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RIFAMPIN-RESISTANT TUBERCULOSIS IN THE UNITED STATES, 1998–2014

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Abstract

Background—Monoresistance to rifamycins necessitates longer and more toxic regimens for tuberculosis (TB). We examined characteristics and mortality associated with rifampin-monoresistant (RMR) TB in the United States.

Methods—We analyzed *Mycobacterium tuberculosis* culture-positive cases reported to the National TB Surveillance System (excluding California because HIV infection was not reported to CDC during 2005-2010) between 1998 and 2014. We defined: (1) RMR TB found on initial drug susceptibility testing (DST), and (2) possible acquired rifampin-resistant (ARR) TB. We assessed temporal trends in RMR TB. For both classifications of rifampin resistance, we calculated adjusted risk ratios (adjRR) and 95% confidence intervals (CI) for social and clinical characteristics associated with mortality when compared to drug-susceptible TB in multivariable models using backwards selection.

Results—Of 180,329 TB cases, 126,431 (70%) cases were eligible for analysis, with 359 (0.28%) of eligible cases reported as RMR. The percentage of RMR TB cases with HIV declined 4% annually during 1998–2014. Persons with HIV and prior TB were more likely to have RMR TB (adjRR=25.9, CI=17.6–38.1), as were persons with HIV and no prior TB (adjRR=3.1, CI=2.4–4.1), versus those without either characteristic, controlling for other statistically significant variables. RMR cases had greater mortality (adjRR=1.4, CI=1.04–1.8), controlling for HIV and other variables. Persons with HIV had greater risk of ARR than persons without HIV (adjRR=9.6,

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POTENTIAL CONFLICTS OF INTEREST
All authors: No reported conflicts.

CI=6.9–13.3) and ARR was also associated with increased mortality, controlling for HIV and other variables.

Conclusions—All forms of rifampin resistance were positively associated with HIV infection and increased mortality.

Summary:

We examined cases of rifampin-monoresistant (RMR) and acquired rifampin-resistant (ARR) tuberculosis (TB) in the United States during 1998–2014. All forms of rifampin resistance were positively associated with HIV infection, delayed culture conversion and increased mortality.

Keywords

tuberculosis; rifampin; isoniazid; HIV; drug resistance

INTRODUCTION

From reports to the U.S. National TB Surveillance System (NTSS) by the 50 states and District of Columbia over the previous two decades, the percentage of TB cases that were drug resistant remained stable[1]. Nevertheless, drug resistance poses significant barriers to identification of appropriate treatment and treatment completion and to achievement of the U.S. Centers for Disease Control and Prevention (CDC) goal of TB elimination[2].

Rifampin is effective against *Mycobacterium tuberculosis (Mtb)* organisms throughout the course of TB infection with bactericidal activity both in the stationary and log growth phases, and is the principal rifamycin antibiotic used worldwide[3]. The inclusion of rifampin with pyrazinamide has reduced drug susceptible TB treatment duration from 18 months to 6 months[4]. The consequences of rifampin resistance include fewer and more expensive therapeutic options, prolonged treatment, greater toxicity, and poorer clinical outcomes[5–9].

The NTSS captures demographic, clinical, and laboratory information for each reported TB case, including initial drug susceptibility testing (DST) results (usually performed within 30 days of TB diagnosis). Of *Mtb* culture-positive U.S. TB cases, initial DST for isoniazid and rifampin was reported for 91% of cases in 1998 and 96% in 2014[10, 11]. The HIV status of TB patients was known for 47% of reported cases in 1998 and 89% in 2014[1]. Previous studies using the NTSS have examined frequency and determinants of drug-resistant TB, including isoniazid monoresistance[12] and primary and acquired extensively drug-resistant TB[13]. A study of rifampin monoresistant (RMR) TB in California found an association with HIV infection and increased mortality[8]. Highly intermittent (such as once- or twice-weekly) rifampin-based treatment regimens, HIV infection, previous occurrence of TB disease (i.e., prior TB), extrapulmonary or disseminated TB, malabsorption/low serum levels, and patient nonadherence have been associated with acquired rifampin-resistant (ARR) TB, treatment failure, and relapse[8, 14–23]. Further investigation of factors associated with rifampin resistance using national surveillance data might help to further characterize RMR and ARR TB in the United States.

Using the NTSS database from 1998–2014, we examined the associated characteristics and trends over time for two classifications of rifampin-resistant cases: (1) RMR TB found on initial DST, and (2) possible ARR TB.

METHODS

Population

We analyzed *Mtb* culture-positive cases alive at diagnosis reported to the NTSS by 49 states and the District of Columbia between 1998 and 2014. Cases reported by California were excluded because only TB cases matched to the California AIDS registry were reported to the NTSS from 1993–2004 as HIV positive, and no HIV infection status of TB cases was reported during 2005–2010.

Ethical review

This study was approved in ethical review by CDC as a secondary analysis of public health surveillance data that did not require informed consent or further institutional review board approval.

Definitions, Inclusion, and Exclusion Criteria

We included *Mtb* culture-positive cases that had initial DST results for isoniazid, rifampin, and ethambutol. Reported DST results include phenotypic drug susceptibility testing only. We did not include DST for pyrazinamide as an eligibility criterion because results were missing for approximately 25% of cases. We categorized cases as RMR TB, isoniazid-monoresistant (IMR) TB, or multidrug-resistant TB (resistant to at least isoniazid and rifampin, MDR) using initial DST reports (Table 1, Figure 1a). Possible ARR was defined as rifampin susceptibility on the initial DST and resistance on the final DST (Table 2; Figure 1b). Based on evidence that risk factors for ARR may be distinct from those associated with acquired MDR TB[20–22, 24–26], cases of possible ARR TB were further classified according to the presence of isoniazid resistance (Table 2; Figure 1b). The outcome of mortality was compared to a combined outcome of treatment completion or stopping therapy due to adverse treatment event; other outcomes (i.e., lost, refused treatment, other, unknown) were excluded.

Statistical Analysis

Cochran-Mantel-Haenszel methods were used to calculate risk ratios (RRs) and 95% confidence intervals (CIs) for bivariate associations of sociodemographic and clinical variables with RMR TB, IMR TB, and MDR TB compared to DS TB, and for associations with ARR TB (and each of the three sub-classes) compared to rifampin- and isoniazid-susceptible cases. EpiTable (v1.0.1,© 2013, Tap Semiotic LLC) was used to calculate Fishers' Exact CIs for bivariate associations where cells had <5 counts. We report statistically significant unadjusted risk ratios (RR) and adjusted risk ratios (adjRR) and associated CIs of sociodemographic and clinical characteristics with the occurrence of RMR TB and ARR TB, and the outcome of death from any cause during treatment (cause of death may be unrelated to TB). Multivariable logistic regression was used with backwards elimination of variables based on *P*-value cutoff of .05 to select variables for log binomial

models to obtain adjRRs. Variables in initial models were selected based on expert opinion or bivariate statistical significance at the 95% confidence level. In multivariable analyses, dummy variable coding was used to create mutually exclusive categories (e.g., 1 for the factor, 0 for all else) within polytomous factors. For HIV, both HIV positive versus all else, and HIV unknown versus all else were included in initial models. Observations with unknown prior TB were excluded from analysis. For multivariable models of mortality and ARR, we analyzed association with any use of directly observed therapy (DOT). For ARR, small sample sizes precluded systematic testing of interaction terms.

To compare time from treatment start to sputum culture conversion for pulmonary DS cases and drug-resistant cases that were initially sputum culture positive, a one-sided Wilcoxon two-sample test was used. The statistical significance of trends in the change of proportions over time was assessed using the t statistic for year in linear regression of the outcome. We report *P* values for differences at the 95% confidence level and interquartile ranges (IQR).

RESULTS

Rifampin Monoresistance at Initial DST

Between 1998 and 2014, 228,473 TB cases were reported to CDC from all 50 U.S. states. After exclusion of 48,144 cases from the state of California, 180,329 cases were included. Seventy-eight percent (141,428) of 180,329 potentially eligible TB cases had a positive culture for *Mtb* (Figure 1a). Of all culture-positive TB cases, 126,431 (89.4%) had an initial DST result reported for rifampin, isoniazid, and ethambutol and met one of the resistance patterns included in this analysis. Of the 126,431 eligible cases, 0.28% (359) were RMR at initial DST (primary RMR), 1.25% (1,575 cases) were MDR and 4.10% (5,184 cases) were IMR. The remaining 119,313 (94.37%) cases were drug-susceptible. Between 1998 and 2014, the proportion of RMR TB cases among all culture positive cases for which an initial DST result was reported for rifampin, isoniazid, and ethambutol varied between 0.16% and 0.40% (Figure 2a). The proportion of IMR TB cases varied between 3.1% and 5.0% (Figure 2b) and the proportion of MDR TB cases varied between 0.97% and 1.53% (Figure 2c).

The sociodemographic and clinical characteristics of RMR, IMR, and MDR TB cases are summarized with unadjusted risk ratios compared to DS TB in Supplementary Tables 1 and 2. Although the proportion of pulmonary RMR TB cases with reported sputum culture conversion was not significantly different from that of pulmonary DS cases (84% vs. 82%, Supplementary Table 2), there was a significant (P<.01) delay in sputum culture conversion for RMR TB cases (median 60 days, IQR 33–95 days), compared with median time for DS cases (49 days, IQR 26–77 days). The delay in sputum culture conversion was also significantly longer for MDR TB cases (median, 68 days; IQR 37–114 days; P<.01) compared with that of DS cases. However, no statistically significant difference was found for median time for sputum culture conversion between the MDR-TB and RMR-TB cases (P = 0.11).

Persons with HIV and prior TB were most likely to have RMR TB (adjRR=25.9, CI=17.6-38.1), and persons with HIV and no prior TB (adjRR=3.1, CI=2.4–4.1) were also more likely to have RMR TB compared to those without either, controlling for the other

variables remaining in the model (Table 3). The percentage of RMR cases with HIV infection declined significantly (P=.02) between 1998 and 2014 (at approximately 3.7% annually), but not the percentage of HIV/TB cases with RMR (P=.67) (Figure 3). Compared to the age category <64 years, the risk of RMR was lower among those aged ≥ 65 years (adjRR=0.4, CI=0.3–0.6).

Eleven percent (39/359) of RMR TB cases, compared with 8% (10,023/119,313) of persons with DS TB, died and did not complete treatment; the corresponding proportions for persons with IMR TB and MDR TB were 6% (331/5,184) and 10% (161/1,575), respectively (Supplementary Table 2). Multivariable analysis of mortality during TB treatment showed that cases with RMR TB had a statistically significant greater mortality than DS TB cases (adjRR=1.4, CI= 1.04–1.8) (Table 4). Patients with MDR TB (adjRR=2.0, CI=1.8–2.2) also had greater mortality than those with DS TB, controlling for HIV infection (adjRR=2.9, CI=2.7–3.0), and for TB that was both extrapulmonary and pulmonary (versus pulmonary only or extrapulmonary only, adjRR=1.4, CI=1.3–1.45), controlling for the other variables remaining in the model. Other characteristics associated with higher mortality included: unknown HIV status (compared to known HIV status), male sex, American Indian or Alaskan Native race, black or African American race and Hispanic, with all race/ethnic groups compared with non-Hispanic Asians. Persons aged ≥25 years were also at greater risk of mortality than those of younger ages. Those with less mortality included non-U.S.–born origin (compared to U.S.-born), correctional facility inmates, and patients who received any DOT (Table 4).

Acquired Rifampin Resistance

Of 141,428 culture-positive TB cases, reported to the NTSS between 1998 and 2014 from all states except California, 12,236 (8.7%) had both initial and final DST results reported, of which 10,168 met one of the case definitions included in this analysis (Figure 1b; Table 2). Of the 10,168 cases analyzed, 10,015 remained rifampin- and isoniazid-susceptible (98.5%) and 153 (1.5%) were possible ARR TB cases; 43 (0.4%) ARR-TB cases were isoniazid-susceptible at initial DST, but isoniazid-resistant at final DST (ARR-MDR); 59 (0.6 %) were isoniazid-resistant at initial DST (ARR-INH-R), and 51 (0.5%) cases were isoniazid-susceptible at both initial and final DST (ARR-INH-S; acquired rifampin monoresistance) (Figure 1b). Cases with an alternative drug resistance pattern (2,068) were excluded.

The sociodemographic and clinical characteristics of ARR TB (and the three subclasses) are summarized with unadjusted risk ratios compared to rifampin- and isoniazid-susceptible cases in Supplementary Tables 3 and 4. While the proportion of pulmonary ARR TB cases with reported culture conversion was greater (RR=1.02, CI=1.00-1.03) than for rifampin- and isoniazid-susceptible cases, there was a significant (P<.01) delay in time to sputum culture conversion for ARR TB cases (median 190 days, IQR 75–362 days) compared with time to sputum culture conversion of rifampin- and isoniazid-susceptible cases (median 76 days, IQR 53–110 days) (Table 4). For all subclasses of ARR, there was a significant delay in sputum culture conversion.

Persons with HIV were most likely to have ARR TB (adjRR=9.56, CI=6.89–13.28) compared to persons without HIV, controlling for Asian race, birth origin, having resided in

a correctional facility at TB diagnosis, and receipt of treatment with any DOT (Table 5). Noteworthy was the high proportion (78%) of persons with HIV among the ARR-INH-S subclass; the proportions of persons with HIV for the ARR-INH-R and ARR-MDR subclasses were lower at 34% and 26% respectively (Supplementary Table 4). Compared to cases of all other race/ethnicities, Asians had a 90% greater risk of ARR TB (adjRR=1.9, CI=1.2-3.05) (Table 5); of the 3 subclasses of ARR, ARR-INH-R cases had the highest proportion of Asians (34%) (Supplementary Table 3). Compared to U.S.-born cases, non-U.S.–born cases had a 60% greater risk of ARR TB (adjRR=1.6, CI=1.1–2.3). The risk for ARR TB was more than two times higher among correctional facility inmates than among nonincarcerated persons (adjRR=2.4, CI=1.4–4.0) (Table 5).

Seventeen percent (26/153) of ARR TB patients died before completing TB treatment, compared with 5% (519/10,015) of rifampin- and isoniazid-susceptible cases (Supplementary Table 4). Death from any cause during TB treatment, compared with completion of treatment or stopping treatment for adverse event was more than twice as likely among ARR cases than among rifampin- and isoniazid-susceptible-TB cases (adjRR=2.4, CI=1.8-3.4), while controlling for the greater risk with age ≥65 (adjRR=6.8, CI=5.4–8.6, compared to ages <45), age 45–64 (adjRR=2.2, CI=1.7–2.7, compared to ages <45), HIV (adjRR=4.8, CI=3.9–6.0, compared to HIV negative), correctional facility residence (adjRR=1.6, CI=1.1–2.4), and unknown HIV status (adjRR=1.4, CI=1.1–1.7, compared to HIV negative). Prior TB disease (adjRR=1.4, CI=1.1–1.8, compared to no prior TB) and both extrapulmonary and pulmonary TB (adjRR=1.6, CI=1.3–2.0, compared to pulmonary-only, extrapulmonary-only or unknown sites of disease) were also associated with greater mortality during TB treatment. Characteristics associated with less mortality included: being non-U.S.–born (adjRR=0.6, CI=0.4–0.7, compared to U.S.-born) and receipt of treatment with any DOT (adjRR=0.5, CI=0.4–0.6, compared to no DOT) (Table 6).

DISCUSSION

Analysis of data from all *Mtb* culture-positive cases reported to the NTSS (excluding California) between 1998 and 2014 indicated that persons with HIV, especially those with prior TB, were at greatest risk of having RMR TB at initial DST. Although we excluded California TB cases because of gaps in HIV reporting to CDC, studies from California[8, 23, 27] of all HIV/TB cases have found similar results.

In 1998, the proportion of persons with HIV who had RMR TB was less than 1% and had not changed significantly over the study period, but 52% of RMR TB cases having known HIV status were persons with HIV and that proportion declined (3.7%, or approximately 4%, annually) over the period. This decline might reflect the overall decline (4.4%, or approximately 4% annually, Robert Pratt, CDC, personal communication) in the percentage of TB with HIV because of improved HIV treatment and treatment for latent TB infection. However, HIV is still a risk for RMR TB at TB diagnosis. Rifabutin (another rifamycin) had been used for prevention of infection with *Mycobacterium avium* complex (MAC, a common opportunistic respiratory tract pathogen), until azithromycin was found to be superior (1996) and routine MAC prophylaxis was no longer recommended (1999)[28, 29]. Without individual patient data on previous medications, antiretroviral treatment, or

immunosuppression, we could not determine whether rifabutin MAC prophylaxis contributed to RMR TB. Low serum levels of rifampin have also been described in persons with HIV[30, 31], and may contribute to the development of resistance. Therapeutic drug monitoring to assure adequate drug levels could help prevent the emergence of acquired rifampin resistance. Another possibility is that persons with HIV became infected with RMR TB through primary transmission. Because of heightened susceptibility to rapid TB progression, persons with HIV have higher rates of recent TB transmission[32]. Additional research is needed in this area. We found that persons with HIV were also at high risk for developing ARR. ARR TB was twice as common among inmates diagnosed in correctional settings, and mortality was greater.

There was a significant delay in median time to sputum culture conversion for RMR TB cases compared to DS cases, which was comparable to MDR TB and supports rifampin being the main driver of the delay for MDR TB. There was also a delay in culture conversion for ARR TB cases compared with rifampin- and isoniazid-susceptible cases. This suggests a delay in placing RMR TB and ARR TB cases on effective TB therapy, or inadequate dosing or adherence to TB medications. The use of rapid TB diagnostics (nucleic acid amplification tests [NAATs], such as the Xpert® MTB/RIF assay (Cepheid, Inc., Sunnyvale, CA) could reduce time to diagnosis of both TB disease and rifampin resistance in cases with RMR, and thus time to effective treatment[33, 34]. Because studies found poor TB outcomes among persons with HIV receiving intermittent dosing of anti-TB medications, daily dosing is now recommended[35]. Unfortunately, adherence to medications through culture conversion could not be assessed using NTSS data, and additional studies are needed to assess adherence to anti-TB drug regimens.

In our data, controlling for treatment using DOT and for HIV infection and other drug resistance, RMR TB was associated with 40% increased mortality. Controlling for HIV, DOT, sites of disease, and age ≥65, ARR was also associated with a more than 2-fold increased mortality. One limitation of this finding is that we did not control for duration of treatment; the 12-month treatment regimen for rifampin-resistant TB, compared with 6–10 months for DS TB, might have increased the opportunity for death during treatment compared to DS TB. We excluded patients who were lost to follow up in mortality analyses; while it allowed a clean comparison of mortality with treatment completion, results for patient populations that have large lost to follow up (e.g., correctional) might show considerable bias. However, our findings are similar to studies examining TB mortality using NTSS data[36, 37] and one that combined medical record reviews with surveillance data[38].

Further limitations of our analysis included its retrospective nature and limited variables collected by the NTSS, including only initial and final DSTs (despite many DSTs occurring during treatment), lack of genotyping comparison at diagnosis and at acquired resistance, and data only on initial TB treatment regimens. However, given the low prevalence of RMR TB in the United States, prospective studies would require potentially unattainably large sample sizes. Final DSTs were reported for less than 10% of patients, which may have biased the acquired resistance results unpredictably. The small number of cases with a final DST limited statistical power to identify statistically significant associations since ARR is

rare. Failure to detect rifampin drug resistance has been found to be more common than false identification of resistance, which if applicable to our data would have attenuated our findings[39]. Finally, variability in methods used for *Mtb* culture and DST may have influenced temporal trends in drug resistance.

Conclusions

This study of 17 years of surveillance data is the largest identified study of rifampin resistance performed in the United States. Persons with HIV were found to be at greatest risk of RMR and ARR. All forms of rifampin resistance were positively associated with HIV infection, delayed culture conversion and increased mortality. Although the prevalence of rifampin-resistant TB is lower than that of isoniazid-resistant TB, RMR mortality was greater than for IMR, and comparable to that of MDR TB cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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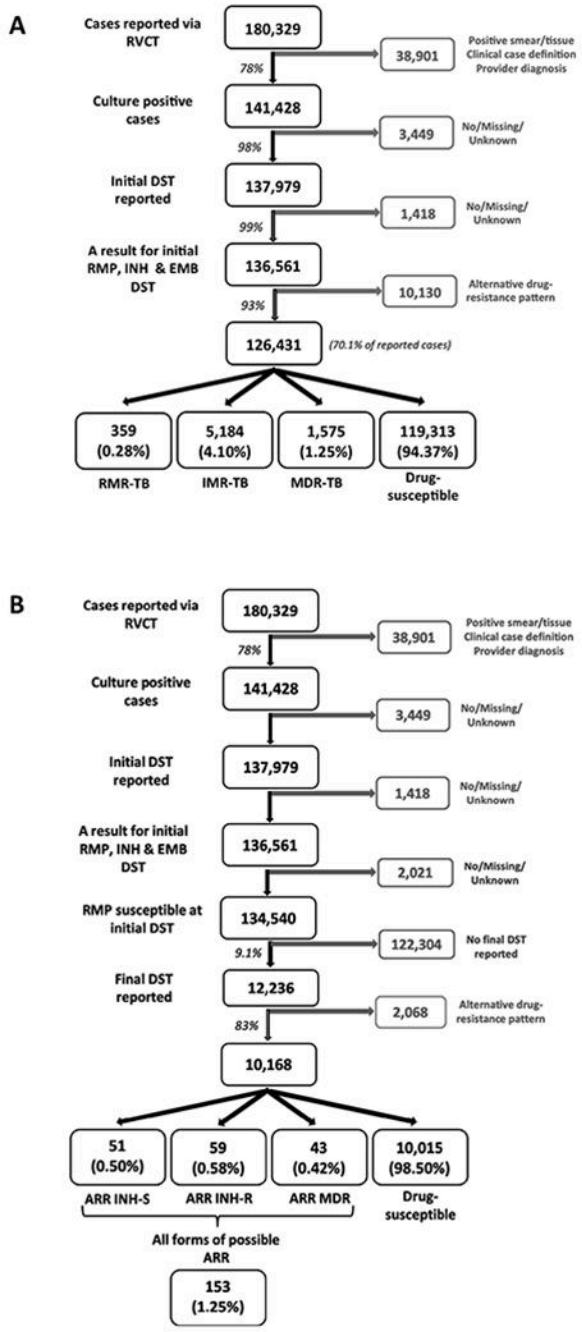

Figure 1. Selection of rifampin-resistant tuberculosis cases (1998–2014)

A total of 228,473 tuberculosis cases were reported to CDC from all 50 US states 1998–2014; 48,144 cases from the state of California were excluded due to incomplete reporting of HIV status during the time period analyzed, resulting in 180,329 potentially eligible cases. A) Rifampin-monoresistant tuberculosis (RMR TB), isoniazid-monoresistant tuberculosis (IMR TB), multidrug-resistant tuberculosis (MDR TB) at initial drug susceptibility testing (DST). Cases with reported resistance to rifabutin and susceptibility to rifampin were excluded due to suspected lab errors and are included with the cases with an

'alternative drug resistance pattern'. RMP; rifampin, INH; isoniazid, EMB; ethambutol. **B)** Three subclasses of possible acquired rifampin-resistant (ARR) TB were defined based on isoniazid susceptibility at initial and final DST, isoniazid-susceptible at both initial and final DST (ARR-INH-S), isoniazid-resistant at initial DST (ARR-INH-R) and isoniazid-susceptible at initial DST, but isoniazid-resistant at final DST (ARR-MDR).

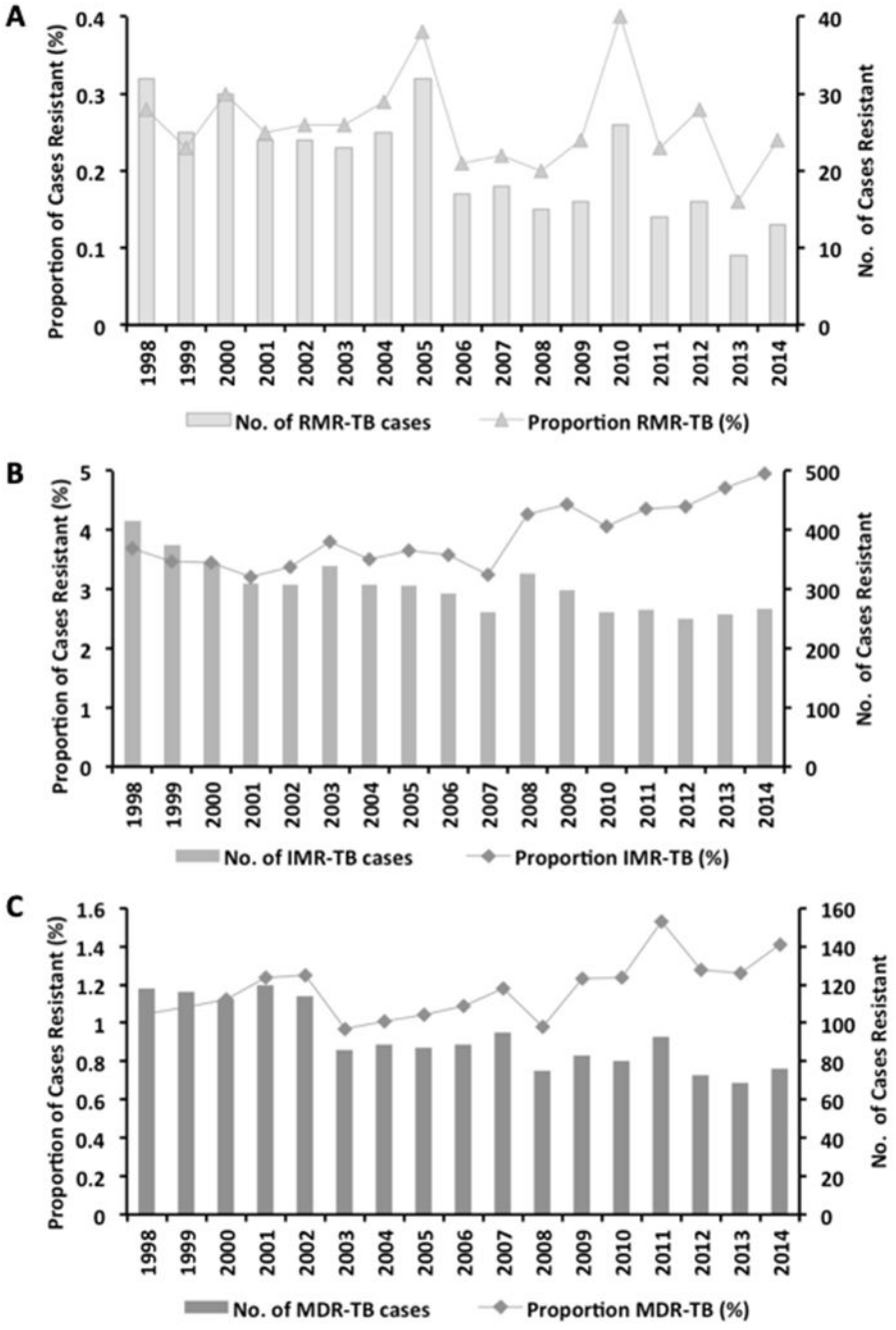

Figure 2. Proportion of tuberculosis cases that were reported as rifampin-monoresistant, isoniazid-monoresistant and multidrug-resistant at initial drug susceptibility testing in the United States*, 1998–2014

The proportion of resistant cases was calculated among all culture positive cases for which an initial susceptibility result was reported for rifampin, isoniazid, and ethambutol. Rifampin-monoresistant tuberculosis (RMR TB), isoniazid-monoresistant tuberculosis (IMR TB), multidrug-resistant tuberculosis (MDR TB) at initial final drug susceptibility testing. *Excludes the state of California due to incomplete reporting of HIV status during the time period analyzed.

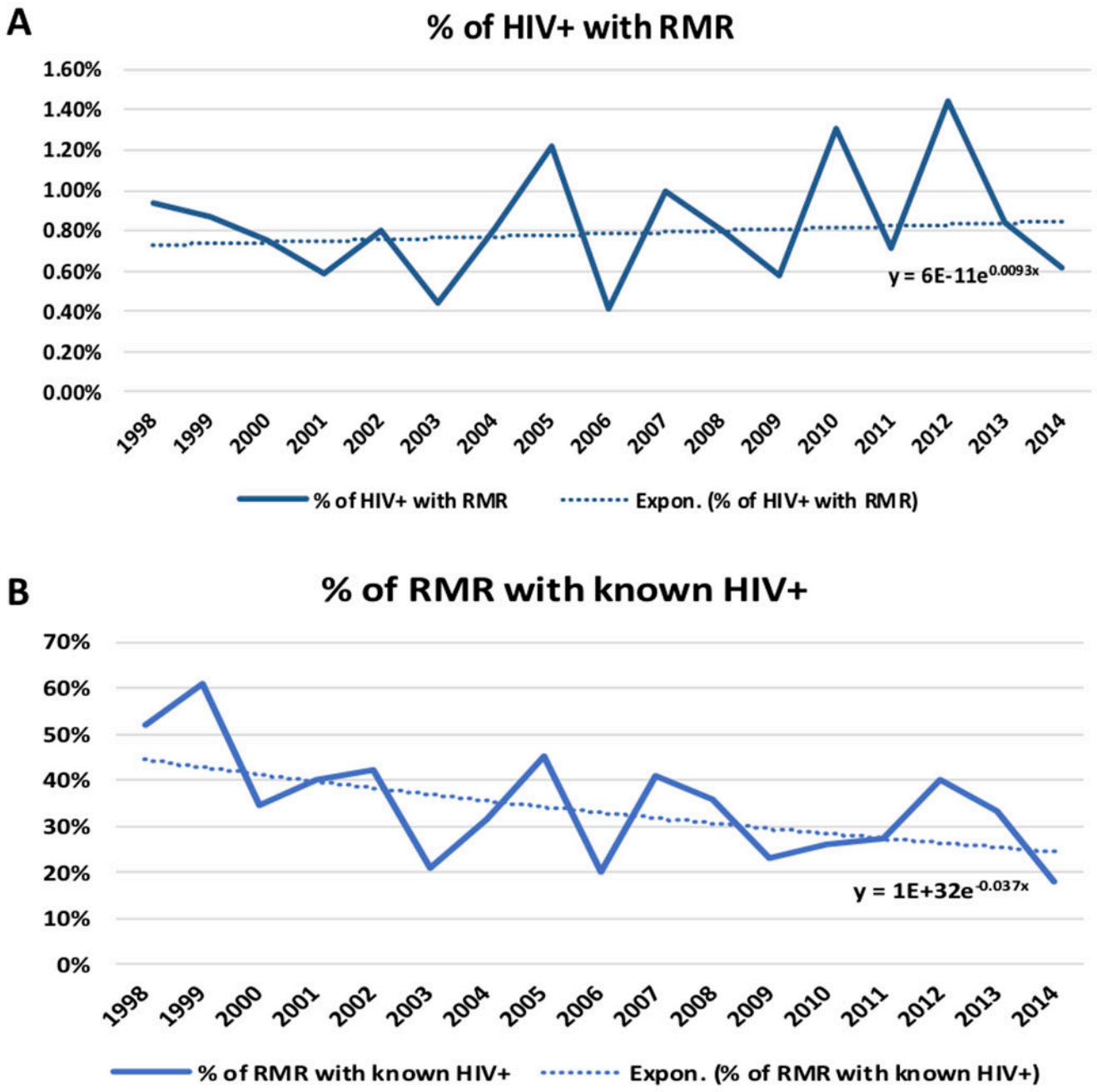

Figure 3. Temporal trends in HIV-infection and RMR-TB in the United States*, 1998–2014

*Excludes the state of California due to incomplete reporting of HIV status during the period analyzed.

Table 1.

Mycobacterium tuberculosis resistance patterns at initial drug susceptibility testing (DST)

Pattern	Resistance at initial DST	Susceptibility at initial DST
RMR TB	Rifampin-resistant	Susceptible to isoniazid and ethambutol. No resistance reported to pyrazinamide, ethionamide, kanamycin, para-aminosalicylic acid, levofloxacin, moxifloxacin, ofloxacin, other quinolones or streptomycin *
IMR TB	Isoniazid-resistant	Susceptible to rifampin and ethambutol. No resistance reported to pyrazinamide, ethionamide, kanamycin, para-aminosalicylic acid, levofloxacin, moxifloxacin, ofloxacin, other quinolones or streptomycin *
MDR TB	Resistance to at least isoniazid and rifampin	No consideration for resistance or susceptibility to drugs other than rifampin and isoniazid
Drug-susceptible	No reported resistance to any drug	Susceptible to isoniazid, rifampin, and ethambutol, and no resistance reported to pyrazinamide, ethionamide, kanamycin, para-aminosalicylic acid, levofloxacin, moxifloxacin, ofloxacin, other quinolones or streptomycin *

* Including lack of a DST result.

Rifampin-monoresistant tuberculosis (RMR TB), isoniazid-monoresistant tuberculosis (IMR TB), multidrug-resistant tuberculosis (MDR TB).

Table 2.

Patterns of acquired *Mycobacterium tuberculosis* rifampin resistance (ARR)

Pattern	Initial DST	Final DST	Other drug susceptibility testing results
ARR-INH-S	Rifampin-susceptible Isoniazid-susceptible	Rifampin-**resistant** Isoniazid-susceptible	Resistance to other drugs was not considered due to the small number of eligible cases with initial and final drug susceptibility testing
ARR-INH-R	Rifampin-susceptible Isoniazid-**resistant**	Rifampin-**resistant** Isoniazid-**resistant**	
ARR-MDR	Rifampin-susceptible Isoniazid-susceptible	Rifampin-**resistant** Isoniazid-**resistant**	
All Forms ARR	Includes the three patterns of acquired rifampin resistance (ARR-INH-S, ARR-INH-R and ARR-MDR)		
Rifampin & isoniazid susceptible	Rifampin-susceptible Isoniazid-susceptible	Rifampin-susceptible Isoniazid-susceptible	

Three subclasses of possible acquired rifampin-resistant (ARR) TB were defined based on isoniazid resistance at initial and final drug susceptibility testing (DST), isoniazid-susceptible at both initial and final DST (ARR-INH-S), isoniazid-resistant at initial DST (ARR-INH-R) and isoniazid-susceptible at initial DST, but isoniazid-resistant at final DST (ARR-MDR).

Table 3.

Multivariable analysis of factors associated with RMR-TB compared to drug susceptible TB, United States*, 1998–2014.

Characteristics	RR	LCI	UCI	adjRR	LCI	UCI
HIV Positive, with a prior TB diagnosis	**25.42**	**17.53**	**36.85**	**25.93**	**17.65**	**38.11**
HIV Positive, without a prior TB diagnosis	**3.17**	**2.44**	**4.12**	**3.12**	**2.36**	**4.11**
HIV Negative/Unknown, with a prior TB diagnosis	**2.62**	**1.75**	**3.93**	**2.81**	**1.88**	**4.22**
Age 65 or older	**0.36**	**0.25**	**0.51**	**0.43**	**0.30**	**0.62**
Black or African American, non-Hispanic	1.03	0.83	1.28	**0.68**	**0.54**	**0.86**

Results from a log binomial model including 353 RMR TB and 117,534 DS observations (referent group). Dummy variable coding was used for race/ethnic, age group, and site of disease variables (e.g., non-Hispanic Asian race versus all other race/ethnicities) to assess differences among categories within the variables. For HIV, both HIV positive versus all else, and HIV unknown versus all else were included in initial models, but HIV unknown status was dropped from the final model; thus, the referent in this model for HIV positive is HIV negative or unknown status. Interaction was evident between HIV positivity and a prior TB diagnosis. Univariate analyses for the variables are included in the model are reported in Supplement Tables 1,2.

adjRR, adjusted risk ratio; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval.

*Excludes the state of California due to incomplete reporting of HIV status over the time period analyzed.

Table 4.

Initial drug-resistance and other factors associated with mortality, United States*, 1998–2014

Characteristics	RR	LCI	UCI	adjRR	LCI	UCI
RMR TB	**1.36**	**1.01**	**1.83**	**1.36**	**1.04**	**1.78**
IMR TB	**0.76**	**0.68**	**0.84**	0.99	0.90	1.09
MDR TB	**1.35**	**1.17**	**1.56**	**1.99**	**1.84**	**2.16**
HIV positive	**2.90**	**2.76**	**3.06**	**2.87**	**2.74**	**3.02**
HIV unknown	**2.59**	**2.48**	**2.70**	**1.80**	**1.72**	**1.87**
Male	**1.25**	**1.20**	**1.30**	**1.18**	**1.14**	**1.23**
White, non-Hispanic	**1.62**	**1.56**	**1.69**	1.03	0.96	1.11
Hispanic	**0.63**	**0.60**	**0.67**	**1.20**	**1.12**	**1.29**
Black or African American, non-Hispanic	**1.23**	**1.19**	**1.28**	**1.22**	**1.13**	**1.32**
American Indian or Alaska Native, non-Hispanic	**1.47**	**1.32**	**1.65**	**1.31**	**1.16**	**1.49**
Age 25-44	**0.30**	**0.29**	**0.32**	**2.89**	**2.45**	**3.42**
Age 45-64	0.98	0.94	1.02	**6.66**	**5.66**	**7.84**
Age 65 or older	**4.27**	**4.12**	**4.43**	**16.39**	**13.95**	**19.27**
Non-US-born	**0.40**	**0.39**	**0.42**	**0.62**	**0.59**	**0.66**
Correctional facility resident	**0.56**	**0.48**	**0.64**	**0.84**	**0.73**	**0.96**
Extrapulmonary & pulmonary TB	**1.57**	**1.49**	**1.65**	**1.39**	**1.33**	**1.45**
Any DOT	**0.56**	**0.54**	**0.58**	**0.79**	**0.76**	**0.82**

Rifampin-monoresistant tuberculosis (RMR TB), isoniazid-monoresistant tuberculosis (IMR TB), multidrug-resistant tuberculosis (MDR TB); Directly observed therapy (DOT). Results from a log binomial model including 10,468 cases that died due to any cause (death may have been due to causes not related to TB disease), and 103,271 cases that completed TB treatment or stopped therapy due to adverse treatment event (referent group). Dummy variable coding was used for race/ethnic, age group, and site of disease variables to assess differences among categories within the variables. The race/ethnic referent in the final model was non-Hispanic Asian. The referent for age group was ages < 25 years. For HIV, both HIV positive versus all else, and HIV unknown versus all else were included in initial models; as both variables were significant, the referent is HIV negative status. Dummy variable coding was also used for DOT use (any DOT versus other). The referent for extrapulmonary and pulmonary sites of disease was all other sites. RR, unadjusted risk ratio; adjRR, adjusted risk ratio; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval.

*Excludes the state of California due to incomplete reporting of HIV status during the time period analyzed.

Table 5.

Multivariable analysis of factors associated with possible acquired rifampin-resistant TB (all forms ARR) to drug susceptible TB, United States*, 1998–2014.

Characteristics	RR	LCI	UCI	adjRR	LCI	UCI
HIV positive	**8.39**	**6.01**	**11.72**	**9.56**	**6.89**	**13.28**
Asian, non-Hispanic	1.46	0.96	2.20	**1.90**	**1.18**	**3.05**
Non-US born	**1.43**	**1.05**	**1.96**	**1.60**	**1.13**	**2.27**
Correctional facility resident	**2.73**	**1.61**	**4.60**	**2.39**	**1.43**	**3.99**
Any DOT	**0.55**	**0.34**	**0.88**	0.67	0.41	1.09

Directly observed therapy (DOT). Results from a log binomial model including 151 ARR TB cases and 9,991 rifampin- and isoniazid-susceptible cases (referent group). Dummy variable coding was used for race/ethnic, age group, and site of disease variables to assess differences among categories within the variables. In the final model, the referent for non-Hispanic Asian is all other race/ethnicities. For HIV, both HIV positive versus all else, and HIV unknown versus all else were included in initial models, however only HIV positive was significant in the final model; the referent is HIV negative or unknown status. Dummy variable coding was also used for DOT use (any DOT versus other). Bivariate analyses of the variables included in the model are reported in Supplement Tables 3,4. adjRR, adjusted risk ratio; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval.

*Excludes the state of California due to incomplete reporting of HIV status during the time period analyzed.

Table 6.

Association of possible acquired rifampin-resistant TB with mortality, United States*, 1998–2014

Characteristics	RR	LCI	UCI	adjRR	LCI	UCI
All forms ARR	**3.67**	**2.58**	**5.23**	**2.45**	**1.78**	**3.37**
ARR-INH-S	**3.21**	**1.63**	**6.32**			
ARR-INH-R	**4.76**	**3.01**	**7.52**			
ARR-MDR	**2.55**	**1.12**	**5.77**			
Age 45–64	0.89	0.75	1.06	**2.15**	**1.71**	**2.72**
Age 65 or older	**3.65**	**3.11**	**4.29**	**6.79**	**5.36**	**8.60**
Non-US born	**0.42**	**0.35**	**0.51**	**0.55**	**0.45**	**0.67**
Correctional facility resident	1.30	0.88	1.93	**1.63**	**1.11**	**2.40**
HIV positive	**4.38**	**3.60**	**5.34**	**4.84**	**3.91**	**5.98**
HIV unknown	**1.77**	**1.47**	**2.14**	**1.36**	**1.10**	**1.68**
Extrapulmonary & pulmonary TB	**2.21**	**1.78**	**2.74**	**1.60**	**1.30**	**1.98**
Prior TB	**1.72**	**1.29**	**2.29**	**1.40**	**1.06**	**1.84**
Any DOT	**0.39**	**0.31**	**0.48**	**0.52**	**0.42**	**0.65**

Three subclasses of possible acquired rifampin-resistant (ARR) TB were defined based on isoniazid resistance at initial and final drug susceptibility testing (DST), isoniazid-susceptible at both initial and final DST (ARR-INH-S), isoniazid-resistant at initial DST (ARR-INH-R) and isoniazid-susceptible at initial DST, but isoniazid-resistant at final DST (ARR-MDR). Directly observed therapy (DOT). Dummy variable coding was used for race/ethnic, age group, and site of disease variables to assess differences among categories within the variables. In the final model, the referent for age is age < 45 years. For HIV, both HIV positive versus all else, and HIV unknown versus all else were included in initial models; both were significant in the final model and the referent is HIV negative status. The referent for extrapulmonary and pulmonary sites of disease was all other sites. Observations with unknown prior TB were excluded from analysis; the referent for prior TB is no prior TB. Dummy variable coding was also used for DOT use (any DOT versus other). Results from a log binomial model including 532 cases that died due to any cause (death may have been due to causes not related to TB disease), and 9,014 cases that completed TB treatment or stopped therapy due to adverse event (referent group).

*The subclasses of ARR; ARR-INH-S, ARR-INH-R, ARR-MDR were not included in the log binomial model, only their unadjusted RR is reported. RR, unadjusted risk ratio; adjRR, adjusted risk ratio; LCI, lower 95% confidence interval; UCI, upper 95% confidence interval. *Excludes the state of California due to incomplete reporting of HIV status during the time period analyzed.