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BRIEF REPORT

Increasing Drug Resistance Among Persons With Tuberculosis in Massachusetts, 2009–2018

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We examined Massachusetts tuberculosis surveillance data from to 2009 to 2018. Of 1533 culture-confirmed cases, 190 (12.4%) demonstrated resistance to isoniazid including 32 (2.1%) with rifampin resistance. In multivariable analysis, isoniazid resistance increased significantly over time (per-year odds ratio = 1.07, 95% confidence interval = 1.01–1.13, $P = .018$) and was associated with younger age, foreign birth, and prior tuberculosis treatment.

Keywords. drug resistance; epidemiology; isoniazid resistance; Massachusetts; tuberculosis.

Data from the Centers for Disease Control and Prevention (CDC) indicate that resistance to first-line tuberculosis (TB) drugs remains important in the United States [1]. Nationally, in individuals with no reported prior TB episode (ie, new TB), resistance to both isoniazid (INH) and rifampin (RIF) (ie, multidrug resistance [MDR]) remains low (1.3% of cases in 2018). However, resistance to at least INH occurs in almost one tenth of all new TB cases (9.0% in 2018) [1]. Moreover, INH monoresistance increased significantly from 4.1% of all TB cases in 1993 to 4.9% in 2016 [2]. Although no significant change occurred among non-US-born persons, a 2.8% annual percentage increase was reported among US-born individuals [2].

Provider awareness of the potential for drug resistance in the United States is important because identification of resistance allows for tailored therapies that lead to improved outcomes [3]. There is increasing evidence that this is true for INH resistance without RIF resistance as well as for MDR-TB [18]. Evaluation of drug-resistant TB rates at the individual state level, including states with higher rates of citizens or visitors born outside the United States, has not been frequently reported but is essential for control measures.

The Massachusetts TB case rate (2.9 per 100 000 residents [4]) is similar to the national case rate, demonstrating a slow decline over the past decade. The majority (86%) of TB cases in Massachusetts occur among individuals born outside the United States 4]. In this retrospective study utilizing Massachusetts surveillance data, we assessed how the percentage of drug-resistant (ie, INH resistance with or without RIF resistance) TB cases changed from 2009 to 2018, and we identified characteristics associated with INH resistance.

METHODS

We obtained deidentified TB surveillance case data for the years 2009–2018 from the Massachusetts Virtual Epidemiologic Network (MAVEN) [5] (1) to retrospectively identify predictors of INH resistance compared with TB susceptible to both INH and RIF and (2) to evaluate time trends. Resistance was defined by phenotypic drug-susceptibility testing (DST) performed at the Massachusetts State Laboratory, involving both Mycobacteria Growth Indicator Tubes (MGIT) and the agar proportion method on 7H10 plates. Discordances between these methods for INH resistance are extremely rare, and in these instances the agar proportion method is reported as the gold standard. All culture-positive cases in Massachusetts have DST performed automatically with a panel of 11 first-line and second-line antimicrobial drugs. Decisions are made on a case-by-case basis at the Massachusetts Department of Public Health to send specimens to the CDC for molecular detection of drug resistance (MDDR) when drug resistance is suspected. Massachusetts clinicians during this time frame would have looked for treatment guidance for INH-resistant TB without RIF resistance from several different organizations with variable regimens [6–8]. The World Health Organization (WHO) in 2014 described 6–9 months of RIF, pyrazinamide (PZA), and ethambutol (EMB) plus or minus a fluoroquinolone [9]. Clinicians in 2017–2018 may have substituted levofloxacin for INH to complete 6 months together with RIF, PZA, and EMB, following the 2018 WHO updated guidance [10].

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In bivariable analyses, variables that differed between individuals with TB resistant to INH and those with TB susceptible to both INH and RIF at a significance level of $P \leq .2$ were considered potential confounders and were assessed in multivariable logistic regression models. Continuous variables included age at TB diagnosis and calendar year of TB diagnosis. Categorical variables were dichotomous with the exception of race (white, black, Asian). Backward selection was used to achieve the most parsimonious multivariable model by initially including all potential confounders and then removing one at a time in order of decreasing P value while monitoring for changes. Because we could not differentiate between unknown status and negative test results, human immunodeficiency virus (HIV) could not be included in the final model.

A second multivariable model was generated for the subset of non-US-born individuals. Given that preliminary testing showed the greatest levels of drug resistance for Vietnam, this model used the dichotomous variable "Vietnam" (ie, birth in Vietnam versus in other countries) in lieu of birth in or outside the United States, and it separately tested the following continuous variables: arrival year in the United States and years since arrival (ie, years between arrival in the United States and TB diagnosis). Wilcoxon tests were used to compare the medians of continuous variables.

We also examined whether Xpert MTB/RIF (Cepheid), a molecular diagnostic test to detect RIF resistance, significantly affected the median time to effective therapy for patients with RIF resistance (by DST) using a Wilcoxon test. Effective therapy was defined as a regimen that included ≥3 drugs to which the patient's isolate was susceptible. Time to treatment was calculated in days by subtracting the date at which effective therapy was started from the date of the first acid-fast bacilli smear collection. Statistical Analysis System (SAS) version 9.3 was used for all analyses.

RESULTS

In Massachusetts, 1533 cases of culture-confirmed TB were identified between 2009 and 2018. DST results were unavailable for 26 cases, most frequently due to insufficient growth. Of the remaining 1507, there were 4 cases (0.3%) with RIF resistance without INH resistance and 190 (12.6%) with INH resistance. In 2014 and 2017, 18% of all TB cases with DST in each of those years had INH resistance (Supplementary Table 1). Thirty-two cases (2.1% of all TB cases with DST) were MDR-TB (INH- and RIF-resistant), and 158 (10.5% of all TB cases with DST) had INH resistance without RIF resistance (Figure 1). Approximately half of INH-resistant cases were resistant to INH alone (n = 73). Those INH-resistant isolates with additional resistance other than RIF included streptomycin (n = 57), EMB (n = 19), and PZA (n = 6) resistance. Twenty-five specimens were sent to the CDC for MDDR by pyrosequencing and/or Sanger sequencing [11]. No discordances with phenotypic DST were observed for INH, although 4 and 2 specimens were discordant with regards to EMB and PZA, respectively (ie, susceptible by DST but resistant by Sanger sequencing). The population diagnosed with TB was predominantly born outside the United States (85.6%), especially in India (9.4%), China (8.4%), Haiti (7.7%), and Vietnam (7.6%).

The following variables showed positive associations with INH resistance with or without RIF resistance (ie, odds ratio [OR], >1.0) in bivariable analyses: calendar year

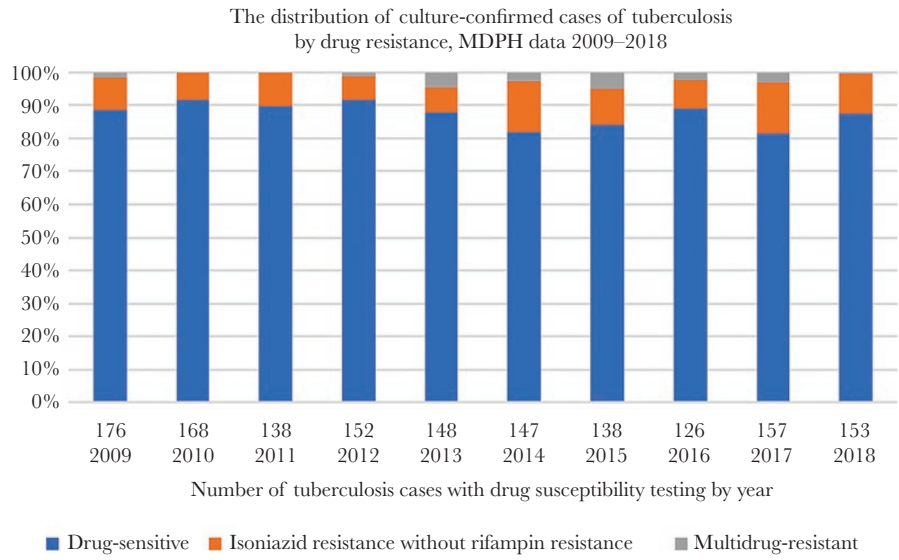

Figure 1. The distribution of culture-confirmed cases of tuberculosis (TB) by drug resistance to isoniazid and rifampin (Massachusetts Data 2009–2018; total N = 1503). Drug resistance is here defined by resistance to either isoniazid or rifampin, or both, without regard to other TB drugs. This figure does not show the 4 cases that were susceptible to isoniazid but resistant to rifampin (1 in 2009, 2 in 2010, and 1 in 2017; Supplementary Table 1). MDPH, Massachusetts Department of Public Health.

of TB diagnosis (ie, per-year change), race (Asian versus white), birth outside the United States, and prior TB treatment. Negative association (ie, OR, <1.0) was seen for each 10-year increase in age at TB diagnosis. Other variables did not show significant associations (Table 1). Median age was significantly younger for those with INH-resistant TB versus those with INH-susceptible TB (37 and 46 years, respectively, $P < .001$). In addition, a Cochran-Armitage test for trend showed that INH resistance increased significantly over time ($P = .028$).

In multivariable analysis (Table 1), only 4 variables demonstrated statistically significant associations with INH resistance: each 10-year increase in age at TB diagnosis (OR, 0.92; 95% CI, 0.89–0.96; $P < .001$), prior TB treatment (OR, 2.77; 95% CI, 1.49–5.17; $P = .001$), birth outside the United States (OR, 2.19; 95% CI, 1.24–3.88; $P = .007$), and calendar year of TB diagnosis (ie, per-year change) (OR, 1.07; 95% CI, 1.01–1.13; $P = 018$). Race showed a trend toward significance (type 3 $P = .055$; Asian versus white OR = 1.65, 95% CI = 1.08–2.52, $P = .021$).

The second model incorporating only those born outside the United States revealed significant associations between INH resistance with or without RIF resistance and the following: each 10-year increase in age at diagnosis (OR, 0.92; 95% CI, 0.88–0.95; $P < .001$), birth in Vietnam (OR, 3.33; 95% CI, 2.10–5.26; $P < .001$), and prior treatment (OR, 2.93; 95% CI, 1.53–5.61; $P = .001$). Rifampin-resistant cases without a molecular test for RIF resistance (N = 19) had a significantly longer median time to effective treatment of 19.0 days versus 2.0 days for cases in which Xpert MTB/RIF detected RIF resistance (N = 17, $P = .009$).

DISCUSSION

Early recognition of drug-resistant TB allows providers to give the most effective therapy quickly, leading to improved individual outcomes and decreased community spread [3]. We found that TB with resistance to INH in Massachusetts increased significantly over 2009–2018 (per-year OR = 1.07, 95% CI = 1.01–1.13, $P = .018$), with rates as high as 18% of all TB

Table 1. Bivariable and Multivariable Predictors of TB Resistant INH With or Without Resistance to RIF (Massachusetts Data 2009–2018; Total N = 1503)

Predictor of TB Resistant to INH[a]	Resistance to INH N = 190 (%)	Susceptible to INH and RIF N = 1313 (%)	Bivariable OR (95% CI)	Bivariable *P* Value	Multivariable OR (95% CI)	Multivariable *P* Value
Age at Time of TB Diagnosis (Years)	--	--	0.93 (0.90–0.96)[b]	<.001	0.92 (0.89–0.96)[b]	<.001
Calendar Year of TB Diagnosis	--	--	1.07 (1.01–1.12)	.017	1.07 (1.01–1.13)	.018
Sex						
Male	107 (56.3%)	731 (55.7%)	1.02 (0.75–1.39)	.885		
Race				.004[c]		
White	36 (18.9%)	395 (30.1%)	REF	--		
Black	54 (28.4%)	377 (28.7%)	1.57 (1.01–2.45)	.046		
Asian	94 (49.5%)	516 (39.3%)	2.00 (1.33–3.00)	<.001		
Ethnicity						
Hispanic	35 (18.4%)	201 (15.3%)	1.25 (0.84–1.85)	.275		
Other Characteristics						
Born outside of the United States	176 (92.6%)	1110 (84.5%)	2.28 (1.29–4.00)	.004	2.19 (1.24–3.88)	.007
Homeless	6 (3.2%)	54 (4.1%)	0.76 (0.32–1.79)	.527		
Substance use	11 (5.8%)	110 (8.4%)	0.67 (0.36–1.27)	.223		
Incarceration history	5 (2.6%)	19 (1.4%)	1.85 (0.68–5.01)	.228		
Prior treatment of TB	15 (7.9%)	44 (3.4%)	2.46 (1.34–4.50)	.004	2.77 (1.49–5.17)	.001
Extrapulmonary TB[d]	48 (25.3%)	308 (23.5%)	1.11 (0.78–1.57)	.573		
Cavitary TB	58 (30.5%)	344 (26.2%)	1.23 (0.88–1.71)	.229		
Miliary TB on chest x-ray	11 (5.8%)	62 (4.7%)	1.23 (0.64–2.38)	.537		
Diabetes	18 (9.5%)	174 (13.3%)	0.69 (0.41–1.14)	.147		
Malignancy	7 (3.7%)	47 (3.6%)	1.03 (0.46–2.31)	.942		
Immunosuppression (non-HIV)	7 (3.7%)	63 (4.8%)	0.76 (0.34–1.68)	.498		
HIV positive[e]	6	50	--	--		
HIV negative/unknown[e]	188	1263	--	--		

Abbreviations: 95% CI, 95% Wald confidence limits; HIV, human immunodeficiency virus; INH, isoniazid; OR, odds ratio; RIF, rifampin; TB, tuberculosis.

Bivariable and multivariable predictors of TB resistant to isoniazid (INH) with or without resistance to rifampin (RIF) (Massachusetts Data 2009–2018; total N = 1503).

[a]Data were missing for most variables (number of cases missing in parentheses): age at time of TB diagnosis (0), calendar year of TB diagnosis (0), sex (2), race (31), ethnicity (2), birth outside of the United States (2), homeless (4), substance use (0), incarceration history (4), prior treatment of TB (9), extrapulmonary TB (5), cavitary TB (9), miliary TB on chest x-ray (9), diabetes (0), malignancy (0), non-HIV immunosuppression (0), and HIV status (0).

[b]Odds ratio is given for a 10-year change.

[c]Type 3 analysis of effects *P* value.

[d]Extrapulmonary TB indicates both extrapulmonary TB alone and extrapulmonary TB with pulmonary TB; the reference group was pulmonary TB alone.

[e]The HIV cells for "resistance to INH" also include 4 cases of INH-susceptible/RIF-resistant TB in addition to the total N of 1503.

cases with DST in 2 individual years and most recently 12.4% in 2018. These numbers are higher than national data from the CDC (10.9% resistance to at least INH in 2018) [1] and highlight the need to evaluate more granular state-level data to keep providers adequately informed of risk [12]. In 2018, 70.2% (6335 of 9025) of US-reported cases occurred among non-US-born persons [1], whereas in Massachusetts this statistic was 86% (172 of 200) in 2018 [4]. Our multivariable model supported the hypothesis that the higher percentage of individuals born outside the United States among TB cases in Massachusetts compared with the larger nation may explain some of the higher proportion of INH resistance among Massachusetts cases.

Resistance to INH without resistance to RIF remains the most common TB drug resistance type globally and also in our state, comprising 10.5% of all cases in our cohort and as much as 15% in some years. Of the INH-resistant cases, 92.1% were in patients with their first TB episode, indicating that their resistance was transmitted and could not be predicted from prior history. In addition, patients with INH resistance were younger and born outside the United States, suggesting that increasing drug resistance in Massachusetts reflects the rise in transmitted drug resistance in their countries of origin [13]. Our findings argue for the development and inclusion of practices that consider migrant populations in the WHO End TB strategy. Improvements in drug-resistant TB care in high-burden settings have global impact in today's increasingly connected world, including for low-burden settings [14].

Other risk factors for drug resistance largely reflected those previously reported in the United States. A national US study of INH monoresistance in 1993–2016 found associations with age <65 years, and Asian race in both US-born and foreign-born populations, and prior TB therapy in the latter [2]. We did not find associations with previously reported social risk factors such as substance use, incarceration, or homelessness [2, 15], and we could not assess HIV status. Among those born outside the United States, birth in Vietnam was strongly associated with all forms of drug resistance, consistent with increasing INH resistance reported in Vietnam [16]. Our study is limited in its size and in lack of completeness of some variables, particularly HIV status. Our findings are likely generalizable to states of comparable size and those that contain a significant number of individuals born outside the United States

Finally, our study has important clinical implications for the treatment of INH-resistant TB. Similar to other studies, we found that molecular testing (Xpert MTB/RIF) significantly decreased the median time to appropriate therapy for patients with RIF-resistant TB [17]. Rapid tests for RIF have been available in Massachusetts since 2012. However, rapid INH molecular testing is not currently performed, except by individual request at the CDC, even though INH resistance is the more common drug resistance. Given that the great majority of patients are started on standard therapy before detection of INH resistance and given recent support for modified regimens for INH-resistant TB, prompt identification of INH resistance is essential to avoid treatment delays lasting as long as months that occur with phenotypic DST [18]. Moreover, the fact that several INH-resistant cases were also resistant to EMB and/or PZA argues for rapid molecular testing for resistance to all first-line drugs.

CONCLUSIONS

This study showed that INH-resistant TB increased in Massachusetts between 2009 and 2018. Rapid molecular tests to detect resistance to INH should be implemented at the state and local level to quickly implement effective treatment regimens.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. K. R. J. conceived the idea and supervised the project with C. R. H. K. M. G. cleaned the data for analysis. J. J. E. processed and analyzed the data with assistance from K. M. G. who worked out many technical details under the supervision of A. T. L. F. W. provided guidance for statistical analysis. J. J. E. wrote the manuscript with input from all authors. All authors discussed the results and contributed to the final manuscript.

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