Extensively Drug-Resistant Tuberculosis: "There must be some kind of way out of here"

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Over the past 7 decades, *Mycobacterium tuberculosis* has developed resistance to virtually every new drug used to treat tuberculosis, resulting recently in the global emergence of extensively drug-resistant tuberculosis. In an individual, treatment with a single new drug results in acquired drug resistance within weeks to months. On a population basis, the pattern is just as consistent. After a new drug is introduced, drug-resistant cases or case series are reported within months to years, typically leading to focused surveys, and within several years, dramatic outbreaks with extraordinary mortality occur. Invariably, such outbreaks prove to be the tip of the iceberg. Incomplete and delayed diagnoses, drug costs, and drug supplies are frequently implicated. With new drugs and new diagnostics on the horizon, we must develop new ways of incorporating them into public health practice, basing treatment on rapid drug-susceptibility tests, ensuring that effective drugs are always used in combination, and making these drug available to persons who need them.

SETTING THE STAGE: EMERGENCE OF RESISTANCE TO THE FIRST ANTITUBERCULOSIS DRUGS

Taped to the door of a national tuberculosis (TB) program director's office is a famous quotation often attributed to Albert Einstein, "Insanity is doing the same thing over and over and expecting different results." In accordance with this quotation, the global emergence of extensively drug-resistant (XDR) TB reaffirms the collective insanity associated with TB prevention and control and perhaps that associated with prevention and control of microbial diseases in general. Why? Since the first human trials of streptomycin for TB in 1947 and isoniazid in 1952, *Mycobacterium tuberculosis* has demonstrated its ability to evade our biochemical bullets through genetic mutation and "unnatural" selection resulting from the fact that mutants are selected by deliberate, albeit insufficient, exposure to anti-TB drugs [1, 2]. *Homo sapiens* countered by combining 2 and then all 3 available drugs, streptomycin, para-aminosalicylic acid, and isoniazid, which cured 90%–100% of patients in controlled clinical trials, that proved treatment failure because of acquired drug resistance could be prevented [3–5].

Scientific proof, however, did not translate instantly into universal availability and clinical practice. Scale-up of manufacturing and distribution took time. Drug discovery and development continued for many years, and clinical trials continued for decades, each one building on previous results. Imagine the process, in the 1950s, of assimilating and disseminating this information. Medical practitioners treated patients with drugs that they had available, and monotherapy was common practice [6]. At the time, public health authorities, including the World Health Organization (WHO), promoted isoniazid monotherapy, especially in locations without satisfactory alternatives. Treatment failures associated with drug resistance proliferated, including resistance to multiple drugs [6, 7]. Within a few short years after TB drugs were first used in humans, drug-resistant TB was geographically widespread. Drug-resistant TB was the fly in the soup. For the first time in history, TB could be cured in a large majority of patients, but these miraculous drugs failed in a proportion of patients.

RIFAMPIN AND MULTIDRUG-RESISTANT (MDR) TB

Fast-forwarding through the decades, we see this scenario playing itself out again and again throughout the heyday of TB drug discovery and development (from the 1940s through the 1970s). As new anti-TB drugs were introduced, strains of *M. tuberculosis* emerged with resistance to each of them and eventually to all of them. Before XDR-TB, the most dramatic example was rifampin leading to what later came to be defined as MDR-TB (ie, re-

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sistance to at least rifampin and isoniazid). Rifampin was developed in the early 1960s [8]. Controlled clinical trials soon proved that combinations of rifampin, isoniazid, and pyrazinamide (another drug from the 1950s) safely cured 90%–100% of patients with as little as 6 months of treatment, compared with 18–24 months in the pre-rifampin era. The US Food and Drug Administration approved rifampin for TB treatment in 1971.

These advances in chemotherapy led to the widespread belief that TB had been conquered and was a disease of the past. Categorical federal funding for TB control was eliminated in 1972 and was replaced by public health block grants to states with no specific requirement for TB control. Funding for TB research dropped to near zero. Drug discovery, development of diagnostics, and vaccine research nearly stopped. Except for 2 chemical siblings of rifampin, no new drugs have been approved for tuberculosis since 1971. Why should government and industry invest in TB research when there would be no market for new products in the future? At the WHO, the prevailing outlook was that existing tools were sufficient and only needed to be applied diligently at the local level [9]. An analysis of primary health care interventions concluded that TB control was too costly and too complex to be a high priority [9]. By the late 1980s, the WHO's TB program was reduced to 2 individuals.

These cutbacks proved to be premature. Rifampin-resistant *M. tuberculosis* isolates from patients with TB who received rifampin monotherapy were reported in Europe in the late 1960s and in the United States as early as 1975 [10–14]. At the height of a generalized resurgence of TB in the United States from 1985 through 1992, lethal outbreaks of MDR-TB were reported in Florida, New York, and other states, especially among human immunodeficiency virus (HIV)–infected persons [15–17]. MDR-TB epidemics were reported in country after country, proving to be the tip of a massive iceberg and attracting worldwide attention to the menace of TB, especially the threat of MDR-TB. Wisely, the WHO and the International Union Against Tuberculosis and Lung Disease launched a massive, ongoing series of drug-resistance surveys to determine accurately the magnitude, distribution, and trends of this pandemic [18–21]. Before rifampin, MDR-TB did not exist. Within 40 years after introduction of rifampin, ~490,000 individuals were developing MDR-TB each year, and MDR-TB affected virtually every country surveyed.

US RESPONSE TO MDR-TB

The US domestic response to MDR-TB and to TB in general was decisive, successful, and costly [22–25]. In 1993, the US Congress appropriated emergency funds to address the domestic resurgence of TB and ramped up appropriations to the Centers for Disease Control and Prevention (CDC) for TB control from <$10 million/year to ~$142 million/year. These resources were used to strengthen surveillance, expand directly observed treatment, improve infection-control measures preventing airborne spread in institutions, and invigorate contact investigation for case finding and prevention of future TB cases through treatment of latent TB infection. Education and training programs were disseminated widely. Clinical research for improving diagnosis, treatment, and prevention was revitalized. New technologies were developed and widely implemented for rapidly identifying *M. tuberculosis,* including drug-resistant strains. Federal funding to the National Institutes of Health (NIH) for TB research and education increased to ~$170 million from <$20 million in 1992, focusing on better diagnostics, better treatment, better vaccines, better understanding of the basic biology of TB, and better training for health care professionals [26, 27].

The annual number of reported TB cases in the United States decreased by >39% from 1992 through 2000 (from 26,673 cases to 16,309 cases, respectively), and the case rate decreased by 44% (from 10.4 to 5.8 cases per 100,000 population per year, respectively) [22, 28]. The number of MDR-TB cases decreased from 407 (2.5% of TB cases) in 1993 (the first year of nationwide drug resistance surveillance) to 120 cases (1.0% of TB cases) in 2000. Unfortunately, the annual decrease in the number of cases slowed to 3.8% per year from 2000 through 2007. The number of MDR-TB cases actually increased slightly to 125 cases in 2007, and the prevalence of isoniazid resistance increased from a nadir of 7.3% in 2001 to 8.2% in 2008, reminding us that progress against TB is tenuous and much remains to be done [22, 28].

Decreases in the incidence of TB disease and advancements in science and technology show what can be achieved with determined effort and represent a measurable return on the resources invested to achieve these goals. The investment was substantial. In the 1990s, an estimated $1 billion was spent on bringing TB under control in New York City alone [24]. Currently, an estimated $1 billion from all sources combined is spent annually for TB control in the United States [25, 29]. In retrospect, it is easy to ask how much cheaper would it have been not to lose control of TB in the first place. How many lives would not have been ruined had we not allowed ourselves to become the victims of our own success?

INTERNATIONAL RESPONSE TO MDR-TB

Internationally, the worldwide threat of MDR-TB galvanized support for TB control, and the global public health response was no less decisive and no less successful under more challenging circumstances [30–33]. Pioneered by the International Union Against Tuberculosis and Lung Disease, implemented worldwide with WHO's leadership, the DOTS (directly observed therapy short-course) strategy has been hailed as one of the most cost-effective health interventions of the 20th Century [34, 35].

Unlike in affluent countries, however,

the large majority of persons with MDR-TB worldwide do not receive a diagnosis and remain untreated. Sophisticated microbiology laboratories and complex combinations of expensive second-line drugs are not available to them, and the disease spreads unchecked. Blower et al [36] developed mathematical models that predicted that MDR-TB could eventually replace common drug-susceptible TB in the absence of vigorous countermeasures. In certain regions, these predictions have already occurred and are the reality for patients with TB and local TB-control programs. Before 2006, the DOTS strategy obstinately neglected MDR-TB, as shown by 2 salient examples. Because guidelines for national TB programs insisted chiefly on microscopy as the basis for case detection, laboratory services in many countries were unable to develop additional capabilities, resulting in grossly underdeveloped global laboratory capacity, because, currently, drug-susceptibility testing is so vital. As for treatment, we learned the hard way that monotherapy is taboo. In the same way, adding a single drug to an unsuccessful treatment regimen results in the serial accumulation of resistance to even more drugs [37]. However, that was precisely the global recommendation for retreatment of previously treated patients [38]. International public health leaders asserted that MDR-TB was too costly and too complex, that if we just applied the basic principles of TB control diligently, MDR-TB would go away by itself [39]. Sound familiar?

Instead, real leadership in relation to MDR-TB came from collaborative partnerships between the countries affected and nongovernmental organizations, especially humanitarian and nonprofit organizations, academic institutions, and philanthropies, such as Médecins Sans Frontières, Harvard University–Partners in Health, the Royal Dutch TB Foundation, the Bill & Melinda Gates Foundation, the Tropical Disease Foundation, the International Dispensary Association, and the International Working Group on MDR-TB of the Stop TB Partnership.

Before the Global Fund Against AIDS, TB, and Malaria, US government economic assistance to global TB control was not proportional to the burden of disease. The CDC's contributions were constrained by 2 considerations. First, the CDC's mandate on TB control was largely domestic, and its international activities were supported largely from extramural sources, especially the US Agency for International Development (USAID). The primary role of the CDC was technical assistance to the WHO for supporting the highly effective aspects of the WHO program. Its capacity in international TB activities was limited to a handful of full-time staff supporting TB-control activities in India, the Russian Federation, southern Africa, Vietnam, the Philippines, and a few other countries. Second, direct US government support for international TB-control programs was channeled primarily through USAID in general, an agency of the Department of State. These activities were influenced by bilateral relationships with individual countries. Federal support for international research and training related to TB was channeled largely through the NIH, especially the National Institute of Allergy and Infectious Diseases and the John E. Fogarty International Center.

FLUOROQUINOLONES AND XDR-TB

The worldwide emergence of XDR-TB, first described in 2005, paralleled the MDR-TB story of the previous decade in many ways, but the differences are highly informative. When systemic fluoroquinolones were developed in the 1980s, they could have been a silver lining to the MDR-TB–control cloud. Their bactericidal effect on *M. tuberculosis* was reported as early as 1984 [40]. Ciprofloxacin was first approved by the US Food and Drug Administration in 1987, and ofloxacin was first approved in 1990. These drugs were reportedly used in patients with chronic, drug-resistant TB as early as 1990 [41]. Combining a fluoroquinolone with one of the older, second-line injectable drugs (eg, kanamycin, amikacin, or capreomycin) and $\geqslant 2$ of the older oral drugs cured 60%–70% of patients in middle- and low-income countries [42].

A "Green Light Committee" was set up by the Stop TB Partnership in 2000 to increase access to high-quality MDR-TB treatment in middle- and low-income countries at reduced cost [43, 44]. By working with nascent MDR-TB programs in dozens of countries, it became apparent by 2004 that physicians and patients everywhere were already faced with TB that was resistant to every available drug. In collaboration with supranational TB reference laboratories worldwide and the WHO, the CDC first reported the global emergence of XDR-TB; the abbreviation "XDR-TB" was coined to help focus public and professional attention [45, 46]. Within months, a devastating outbreak of XDR-TB was reported from South Africa, and more reports followed [47–52]. One had to wonder whether we were living through an episode of *The Twilight Zone.* The public news media latched on, and suddenly the world awoke to the possibility of a pandemic of untreatable TB.

INTERNATIONAL AND US RESPONSES TO XDR-TB

The global public health community mobilized with phenomenal speed. The South African Medical Research Council convened an emergency consultation on XDR-TB, attracting worldwide public attention and outlining the essential elements of a global response plan: surveillance, laboratory capacity, patient care, outbreak response, infection control, new drugs, new rapid diagnostics, and universal access to antiretroviral drugs for HIV-infected persons who needed them [53]. In record time, the WHO convened an Emergency Task Force on XDR-TB, reaffirming the action plan and redefining XDR-TB for practical and political purposes [53–55]. Separately, the WHO announced it was no longer neglecting pre-

viously treated TB cases, explicitly including drug-resistant TB in its revised Stop TB Strategy [56, 57]. The WHO's Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis were crucial in this respect. In the absence of rigorous evidence from controlled clinical trials, these guidelines provided an algorithmic approach to treatment of MDR-TB and XDR-TB that was based on a consensus of international experts. Patients should be treated with at least 4 effective drugs chosen on the basis of in vitro drug-susceptibility testing and treatment history, prescribed in a specific priority order, including contingencies for unproven drugs in instances in which <4 effective drugs are available [58]. The international Stop TB Partnership released an updated Global Plan to Stop TB (2006–2015) that explicitly addressed drug-resistant TB [59]. Moreover, the Global Fund Against AIDS, TB, and Malaria completely changed the economic landscape of drug-resistant TB control. For the first time, the necessary financial resources were available to middle- and low-income countries, and the lack of such resources was no longer an excuse. Since its inception in 2002, the Global Fund has approved >$2.26 billion in funding for TB control in >100 countries and has disbursed >$1.26 billion of these funds [60]. These funds represent a sound investment not only in terms of TB-related morbidity and mortality, but also in much broader socioeconomic terms, because >75% of TB-related disease and death occur among young and middle-aged adults, the economically productive age groups. One adult with TB, on average, results in the loss of 20%–30% of annual household income. Consequently, TB is estimated to be related to a loss of income of $12 billion in the world's poorest communities [60].

Apart from US government contributions to the Global Fund Against AIDS, TB, and Malaria, the USAID is the lead US government agency in international TB-control programming (except for HIV-TB programming, which is led by the Department of State's Office of the Global AIDS Coordinator). Through the USAID, the US government is the leading bilateral donor in the world for TB and supports the expansion and strengthening of TB control in 40 countries. From 2000 through 2008, the USAID provided ~$777 million to support TB programs worldwide [61]. The CDC provides critical technical assistance to global and country-level initiatives, including research, evaluation, training, consultation, surveillance, and program strengthening. The National Institute of Allergy and Infectious Diseases's research agenda on MDR-TB and XDR-TB, released in 2008, targets 6 strategic areas—diagnostics, chemotherapy and clinical management, basic biology, epidemiology, HIV coinfection, and vaccine development—supported with a $120 million portfolio of >300 active projects [26, 27]. The Federal Tuberculosis Task Force, led by the CDC and the NIH, developed the Plan to Combat Extensively Drug-Resistant Tuberculosis, detailing concrete action steps outlined under 9 key components: diagnostic laboratory; surveillance, epidemiology, and outbreak containment; infection control; clinical and programmatic interventions; ethical and legal issues; communication and education; research; partnerships; and cost analysis [62].

NEW RESOURCES, NEW TOOLS, AND NEW STRATEGIES AGAINST TOMORROW'S DRUG-RESISTANT TB

President Obama's Global Health Initiative provides an opportunity for a new focused approach to accelerate TB case finding, scale up services for drug-resistant TB, scale up laboratory networks with rapid diagnostic testing and biosafe working conditions, scale up infection-control measures to prevent airborne disease transmission, and strengthen information systems and data analysis [63]. Although details have not yet been released, the Global Health Initiative shows promise for increasing US support for international TB-control programs, because TB, in addition to HIV infection and AIDS and malaria, is at the center of this initiative.

Academic leaders, nongovernmental organizations, humanitarian organizations, and philanthropies have continued and expanded their pivotal role in international efforts to control drug-resistant TB. International partnerships have played an unprecedented role advancing both public health programs and scientific research focused on drug-resistant TB. Too numerous to name without omitting many worthy organizations, some of the leading groups include the Foundation for Innovative New Diagnostics, the Bill & Melinda Gates Foundation, Eli Lilly, the Global Alliance for TB Drug Development, Médecins Sans Frontières, the Royal Dutch Tuberculosis Foundation, the Supranational TB Reference Laboratory Network, the Japan Anti-Tuberculosis Association, the American Thoracic Society, the Stop TB Partnership and its Green Light Committee, the Treatment Action Group, Harvard University–Partners in Health, the Infectious Diseases Society of America, and the International Union Against Tuberculosis and Lung Disease.

New diagnostic tools have the potential to eliminate the traditional diagnostic delay of weeks or months, identifying *M. tuberculosis* and drug resistance–associated genetic mutations in a matter of hours in many instances. As the genetic basis of drug resistance is further unraveled, the paradigm for detecting drug resistance may well shift from time-consuming, complex, and hazardous phenotypic testing to molecular genetic methods. Because of historical and intrinsic limitations of conventional phenotypic methods against which newer technologies are validated, these newer methods must be evaluated rigorously against clinical and programmatic end points.

Promising new drugs and vaccines are

being developed, including several candidates already in human trials. But, according to industry experts, there are not nearly enough new products in the pipeline to guarantee that at least one of them will be ready in the next 5–10 years [64, 65]. Support for drug discovery and development must be ramped up substantially, as must investigations into novel approaches to treatment with already existing drugs. From a broader perspective, on the basis of the lessons of the past 60 years, cooperative clinical trials of entirely new drug regimens are essential; these trials should combine at least 3 novel drugs, develop a new approach to regulatory affairs, and emphasize long-term public health over short-term economic returns. Otherwise, if researchers continue to introduce new drugs one at a time, the enduring wisdom of Einstein about doing the same thing and expecting a different result will be reaffirmed.

Humans, like all animals, are neurologically hard-wired to react to sudden change. Outbreaks capture public attention. New resources are brought to bear, and efforts are redoubled to control an imminent threat. Decreases in TB disease, coupled with advances in science and technology, reveal what can be achieved with determined effort and represent a measurable return on investment in economic and humanitarian terms. The question remains whether we will sustain this progress, learning the hard lessons of history, or whether we will allow ourselves to be sidetracked and repeat the same mistakes.

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