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

(Received in original form May 14, 2021; accepted in final form December 22, 2021)

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All authors are employees of the U.S. government. The findings and conclusions of this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Data availability statement: No additional data are available.

Author Contributions: Conception and design: Y.L., D.L.P., Q.Y., and C.R.P. Analysis and interpretation: Y.L., D.L.P., Q.Y., M.S.W., S.A.M., L.A.L., L.S.O., N.M., M.S.C., and C.R.P. Drafting the manuscript for important intellectual content: Y.L., D.L.P., and C.R.P. Critical revision and final approval of manuscript: all authors.

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Ann Am Thorac Soc Vol 19, No 6, pp 943–951, June 2022
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DOI: 10.1513/AnnalsATS.202105-580OC
Internet address: www.atsjournals.org
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(d); 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 TB.

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

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

| Year of Arrival | MDR-TB | Rifampicin-Resistant TB | Isoniazid-Resistant TB | Rifampicin- and Isoniazid-Susceptible TB |
|----------------|--------|------------------------|------------------------|----------------------------------------|
|                | No. (%95 CI) | No. (%95 CI) | No. (%95 CI) | No. (%95 CI) |
| 2015           | 683 (20) 2.9 (1.7–4.2) | 4 (0.6–1.5) | 72 (10.5–12.8) | 587 (85.9–88.6) |
| 2016           | 808 (35) 4.3 (2.9–5.7) | 4 (0.5–1.9) | 97 (12.0–14.2) | 672 (83.2–85.7) |
| 2017           | 660 (16) 2.4 (1.3–3.6) | 6 (0.9–1.6) | 74 (11.2–13.6) | 564 (85.5–88.1) |
| 2018           | 648 (25) 3.9 (2.4–5.3) | 3 (0.5–1.4) | 77 (11.9–14.4) | 543 (83.8–86.6) |
| 2019           | 501 (26) 5.2 (3.2–7.1) | 3 (0.6–1.7) | 62 (12.4–15.3) | 410 (81.8–85.2) |

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

| Year of Arrival | MDR-TB | Rifampicin-Resistant TB | Isoniazid-Resistant TB | Rifampicin- and Isoniazid-Susceptible TB |
|----------------|--------|------------------------|------------------------|----------------------------------------|
|                | No. (%95 CI) | No. (%95 CI) | No. (%95 CI) | No. (%95 CI) |
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| 2018           | 648 (25) 3.9 (2.4–5.3) | 3 (0.5–1.4) | 77 (11.9–14.4) | 543 (83.8–86.6) |
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**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/.
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 an average of 24.4 MDR-TB cases per year from arriving in the United States. For context, the mean annual number of MDR-TB cases reported in the United States during 2015–2019 was 100.2. If importation had not been prevented, these 24.4 additional cases would represent a 24.4% increase in the total annual number of U.S.-based MDR-TB cases. Our analysis supported the findings 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 in the United States, which decreased from 182 cases in 2006 to 117 cases in 2013 (25). Our analysis indicated that the use of the culture-based algorithm in overseas TB screening could contribute to the decline in newly arrived non-U.S.-born persons in the United States. Other factors could also contribute to the decline in MDR-TB among newly arrived non-U.S.-born persons in the United States. Other factors could also contribute to the decline in MDR-TB among newly arrived non-U.S.-born persons in the United States.

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           | 0 (0)                              | 382          | 0 (0)                             | 2,776        | —                                  |
| Ethambutol                        | 119          | 27 (22.7)                          | 19           | 1 (5.6)                            | 377          | 5 (13.9)                          | 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       | 88           | 53 (60.2)                          | 11           | 2 (18.1)                           | 297          | 98 (33.0)                         | 2,028        | 140 (6.9)                          |
| Streptomycin                      | 71           | 0 (0)                              | 1            | 0 (0)                              | 12           | 0 (0)                             | 20           | 1 (5.0)                            |
| Amikacin                          | 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                                | 2            | 1 (50.0)                          | 5            | 0 (0)                              |
| Second-line injectable agents     |              |                                   |              |                                   |              |                                   |              |                                   |
| Amikacin                          | 88           | 53 (60.2)                          | 11           | 2 (18.1)                           | 297          | 98 (33.0)                         | 2,028        | 140 (6.9)                          |
| Capreomycin                       | 71           | 0 (0)                              | 1            | 0 (0)                              | 12           | 0 (0)                             | 20           | 1 (5.0)                            |
| Kanamycin                         | 43           | 2 (4.7)                            | 2            | 0 (0)                              | 10           | 0 (0)                             | 19           | 0 (0)                              |
| Fluoroquinolones                  | 48           | 5 (10.4)                           | 1            | 0 (0)                              | 6            | 0 (0)                             | 3            | 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.
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 nonimmigrant 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/riafamicin-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, 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

### 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

| Overseas TB Classification† | Total No. of Arrivals | Sputum Culture–Positive TB | 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.

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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.

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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 after full implementation of a culture-based algorithm in overseas TB screening (2014–2019) 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

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.
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 | 24.4 |
| Mean annual number of cases prevented by culture-based overseas TB screening during 2015–2019 | 6.2 |
| Estimated mean annual number of cases prevented by smear-based overseas TB screening* | 18.2 |
| Difference | 12.8 (P < 0.001)† |
| Difference between 1996–2006 and 2007–2013 | 34.6 |
| Mean annual number of cases during 1996–2006 (when overseas TB screening followed a smear-based algorithm) | 21.8 |
| Mean annual number of cases during 2007–2013 (during phased implementation of a culture-based algorithm) | 19.5 |
| Mean annual number of cases during 2014–2019 (after full implementation of a culture-based algorithm) | 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% 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.

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Mr. Robert Pratt of CDC’s Division of TB Elimination for reviewing the manuscript. They also thank the staff of CDC’s Electronic Disease Notification team for updating and managing CDC’s notification system for TB in immigrants and refugees; the staff of CDC’s Quarantine Stations for collecting information of overseas medical examination; the panel physicians for performing overseas TB screening; and the staff of state and local health departments for conducting postarrival evaluations in the United States.

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