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# Epidemiology & Background

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## SUMMARY OF KEY UPDATES (2022)

- Updated pre-XDR and XDR definitions from WHO and CDC
- Updated data on global and U.S. burden of drug-resistant TB

# Drug-resistant TB threatens TB control efforts throughout the world.

Drug-resistant tuberculosis (DR-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.

Accepted definitions of types of DR-TB have changed and should be considered when comparing past epidemiologic data to current information. Updated World Health Organization (WHO) definitions were changed in January 2021 and Centers for Disease Control and Prevention (CDC) definitions changed in January 2022 (applied to 2021 data analysis) as seen below.

## Definitions

| | |
|---|---|
| **Drug-resistant (DR)** | Refers to TB that is resistant to at least one anti-TB medication |
| **Rifampin resistant (RR)*** | Refers to TB that is resistant to rifampin but is not (or is not known to be) resistant to INH* |
| **Multidrug-resistant (MDR)** | Refers to TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) that is resistant to at least:<br>• Isoniazid (INH) and rifampin (RIF) |
| **Pre-extensively drug-resistant (Pre-XDR)** | Refers to MDR-TB plus resistance to:<br>• Fluoroquinolones WHO January 2021<br>• Fluoroquinolones or second-line injectable CDC January 2022 |
| **Extensively drug-resistant (XDR)**** | Refers to MDR-TB plus resistance to:<br>• Fluoroquinolones + [bedaquiline (BDQ) or linezolid (LZD)] WHO January 2021<br>• Fluoroquinolones + [BDQ or LZD or second-line injectable] CDC January 2022 |

* Considered by WHO to be equivalent to MDR because only molecular tests like Xpert MTB/RIF are available in many settings.
** Fluoroquinolones + second-line injectable only (Prior WHO and CDC definitions)

# DR-TB across the globe

WHO global estimates are that **450,000 people developed MDR- or rifampin-resistant TB (MDR/RR-TB) in 2021, an increase of 3.1% over 2020.** The proportion of MDR/RR-TB was 3.6% in new TB cases and 18% presenting in those with prior TB treatment. The same report shared that approximately two-thirds of the global burden of MDR-TB is currently in seven countries: India, Russian Federation, Pakistan, China, Philippines, Indonesia, and South Africa. Estimates based on 2018 data show 20.8% of MDR-TB cases worldwide have additional resistance to a fluoroquinolone, and 6.2% have XDR-TB.

In the 2021 WHO report, the detrimental effect of the COVID-19 pandemic on TB services was evident with an overall 18% decrease in reported TB diagnoses and the first year-on-year increase in TB deaths since 2005. The impact for DR-TB was a 22% reduction in DR-TB case detection (from 201,997 in 2019 to 156,982 in 2020) and a 15% reduction in treatment initiation (from 177,000 to 150,469). 2021 saw a partial return toward 2019 numbers with 166,991 cases of MDR/RR-TB detected and 161,746 people enrolled in treatment. Estimates predicted only 1 in 3 persons with DR-TB was enrolled on treatment.

**Approximately two-thirds of the global burden of MDR-TB is currently in seven countries.**

Despite those setbacks, two improvements can be cited. WHO estimated that in 2020 and 2021, **71% of those with bacteriologically confirmed TB were tested for rifampin resistance** (up from 50% in 2018). Progress in the identification of RR-TB reflects global efforts to scale-up implementation of rapid molecular tests for early detection of both the presence of TB and, at a minimum, rifamycin resistance in many high-burden countries. In addition, 2019 data (latest patient cohort with available data) for MDR/RR-TB reported an **improved treatment success rate of 60%** as compared to 50% treatment success in 2012.

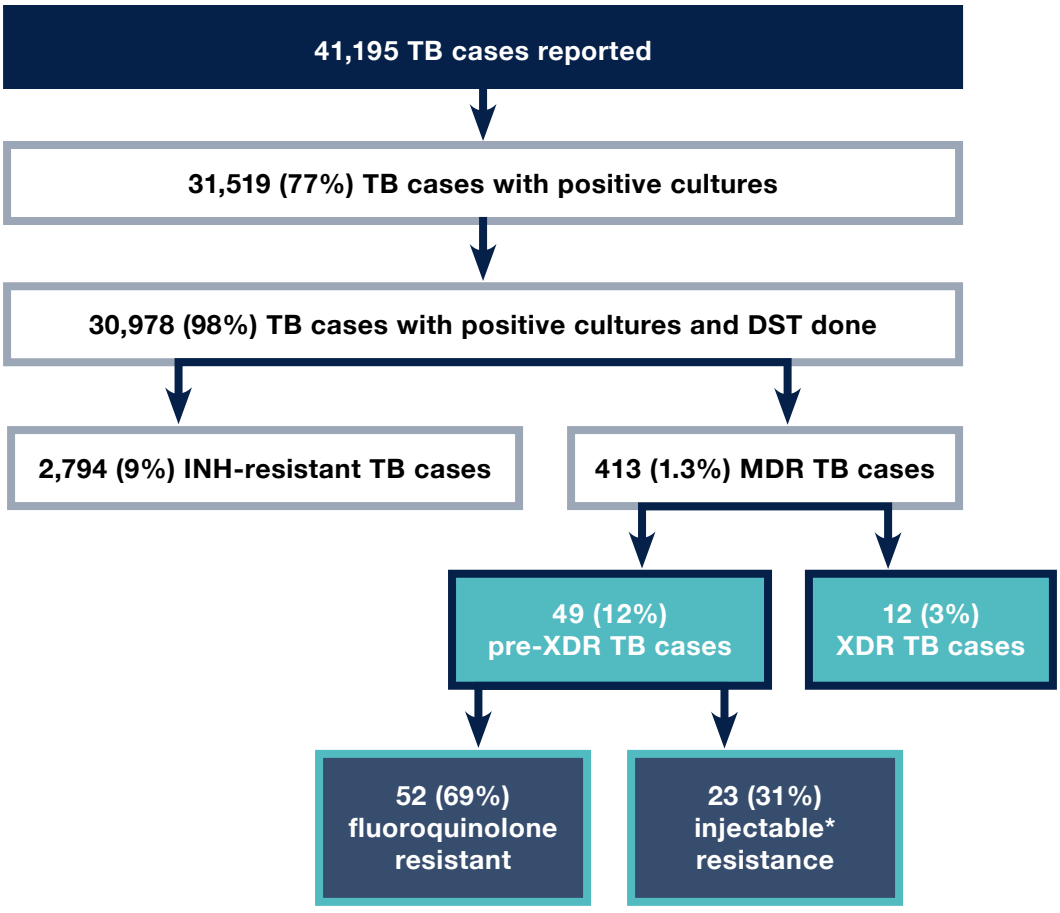
A milestone for MDR-TB care occurred in 2012 when **bedaquiline (BDQ) fumarate** (Janssen) became the first TB drug in a novel class to be approved in 40 years. WHO reports that in 2021, 124 countries were using BDQ as part of MDR-TB regimens. An additional breakthrough occurred in August 2019 when the FDA approved the new drug, **pretomanid** (TB Alliance/Mylan), for use in combination with BDQ and LZD for cases of XDR-TB. As a cautionary note, BDQ resistance is being recognized globally as an emerging issue. Surveillance analysis of isolates in South Africa from 2015-2019 revealed a 3.8% (76 of 2023 patients; 95% CI 2.9-4.6) prevalence of BDQ resistance. Emergence of resistance was associated with prior exposure to BDQ or clofazimine (known cross-resistance with BDQ; among the 19 patients with previous exposure to either BDQ or CFZ, 4 [21%] had BDQ resistance.), as well as baseline resistance to a fluoroquinolone.

# DR-TB in the United States

In the United States (U.S.) during 2016-2020:

- 477 TB patients had MDR-TB based on initial drug susceptibility testing (DST). Of these, 75 patients had pre-XDR-TB (52 had fluoroquinolone resistance), and 10 patients had XDR-TB. In other words, 18% of U.S. MDR-TB patients had pre-XDR or XDR. See **Figure 1**.
- Forty-two states plus the District of Columbia reported at least 1 MDR-TB case; 21 states reported at least 1 pre-XDR-TB case; and 6 states reported at least 1 XDR-TB case.

FIGURE 1. **DR-TB in U.S., 2016-2020**




* injectables = amikacin, capreomycin, or kanamycin

Although the number of DR-TB cases in the U.S. declined as the number of total reported TB cases decreased, there has been little change in the percentage (1.0 – 1.9%) of persons with MDR-TB during 2000-2020.

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

- During 2016-2020, 88.5% of MDR-TB cases in the U.S. were among non-U.S.-born persons. During this time, 1.8% of non-U.S.-born persons with TB had MDR-TB compared with 0.6% of U.S.-born patients. (**Figure 2**).
- Over time, the percentage of U.S.-born TB patients with MDR-TB remained small, declining from 0.6% (n=42) in 2000 to 0.2% (n=3) in 2020, while the percentage of non-U.S.-born TB patients with MDR-TB (<2.0%) remained stable over the same time period.
- Among non-U.S.-born patients who arrived in the U.S. within 9 years of TB diagnosis, 1.9-2.9% had MDR-TB, compared to 1.0-1.1% of those diagnosed with TB more than 9 years after they arrived (**Figure 3**).

FIGURE 2. **Percent INH monoresistant and MDR by U.S. birth** (U.S., 2016-2020)

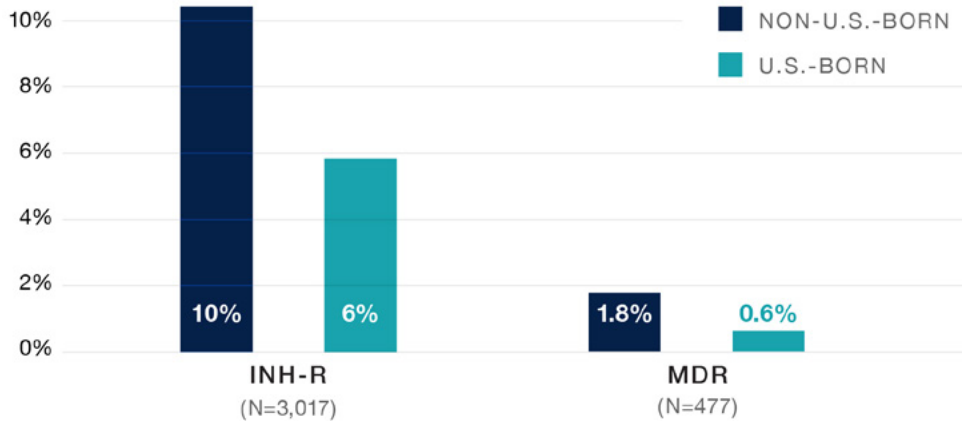
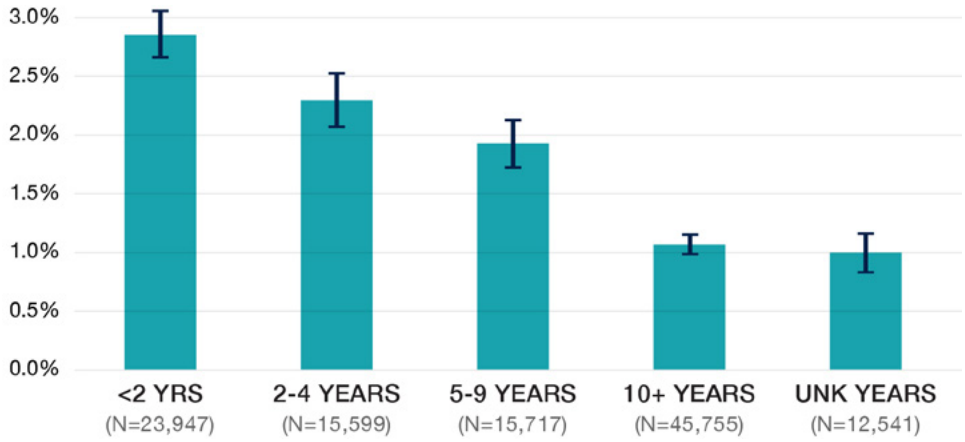



FIGURE 3. **Percent TB cases that are MDR among non-U.S. born people by years in U.S.** (U.S., 2000-2020)



## INH monoresistance

- INH monoresistance is much more common than MDR, with a range of 8-10% during 2000-2020.
- INH monoresistance is more common among people born outside the U.S. with 10% of cases being INH monoresistant among non-U.S.-born compared with 6% among U.S.-born people. (**Figure 2**). Like MDR-TB, the percent of cases in the U.S. that are INH monoresistant varies by country of birth. (**Table 1**)
- Overall, DR-TB is more common among people who were born in countries with a high prevalence of drug resistance. Published estimates of MDR-TB by country, such as those from WHO, may be different from data on MDR-TB prevalence among immigrants to the U.S. by country of origin from the U.S. National TB Surveillance System (NTSS). These differences may reflect variations in risk among people who immigrate, risk of MDR-TB at the time of immigration, or other differences. Where available, U.S. data by country of origin (**Table 1**) may be a better predictor of MDR-TB in non-U.S.-born U.S. residents than global estimates.

Of the 422 non-U.S.-born patients diagnosed with MDR-TB in the U.S. from 2016 to 2020, 336 (80%) were born in only 15 countries, and 362 (86%) were born in 20 countries. **Table 1** shows the drug resistance pattern for the 19 countries of origin (with at least 5 cases of MDR-TB) in the U.S. during 2016-2020. **More than 5% of people with TB born in Ukraine, Laos, Mongolia, the Russian Federation, and the Dominican Republic had MDR-TB.** The percentage of TB cases that were drug resistant from each country of origin can be used to estimate pretest probability of drug resistance. The provider who diagnoses TB in a patient whose birth country has a high proportion of MDR-TB (>2%) should seek rapid DST for patients' specimens if that is not universally done.

TABLE 1. **Drug resistance among non-U.S.-born TB patients in the U.S., 2016-2020**
(Countries with five or more cases of MDR-TB according to the NTSS)

| Country of origin | Total TB cases[1] | MDR | | Any resistance[2] | | INH resistance[3] | |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | No. | % |
| Ukraine | 74 | 10 | 13.5% | 19 | 25.7% | 19 | 25.7% |
| Laos | 267 | 33 | 12.4% | 77 | 28.8% | 58 | 21.7% |
| Mongolia | 42 | 5 | 11.9% | 11 | 26.2% | 11 | 26.2% |
| Russian Federation | 72 | 5 | 6.9% | 12 | 16.7% | 10 | 13.9% |
| Dominican Republic | 231 | 12 | 5.2% | 35 | 15.2% | 34 | 14.7% |
| Peru | 288 | 14 | 4.9% | 41 | 14.2% | 39 | 13.5% |
| Nepal | 344 | 14 | 4.1% | 41 | 11.9% | 25 | 7.3% |
| Burma | 258 | 9 | 3.5% | 55 | 21.3% | 36 | 14.0% |
| Thailand | 145 | 5 | 3.5% | 33 | 22.8% | 19 | 13.1% |
| Ecuador | 269 | 7 | 2.6% | 28 | 10.4% | 26 | 9.7% |
| India | 2,195 | 53 | 2.4% | 351 | 16.0% | 220 | 10.0% |
| Vietnam | 2,011 | 49 | 2.4% | 443 | 22.0% | 358 | 17.8% |
| Ethiopia | 537 | 11 | 2.1% | 62 | 11.6% | 54 | 10.1% |
| China | 1,522 | 30 | 2.0% | 200 | 13.1% | 165 | 10.8% |
| South Korea | 352 | 7 | 2.0% | 48 | 13.6% | 45 | 12.8% |
| Philippines | 3,204 | 55 | 1.7% | 687 | 15.5% | 492 | 15.4% |
| Guatemala | 757 | 8 | 1.7% | 71 | 9.4% | 63 | 8.3% |
| Haiti | 547 | 7 | 1.3% | 63 | 11.5% | 60 | 11.0% |
| Mexico | 4,423 | 24 | 0.5% | 687 | 15.5% | 302 | 6.8% |

1 Total cases with positive cultures and initial susceptibilities performed

2 TB isolates with any first-line drug resistance (INH, RIF, ethambutol [EMB], pyrazinamide [PZA])

3 Resistance to at least INH among cases with susceptibility testing complete for at least INH and RIF. Excludes cases with susceptibility testing missing, not done or unknown for INH or RIF. Isolates may be resistant to other drugs.

**Drug resistance is also more common in persons with TB who reported having had TB previously.** In the U.S. during 2016-2020, 6.4% 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 (1.4% with previous TB vs 0.6 without previous TB) and non-US-born patients (7.8% with previous TB vs. 1.5% non-U.S.-born patients without previous TB). [Unpublished data, CDC, Division of TB Elimination, August 2022.]

### MDR-TB: A staggering cost for a small percentage of TB cases

CDC estimated that in 2020 the direct costs to treat DR-TB averaged **$182,186** per MDR-TB patient and **$567,708** per XDR-TB patient. In contrast, the estimated cost per non-MDR-TB patient was **$20,211**.

# Sources of DR-TB in the U.S.

Four primary sources explain the epidemiology of DR-TB in the U.S.:

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

A cross-sectional study of 92 MDR-TB cases reported in the U.S. 2007-2009 determined that:

- 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 U.S.).
- 22% of MDR-TB cases were the result of **recent transmission.**
- Another 22% occurred in **persons originating from another country who entered the U.S. with active TB disease.**
- 5% of patients had a documented **previous episode of TB in the U.S. and likely relapsed with acquired drug-resistant disease.**
- 10% could not be classified because there were insufficient data.

A 2019 modelling study estimated that, worldwide, 19.1 million people were latently infected with MDR-TB in 2014, and that MDR strains of *M. tuberculosis* were responsible for: 1.2% of the total global burden of latent TB infection (LTBI), and 2.9% of the burden was among children younger than 15 years. Estimates for the percentage of LTBI caused by MDR strains of TB in the U.S. were 0.4% (95% uncertainty interval [UI] 0.1-1.0) to 0.7% (95% UI 0.2-1.7).

# 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., *rpoB* for rifampin) of *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 2. **Select anti-tuberculosis drugs and prevalence of resistant mutants**

| Drug | Year introduced | Prevalence of resistant mutants within a wild-type population of *M. tuberculosis* bacteria |
|---|---|---|
| **Streptomycin** | 1945 | $3.8 \times 10^{-6}$ |
| **Isoniazid** | 1952 | $3.5 \times 10^{-6}$ |
| **Pyrazinamide** | 1952 | $1.0 \times 10^{-5}$ |
| **Ethambutol** | 1962 | $3.1 \times 10^{-5}$ |
| **Rifampin** | 1967 | $1.2 \times 10^{-8}$ |
| **Bedaquiline** | 2013 | ? |
| **Pretomanid** | 2019 | ? |

Within wild-type populations, resistance to more than one TB drug is even rarer as resistance to the various drugs is not linked genetically. 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 *M. tuberculosis* become important for the person with TB when amplified by health care system and patient factors. 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, delayed access to medication (e.g., bedaquiline), 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 **person with active TB disease,** factors that create or amplify drug resistance include:

- Not taking all the drugs prescribed, often because of comorbidities, side effects, miscommunication, or other medical or social factors.
- There may be a dispensing or administration error regarding the correct dose.
- The person with TB may not be prescribed the appropriate dose.
- The person with TB 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 person with TB may have been incorrectly diagnosed as having LTBI, rather than active TB disease, and treated with monotherapy.
- The person with TB may be taking therapy for another disease. That therapy may coincidentally contain a single drug active against TB (rifabutin in a person with HIV 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 U.S.) or taking medications belonging to someone else.
- The TB medicines may interact with other drugs being taken by the person.

**If a person 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 person 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 person with TB 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 but has occurred more quickly for fluoroquinolones when used as monotherapy** (e.g., empiric treatment of community acquired pneumonia).

## SUMMARY

- Globally in 2019, an estimated 465,000 people developed MDR-TB. Approximately 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.
- Nine of every 10 MDR-TB cases in the U.S. occur among people born outside the U.S.
- Sixteen percent of MDR-TB patients in the U.S. had pre-XDR TB. (only 2% of MDR-TB patients had XDR-TB).
- The percentage of TB patients with MDR-TB or INH-resistant TB is not increasing in the U.S.
- Risk factors for INH-resistant and MDR-TB in the U.S. include country-of-origin, recent arrival (within 9 years) in the U.S., previous TB, and exposure to an individual with infectious INH-resistant or MDR-TB.
- MDR-TB can be generated by inadequate treatment regimen or poor adherence to treatment. It is essential to implement strategies to support and ensure completion of an adequate regimen.

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