Increasing Drug Resistance Among Persons with Tuberculosis in Massachusetts, 2009-2018

**Jared J. Eddy**, Postdoctoral Research Fellow, Section of Infectious Diseases, Boston Medical Center, Boston, U.S.A., eddyj@njhealth.org

**Kavita M. Gadani**, Epidemiologist, Massachusetts Department of Public Health, Boston, U.S.A., kavita.m.gadani@state.ma.us

**Andrew Tibbs**, Director of Epidemiology, Surveillance and Research, Division of Global Populations, Massachusetts Department of Public Health, Boston, U.S.A., andrew.tibbs@state.ma.us

**John Bernardo**, Tuberculosis Medical Officer, Division of Global Populations and Infectious Disease Prevention, Massachusetts Department of Public Health; Professor of Medicine, Boston University School of Medicine, Boston, U.S.A., jbernard@bu.edu

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Jennifer Cochran, Director, Division of Global Populations and Infectious Disease Prevention, Massachusetts Department of Public Health, Boston, U.S.A., jennifer.cochran@state.ma.us

Laura F. White, Associate Professor of Biostatistics, Boston University, Boston, U.S.A., lfwhite@bu.edu

C. Robert Horsburgh, Jr., Professor, Epidemiology, Biostatistics, Global Health and Medicine, Boston University Schools of Public Health and Medicine, Boston U.S.A., rhorsbu@bu.edu

Karen R. Jacobson, Assistant Professor of Medicine, Section of Infectious Diseases, Boston University School of Medicine, Boston, U.S.A., Karen.Jacobson@bmc.org

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.R.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.
Contact Information (corresponding author):

Jared J. Eddy, National Jewish Health, Division of Mycobacterial and Respiratory Infections, 1400 Jackson Street, J200c, Denver, CO 80206

Tel. (303) 398-1667, Fax: (303) 398-1780, Email: eddyj@njhealth.org

Contact Information (alternate corresponding author):

Karen R. Jacobson, Section of Infectious Diseases, Department of Medicine 801 Massachusetts Avenue, 2nd Floor, Boston, MA 02118

Tel. (617) 414-5213, Fax: (617) 638-8070, Email: Karen.Jacobson@bmc.org
Abstract:

We examined Massachusetts tuberculosis surveillance data (2009-2018). Of 1,533 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 OR 1.07, 95%CI 1.01-1.13, p=0.018) and was associated with younger age, foreign birth, and prior tuberculosis treatment.

Keywords: Tuberculosis, epidemiology, drug resistance, isoniazid resistance, Massachusetts
Introduction:

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 (U.S) [1]. Nationally, in individuals with no reported prior TB episode (i.e., new TB), resistance to both isoniazid (INH) and rifampin (RIF) (i.e., multidrug resistance, MDR) remains low (1.3% of cases in 2018). However, resistance to at least INH occurs in almost a 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-U.S.-born persons, a 2.8% annual percentage increase was reported among U.S.-born individuals [2].

Provider awareness of the potential for drug resistance in the U.S. is important since 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 U.S., 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 U.S [4]. In this retrospective study utilizing Massachusetts surveillance data, we assessed how the percentage of drug-resistant (i.e., INH resistance with or without RIF resistance) TB cases changed from 2009 to 2018 and identified characteristics associated with INH resistance.
Methods:

We obtained de-identified TB surveillance case data for the years 2009-2018 from the Massachusetts Virtual Epidemiologic Network (MAVEN) [5] to retrospectively identify predictors of INH resistance compared to TB susceptible to both INH and RIF, and 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 antimicrobials. Decisions are made on a case-by-case basis at the Massachusetts Department of Public Health (MDPH) 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 tuberculosis without RIF resistance from a number of different organizations with variable regimens [6, 7, 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].

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 \( p \leq 0.2 \) 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 utilized 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. Since 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-U.S.-born individuals. Given that preliminary testing showed the greatest levels of drug resistance for Vietnam, this model utilized the dichotomous variable “Vietnam” (i.e., birth in Vietnam versus in other countries) in lieu of birth in or outside the U.S., and separately tested the following continuous variables: arrival year in the U.S. and years since arrival (i.e., years between arrival in the U.S. and TB diagnosis). Wilcoxon tests were employed 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, 1,533 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 1,507, 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). Almost 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 (i.e., susceptible by DST but resistant by Sanger sequencing). The population diagnosed with TB was predominantly born outside the U.S. (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 (i.e., odds ratio [OR] > 1.0) in bivariable analyses: calendar year of TB diagnosis (i.e., per-year change), race (Asian versus white), birth outside the U.S., and prior TB treatment. Negative association (i.e., 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<0.001). Additionally, a Cochran-Armitage test for trend showed that INH resistance increased significantly over time (p=0.028).

In multivariable analysis (Table 1) only four 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<0.001), prior TB treatment (OR 2.77, 95%CI 1.49-5.17, p=0.001), birth outside the U.S. (OR 2.19, 95%CI 1.24-3.88, p=0.007), and calendar year of TB diagnosis (i.e., per-year change) (OR 1.07, 95%CI 1.01-1.13, p=0.018). Race showed a trend toward significance (type 3 p=0.055; Asian versus white OR 1.65, 95%CI 1.08-2.52, p=0.021).

The second model incorporating only those born outside the U.S. 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 < 0.001), birth in Vietnam (OR 3.33, 95%CI 2.10-5.26, p<0.001), and prior treatment (OR 2.93, 95%CI 1.53-5.61, p=0.001).

RIF-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=0.009).
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=0.018), with rates as high as 18% of all TB 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% (6,335/9,025) of U.S.-reported cases occurred among non-U.S.-born persons [1], whereas in Massachusetts this statistic was 86% (172/200) in 2018 [4]. Our multivariable model supported the hypothesis that the higher percentage of individuals born outside the U.S. among TB cases in Massachusetts compared to 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. Additionally, patients with INH resistance were younger and born outside the U.S., 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 World Health Organization 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 U.S. A national U.S. study of INH mono-resistance 1993-2016 found associations with age <65 years, and Asian race in both U.S.-born and foreign-born populations, and prior TB therapy in the latter [2]. We did not find associations with previously reported social risk factors like substance use, incarceration, or homelessness [2, 15], and we could not assess HIV status. Among those born outside the U.S., 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 U.S.

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:**

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 in order to quickly implement effective treatment regimens.
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Conflicts of Interest:

None.

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**Tables:**

**Table 1:** Bivariabale and multivariable predictors of TB resistant to isoniazid (INH) with or without resistance to rifampin (RIF) 
(Massachusetts Data 2009-2018; Total N = 1503):

| Predictor of TB Resistant to | Resistance to | Susceptible to | Bivariable OR (95% CI) | Bivariable p-value | Multi-variable OR (95% CI) | Multi-variable p-value |
|-----------------------------|---------------|----------------|------------------------|-------------------|---------------------------|------------------------|
| INH*                        | INH N=190 (%) | INH and RIF N=1313 (%) | 0.93 (0.90-0.96)        | < 0.001           | 0.92 (0.89-0.95)          | < 0.001                |
| Age at Time of TB Diagnosis | --            | --             | 0.93 (0.90-0.96)        | < 0.001           | 0.92 (0.89-0.95)          | < 0.001                |
| Characteristics         | Reference | Estimate (95% CI) | p-value |
|-------------------------|-----------|------------------|---------|
| Calendar year of TB Diagnosis | -         | 1.07 (1.01-1.12) | 0.017   | 1.07 (1.01-1.13) | 0.018   |
| Sex                     |           |                  |         |                  |
| Male                    | 107 (56.3%) | 731 (55.7%)      | 1.02 (0.75-1.39) | 0.885 |
| Race                    |           |                  |         |                  |
| White                   | 36 (18.9%) | 395 (30.1%)      | REF     | --               |
| Black                   | 54 (28.4%) | 377 (28.7%)      | 1.57 (1.01-2.45) | 0.046 |
| Asian                   | 94 (49.5%) | 516 (39.3%)      | 2.00 (1.33-3.00) | < 0.001 |
| Ethnicity               |           |                  |         |                  |
| Hispanic                | 35 (18.4%) | 201 (15.3%)      | 1.25 (0.84-1.85) | 0.275 |
| Other Characteristics   |           |                  |         |                  |
| Condition                          | Group 1 | Group 2 | OR (95% CI)   | p-value |
|----------------------------------|---------|---------|---------------|---------|
| Born outside of the U.S.         | 176 (92.6%) | 1110 (84.5%) | 2.28 (1.29-4.00) | 0.004   |
| Homeless                         | 6 (3.2%) | 54 (4.1%) | 0.76 (0.32-1.79) | 0.527   |
| Substance Use                    | 11 (5.8%) | 110 (8.4%) | 0.67 (0.36-1.27) | 0.223   |
| Incarceration History            | 5 (2.6%) | 19 (1.4%) | 1.85 (0.68-5.01) | 0.228   |
| Prior Treatment of TB            | 15 (7.9%) | 44 (3.4%) | 2.46 (1.34-4.50) | 0.004   |
| Extrapulmonary TB*               | 48 (25.3%) | 308 (23.5%) | 1.11 (0.78-1.57) | 0.573   |
| Cavitary TB                      | 58 (30.5%) | 344 (26.2%) | 1.23 (0.88-1.71) | 0.229   |
| Miliary TB on Chest X-ray        | 11 (5.8%) | 62 (4.7%) | 1.23 (0.64-2.38) | 0.537   |
| Diabetes                         | 18 (9.5%) | 174 (13.3%) | 0.69 (0.41-1.14) | 0.147   |
| Malignancy                       | 7 (3.7%) | 47 (3.6%) | 1.03 (0.46-2.31) | 0.942   |
| Immunosuppression (non-          | 7 (3.7%) | 63 (4.8%) | 0.76 (0.34-1.68) | 0.498   |
HIV positive

HIV negative/unknown

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

Data was 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 U.S. (2), homeless (4), substance use (0), incarceration history (4), prior treatment of TB (9), extrapulmonary TB (5), cavitory TB (9), miliary TB on chest X-ray (9), diabetes (0), malignancy (0), non-HIV immunosuppression (0), and HIV status (0).

OR = Odds Ratio; 95% CI = 95% Wald Confidence Limits.

OR is given for a 10-year change.

Type 3 analysis of effects p-value.

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

The HIV cells for “Resistance to INH” also include 4 cases of INH-susceptible/RIF-resistant tuberculosis in addition to the total N of 1503.
**Figure 1 Legend:**

The distribution of culture-confirmed cases of tuberculosis 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.
Figure 1

The Distribution of Culture-Confirmed Cases of Tuberculosis by Drug Resistance, MDPH Data 2009-2018

- **Drug-sensitive**
- Isoniazid resistance without rifampin resistance
- Multidrug-resistant

Number of Tuberculosis Cases with Drug Susceptibility Testing by Year

| Year | Cases |
|------|-------|
| 2009 | 176   |
| 2010 | 168   |
| 2011 | 138   |
| 2012 | 152   |
| 2013 | 148   |
| 2014 | 147   |
| 2015 | 138   |
| 2016 | 126   |
| 2017 | 157   |
| 2018 | 153   |