Epidemiology & Background

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Efforts to control TB throughout the world have been challenged in recent decades by the emergence of drug-resistant TB.

Drug-resistant tuberculosis (TB) is a deadly communicable disease that poses a serious global health threat. It impacts not only individual patients and their families, but also imposes tremendous burdens on overextended public health systems that may lack the resources needed to contain it.

**DEFINITIONS**

- **Multidrug-resistant (MDR)** refers to TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) that is resistant to at least isoniazid (INH) and rifampin (RIF).

- **Pre-extensively drug-resistant (Pre-XDR)** refers to MDR-TB that is also resistant to either a fluoroquinolone or a second-line injectable anti-TB drug (kanamycin, capreomycin, or amikacin), but not both.

- **Extensively drug-resistant (XDR)** refers to MDR-TB that is also resistant to both a fluoroquinolone and a second-line injectable anti-TB drug.

**Drug-resistant TB across the globe**

In 2014, an estimated 480,000 people developed MDR-TB and 190,000 people died from MDR-TB. By 2015, 105 countries had reported at least one case of XDR-TB. An estimated 21% of MDR-TB cases worldwide have additional resistance to a fluoroquinolone, and 9.7% have XDR-TB. According to the World Health Organization (WHO), more than half of the global burden of MDR-TB is currently in three countries: India, China, and the Russian Federation.

Worldwide and in most countries with a high burden of MDR-TB, WHO estimates that in 2014 only 41% of those with MDR-TB were actually diagnosed by laboratory testing.

Fortunately, there are new and vigorous efforts for control of TB and for early diagnosis and treatment of drug-susceptible and drug-resistant TB worldwide. Large-scale implementation of rapid molecular tests for early detection of both the presence of TB and, at
a minimum, rifamycin resistance has occurred in many high-burden countries. The Patients’ Charter for Tuberculosis Care, developed by the World Care Council, promotes a “patient-centered” approach to tuberculosis care. The updated International Standards for Tuberculosis Care (iSTC) presents a set of widely accepted, evidence-based standards describing a level of care that all practitioners, public and private, should seek to achieve in managing patients with, or suspected of having, TB.

WHO reported improvements in detection and treatment of MDR-TB in 2014: 111,000 people with MDR-TB were started on second-line treatment, equivalent to 90% of the 123,000 newly-detected cases that were reported and eligible for treatment globally. However, treatment coverage gaps for detected cases were much larger in some countries, notably the high-burden countries of China (49%), Myanmar (44%), and Nigeria (53%).

Finally, improvements in early identification and enrollment into treatment must also be followed by quality of care measures that ensure treatment success. Only three high-burden countries reported a treatment success rate for MDR-TB of 75% or higher. On average, only 50% of MDR-TB patients in the 2012 cohort of detected cases were treated successfully. Many countries lack the resources needed to provide sufficient quality of care. These disparities must be addressed to prevent further transmission of disease and more extensive resistance.

In many high-burden countries, a standardized MDR-TB regimen is used due to the lack of routine access to second-line drug-susceptibility testing (DST). The success or failure of treatment of these cases overseas can impact the presentation of drug resistance in the United States (U.S.) through immigration. It is important for U.S. clinicians to understand the diversity of global practices.

A milestone for improved MDR-TB care occurred in 2012 when bedaquiline (BDQ) fumarate (Sirturo, Janssen) became the first TB drug in a novel class to be approved in 40 years. In October 2013, the U.S. Centers for Disease Control and Prevention (CDC) issued provisional guidance for its use in the treatment of MDR-TB. A second new drug, delamanid (Deltyba, Otsuka), also gained provisional approval for use in the European Union in 2014, and additional drugs are in the development pipeline.

Drug-resistant TB in the United States

In the United States in 2010-2013:

- 413 TB patients had MDR-TB based on initial DST. Of these, 49 patients had pre-XDR-TB, and 12 patients had XDR-TB. In other words, 15% of U.S. MDR-TB patients had pre-XDR or XDR.

- Thirty-eight states plus the District of Columbia reported at least 1 MDR-TB case; 19 states reported at least 1 pre-XDR-TB case; and 8 states reported at least 1 XDR-TB case. See Figure 1.
Although the number of drug-resistant cases of TB in the United States declined as the number of total reported TB cases decreased, there has been little change in the percentage (1.0–1.6%) of TB patients with MDR-TB during 2000-2013. On the other hand, the percentage of patients with INH resistance has increased from 7.9% in 2000 to 9.2% in 2013. The increase in INH-resistant TB is troubling because it is one mutation away from becoming MDR-TB.

In recent years, the percentage of patients with pyrazinamide (PZA)-resistant TB has also increased (from 2.0% to 3.3% during 1999-2009). TB patients with PZA resistance include those with TB infections caused by *M. bovis* (a member of the *M. tuberculosis* complex that is intrinsically resistant to PZA) and *M. tuberculosis*. *M. bovis* accounted for an average of 1.7% of culture proven cases from 2008-2013.

In the United States, drug resistance in foreign-born persons with TB is much more common than in U.S.-born persons with TB, corresponding to the higher rates of drug resistance in the countries of origin.

- In 2013, 90% of MDR-TB cases in the United States were among foreign-born persons.
- Among foreign-born patients who arrived in the United States within 2 years of TB diagnosis (recent arrivers), 3.2% had MDR-TB, compared to 1.4% of those diagnosed with TB more than 2 years after they arrived (remote arrivers).
Figure 2 shows that the percentage of U.S.-born TB patients with INH resistance increased from 4.5% to 5.8% from 2000 to 2013. Among foreign-born TB patients over the same time period, the percentage of INH-resistant TB remained the same, at about 11% in both recent and remote arrivers.

The small percentage of U.S.-born TB patients with MDR-TB slightly declined from 2000 (0.6%, N=42) to 2013 (0.4%, N=9), while the percentage of foreign-born recent (3%, N=33) and remote (1.4%, N=47) arrivers with MDR-TB remained stable over the same time period.

Overall, drug-resistant TB is also more common among TB patients who were born in countries with an estimated high prevalence of drug resistance. Discordance between WHO and U.S. estimates of MDR-TB by country-of-origin was documented in a recent study that demonstrated that the U.S. National TB Surveillance system (NTSS) better predicted the prevalence of drug resistance in foreign-born U.S. residents with TB than the WHO/International Union Against Tuberculosis and Lung Diseases (IUATLD) Global Project on Anti-Tuberculosis Drug Resistance Surveillance (Global DRS). Of the 413 foreign-born patients diagnosed with MDR-TB in the United States from 2010 to 2013, 75% were born in only 15 countries. Table 1 shows the drug resistance pattern for the top 15 countries of origin for cases of drug-resistant TB in the United States.

**INH-resistant TB among U.S.-born patients slightly increased from 2000-2013. Rates of INH-resistant and MDR-TB among all groups have otherwise remained stable during this period.**
# Drug resistance among foreign-born TB patients in the United States, 2010-2013 (Top 15 countries)

<table>
<thead>
<tr>
<th>Country of origin</th>
<th>Total TB cases*</th>
<th>MDR</th>
<th>Any resistance**</th>
<th>INH resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>India</td>
<td>2,122</td>
<td>40</td>
<td>1.9</td>
<td>258</td>
</tr>
<tr>
<td>Philippines</td>
<td>3,068</td>
<td>39</td>
<td>1.3</td>
<td>484</td>
</tr>
<tr>
<td>Mexico</td>
<td>5,542</td>
<td>37</td>
<td>0.7</td>
<td>652</td>
</tr>
<tr>
<td>Vietnam</td>
<td>2,002</td>
<td>32</td>
<td>1.6</td>
<td>365</td>
</tr>
<tr>
<td>China</td>
<td>1,478</td>
<td>23</td>
<td>1.6</td>
<td>162</td>
</tr>
<tr>
<td>Peru</td>
<td>373</td>
<td>14</td>
<td>3.8</td>
<td>51</td>
</tr>
<tr>
<td>Laos</td>
<td>284</td>
<td>12</td>
<td>4.2</td>
<td>49</td>
</tr>
<tr>
<td>Ukraine</td>
<td>93</td>
<td>12</td>
<td>12.9</td>
<td>21</td>
</tr>
<tr>
<td>Haiti</td>
<td>753</td>
<td>11</td>
<td>1.5</td>
<td>58</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>461</td>
<td>11</td>
<td>2.4</td>
<td>56</td>
</tr>
<tr>
<td>Burma / Myanmar</td>
<td>426</td>
<td>9</td>
<td>2.1</td>
<td>60</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>296</td>
<td>8</td>
<td>2.7</td>
<td>31</td>
</tr>
<tr>
<td>Ecuador</td>
<td>307</td>
<td>8</td>
<td>2.6</td>
<td>31</td>
</tr>
<tr>
<td>Guatemala</td>
<td>777</td>
<td>8</td>
<td>1.0</td>
<td>61</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>635</td>
<td>7</td>
<td>1.1</td>
<td>60</td>
</tr>
</tbody>
</table>

*Total cases with positive cultures and initial susceptibilities performed
**TB isolates with any first-line drug resistance (INH, RIF, ethambutol [EMB], PZA)
Source: Robert H. Pratt, National Tuberculosis Surveillance System, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention (email communication, November 14, 2014).
Drug resistance is also more common in TB patients who reported having had previous TB. In the United States in 2013, 4.2% of all patients who reported previous TB had MDR-TB, whereas only 1.2% of patients who did not report previous TB had MDR-TB. These differences in percentages with MDR-TB were evident among both U.S.-born patients (2.2% with previous TB vs. 0.3% without previous TB) and foreign-born patients (5.1% with previous TB vs. 1.7% foreign-born patients without previous TB).

Sources of drug-resistant TB in the United States

There are 4 primary sources that explain the epidemiology of drug-resistant TB in the United States:

- Resistance acquired during treatment in the United States
- Recent transmission of drug-resistant *M. tuberculosis*
- Reactivation of latent drug-resistant TB infection
- Entry of patients into the United States with active drug-resistant *M. tuberculosis* disease

A cross-sectional study of 92 MDR-TB cases reported in the United States 2007-2009 determined that:

- 5% of patients had a documented previous episode of TB in the United States and likely relapsed with acquired drug-resistant disease.
- 22% of MDR-TB cases were the result of recent transmission.
- 41% had reactivation disease (one-third of those with reactivation disease had a previous episode of TB in another country, indicating possible acquired resistance outside of the United States).
- Another 22% occurred in patients originating from another country who entered the United States with active TB disease.
- 10% could not be classified because there were insufficient data.

MDR-TB transmission has been documented across the world, with a 2010 report of half of MDR-TB cases occurring within individuals with newly-identified TB (rather than previously-treated TB), in 30 countries.
How is drug resistance generated?

Drug resistance is generated at the molecular level when genes responsible for the specific form of drug resistance (e.g., \textit{rpoB} for rifampin) of \textit{M. tuberculosis} develop a spontaneous mutation. The prevalence of resistant mutants associated with each first-line drug used to treat TB has been estimated, and resistance to new drugs (e.g., bedaquiline) has already been identified. A typical pulmonary cavity will contain an estimated $10^7$ to $10^9$ organisms, therefore making it likely that some organisms in these cases may exhibit a spontaneous mutation for resistance. See Table 2.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year introduced</th>
<th>Prevalence of resistant mutants within a wild-type population of \textit{M. tuberculosis} bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>1945</td>
<td>$3.8 \times 10^{-6}$</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>1952</td>
<td>$3.5 \times 10^{-6}$</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1952</td>
<td>$1.0 \times 10^{-5}$</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>1962</td>
<td>$3.1 \times 10^{-5}$</td>
</tr>
<tr>
<td>Rifampin</td>
<td>1967</td>
<td>$1.2 \times 10^{-8}$</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>2013</td>
<td>?</td>
</tr>
</tbody>
</table>

Within wild-type populations, resistance to more than one TB drug is even rarer as resistance to the various drugs is not linked genetically. Inherent resistance to more than one TB drug is the product of the prevalence of resistance to the individual drugs.

- INH and RIF: $3.5 \times 10^{-6} \times 1.2 \times 10^{-8}$ equals $4.2 \times 10^{-14}$

Mutations conferring drug resistance to \textit{M. tuberculosis} become important for the TB patient when amplified by health care system-related factors and/or patient behaviors. Contributors to the development of acquired resistance during treatment for TB include: inadequate clinical management, poor adherence, drug malabsorption, and unstable drug supply. Enhancers of transmission of MDR-TB include factors that extend the infectious period; e.g., delayed diagnosis and/or delayed treatment initiation with an appropriate regimen, and delayed bacteriological conversion of sputum. Inadequate infection control can also contribute to transmission of MDR-TB.
In a patient with active TB disease, factors that create or amplify drug resistance include:

- The patient may not take all the drugs prescribed, due to any of the following factors:
  - Lack of resources
  - Intolerance/toxicity
  - Misunderstanding
  - Interrupted drug supply
  - Disbelief in the diagnosis
  - Disbelief in the efficacy or necessity of the treatment
  - Chaotic lifestyle; substance abuse
  - Cultural issues
  - Pregnancy
  - Neuropsychiatric disease
- There may be a dispensing or administration error regarding the correct dose.
- The patient may not be prescribed the appropriate dose.
- The patient may not absorb the full dose of medication and/or have disease in areas where the penetration of one or more of the drugs may be impaired.
- The provider may not prescribe an adequate TB regimen.
- The patient’s organism may already be resistant to one of the TB drugs prescribed, leaving an unrecognized suboptimal TB regimen.
- The patient may have been incorrectly diagnosed as having latent TB infection (LTBI), rather than active TB disease, and treated with monotherapy.
- The TB patient may be taking therapy for another disease. That therapy may coincidentally contain a single drug active against TB (rifabutin in an HIV patient for Mycobacterium avium complex [MAC] prophylaxis; a fluoroquinolone for community-acquired pneumonia).
- The patient may take TB medicines without a prescription (sometimes available over-the-counter outside the United States, or if taking medications belonging to someone else).
- The TB medicines may interact with other drugs being taken by the patient.

If the patient starts an effective TB regimen and then stops taking all the TB drugs at the same time, the population of bacteria usually remains susceptible.

This is one of the major advantages of directly observed therapy (DOT): either the patient takes all the drugs or none of the drugs. This is also the benefit of combination formulations such as INH/RIF or INH/RIF/PZA in a single product. The patient either takes all drugs or none—reducing risk of development of resistance.

Clinically significant drug resistance usually emerges after 1 to 3 months of administration of an inadequate drug regimen.
Summary

• Globally in 2014, an estimated 480,000 people developed MDR-TB and 190,000 people died from MDR-TB. By 2015, 105 countries had reported at least one case of XDR-TB. More than half of the global burden of MDR-TB is currently in three countries: India, China, and the Russian Federation.

• Despite recent improvements in early identification and enrollment into treatment, high-burden countries often lack the resources needed to ensure quality of care for treatment success.

• Ninety percent of MDR-TB cases in the United States occur among the foreign-born.

• Fifteen percent of MDR-TB patients in the United States had pre-XDR or XDR-TB.

• Risk factors for INH-resistant and MDR-TB in the United States include country-of-origin, recent arrival (within 2 years) in the United States, previous TB, and exposure to an individual with INH-resistant or MDR-TB during the infectious period.

• The percentage of TB patients with MDR-TB is not increasing in the United States, but the percentage of U.S.-born TB patients with INH resistance, and PZA resistance overall, is increasing in the United States.

• The increase in INH-resistant TB is troubling because it is one mutation away from becoming MDR-TB.

• It is essential to implement strategies to assure DOT and completion of an adequate regimen in order to reduce development or amplification of drug resistance.
References
