

# Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: The National Institute of Allergy and Infectious Diseases Research Agenda and Recommendations for Priority Research

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Globally, tuberculosis (TB) is one of the leading causes of death due to an infectious disease, second only to HIV/AIDS [1, 2]. Estimates suggest that approximately one-third of the world's population is infected with *Mycobacterium tuberculosis*, the microbe that causes TB, and 10% of infected individuals will develop active TB at some point in their lives. For individuals also infected with HIV, the likelihood of developing active TB after infection is much higher [3, 4]. In 2006, 9.2 million people globally developed active TB, and it is estimated that 1.7 million people died as a result of TB, including 200,000 HIV-infected individuals [1]. Although estimates suggest that the rates of new cases and deaths due to TB show signs of slowing throughout the world, recent increases in rates of drug-resistant TB have the potential to reverse these gains [1, 3].

In 2006, an estimated 500,000 individuals throughout the world developed mul-

tidrug-resistant (MDR) TB, which, at a minimum, is refractory to treatment with isoniazid and rifampin, the 2 first-line antibiotics for treating TB [4, 5]. Extensively drug-resistant (XDR) TB, a form of MDR TB that is much more difficult to treat, has recently been described; by February 2008, it had been detected in at least 46 countries [6]. XDR TB is MDR TB with concomitant resistance to any fluoroquinolone and to at least 1 of 3 injectable second-line anti-TB drugs: amikacin, kanamycin, or capreomycin [4, 5].

The National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), recently convened a working group to review its TB programs and determine its most effective contributions to the global fight against MDR/XDR TB. The *NIAID Research Agenda for Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis* [7], developed by the NIAID TB Working Group, complements other domestic and international efforts to prevent and control the spread of MDR/XDR TB. Representing international efforts, the World Health Organization (WHO) together with the Stop TB Partnership recently released *The Global MDR-TB and XDR-TB Response Plan* [8], and the US Federal Tuberculosis Task Force will soon publish its *Plan to Combat Extensively Drug-Resistant Tuberculosis* (in

preparation). All 3 documents emphasize the urgency of the MDR/XDR TB situation and the need to take immediate action. Whereas the WHO/Stop TB plan emphasizes the need to increase surveillance, control, and treatment efforts, the NIAID plan focuses specifically on areas of biomedical research to which increased attention is needed to improve current diagnostics, treatment, and preventive measures aimed at halting the threat of drug-resistant TB. Here, we summarize the issues and considerations that underlie the NIAID research agenda for MDR/XDR TB, the goal of which is to contribute substantively to the global fight against this emerging threat.

## THE GLOBAL BURDEN OF MDR/XDR TB

The threat of drug-resistant TB that is refractory to current treatment strategies was highlighted by an outbreak of XDR TB at a hospital in Tugela Ferry, KwaZulu-Natal, South Africa, between January 2005 and March 2006 [9]. Of 53 patients with XDR TB, 52 died within a median of 16 days from the time of diagnosis. Forty-four patients were tested for HIV, and all were found to be infected with the virus. In 2004–2005, a global survey of international reference laboratories was conducted by the WHO and the US Centers for Disease Control and Prevention

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(CDC) [10, 11] to examine the prevalence of drug resistance among isolates of *M. tuberculosis* from patient samples collected in 2000–2004. The study included samples from countries in Africa and Asia with a high prevalence of HIV infection, as well as samples from countries with a low prevalence of HIV infection, such as South Korea, Latvia, Iran, and the United States. Overall, 20% of the 17,690 isolates examined were MDR *M. tuberculosis*, and, after re-examination, 2% of all isolates met the definition of XDR *M. tuberculosis*. (Note that these estimates are based on the initial CDC/WHO definition of XDR TB developed 24 March 2006: XDR TB was defined as TB resistant to isoniazid and rifampin and at least 3 of the 6 main classes of second-line drugs [aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicylic acid]. In November 2006, the definition of XDR TB was updated. The current definition of XDR TB includes all cases of TB that are resistant to isoniazid, rifampin, and any fluoroquinolone and at least 1 second-line injectable drug [amikacin, kanamycin, or capreomycin]. Unless otherwise stated, reference to XDR TB throughout the present article reflects the updated definition of XDR TB.) However, the true global prevalence of XDR TB and MDR TB is unknown, because drug susceptibility testing, even for first-line drugs, is not routinely performed in most TB-endemic countries, and many cases likely are undetected [10, 11]. This situation was underscored by the fact that, although a significant number of global TB cases occur in Africa, only a small sample of drug-resistant *M. tuberculosis* isolates was included in the survey, because only 2 reference laboratories are available to serve the entire African continent.

The appearance of drug-resistant TB is not a recent occurrence, but, rather, an unfortunate and expected consequence of the adaptation of *M. tuberculosis* to the use of antibiotics. Progressive development of drug resistance can be expected if we fail to improve treatment and control mea-

asures for TB. Recently, the first cases of *completely* drug-resistant TB were reported from Italy, where 2 HIV-negative patients were diagnosed with TB that was resistant to all known anti-TB drugs [12, 13].

Although the initial development of drug resistance in patients receiving anti-TB therapy is often due to multiple factors—primarily suboptimal drug concentrations and varying degrees of nonadherence to therapy—transmission of drug-resistant *M. tuberculosis* has been observed, particularly in countries with high numbers of patients coinfecting with HIV [14]. These patients, because of their compromised immune systems, are at higher risk for developing active TB infection and therefore could contribute significantly to the spread of MDR/XDR TB [3]. Drug-resistant TB is already highly prevalent in eastern Europe, and its prevalence is increasing disproportionately in African countries, where the coepidemics of TB and HIV/AIDS are fueling each other; thus, anti-TB drug resistance has the potential to take on crisis proportions [15].

Although it has been known for years that standard anti-TB therapy is gradually losing its effectiveness and that existing control programs for TB have been seriously compromised in the setting of widespread HIV infection, it took reports of patients with AIDS in South Africa rapidly dying of TB despite receiving antiretroviral and anti-*M. tuberculosis* agents [7], as well as a highly publicized case in the United States [16], to raise global awareness of the continuing threat of drug-resistant TB.

The large global burden of TB and the fact that MDR TB and XDR TB have likely existed for years in most countries highlight serious limitations in the quality of national TB programs in those countries and follow-up efforts to ensure cure. These limitations may have arisen because therapies to cure TB have been available for decades. After the establishment of global control programs, TB was considered to have been managed, and efforts to

develop new drugs and diagnostics were not considered to be of great importance. Furthermore, because success has been measured primarily as completion of treatment, a thorough and realistic assessment of cure and consideration of drug resistance have been minimal [17, 18]. As a result of limited attention given by pharmaceutical companies, few new anti-TB drugs have been added to the armamentarium of TB treatment in the 37 years since rifampin was approved by the US Food and Drug Administration (FDA) in 1971 [19]. To keep anti-TB drug discovery and development from disappearing completely, government-sponsored research organizations, philanthropic donors, and public-private partnerships have shouldered most of the responsibility to continue research and development efforts for new anti-TB agents.

Clearly, the existence of drug-resistant TB—and of XDR TB, in particular—can no longer simply be measured and documented and ultimately ignored; it requires our urgent attention and a tangible response.

## THE ROLE OF THE NIAID IN ADDRESSING MDR/XDR TB

The NIAID supports a global TB research agenda through its extramural and intramural programs [20]. The NIAID extramural portfolio of grants and contracts supports all aspects of TB research, ranging from studying the basic biology of *M. tuberculosis* and its interaction with the host to investigating the various manifestations of TB (pulmonary, extrapulmonary, and latent) in adult and pediatric populations, including HIV-coinfecting individuals, to conducting research aimed at developing new health care interventions, including diagnostics, drugs, and vaccines, several of which are already in clinical trials (table 1).

In fiscal year 2007, NIAID intramural and extramural TB expenditures totaled approximately \$131.1 million, supporting 257 research projects. Of these, 146 projects (\$60.6 million) were funded in basic

**Table 1. Examples of how US government funding for tuberculosis (TB) research has contributed to new drug, vaccine, and diagnostic candidates that are currently being evaluated for use in TB medicine.**

Candidate	Stage of development	Sponsor(s)	Description
<b>Drugs</b>			
SQ109	Phase 1	Sequella	Discovered in NIAID intramural laboratories; preclinical development funded in part through grants, cooperative agreements, and services provided through NIH contracts; phase 1b clinical trial to be conducted in collaboration with the NIH Clinical Center
PA-824	Phase 2	Global Alliance for TB Drug Development	Preclinical development and clinical preparation funded in part through services provided by NIAID contracts; development of second-generation drug candidates being conducted in NIAID intramural laboratories
Moxifloxacin	Phase 2–3	Open access; Global Alliance for TB Drug Development	Preclinical animal models and clinical trials to assess contribution of moxifloxacin to anti-TB drug regimens funded in part through NIAID contracts; studies to assess best use of fluoroquinolones as part of anti-TB therapy funded through NIAID grants
FAS 20013	Preclinical	FasGen	Developed through NIAID Small Business Innovation Research Grant and with services provided through NIAID contracts
TMC 207	Phase 2	Tibotec (Johnson & Johnson)	Preclinical studies conducted in part through services provided by NIAID contracts
<b>Vaccines</b>			
Recombinant BCG	Preclinical–phase 1	University of California, Los Angeles; Vanderbilt University; Aeras Global TB Vaccine Foundation	Discovery, preclinical development, and follow-on candidates funded in part through NIAID grants and services provided through NIAID contracts
Mtb72f	Phase 2	GlaxoSmithKline; Corixa; Infectious Disease Research Institute	Discovered and developed in part through NIAID grants and cooperative agreements and through services provided by NIAID contracts; follow-on strategies developed with contributions from NIAID grants and contracts
Live attenuated <i>Mycobacterium tuberculosis</i>	Preclinical	Albert Einstein College of Medicine	Developed in part through NIAID grants and services provided by NIAID contracts
<i>Mycobacterium vaccae</i>	Phase 3	Dartmouth-Hitchcock Medical Center	Evaluated in HIV-positive patients under an NIAID grant
<b>Diagnostics</b>			
Patch Test	Phase 2	Sequella	Developed in part through NIAID grants and cooperative agreements
Automated nucleic acid amplification test with integrated sputum processing for detection of drug-susceptible and drug-resistant TB	Preclinical	Cepheid; University of Medicine and Dentistry, New Jersey	Developed in part through NIAID Small Business Innovation Research Grants
Microscopic-Observation Drug-Susceptibility Test (MODS)	Phase 2/3	Johns Hopkins University	Developed and evaluated in part through NIAID grants

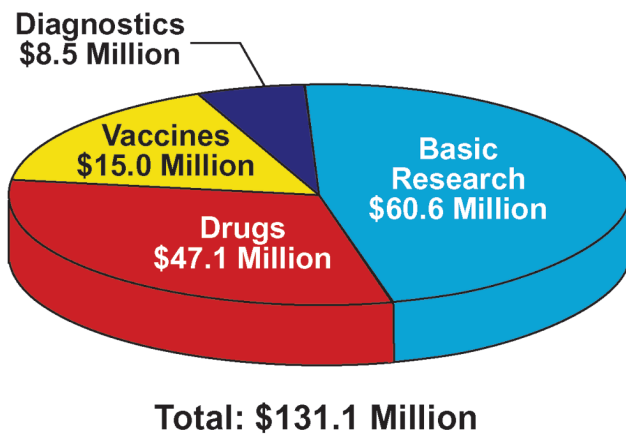
**Note.** BCG, bacille Calmette-Guérin; NIAID, National Institute of Allergy and Infectious Diseases; NIH, National Institutes of Health.

research, 67 projects (\$47.1 million) were funded in drug discovery and development, 22 projects (\$15.0 million) were funded in vaccine discovery and development, and 22 projects (\$8.5 million)

were funded in the discovery and development of diagnostics (figure 1).

Other NIH institutes and centers, including the National Heart, Lung, and Blood Institute, the National Institute of

Child Health and Human Development, and the Fogarty International Center, contribute to these efforts by supporting projects that target specific aspects of TB research. NIH-funded biomedical research,



**Figure 1.** National Institute of Allergy and Infectious Diseases (NIAID) tuberculosis (TB) funding for fiscal year 2007. NIAID total TB expenditures of \$131.1 million supported 257 intramural and extramural research projects in fiscal year 2007. Approximately 16% of funds were allocated to intramural projects, and 84% were allocated to extramural projects. Funds supported 146 projects in basic research, 67 projects in drug discovery and development, 22 projects in vaccine discovery and development, and 22 projects in the discovery and development of diagnostics.

together with research conducted and supported by the CDC, constitute the primary TB research efforts in the United States. The CDC also conducts and supports TB surveillance, epidemiology, and control activities in collaboration with state, local, and international health officials.

Although the NIAID's long-standing commitment to TB research has always included efforts to improve the diagnosis, prevention, and control of all forms of TB, it has recently made the development of new strategies to prevent the further emergence and spread of MDR/XDR TB a top priority. As noted above, the NIAID Tuberculosis Working Group, which includes representatives from each of its extramural, intramural, and clinical research divisions, conducted a review of the NIAID TB research portfolio in 2007. The group, with input from external advisors and TB experts, identified areas of science that have the potential, if given additional attention, to contribute substantially to a global public health response. The areas that are articulated in the *NIAID Research Agenda for Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis* [7] were chosen because they can build on existing efforts supported by the NIAID and its collaborators within the complex inter-

national network of TB research. They are organized into the following broad objectives that apply to adult and pediatric populations, as well as persons with HIV infection and other comorbidities:

1. Develop and test reliable technologies to rapidly diagnose TB and to identify drug resistance
2. Define the most effective use of existing second-line anti-TB therapies and other antimicrobials available to treat drug-resistant TB and develop new chemotherapeutic agents, particularly against MDR/XDR TB
3. Understand the basic biology and immunology of host and pathogen that underlie the development and spread of MDR TB
4. Understand the epidemiology of *M. tuberculosis*, including host and strain characteristics that contribute to the development and spread of MDR TB
5. Determine the influence of the overall immune status of the infected individual, other host factors, and HIV coinfection on drug resistance and the outcome of TB chemotherapy
6. Develop effective chemopreventive and immunopreventive strategies for drug-susceptible and drug-resistant TB

The objectives proposed in the research agenda are expected to leverage a combination of existing resources, collaborations, and infrastructure and to provide targeted opportunities to expedite ongoing research programs and product-development efforts that could be realized if additional financial resources become available. These programs will complement ongoing NIAID efforts in the most critical areas of TB research, such as understanding latency; developing surrogate markers of infection, disease, and response to therapy; identifying correlates of immunity and markers that signal transition from latent to active TB; and discovering and developing new diagnostics, drugs, and vaccines for TB that are relevant to all persons at risk, including children and those coinfecting with HIV.

The NIAID's contributions to the global MDR/XDR TB response are based on the distinct role the institute plays as part of a continuum of research and development efforts that range from fundamental science to the implementation of new and improved health care interventions for TB. The NIAID's support focuses on leading and sponsoring research activities to create a foundation of knowledge for the discovery of new diagnostics, drugs, and vaccines, with an expectation that these products will be further developed by other organizations, such as drug companies and public-private partnerships, into tools and approaches that enhance the quality of care for patients with TB.

**Diagnostics.** Proper treatment of drug-resistant TB depends on the ability to identify persons with active disease and to rapidly determine the "cocktail" of drugs to which a specific drug-resistant form of TB may still respond. Despite numerous initiatives by the NIAID and other organizations, diagnostics research and development remain underrepresented in research programs throughout the world. In particular, fundamental and applied research in TB diagnostics is needed for (1) rapid identification of *M. tuberculosis*, (2) determination of its drug resistance pro-

file, (3) rapid diagnosis or ruling out of TB in patients and their contacts, and (4) overall studies to improve the state of the art in TB diagnosis. To achieve these goals, we may need to change the way partnerships between basic research scientists and biotechnology companies are structured, to ensure that promising new diagnostics progress into clinical development and to the marketplace within a reasonable amount of time and at a reasonable cost. In addition, we must proactively identify and embrace innovation in diagnostics research. Diagnostic advances suitable for adaptation to TB are likely to emerge from platform technologies supported for other infectious diseases, such as those being developed by the biodefense and emerging infectious diseases program at the NIAID. Creating diagnostic tools that are suitable for field use in sites with limited infrastructure will constitute an additional challenge.

**Improving chemotherapy for MDR/XDR TB.** The most critical need for patients with drug-resistant TB is access to new drugs. Several new therapies are in clinical trials, some of which are the direct result of NIAID research efforts and partnerships [21] (table 1). The NIAID has focused its drug discovery efforts on studies of the physiology of *M. tuberculosis* and its interaction with the host to identify suitable points of intervention against which new drug candidates can be developed. Unfortunately, new TB therapeutics are not expected to be widely available in the immediate future. In the interim, it has been recognized that even the current first- and second-line therapies for TB are likely not fully optimized and need to be reexamined to determine whether adequate drug levels are being achieved in patients with advanced disease, in children, in those receiving antiretroviral therapies, and in those with other comorbidities [22–24]. Furthermore, FDA-approved antibiotics not currently used for treatment of TB should be tested clinically to determine whether they can

contribute to treatment approaches for drug-resistant and drug-susceptible TB; if this is the case, additional drugs with anti-*M. tuberculosis* activity might be made available in a timely manner to address the global threat of MDR/XDR TB [7].

**Basic biology.** It is still not known whether strains of MDR and XDR *M. tuberculosis* are more transmissible or more virulent than their drug-susceptible counterparts, particularly among HIV-infected individuals. Programs for the genetic sequencing of representative *M. tuberculosis* strains are ongoing, and drug resistance markers are beginning to be identified; it is also important to understand how host factors contribute to the development of drug resistance in TB. Answers to these research questions will not only improve our understanding of the pathogenesis of TB and provide additional drug targets and potential diagnostic and immunological markers but, hopefully, will also help to prevent development of drug resistance in the future.

**Epidemiology.** MDR/XDR TB already constitutes a significant threat to global TB and HIV/TB programs, yet we lack complete information on how drug-resistant strains develop and are transmitted and how drug resistance varies in different regions of the world. Data from basic biological studies to better understand the transmissibility and virulence of MDR/XDR TB will be critical to the design and implementation of epidemiological studies to ascertain the true burden, risk, and impact of MDR/XDR TB; improvements in the identification and treatment of MDR TB will depend on understanding the dynamics of these interactions.

**Clinical management of MDR/XDR TB in patients coinfecting with HIV.** The clinical management of MDR/XDR TB in patients coinfecting with HIV is particularly challenging. Immunocompromised individuals, including those with advanced HIV infection, are at greatly increased risk of developing active TB caused by either a new *M. tuberculosis* in-

fection or reactivation of latent TB. HIV/*M. tuberculosis*-coinfecting individuals are, therefore, more likely to transmit both drug-susceptible and drug-resistant *M. tuberculosis* to others. Although management of drug-susceptible TB in HIV-coinfecting patients is very complex, and solid data to guide treatment, particularly in the presence of additional comorbidities, remain inadequate, we know even less about the treatment of drug-resistant TB in these patients. For second-line therapies, many basic facts regarding drug-drug interactions, toxicities, achievable drug levels, and drug metabolism remain to be determined in HIV-coinfecting individuals to ensure that the treatment options currently available are applied optimally and provide acceptable efficacy.

**TB prevention and adjuncts to therapy.** The largest potential impact on TB control and the development of drug resistance would come from effective vaccines to prevent all forms of TB. The currently available vaccine, bacille Calmette-Guérin, does not provide adequate protection against pulmonary TB, particularly in adults, and therefore has limited utility for the control of TB transmission. Development of new vaccines and vaccination strategies has been stymied by a lack of understanding of the nature and mechanisms of immune protection that would have to be elicited by an effective vaccine. Clinical studies of new vaccine candidates are hampered by a limited understanding of surrogate markers of infection and correlates of immune protection. Vaccine development will continue to be empirical until phase 3 clinical trials have been completed to validate available markers. Combining chemotherapy with various vaccines has the theoretical potential to contribute to the increased effectiveness of drug regimens, to provide alternative strategies for limiting the duration of infectiousness of patients with TB, and to contribute to chemopreventive strategies for latent infection with MDR *M. tuber-*

culosis and to protect contacts of patients with MDR/XDR TB.

## CONCLUSION

The NIAID MDR/XDR TB research agenda outlines strategies in biomedical research based on the role of the institute as a partner in global TB research. To ensure that diagnostics, drugs, and vaccines can be developed in an effective manner, already-strong collaborations among US and international partners need to be expanded to include a clear articulation of the role and practical commitment of each entity in filling specific gaps along the product-development continuum from basic science to late-stage clinical trials. Only a concerted global effort will successfully counteract the remarkable resilience of *M. tuberculosis*.

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