SPECIAL REPORT

Twenty Years of Global Surveillance of Antituberculosis-Drug Resistance

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Antimicrobial resistance represents a major threat to global health and security. In 2014, the World Health Assembly called on all nations and the international community to take every necessary measure to control it, including surveillance of its emergence and spread.[1]

The development of drug resistance in *Mycobacterium tuberculosis* was first documented in the late 1940s, soon after antibiotic therapy was introduced for tuberculosis treatment.[2] It quickly became obvious that combination chemotherapy could prevent the emergence of drug resistance[3] and that patients infected with drug-resistant strains were less likely to be cured.[4] Nevertheless, it was only in the early 1990s that drug-resistant tuberculosis began to receive global attention as a public health threat. This coincided with the detection of outbreaks of multidrug-resistant (MDR) tuberculosis (defined as resistance to at least rifampin and isoniazid) that were associated with high mortality among patients coinfected with the human immunodeficiency virus (HIV).[5-8] The urgent need for a global mechanism to monitor the emergence and spread of resistance to antituberculosis drugs became clear.

In 1994, the Global Tuberculosis Program of the World Health Organization (WHO), with the support of the International Union against Tuberculosis and Lung Disease (the Union), established the Global Project on Anti-Tuberculosis Drug Resistance Surveillance (hereafter referred to as "the project") to measure the magnitude of drug resistance and to monitor trends. This project remains the oldest and largest initiative on the surveillance of antimicrobial resistance in the world.[9] In this article, we describe the history of global surveillance of drug resistance in tuberculosis and discuss methods for surveillance, the quality of available data, the key achievements and findings to date, the main challenges that remain, and future directions.

HISTORY OF GLOBAL SURVEILLANCE OF RESISTANCE TO ANTITUBERCULOSIS DRUGS

Throughout its existence, the project has been hosted by the WHO and supported by the TB Supranational Reference Laboratory (SRL) Network and several technical agencies. Funding has been continuously provided by the U.S. Agency for International Development.

The foundations of the project were laid in 1993 and 1994. A first meeting of interested partners was organized at the annual international conference of the Union in October 1993. Investigators from the Dominican Republic, Kenya, and Zimbabwe committed to implement the first drug-resistance surveys using a standardized approach. In June 1994, at a meeting organized by the WHO and the Union in Mainz, Germany, a group of 14 laboratories established the SRL Network to conduct and ensure quality-assured testing of drug susceptibility, under the leadership of the Laboratory Centre for Disease Control in Ottawa. Meanwhile, the WHO issued guidelines on standardized methods for conducting surveys of antituberculosis-drug resistance, which have been regularly updated.[10-14] Surveillance data are collected either through continuous surveillance systems based on routine testing of all patients with tuberculosis or periodic surveys, which are discrete studies measuring

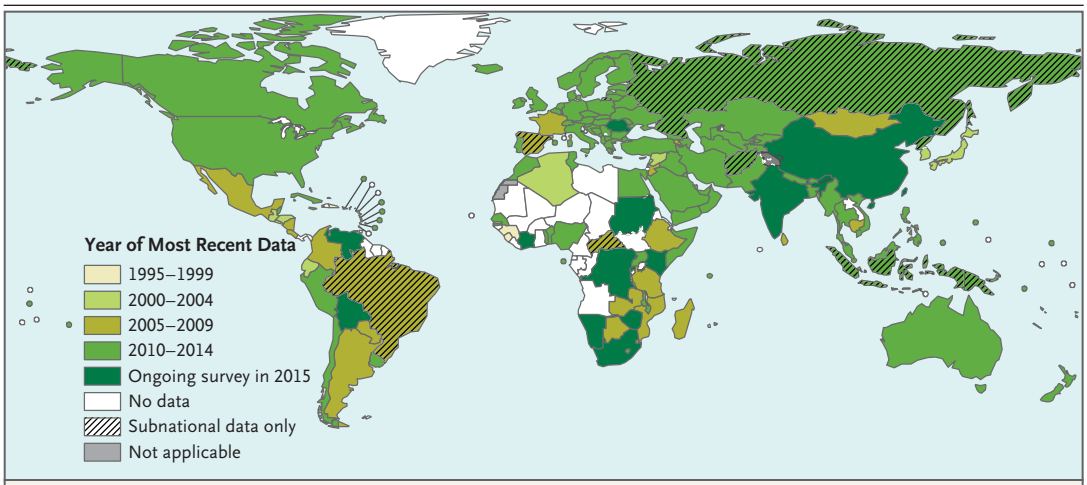

Figure 1. Global Coverage of Surveillance Data on Resistance to First-Line Antituberculosis Drugs, 1995–2015.

drug resistance among a selected sample of patients who are representative of an entire population of patients with tuberculosis. These standardized methods allow comparability of data within countries over time as well as between countries.

Since 1999, the SRL Network has been coordinated by the Institute of Tropical Medicine in Antwerp, Belgium, and it currently comprises 33 laboratories distributed across all continents. Proficiency testing is conducted annually, and results are published regularly.[15-17] Starting in 2006, soon after the recognition of extensively drug-resistant (XDR) tuberculosis (defined as MDR tuberculosis plus resistance to a fluoroquinolone and at least one second-line injectable agent: amikacin, kanamycin, or capreomycin) as an emerging threat worldwide,[18,19] the panel of drugs tested as part of the project was expanded to include fluoroquinolones and second-line injectable agents for all patients who had received a diagnosis of MDR tuberculosis.

The first global report on antituberculosis-drug resistance was published by the WHO in 1997 with results from surveys conducted in 35 countries. By 2010, a total of five global reports had been published.[20-24] Subsequently, drug-resistance surveillance data have been published annually in the WHO Global Tuberculosis Report, allowing rapid sharing of data soon after they become available by incorporating them alongside other aspects of tuberculosis surveillance. To ensure wide dissemination and allow in-depth analysis of specific topics, including trends, data have also been regularly published in peer-reviewed journals.[25-32]

KEY ACHIEVEMENTS

WIDE GEOGRAPHIC COVERAGE OF DATA ON ANTITUBERCULOSIS-DRUG RESISTANCE

By 2014, representative data on antituberculosis-drug resistance that were derived from continuous surveillance or periodic surveys conducted with the use of standardized methods had been made available from 153 countries, covering 96% of the world's population and incident tuberculosis cases (Fig. 1). Only 41 countries, accounting for 4% of the world's population and incident tuberculosis cases, have never conducted a survey and therefore still rely on weaker model-based estimates of the prevalence of drug resistance. A total of 80 of the 153 countries have continuous surveillance systems, and the remaining 73 have relied on periodic surveys. The latter group includes most resource-limited settings, in which the burden of tuberculosis and MDR tuberculosis is the highest but a shortage of laboratory capacity and inadequate financial and human resources have precluded testing every patient with tuberculosis for drug resistance.[33]

MEASUREMENT OF LEVELS OF MDR TUBERCULOSIS IN 153 COUNTRIES

The most recent data on the percentage of patients with newly diagnosed tuberculosis who have MDR tuberculosis are shown in Figure 2. The percentage remains stable, at 3% or lower,

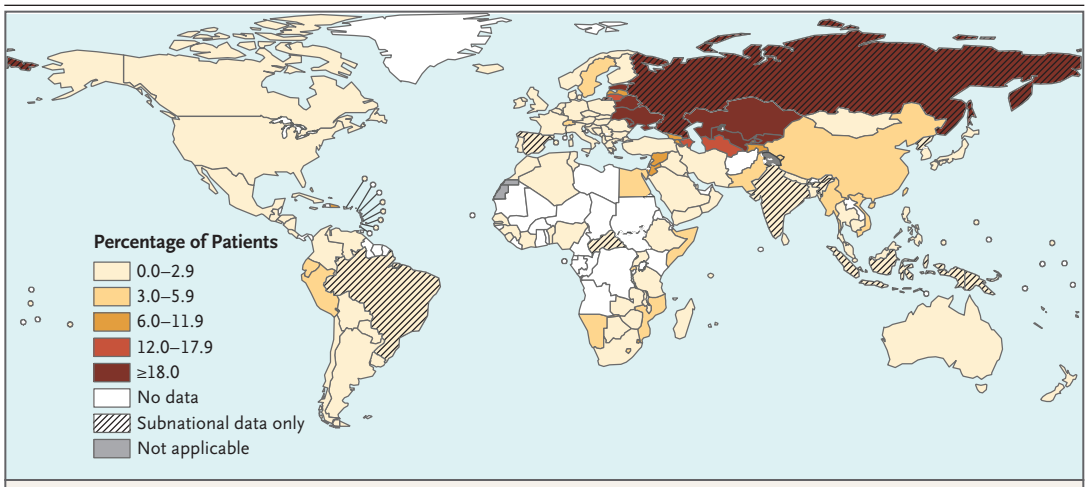

Figure 2. Percentage of Patients with Newly Diagnosed Tuberculosis Who Have Multidrug-Resistant (MDR) Tuberculosis.
The figure reflects the most recent year for which data have been reported, which varies among countries.

in most parts of the world. However, countries in Eastern Europe and central Asia have serious MDR tuberculosis epidemics. This suggests that the severe disruptions of drug supply after the collapse of the Soviet Union may have led to mismanagement of patient care, generating high levels of MDR tuberculosis. The highest measured levels of MDR tuberculosis among patients with newly diagnosed tuberculosis are in Belarus (34.1% in 2014), Estonia (19.5% in 2014), Kazakhstan (25.2% in 2013), Kyrgyzstan (26.4% in 2011), Moldova (23.7% in 2012), Russia (average across regions with data, 19.3% in 2012), Ukraine (24.0% in 2014), and Uzbekistan (23.2% in 2011).[33]

Among patients with previously diagnosed tuberculosis, the percentages with MDR tuberculosis were the highest in Belarus (69.1% in 2014), Estonia (62.1% in 2014), Kazakhstan (57.8% in 2013), Kyrgyzstan (55.1% in 2013), Moldova (62.3% in 2012), Tajikistan (52.2% in 2014), and Uzbekistan (62.0% in 2011). In Russia, even though the average percentage of patients with previously treated tuberculosis who have MDR tuberculosis does not exceed 50%, the percentage is well above 50% in several regions.[34]

A TIME-TREND ANALYSIS BASED ON DATA FROM 100 COUNTRIES

During the previous two decades, 100 countries have repeated a drug-resistance survey at least once; of these, 65 have at least 3 years of data. For settings with three or more data points, per capita rates of MDR tuberculosis between 1999 and 2014 were calculated by multiplying the notification rate of new cases of tuberculosis reported annually to the WHO by the percentage of patients with MDR tuberculosis among patients with newly diagnosed tuberculosis reported in the same setting and year. The rate of MDR tuberculosis is defined as the annual number of estimated new cases of MDR tuberculosis per 100,000 population, and the notification rate of new cases of tuberculosis is defined as the annual number of new cases of tuberculosis occurring in notified patients per 100,000 population. The statistical significance of trends were assessed by testing the null hypothesis of no linear trend. More details on the methods are described elsewhere.[32,35] The average annual percentage change in the rates of tuberculosis and MDR tuberculosis were calculated for all countries and subnational settings with significant linear trends (Fig. 3).

Significant trends in per capita rates of MDR tuberculosis among notified patients with newly diagnosed tuberculosis were detected in 12 countries. Decreasing trends were found in Australia, Estonia, Hong Kong, Israel, Latvia, Portugal, and the United States, ranging from a change of –5% to –9% per annum. Increasing trends were detected in the Tomsk Oblast region of Russia (13% per annum) and also in Austria, Finland, Sweden, and the United Kingdom. In this group of western European countries, increasing trends are associated with immigration.[36] Limited data on trends are available from African and Asian

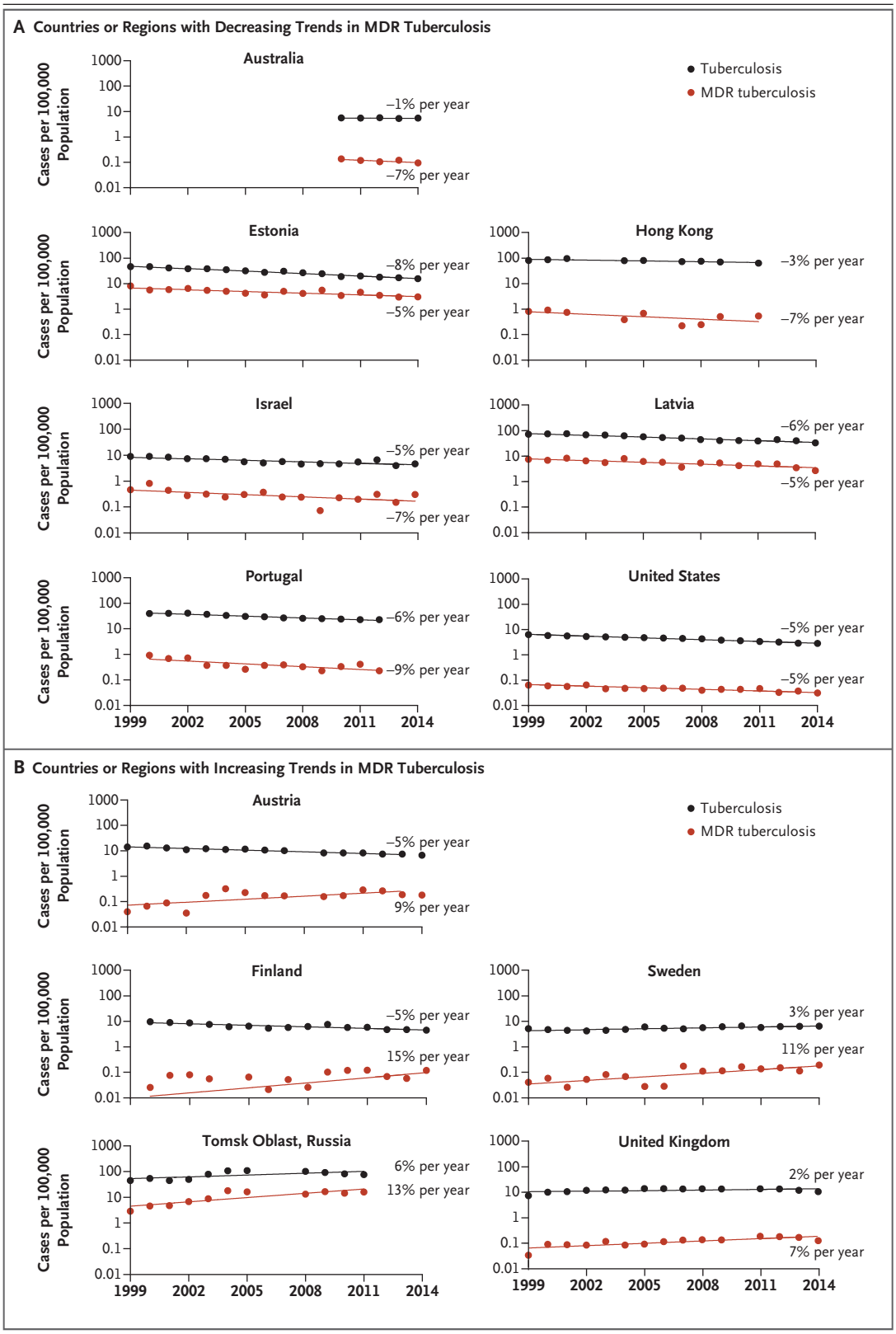
A Countries or Regions with Decreasing Trends in MDR Tuberculosis
Australia
Tuberculosis
MDR tuberculosis
–1% per year
–7% per year
Estonia
–8% per year
–5% per year
Hong Kong
–3% per year
–7% per year
Israel
–5% per year
–7% per year
Latvia
–6% per year
–5% per year
Portugal
–6% per year
–9% per year
United States
–5% per year
–5% per year
Cases per 100,000 Population
1000
100
10
1
0.1
0.01
1999
2002
2005
2008
2011
2014
B Countries or Regions with Increasing Trends in MDR Tuberculosis
Austria
–5% per year
9% per year
Finland
–5% per year
15% per year
Sweden
3% per year
11% per year
Tomsk Oblast, Russia
6% per year
13% per year
United Kingdom
2% per year
7% per year

Figure 3 (facing page). Time Trends in MDR Tuberculosis.
Shown are rates per 100,000 population of new cases of tuberculosis (black circles) and cases of MDR tuberculosis among patients with newly diagnosed tuberculosis (red circles) in countries or regions with significant linear decreasing trends (Panel A) or increasing trends (Panel B) in MDR tuberculosis. The mean change per year is given as a percentage. The y axes are on a log scale.

countries owing to the challenges in repeating surveys at regular intervals or establishing continuous surveillance. As a consequence, our understanding of the evolution of the MDR tuberculosis epidemic in these regions is very limited.

EVIDENCE OF AN ASSOCIATION BETWEEN MDR TUBERCULOSIS AND OTHER FACTORS

The association between MDR tuberculosis and HIV infection at the population level varies from setting to setting. A positive association has been found in Eastern European countries,[31,37] and a recent systematic review showed a moderate association with HIV infection, particularly in patients with newly diagnosed tuberculosis.[38] However, on a global level, currently available data do not show a clear, consistent relationship between the levels of HIV infection and MDR tuberculosis in a population.

An analysis of the levels of MDR tuberculosis in different age groups suggested that children with tuberculosis did not have a lower risk of MDR tuberculosis than adult patients, with similar percentages of patients with MDR tuberculosis in both groups.[30] This finding should, however, be interpreted with caution, because any analysis of surveillance data on childhood tuberculosis is limited by the challenges associated with the bacteriologic diagnosis of tuberculosis and the detection of drug resistance in children.

RELIABLE ESTIMATES OF THE GLOBAL BURDEN OF MDR TUBERCULOSIS (CASES AND DEATHS)

On average worldwide, 3.3% of patients with newly diagnosed tuberculosis (95% confidence interval [CI], 2.2 to 4.4) and 20.1% of those with previously treated tuberculosis (95% CI, 13.8 to 27.5) are estimated to have MDR tuberculosis.[33] Data on levels of drug resistance in patients with newly diagnosed and previously treated tuberculosis can be combined with other data on tuberculosis incidence and mortality to produce global estimates of the disease burden associated with MDR tuberculosis. The latest estimates suggest that there were 480,000 incident cases of MDR tuberculosis (range, 360,000 to 600,000) and 190,000 deaths from the disease (range, 120,000 to 260,000) in 2013. The methods used to produce these estimates are described in detail elsewhere.[33]

XDR TUBERCULOSIS REPORTED FROM 105 COUNTRIES

By December 2014, cases of XDR tuberculosis had been reported by 105 countries. A total of 83 countries reported representative data from continuous surveillance or periodic surveys on the percentage of patients with MDR tuberculosis who had XDR tuberculosis. When these data were combined, the average percentage was 9.7% (95% CI, 7.4 to 12.1). Fourteen of these countries reported 10 or more cases of XDR tuberculosis in the most recent year for which data were available. Among these countries, the percentage of patients with MDR tuberculosis who had XDR tuberculosis was highest in Belarus (29.3% in 2014), Georgia (15.1% in 2014), Latvia (18.6% in 2014), and Lithuania (24.7% in 2013).[33]

INCREASE IN PATIENTS WITH MDR TUBERCULOSIS WHO WERE RECEIVING SECOND-LINE THERAPY

Globally in 2014, a total of 123,000 patients with MDR or rifampin-resistant tuberculosis were notified. This was equivalent to 41% of the patients estimated to have MDR tuberculosis among those who were reported to have pulmonary tuberculosis in the same year (see the Global Tuberculosis Report 2015[33] for the details of this estimate). This is a reflection of the still very limited access to drug-susceptibility testing in most countries: globally in 2014, only 12% of patients with newly diagnosed tuberculosis and 58% of those with previously treated tuberculosis underwent testing for drug resistance. Patients with MDR tuberculosis or rifampin-resistant tuberculosis would be treated with second-line drugs. A total of 111,000 patients with tuberculosis began second-line therapy in 2014, an increase of 14% as compared with 2013. Globally, the ratio of patients receiving second-line therapy to notified patients with MDR tuberculosis was 90%. Although the rate of treatment success remained stagnant at around 50% between 2007

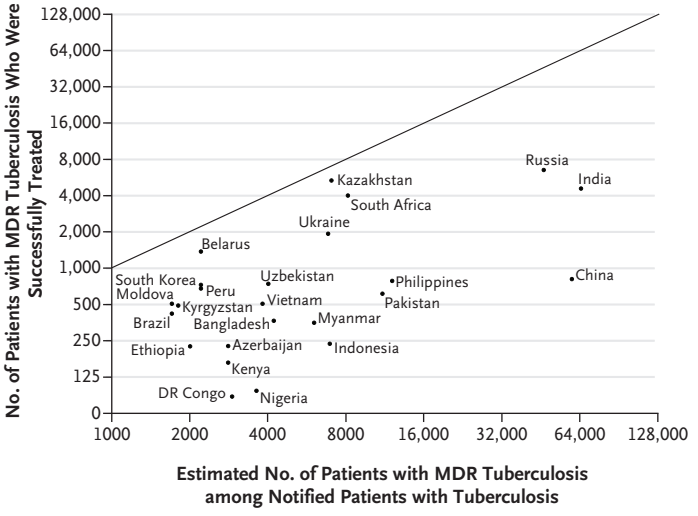

Figure 4. Estimated Number of Patients with MDR Tuberculosis and Number of Patients Who Were Successfully Treated (2012 Cohort).

Countries with more than 1000 estimated patients with MDR tuberculosis and more than 0 patients who were successfully treated with second-line therapy are presented. The diagonal line represents the line of identity. Both axes of the graph are on a log scale. DR Congo denotes the Democratic Republic of Congo.

and 2012, more than 100,000 patients worldwide were successfully treated in these six annual cohorts alone.[33]

Figure 4 compares the number of patients who were successfully treated with second-line regimens with the estimated number of patients with MDR tuberculosis among patients with pulmonary tuberculosis notified in 2012. None of these countries have managed to cure all of their estimated MDR tuberculosis burden, reflecting persistent barriers to the diagnosis of cases and the initiation of appropriate treatment, as well as the relative ineffectiveness of second-line regimens for MDR tuberculosis.[39] Only if more countries, especially those with large numbers of patients with MDR tuberculosis, take bold actions to address these three critical points separately will there be any substantial effect on the global burden of disease and death due to MDR tuberculosis. In addition, more efforts are needed to find more cases of tuberculosis: 9.6 million cases of tuberculosis were estimated to have occurred in 2014, but one third of the patients were not notified and the burden of resistance among these patients is unknown.

REMAINING CHALLENGES

After 20 years of global surveillance of resistance to antituberculosis drugs, three main challenges remain. These are a lack of trend data for many resource-limited countries (particularly in Africa and Asia), owing to insufficient capacity to conduct repeat surveys at regular intervals or to establish continuous surveillance of drug resistance; limited understanding of in-country geographic distribution of drug resistance and limited capacity to detect outbreaks and hot-spot areas; and limited engagement of private health providers in surveys, resulting in an inability to assess the scale of drug resistance outside cases detected in the public sector.

Routine testing of all patients with tuberculosis is widely recognized as the most appropriate surveillance approach for monitoring trends in drug resistance and detecting outbreaks and hot-spot regions.[40] However, in most resource-limited countries in which the burden of tuberculosis and MDR tuberculosis is the highest, routine drug-susceptibility testing is not yet accessible to all patients owing to insufficient laboratory capacity, infrastructure (including deficiencies in transportation of specimens and in data collection and management), or resources. Although a surveillance system for tuberculosis exists in most countries, the complexities associated with drug-resistance testing do not permit routine drug-susceptibility testing on all patients with newly diagnosed tuberculosis. The establishment of continuous surveillance systems for drug resistance can overcome two of the above-mentioned major challenges: a lack of understanding of trends in drug resistance and the inability to accurately describe the heterogeneity of the epidemic within countries and detect hot-spot areas and disease outbreaks.

The third major challenge is a general lack of data on the magnitude of drug resistance outside the public sector. In large parts of the world, particularly in Asia, many patients with symptoms of tuberculosis seek care from private health care providers and may never reach public facilities or reach those linked to the national tuberculosis-control program only at a later stage, if the treatment they received from private providers was ineffective or too costly.[41] Private providers are involved in drug-resistance surveys

only if they are linked to the national tuberculosis-control program through formal agreements. As a result, current drug-resistance surveillance data may underestimate or overestimate the true magnitude of the problem, especially in countries with a large private health sector that is involved in tuberculosis care.

THE NEXT DECADE

The next 10 years of surveillance of antituberculosis-drug resistance should see considerable evolution, including developments that address the three main challenges that exist today. Since 2009, molecular technologies have been increasingly incorporated into drug-resistance surveys. In particular, Xpert MTB/RIF (Cepheid) is being used in several Asian and African countries to detect specimens with rifampin resistance and identify those requiring testing for additional drugs at a reference laboratory. Rifampin resistance is the most important indicator of MDR tuberculosis and has implications for treatment regimens. This approach simplifies logistics (e.g., sample transportation), greatly reduces laboratory workload, and cuts costs.[14,42] In the future, it is likely that molecular technologies will replace conventional phenotypic testing in drug-resistance surveys and surveillance. This includes high-throughput sequencing-based technologies, which are already used for research purposes in some reference laboratories of resource-limited countries. These technologies are expected to become standard tools for surveillance as the costs of equipment and tests continue to fall and understanding of the clinical significance of mutations in the *M. tuberculosis* genome improves.[43]

The use of molecular technologies could resolve the persistent difficulties that have constrained monitoring of drug-resistance trends in most resource-constrained countries and have limited the ability to detect disease outbreaks. For example, the establishment of continuous surveillance systems using Xpert MTB/RIF would allow the monitoring of trends in rifampin resistance, an accurate description of variations in the levels of resistance within a country, and prompt detection of hot-spot regions.[14]

Rifampin and isoniazid remain the most powerful bactericidal first-line antituberculosis drugs. However, promising shorter treatment regimens with fluoroquinolones and pyrazinamide are currently being evaluated and could become the cornerstones of tuberculosis treatment in the future.[44] Data on the background prevalence of resistance to fluoroquinolones (in particular, moxifloxacin and gatifloxacin) and pyrazinamide are therefore essential for assessing the feasibility of introducing new treatment regimens and guiding laboratory practices and diagnostic algorithms. Testing of these drugs should become a routine component of surveillance activities.[45]

For the first time since the introduction of rifampin in the late 1960s, two new drugs for the treatment of tuberculosis, bedaquiline and delamanid, became available in 2013 and 2014, respectively. They have recently been approved for the treatment of MDR tuberculosis and are already being used in several countries.[33] The swift establishment of surveillance mechanisms to monitor the acquisition of resistance to these drugs in patients with MDR tuberculosis and the transmission of resistance in the community will be of paramount importance to preserve the effectiveness of these new agents.

Finally, although challenges exist, future surveys should involve private practitioners, particularly in countries with a large private sector. In these settings, drug-resistance surveys in the public sector could be complemented by surveys in the private sector to determine the magnitude of drug resistance as well as the existence and direction of any bias introduced by excluding private providers from assessments.[46] Another option is to include private facilities in the survey sampling frame and provide incentives for private clinics to participate, with the aim of having a representative sample.

CONCLUSIONS

Data generated at national and global levels have allowed the development of an evidence-based response to the public health threat posed by drug-resistant tuberculosis.[47-49] The diagnosis and treatment of tuberculosis, including drug-resistant forms, continue to evolve. It is critical that methodologic advances be incorporated into the approach to ensure that surveillance continues to be a key tool to inform policy that is conducive to better control of tuberculosis and drug-resistant tuberculosis.[40]

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the views and opinions of the World Health Organization or of the U.S. Agency for International Development.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMsr1512438