Extensively Drug-Resistant Tuberculosis: Are We Learning from History or Repeating It?

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Tuberculosis (TB) is an enormous global public health problem. Cases of extensively drug-resistant TB (XDR-TB) are being reported in increasing numbers across the globe. A large outbreak of XDR-TB associated with rapid and nearly universal mortality has been reported among patients with human immunodeficiency virus infection or acquired immunodeficiency disease in South Africa who have been receiving standard TB therapy and antiretrovirals. Epidemiologic features of this outbreak make it highly suspicious for health care–associated transmission. We urge the Infectious Diseases Society of America and its members to increase involvement in ongoing international TB prevention and treatment efforts and to develop a registry of experts in infection control and laboratory and disease management. We urge advocacy for increased funding for domestic and global TB control programs, including expanded access to sputum culture and drug susceptibility testing, as well as funding for TB clinical trials and research capacity. We believe that substandard TB diagnostic tests are not acceptable for TB control in resource-poor countries. We urge the development of shorter, less toxic TB treatment and prevention regimens. Funding of TB control and research should be reassessed to prevent budget cuts at a time when the disease is killing as many as 2 million people a year.

Tuberculosis (TB) is an enormous global public health problem that has spawned new and urgent issues that deserve our attention and response. Close to 9 million new cases of TB disease and 1.2 million TB-related deaths are reported annually, making TB the second leading cause of infectious disease–related death after HIV infection/AIDS [1]. TB is curable and preventable if the infrastructure is in place to accurately and promptly diagnose active disease and to ensure full treatment for active and latent TB. Without adequate diagnostics, however, cases of TB go unnoticed until they are too advanced for treatment to be effective. In addition, drug resistance is likely to develop when cases of TB are treated without an adequate supply of the drugs needed in the multidrug treatment regimen, when nonstandard regimens are prescribed, or when staff oversight of therapy is lacking. Resistance to available TB therapy is on the rise around the world and is the primary focus of this article. We will review recent developments and propose steps that we, as infectious diseases, pulmonary, or public health professionals, can take to help improve TB prevention and treatment.

The emergence of what has been termed extensively drug-resistant TB (XDR-TB) [2, 3] threatens to return TB treatment to the preantibiotic era, when 50% of patients with TB died of the disease. The revised definition of XDR-TB is disease caused by bacteria that are resistant to at least isoniazid and rifampin—both first-line TB drugs, resistance to which defines multidrug-resistant TB (MDR-TB)—plus resistance to any fluoroquinolones and resistance to at least 1 second-line injectable drug (amikacin, capreomycin, or kanamycin) [4]. Losing the fluoroquinolones and the injectable agents means losing the most potent and least toxic options for second-line drug therapy. Unfortunately, a significant number of the XDR-TB strains go beyond the definition of XDR-TB and are essentially untreatable, being resistant to numerous other second-line drugs. XDR-TB is now documented in countries throughout the world, with the highest known rates in Eastern Europe and Asia.

Why should North American and European physicians, scientists, citizens, and policymakers be concerned about increas-
ing rates of drug-resistant TB overseas? Increasing rates of drug-resistant TB directly reflect a breakdown in the adequacy of TB control programs. The breakdown may occur at a local, regional, or national level; an example of the latter can be found in the outbreak of MDR-TB after the collapse of the former Soviet Union. Thus, we should be very concerned that our investments in TB control worldwide—which have paid off, with steady decreases in TB case rates in many countries—may evaporate. We have already watched the reversal of success in TB control in southern Africa, where the number of cases of TB has skyrocketed in the wake of HIV/AIDS-associated immunosuppression [1]. Another obvious reason for concern lies in the increasingly global nature of business, finance, trade, and education. Drug-resistant TB is as close as the next international flight, which could be bringing the newest engineering talent to a high-tech firm in the United States, or which could be taking our sons and daughters to their new assignments in southeast Asia. And finally, immigrants constitute >50% of the persons with active TB in North America and many European Union countries [5, 6], and the percentage increases each year. Combined, US residents from Asian countries (e.g., The Philippines, Vietnam, India, China, and South Korea) make up >35% of the persons with reported TB in the United States [7].

Data from KwaZulu Natal province in South Africa (reported as abstracts at the 2006 meeting of the International AIDS Conference and recently reported in the literature [8]) show what can happen when a strain of highly drug-resistant TB is introduced into a particularly vulnerable population. Staff and investigators noted excessive mortality among patients with TB and HIV/AIDS, despite the use of standard TB therapy; in several individuals, they documented robust viral response to antiretrovirals (N. Gandhi, Albert Einstein College of Medicine, Bronx, NY; personal communication). Investigators found the cause to be undiagnosed XDR-TB. A subsequent cross-sectional study of inpatients with suspected TB found 544 culture-positive cases of TB, 40% of which were MDR-TB. Shockingly, 53 of these culture-positive cases (24% of the MDR-TB cases) were resistant to all of the drugs tested.

Fifty-two of the 53 patients with XDR-TB died, with a median time from diagnosis to death of only 16 days. The majority of the isolates matched genotypically, and a large percentage of the patients had been hospitalized previously, making it very likely that the mode of transmission was health care associated. These reports are strikingly similar to reports from the epidemic of health care–associated MDR-TB in the United States during the late 1980s and early 1990s [9, 10]. When resources were provided to reconstitute and strengthen local and state TB programs, such that standard principles of TB treatment and containment could be implemented, rates of TB and drug resistance decreased. Fifteen years later, in 2005, the United States posted the lowest number of TB cases in its history [7]. Ironically, this success has resulted in cuts to the TB budget for the Centers for Disease Control and Prevention (CDC), which finances each state’s TB program, and TB control programs are being asked to consider the possibility of additional cuts of up to 25% over the next 5 years (Kenneth Castro, Division of TB Elimination, CDC, personal communication; Dr. Castro also suggested changing the name of his division from “Division of TB Elimination” to “Division of TB Control,” to bring attention to the effects of cumulative budget rescissions over the past several years).

What are the established principles critical to preventing the development and spread of drug-resistant TB? The cornerstone is prompt and accurate diagnosis and initiation of therapy to which the organism is susceptible. Currently available TB treatment regimens require strict adherence to a multidrug regimen with agents that are often toxic; furthermore, directly observed therapy is required to ensure that all doses are taken, to prevent the development of drug resistance. To curtail disease spread, patients must be identified quickly and quarantined until they are no longer infectious. Thus, TB programs need to have a steady supply of TB drugs and modern diagnostic services, and they must understand and implement core infection control practices.

The Global Stop TB Partnership (of which the Infectious Diseases Society of American [IDSA] is a member) and others have worked to standardize TB treatment strategies [11], to improve case detection, and to decrease rates of treatment default. However, insufficient political will and financial support have frustrated their success. In particular, the resources to support diagnostics and infection control are extremely limited in developing countries. Patient-specific, real-time cultures and TB drug susceptibility tests are rarely performed. In fact, the “direct observation of therapy (short course)” (DOTS) strategy supported by the World Health Organization [12] is based on diagnosis by sputum-smear microscopic examination alone, usually using unconcentrated sputum specimens. This strategy is practical and potentially attainable in every locale, with the caveat that ~50% of active TB cases may remain undetected [13, 14] until such time that individuals either die of TB [15–17], spontaneously heal, or develop more severe—and more contagious—sputum-smear-positive disease [18, 19]. If an astute local physician strongly suspects that a patient has TB despite a negative sputum smear result, an individual may receive empirical treatment before he or she develops any of these dire consequences. Nevertheless, it is feared that this strategy allows the disease to incubate and spread in the community until it becomes severe enough to be diagnosed by smear microscopy. The other failure of the current DOTS strategy is that the rigor of its implementation—in particular, the “direct observation” part of DOTS—may differ from location to location, depending on local resources and opinions about its
effectiveness [20]. Poor or intermittent adherence to TB treatment is the most important risk factor for development of drug-resistant disease. Finally, because most TB programs do not have access to culture results, they also do not have access to patient-specific, real-time drug susceptibility test results, such that even the best DOTS program providing standard therapy to individuals with undiagnosed, drug-resistant disease is doomed to fail [21, 22].

TB infection control, which requires a system-wide approach that is visibly and financially supported from the top down, has been widely ignored in the health care systems in resource-limited countries; even simple practices, such as screening patients for symptoms of TB before admitting them to a crowded clinic or ward, are also overlooked. Patients with suspected TB are placed in crowded wards for days (often next to HIV-infected patients) or are required to return to bustling clinics repeatedly, thereby facilitating transmission of infection among ill patients in health care settings. Given the experience in KwaZulu Natal province of South Africa, attention to TB infection control measures is essential to prevent transmission of TB—especially XDR-TB—with particular attention paid to HIV-infected patients receiving care.

What can public health systems, infectious diseases experts, and microbiologists do, and what can the IDSA do to effect change? Below are some preliminary suggestions, and we hope to use this forum to stimulate more ideas and action.

IDSA REPRESENTATION IN ONGOING INTERNATIONAL TB CONTROL EFFORTS

The IDSA can increase its engagement in the international efforts to enhance TB control. A number of IDSA members are involved in TB-related work in the international arena; however, professional society endorsement and commitment are very important. The Global Stop TB Partnership (http://www.stoptb.org/) has working groups that focus on advocacy, expansion of DOTS programs, MDR-TB, new TB diagnostics, new TB drugs, new TB vaccines, and the interaction of TB and HIV infection. We suggest that the IDSA seek to appoint knowledgeable and interested members of the IDSA and the American Society of Microbiologists—in particular, medical microbiologists—may be able to assist programs in planning, seeking funding for, and improving current diagnostics. Those who have actually organized TB laboratories from the ground up may have practical ideas, contacts, standard operating procedures, and to-do lists that could be useful. There are efforts by the Foundation for Innovative New Diagnostics (see the Web site at http://www.finddiagnostics.org/) and others [23] to develop affordable diagnostics. It is critical that, as these diagnostics are developed, there is adequate funding and commitment to operational research that will demonstrate the utility and cost-effectiveness of new diagnostic tools and lay the groundwork for more rapid uptake of new technologies where they are most critically needed. In the meantime, the IDSA should strongly advocate for TB programs in developing countries to have access to patient-specific, real-time TB culture and susceptibility testing.

DEVELOP A REGISTRY OF EXPERTS IN INFECTION CONTROL AND LABORATORY AND DISEASE MANAGEMENT

We propose developing a registry of interested members of the IDSA—perhaps in partnership with the Society for Healthcare Epidemiology of America and the Association for Professionals in Infection Control and Epidemiology—who would be willing to work with overseas programs to review or develop infection control plans and to formulate quickly achievable procedures in clinics and hospitals. This undertaking should be closely coordinated with the STOP-TB Partnership, the World Health Organization, the National Institute for Occupational Safety and Health at the CDC, the American Thoracic Society, and other lead agencies. Similarly, members of the IDSA and the American Thoracic Society who have experience managing MDR-TB and XDR-TB could make themselves available for consultation. A registry may help develop working partnerships, using E-mail and voice-over-Internet as affordable mechanisms for assistance. Finally, colleagues in the...
of developing drug resistance, but at increased programmatic costs. Two years of therapy are required for treatment of MDR-TB, with frequent interruptions and substitutions to manage serious drug toxicities and only a modest chance of cure. However, new animal model studies and phase 2 clinical trials, plus reports of novel antitubercular compounds, offer hope that a drug regimen that cures TB in ≤2 months may be an attainable goal, if there is adequate research funding [24–26].

We urge the IDSA and other relevant professional organizations to advocate vigorously for significant increases in domestic and global TB funding. The CDC’s Division of TB Elimination funds state-based TB prevention and control efforts and conducts the majority of TB clinical trials and epidemiological research in the United States. The National Institutes of Health (NIH) pursues critically important basic science TB research. Although the NIH remains the largest funding agency for TB research and development in the world, its contribution to TB programs ($158 million in 2005)—a disease that kills 2 million people per year—is less than what was spent on smallpox ($187 million) or anthrax ($183 million) in 2005 and represents a mere 5% of the funding available for HIV/AIDS ($2.9 billion in 2005). These figures, gathered in a recent report by the Treatment Action Group [27], highlight the huge funding gap that prevents rapid development of new TB drugs, diagnostics, and vaccines. Private-public partnerships, such as the TB Alliance for TB Drug Development (http://new.tb alliance.org/home/home.php), the Foundation for Innovative New Diagnostics (http://www.finddiagnostics.org/), and Aeras (http://www.aeras.org/), are largely funded by the Bill and Melinda Gates Foundation and serve as tremendous catalysts for advances in TB treatment, diagnostics, and vaccines. However, drug and device pipelines have to be even more robust to have a chance for success [28]. It is clear that definitive, phase 3, randomized clinical trials and treatment strategy trials will eventually require public funding, including funding to develop and support high-quality clinical research sites in high-burden countries. Perhaps most importantly, advocacy is also needed for increased funding for the NIH Fogarty International Center, which has the smallest budget of any NIH institute while supporting research training for scientists in resource-limited areas. With appropriate training, these colleagues can form the nidus to develop and implement improved treatment, diagnosis, and prevention strategies.

**VISIBILITY AND FOCUS WITHIN THE IDSA**

The IDSA’s journal *Clinical Infectious Diseases* could introduce a recurring or standing TB section that could feature research, news, reviews articles, or commentaries on specific areas of focus, such as improved diagnostics; TB research for new treatment, prevention, and diagnostic options; infection control as it exists in resource-poor countries; and nascent projects that are working toward improvement. Now that some pharmaceutical companies are bringing TB treatment compounds and diagnostic devices forward, they may have interest in supporting supplements or symposia for *Clinical Infectious Diseases*. Finally, the IDSA’s Web site (http://www.idsociety.org) features hot links to issues it deems of interest and importance, such as avian/pandemic flu, bioterrorism, and HIV. A “Global TB Epidemic” hot link to information, published research, and advocacy groups could be developed with modest support.

The global HIV/AIDS treatment and advocacy community did an amazing thing several years ago when they stopped accepting the mantra that HAART was not affordable to people in poor countries. It is time for the TB community to stop accepting an even longer-running refrain that says that substandard diagnostics are acceptable in countries where TB and HIV/AIDS are ravaging the population; stop accepting a decades-old, toxic, and lengthy treatment regimens that create XDR-TB when recipients do not meticulously adhere to them; stop accepting that the bacille Calmette-Guérin vaccine developed by Calmette and Guérin in 1921 is as good as it gets. Perhaps now that we see the specter of untreatable TB, which is contagious to rich and poor alike, there will be enough willpower to effectively confront this bona fide agent of mass destruction.

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