Resistance to First-Line Antituberculosis Drugs in Washington State by Region of Birth and Implications for Latent Tuberculosis Treatment among Foreign-Born Individuals

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Abstract. The United States has a low burden of drug resistance among tuberculosis (TB) cases compared with other world regions. TB is increasingly concentrated among foreign-born individuals who have higher rates of drug resistance than U.S.-born individuals. While universal drug susceptibility testing is the standard for detecting active tuberculosis, there are limited guidelines for latent tuberculosis infection (LTBI) treatment based on risk factors for drug resistance. To quantify the variable risk of drug resistance among foreign-born individuals, all TB cases in Washington State between 1994 and 2014 with drug resistance data for isoniazid, rifampin, pyrazinamide, and ethambutol were divided into eight regions of birth. Logistic regression was used to characterize regional differences in resistance patterns. Genotypic cluster and lineage data were compared against drug resistance in a subanalysis. Among 4,298 cases, isoniazid resistance was more common in foreign-born individuals (12.6% versus 4.8%; $P < 0.001$), with the highest burden among individuals from the Asia-Pacific (14.8%) region. Rifampin resistance was slightly higher among foreign-born individuals (1.9% versus 1.1%; $P = 0.063$). Multivariate logistic regression demonstrated that older age was associated with a lower risk of resistance to isoniazid and rifampin (odds ratio [OR] = 0.86, $P = 0.006$ and OR = 0.64, $P = 0.003$ for each 20-year interval, respectively). These data suggest drug resistance in LTBI will remain a challenge and that rifampin-based regimens for treatment of LTBI in non-human immunodeficiency virus-infected adults may be preferable for individuals born in regions with high levels of isoniazid resistance. However, further research is needed to demonstrate whether LTBI treatment based on region of birth further decreases TB reactivation.

INTRODUCTION

While there have been continued improvements in the diagnosis, treatment, and prevention of *Mycobacterium tuberculosis* (TB) in the years since the implementation of Directly Observed Therapy, Short Course (DOTS), the growing danger of drug-resistant TB threatens to undermine these advances.¹ Globally, it is estimated that 5% of TB cases were multidrug-resistant TB (MDR-TB), which is significant because MDR-TB is more difficult to treat and is associated with worse treatment outcomes.²

In the United States, TB remains a rare disease with an incidence of 2.96 cases per 100,000 persons.³ In the United States, 66% of the TB originates from foreign-born individuals, most of whom have reactivation of their TB after immigration to the United States.⁴ In 2008, the United States revised its overseas immigration protocol to include culture methods in its screening program due to cases of TB missed by conventional microscopy-based diagnostic algorithms.⁵ The new protocol found that approximately 60% of TB cases were smear negative, and its implementation resulted in a decrease of imported cases of active TB.^{5,6} Since 2008, TB incidence in the United States has steadily decreased due to the improved overseas culture-based TB screening protocol, declined immigration from high-burden countries, and decreased transmission from recent entrants.⁷ However, reactivation of latent tuberculosis infection (LTBI) among foreign-born individuals accounts for the majority of incident TB cases and has not declined to the same degree as it has among recent arrivals.

Drug-resistance in the United States remains low with only 1.3% of cases being MDR-TB, but it has the potential to rise in parallel with regions with increasing drug resistance as TB becomes more concentrated in foreign-born individuals from these populations.³ Indeed, the proportion of MDR-TB occurring among foreign-born individuals has increased from 31% in 1993 to 88% in 2014.³ These trends offer a means of predicting drug resistance based on the resistance profile of the region of the world the foreign-born individual was born.^{1,8–11} This is particularly relevant in LTBI where drug susceptibility testing is not possible. The ability to predict drug resistance may improve the efficacy of LTBI treatment in foreign-born populations at highest risk for drug-resistant TB.¹²

Washington State, in many ways, reflects the situation of TB in the United States with an incidence of 2.8 cases per 100,000 persons with 1.3% of cases being MDR-TB.¹³ In Washington, the 13.2% of the population is foreign born and account for 72% of the cases of TB.^{13,14} This study describes the differing rates of drug resistance between the United States and foreign-born individuals in Washington State to identify individuals at highest risk for harboring drug-resistant TB.

METHODS

Data sources. In the United States, TB is a reportable disease with individual counties or states being responsible for conducting case investigations, treating TB among contacts, and preventing future cases.¹⁵ Verified cases of TB are reported to the state and then subsequently reported to the U.S. Centers for Disease Control and Prevention (CDC) via the standardized Report of Verified Case of Tuberculosis (RVCT). The state facilitates drug resistance testing and genotyping of each positive culture and reports the result to the CDC using a separate database.

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Demographic and risk factor data from the RVCT form was compiled for all cases of TB in Washington State from 1994 to 2014 and were paired with corresponding drug resistance and genotype data. Genotype data were universally available from 2004 onward. TB genotype has been determined through a number of molecular techniques including restriction fragmentation length polymorphism, spoligotyping, and *Mycobacterium* interspersed repetitive unit (MIRU) analyses.¹⁶ The spoligotyping and MIRU loci typing results are combined to generate a genotypic identity. TB samples from different individuals with the same genotypic identity are categorized into a genotypic cluster, which in turn is used as evidence of direct transmission in the context of epidemiologic investigations.

A separate method of genetic classification involves analysis of DNA large sequence polymorphisms and division into one of five lineages: IndoOceanic, East Asian, East-African-Indian, EuroAmerican, or Africanum. *Mycobacterium bovis*, which also causes clinical tuberculosis, is identified as a distinct species in genotypic lineage analysis.

Study population. Cases were included if an RVCT form was completed, they were counted as a TB case between 1994 and 2014, and they had a positive culture with a phenotypic drug resistance profile including isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). Cases were excluded if they were counted as a case outside the jurisdiction of Washington State, had started TB treatment in another country, had recurrent TB within the last 12 months, or did not have complete first-line drug resistance data. This study was exempt from institutional ethical review as a deidentified database was used.

Individuals were stratified into eight regions of birth: United States and Canada, Latin America and Caribbean, western Europe and Scandinavia, eastern Europe and north-central Asia, Middle East and northern Africa, sub-Saharan Africa, south Asia, and Asia-Pacific (Supplemental Figure 1). Decision to divide the world regions in this manner reflects consideration of regional resistance rates^{1,17} and geographic, political, and ethnic similarities.

Statistical analysis. Demographics and risk factors for TB drug resistance included gender, age, previous TB infection, and human immunodeficiency virus status. Age was stratified by 20-year increments and year of diagnosis was divided into four intervals. These variables were compared against region of birth using χ^2 analysis and analysis of variance (ANOVA) to assess for association. Gender, age, year of diagnosis, previous TB infection, and HIV status were included in a multivariate logistic regression to assess the adjusted odds of drug resistance by region of birth for each first-line tuberculosis drug.

In a subanalysis, the most common genotypic clusters in Washington State containing more than 20 individuals were compiled and analyzed for their proportion of foreign-born individuals and rates of drug resistance to first-line drugs. ANOVA was used to compare the differences in the proportion of foreign-born individuals and rates of drug resistance. χ^2 analysis was used to assess whether genotypic lineage served as a predictor or region of birth and drug resistance. Given *M. bovis* has intrinsic resistance to PZA, demographic factors, country of birth, and PZA resistance among *M. bovis* cases were separately compared against the cohort with χ^2 and ANOVA.

RESULTS

From January 1994 to December 2014, there were 5,229 counted cases of tuberculosis in Washington State. Of these, 4,298 TB cases had complete first-line drug resistance profiles and were included in the analysis. Demographics of all the TB cases stratified by region of birth are summarized in Table 1. The top countries of origin for foreign-born individuals were the Philippines, Vietnam, and Mexico. Foreign-born individuals tended to be more male and had higher rates of prior TB infection. From 1994 to 1999, 59% of TB cases were foreign born compared with 81% during 2010–2014. Rates of HIV positivity were highest among sub-Saharan African (8.7%) and U.S.-born individuals (7.0%). INH resistance was low among U.S.-born individuals (4.8%) compared with Asia-Pacific- (14.8%), south Asian- (11.3%), Latin American- (10.5%), and sub-Saharan Africa- (9.6%) born individuals. RIF, PZA, and EMB resistance was slightly higher among foreign-born individuals but overall quite rare.

The adjusted multivariate logistic regression assessing region of birth as a predictor of drug resistance for each of the first-line TB drugs is summarized in Table 2. Older age was associated with a decreased risk of drug resistance for INH (odds ratio [OR] = 0.86, P = 0.006) and RIF (OR = 0.64, P = 0.003) for each 20-year interval difference. Rates of INH and RIF resistance did not change over time, but there was a trend toward increasing PZA (OR = 1.29, P = 0.529) and decreasing EMB (OR = 0.76, P = 0.013) for each additional 5-year interval in time. Previous TB was a significant predictor of INH and RIF resistance but not of PZA or EMB resistance. HIV positivity was only associated with higher RIF resistance.

In the adjusted logistic regression, INH resistance was significantly higher among foreign-born individuals from Asia-Pacific (OR = 3.36, P < 0.001), south Asia (OR = 2.34, P = 0.001), eastern Europe (OR = 2.29, P = 0.006), Latin America (OR = 2.14, P < 0.001), and sub-Saharan Africa (OR = 1.88, P = 0.003) compared with U.S.-born individuals. Given the infrequency of RIF, PZA, and EMB resistance, there were only insignificant trends toward higher resistance among foreign-born individuals with the exception of higher PZA resistance among individuals from Latin America (OR = 2.81, P < 0.001) and higher EMB resistance among individuals from south Asia (OR = 4.48, P < 0.001), eastern Europe (OR = 3.81, P = 0.011), and Asia-Pacific (OR = 2.26, P = 0.016).

From 1994 to 2014, there were eight circulating genotypic clusters in Washington State with more than 20 individuals. The proportion of foreign-born individuals and INH resistance varied significantly between each cluster, but RIF, PZA, or EMB differences were not detected by χ^2 analysis (Table 3). INH resistance was significantly higher in strains circulating among individuals from the Asia-Pacific region (PCR00117 = 22.2% and PCR00093 = 21.9%) compared with strains circulating among U.S.-born individuals (PCR00036 = 0% and PCR00001 = 1.4%).

Genotypic lineage varied with region of birth with the IndoOceanic strain being predominant in south Asia and Asia-Pacific region, the East Asian strain being common in the Asia-Pacific region, the East-African-Indian strain being common in sub-Saharan African and south Asian regions,

TABLE 1
Demographics and drug resistance by region of birth of TB cases in Washington State, 1994–2014

	United States and Canada (N = 1,288)	Latin America and Caribbean (N = 532)	Western Europe and Scandinavia (N = 26)	Eastern Europe and north-central Asia (N = 150)	Middle East and north Africa (N = 24)	Sub-Saharan Africa (N = 458)	Asia-Pacific (N = 1,607)	South Asia (N = 213)	P value*
Most common countries of origin (n)	United States (1,277) Canada (11)	Mexico (425) Guatemala (33) El Salvador (16)	United Kingdom (8) Germany (5) Ireland (3)	Ukraine (52) Russia (42) Bosnia Herzegovina (15)	Iran (8) Afghanistan (5) Algeria (3)	Ethiopia (192) Somalia (142) Kenya (39)	Philippines (482) Vietnam (468) South Korea (144)	India (185) Pakistan (13) Nepal (12)	
Female gender, %	32.1	32.7	65.4	50.7	50.0	46.9	49.9	45.1	< 0.001
Age at diagnosis (years), n (%)									< 0.001
0–19	121 (9.4)	36 (6.8)	2 (7.7)	5 (3.3)	1 (4.2)	57 (12.5)	69 (4.3)	9 (4.2)	
20–39	259 (20.1)	277 (52.1)	5 (19.2)	50 (33.3)	3 (12.5)	270 (59.0)	524 (32.6)	129 (60.6)	
40–59	525 (40.8)	146 (27.4)	2 (7.7)	25 (16.7)	4 (16.7)	93 (20.3)	488 (30.4)	28 (13.2)	
60–79	264 (20.5)	63 (11.8)	13 (50.0)	45 (30.0)	9 (37.5)	31 (6.8)	427 (26.6)	32 (15.0)	
≥ 80	119 (9.2)	10 (1.9)	4 (15.4)	25 (16.7)	7 (29.2)	7 (1.5)	99 (6.12)	15 (7.0)	
Year of diagnosis, n (%)									
1994–1999	505 (39.2)	142 (26.7)	8 (30.8)	52 (34.7)	3 (12.5)	55 (12.0)	435 (27.1)	32 (15.0)	
2000–2004	334 (25.9)	130 (24.4)	8 (30.8)	34 (22.7)	8 (33.3)	127 (27.7)	399 (24.8)	51 (23.9)	
2005–2009	295 (22.9)	159 (29.9)	6 (23.1)	43 (28.7)	6 (25.0)	155 (33.8)	399 (24.8)	69 (32.4)	
2010–2014	154 (12.0)	101 (19.0)	4 (15.4)	21 (14.0)	7 (29.2)	121 (26.4)	374 (23.3)	61 (28.6)	
Previous TB, %	4.6	4.7	11.5	14	8.3	5.2	7.3	3.8	< 0.001
HIV status at diagnosis, n (%)									< 0.001
Positive	90 (7.0)	35 (6.6)	0	0	1 (4.2)	40 (8.7)	12 (0.8)	2 (0.9)	
Negative	785 (61.0)	393 (73.9)	16 (61.5)	106 (70.7)	12 (50.0)	375 (81.9)	1,175 (73.1)	164 (77.0)	
Unknown	413 (32.1)	104 (19.6)	10 (38.5)	44 (29.3)	11 (45.8)	43 (9.4)	420 (26.14)	47 (22.1)	
Drug resistance, n (%)									
Isoniazid	62 (4.8)	56 (10.5)	1 (3.9)	16 (10.8)	1 (4.2)	44 (9.6)	238 (14.8)	24 (11.3)	< 0.001
Rifampin	14 (1.1)	10 (1.9)	0	5 (3.3)	0	10 (2.2)	27 (1.7)	5 (2.4)	0.37
Pyrazinamide	20 (1.6)	24 (4.5)	0	5 (3.3)	2 (8.3)	9 (2.0)	30 (1.9)	4 (1.9)	0.002
Ethambutol	12 (0.9)	7 (1.3)	1 (3.9)	6 (4.0)	0	6 (1.3)	35 (2.2)	9 (4.2)	0.004

HIV = human immunodeficiency virus; TB = tuberculosis.

*P values for "female," "previous TB," "HIV status," and "drug resistance" were calculated by χ^2 analysis and for "age at diagnosis" was calculated by one-way analysis of variance.

TABLE 2
Adjusted multivariable logistic regression odds ratios of drug resistance and region of birth for each first-line tuberculosis drug.

	Isoniazid	Rifampin	Pyrazinamide	Ethambutol
Female gender	1.03 (95% CI: 0.84, 1.27; $P = 0.764$)	1.35 (95% CI: 0.82, 2.24; $P = 0.241$)	1.26 (95% CI: 0.82, 1.95; $P = 0.286$)	1.51 (95% CI: 0.95, 2.41; $P = 0.085$)
Age at diagnosis (years)				
0–19	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
20–39	1.03 (95% CI: 0.68, 1.57; $P = 0.874$)	1.02 (95% CI: 0.44, 2.42; $P = 0.949$)	0.79 (95% CI: 0.36, 1.73; $P = 0.550$)	0.73 (95% CI: 0.32, 1.69; $P = 0.466$)
40–59	0.88 (95% CI: 0.57, 1.35; $P = 0.550$)	0.32 (95% CI: 0.11, 0.91; $P = 0.032$)	0.74 (95% CI: 0.32, 1.72; $P = 0.491$)	0.45 (95% CI: 0.18, 1.14; $P = 0.093$)
60–79	0.71 (95% CI: 0.45, 1.12; $P = 0.114$)	0.44 (95% CI: 0.15, 1.31; $P = 0.140$)	0.93 (95% CI: 0.38, 2.27; $P = 0.873$)	0.69 (95% CI: 0.26, 1.79; $P = 0.444$)
≥ 80	0.64 (95% CI: 0.35, 1.19; $P = 0.157$)	0.28 (95% CI: 0.05, 1.52; $P = 0.141$)	0.59 (95% CI: 0.17, 2.05; $P = 0.402$)	0.58 (95% CI: 0.15, 2.23; $P = 0.426$)
Each additional 20 years of age	0.86 (95% CI: 0.78, 0.96; $P = 0.006$)	0.64 (95% CI: 0.48, 0.86; $P = 0.003$)	0.97 (95% CI: 0.77, 1.21; $P = 0.762$)	0.89 (95% CI: 0.68, 1.15; $P = 0.365$)
Year of diagnosis				
1994–1999	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
2000–2004	0.95 (95% CI: 0.72, 1.26; $P = 0.729$)	0.69 (95% CI: 0.35, 1.37; $P = 0.292$)	2.55 (95% CI: 1.29, 5.01; $P = 0.007$)	0.79 (95% CI: 0.43, 1.43; $P = 0.430$)
2005–2009	0.95 (95% CI: 0.72, 1.27; $P = 0.761$)	0.78 (95% CI: 0.40, 1.51; $P = 0.456$)	2.61 (95% CI: 1.31, 5.20; $P = 0.006$)	0.66 (95% CI: 0.35, 1.21; $P = 0.179$)
2010–2014	1.03 (95% CI: 0.75, 1.39; $P = 0.862$)	0.81 (95% CI: 0.40, 1.62; $P = 0.546$)	2.96 (95% CI: 1.43, 6.13; $P = 0.003$)	0.40 (95% CI: 0.19, 0.85; $P = 0.018$)
Each additional 5 years in time	1.01 (95% CI: 0.91, 1.11; $P = 0.897$)	0.93 (95% CI: 0.74, 1.18; $P = 0.570$)	1.33 (95% CI: 1.10, 1.61; $P = 0.003$)	0.76 (95% CI: 0.61, 0.94; $P = 0.013$)
Previous tuberculosis	1.66 (95% CI: 1.16, 2.38; $P = 0.005$)	4.08 (95% CI: 2.11, 7.87; $P < 0.001$)	1.29 (95% CI: 0.58, 2.86; $P = 0.529$)	1.25 (95% CI: 0.54, 2.89; $P = 0.603$)
HIV status at diagnosis				
Negative	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Positive	1.08 (95% CI: 0.61, 1.89; $P = 0.793$)	3.75 (95% CI: 1.66, 8.54; $P = 0.001$)	1.15 (95% CI: 0.40, 3.30; $P = 0.794$)	0.86 (95% CI: 0.20, 3.64; $P = 0.833$)
Unknown	1.06 (95% CI: 0.82, 1.36; $P = 0.664$)	0.85 (95% CI: 0.44, 1.66; $P = 0.642$)	1.36 (95% CI: 0.80, 2.30; $P = 0.256$)	0.57 (95% CI: 0.77, 1.06; $P = 0.077$)
Region of birth				
United States and Canada	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Latin America and Caribbean	2.14 (95% CI: 1.46, 3.14; $P < 0.001$)	1.30 (95% CI: 0.66, 2.93; $P = 0.534$)	2.81 (95% CI: 1.58, 5.00; $P < 0.001$)	1.32 (95% CI: 0.52, 3.33; $P = 0.560$)
Western Europe and Scandinavia	0.82 (95% CI: 0.11, 6.20; $P = 0.849$)	Insufficient data	Insufficient data	3.63 (95% CI: 0.43, 30.8; $P = 0.238$)
Eastern Europe and north-central Asia	2.29 (95% CI: 1.27, 4.13; $P = 0.006$)	2.56 (95% CI: 0.82, 7.95; $P = 0.104$)	1.98 (95% CI: 0.68, 5.80; $P = 0.210$)	3.81 (95% CI: 1.36, 10.7; $P = 0.011$)
Middle East and north Africa	0.93 (95% CI: 0.13, 6.83; $P = 0.945$)	Insufficient data	4.26 (95% CI: 0.88, 20.5; $P = 0.071$)	Insufficient data
Sub-Saharan Africa	1.88 (95% CI: 1.24, 2.85; $P = 0.003$)	1.34 (95% CI: 0.58, 3.09; $P = 0.492$)	1.03 (95% CI: 0.46, 2.33; $P = 0.930$)	1.20 (95% CI: 0.44, 3.26; $P = 0.720$)
Asia-Pacific	3.36 (95% CI: 2.49, 4.52; $P < 0.001$)	1.49 (95% CI: 0.76, 2.92; $P = 0.246$)	1.05 (95% CI: 0.59, 1.90; $P = 0.861$)	2.26 (95% CI: 1.16, 4.40; $P = 0.016$)
South Asia	2.34 (95% CI: 1.41, 3.90; $P = 0.001$)	1.83 (95% CI: 0.66, 5.13; $P = 0.248$)	1.01 (95% CI: 0.34, 2.95; $P = 0.993$)	4.48 (95% CI: 1.81, 11.1; $P < 0.001$)

CI = confidence interval; HIV = human immunodeficiency virus.

TABLE 3
Rates of foreign birth and drug resistance among the eight most common genotype clusters

	PCR00036 (N = 57)	PCR00001 (N = 73)	PCR00309 (N = 21)	PCR00002 (N = 105)	PCR00093 (N = 32)	PCR00117 (N = 27)	PCR00041 (N = 115)	PCR00803 (N = 47)	P value*
Foreign born, %	12.3	27.4	57.1	70.5	78.1	81.5	90.4	93.6	< 0.001
Most common countries of origin (n)	United States (50)	United States (53)	United States (9)	United States (31)	Vietnam (20)	Philippines (13)	Philippines (86)	Marshall Islands (32)	
	Mexico (5)	Vietnam (2)	Vietnam (5)	Vietnam (22)	United States (7)	United States (3)	United States (11)	United States (3)	
	Ethiopia (1)	Guatemala (2)	Hong Kong (4)	China (14)	Peru (2)	Mexico (3)	Mexico (11)	Micronesia (3)	
Drug resistance, %									
Isoniazid	0	1.4	4.8	10.5	21.9	22.2	13.9	2.1	< 0.001
Rifampin	0	0	0	2.9	3.1	3.7	0	0	0.161
Pyrazinamide	0	0	0	3.8	0	0	0	0	0.380
Ethambutol	1.8	0	4.8	4.8	6.3	0	1.7	0	0.229

*P value for foreign born is generated with one-way analysis of variance, and for drug resistance generated with χ^2 analysis.

TABLE 4
Region of birth and rates of drug resistance by genotypic lineage

	IndoOceanic (L1) (N = 586)	East Asian (L2) (N = 543)	East-African-Indian (L3) (N = 127)	EuroAmerican (L4) (N = 866)	Africanum (L5/L6) (N = 7)	<i>Mycobacterium bovis</i> (N = 33)	P value*
World region of birth (%)							< 0.001
United States and Canada	45 (7.7)	189 (34.8)	7 (5.5)	265 (30.5)	1 (14.3)	5 (15.2)	
Latin America and Caribbean	37 (6.3)	27 (5.0)	1 (0.8)	203 (23.4)	0	20 (60.6)	
Western Europe and Scandinavia	0	0	0	9 (1.0)	0	0	
Eastern Europe and north-central Asia	4 (0.7)	10 (1.8)	0	54 (6.2)	0	2 (6.1)	
Middle East and north Africa	0	0	2 (1.6)	9 (1.0)	0	2 (6.1)	
Sub-Saharan Africa	35 (6.0)	23 (4.2)	68 (53.5)	170 (19.6)	6 (85.7)	3 (9.1)	
Asia-Pacific	411 (70.1)	283 (52.1)	7 (5.5)	138 (15.9)	0	1 (3.0)	
South Asia	54 (9.2)	11 (2.0)	42 (33.1)	19 (2.2)	0	0	
Drug resistance, %							
Isoniazid	13.5	9.2	8.7	9.5	0	15.2	0.090
Rifampin	1.2	1.8	0.8	1.9	0	0	0.797
Pyrazinamide	1.7	1.5	0	1.2	0	78.8	< 0.001
Ethambutol	1.7	2.6	0	1.2	0	0	0.202

*P values for region of birth and drug resistance are generated with χ^2 analysis.

and the EuroAmerican strain being prevalent in the Americas (Table 4). However, genotypic lineage did not correlate with drug resistance. The 33 *M. bovis* cases, which accounted for the 48% of phenotypic PZA resistance in the genotype sample, were most prevalent in the Latin America region. Most *M. bovis* cases (67%) occurred during 2005–2009, and 58% of cases were in individuals originally born in Mexico (Table 5).

DISCUSSION

While TB incidence in the United States has fallen in the past decade through improvements in the pre-entry culture-based screening of immigrants and decreased arrival of immigrants from high-burden regions, the remaining TB

cases are increasing due to reactivation of LTBI among foreign-born individuals.⁷ Increasing drug resistance abroad may foreshadow a parallel rise in drug resistance in the United States as foreign-born individuals are more likely to be infected with a latent TB strain from their region of origin. Further progress in eliminating TB in the United States therefore depends on the ability to more effectively prevent LTBI reactivation.^{7,18}

This study seeks to describe trends in drug resistance and guide LTBI management based on risk factors for resistance. While resistance to RIF, PZA, and EMB remains low, our study identified significant differences in INH resistance based on region of birth. In the adjusted analysis, INH resistance was significantly higher among individuals from the Asia-Pacific, south Asian, eastern Europe, Latin American, and sub-Saharan African regions, which corresponds to the higher rates drug resistance in these regions.^{1,11}

While the year of diagnosis was not significantly associated with INH or RIF resistance, it is troubling that younger individuals had significantly higher rates of INH and RIF resistance. This suggests that individuals more recently infected with latent TB have higher rates of drug resistance. As they become older and develop reactivated TB, the prevalence of drug resistance may therefore increase compared with previous generations.

This trend is further demonstrated by the genotypic cluster data that show significant differences in INH resistance between strains originating from abroad and strains transmitted in the United States. The PCR00036 and PCR00001 clusters with low INH resistance represent a strain spread among Whites and American Indians in eastern Washington and a strain spreading locally in the Seattle metropolitan region, respectively. Conversely, the clusters with the highest INH resistance, PCR00117 and PCR00093, represent strains from foreign-born individuals from the Philippines and Vietnam, respectively.

An exception to this trend was a genotypic cluster of cases among individuals from the Marshall Islands, which for the purposes of this analysis were included in the Asia-Pacific region. Interestingly, the Marshall Islands cluster (PCR00803) had low rates of resistance, similar to U.S.-born individuals. This may reflect the ease of visa-free travel between the Marshall Islands and the United States given its status as a

TABLE 5
Demographics of *Mycobacterium bovis* infections

	<i>M. bovis</i> (N = 33)	Non- <i>M. bovis</i> (N = 2,129)	P value*
Female, %	45.5	43.3	0.805
Age at diagnosis (years), n (%)			0.558
0–19	4 (12.1)	161 (7.6)	
20–39	12 (36.4)	760 (35.7)	
40–59	7 (21.2)	611 (28.7)	
60–79	9 (27.3)	442 (20.8)	
≥ 80	1 (3.0)	155 (7.3)	
Year of diagnosis, n (%)			0.336
1994–1999	0	6 (0.3)	
2000–2004	3 (9.1)	235 (11.0)	
2005–2009	22 (66.7)	1,083 (50.9)	
2010–2014	8 (24.2)	805 (37.8)	
Previous TB, %	3 (9.1)	5.5	0.536
HIV status at diagnosis, n (%)			0.949
Positive	1 (3.0)	81 (3.8)	
Negative	27 (81.8)	1,757 (82.5)	
Unknown	5 (15.2)	291 (13.7)	
Country of birth, n (%)			< 0.001
Mexico	19 (57.6)	205 (9.6)	
United States	5 (15.2)	500 (23.5)	
Ethiopia	2 (6.1)	119 (5.6)	
Other	7 (21.2)	1,305 (61.3)	
Drug resistance, %			
Pyrazinamide	78.8	1.3	< 0.001

HIV = human immunodeficiency virus; TB = tuberculosis.

*P values for "female," "previous TB," "HIV status," and "drug resistance" were calculated by χ^2 analysis and for "age at diagnosis" was calculated by one-way analysis of variance.

Freely Associated State or alternatively indicate a locally circulating strain in Washington State.

Analysis of genotypic lineage did not show a correlation with drug resistance with the exception of PZA resistance among foreign-born individuals predominantly from Mexico infected with *M. bovis*. The timing of these cases coincide with a circulating strain of *M. bovis* present among Mexican cattle and spread to humans through consumption of unpasteurized milk between 2004 and 2007.¹⁹

A significant limitation of this analysis is that it only represents the foreign-born population in Washington State. Regional trends in immigration result in overrepresentation of foreign-born individuals from certain regions of the world. Washington State has a large population of foreign-born individuals from Mexico, China, the Philippines, Vietnam, and east Africa. So while resistance in the Asia-Pacific and Latin American regions may be well defined, resistance data in the eastern Europe, Middle East, and western European regions are limited due to few individuals from these regions. Further, a majority of the TB cases from sub-Saharan Africa are from eastern Africa that has significantly lower drug resistance (MDR-TB: 1–3% of new TB cases) compared with southern Africa (MDR-TB: 2–8% of new TB cases).^{1,2} Thus, the risk of drug resistance in our analysis in those born in sub-Saharan Africa more closely resembles the risk of an individual born in eastern Africa. Finally, the infrequency of RIF, PZA, and EMB resistance limits the precision of risk factors for resistance to these drugs.

While the standard treatment of LTBI among individuals is 9 months of INH therapy, the RIF-based regimens of 4 months or 3 months of weekly INH and rifapentine are acceptable alternatives for nonpregnant, HIV-negative individuals.²⁰ Currently, there are limited guidelines on LTBI treatment regimen choice incorporating risk of resistance.^{20,21} Due to the significantly higher rates of INH resistance among certain foreign-born groups, RIF-based LTBI regimens in these groups may be more effective in preventing TB reactivation. However, further research is needed to clarify whether an LTBI treatment strategy based on drug resistance risk stratification conveys meaningful reductions in progression to active TB.

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