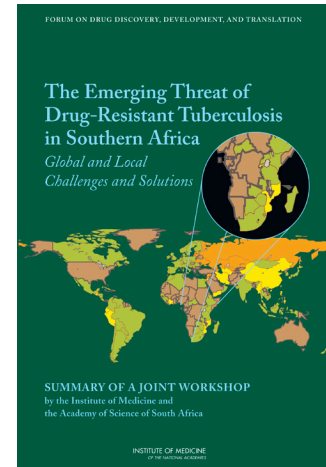


The Emerging Threat of Drug-Resistant Tuberculosis in Southern Africa

Summary of a Joint Workshop



Tuberculosis (TB) kills approximately 4,500 people worldwide every day. TB is the leading killer of people with HIV, and it also is a disease of poverty—the majority of TB deaths occur in the developing world. Although antibiotics are effective in treating many cases, some strains have developed resistance to these drugs. The treatments for drug-resistant TB are less effective, more expensive, and more toxic to the patient than antibiotics are for drug-susceptible TB.

The Institute of Medicine (IOM) Forum on Drug Discovery, Development, and Translation and the Academy of Science of South Africa (ASSAf) held a workshop March 3–4, 2010, in Pretoria, South Africa—the first in a series of international meetings designed to gather information from experts on the threat of drug-resistant TB and ways it can be combated. Representatives from the African public health community shared their experiences in fighting drug-resistant TB, and participants discussed lessons learned, best practices, and new approaches that can be used worldwide for treating and preventing drug-resistant TB. The workshop was co-hosted by the IOM and ASSAf.

The Nature of the Threat

Multidrug-resistant TB (MDR TB) is caused by bacteria resistant to isoniazid and rifampicin, the two most effective first-line anti-TB drugs. Extensively drug-resistant TB (XDR TB) is resistant to the same drugs as MDR TB, as well as any fluoroquinolone and at least one second-line injectable drug. Totally drug-resistant TB (TDR TB) is TB for which no effective treatments are avail-

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able. As outlined in a white paper authored by Partners In Health commissioned by the Forum in support of this workshop series, treatment of MDR and XDR TB requires two years or more of daily, directly observed treatment with drugs that are less potent, more toxic, and much more expensive than those used to treat drug-susceptible TB.

Workshop chair Gail Cassell, Eli Lilly & Co. (retired), emphasized that the failure to acknowledge the new realities of drug-resistant TB and to act rapidly will be catastrophic for many countries. Furthermore, the volume of international travel and immigration, legal and otherwise, means that drug-resistant TB represents a grave threat to the public health of all countries, not just those in which TB is prevalent today.

The Alarming Incidence, Epidemiology, and Spread of Drug-Resistant TB

Several workshop presenters described the tremendous health burden posed by drug-resistant TB throughout southern Africa, including the unmanageable number of patients presenting to the health care system as a result of the disease. Since 2006, cases of XDR TB have occurred in all provinces of South Africa and in all surrounding countries. The HIV epidemic in southern Africa has exacerbated the spread and virulence of drug-resistant TB.

As noted by Gerald Friedland, Yale School of Medicine, knowledge of the true extent of the MDR/XDR TB epidemic is hampered by a lack of in-country laboratory capacity and the inadequacies of the existing health system infrastructure. Dale Nordenberg, Novosano Health and Science, noted that a strengthened information infrastructure—an “information supply chain”—for TB laboratories could support both the detection and treatment of drug-resistant TB.

Rob Warren, Stellenbosch University, presented findings from a study of the drug-resistant strains in the Western Cape Province. The num-

ber of identified cases was found to be doubling approximately every eight years. Ninety percent of all drug-resistant cases tested were smear positive and thus indicative of being highly infectious. Stratification of the data by drug resistance pattern showed that the observed increase was strongly driven by MDR TB. The “Beijing” strain under investigation in this study contributed to 42 percent of this increase, with a doubling time of 2.4 years. Warren also noted that XDR TB is a major component of the drug-resistant TB epidemic in the Eastern Cape Province, and that pre-XDR and XDR TB strains are moving between provinces, emphasizing the need for rigorous TB control in both the Eastern and Western Capes.

Speakers noted that MDR TB is transmitted through the air, with the Tugela Ferry XDR TB outbreak demonstrating the threat of XDR TB transmission in a health care setting. Their key messages regarding infection control included

- The infection control program in Tugela Ferry has demonstrated that transmission can be substantially reduced through administrative, environmental, and personal protection controls.
- By improving cure rates and decreasing default rates, community-based care and treatment in Tugela Ferry has likely reduced the transmission of drug-susceptible and drug-resistant TB.
- Health care workers are at particular risk for contracting TB and need much higher levels of education and environmental protection than they currently receive.
- Household contacts of active TB cases, vulnerable populations in poorly ventilated congregate settings (such as prisons and drug treatment programs), and certain vocational workers, particularly migrant workers and miners, also are at a high risk of contracting TB. Special efforts are warranted to reach and protect such groups.

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Needs for Diagnosis and Treatment of Drug-Resistant TB

A number of workshop participants observed that an inability to diagnose drug-resistant TB rapidly and accurately is contributing to the severity of the DR TB epidemic. Paul van Helden, Stellenbosch University, noted that studies of the current system for diagnosis indicate that 20 percent of patients fail to return after their first visit to a clinic and thus are lost to follow-up. He added that a point-of-care diagnostic device could prevent those patients from being lost to follow-up at that early stage of diagnosis and treatment of their TB.

Gerrit Coetzee, National Health Laboratory Services, South Africa, observed that South Africa's response to MDR TB has been limited by the unsatisfactory performance of its laboratory services and inadequate human resources.

The workshop presentations and discussions highlighted a number of challenges and open questions for consideration in efforts to improve the treatment of drug-resistant TB, including

- Early diagnosis of drug-resistant TB is an essential precursor to successful treatment.
- With HIV coinfection, drug-resistant TB appears to take a different and more aggressive course.
- Differing approaches with respect to the locus of treatment were considered. It was noted that XDR TB treatment, especially in the earliest stages, should take place in a hospital

to ensure management of side effects, treatment literacy in patients, nutritional support, and infection control. A different perspective was noted that a move toward a decentralized model of care is necessary for prevention of transmission.

The Devastating Spread and Unique Challenges of Drug-Resistant TB in Children

The workshop presenters highlighted that an increasing number of children in southern Africa are contracting drug-resistant TB, primarily through transmission. Their key messages included the following:

- Diagnosis of drug-resistant TB and assessment of side effects are often more difficult in children than in adults;
- The optimal duration of treatment in children is unknown but is likely shorter than in adults;
- Better data on mortality and causes of death would clarify the extent of the epidemic among children.

Research Needs

Over the course of the workshop, individual participants suggested a number of research questions that, in their judgment, need to be pursued,



such as the following:

- What is the current extent of MDR, XDR, and TDR TB? What are the cure rates for MDR and XDR TB?
- How many cases of drug-resistant TB are occurring in southern Africa that are not being diagnosed? How can cases be identified more rapidly?
- What proportion of cases can be attributed to transmission in health care facilities, transmission in the community, or evolution of the organism?
- What is the benefit of intensive case finding in health care facilities and community settings in terms of earlier detection, improved outcomes, and reduced transmission of drug-resistant TB?
- How should information systems be developed and implemented for the management of laboratory and surveillance data?
- What are the best currently available and future treatment regimens? How can clinical trials be designed and executed to test existing drugs, new drugs, and drug combinations to optimize treatment of MDR and XDR TB?
- How can TB programs be strengthened and suboptimal adherence to treatment regimens be addressed?
- How can preventive, diagnostic, and therapeutic operations in health care facilities, including infection control, be changed and improved? How can households be reached? How can the protection of health care workers be enhanced?

Need for Communication and a Public Health Approach

Queta Bond, QE Philanthropic Advisors, remarked that TB is not just a medical problem. Many of the challenges involve social issues such as poverty, migrant labor, overcrowding, poor nutrition, and inadequate ventilation. Solutions entail not just new diagnostics, vaccines, and treatments but also behaviors of patients and health care workers, health systems, political commitments, and social mobilization. Salim Abdool Karim, University of KwaZulu-Natal, noted that members of the scientific and medical communities must communicate the realities of drug-resistant TB to the public and to policy makers, and they must translate data into policies commensurate with the magnitude of the problem.

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