for TB (16% vs 5%; POR, 3.99; 95% CI, 2.55-6.25). The association was statistically significant for each of the three subclasses, with the cumulative mortality (POR estimates) of 13%; (POR, 3.32; 95% CI, 1.46-7.53) for Aqrd-RIF INH-S, 23% (POR, 5.51; 95% CI, 2.92-10.43) for Aqrd-RIF INH-R and 12% (POR, 2.78; 95% CI, 1.07-7.22) for Aqrd MDR.

DISCUSSION

This study found all forms of RIF-resistant TB examined to be positively associated with HIV co-infection and the association was strongest for cases of possible acquired RIF-monoresistance (the Aqrd RIF INH-S subclass). HIV co-infection was also associated with MDR-TB, however the association was less pronounced.

Another risk factor for RIF monoresistance at initial DST (RMR), but not for possible acquired RIF resistance (or any of the subclasses) was prior diagnosis of TB. This raises the possibility that for a significant portion of RMR-TB cases the initial DST was performed following relapse of disease or treatment failure. According to the NTSS guidelines, multiple TB episodes diagnosed more than 12 months apart in the same patient should be reported as separate cases. It is therefore possible that initial drug susceptibility testing could be performed on *M. tuberculosis* isolated from recurrent infection, e.g., during relapse or treatment failure. This possibility is supported by our multivariate logistic regression analysis, which demonstrated a significant interaction between HIV co-infection and a prior TB diagnosis. Among cases with a prior TB diagnosis the association with HIV was markedly stronger than in patients with no prior TB. A comparison of cases who were HIV co-infected and had a prior TB diagnosis compared to cases without these exposures showed the magnitude of the POR to be comparable to cases with possible acquired RIF mono-resistance (the Aqrd RIF INH-S subclass).

Alternatively it is possible that a prior TB diagnosis be reported due to multiple independent infections with distinct *M. tuberculosis* genotypes. This is unlikely for patients born in the United States who travel infrequently to high TB incidence countries

because of the low TB incidence rate in the United States. In this study half of RMR-TB cases were foreign born, but being foreign born was not associated with RMR-TB.

The mechanism by which HIV co-infection increases the likelihood of RIF resistance has not been elucidated, although several risk factors related to HIV infection have been studied (Table 1). Malabsorption [30], gastrointestinal symptoms [19, 25] or drug-drug interactions involving the complex HIV and TB treatment regimens [30] may result in sub-therapeutic serum concentrations for one or more drugs. A low CD4 count (<100-200/mm^3) among HIV co-infected patients has also consistently been found to be associated with RIF resistance [18-20, 25-30, 32, 41]. It is plausible that for immune compromised patients carrying a higher bacterial load a mutation conferring drug resistance occurs, before treatment controls the infection, more frequently. Although the mutation rate in the gene conferring RMP resistance is approximately 100-fold lower than that for the gene conferring resistance to INH [42] it is not clear why all forms of drug resistance (for example IMR-TB) would not be more strongly associated with HIV co-infection. To gain further insight into the possible mechanism by which HIV co-infection increases the likelihood of RMR-TB, the CDC is now conducting a review of medical records at selected high incidence sites.

RMR-TB cases were less likely to have reported receiving full DOT and were more likely to have received partial DOT. This is in agreement with previous studies showing non-adherence to treatment to be a risk factor for drug resistance [20, 25, 31]**.** Overall, compared to IMR-TB and MDR-TB cases, patients with RMR-TB appeared quite different in terms of the proportions of foreign-born, and the distribution of the race/ethnicity variable. As previously indicated [41] treatment outcomes for IMR-TB

cases were found to be comparable to drug-susceptible TB cases, whereas treatment outcomes for RMR-TB and MDR-TB were similar. In future studies it would be interesting to determine whether the increased likelihood of death during treatment for RMR-TB is confounded by the high prevalence of HIV infection.

Strengths and Limitations

This is the first report of the epidemiology of RIF-resistant TB on the national level in the United States. The national TB surveillance system is estimated to capture approximately 98% of TB cases such that the sample of RIF-resistant TB cases analyzed in this study is likely representative of the underlying population. Furthermore the validity and completeness of the NTSS data collected has been reported to be excellent [44]. On the other hand, due to confidentiality agreements between the CDC and states, a significant limitation of the national TB surveillance data is the inability to ensure that each observation is independent.

Another limitation of the NTSS dataset most relevant to this study was the lack of *M. tuberculosis* genotyping information. It was not possible to confirm whether a change from RMP susceptibility reported at initial DST to RMP resistance at final DST was based on the same *M. tuberculosis* strain. However, since the incidence rates of TB and RIF resistance in the United States are very low, the likelihood of re-infection with a RIF-resistant TB strain following initial infection with a RIF-susceptible strain is also unlikely.

The state of California does not report the HIV status of TB cases and since California is a high TB incidence state, 36% and 27% of RMR-TB and possible ARR-TB

cases respectively had missing data for the main exposure variable of interest. This high proportion of missing data for HIV status may impact the generalizability of this study's findings. Furthermore the 2002 CDC treatment guidelines for HIV co-infected patients recommended the treatment regimen be taken daily for patients with low CD4 counts [22]**.** As the NTSS does not collect information on the intermittency of the treatment regimen we were unable to assess the impact of regimen intermittency on RMR-TB.

Since there is variability in the methodology of *M. tuberculosis* culture and drug susceptibility testing across TB control programs and these methodologies continue to be improved, it is possible that drug susceptibility testing performance could have changed during the study period. Changes in methodology could have influenced the apparent temporal trends in drug resistance.

Overall relatively few cases met the case definition of possible acquired RIF resistance, therefore analyses involving these cases may have suffered from limited statistical power. Our *a priori* decision to further group the cases into three subclasses resulted in even smaller sample sizes and precluded us from conducting multivariate analysis of acquired RIF-resistant-TB. However as the effect sizes in these analyses were very large, it appears unlikely that associations of this magnitude could be explained solely by confounding.

Public Health Significance

Our study has confirmed that HIV co-infection is strongly associated with all forms of RIF resistance. These findings should aid in supporting recommendations for the case management of HIV co-infected patients. Our study results also highlight the

significant burden of RIF resistance on the patient and on local TB control programs.

Interestingly, during the course of completing this study a significant advance in TB diagnostics, the GeneXpert MTB/RIF rapid test [45], was made. This advancement subsequently made our findings more timely than anticipated. The GeneXpert MTB/RIF rapid test is a cartridge-based, automated diagnostic test that can identify *M. tuberculosis* and resistance to RMP within hours of specimen collection. However, since there is no rapid test for INH resistance and the incidence rate of RIF resistance (without INH resistance) is significantly lower than MDR rates it has been presumed that a GeneXpert test indicating RIF resistance will be a marker of MDR. As the GeneXpert MTB/RIF rapid test is rolled out, studies such as this will be critical for the development of the guidelines for its use, especially in settings where HIV prevalence is high and in low resource settings where follow-up confirmatory culture-based drug susceptibility testing is not available.

REFERENCES

1. WHO, *Global tuberculosis control: a short update to the 2009 report*. 2009, World Health Organization.
2. WHO. *Tuberculosis global report, 2006.* 2006.
3. Quy, H.T., et al., *Treatment outcomes by drug resistance and HIV status among tuberculosis patients in Ho Chi Minh City, Vietnam.* Int J Tuberc Lung Dis, 2006. **10**(1): p. 45-51.
4. Johnston, J.C., et al., *Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis.* PLoS One, 2009. **4**(9): p. e6914.
5. Goble, M., et al., *Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin.* N Engl J Med, 1993. **328**(8): p. 527-32.
6. Lockman, S., et al., *Clinical outcomes of Estonian patients with primary multidrug-resistant versus drug-susceptible tuberculosis.* Clin Infect Dis, 2001. **32**(3): p. 373-80.
7. Mitchison, D.A. and A.J. Nunn, *Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis.* Am Rev Respir Dis, 1986. **133**(3): p. 423-30.
8. Wells, C.D., et al., *HIV infection and multidrug-resistant tuberculosis: the perfect storm.* J Infect Dis, 2007. **196 Suppl 1**: p. S86-107.
9. *Trends in tuberculosis--United States, 2008.* MMWR Morb Mortal Wkly Rep, 2009. **58**(10): p. 249-53.
10. Migliori, G.B., et al., *Multidrug-resistant and extensively drug-resistant tuberculosis in the West. Europe and United States: epidemiology, surveillance, and control.* Clin Chest Med, 2009. **30**(4): p. 637-65, vii.
11. Granich, R.M., et al., *Multidrug resistance among persons with tuberculosis in California, 1994-2003.* JAMA, 2005. **293**(22): p. 2732-9.
12. Dickinson, J.M. and D.A. Mitchison, *Experimental models to explain the high sterilizing activity of rifampin in the chemotherapy of tuberculosis.* Am Rev Respir Dis, 1981. **123**(4 Pt 1): p. 367-71.
13. Blumberg, H.M., et al., *American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis.* Am J Respir Crit Care Med, 2003. **167**(4): p. 603-62.
14. Bloch, A.B., et al., *Nationwide survey of drug-resistant tuberculosis in the United States.* JAMA, 1994. **271**(9): p. 665-71.
15. LoBue, P.A. and K.S. Moser, *Isoniazid- and rifampin-resistant tuberculosis in San Diego County, California, United States, 1993-2002.* Int J Tuberc Lung Dis, 2005. **9**(5): p. 501-6.
16. Moore, M., et al., *Trends in drug-resistant tuberculosis in the United States, 1993-1996.* JAMA, 1997. **278**(10): p. 833-7.
17. CDC., *Reported Tuberculosis in the United States, 2008. Atlanta, GA: U.S.* 2009.
18. Vernon, A., et al., *Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium.* Lancet, 1999. **353**(9167): p. 1843-7.

19. Ridzon, R., et al., *Risk factors for rifampin mono-resistant tuberculosis.* Am J Respir Crit Care Med, 1998. **157**(6 Pt 1): p. 1881-4.
20. Munsiff, S.S., et al., *Rifampin-monoresistant tuberculosis in New York City, 1993-1994.* Clin Infect Dis, 1997. **25**(6): p. 1465-7.
21. Burwen, D.R., J.L. Jones, and T.H.S. Group, *Epidemiology and diagnosis of tuberculosis (abstract).* Am. J. Respir. Crit. Care Med. , 1995. **151(Suppl.)**: p. A144.
22. MMWR, *Notice to Readers: Acquired Rifamycin Resistance in Persons with Advanced HIV Disease Being Treated for Active Tuberculosis with Intermittent Rifamycin-Based Regimens.* . 2002, CDC. p. 214-5.
23. Hoopes, A.J., et al., *Isoniazid-monoresistant tuberculosis in the United States, 1993 to 2003.* Arch Intern Med, 2008. **168**(18): p. 1984-92.
24. Shah, N.S., et al., *Extensively drug-resistant tuberculosis in the United States, 1993-2007.* JAMA, 2008. **300**(18): p. 2153-60.
25. Bradford, W.Z., et al., *The changing epidemiology of acquired drug-resistant tuberculosis in San Francisco, USA.* Lancet, 1996. **348**(9032): p. 928-31.
26. Burman, W., et al., *Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis.* Am J Respir Crit Care Med, 2006. **173**(3): p. 350-6.
27. el-Sadr, W.M., et al., *Evaluation of an intensive intermittent-induction regimen and duration of short-course treatment for human immunodeficiency virus-related pulmonary tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG).* Clin Infect Dis, 1998. **26**(5): p. 1148-58.
28. Jenny-Avital, E.R. and K. Joseph, *Rifamycin-resistant Mycobacterium tuberculosis in the highly active antiretroviral therapy era: a report of 3 relapses with acquired rifampin resistance following alternate-day rifabutin and boosted protease inhibitor therapy.* Clin Infect Dis, 2009. **48**(10): p. 1471-4.
29. Li, J., et al., *Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifabutin-based regimens in New York City, 1997-2000.* Clin Infect Dis, 2005. **41**(1): p. 83-91.
30. March, F., et al., *Acquired drug resistance in Mycobacterium tuberculosis isolates recovered from compliant patients with human immunodeficiency virus-associated tuberculosis.* Clin Infect Dis, 1997. **25**(5): p. 1044-7.
31. Sandman, L., et al., *Risk factors for rifampin-monoresistant tuberculosis: A case-control study.* Am J Respir Crit Care Med, 1999. **159**(2): p. 468-72.
32. Weiner, M., et al., *Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis.* Clin Infect Dis, 2005. **40**(10): p. 1481-91.
33. Migliori, G.B., et al., *Review of multidrug-resistant and extensively drug-resistant TB: global perspectives with a focus on sub-Saharan Africa.* Trop Med Int Health, 2010.
34. Uzun, M., Z. Erturan, and O. Ang, *Investigation of cross-resistance between rifampin and rifabutin in Mycobacterium tuberculosis complex strains.* International Journal of Tuberculosis and Lung Disease, 2002. **6**(2): p. 164-165.

35. Yang, B., et al., *Relationship between antimycobacterial activities of rifampicin, rifabutin and KRM-1648 and rpoB mutations of Mycobacterium tuberculosis.* Journal of Antimicrobial Chemotherapy, 1998. **42**(5): p. 621-628.
36. Rastogi, N., et al., *Activity of rifapentine and its metabolite 25-O-desacetylrifapentine compared with rifampicin and rifabutin against Mycobacterium tuberculosis, Mycobacterium africanum, Mycobacterium bovis and M-bovis BCG.* Journal of Antimicrobial Chemotherapy, 2000. **46**(4): p. 565-570.
37. Cavusoglu, C., Y. Karaca-Derici, and A. Bilgic, *In-vitro activity of rifabutin against rifampicin-resistant Mycobacterium tuberculosis isolates with known rpoB mutations.* Clinical Microbiology and Infection, 2004. **10**(7): p. 662-665.
38. Dickinson, J.M. and D.A. Mitchison, *Invitro Activity of New Rifamycins against Rifampicin-Resistant Mycobacterium-Tuberculosis and Mais-Complex Mycobacteria.* Tubercle, 1987. **68**(3): p. 177-182.
39. Lutfey, M., et al., *Independent origin of mono-rifampin-resistant Mycobacterium tuberculosis in patients with AIDS.* Am J Respir Crit Care Med, 1996. **153**(2): p. 837-40.
40. Zack, M., J. Singleton, and C. Satterwhite, *Collinearity macro (SAS), Unpublished, Department of Epidemiology RSPH at Emory University, (contact dkleinb@sph.emory.edu).* 2009.
41. Nettles, R.E., et al., *Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a comparison by HIV serostatus and rifamycin use.* Clin Infect Dis, 2004. **38**(5): p. 731-6.
42. David, H.L., *Probability distribution of drug-resistant mutants in unselected populations of Mycobacterium tuberculosis.* Appl Microbiol, 1970. **20**(5): p. 810-4.
43. Cattamanchi, A., et al., *Clinical characteristics and treatment outcomes of patients with isoniazid-monoresistant tuberculosis.* Clin Infect Dis, 2009. **48**(2): p. 179-85.
44. Sprinson, J.E., et al., *Assessing the validity of tuberculosis surveillance data in California.* BMC Public Health, 2006. **6**: p. 217.
45. Hillemann, D., et al., *Rapid Molecular Detection of Extrapulmonary Tuberculosis by the Automated GeneXpert MTB/RIF System.* J Clin Microbiol. **49**(4): p. 1202-5.
46. Swaminathan, S., et al., *Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial.* Am J Respir Crit Care Med, 2010. **181**(7): p. 743-51.
47. Menzies, D., et al., *Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis.* PLoS Med, 2009. **6**(9): p. e1000146.

TABLES AND FIGURES

Figure 1. Defining Possible Cases of Acquired RIF-resistant TB with Consideration for Initial and Acquired INH Resistance

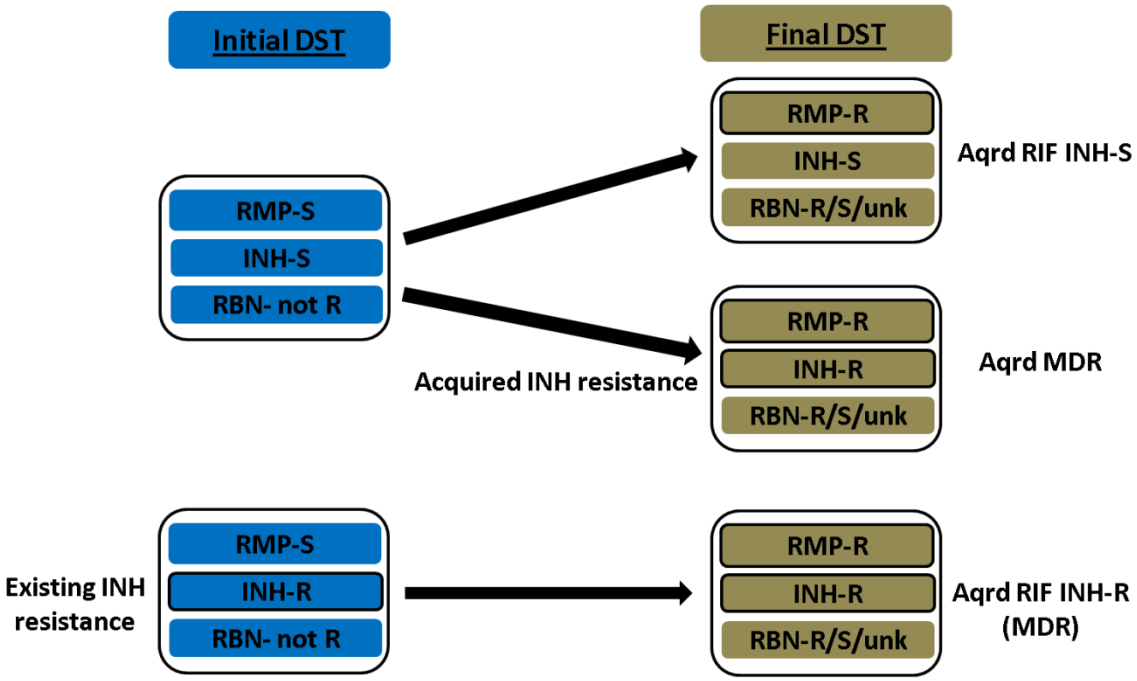


Figure 2. Selection of RIF-monoresistant Cases at Initial DST (1998–2008)

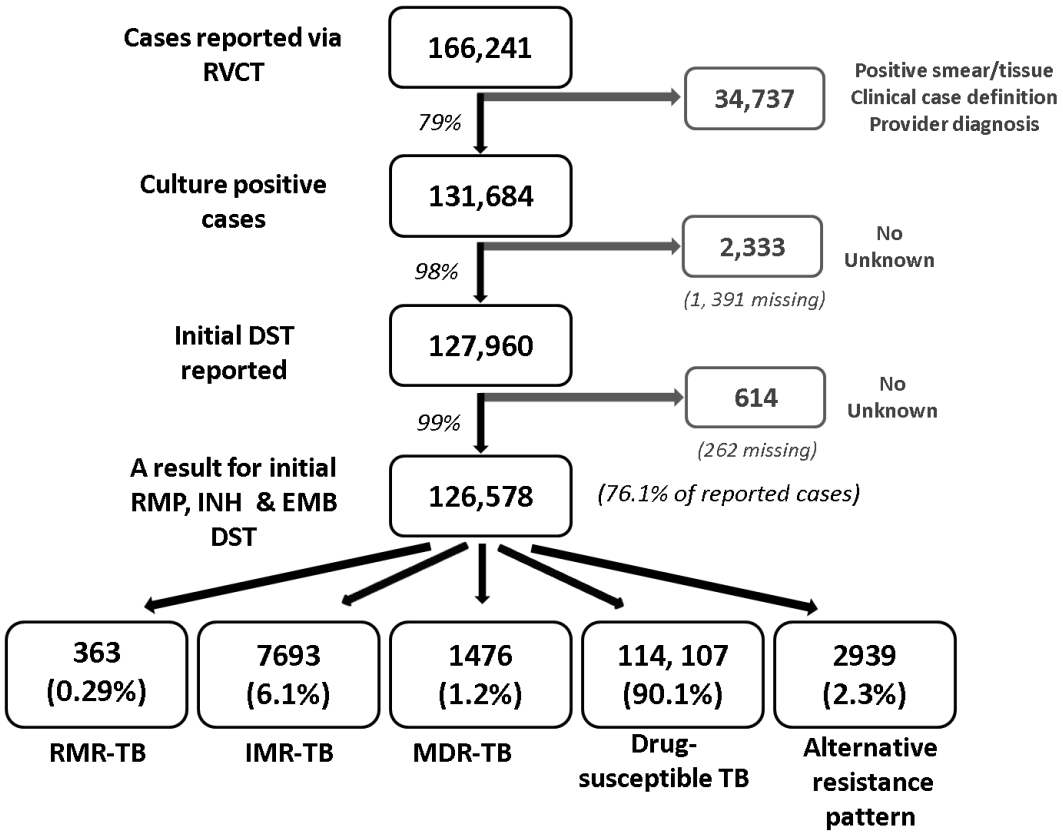


Figure 3. Selection of Possible Cases of Acquired RIF-resistant TB (1998–2008)

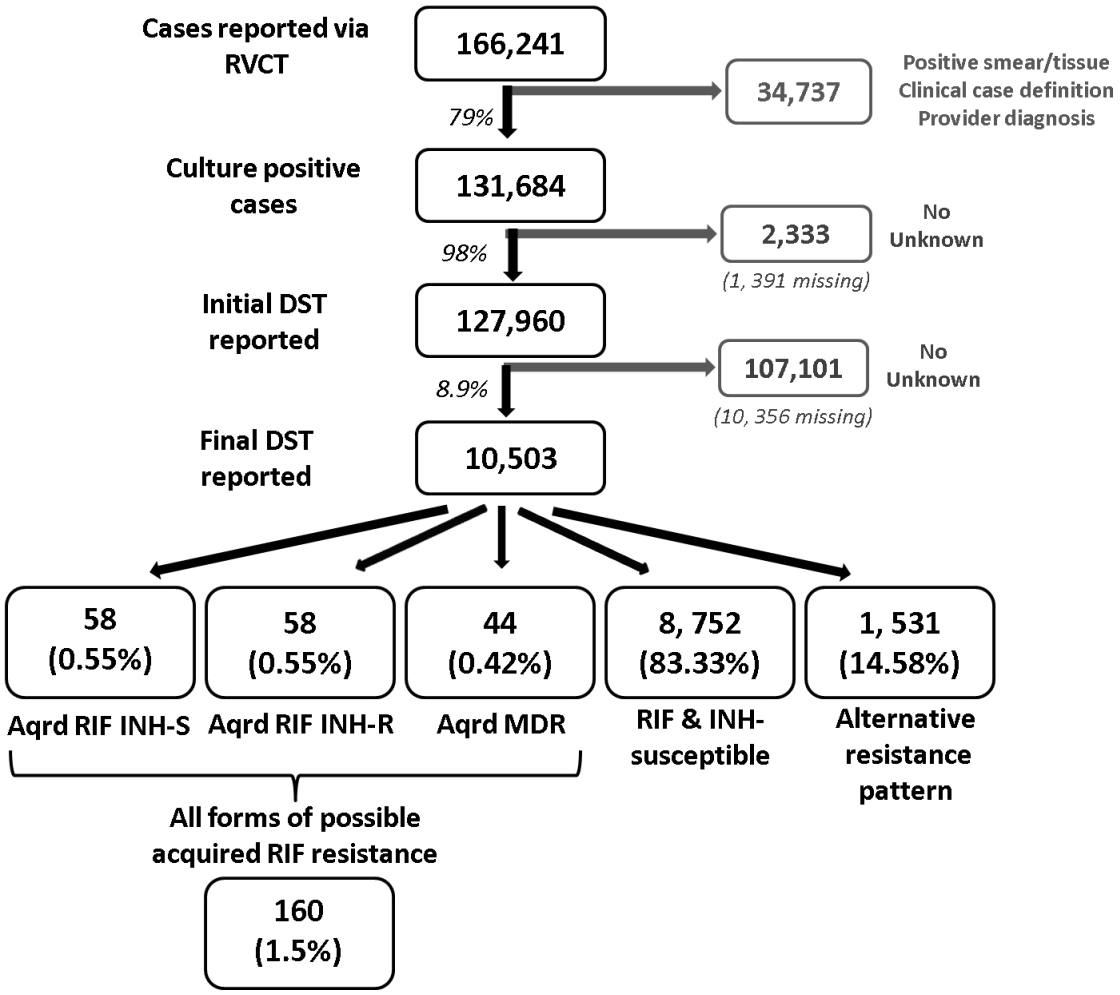
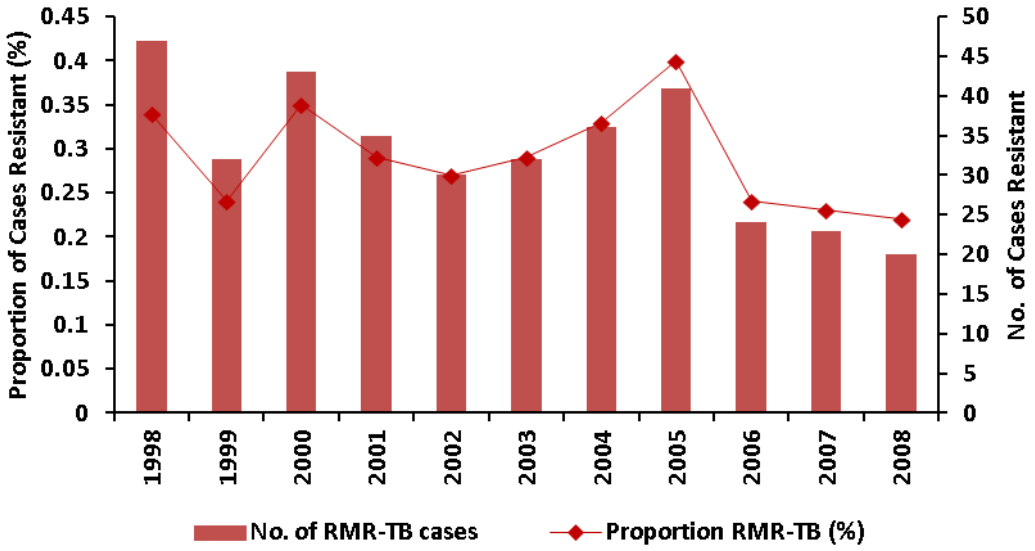
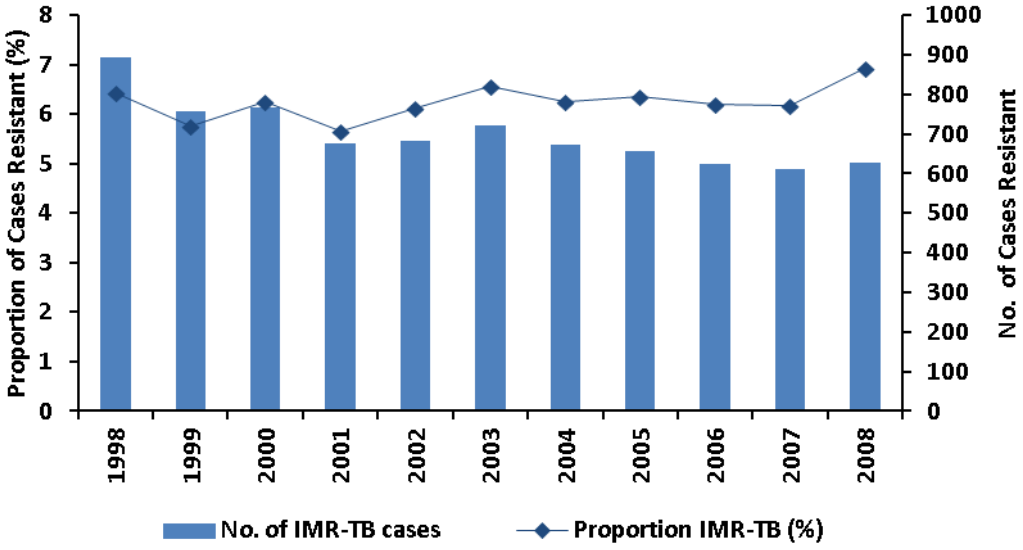


Figure 4. RIF-Monoresistant Tuberculosis Reported at Initial Drug Susceptibility Test in the United States, 1998 to 2008



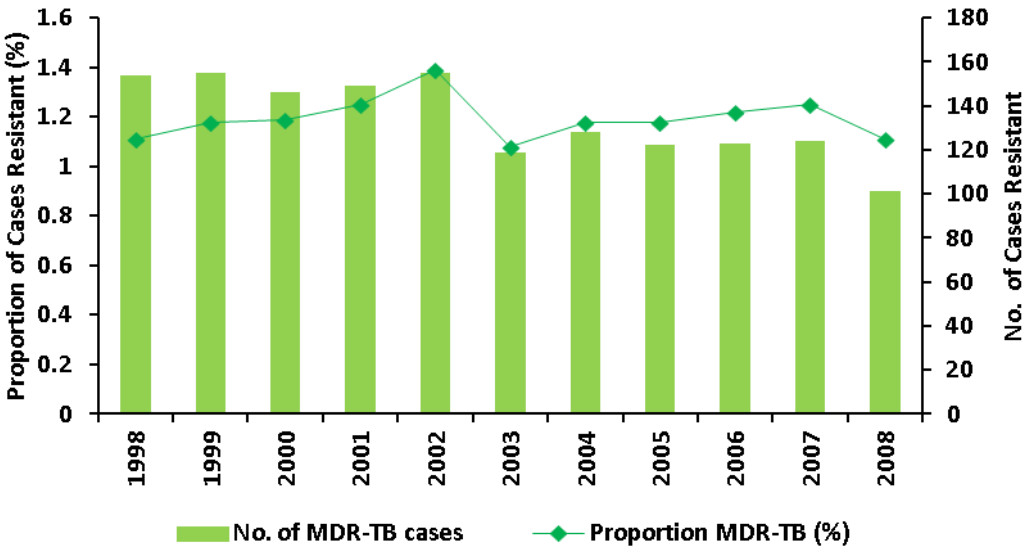
The proportion of resistant cases was calculated among all culture positive cases for which an initial susceptibility result was reported for rifampin, izoniazid, and ethambutol.

Figure 5. INH-Monoresistant Tuberculosis Reported at Initial Drug Susceptibility Test in the United States, 1998 to 2008



The proportion of resistant cases was calculated among all culture positive cases for which an initial susceptibility result was reported for rifampin, izoniazid, and ethambutol.

Figure 6. Multidrug-Resistant Tuberculosis Reported at Initial Drug Susceptibility Test in the United States, 1998 to 2008



The proportion of resistant cases was calculated among all culture positive cases for which an initial susceptibility result was reported for rifampin, izoniazid, and ethambutol.

Table 1. Predictive Factors for Acquired RIF Resistance and Relapse or Treatment Failure.

Potential factor	Report
CD4 count <100/mm^3	[18-20, 25-32, 41]
Non-adherence to treatment regimen	[20, 25, 31]
Extrapulmonary or disseminated TB	[18, 30, 31]
Duration and intermittency of rifamycin-based therapy	
*Twice-weekly RMP & INH **	[27]
*Twice or thrice-weekly RMP in initiation phase**	[29]
*Thrice-weekly RMP in initiation & continuation phase in antiretroviral therapy naïve patients**	[46]
*Once-weekly rifapentine & INH**	[18]
*Twice-weekly rifabutin & INH in initiation phase**	[26]
RMP in the initiation phase, but not the continuation phase	[47]
*6-month and 9-months RIF-based therapy comparable**	[46]
Malabsorption of TB medications or gastrointestinal symptoms	[19, 25]
Use of azole antifungal drugs	[16, 19, 31]
Prior history of TB	[19, 31]
Prior rifabutin therapy	[19]
Baseline INH resistance	[46, 47]
Younger age	[18]
Drug level	[26, 28, 32]

*Study population was HIV positive.

Table 2. RIF-Monoresistant Tuberculosis Reported at Initial Drug Susceptibility Test before and after 2003.

Years	No. of eligible cases	RMR-TB No.	RMR-TB % of eligible cases	IMR-TB No.	IMR-TB % of eligible cases	MDR-TB No.	MDR-TB % of eligible cases
1998-2002	63826	187	0.30	3778	6.05	759	1.22
2003-2008	62752	176	0.29	3915	6.40	717	1.17
P-value*	-	0.677		0.017		0.440	

* P-value for a one-sided, two-sample t-test comparing the proportion of resistant cases before 2002 (1998-2002 inclusive) and after 2002 (2003-2008 inclusive).

Table 3. Sociodemographic Characteristics of RIF-Monoresistant Tuberculosis (RMR-TB), INH-Monoresistant Tuberculosis (IMR-TB), Mutidrug-Resistant Tuberculosis (MDR-TB) and Drug Susceptible TB Cases at Initial Drug Susceptibility Test, United States, 1998-2008

Characteristics	No. (%)					Prevalence Odds Ratio (95% Confidence Interval)		
	RMR-TB (n = 363)	IMR-TB (n = 7693)	MDR-TB (n = 1476)	Drug-susceptible-TB (n =114 107)	Alternative resistance pattern (n =2939)	RMR-TB vs Drug susceptible	IMR-TB vs Drug susceptible	MDR-TB vs Drug susceptible
Age categories, y								
0-14	9 (2)	118 (2)	40 (3)	2038 (2)	183 (6)	1.12 (0.57-2.19)	0.71 (0.59-0.86)[a]	1.12 (0.81-1.55)
15-24	38 (10)	943 (12)	230 (16)	11684 (10)	385 (13)	0.82 (0.58-1.18)	1.00 (0.92-1.07)	1.12 (0.97-1.31)
25-44	157 (43)	3225 (42)	697 (47)	39778 (35)	1114 (38)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
45-64	122 (34)	2321 (30)	388 (26)	35060 (31)	714 (24)	0.88 (0.70- 1.13)	0.82 (0.77-0.86)[a]	0.63 (0.56-0.72)[a]
≥65	37 (10)	1086 (14)	121 (8)	25547 (22)	543 (18)	0.37 (0.26-0.53)[a]	0.52 (0.49-0.56)[a]	0.27 (0.22-0.33)[a]
Gender[b]								
Female	121 (33)	2919 (38)	632 (43)	41979 (37)	1164 (40)	0.86 (0.69-1.07)	1.05 (1.00-1.10)	1.29 (1.16-1.43)[a]
Male	242 (67)	4774 (62)	844 (57)	72115 (63)	1775 (60)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Race/ethnicity[c]								
Hispanic	129 (36)	1920 (25)	420 (28)	28245 (25)	1438 (49)	1.66 (1.24-2.24)[a]	1.75 (1.62-1.90)[a]	2.34 (1.94-2.81)[a]
American Indian	6 (2)	34 (0)	3 (0)	1607 (1)	20 (1)	1.36 (0.59-3.24)	0.55 (0.39-0.77)[a]	0.29 (0.09-0.92)[a]
Asian	51 (14)	3035 (39)	589 (40)	24833 (22)	648 (22)	0.75 (0.52-1.08)	3.15 (2.92-3.40)[a]	3.73 (3.12-4.45)[a]
Non-Hispanic Black	109 (30)	1700 (22)	297 (20)	34392 (30)	391 (13)	1.15 (0.85-1.57)	1.27 (1.17-1.38)[a]	1.36 (1.12-1.65)[a]
Non-Hispanic White	66 (18)	932 (12)	153 (10)	24027 (31)	426 (14)	1.00 [Reference]	1.00 [Reference][a]	1.00 [Reference]
Foreign-born nationality[d]								
Foreign-born	175 (48)	5473 (71)	1104 (75)	57170 (50)	2000 (68)	0.93 (0.75-1.14)	2.47 (2.34-2.60)[a]	2.95 (2.62-3.32)[a]
US-born	187 (52)	2197 (29)	370 (25)	56593 (50)	928 (32)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Occupation during 2 years prior to diagnosis[e]								
Unemployed	198 (55)	3507 (46)	761 (52)	60415 (53)	1527 (52)	1.08 (0.87-1.35)	0.74 (0.71-0.78)[a]	0.96 (0.86-1.07)
Health care worker	11 (3)	278 (4)	55 (4)	3226 (3)	69 (2)	1.12 (0.61-2.08)	1.10 (0.97-1.25)	1.30 (0.99-1.72)
Other low-risk employment	133 (37)	3423 (44)	574 (39)	43802 (38)	1155 (39)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Missing/Agricultural/Correctional facility workers	21 (6)	485 (6)	86 (6)	6664 (6)	188 (6)	n.d	n.d	n.d

Correctional facility resident[f]								
Yes	19 (5)	289 (4)	40 (30)	4102 (4)	61 (2)	1.49 (0.94-2.36)	1.05 (0.93-1.18)	0.75 (0.55-1.03)
No	342 (94)	7391 (96)	1433 (97)	109847 (96)	2873 (98)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Homeless in the year prior to diagnosis[g]								
Yes	27 (7)	388 (5)	61 (4)	7856 (7)	2798 (95)	1.10 (0.74-1.63)	0.72 (0.65-1.63)	0.59 (0.45-0.76)[a]
No	327 (90)	7200 (94)	1389 (94)	104755 (92)	95 (3)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]

[a] Statistically significant at $P < 0.05$.

[b] For drug-susceptible cases gender was unknown for 9 cases and missing for 4.

[c] Two RMR-TB cases (1%), 72 IMR-TB cases (1%), 14 MDR-TB (1%) cases, 1003 drug-susceptible cases (1%) and 16 cases with an alternative drug resistance pattern (1%) were either Native Hawaiian or had multiple or unknown racial/ethnic designations.

[d] One RMR-TB cases (0%), 23 IMR-TB cases (0%), 2 MDR-TB (0%) cases, 344 drug-susceptible cases (0%) and 11 cases with an alternative drug resistance pattern (0%) had multiple or unknown/missing racial/ethnic designations.

[e] Occupation was unknown or missing for 15 RMR-TB cases (4%), 357 IMR-TB cases (5%), 68 MDR-TB (5%) cases, 5208 drug-susceptible cases (5%) and 188 cases with an alternative drug resistance pattern (6%).

[F] Correctional facility residence history was unknown or missing for 2 RMR-TB cases (1%), 13 IMR-TB cases (0%), 3 MDR-TB (0%) cases, 158 drug-susceptible cases (0%) and 5 cases with an alternative drug resistance pattern (0%).

[g] Homelessness history was unknown or missing for 9 RMR-TB cases (2%), 105 IMR-TB cases (1%), 26 MDR-TB (1%) cases, 1496 drug-susceptible cases (1%) 46 cases with an alternative drug resistance pattern (1%).

n.d = not determined.

Table 4. Clinical Characteristics of RIF-Monoresistant Tuberculosis (RMR-TB), INH-Monoresistant Tuberculosis (IMR-TB), Mutidrug-Resistant Tuberculosis (MDR-TB) and Drug Susceptible TB Cases at Initial Drug Susceptibility Test, United States, 1998-2008

Characteristics	No. (%)					Prevalence Odds Ratio (95% Confidence Interval)		
	RMR-TB (n = 363)	IMR-TB (n = 7693)	MDR-TB (n = 1476)	Drug-susceptible-TB (n =114 107)	Alternative resistance pattern (n =2939)	RMR-TB vs Drug susceptible	IMR-TB vs Drug susceptible	MDR-TB vs Drug susceptible
Prior TB diagnosis								
Yes	52 (14)	499 (6)	258 (17)	5233 (5)	133 (5)	3.50 (2.61-4.71)[a]	1.45 (1.32-1.59)[a]	4.43 (3.86-5.08)[a]
No	306 (84)	7108 (92)	1202 (81)	107849 (95)	2783 (5)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Location of TB disease[b]								
Pulmonary alone	270 (74)	5819 (76)	1203 (82)	84062 (74)	1612 (55)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Extrapulmonary alone	55 (15)	1259 (16)	150 (10)	19695 (17)	925 (31)	0.87 (0.65-1.16)	0.92 (0.87-0.98)[a]	0.53 (0.45-0.63)[a]
Pulmonary and extrapulmonary	38 (10)	614 (8)	122 (8)	10325 (9)	402 (14)	1.15 (0.82-1.61)	0.86 (0.79-0.94)[a]	0.83 (0.69-1.00)
Sputum microscopy result for acid-fast bacilli[c]								
Positive	190 (62)	3703 (58)	859 (65)	51543 (55)	1219 (5)	1.27 (1.00-1.62)	1.03 (0.98-1.09)	1.41 (1.25-1.59)[a]
Negative	97 (31)	2326 (36)	395 (30)	33455 (35)	8897 (37)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Chest radiograph result[d]								
Abnormal	315 (87)	6616 (86)	1339 (91)	98103 (86)	2133 (73)	1.11 (0.80-1.56)	0.96 (0.89-1.03)	1.47 (1.22-1.78)[a]
Normal	38 (10)	927 (12)	122 (8)	13189 (12)	740 (25)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Cavitary disease[e]								
Yes	100 (32)	2022 (31)	489 (45)	28904 (32)	562 (26)	1.12 (0.88-1.43)	1.04 (0.99-1.10)	1.36 (1.21-1.52)[a]
No	206 (65)	4479 (68)	835 (76)	66853 (73)	1556 (73)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
HIV test result[f]								
Negative	145 (49)	3468 (62)	693 (63)	53747 (59)	1032 (60)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Positive	87 (29)	564 (10)	170 (15)	9328 (10)	173 (10)	3.46 (2.65-4.51)[a]	0.94 (0.86-1.03)	1.41 (1.19-1.67)[a]
Unknown/missing	65 (22)	1518 (27)	235 (21)	28414 (31)	526 (30)	n.d.	n.d.	n.d.
Vital Status at diagnosis[g]								
Alive	355 (98)	7591 (99)	1459 (99)	111101 (97)	2876 (98)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Dead	8 (2)	99 (1)	16 (1)	2954 (3)	61 (2)	0.85 (0.42-1.71)	0.49 (0.40-0.60)[a]	0.41 (0.25-0.68)[a]

[a] Statistically significant at $P < 0.05$.

[b] Location of disease was unknown for 1 IMR -TB cases (0%), 1 MDR-TB (0%) cases and 25 drug-susceptible cases (0%).

[c] Percentage is based on the number of cases with any pulmonary disease; n= 308 for RMR-TB cases, n= 6433 for IMR-TB cases, n= 1325 for MDR-TB cases, n= 94 387 for drug-susceptible TB cases and n= 2014 cases with an alternative drug resistance pattern. Sputum microscopy result was unknown or missing for 21 RMR-TB cases (7%), 404 IMR-TB cases (6%), 71 MDR-TB (5%) cases, 9389 drug-susceptible cases (10%) and 14009 cases with an alternative drug resistance pattern (58%).

[d] A chest radiograph result was missing or unknown for 10 RMR-TB cases (3%), 150 IMR-TB cases (2%), 15 MDR-TB (1%) cases, 2815 drug-susceptible cases (2%) and 66 cases with an alternative drug resistance pattern (2%).

[e] Percentage is based on the number of cases with abnormal chest radiograph findings (provided in table). Cavitary disease diagnosis was missing or unknown for 9 RMR-TB cases (3%), 115 IMR-TB cases (2%), 15 MDR-TB (1%) cases, 2346 drug-susceptible cases (3%) and 15 cases with an alternative drug resistance pattern (1%).

[f] Number and percentage are based on non-Californian cases (n= 297 for RMR-TB, n= 5550 for IMR-TB, n= 1098 for MDR-TB, n= 91 489 for drug-susceptible TB and n= 1731 cases with an alternative drug resistance pattern).

[g] Vital status at diagnosis was missing for 3 IMR-TB cases (0%), 1 MDR-TB (0%) cases, 52 drug-susceptible cases (0%) and 2 cases with an alternative drug resistance pattern (0%).

n.d = not determined.

Table 5. Directly Observed Therapy (DOT) Use and Treatment Outcomes of RIF-Monoresistant Tuberculosis (RMR-TB), INH-Monoresistant Tuberculosis (IMR-TB), Mutidrug-Resistant Tuberculosis (MDR-TB) and Drug Susceptible TB Cases at Initial Drug Susceptibility Test, United States, 1998-2008

	No. (%)[a]					Prevalence Odds Ratio (95% Confidence Interval)		
Characteristics	RMR-TB (n = 310)	IMR-TB (n = 6318)	MDR-TB (n = 11224)	Drug-susceptible-TB (n =93 154)	Alternative resistance pattern (n =2939)	RMR-TB vs Drug susceptible	IMR-TB vs Drug susceptible	MDR-TB vs Drug susceptible
DOT[b]								
No DOT (Self administered therapy only)	37 (12)	1046 (17)	112 (9)	16524 (18)	479 (16)	0.72 (0.51-1.04)	0.97 (0.90-1.04)	0.57 (0.47-0.70)[c]
Partial DOT (DOT combined with some self administered therapy)	108 (35)	1934 (31)	480 (39)	25313 (27)	1403 (48)	1.38 (1.08-1.76)[c]	1.17 (1.11-1.24)[c]	1.60 (1.42-1.81)[c]
Complete DOT	155 (50)	3264 (52)	594 (49)	50085 (54)	781 (27)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Sputum culture conversion[d]								
Yes	184 (78)	3922 (82)	833 (81)	52802 (79)	1111 (79)	0.99 (0.71-1.37)	1.23 (1.14-1.33)[c]	1.41 (1.18-1.68)[c]
No	45 (19)	768 (16)	143 (14)	12739 (19)	248 (18)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Time to conversion, median (interquartile range), d[e]	63 (35-114)	50 (27-82)	79 (42-127)	51 (28-81)	67 (26-83)	P <0.001	P = 0.202	P <0.001
Treatment outcomes[f]								
Death due to any cause	41 (13)	425 (7)	139 (11)	8484 (9)	209 (9)	1.66 (1.19-2.32)[c]	0.73 (0.66-0.80)[c]	1.48 (1.24-1.77)[c]
Other, unknown, or missing[g]	42 (14)	501 (8)	219 (18)	6487 (7)	209 (9)	2.23 (1.60-3.10)[c]	1.12 (1.02-1.23)[c]	3.05 (2.62-3.54)[c]
Completion of therapy	227 (73)	5392 (85)	866 (71)	78183 (84)	1914 (82)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]

[a] Number and percentages are based on cases who were alive at diagnosis and initially treated with 1 or more TB drugs. Case counts have been censored at 2006 to allow sufficient time for the reporting of end-of-treatment results.

[b] Information regarding DOT was missing for 10 RMR-TB cases (3%), 74 IMR-TB cases (1%), 38 MDR-TB (3%) cases , 1232 drug-susceptible cases (1%) and 276 cases with an alternative drug resistance pattern (9%).

[c] Statistically significant at $P < 0.05$.

[d] Number and percentage are based on cases with baseline positive sputum culture result (n= 237 for RMR-TB, n= 4086 for IMR-TB, n= 1025 for MDR-TB, n= 67 081 for drug-susceptible TB and n=1398 for cases with an alternative drug resistance pattern). Culture conversion results were missing or unknown for 6 RMR-TB cases (3%), 72 IMR-TB cases (2%), 41 MDR-TB (4%) cases, 1088 drug-susceptible cases (2%) and 39 cases with an alternative drug resistance pattern (3%).

[e] Time to conversion is defined as the time from TB treatment start to the first negative culture, after which there were no more positive cultures. Median time is based in cases with sputum culture conversion documented and in whom culture conversion was reported (n= 184 for RMR-TB, n=3904 for IMR-TB, n=831 for MDR-TB, n= 52 454 for drug-susceptible TB and n=1108 for cases with an alternative drug resistance pattern). The p-value is for a one-sided Wilcoxon two-sample test.

[f] Treatment outcome is recorded as the reason a patient stopped TB therapy. Death may include patients who died of causes not related to TB disease.

[g]Includes cases who moved, were lost, were uncooperative or refused, or had some other reason to stop therapy.

Table 6. Model Fit Statistics for the final logistic model

Parameter	Estimate	P-value
Intercept	-5.9611	<.0001
PRR	1.1012	<.0001
hiv1	1.1293	<.0001
hiv2	0.1097	0.5025
hiv1prr	0.7997	0.0321
hiv2prr	-0.3883	0.4705
dot1	-0.3313	0.1307
dot2	0.3325	0.0082
ETH	-0.1521	0.7239
ETH	0.2054	0.2381
ETH	-0.1649	0.4396
ETH	-0.3774	0.0289
AGE4	0.0537	0.7867
AGE4	0.1154	0.3915
AGE4	-0.8556	0.0003

*P-value for the Wald test for significant effect of the independent variable.

Table 7. Summary Prevalence Odds Ratio Estimates for Exposure variables.

Contrast Title	Previous TB diagnosis	HIV status	POR Estimate	95% Wald Confidence interval	
Referent	No	Negative	-	-	-
1		Positive	3.09	2.26	4.24
2		Unknown	1.12	0.81	1.54
Referent	Yes	Negative	-	-	-
3		Positive	6.88	3.50	13.52
4		Unknown	0.76	0.27	2.09

Table 8. Summary Prevalence Odds Ratio Estimates for Control Variables.

Effect	POR Estimate	95% Wald Confidence Intervals	
dot1	0.72	0.47	1.10
dot2	1.39	1.09	1.78
ETH 1 vs 5	0.86	0.37	2.00
ETH 2 vs 5	1.23	0.87	1.73
ETH 3 vs 5	0.85	0.56	1.29
ETH 4 vs 5	0.69	0.49	0.96
AGE4 1 vs 4	1.06	0.72	1.56
AGE4 2 vs 4	1.12	0.86	1.46
AGE4 3 vs 4	0.43	0.27	0.68

Table 9. Sociodemographic Characteristics of All Forms of Possible Acquired RIF-resistant (ARR) TB and 3 Sub-categories of Acquired RIF-resistant TB with consideration for INH susceptibility, and RIF and INH Susceptible TB Cases, United States, 1998-2008

	No. (%)						Prevalence Odds Ratio (95% Confidence Interval)			
Characteristics	All forms ARR (N=160)	Aqrd RIF INH-S (n =58)	Aqrd RIF INH-R (n =58)	Aqrd MDR (n =44)	RIF & INH-susceptible (n =8752)	Other (n =1531)	Aqrd RIF INH-S vs Drug susceptible	Aqrd RIF INH-R vs Drug susceptible	Aqrd MDR vs Drug susceptible	All forms of ARR vs Drug susceptible
Age categories, y										
0-14	0 (0)	0 (0)	0 (0)	0 (0)	43 (0)	14 (1)	n.d.	n.d.	n.d.	n.d.
15-24	12 (8)	3 (5)	4 (7)	5 (11)	718 (8)	181 (12)	0.41 (0.13-1.34)	0.60 (0.21-1.71)	0.98 (0.37-2.58)	0.63 (0.34-1.15)
25-44	86 (54)	33 (57)	30 (52)	23 (52)	3224 (37)	631 (14)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
45-64	47 (28)	20 (34)	19 (33)	8 (18)	3279 (37)	533 (35)	0.60 (0.34-1.04)	0.62 (0.35-1.11)	0.34 (0.15-0.77)[a]	0.54 (0.38-0.77)[a]
≥65	15 (9)	2 (3)	5 (9)	8 (18)	1488 (17)	172 (11)	0.13 (0.03-0.55)[a]	0.36 (0.14-0.93)[a]	0.75 (0.34-1.69)	0.38 (0.22-0.66)[a]
Gender										
Female	45 (28)	10 (17)	20(34)	15 (34)	2531 (29)	529(35)	0.51 (0.26-1.01)	1.29 (0.75-2.23)	1.27 (0.68-2.38)	0.96 (0.68-1.36)
Male	115 (72)	48 (83)	38 (66)	29 (66)	6221 (71)	1002 (65)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Race/ethnicity[b]										
Hispanic	50 (31)	21 (36)	15 (26)	14 (32)	2579 (30)	469 (31)	1.77 (0.83-3.77)	1.27 (0.57-2.82)	1.97 (0.76-5.13)	1.62 (1.01-2.62)[a]
American Indian	1 (1)	0 (0)	0 (0)	1 (2)	85 (1)	7 (0)	n.d.	n.d.	n.d	n.d
Asian	26 (16)	3 (5)	20 (34)	3 (7)	1207 (14)	452(30)	0.54 (0.15-1.97)	3.61 (1.68-7.73)[a]	0.90 (0.23-3.61)	1.80 (1.04-3.12)[a]
Non-Hispanic Black	57 (36)	24 (41)	13 (22)	20 (45)	2675 (31)	352 (23)	1.95 (0.93-4.09)	1.06 (0.46-2.42)	2.71 (1.09-6.77)[a]	1.78 (1.12-2.85)[a]
Non-Hispanic White	26 (16)	10 (17)	10 (17)	6 (14)	2177 (25)	236 (16)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Foreign-born nationality[c]										
Foreign-born	80 (50)	22 (38)	42 (72)	16 (36)	3719 (42)	978 (64)	0.83 (0.49-1.41)	3.55 (1.99-6.32)[a]	0.77 (0.42-1.43)	1.35 (0.99-1.85)
US-born	80(50)	36 (62)	16 (28)	28 (64)	5024 (57)	550 (36)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Occupation during 2 years prior to diagnosis[d]										
Unemployed[e]	86 (54)	29 (50)	32 (55)	25 (57)	4567 (52)	772(50)	0.89 (0.53-1.52)	1.51 (0.83-2.72)	1.43 (0.74-2.76)	1.21 (0.86-1.70)
Health care worker	3 (2)	1 (2)	1 (2)	1 (2)	182 (2)	47 (3)	0.77 (0.10-5.73)	1.18 (0.16-8.93)	1.44 (0.19-10.98)	1.06 (0.33-3.41)
Low--risk employment	57 (36)	26 (45)	17 (29)	14 (32)	3660 (42)	652 (43)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Agricultural/Correctional facility worker/Missing	14 (9)	2(3)	8 (14)	4 (9)	343 (4)	60 (4)	n.d	n.d	n.d	n.d

Correctional facility resident[d]										
Yes	14 (9)	6 (10)	2 (3)	6 (14)	349 (4)	47 (3)	2.78 (1.19-6.51)[a]	0.86 (0.21-3.54)	3.80 (1.60-9.06)[a]	2.31 (1.32-4.04)[a]
No	146 (91)	52 (90)	56 (97)	38 (86)	8402 (96)	1481 (97)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Homeless[e]										
Yes	23 (14)	12 (21)	5 (9)	6 (14)	923 (11)	97 (6)	2.23 (1.18-4.23)[a]	0.80 (0.32-2.02)	1.32 (0.56-3.13)	1.42 (0.91-2.23)
No	135 (84)	45 (78)	52 (90)	28 (86)	7708 (88)	1405 (92)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]

[a] Statistically significant at $P < 0.05$.

[b] Seven RIF/INH-susceptible TB cases (0%) and 8 other resistance pattern cases (1%) were either Native Hawaiian or had multiple or unknown racial/ethnic designations.

[c] Nationality was unknown for 9 RIF/INH-susceptible TB cases (0%) and 3 TB cases with other resistance pattern (0%).

[d] Correctional facility residence history was unknown or missing for 1 RIF/INH-susceptible TB cases (0%) and 3 TB cases other resistance patterns (0%).

[e] Homelessness was defined as homeless in the year prior to diagnosis. Homelessness history was unknown or missing for 2 all forms of acquired RIF resistant TB cases (1%), 1 acquired mono-RIF/INH-S TB cases (2%), 1 acquired mono-RIF/INH-R TB cases (2%), 121 RIF/INH-susceptible TB cases (1%) and 29 TB cases with other resistance patterns (2%).

n.d = not determined.

Table 10. Clinical Characteristics of All Forms of Possible Acquired RIF-resistant (ARR) TB and 3 Sub-categories of Acquired RIF-resistant TB with consideration for INH susceptibility, and RIF and INH Susceptible TB Cases, United States, 1998-2008

	No. (%)						Prevalence Odds Ratio (95% Confidence Interval)			
Characteristics	All forms ARR (N=160)	Aqrd RIF INH-S (n = 58)	Aqrd RIF INH-R (n = 58)	Aqrd MDR (n = 44)	RIF & INH-susceptible (n = 8752)	Other (n =1531)	Aqrd RIF INH-S vs Drug susceptible	Aqrd RIF INH-R vs Drug susceptible	Aqrd MDR vs Drug susceptible	All forms of ARR vs Drug susceptible
Prior TB diagnosis										
Yes	15 (9)	4(7)	6 (10)	5 (11)	494 (6)	149 (10)	1.23 (0.44-3.41)	1.92 (0.82-4.49)	2.13 (0.84-5.43)	1.72 (1.00-2.95)
No	*145 (91)*	54 (93)	52 (90)	39 (89)	8207 (94)	1367 (89)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Location of TB disease										
Pulmonary alone	119 (74)	36 (62)	48 (83)	35 (80)	7596 (87)	1323 (86)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Extrapulmonary alone	6 (4)	3 (5)	1 (2)	2 (5)	424 (5)	82 (5)	1.49 (0.46-4.87)	0.37 (0.05-2.71)	1.02 (0.25-4.27)	0.90 (0.40-2.06)
Pulmonary and extrapulmonary	35 (22)	19 (33)	9 (16)	7 (16)	731 (8)	126 (8)	5.48 (3.13-9.61)[a]	1.95 (0.95-3.99)	2.08 (0.92-4.70)	3.06 (2.08-4.49)[a]
Sputum microscopy result for acid-fast bacilli[b]										
Positive	122 (79)	38 (69)	49 (86)	35 (83)	6219 (75)	1077 (74)	0.76 (0.42-1.38)	2.45 (1.05-5.72)	1.50 (0.67-3.38)	1.22 (0.80-1.85)
Negative	*28 (18)*	15 (27)	6 (11)	7 (17)	1864 (22)	331 (23)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Chest radiograph result										
Abnormal	144 (90)	49 (84)	54 (93)	41 (93)	8172 (93)	1432 (94)	0.36 (0.16-0.80)[a]	0.93 (0.29-2.98)	0.70 (0.22-2.28)	0.57 (0.32-1.02)
Normal	*13 (8)*	7 (12)	3 (5)	3 (7)	421 (5)	77 (5)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Cavitary disease[c]										
Yes	46 (32)	12 (24)	22 (41)	12 (29)	3655 (45)	633 (44)	0.42 (0.22-0.82)[a]	0.80 (0.46-1.38)	0.48 (0.25-0.94)[a]	0.54 (0.38-0.79)[a]
No	*94 (65)*	33 (67)	32 (59)	29 (71)	4249 (52)	765 (53)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
HIV test result[d]										
Negative	49 (37)	8 (17)	23 (49)	18 (46)	5078 (67)	849 (68)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Positive	65(49)	37 (79)	17 (36)	11 (28)	738 (10)	135 (11)	31.82 (14.76-68.59)[a]	5.09 (2.70-9.57)[a]	4.21 (1.98-8.94)[a]	9.13 (6.25-13.33)[a]
Unknown/missing	*19 (14)*	2 (4)	7 (15)	10 (26)	1812 (24)	257 (21)	n.d.	n.d.	n.d.	n.d.

[a] Statistically significant at $P < 0.05$.

[b] Percentage is based on the number of cases with any pulmonary disease; n= 154 for all forms of acquired RIF resistant TB, n=55 for acquired mono-RIF resistant/INH-S TB, n=57 for acquired mono-RIF resistant /INH-R TB, n=42 for acquired MDR-TB, n=8751 for RIF/INH-susceptible TB and n=1449 for cases with other resistance patterns.

[c] Percentage is based on the number of cases with abnormal chest radiograph findings (provided in table).

[d] Number and percentage are based on non-Californian cases (n= 133 for all forms of acquired RIF resistant TB, n=47 for acquired mono-RIF resistant/INH-S TB, n=47 for acquired mono-RIF resistant /INH-R TB, n=39 for acquired MDR-TB, n=7628 for RIF/INH-susceptible TB and n=1241 for cases with other resistance patterns).

n.d = not determined.

Table 11. Directly Observed Therapy (DOT) Use and Treatment Outcomes of All Forms of Possible Acquired RIF-resistant (ARR) TB and 3 Sub-categories of Acquired RIF-resistant TB with consideration for INH susceptibility, and RIF and INH Susceptible TB Cases, United States, 1998-2008

	No. (%)[a]						Prevalence Odds Ratio (95% Confidence Interval)			
Characteristics	All forms ARR (N=160)	Aqrd RIF INH-S (n = 58)	Aqrd RIF INH-R (n = 58)	Aqrd MDR (n = 44)	RIF & INH-susceptible (n = 8752)	Other (n=1531)	Aqrd RIF INH-S vs Drug susceptible	Aqrd RIF INH-R vs Drug susceptible	Aqrd MDR vs Drug susceptible	All forms of ARR vs Drug susceptible
DOT[b]										
No DOT (Self administered therapy only)	9 (6)	2 (4)	5 (9)	2 (5)	621 (8)	89 (6)	0.47 (0.11-1.96)	1.25 (0.48-3.24)	0.58 (0.14-2.46)	0.77 (0.39-1.54)
Partial DOT (DOT combined with some self administered therapy)	52 (34)	17 (31)	23 (40)	12 (29)	2476 (32)	506 (37)	1.00 (0.55-1.81)	1.44 (0.83-2.50)	0.87 (0.44-1.74)	1.11 (0.79-1.58)
Complete DOT	85 (56)	31 (57)	29 (51)	25 (61)	4503 (59)	761 (55)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Sputum culture conversion[d]										
Yes	114 (81)	39 (81)	46 (87)	29 (74)	6295 (89)	1127 (89)	0.73 (0.31-1.73)	0.86 (0.37-2.02)	0.54 (0.22-1.31)	0.71 (0.43-1.18)
No	18 (13)	6 (13)	6 (11)	6 (15)	706 (10)	116 (9)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Time to conversion, median (interquartile range), d[e]	217 (88-410)	245 (86-435)	226 (108-417)	152 (75-321)	79 (54-113)	84 (54-136)	P <0.001	P <0.001	P <0.001	P <0.001
Treatment outcomes[f]										
Death due to any cause	25 (16)	7 (13)	13 (23)	5 (12)	422 (5)	99 (7)	3.32 (1.46-7.53)[c]	5.51 (2.92-10.43)[c]	2.78 (1.07-7.22)[c]	3.99 (2.55-6.25)[c]
Other, unknown, or missing[g]	26 (17)	13 (24)	6 (11)	7 (17)	451 (6)	130 (9)	5.77 (3.02-11.00)[c]	2.38 (1.00-5.66)[c]	3.64 (1.59-8.36)[c]	3.88 (2.50-6.04)[c]
Completion of therapy	*101 (66)*	34 (63)	38 (67)	29 (71)	6802 (89)	1148 (83)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]

[a] Number and percentages are based on cases who were alive at diagnosis and initially treated with 1 or more TB drugs. Case counts have been censored at 2006 to allow sufficient time for the reporting of end-of-treatment results.

[b] Information regarding DOT was missing for 6 all forms of acquired RIF resistant TB (4%), 4 acquired mono-RIF/INH-S TB (7%), 0 acquired mono-RIF/INH-R TB (0%), 2 acquired MDR-TB (5%) cases, 75 RIF/INH-susceptible TB (1%) and 21 TB cases with other resistance patterns (2%).

[c] Statistically significant at $P < 0.05$.

[d] Number and percentage are based on cases with baseline positive sputum culture result (n= 140 for all forms of acquired RIF resistant TB, n=48 for acquired mono-RIF resistant/INH-S TB, n=53 for acquired mono-RIF resistant /INH-R TB, n=39 for acquired MDR-TB, n=7067 for RIF/INH-susceptible TB and n=1267 for TB cases with other resistance patterns). Culture conversion results were missing or unknown for 8 all forms of acquired RIF resistant TB (6%), 3 acquired mono-RIF/INH-S TB (6%), 1 acquired mono-RIF/INH-R TB (2%), 4 acquired MDR-TB (10%) cases, 66 RIF/INH-susceptible TB (1%) and 22 TB cases with other resistance patterns (2%).

[e] Time to conversion is defined as the time from TB treatment start to the first negative culture, after which there were no more positive cultures. Median time is based in cases with sputum culture conversion documented and in whom culture conversion was reported (n=112 for all forms of acquired RIF resistant TB, n=37 for acquired mono-RIF resistant/INH-S TB, n=46 for acquired mono-RIF resistant /INH-R TB, n=29 for acquired MDR-TB, n=6231 for RIF/INH-susceptible TB and n=1118 for TB cases with other resistance patterns). The p-value is for a one-sided Wilcoxon two-sample test.

[f] Treatment outcome is recorded as the reason a patient stopped TB therapy. Death may include patients who died of causes not related to TB disease.

[g] Includes cases who moved, were lost, were uncooperative or refused, or had some other reason to stop therapy.

APPENDICES

Appendix A. CDC Report of a Verified Case of Tuberculosis Form in Use 1993 through 2008

Patient's Name: _____ (Last) (First) (M.I.)

Street Address: _____ (Number, Street, City, State) Zip Code)

REPORT OF VERIFIED CASE OF TUBERCULOSIS

CDC Centers for Disease Control and Prevention

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)
ATLANTA, GEORGIA 30333

FORM APPROVED OMB NO. 0920-0026 Exp. Date 09/30/2005

REPORT OF VERIFIED CASE OF TUBERCULOSIS

SOUNDEX ☐☐☐☐

1. State Reporting:
Specify: _____
Alpha State Code ☐☐

2.
State Case Number: ☐☐☐☐☐☐☐☐☐☐
City/County Case Number: ☐☐☐☐☐☐☐☐☐☐

3. Date Submitted: Mo. ☐☐ Day ☐☐ Yr. ☐☐
By: _____

4. Address for Case Counting:
City ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Within City Limits 1 ☐ Yes 2 ☐ No
County ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Zip Code ☐☐☐☐☐ – ☐☐☐☐

5. Month-Year Reported: Mo. ☐☐ Yr. ☐☐☐☐

6. Month-Year Counted: Mo. ☐☐ Yr. ☐☐☐☐

7. Date of Birth: Mo. ☐☐ Day ☐☐ Yr. ☐☐☐☐

8. Sex:
1 ☐ Male
2 ☐ Female

9. Ethnicity: *(Select one)*
1 ☐ Hispanic or Latino
2 ☐ Not Hispanic or Latino

10. Race: *(Select one or more)*
1 ☐ American Indian or Alaska Native
2 ☐ Asian *Specify (Optional):* _____
3 ☐ Black or African American
4 ☐ Native Hawaiian or Other Pacific Islander *Specify (Optional):* _____
5 ☐ White

11. Country of Origin:
If U.S., check here ☐ If not U.S., enter country code (see list) ☐☐

12. Month-Year Arrived in U.S.: Mo. ☐☐ Yr. ☐☐☐☐

13. Status at Diagnosis of TB:
1 ☐ Alive 2 ☐ Dead

14. Previous Diagnosis of Tuberculosis:
1 ☐ Yes
2 ☐ No
Yr. ☐☐☐☐ If yes, list year of previous diagnosis
1 ☐ If more than one previous episode, check here

15. Major Site of Disease:
00 ☐ Pulmonary
10 ☐ Pleural
21 ☐ Lymphatic: Cervical
22 ☐ Lymphatic: Intrathoracic
23 ☐ Lymphatic: Other
29 ☐ Lymphatic: Unknown
30 ☐ Bone and/or Joint
40 ☐ Genitourinary
50 ☐ Miliary
60 ☐ Meningeal
70 ☐ Peritoneal
80 ☐ Other*
90 ☐ Site not Stated
*If site is "Other", enter anatomic code (see list) ☐☐

16. Additional Site of Disease:
00 ☐ Pulmonary
10 ☐ Pleural
21 ☐ Lymphatic: Cervical
22 ☐ Lymphatic: Intrathoracic
23 ☐ Lymphatic: Other
29 ☐ Lymphatic: Unknown
30 ☐ Bone and/or Joint
40 ☐ Genitourinary
50 ☐ Miliary
60 ☐ Meningeal
70 ☐ Peritoneal
80 ☐ Other*
*If site is "Other", enter anatomic code (see list) ☐☐
If more than one additional site, check here ☐ 88

17. Sputum Smear:
1 ☐ Positive 3 ☐ Not Done
2 ☐ Negative 9 ☐ Unknown

18. Sputum Culture:
1 ☐ Positive 3 ☐ Not Done
2 ☐ Negative 9 ☐ Unknown

19. Microscopic Exam of Tissue and Other Body Fluids:
1 ☐ Positive 3 ☐ Not Done
2 ☐ Negative 9 ☐ Unknown
If positive, enter anatomic code(s) (see list) ☐☐ ☐☐

20. Culture of Tissue and Other Body Fluids:
1 ☐ Positive 3 ☐ Not Done
2 ☐ Negative 9 ☐ Unknown
If positive, enter anatomic code(s) (see list) ☐☐ ☐☐

21. Chest X-Ray:
1 ☐ Normal 2 ☐ Abnormal 3 ☐ Not Done 9 ☐ Unknown
If Abnormal *(check one)* 1 ☐ Cavitary 2 ☐ Noncavitary Consistent with TB 3 ☐ Noncavitary Not Consistent with TB
If Abnormal *(check one)* 1 ☐ Stable 3 ☐ Improving 2 ☐ Worsening 9 ☐ Unknown

22. Tuberculin (Mantoux) Skin Test at Diagnosis:
1 ☐ Positive 3 ☐ Not Done
2 ☐ Negative 9 ☐ Unknown
Millimeters (mm) of Induration ☐☐
If Negative, was patient anergic? 1 ☐ Yes 2 ☐ No 9 ☐ Unknown

Public reporting burden of this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to CDC, Project Clearance Officer, 1600 Clifton Road, MS D-24, Atlanta, GA 30333, ATTN: PRA (0920-0026). Do not send the completed form to this address.

Information contained on this form which would permit identification of any individual has been collected with a guarantee that it will be held in strict confidence, will be used only for surveillance purposes, and will not be disclosed or released without the consent of the individual in accordance with Section 308(d) of the Public Health Service Act (42 U.S.C. 242m).

REPORT OF VERIFIED CASE OF TUBERCULOSIS

23. HIV Status: 0 ☐ Negative 1 ☐ Positive 2 ☐ Indeterminate 3 ☐ Refused 4 ☐ Not Offered 5 ☐ Test Done, Results Unknown 9 ☐ Unknown

If Positive, Based on: 1 ☐ Medical Documentation 2 ☐ Patient History 9 ☐ Unknown

If Positive, List: CDC AIDS Patient Number ☐☐☐☐☐☐☐ (If AIDS Reported before 1993)

State HIV/AIDS Patient Number ☐☐☐☐☐☐☐☐☐☐ (If AIDS Reported 1993 or Later)

City/County HIV/AIDS Patient Number ☐☐☐☐☐☐☐☐☐☐ (If AIDS Reported 1993 or Later)

24. Homeless Within Past Year: 0 ☐ No 1 ☐ Yes 9 ☐ Unknown

25. Resident of Correctional Facility at Time of Diagnosis: 0 ☐ No 1 ☐ Yes 9 ☐ Unknown

If Yes, 1 ☐ Federal Prison 2 ☐ State Prison 3 ☐ Local Jail 4 ☐ Juvenile Correctional Facility 5 ☐ Other Correctional Facility 9 ☐ Unknown

26. Resident of Long-Term Care Facility at Time of Diagnosis: 0 ☐ No 1 ☐ Yes 9 ☐ Unknown

If Yes, 1 ☐ Nursing Home 2 ☐ Hospital-Based Facility 3 ☐ Residential Facility 4 ☐ Mental Health Residential Facility 5 ☐ Alcohol or Drug Treatment Facility 6 ☐ Other Long-Term Care Facility 9 ☐ Unknown

27. Initial Drug Regimen:

	NO	YES	UNK.		NO	YES	UNK.		NO	YES	UNK.
Isoniazid	0 ☐	1 ☐	9 ☐	Ethionamide	0 ☐	1 ☐	9 ☐	Amikacin	0 ☐	1 ☐	9 ☐
Rifampin	0 ☐	1 ☐	9 ☐	Kanamycin	0 ☐	1 ☐	9 ☐	Rifabutine	0 ☐	1 ☐	9 ☐
Pyrazinamide	0 ☐	1 ☐	9 ☐	Cycloserine	0 ☐	1 ☐	9 ☐	Ciprofloxacin	0 ☐	1 ☐	9 ☐
Ethambutol	0 ☐	1 ☐	9 ☐	Capreomycin	0 ☐	1 ☐	9 ☐	Ofloxacin	0 ☐	1 ☐	9 ☐
Streptomycin	0 ☐	1 ☐	9 ☐	Para-Amino Salicylic Acid	0 ☐	1 ☐	9 ☐	Other	0 ☐	1 ☐	9 ☐

28. Date Therapy Started: Mo. ☐☐ Day ☐☐ Yr. ☐☐

29. Injecting Drug Use Within Past Year: 0 ☐ No 1 ☐ Yes 9 ☐ Unknown

30. Non-Injecting Drug Use Within Past Year: 0 ☐ No 1 ☐ Yes 9 ☐ Unknown

31. Excess Alcohol Use Within Past Year: 0 ☐ No 1 ☐ Yes 9 ☐ Unknown

32. Occupation *(Check all that apply within the past 24 months):*

1 ☐ Health Care Worker
2 ☐ Correctional Employee
3 ☐ Migratory Agricultural Worker
4 ☐ Other Occupation
5 ☐ Not Employed within Past 24 Months
9 ☐ Unknown

Comments:

Patient's Name: _____ (Last) (First) (M.I.)

Street Address: _____ (Number, Street, City, State) _____ Zip Code)

REPORT OF VERIFIED CASE OF TUBERCULOSIS

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)
ATLANTA, GEORGIA 30333

CENTERS FOR DISEASE CONTROL AND PREVENTION

REPORT OF VERIFIED CASE OF TUBERCULOSIS

FORM APPROVED OMB NO. 0920-0026 Exp. Date 09/30/2005

Initial Drug Susceptibility Report

(Follow Up Report – 1)

SOUNDEX

State Reporting:
Specify: _____
Alpha State Code

Year Counted:

State Case Number:

City/County Case Number:

Submit this report for all culture-positive cases.

33. Initial Drug Susceptibility Results:

Was Drug Susceptibility Testing Done: 0 No 1 Yes 9 Unknown

If answer is No or Unknown, do not complete rest of report.

If Yes, Enter Date First Isolate Collected for Which Drug Susceptibility Was Done? Mo. Day Yr.

34. Susceptibility Results:

	Resistant	Susceptible	Not Done	Unknown
Isoniazid	1	2	3	9
Rifampin	1	2	3	9
Pyrazinamide	1	2	3	9
Ethambutol	1	2	3	9
Streptomycin	1	2	3	9
Ethionamide	1	2	3	9
Kanamycin	1	2	3	9
Cycloserine	1	2	3	9
Capreomycin	1	2	3	9
Para-Amino Salicylic Acid	1	2	3	9
Amikacin	1	2	3	9
Rifabutine	1	2	3	9
Ciprofloxacin	1	2	3	9
Ofloxacin	1	2	3	9
Other	1	2	3	9

Comments:

Patient's Name: _____ (Last) (First) (M.I.)

Street Address: _____ (Number, Street, City, State) Zip Code)

REPORT OF VERIFIED CASE OF TUBERCULOSIS

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

REPORT OF VERIFIED CASE OF TUBERCULOSIS

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL
AND PREVENTION (CDC)
ATLANTA, GEORGIA 30333

FORM APPROVED OMB NO. 0920-0026 Exp. Date 09/30/2005

Case Completion Report

(Follow Up Report – 2)

SOUNDEX

State Reporting:
Specify: _____
Alpha State Code

Year Counted:

State Case Number:

City/County Case Number:

Submit this report for all cases in which the patient was alive at diagnosis.

35. Sputum Culture Conversion Documented:
0 No 1 Yes 9 Unknown

If Yes, Date Specimen Collected on Initial Positive Sputum Culture: Mo. Day Yr.

If Yes, Date Specimen Collected on First Consistently Negative Culture: Mo. Day Yr.

36. Date Therapy Stopped: Mo. Day Yr.

37. Reason Therapy Stopped:
1 Completed Therapy 3 Lost 5 Not TB 7 Other
2 Moved 4 Uncooperative or Refused 6 Died 9 Unknown

38. Type of Health Care Provider:
1 Health Department
2 Private/Other
3 Both Health Department and Private/Other
9 Unknown

39. Directly Observed Therapy:
0 No, Totally Self-Administered
1 Yes, Totally Directly Observed
2 Yes, Both Directly Observed and Self-Administered
9 Unknown

If Yes, Give Site(s) of Directly Observed Therapy:
1 In Clinic or Other Facility
2 In the Field
3 Both in Facility and in the Field
9 Unknown

Number of Weeks of Directly Observed Therapy: Weeks

40. Final Drug Susceptibility Results:
Was Follow-up Drug Susceptibility Testing Done? 0 No 1 Yes 9 Unk.
If answer is No or Unknown, do not complete rest of report.

If Yes, Enter Date Final Isolate Collected for Which Drug Susceptibility Was Done: Mo. Day Yr.

41. Final Susceptibility Results:

	Resistant	Susceptible	Not Done	Unknown
Isoniazid	1	2	3	9
Rifampin	1	2	3	9
Pyrazinamide	1	2	3	9
Ethambutol	1	2	3	9
Streptomycin	1	2	3	9
Ethionamide	1	2	3	9
Kanamycin	1	2	3	9
Cycloserine	1	2	3	9
Capreomycin	1	2	3	9
Para-Amino Salicylic Acid	1	2	3	9
Amikacin	1	2	3	9
Rifabutine	1	2	3	9
Ciprofloxacin	1	2	3	9
Ofloxacin	1	2	3	9
Other	1	2	3	9

Comments:

Appendix B. Emory University IRB Exemption Letter

EMORY UNIVERSITY | Institutional Review Board

October 15, 2010

Lisa Sharling, PhD
Rollins School of Public Health, Department of Epidemiology
1518 Clifton Rd
Atlanta, GA 30022

RE: Determination: No IRB Review Required
Rifamycin-resistant tuberculosis in the United States: 1998–2008
PI: Lisa Sharling, PhD

Dear Dr. Sharling:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because Emory is not engaged in this research project. Specifically, in this project, you are acting as an intern at the CDC, performing research and public health surveillance work as dictated by the needs of the CDC. All of your work on this project that involves access to identifiable data will be done at the CDC under the terms of your internship. You will write up the results of this work for the CDC and for your thesis as a Masters of Public Health student, but no separate, original research aims will be pursued for your thesis.

This determination could be affected by substantive changes in the study design and research aims, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Rebecca Rousselle

Rebecca Rousselle, CIP
Lead Research Protocol Analyst

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu

Appendix C. Signed Assurance of Confidentiality for Non CDC/NCHHSTP Employees With Access to the National Tuberculosis Surveillance System

Agreement to abide by policies and procedures to maintain confidentiality and data security and restrictions on release of data from the national TB surveillance system

I, Lisa Sharling, understand that data collected by CDC through the national TB surveillance system is protected by an Assurance of Confidentiality that prohibits disclosure of any information that could be used to directly or indirectly identify any individual on whom a record is maintained at CDC. I agree to adhere to the policies and procedures outlined in the attached document and specified below.

I agree to the following (check each item):

☑ I will not give my access password to anyone.

☑ I will treat all data at my desk site confidentially and maintain records that could be used to directly or indirectly identify any individual on whom CDC maintains a record in a locked file cabinet.

☑ I will keep all hard copies of data runs containing record-level or line listed data or other data containing potentially patient identifiable information locked in a file cabinet when not in use. Files will be maintained in accordance with CDC file management policy.

☑ I will not produce a "back-up" copy of RVCT data, or other related databases maintained by Surveillance, Epidemiology, and Outbreak Investigations Branch (SEOIB), DTBE, NCHHSTP to store in locations other than the designated LAN workspace for use in this project.

☑ I will not remove electronic files, records or databases from the worksite (CDC/NCHHSTP/DTBE). I will not remove electronic files, records or databases from the worksite (CDC/NCHHSTP/DTBE).

☑ I will not copy potentially identifiable data onto, including but not limited to, laptops, desktop hard drives, flash drives, compact disks, unless the file is password protected, or transmit data by e-mail or internet that is not a certified secure server, such as the Secure Data Network.

☑ I will not remove hard copies of case reports, lab reports, or any records containing sensitive data and information or the like from the worksite.

☑ I will not remove from the worksite (CDC/NCHHSTP/DTBE) tabulations or data in any format that could directly or indirectly identify any individual.

☑ I will maintain confidentiality of records on individuals in all discussions, communications, emails, tabulations, presentations, and publications by using only the minimum information necessary to describe an individual case.

☑ I will not release any national or regional tabulation from the RVCT database in either narrative or tabular format without the express permission of my CDC project supervisor and the Surveillance Team Leader.

☑ I will not release, either inside or outside CDC, State/Territorial, city or county specific data (line list or in tabular form) in any format (e.g., publications, presentations, slides, interviews) without the written consent of the Surveillance Team Leader, and the Chief, SEOIB, DTBE, NCHHSTP.

☑ When presenting or publishing site-specific data in accordance with the restrictions outlined above, I will inform and obtain appropriate permission from the appropriate state and local health departments in advance of the release of state or local data, so as to afford them the opportunity to review for accuracy, and anticipate local queries and prepare their response.

☑ When presenting or publishing data from analyses of RVCT data, I will adhere to the principles and guidelines outlined in this agreement as well as CDC clearance procedures.

☑ I understand that release of data not specifically permitted by this agreement is prohibited unless written permission is first obtained from the Surveillance Team Leader.

☑ I will not release data to the press or media without prescreening and approval of the request by the Office of Communications, NCHHSTP and the Chief of SEOIB, DTBE, NCHHSTP.

☑ **I have read this document "Agreement to abide by policies and procedures to maintain confidentiality and data security and restrictions on release of data from the national TB surveillance system" and the attached documents, "Protocol to Maintain Data Security and Confidentiality for the National TB Surveillance System" and "Assurance of Confidentiality for Reports of Verified Case of Tuberculosis (RVCT)," and I agree to abide by them. For CDC employees, failure to comply with this agreement may result in disciplinary action, including possible termination of employment.**

Safeguards for Individuals and Establishments Against Invasions of Privacy
(308(d) Assurance of Confidentiality for Non CDC /NCHHSTP Employees With Access to the National Tuberculosis Surveillance System

In accordance with the Privacy Act of 1974 (5 U.S.C. 552a), I, as a non-CDC Employee (Guest Researcher, Visiting Fellow, Student, etc.) may be given access to personally identifiable and indirectly identifiable data that is covered by the Privacy Act and/or Section 308(d) of the Public Health Service Act (42 U.S.C. 242m). As a condition of this access and my participation in this

project, I am required to comply with the following safeguards for individuals and establishments against invasions of privacy.

1. I agree to be bound by the following assurance:

   In accordance with Section 308(d) of the Public Health Service Act (42 U.S.C. 242m), all respondents are assured that the confidentiality of their responses to this information request will be maintained and that no information obtained in the course of this activity will be disclosed in a manner in which the individual or establishment is identifiable, unless the individual or establishment has consented to such disclosure, to anyone other than authorized staff of CDC.

2. I agree to maintain the following safeguards to assure that confidentiality is protected and to provide for the physical security of the records:

   To preclude observation of confidential information by persons not authorized to have access to the information on the project, I shall maintain all records that identify individuals or establishments or from which individuals or establishments could be identified in locked containers or protected computer files when not under immediate supervision by me or another authorized member of the project. The keys or means of access to these containers or files are not to be given to anyone other than CDC authorized staff. I further agree to abide by any additional requirements imposed by CDC for safeguarding the identity of individuals and establishments.

☑ By checking this box, I indicate that I have carefully read and understand this agreement and the assurance which pertains to the confidential nature of all records to be handled in regard to this project. As a(n) (Non-CDC employee) (guest researcher, student, etc.), I understand that I am prohibited from disclosing any such confidential information that has been obtained under this project to anyone other than authorized staff of CDC. I understand that any disclosure in violation of this Confidentiality Pledge will lead to termination of my employment as well as other penalties.