ORIGINAL RESEARCH

Multidrug-Resistant Tuberculosis in U.S.-Bound Immigrants and Refugees

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Abstract

Rationale: Approximately two-thirds of new cases of tuberculosis (TB) in the United States are among non–U.S.-born persons. Culture-based overseas TB screening in U.S.-bound immigrants and refugees has substantially reduced the importation of TB into the United States, but it is unclear to what extent this program prevents the importation of multidrug-resistant TB (MDR-TB).

Objectives: To study the epidemiology of MDR-TB in U.S.-bound immigrants and refugees and to evaluate the effect of culture-based overseas TB screening in U.S.-bound immigrants and refugees on reducing the importation of MDR-TB into the United States.

Methods: We analyzed data of immigrants and refugees who completed overseas treatment for culture-positive TB during 2015–2019. We also compared mean annual number of MDR-TB cases in non–U.S.-born persons within 1 year of arrival in the United States between 1996–2006 (when overseas screening followed a smear-based algorithm) and 2014–2019 (after full implementation of a culture-based algorithm).

Results: Of 3,300 culture-positive TB cases identified by culture-based overseas TB screening in immigrants and refugees during 2015–2019, 122 (3.7%; 95% confidence interval [CI], 3.1–4.1) had MDR-TB, 20 (0.6%; 95% CI, 0.3–0.9) had rifampicin-resistant TB, 382 (11.6%; 95% CI, 10.5–12.7) had isoniazid-resistant TB, and 2,776 (84.1%; 95% CI, 82.9–85.4) had rifampicin- and isoniazid-susceptible TB. None were diagnosed with extensively drug-resistant TB. All 3,300 persons with culture-positive TB completed treatment overseas; of 70 and 11 persons who were treated overseas for MDR-TB and rifampicin-resistant TB, respectively, none were diagnosed with TB disease at postarrival evaluation in the United States. Culture-based overseas TB screening in U.S.-bound immigrants and refugees prevented 24.4 MDR-TB cases per year from arriving in the United States, 18.2 cases more than smear-based overseas TB screening. The mean annual number of MDR-TB cases among non–U.S.-born persons within 1 year of arrival in the United States decreased from 34.6 cases in 1996–2006 to 19.5 cases in 2014–2019 (difference of 15.1; $P < 0.001$).

Conclusions: Culture-based overseas TB screening in U.S.-bound immigrants and refugees substantially reduced the importation of MDR-TB into the United States.

Keywords: tuberculosis; multidrug-resistant tuberculosis; immigrants and refugees

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Multidrug-resistant tuberculosis (MDR-TB) is defined as disease caused by strains of *Mycobacterium tuberculosis* complex that are at least resistant to treatment with isoniazid and rifampicin; extensively drug-resistant TB (XDR-TB) is defined as disease caused by MDR strains that are also resistant to any fluoroquinolones and any second-line injectable drugs (amikacin, capreomycin, and kanamycin) (1). The spread of MDR- and XDR-TB is a threat to achieving global TB control and elimination (2–12). Globally in 2018, there were 484,000 incident cases of MDR/rifampicin-resistant TB estimated by the World Health Organization; of these, 78.0% had MDR-TB (10). As mycobacterial culture and drug susceptibility testing are not routinely completed for TB cases in all countries, this is most likely an underestimate of the true global incidence of MDR/rifampicin-resistant TB. In the United States, where culture and drug susceptibility testing are the standard of care and completed for the vast majority of TB cases, 102 cases of MDR-TB and one case of XDR-TB were reported in 2018 (13). Direct treatment costs per case in the United States average $175,000 and $544,000 for MDR- and XDR-TB, respectively (14). Although the case burden is relatively low in the United States, applying these estimates to the number of cases suggests $18.4 million in direct treatment costs for MDR- and XDR-TB in 2018.

Approximately two-thirds of new cases of TB in the United States are among non–U.S.-born persons (13, 15). In 2018, 88 (86.3%) of the 102 MDR-TB cases and the one XDR-TB case reported to the U.S. National TB Surveillance System were among non–U.S.-born persons (13). Each year, approximately a half million immigrants and 50,000–70,000 refugees migrate to the United States from overseas (including Mexico and Canada); to reduce the importation of TB into the United States, all such U.S.-bound immigrants and refugees are required to undergo overseas TB screening (16). Before 2007, overseas TB screening used a sputum smear-based algorithm that could not identify smear-negative but culture-positive TB (17–19). In 2007, the U.S. Centers for Disease Control and Prevention (CDC) developed a culture-based algorithm. The culture-based algorithm was implemented initially in Thailand, Mexico, the Philippines, Belize, and Qatar in 2007 and was fully implemented in all countries by 2013 (19).

Culture-based overseas TB screening in U.S.-bound immigrants and refugees is effective in diagnosing and treating TB (19), but it is unclear to what extent this program reduces the importation of MDR-TB into the United States. To evaluate its impact on MDR-TB, we analyzed data from the CDC's Electronic Disease Notification System and the U.S. National TB Surveillance System.

Methods

Overseas TB Screening

Overseas TB screening in U.S.-bound immigrants and refugees is performed by panel physicians, licensed local physicians who are appointed by U.S. embassies and consulates (20). During the analysis period (2015–2019), overseas TB screening, which used the culture-based algorithm, required all persons aged ⩾15 years to have a chest radiograph and those aged 2–14 years in countries with a TB incidence ⩾20 cases/100,000 population/year to undergo a tuberculin skin test or interferon-γ release assay and, if positive, to have a chest radiograph (16). Persons with a chest radiograph or clinical signs or symptoms suggestive of TB had to provide three sputum specimens to undergo microscopy for acid-fast bacilli, culture for mycobacteria, confirmation of the *Mycobacterium* species at least to the *M. tuberculosis* complex level, and drug susceptibility testing for positive cultures (16). Those receiving TB disease diagnoses were not permitted to travel to the United States until they had completed a course of directly observed therapy for TB overseas and were considered cured (16). Treatment of rifampin-resistant disease, including MDR-TB, must be done in close consultation with TB Center of Excellence experts (21) and in coordination with the CDC. If treatment is managed by a national program, the panel physician is required to follow the treatment course, consult TB Center of Excellence experts, and alert the CDC if the treatment is not consistent with U.S. requirements (16).

Analysis Population

We obtained overseas TB screening data from the CDC's Electronic Disease Notification System to study the epidemiology of MDR-TB in U.S.-bound immigrants and refugees (22). This analysis included persons who received sputum culture–positive TB diagnoses overseas, completed treatment by directly observed therapy, had drug susceptibility testing performed for at least isoniazid and rifampin, and arrived in the United States during 2015–2019.

We also obtained publicly available data from the U.S. National TB Surveillance System (23) and compared mean annual number of MDR-TB cases in non–U.S.-born persons within 1 year of arrival in the United States among three time periods of 1996–2006 (when overseas TB screening followed a smear-based algorithm), 2007–2013 (during phased implementation of a culture-based algorithm), and 2014–2019 (after full implementation of a culture-based algorithm).

Sputum Culture–Positive TB

Based on the results of overseas drug susceptibility testing for isoniazid and rifampin, we categorized sputum culture–positive TB as *1*) "MDR-TB" if the testing results were resistant to both isoniazid and rifampin, *2*) "rifampin-resistant TB" if the testing results were resistant to rifampin but susceptible to isoniazid, *3*) "isoniazid-resistant TB" if the testing results were resistant to isoniazid but susceptible to rifampin, and *4*) "rifampin- and isoniazid-susceptible TB" if the testing results were susceptible to both isoniazid and rifampin. MDR-TB was further categorized as "XDR-TB" if patients also had resistance to any fluoroquinolones and any second-line injectable drugs (amikacin, capreomycin, and kanamycin).

Postarrival Evaluation in the United States

The CDC routinely notifies state and local health departments of arriving immigrants and refugees at risk for TB and recommends health department physicians to conduct a postarrival evaluation in the United States (24). When health department physicians suspect pulmonary TB disease, three sputum specimens are obtained on three consecutive days for mycobacterial culture. Drug susceptibility testing is performed for those who have positive culture results.

Ethics Review

This activity was reviewed by CDC and was conducted consistent with applicable federal

law and CDC policy (*see* e.g., 45 C.F.R. part 46.102(l) (2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 *et seq*.).

Statistical Analysis

We calculated the proportions of drug-resistant TB among U.S.-bound immigrants and refugees who received overseas diagnoses of sputum culture–positive TB. We also calculated the proportions of TB disease among those who completed a postarrival evaluation in the United States.

U.S.-bound immigrants and refugees receiving diagnoses of TB by overseas TB screening are required to complete their treatment and cure before they can apply for a visa to the United States. In this analysis, we assumed annual arrivals of immigrants and refugees who completed overseas treatment for MDR-TB and were cured as annual number of MDR-TB cases prevented by culture-based overseas TB screening.

Data on MDR-TB are unavailable for U.S.-bound immigrants and refugees who were screened before 2007 by smear-based overseas TB screening. Without performing drug susceptibility testing, persons with MDR-TB were likely treated overseas with first-line drugs initially. A study of U.S.-bound immigrants and refugees found that of 2,946 sputum culture–positive TB cases diagnosed by culture-based overseas screening during 2007–2012, 25.5% (751) also had sputum smear–positive results (19). This result indicates that smear-based overseas TB screening identified 25.5% of persons with sputum culture–positive TB. In this analysis, we assumed that of the MDR-TB cases diagnosed by culture-based overseas TB screening, 25.5% were among persons with sputum smear–positive and culture-positive TB. Using this assumption, we estimated the number of MDR-TB cases prevented by smear-based overseas TB screening (as 25.5% of that prevented by culture-based overseas TB screening).

Using data from the U.S. National TB Surveillance System for non–U.S.-born persons within 1 year of arrival in the United States, we applied the Student's *t* test to compare the mean annual number of MDR-TB cases among 1996–2006 (when overseas TB screening followed a smear-based algorithm), 2007–2013 (during phased implementation of a culture-based algorithm), and 2014–2019 (after full implementation of a culture-based algorithm). We used the chi-square test to compare proportions of MDR-TB in non–U.S.-born persons with sputum culture–positive TB within 1 year of arrival in the United States among 1996–2006, 2007–2013, and 2014–2019.

Results

Sputum Culture–Positive TB Cases Prevented from Arriving in the United States by Culture-based Overseas TB Screening

Of 3,300 culture-positive TB cases identified by culture-based overseas TB screening during 2015–2019, 122 (3.7%; 95% confidence interval [CI], 3.1–4.1) had MDR-TB, 20 (0.6%; 95% CI, 0.3–0.9) had rifampicin-resistant TB, 382 (11.6%; 95% CI, 10.5–12.7) had isoniazid-resistant TB, and 2,776 (84.1%; 95% CI, 82.9–85.4) had rifampicin- and isoniazid-susceptible TB (Table 1). None were diagnosed with XDR-TB (Table 1). Collectively, persons from Vietnam, Philippines, Burma, and China accounted for 82.8% of the MDR-TB cases, 75.0% of the rifampicin-resistant TB cases, 89.5% of the isoniazid-resistant TB cases, and 75.0% of the rifampicin- and isoniazid-susceptible TB cases (Table 1).

Between 2015 and 2019, culture-based overseas TB screening in U.S.-bound immigrants and refugees prevented 24.4 cases of MDR-TB, 4.0 cases of rifampicin-resistant TB, 76.4 cases of isoniazid-resistant TB, and 555.2 cases of rifampicin- and isoniazid-susceptible TB on average per year from arriving in the United States.

Resistance to First- and Second-Line Drugs

Of persons who had MDR-TB, resistance to additional first-line drugs was found in 60.2% (53/88) to streptomycin, 40.9% (47/115) to pyrazinamide, and 22.7% (27/119) to ethambutol; resistance to second-line injectable drugs was found in 4.7% (2/43) to capreomycin, 2.4% (1/42) to kanamycin, 0% (0/71) to amikacin; resistance to fluoroquinolones was found in 25.0% (1/4) to moxifloxacin, 10.4% (5/48) to ofloxacin, 4.8% (1/21) to levofloxacin; and resistance to other second-line drugs was found in 33.3% (1/3) to cycloserine, 23.6% (17/72) to ethionamide, and 11.9% (7/59) to para-aminosalicylic acid (Table 2). Of those who had rifampicin-resistant TB, resistance was found in 18.1% (2/11) to streptomycin, 10.5% (2/19) to ethambutol, and 5.6% (1/18) to pyrazinamide (Table 2). Of those who had isoniazid-resistant TB, resistance was found in 33.0% (98/297) to streptomycin, 7.4% (27/367) to pyrazinamide, and 1.3% (5/377) to ethambutol (Table 2). Of those who had rifampicin- and isoniazid-susceptible TB, resistance was found in 6.9% (140/2,028) to streptomycin, 1.4% (36/2,641) resistant to pyrazinamide, and 0.2% (5/2,728) to ethambutol (Table 2).

Postarrival Evaluation in the United States

Among 122 persons who were treated for MDR-TB overseas, 70 (57.4%) completed a postarrival evaluation; of these, none received a diagnosis of TB disease (Table 3). Of 20 persons who were treated for rifampicin-resistant TB overseas, 11 (55.0%) completed a postarrival evaluation; of these, none received a diagnosis of TB disease (Table 3). Of 382 persons treated for isoniazid-resistant TB overseas, 262 (68.6%) completed a postarrival evaluation; of these, 2 (0.8%) received a diagnosis of TB disease (one was culture positive but susceptible to first-line drugs, and the other one was culture negative; Table 3). Of 2,776 persons who were treated for rifampicin- and isoniazid-susceptible TB overseas, 1,955 (70.4%) completed a postarrival evaluation; of these, 14 (0.7%) received a diagnosis of TB disease (1 had MDR-TB, 1 was culture-positive but susceptible to first-line drugs, 9 were culture-negative, and 3 had unavailable culture results; Table 3).

Annual Number of MDR-TB Cases Prevented from Arriving in the United States by Culture- or Smear-based Overseas TB Screening

During 2015–2019, culture-based overseas TB screening prevented 24.4 MDR-TB cases on average per year from arriving in the United States (Table 4). We estimated that if the smear-based algorithm had continued to be used during the same period, overseas TB screening in U.S.-bound immigrants and refugees would have prevented just 6.2 MDR-TB cases on average per year and missed 18.2 cases among those with smear-negative but culture-positive TB (Table 4).

Table 1. Sputum culture–positive TB cases prevented by culture-based overseas TB screening in U.S.-bound immigrants and refugees, 2015–2019

		Overseas TB Classification*							
		MDR-TB		Rifampicin-Resistant TB		Isoniazid-Resistant TB		Rifampicin- and Isoniazid-Susceptible TB	
Variable	Total	No.	Percentage of Total (95% CI)†	No.	Percentage of Total (95% CI)†	No.	Percentage of Total (95% CI)†	No.	Percentage of Total (95% CI)†
Year of arrival									
2015	683	20	2.9 (1.7–4.2)	4	0.6 (0.2–1.5)	72	10.5 (8.2–12.8)	587	85.9 (83.3–88.6)
2016	808	35	4.3 (2.9–5.7)	4	0.5 (0.1–1.3)	97	12.0 (9.8–14.2)	672	83.2 (80.6–85.7)
2017	660	16	2.4 (1.3–3.6)	6	0.9 (0.2–1.6)	74	11.2 (8.8–13.6)	564	85.5 (82.8–88.1)
2018	648	25	3.9 (2.4–5.3)	3	0.5 (0.1–1.4)	77	11.9 (9.4–14.4)	543	83.8 (81.0–86.6)
2019	501	26	5.2 (3.2–7.1)	3	0.6 (0.1–1.7)	62	12.4 (9.5–15.3)	410	81.8 (78.5–85.2)
Visa type									
Immigrant	2,625	96	3.7 (2.9–4.4)	15	0.6 (0.3–0.9)	343	13.1 (11.8–14.4)	2,171	82.7 (81.3–84.2)
Refugee	675	26	3.9 (2.4–5.3)	5	0.7 (0.2–1.7)	39	5.8 (4.0–7.5)	605	89.6 (87.3–91.9)
Sex									
Male	1,991	69	3.5 (2.7–4.3)	10	0.5 (0.2–0.8)	244	12.3 (10.8–13.7)	1,668	83.8 (82.2–85.4)
Female	1,309	53	4.0 (3.0–5.1)	10	0.8 (0.3–1.2)	138	10.5 (8.9–12.2)	1,108	84.6 (82.7–86.6)
Age, yr									
<2	0	0	N/A	0	N/A	0	N/A	0	N/A
2–14	41	2	4.9 (0.6–16.5)	0	0	0	0	39	95.1 (88.5–100.0)
15–44	1,524	67	4.4 (3.4–5.4)	12	0.8 (0.3–1.2)	154	10.1 (8.6–11.6)	1,291	84.7 (82.9–86.5)
45–64	1,232	46	3.7 (2.7–4.8)	6	0.5 (0.1–0.9)	162	13.1 (11.3–15.0)	1,018	82.6 (80.5–84.7)
⩾65	503	7	1.4 (0.4–2.4)	2	0.4 (0.1–1.4)	66	13.1 (10.2–16.1)	428	85.1 (82.0–88.2)
Country of birth‡									
Mexico	71	0	0	0	0	2	2.8 (0.3–9.8)	69	97.2 (93.3–100.0)
Philippines	1,135	33	2.9 (1.9–3.9)	5	0.4 (0.1–1.0)	161	14.2 (12.2–16.2)	936	82.5 (80.3–84.7)
India	47	3	6.4 (1.3–17.5)	0	0	0	0	44	93.6 (86.6–100.0)
Vietnam	880	47	5.3 (3.9–6.8)	6	0.7 (0.1–1.2)	131	14.9 (12.5–17.2)	696	79.1 (76.4–81.8)
China	186	6	3.2 (0.7–5.8)	2	1.1 (0.1–3.8)	22	11.8 (7.2–16.5)	156	83.9 (78.6–89.2)
Guatemala	5	0	0	0	0	0	0	5	100 (2.5–100.0)
Haiti	42	0	0	0	0	7	16.7 (5.4–27.9)	35	83.3 (72.1–94.6)
Honduras	1	0	0	0	0	0	0	1	100 (2.5–100.0)
Ethiopia	14	2	14.3 (1.8–42.8)	0	0	2	14.3 (1.8–42.8)	10	71.4 (47.8–95.1)
Burma	340	15	4.4 (2.2–6.6)	2	0.6 (0.1–2.1)	28	8.2 (5.3–11.2)	295	86.8 (83.2–90.4)
Other	579	16	2.8 (1.4–4.1)	5	0.9 (0.3–2.0)	29	5.0 (3.2–6.8)	529	91.4 (89.1–93.7)
TB incidence in birth countries§									
0–19	5	0	0	0	0	1	20.0 (18.8–37.5)	4	80.0 (28.4–99.5)
20–99	353	11	3.1 (1.3–4.9)	5	1.4 (0.5–3.3)	30	8.5 (5.6–11.4)	307	87.0 (83.5–90.5)
⩾100	2,940	111	3.8 (3.1–4.5)	15	0.5 (0.3–0.8)	350	11.9 (10.7–13.1)	2,464	83.8 (82.5–85.1)
Unknown	2	0	0	0	0	1	50.0 (1.3–98.7)	1	50.0 (1.3–98.7)
Total	3,300	122	3.7 (3.1–4.1)	20	0.6 (0.3–0.9)	382	11.6 (10.5–12.7)	2,776	84.1 (82.9–85.4)

Definition of abbreviations: CI = confidence interval; MDR-TB = multidrug-resistant tuberculosis; TB = tuberculosis; WHO = World Health Organization.

*Overseas TB classification was based on overseas drug susceptibility testing results for rifampicin and isoniazid; none received a diagnosis of extensively drug-resistant TB.

†For No. ⩽5, CI was calculated by an exact method (i.e., Clopper Pearson Method).

‡Top 10 birth countries of most reported TB cases among non–U.S.-born persons in the United States in 2019.

§2016 WHO-estimated TB incidence (cases/100,000 persons/year) for birth country. WHO TB burden estimates: https://www.who.int/tb/country/data/download/en/.

MDR-TB among Non–U.S.-born Persons within 1 Year of Arrival in the United States

The mean annual number of MDR-TB cases among non–U.S.-born persons within 1 year of arrival decreased from 34.6 cases in 1996–2006 to 21.8 cases in 2007–2013 (difference of 12.8; $P < 0.001$), and to 19.5 cases in 2014–2019 (difference of 15.1; $P < 0.001$; Table 4 and Figure 1). There was a nonsignificant difference in the mean annual number of MDR-TB cases among non–U.S.-born persons within 1 year of arrival between 2007–2013 and 2014–2019 (difference of 2.3; $P = 0.460$; Table 4 and Figure 1). The proportion of MDR-TB in non–U.S.-born persons receiving diagnoses of sputum

Table 2. Overseas drug susceptibility testing results for immigrants and refugees who received a diagnosis of sputum culture–positive TB by culture-based overseas screening, 2015–2019

Drug Susceptibility Test Performed	Overseas TB Classification*								
	MDR-TB†		Rifampicin-Resistant TB		Isoniazid-Resistant TB		Rifampicin- and Isoniazid-Susceptible TB		
	No. of Tests	No. with Resistant Result (%)	No. of Tests	No. with Resistant Result (%)	No. of Tests	No. with Resistant Result (%)	No. of Tests	No. with Resistant Result (%)
First-line oral agents								
Isoniazid	122	122 (100)	20	0 (0)	382	382 (100)	2,776	—
Rifampicin	122	122 (100)	20	20 (100)	382	0 (0)	2,776	—
Ethambutol	119	27 (22.7)	19	2 (10.5)	377	5 (1.3)	2,728	5 (0.2)
Pyrazinamide	115	47 (40.9)	18	1 (5.6)	367	27 (7.4)	2,641	36 (1.4)
First-line injectable agent								
Streptomycin	88	53 (60.2)	11	2 (18.1)	297	98 (33.0)	2,028	140 (6.9)
Second-line injectable agents								
Amikacin	71	0 (0)	1	0 (0)	12	0 (0)	20	1 (5.0)
Capreomycin	43	2 (4.7)	2	0 (0)	10	0 (0)	19	0 (0)
Kanamycin	42	1 (2.4)	0	N/A	2	1 (50.0)	9	0 (0)
Fluoroquinolones								
Levofloxacin	21	1 (4.8)	0	N/A	50	0 (0)	15	0 (0)
Ofloxacin	48	5 (10.4)	1	0 (0)	6	0 (0)	3	0 (0)
Moxifloxacin	4	1 (25.0)	0	N/A	0	N/A	5	0 (0)
Other second-line oral agents								
Ethionamide	72	17 (23.6)	2	0 (0)	16	2 (12.5)	32	0 (0)
Para-aminosalicylic acid	59	7 (11.9)	2	0 (0)	9	1 (11.1)	22	0 (0)
Cycloserine	3	1 (33.3)	0	N/A	2	0 (0)	2	0 (0)

Definition of abbreviations: MDR-TB = multidrug-resistant tuberculosis; N/A = not applicable; TB = tuberculosis.
*Based on overseas drug susceptibility testing results for rifampicin and isoniazid.
†None received a diagnosis of extensively drug-resistant TB.

culture–positive TB within 1 year of arrival was 3.2% (381/11,938) in 1996–2006, compared with 2.9% (153/5,334) in 2007–2013 ($P = 0.257$) and 2.8% (117/4,134) in 2014–2019 ($P = 0.248$).

Discussion

Our analysis demonstrated that culture-based overseas TB screening in U.S.-bound immigrants and refugees substantially reduced the importation of MDR-TB into the United States. During 2015–2019, culture-based overseas TB screening prevented 24.4 MDR-TB cases on average per year from arriving in the United States. For context, the mean annual number of 100.2 MDR-TB cases was reported in the United States during 2015–2019 (23); these 24.4 additional cases, had importation not been prevented, would represent a 24.4% increase in the total annual number of U.S. cases. Our analysis supported the finding of a previous study that overseas treatment for TB effectively limits importation; of 3,005 who were treated overseas for TB disease and completed postarrival evaluation in the United States, only 0.7% were diagnosed with TB disease (0.1% with culture-positive TB) (24). Our analysis showed that overseas treatment for MDR-TB and rifampicin-resistant TB in U.S.-bound immigrants and refugees was also effective. Of 70 and 11 persons who were treated overseas for MDR-TB and rifampicin-resistant TB, respectively, none were diagnosed with TB disease at postarrival evaluation in the United States.

We estimated that culture-based overseas TB screening in U.S.-bound immigrants and refugees, introduced in 2007, prevented 18.2 more cases of MDR-TB per year than smear-based overseas TB screening. This finding is consistent with the change in mean annual number of MDR-TB cases reported among non–U.S.-born persons within 1 year of arrival in the United States, which decreased by 15.1 cases between 1996–2006 (when overseas screening followed a smear-based algorithm) and 2014–2019 (after full implementation of the culture-based algorithm). These results indicated that the use of the culture-based algorithm in overseas TB screening in U.S.-bound immigrants and refugees could contribute to the decline of reported cases of MDR-TB among newly arrived non–U.S.-born persons in the United States. Other factors could also contribute to the decline,

Table 3. Results of postarrival evaluation in the United States of immigrants and refugees who completed overseas treatment for sputum culture–positive TB, 2015–2019

		Completion of Postarrival Evaluation in the United States						
			TB Cases					
			Sputum Culture–Positive TB					
Overseas TB Classification*	Total No. of Arrivals	No. (%)	MDR-TB (%)	Susceptible to First-Line Drugs (%)	Sputum Culture–Negative TB (%)	Unavailable Sputum Culture Results (%)	Total No. of Cases (%)	
MDR-TB†	122	70 (57.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Rifampicin-resistant TB	20	11 (55.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Isoniazid-resistant TB	382	262 (68.6)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	2 (0.8)	
Rifampicin- and isoniazid-susceptible TB	2,776	1,955 (70.4)	1 (0.1)	1 (0.1)	9 (0.5)	3 (0.2)	14 (0.7)	
Total	3,300	2,298 (69.6)	1 (0.04)	2 (0.1)	10 (0.4)	3 (0.1)	16 (0.7)	

Definition of abbreviations: MDR-TB = multidrug-resistant tuberculosis; TB = tuberculosis.
*Based on overseas drug susceptibility testing results for rifampicin and isoniazid.
†None received a diagnosis of extensively drug-resistant TB.

but we did not have data to conduct further analysis. For example, a previous study has reported that the decline of TB cases among non–U.S.-born persons could be caused by a decreased TB rate and fewer newly arrived non–U.S.-born persons in the United States (25), and these factors could also likely cause the decline of MDR-TB among non–U.S.-born persons within 1 year of arrival. The population of non–U.S.-born persons within 1 year of arrival included newly arrived immigrants and refugees and non-immigration visitors (students/exchange visitors, temporary workers, tourists and business travelers, and unauthorized visitors). Length of stay in the United States varies among nonimmigrant visitors, from several days to multiple years. Data are available for annual admissions of nonimmigrant visitors but not for their length of stay in the United States. Because we could not obtain a reliable estimate for the population of newly arrived nonimmigrant visitors, we are not able to calculate and compare rates of MDR-TB among non–U.S.-born persons within 1 year of arrival between 1996–2006 (when overseas screening followed a smear-based algorithm) and 2014–2019 (after full implementation of a culture-based algorithm).

There are a few data reported specifically on yield of MDR-TB for screening programs in migrants to low-incidence countries. Of 15 studies included in a systematic review on preentry screening for TB in migrants, only 3 described yield of MDR-TB (26). In these three studies, only 33 MDR-TB cases were reported among 183 persons with culture-positive TB (27–29). MDR-TB in low-incidence countries in Europe is more prevalent among migrants than among the native population, but the impact of the increase in migration on the MDR-TB epidemiology is unclear (7). Preentry screening in migrants to the UK is effective in finding TB (30, 31), but data of MDR-TB were not reported. Of 736 migrants who received diagnoses of culture-positive TB from the Immigration Medical Examination in Australia during 2014–2017, 10 (1.4%) had MDR-TB; of these, 3 were from the Philippines and another 3 were from China (32). We found a higher proportion of MDR-TB among those with culture-positive TB, and the Philippines and China were two of the four countries that accounted for most MDR-TB cases.

Globally in 2018, 90.5% of 484,000 incident cases of MDR/rifampicin-resistant TB were in the top 30 countries of high TB burden, and 49.0% of these cases were in India, China, and Russia (10). A study estimates that the burden of MDR- and XDR-TB will be increased in India, the Philippines, Russia, and South Africa (8). High proportions of MDR-TB are also reported in Vietnam and China (33, 34). Our analysis showed that 82.8% of the MDR-TB cases were among persons from the Philippines, Vietnam, Burma, and China, reflecting both the high incidence of disease in these countries and the high volume of U.S.-bound immigrants and refugees from these countries. Because the culture-based screening algorithm was implemented early in the Philippines (October 2007), Vietnam (February 2008), Burma (January 2009), and China (July 2009), there was only a small decline of 2.3 MDR-TB cases between 2007–2013 (during phased implementation of the culture-based algorithm) and 2014–2019 (after full implementation of the culture-based algorithm). Although the annual number of MDR-TB cases declined after implementation of the culture-based algorithm, the proportion of MDR-TB in non–U.S.-born persons receiving a diagnosis of sputum-positive TB within 1 year of arrival was relatively constant (3.2% in 1996–2006 vs. 2.8% in 2014–2019), associated with reduced cases of both TB and MDR-TB into the United States.

Newly arrived non–U.S.-born persons contribute substantially to the burden of MDR-TB in the United States (23, 35). The U.S. National TB Surveillance System reported that during 2014–2019, 22.2% (117) of 526 non–U.S.-born persons with MDR-TB were among those within 1 year of arrival (23). In a cross-sectional study, 23.9% (22) of 92 non–U.S.-born persons with MDR-TB were among those within 3 months of arrival in the United States (35). Currently, overseas TB screening is mandated for U.S.-bound immigrants and refugees but not for U.S.-bound students/exchange visitors and temporary workers. In 2019, ~489,000 immigrants and refugees and 6.6 million students/exchange visitors and temporary workers arrived in the United States from overseas (36). Of 291 MDR-TB cases

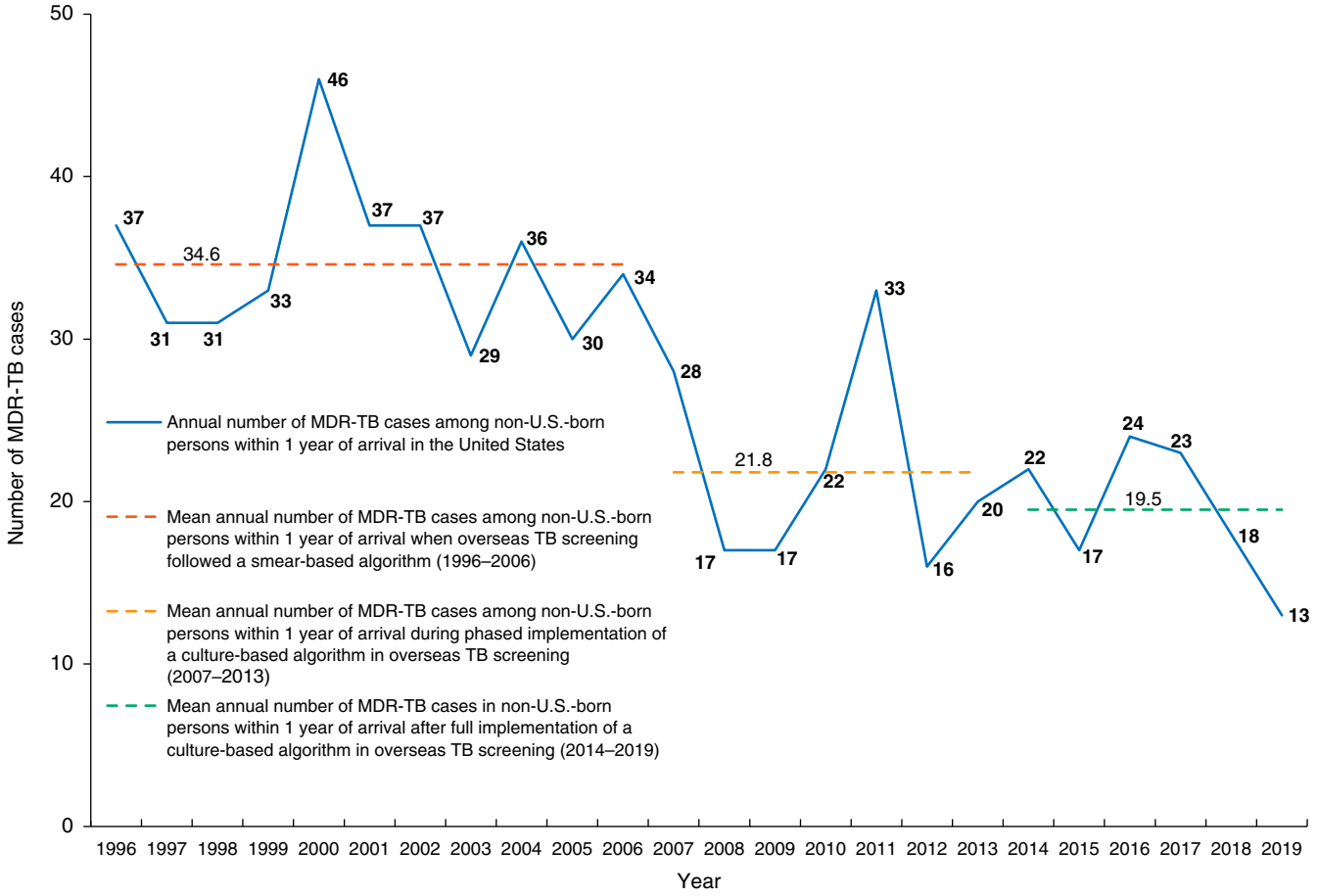

Figure 1. MDR-TB cases among non–U.S.-born persons within 1 year of arrival in the United States that were reported to the U.S. National TB Surveillance System, 1996–2019. MDR-TB = multidrug-resistant tuberculosis; TB = tuberculosis.

estimated among newly arrived non–U.S.-born persons during 2001–2008, 38.1% (111) were among students/exchange visitors and temporary workers (37). More studies are needed to confirm if expansion of overseas TB screening to include U.S.-bound students/exchange visitors and temporary workers from countries with a high incidence of TB can further reduce the importation of TB and MDR-TB into the United States.

We found that 11.6% (382) of 3,330 U.S.-bound immigrants and refugees who received a diagnosis of sputum culture–positive TB overseas had isoniazid-resistant TB. Persons with isoniazid-resistant TB had various proportions of resistance to first-line drugs, and those with MDR-TB had various proportions of resistance to first- and second-line drugs. These susceptibility results underscore the importance of obtaining a full first-line drug susceptibility profile on all patients with TB and a full second-line drug susceptibility profile on all patients with MDR-TB. Although newer molecular tests, such as Cepheid Xpert MTB/RIF Ultra (38), are valuable tools to more quickly identify patients with drug resistance, our analysis indicated that the lack of cultures and full drug susceptibility profiles would have left 11.6% of U.S.-bound immigrants and refugees who received a diagnosis of TB overseas at risk for having an inadequate regimen and at risk for later relapse with increasing drug resistance.

This analysis has two main limitations. First, in comparing the mean annual number of reported MDR-TB cases in non–U.S.-born persons within 1 year of arrival among 1996–2006, 2007–2013, and 2014–2019, we did not adjust for changes in the population size of non–U.S.-born persons within 1 year after arrival during this time as these data are not available. Second, underascertainment of TB disease overseas may occur. Furthermore, some countries may be disproportionately affected. For example, in India, a country with World Health Organization–estimated TB incidence of 193 cases per 100,000 persons per year (39) and the third highest birth countries reported for TB cases among non–U.S.-born persons in the United States in 2019 (13), we found just 47 cases of culture-positive TB diagnosed overseas—a number much lower than expected given 139,134 new immigrant arrivals from India during this period (40). This finding may reflect differences in health status between U.S.-bound immigrants and the general population in India. A previous study also reported low prevalence of bacteriologically confirmed TB (24.4 cases/100,000 persons) among Indian visa applicants who took

Table 4. Mean annual number of MDR-TB cases prevented from arriving in the United States by overseas TB screening in U.S.-bound immigrants and refugees, and mean annual number of MDR-TB cases reported among non–U.S.-born persons within 1 year of arrival in the United States

Variable	No. of MDR-TB Cases
MDR-TB cases among immigrants and refugees in the CDC's Electronic Disease Notification database	
Mean annual number of cases prevented by culture-based overseas TB screening during 2015–2019	24.4
Estimated mean annual number of cases prevented by smear-based overseas TB screening*	6.2
Difference	18.2
MDR-TB cases among non–U.S.-born persons within 1 yr of arrival in the U.S. National TB Surveillance System	
Mean annual number of cases during 1996–2006 (when overseas TB screening followed a smear-based algorithm)	34.6
Mean annual number of cases during 2007–2013 (during phased implementation of a culture-based algorithm)	21.8
Mean annual number of cases during 2014–2019 (after full implementation of a culture-based algorithm)	19.5
Difference between 1996–2006 and 2007–2013	12.8 ($P < 0.001$)†
Difference between 1996–2006 and 2014–2019	15.1 ($P < 0.001$)†
Difference between 2007–2013 and 2014–2019	2.3 ($P = 0.460$)†

Definition of abbreviations: CDC = Centers for Disease Control and Prevention; MDR-TB = multidrug-resistant tuberculosis; TB = tuberculosis.
*Based on the findings of a previous study (19), we assumed that of the MDR-TB cases diagnosed by culture-based overseas TB screening, 25.5% were among persons with sputum smear–positive and culture-positive TB. Using this assumption, we estimated the annual number of MDR-TB cases prevented by smear-based overseas TB screening (as 25.5% of that prevented by culture-based overseas TB screening).
†Tested by the Student's *t* test.

Immigration Medical Examination in Australia during 2014–2017 (32). Alternatively, it may reflect applicants seeking to avoid immigration delays by obtaining treatment, if needed, from their private physician before undergoing medical examination by their panel physician. Additional limitations include small sample size for overseas drug susceptibility testing of several second-line drugs; indirect methods used to estimate MDR-TB cases prevented by smear-based overseas TB screening; and missing postarrival evaluation data for 30.4% of persons who received a diagnosis of sputum culture–positive TB overseas.

Our analysis demonstrated that culture-based overseas TB screening in U.S.-bound immigrants and refugees substantially reduced the importation of MDR-TB into the United States. To further reduce the incidence of TB and MDR-TB among non–U.S.-born persons in the United States, more studies are needed on expansion of culture-based overseas TB screening to include U.S.-bound students/exchange visitors and temporary workers from countries with a high incidence of TB. ■

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