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Risk Factors for and Trends in Isoniazid Monoresistance at Diagnosis of Tuberculosis—United States, 1993-2016

Shareen A. Iqbal, PhD, MPH,
Office of the Associate Director for Science, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia

Lori R. Armstrong, PhD,
Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia.

J. Steve Kammerer, MBA,
Division of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia.

Benedict I. Truman, MD, MPH
Office of the Associate Director for Science, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia.

Abstract

Context—Resistance to isoniazid (INH) only (monoresistance), with drug susceptibility to rifampin, pyrazinamide, and ethambutol at diagnosis of tuberculosis (TB) disease, can increase the length of treatment.

Objective—To describe US trends in INH monoresistance and associated patient characteristics.

Design—We performed trend and cross-sectional analyses of US National Tuberculosis Surveillance System surveillance data. We used Joinpoint regression to analyze annual trends in INH monoresistance and logistic regression to identify patient characteristics associated with INH monoresistance.

Participants—Culture-positive cases reported to National Tuberculosis Surveillance System during 1993–2016 with drug susceptibility test results to INH, rifampin, pyrazinamide, and ethambutol.

Main Outcome Measures—(1) Trends in INH monoresistance; (2) odds ratios for factors associated with INH monoresistance.

Correspondence:*Shareen A. Iqbal, PhD, MPH, Office of the Associate Director for Science, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Rd, NE, Mailstop E-07, Atlanta, GA 30329 (*kqj7@cdc.gov*).*

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Results—Isoniazid monoresistance increased significantly from 4.1% of all TB cases in 1993 to 4.9% in 2016. Among US-born patients, INH monoresistance increased significantly from 2003 onward (annual percentage change = 2.8%; 95% confidence interval: 1.4–4.2). During 2003–2016, US-born persons with INH-monoresistant TB were more likely to be younger than 65 years; to be Asian; to be human immunodeficiency virus–infected; or to be a correctional facility resident at the time of diagnosis. Among non–US-born persons, INH resistance did not change significantly during 1993–2016 (annual percentage change = −0.3%; 95% confidence interval: −0.7 to 0.2) and was associated with being aged 15 to 64 years; being Asian, black, or Hispanic; or having a previous history of TB.

Conclusions—INH-monoresistant TB has been stable since 1993 among non–US-born persons; it has increased 2.8% annually among US-born persons during 2003–2016. Reasons for this increase should be further investigated.

Keywords

antitubercular agents/therapeutic use; bacterial; drug resistance; isoniazid; isoniazid/therapeutic use; *Mycobacterium tuberculosis*; tuberculosis/drug therapy; tuberculosis/epidemiology

Despite substantial improvement since 1993, tuberculosis (TB), an airborne infectious bacterial disease, is still a preventable cause of illness, disability, and death in the United States. During 2018, in a provisional report, a total of 9029 new cases of verified TB disease (2.8 cases per 100 000 population) were reported among US residents.[1] Treatment of TB requires use of first-line drugs (FLDs) (eg, isoniazid [INH], rifampin [RIF], pyrazinamide [PZA], and ethambutol [EMB]) to which *Mycobacterium tuberculosis* complex organisms grown in culture of the patient's clinical specimens are sensitive. Isoniazid and RIF are the 2 most potent FLDs used to treat TB disease caused by *M tuberculosis* that is sensitive to those drugs.[2] Isoniazid monotherapy is also used to treat latent TB infection (LTBI).[3] *M tuberculosis* that is resistant to TB drugs continues to multiply and cause clinical illness in the patient during treatment with those drugs.[4] Tuberculosis drug resistance can develop because of an inadequate number of drugs, ineffective doses or duration of treatment regimens, treatment nonadherence, malabsorption of drugs, and drug-drug interactions that reduce therapeutic drug levels.[5]

Because TB drug resistance caused by random genetic mutation of *M tuberculosis* is rare, increasing temporal trends in resistance might indicate that patient-, treatment-, and organism-related factors are major determinants of those resistance trends. Isoniazid resistance is of particular interest in TB control because INH is one of the treatment regimens for LTBI, an important strategy for preventing progression from infection to TB disease.[6] Isoniazid resistance also has been associated with worse TB treatment outcomes when standard therapy is used to treat TB disease.[7–9]

The global average of INH resistance without concurrent RIF-resistant TB cases during 2002–2016 was 8.5% (95% confidence interval [CI]: 7.4–9.7); among new and previously treated TB cases, the global averages were 7.3% (95% CI: 6.1–8.6) and 14% (95% CI: 12–17), respectively.[10] In the United States, during the respective period, resistance was 8.8%, which includes the 1.3% of total cases with multidrug-resistant (MDR) TB.[11] In contrast, the

global estimate of MDR TB among new cases was 8.1% (95% CI: 7.3–8.9),[10] compared with 1.4% in the United States during 2016.[11]

The majority of TB drug resistance studies have focused on MDR TB.[12] Understanding INH monoresistance is essential because INH resistance has been reported to predate rifampicin resistance in MDR TB patients.[13] Here, we describe trends in INH monoresistance and identify patient-, treatment-, and TB-related attributes associated with resistance among patients with new cases of verified TB disease reported among US residents during 1993–2016.

Methods

Selected analytic samples

We analyzed data from the National Tuberculosis Surveillance System, which is maintained by the Centers for Disease Control and Prevention (Atlanta, Georgia).[11] We defined INH monoresistance as resistance to INH and susceptibility to RIF, PZA, EMB, or any other tested drugs on the basis of initial drug susceptibility testing (DST) results for culture-confirmed cases. We defined MDR TB according to the World Health Organization's definition as resistance to at least INH and RIF.[14] We defined MDR TB as resistance to at least INH and RIF by DST. The number of TB cases available for analysis varied by purpose as follows: *(a)* to assess trends in INH monoresistance by year of diagnosis and patient's birth year; and *(b)* to describe patient's attributes associated with INH-monoresistant disease, compared with INH-sensitive disease, among non–US-born (1993–2016) and US-born (2003–2016) residents. We separated cases by period and patient's nativity because of differences in INH resistance trends by birth origin as reported in the National Tuberculosis Surveillance System data set.[11] We conducted trend analysis by nativity to determine possible period cut points for changes in INH resistance rates and identified an increasing rate of INH monoresistance during 2003–2016 among US-born residents. We restricted patient attribute analysis to the 2003–2016 period to determine which factors might be associated with an increase in INH monoresistance.

We analyzed all verified, culture-positive, TB cases with DST results for all FLDs at diagnosis reported in the 50 states and the District of Columbia during January 1, 1993 to December 31, 2016. We excluded TB cases that became INH-monoresistant or MDR TB disease during TB treatment from our analyses to exclude cases with resistance that might have been associated with drug treatment during the current TB episode. Isoniazid monoresistance, as reported by clinical laboratories through DST results, was the health outcome variable of interest in our regression analyses.

Statistical analyses

Assessing annual trends in INH monoresistance—For each year of 1993–2016, we calculated the annual percentage of TB cases with INH monoresistance among those tested for FLDs. To analyze trends in annual INH monoresistance among selected populations, we used Joinpoint statistical software (version 4.2.0.2, National Cancer Institute, National Institutes of Health, Bethesda, Maryland) to fit Joinpoint regression[15] models and to

estimate annual percentage change (APC) in INH monoresistance. In each model, we assumed a maximum of 3 change points and a minimum of 2 observations from a joinpoint on either end of the data and between 2 joinpoints. We used the slope of the trend lines to compute APCs from year to year and to assess the APC statistical significance, compared with 0. The APC was significantly different from 0 at $P < .05$ on the basis of the *t* test.

Identifying birth cohort effects on INH monoresistance among US-born or non–US-born residents with TB disease—To assess the occurrence of birth cohort effects on INH monoresistance trends, we analyzed data, stratified by nativity, for 1993–2016. For age-specific TB incidence by birth cohort, we classified cases into 12 cohorts by birth decade (ie, 1900: 1900–1909; 1910: 1910–1919; and so forth until 2010: 2010–2016) on the basis of available data by age. The 2010 birth cohort included 7 years (through 2016). We excluded patients born before 1900, because only 1 TB patient with INH monoresistance was reported as having been born before 1900.

Associated factors for INH monoresistance—We selected potential risk factors for INH monoresistance from among covariates previously demonstrated to be risk factors in published research studies.[16] We conducted univariate and multivariate analyses on demographic, treatment outcomes, and risk factor information. To identify associated factors for INH monoresistance, controlling for confounding and adjusting for interaction between covariates, we used the logistic procedure in SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina) to build multivariable logistic regression models by using backward elimination. We eliminated nonsignificant covariates in bivariate analyses with significance levels at $P < .01$. To identify statistically significant effects of the *missing and unknown* category in selected variables with 10% or greater missing or unknown values, we included those observations in the multivariate analyses. We identified significant interaction terms on the basis of the log-likelihood ratio test with levels of significance at $P < .01$, and we tested for multicollinearity among covariates indicated by condition indexes greater than 30 and variance proportions accounted for by principal components greater than 0.50 for 2 or more covariates.[17] We used the Hosmer-Lemeshow test to assess the goodness-of-fit of the final model to the data. For proportion comparison, we used the χ^2 test or the Monte Carlo estimate for Fisher exact test if cells had less than 5 cases. Certain risk factors (eg, TB attributed to recent transmission) began to be measured in all US states in 2011; therefore, those analyses were restricted to 2011–2016 data.

We fit 6 adjusted logistic regression models, 3 among non–US-born and 3 among US-born persons. Among non–US-born persons, the first model started with all observations and variables for 1993–2016 before backward elimination of nonsignificant variables, except for treatment outcome and additional TB risk factor variables available from 2011. A separate model for treatment outcomes, along with age, sex, race/ethnicity, previous TB, and human immunodeficiency virus (HIV) infection status, was fit before backward elimination of nonsignificant variables for 1993–2014. The second model included HIV status because of (*a*) possible reduced absorption of TB drugs or negative treatment and outcome results among persons positive for HIV infection; *(b)* possible inadequate adherence caused by adverse events[18]; or *(c)* pill burden associated with TB and HIV concurrent therapies.[19] To

reduce the number of adjusted regression analyses, we restricted treatment outcome variables for patients who were alive at diagnosis, were prescribed 1 or more drugs, had a positive sputum culture, and were verified during 2014 or earlier, allowing a minimum of 2 years for reporting jurisdictions to submit their information. Treatment outcome variables included receiving initial INH therapy, type of therapy (self-administered compared with directly observed), time to sputum culture negativity, completion of therapy, and type of health care provider. The third model included additional TB risk factor variables available from 2011 and the variables for age, sex, race/ethnicity, and previous TB for 2011–2016. Additional TB risk factor variables included primary occupation in the preceding year, primary reason evaluated for TB disease, TB attributed to recent transmission, contact with an MDR TB patient in the preceding 2 years, contact with a patient with infectious TB in the preceding 2 years, history of incomplete LTBI therapy, recent history of tumor necrosis factor α antagonist therapy, history of receiving a solid organ transplant, diabetes or end-stage renal disease at the time of TB diagnosis, non-HIV/AIDS immune-compromise, other TB risk factor, and no TB risk factor. Similar models were created for US-born persons. Among the models that measured all observations and variables and treatment outcomes, we restricted our analysis to 2003–2016 and 2003–2014, respectively.

Ethics assurances

Institutional review board approval was not required because use of surveillance data in this study did not involve human participant research as determined by the Centers for Disease Control and Prevention's Institutional Review Board.

Results

Trends in INH monoresistance

Of the 360 287 US TB cases verified during 1993–2016, 196 335 (54.5%) had DST results for INH, RIF, PZA, and EMB. Of these, 172 379 (87.8%) persons had TB disease susceptible to FLDs; 15 174 (7.7%) persons had TB disease resistant to RIF, PZA, or EMB; and 8782 (4.5%) persons had INH monoresistance at TB diagnosis (see Supplemental Digital Content Figure 1, available at http://links.lww.com/JPHMP/A601).

Among persons with DST results, INH monoresistance increased from 4.1% in 1993 to 4.9% in 2016, whereas MDR TB decreased from 6.5% in 1993 to 1.5% in 2016 (Figure 1A). The percentage of verified TB cases with INH monoresistance has remained higher among non–US-born persons than among US-born persons each year during 1993–2016 (Figure 1B), with non–US-born residents accounting for 65.3% of the INH-monoresistant TB cases (n = 5737) during 1993–2016. However, the gap in INH monoresistance by nativity has been narrowing since 2003 ($P < .05$). For cohorts born before 1980, the percentage of TB patients with INH monoresistance was higher among non–US-born than among US-born residents; in contrast, for cohorts born after 1980, the frequency of INH monoresistance was higher among US-born than among non–US-born residents (Figure 2).

Trends in INH monoresistance among non–US-born residents, 1993–2016

Among non–US-born residents, trend analysis demonstrated that the percentage of TB patients with INH monoresistance has remained steady (average APC = −0.3; 95% CI: −0.7 to 0.2). Among non–US-born residents, the majority of persons with INH-monoresistant TB (75%) were from 10 countries: the Philippines (22.2%), Mexico (16.4%), Vietnam (10.1%), India (6.8%), China (6.0%), Haiti (4.3%), Republic of Korea (4.0%), Guatemala (1.8%), Somalia (1.8%), and Ethiopia (1.6%) (see Supplemental Digital Content Table 1, available at http://links.lww.com/JPHMP/A601). Among non–US-born persons from the top 10 countries for INH monoresistance, higher than average INH monoresistance (5.2%) was observed for persons from the Philippines (9.1%), Republic of Korea (7.5%), Somalia (6.5%), Haiti (6.3%), Vietnam (6.0%), and China (5.4%).

Trends in INH monoresistance cases among US-born residents, 1993–2016

Trend analysis among US-born residents demonstrated that the percentage of TB patients with INH monoresistance did not change significantly during 1993–2002 (APC = −1.4%; 95% CI: −3.5 to 0.7), but the trend increased during 2003–2016 (APC = 2.8%; 95% CI: = 1.4–4.2). To identify patient attributes associated with the increase in APCs among US-born persons with INH-monoresistant TB since 2003, we compared the distributions of demographic, social, clinical, and treatment attributes from the early (1993–2002) to the late periods (2003–2014) for treatment variables or 2003–2016 for demographic, social, and clinical variables (see Supplemental Digital Content Table 2, available at http://links.lww.com/JPHMP/A601). The late period had higher percentages of patients who were Hispanic, Asian, American Indian/Alaska Natives, and persons aged 5 to 24 years. The later period also had higher percentages of patients with improved treatment outcomes along with lower percentages of patients with previous TB, HIV infection, residency in a long-term care facility, and injection-drug use. A similar distribution of patient attributes was identified when comparing cases during early (1993–2002) and late (2003–2014) periods among patients with drug-susceptible TB disease.

Risk factors for INH-monoresistant TB among non–US-born residents, 1993–2016

Multivariable analyses among non–US-born residents demonstrated that the following risk factors were significantly, positively associated with INH monoresistance TB cases during 1993–2016 (Table): *(a)* age groups of 15–24, 25–44, and 45–64 years; *(b)* Asian, black, and Hispanic race/ethnicity; *(c)* prior TB disease; *(d)* extrapulmonary-only disease site; and *(e)* positive tuberculin skin test. Treatment outcomes and therapy among non–US-born residents during 1993–2014 demonstrated that not receiving initial INH therapy, directly observed therapy, and not completing therapy in less than 1 year were significantly associated with INH monoresistance. Among the additional TB risk factors during 2011–2016 among non–US-born persons, TB not attributed to recent transmission, contact with an MDR TB patient within the previous 2 years, diabetes mellitus, and incomplete LTBI therapy were significantly associated with INH monoresistance.

Risk factors for INH-monoresistant TB among US-born residents, 2003–2016

In multivariable analysis, the following risk factors were significantly associated with INH-monoresistant TB among US-born TB patients during 2003–2016: *(a)* age groups of 0–4, 5–14, 15–24, 25–44, and 45–64 years; *(b)* Asian race; *(c)* HIV infection; and *(d)* residency in a correctional facility at the time of diagnosis. Treatment outcomes and therapy among US-born persons during 2003–2014 demonstrated that not receiving initial INH therapy and not completing therapy in less than 1 year were significantly associated with INH monoresistance. The US-born persons with culture results converting from positive to negative in less than 2 months were inversely associated with INH monoresistance. Among the additional TB risk factors for 2011–2016 among US-born persons, contact with an MDR TB patient within the previous 2 years and TB attributed to recent transmission were significantly associated with INH monoresistance.

Discussion

Trends in INH monoresistance overall

Isoniazid monoresistance increased among TB patients in the United States during 1993–2016 in contrast with stable rates for MDR TB. By nativity, trends in INH monoresistance demonstrate no change in percentage among non–US-born patients during 1993–2016 and US-born patients during 1993–2002. Since 2003, US-born TB patients have had an increasing trend in INH monoresistance.

Trends in and risk factors for INH monoresistance among TB patients

A previous study by Hoopes et al[16] examined the associated characteristics of INH monoresistance in the United States during 1993–2003. We identified similar associations with INH monoresistance to the prior study with an increased likelihood among persons aged 15 to 64 years, US-born Asian/Pacific Islanders, non–US-born blacks and Asian/Pacific Islanders, correctional facility residency, history of TB disease, and not completing therapy in less than 1 year. We also identified a decreased odds of resistance among non–US-born persons who had initially received INH treatment. However, our study differed by finding an increased odds for resistance among US-born persons aged 0 to 14 years or among all US-born persons with positive HIV infection status and among non–US-born Hispanics. These differences might be the result of changing incidence of TB by age groups through time[20] and increased testing and reporting of HIV status among persons with TB[11] since 2003.

We identified an association between having a history of previous TB and INH monoresistance, regardless of nativity. Furthermore, regarding non–US-born persons, we established an association with INH monoresistance among persons who failed to complete LTBI therapy. The association of a history of TB disease or failure to complete LTBI therapy was expected because TB patients who do not complete or have inadequate treatment are at an increased risk for experiencing drug resistance.[5]

Among racial/ethnic groups, INH-monoresistant TB was more likely to be associated with Asians, regardless of nativity. Outside of Eastern European regions, multiple countries in

Asia have reported the highest percentages of INH resistance.[21] Possibly, US-born and non–US-born Asians might have close contact with relatives living in regions of Asia where INH monoresistance is prevalent.

Birth cohort and regression analyses that included a variable for TB attributed to recent transmission appear to support the idea that non–US-born persons are unlikely to have been exposed to INH-monoresistant TB while residing in the United States. Among non–US-born persons with INH monoresistance, a substantial decline among persons born after 1980 and lower odds of TB attributed to recent transmission existed. Therefore, non–US-born persons with INH-monoresistant TB might have had the infection before residing in the United States. Among US-born persons, however, we identified a higher odds of TB attributed to recent transmission and a continued risk for INH monoresistance for persons born among the most recent birth cohorts of 2000 and 2010, indicating transmission of INH-monoresistant strains within the United States. We hypothesized that there were zero cases of INH monoresistance among the 2010 birth cohort of non–US-born pediatric patients for the 2010 birth cohort because they were less likely to have recent transmissions of TB and isolates for DST.

Limitations

Our study had certain limitations. The variables of HIV status, sputum culture, and tuberculin skin test among US- and non–US-born persons and years in the United States among non–US-born persons had more than 10% missing data, which might limit the data's interpretability. Also, although trend analyses revealed an increase in INH monoresistance among US-born persons after 2002, we observed a lower percentage of cases among US-born persons with INH monoresistance for 2015 and 2016, compared with 2014. The decrease could be the result of health care providers prescribing INH-free treatment for LTBI. However, of the 4 LTBI-recommended therapies by the American Thoracic Society and the Centers for Disease Control and Prevention,[22] 3 of the treatment regimens contain INH. We have no empirical evidence that the 2-year decrease in INH monoresistance was caused by prescribers switching from regimens with INH to those without INH. Whether this decreasing trend will continue is unclear. For treatment outcome measures, we restricted the analysis to persons with sputum culture only to reduce the number of adjusted regression analyses. Therefore, treatment completion and outcome were not measured for persons with extrapulmonary TB. The direction of the potential causal association between INH monoresistance and initial drug regimen or not completing therapy in less than 1 year cannot be determined from the analysis. A possible explanation for these associations is that the health care providers knew or suspected that a case was resistant to INH and therefore did not use INH in the initial regimen or prescribed extended treatment for more than 1 year. Finally, National Tuberculosis Surveillance System provides limited longitudinal patient information and does not include detailed information regarding prior treatment for TB disease. Therefore, we were unable to assess the type and completeness of prior TB therapy for patients who had previous TB and were unable to determine whether INH monoresistance was acquired or primary.

Conclusions

Among US-born persons with TB during 2003–2016, INH monoresistance increased and was associated with being younger than 65 years, being of Asian race, being HIV-infected, having resided in a correctional facility at the time of diagnosis, being a recent contact of an MDR TB patient, or having TB attributed to recent transmission. Although INH monoresistance did not increase among non–US-born persons during 1993–2016, the percentage of INH monoresistance was higher each year, compared with US-born persons during the same period. Reducing the incidence of INH-monoresistant TB and improving efforts to ensure treatment completion, particularly among US-born INH-monoresistant TB cases, are a high priority for controlling TB morbidity beyond 2016.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Implications for Policy & Practice

- Reducing isoniazid (INH) monoresistance is essential for TB control and elimination in the United States.
- The findings from this study can guide TB control policies and clinical practice in states and localities with higher burdens of latent TB infection (LTBI) and INH-monoresistant TB disease and disproportionately high concentrations of patients with risk factors for INH monoresistance.
- Policymakers can use these findings to better target resources and support programs for improving completion rates for LTBI and TB disease with recommended treatment regimens.
- Clinicians can use the findings to assess and meet the need for interventions among patients with LTBI and TB disease to prevent development of INH monoresistance.

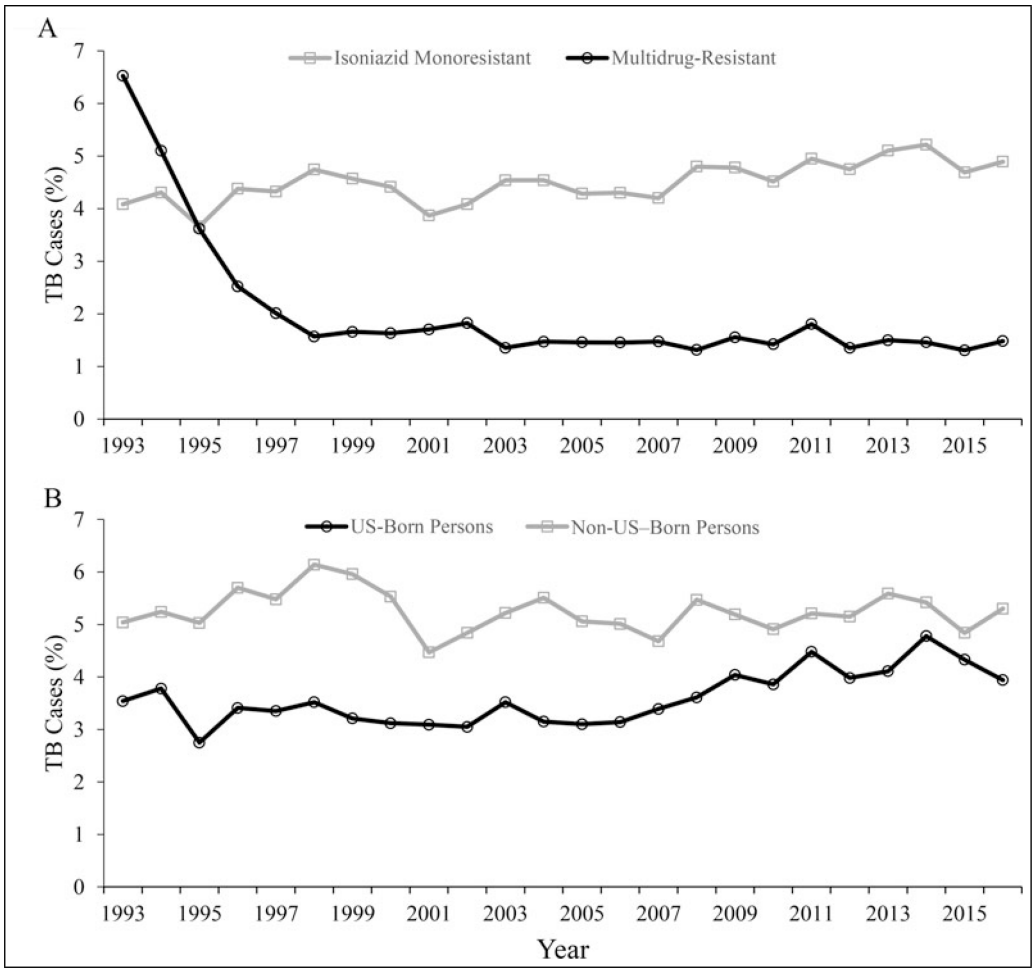

FIGURE 1.

(A) Percentage of Verified Tuberculosis Cases With Isoniazid Monoresistance or Multidrug Resistance, by Year—United States, 1993–2016. (B) Percentage of Verified Isoniazid Monoresistant Tuberculosis Cases Among US-Born and Non–US-Born Persons, by Year—United States, 1993–2016. Abbreviation: TB, tuberculosis.

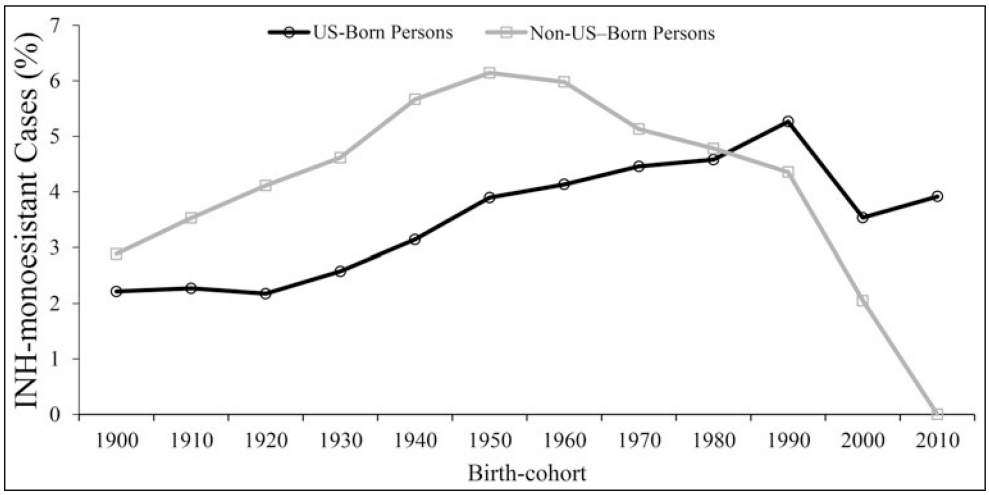

FIGURE 2.

Percentage of Verified Isoniazid (INH)-Monoresistant Tuberculosis (TB) Cases Among US-Born and Non–US-Born Persons, by Decade of Birth Year—United States, 1900–2016.

Abbreviation: INH, isoniazid.

TABLE

Odds Ratios for Demographic, Treatment and Outcome, and Additional Risk Factor Characteristics of Patients With Isoniazid (INH)-Monoresistant Tuberculosis (TB) and Drug-Susceptible TB, by Nativity, United States, 2003–2016[a]

	US-Born (2003–2016)					Non–US-Born (1993–2016)				
	INH-Monoresistant TB (n = 1418)		Drug-Susceptible TB (n = 34 933)		Adjusted Odds Ratio (99% Confidence Interval)	INH-Monoresistant TB (n = 5737)		Drug-Susceptible TB (n = 92 910)		Adjusted Odds Ratio (99% Confidence Interval)
Characteristic	**N**	**%**	**N**	**%**		**N**	**%**	**N**	**%**	
Age, y										
0–4	35	2.5	894	2.6	2.0 (1.2–3.3)	1	0	116	0.1	0.2 (0.03–1.7)
5–14	30	2.1	392	1.1	3.2 (1.9–5.6)	32	0.6	597	0.6	1.2 (0.8–1.8)
15–24	163	11.5	2782	8.0	2.1 (1.6–2.8)	684	11.9	12 125	13.1	1.2 (1.1–1.4)
25–44	424	29.9	8307	23.8	1.7 (1.3–2.2)	2345	40.9	36 529	39.3	1.4 (1.3–1.5)
45–64	538	37.9	13 075	37.4	1.5 (1.2–1.8)	1662	29.0	23 579	25.4	1.4 (1.3–1.6)
≥65	228	16.1	9481	27.1	1 (Reference)	1012	17.6	19 956	21.5	1 (Reference)
Missing/unknown	0	0	2	0	—	1	0	8	0	—
Race/ethnicity										
American Indian/Alaska Native	53	3.7	1333	3.8	0.9 (0.6–1.3)	1	0	48	0.1	0.8 (0.1–6.1)
Asian[b]	66	4.7	943	2.7	1.6 (1.1–2.4)	3236	56.4	42 359	45.6	2.2 (1.9–2.6)
Black	629	44.4	14 868	42.6	1.0 (0.9–1.3)	697	12.2	12 389	13.3	1.6 (1.4–1.9)
Hispanic	215	15.2	4874	14.0	1.0 (0.8–1.3)	1555	27.1	31 154	33.5	1.4 (1.2–1.6)
Native Hawaiian/other Pacific Islander[b]	4	0.3	228	0.7	0.4 (0.1–1.7)	11	0.2	543	0.6	0.5 (0.3–1.1)
White	426	30.0	12 463	35.7	1 (Reference)	201	3.5	5736	6.2	1 (Reference)
Multiple race	9	0.6	146	0.4	1.7 (0.7–4.3)	13	0.2	264	0.3	1.6 (0.9–2.8)
Missing/unknown	16	1.1	78	0.2	—	23	0.4	417	0.5	—
History of previous TB										
No	1324	93.4	33 082	94.7	...	5266	91.8	87 851	94.6	1 (Reference)
Yes	73	5.2	1575	4.5	...	410	7.2	3891	4.2	1.6 (1.5–1.8)
Missing or unknown	21	1.5	276	0.8	...	61	1.1	1168	1.3	—
HIV infection status[c]										

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	N	%	N	%		N	%	N	%	
Negative	941	66.4	22 537	64.5	1 (Reference)	2757	48.1	46 391	49.9	...
Positive	180	12.7	3108	8.9	1.4 (1.1–1.7)	316	5.5	5502	5.9	...
Other[d], missing, or unknown	297	20.9	9288	26.6	0.9 (0.7–1.0)	2664	46.4	41 017	44.2	...
Resident of correctional facility at time of diagnosis										
No	1291	91.0	33 077	94.7	1 (Reference)	5552	96.8	90 252	97.1	...
Yes	108	7.6	1505	4.3	1.6 (1.2–2.1)	143	2.5	1882	2.0	...
Missing/unknown	19	1.3	351	1.0	—	42	0.7	776	0.8	...
Disease site										
Extrapulmonary	1114	78.6	26 840	76.8	...	4299	74.9	64 750	69.7	1 (Reference)
Pulmonary	175	12.3	4723	13.5	...	990	17.3	19 017	20.5	0.8 (0.7–0.8)
Both	129	9.1	3359	9.6	...	446	7.8	9122	9.8	0.7 (0.7–0.8)
Missing/unknown	0	0	11	0	...	2	0	21	0	—
Sputum culture										
Negative	493	34.8	12 054	34.5	1 (Reference)	2296	40.0	37 318	40.2	...
Positive	745	52.5	16 943	48.5	1.1 (0.9–1.3)	2634	45.9	40 153	43.2	...
Not done, missing, or unknown	180	12.7	5936	17.0	0.8 (0.6–1.0)	807	14.1	15 439	16.6	...
Tuberculin skin test										
Negative	227	16.0	5648	16.2	...	451	7.9	9298	10.0	1 (Reference)
Positive	662	46.7	15 423	44.2	...	3145	54.8	48 364	52.1	1.2 (1.1–1.3)
Not done, missing, or unknown	529	37.3	13 862	39.7	...	2141	37.3	35 248	37.9	1.2 (1.04–1.3)
Treatment outcome characteristics[e]										
Received initial isoniazid										
No	43	4.6	253	1.2	4.3 (2.7–6.9)	160	4.1	401	0.7	5.8 (4.7–7.2)
Yes	887	95.2	21 477	98.8	1 (Reference)	3715	95.8	58 336	99.3	1 (Reference)
Missing/unknown	2	0.2	5	0	—	2	0.1	10	0	—
Administration of therapy										
Directly observed (DOT)	590	63.3	13 833	63.6	...	1984	51.2	30 395	51.7	1 (Reference)

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	N	%	N	%		N	%	N	%	
Self-administered	54	5.8	1491	6.9	...	541	14.0	9385	16.0	0.8 (0.7–0.9)
Both DOT and self-administered	279	29.9	6209	28.6	...	1293	33.4	18 164	30.9	1.0 (1.0–1.1)
Missing/unknown	9	1.0	202	0.9	...	59	1.5	803	1.4	—
Time to conversion, months										
<2	466	50.0	9996	46.0	1 (Reference)	2038	52.6	30 256	51.5	...
≥2	283	30.4	7135	32.8	0.8 (0.6–0.95)	1110	28.6	16 589	28.2	...
Did not convert	132	14.2	3649	16.8	0.8 (0.6–1.1)	550	14.2	9257	15.8	...
Missing/unknown	51	5.5	955	4.4	—	179	4.6	2645	4.5	...
Completed therapy in <1 y										
Yes	684	73.4	16 618	76.5	1 (Reference)	2637	6.8	45 219	7.7	1 (Reference)
No	129	13.8	1737	8.0	1.8 (1.4–2.4)	642	16.6	4474	7.6	2.3 (2.1–2.5)
Not eligible[f]	79	8.5	2417	11.1	1.0 (0.7–1.4)	253	6.5	4170	7.1	1.1 (0.9–1.3)
Missing/unknown	40	4.3	963	4.4	—	345	8.9	4884	8.3	—
Additional TB risk factors[g]										
Attributed to recent transmission										
Yes	185	33.8	2827	24.4	1.4 (1.04–1.8)	77	5.5	1793	7.9	0.7 (0.6–0.9)
No	335	61.2	8095	69.7	1 (Reference)	1279	90.6	19 827	87.4	1 (Reference)
Missing or unknown	27	4.9	690	5.9	—	55	3.9	1070	4.7	—
Contact of multidrug-resistant TB patient (within previous 2 y)										
Yes	12	2.2	4	0	40.9 (8.6–195.7)	4	0.3	13	0.1	4.6 (1.3–16.4)
Missing/unknown	535	978	11 608	100.0	1 (Reference)	1407	99.7	22 677	99.9	1 (Reference)
Diabetes mellitus										
Yes	61	11.2	1509	13.0	...	293	20.8	4121	18.2	1.2 (1.02–1.4)
Missing/unknown	486	88.9	10 103	87.0	...	1118	79.2	18 569	81.8	1 (Reference)
Incomplete latent tuberculosis infection therapy										
Yes	20	3.7	415	3.6	...	42	3.0	462	2.0	1.5 (1.1–2.1)
Missing/unknown	527	96.3	11 197	96.4	...	1369	97.0	22 228	97.9	1 (Reference)

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Abbreviations: DOT, directly observed therapy: HIV, human immunodeficiency virus; INH, isoniazid; TB, tuberculosis.

[a]Dashes (—) indicate that the variable level measures of association were not included in the adjusted analysis. Ellipses (...) indicate that the variable measures were not significantly associated with the outcome measure and were not a part of the adjusted model.

[b]Hawaiian/Pacific Islanders were counted as Asians until 2003.

[c]California began reporting HIV test results to the Centers for Disease Control and Prevention in 2011.

[d]Other includes, HIV laboratory tests not offered and offered but unknown or indeterminate.

[e]Persons alive at diagnosis, with an initial regimen of ≥1 drug prescribed and a positive sputum culture. Latest period of measurement ending in 2014. Among US-born persons, INH-monoresistant (n = 932) and drug-susceptible (n = 21 735). Among non–US-born persons, INH-monoresistant (n = 3877) and drug-susceptible TB (n = 58 747).

[f]In this analysis, persons deemed ineligible included those who had died within 1 year of initiating treatment, had bone and joint disease, meningeal disease, or disease of the central nervous system, or pediatric patients (aged 0–14 years) with miliary disease or positive blood culture or a positive nucleic acid amplification test on a blood specimen, and those who had moved out of the country within 1 year after initiating treatment.

[g]During 2011–2016, among US-born persons, INH-monoresistant (n = 547) and drug-susceptible TB (n = 11 612). Among non–US-born persons, INH-monoresistant (n = 1411) and drug-susceptible TB (n = 22 690).