Global Tuberculosis
Perspectives, Prospects, and Priorities

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Despite being nearly 100% curable, tuberculosis remains a major public health problem, representing the second leading cause of death from infectious diseases globally, with drug-resistant tuberculosis increasingly common. In 2012, an estimated 8.6 million people developed tuberculosis worldwide—a global incidence rate of 122 persons per 100 000 population—and 1.3 million people died. Incidence rates vary from high in southern Africa (550/100 000 population in Mozambique and Zimbabwe and 1000/100 000 population in South Africa) to fewer than 10/100 000 population in the United States, Canada, and most of Western Europe.[1] Although the global prevalence of multidrug-resistant tuberculosis was estimated at 3.6% of newly diagnosed and 20.2% of previously treated patients, these rates were 20% to 35% for newly diagnosed cases and 50% to 69% for retreatment cases in the Russian Federation and some other former Soviet republics.

In sub-Saharan Africa, the tuberculosis epidemic is driven by HIV through both increased reactivation of latent tuberculosis infection and the increased risk of rapid development of disease soon after exposure to *Mycobacterium tuberculosis* because of HIV-induced immunodeficiency. There is lower tuberculosis incidence in Asia, but because Asia's population is so much larger than Africa's—more than 4 billion compared with about a billion—75% of the 5 million tuberculosis cases in the 22 highest-burden countries are in Asia. In these countries, crowding, poverty, and inadequate tuberculosis treatment completion rates contribute to the epidemic.[2]

Despite these statistics, marked progress has occurred since the World Health Organization (WHO) declared tuberculosis a global emergency 20 years ago. In 1995, fewer than 2 million patients were successfully treated using the WHO's Directly Observed Treatment, short course (DOTS) strategy, less than a quarter of the estimated total; by 2011, nearly 5 million patients were treated successfully with DOTS. Approximately 56 million patients have been treated successfully since 1995, preventing an estimated 22 million deaths. However, every year about 3 million people with tuberculosis are missed by health systems. Mortality rates are declining, albeit slowly, in all regions of the world. Since 1990, the death rate associated with tuberculosis has decreased 45%, from 25 persons to 14/100 000 population, although rates vary widely between countries.

The greatest risk to tuberculosis control is lack of implementation of effective and currently available strategies and tools. Tuberculosis control rests on 3 fundamental principles: prompt and accurate diagnosis, effective treatment begun immediately upon diagnosis and monitored until completion, and interruption of transmission.

Diagnosis

Microbiological examination of sputum smears for acid-fast bacilli, despite limitations, remains the mainstay of diagnosis. Newer diagnostics provide greater sensitivity, particularly among children and persons with HIV infection (whose sputum smears are often negative), and can also identify rifampin resistance. These newer tests can enhance, but not yet replace, smear microscopy because of expense and requirements for suitable infrastructure, including stable electricity supplies. Early and accurate identification of tuberculosis can result in earlier treatment and decrease transmission, but only if treatment is promptly initiated.[3]

Rapid and Complete Treatment

All patients diagnosed with tuberculosis should receive prompt, complete, and effective treatment. In practice, however, as many as 10% to 30% of patients with laboratory-detected smear-positive sputum do not start treatment,[4] the result of disconnects between laboratories, treating facilities, and patients. Turnaround time between identification of a positive specimen, whether by smear microscopy or molecular diagnostics, and treatment initiation should not be longer than 24 hours. Communication between diagnosing and treating facilities remains problematic, and responsibility for promptly finding patients once there is a positive result remains nebulous in many programs.[5]

Monitoring and evaluation of the diagnosis and treatment cascade within every facility should be routine and performed quarterly, but in practice it is rare for a treating facility to know what percentage of patients diagnosed actually began treatment at the facility to which they were referred, or have information about outcomes of these diagnosed patients, such as cured, died, lost to follow-up, or remaining smear- or culture-positive.

Effective, regular, and structured supervision of tuberculosis diagnostic and treatment facilities and their patients, combined with program management and evaluation, is essential to tuberculosis control. Supervision helps determine why patients do not seek care and how attendance might be improved and teaches staff how to perform essential tasks and keep accurate records. Cohort analysis, performed quarterly and answering 2 simple questions: how many patients were diagnosed with tuberculosis and what happened to them is the hallmark of effective tuberculosis control and a model of accountability for treatment of any chronic illness.

Supportive supervision—helping health workers improve their performance—requires staff trained in specific skills, with central or provincial staff supervising district officers who in turn supervise frontline health staff. Regular, structured field visits to treatment clinics en-

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able supervisory staff to review information in registers and treatment records and interview patients and health care workers and are essential to improve performance.

A specialized central unit to provide leadership, training, supervision, data analysis, evaluation, reporting, and accurate drug forecasting so that medications never run out in any clinic is essential to maintain treatment completion rates as close to 100% as possible. Because a central unit is responsible for countrywide tuberculosis control, such a structure cannot be construed as either inefficient or inappropriate "verticalization." Although there have been major increases globally in tuberculosis-control funding, consistent financial support for program management and supervision is often insufficient.

There is ongoing debate about the need for direct observation of treatment. Although treatment observation is often official policy, it is difficult to implement well and frequently not actually practiced. Randomized clinical trials are the gold standard to evaluate different pharmacological treatments and may provide important information on different program designs, but may not accurately assess the value of treatment observation.[6] A 2007 meta-analysis purporting to show that self-administered treatment is as good as direct observation of treatment included 5 randomized clinical trials.[7] However, none of these trials included data on long-term outcomes such as relapse, additional spread of tuberculosis, or development and spread of drug resistance, all of which are crucial outcomes to evaluate, and relevance to national program scale-up could not be assessed.

Effective treatment observation is an activity that builds, maintains, and strengthens the bond between the patient and the health care worker, ensuring that the patient is the center of the program, thereby increasing the likelihood of cure. It is the concrete expression of the program's acceptance of responsibility—if the patient stops treatment, the program will expend resources to reengage.

Infection Control

In low-resource settings with high HIV prevalence and open, crowded hospital wards, substantial transmission of tuberculosis is likely; in southern Africa, devastating and lethal outbreaks of extensively drug-resistant tuberculosis have occurred. Within hospitals, the simplest ways to reduce tuberculosis spread are often the most effective and least expensive—but the least used. These include increasing the index of suspicion and ensuring that patients who may have tuberculosis are separated from others and tested rapidly, separating patients with suspected drug-resistant tuberculosis from other tuberculosis patients, ensuring that windows remain open, adding windows and skylights, and constructing outdoor waiting areas when possible. Health care workers are at considerable risk, yet few health care systems in high tuberculosis incidence areas monitor tuberculosis among staff, and even when they do, follow-up has been poor.[8]

Drug-Resistant Tuberculosis

The increase in patients who require treatment for drug-resistant tuberculosis is a symptom of 2 different problems: lack of infection control within congregate settings, such as health care facilities and prisons, which leads to primary drug resistance; and inadequate cure rates, particularly of patients who are smear-positive, which leads to acquired drug resistance.

Prompt diagnosis and effective treatment of patients with drug-resistant tuberculosis is essential, especially in areas with high HIV prevalence. Molecular testing will improve diagnosis, but effective treatment depends on drug susceptibility testing. Ideally, all patients with tuberculosis, or at least those who have not responded to prior treatment, should have isolates tested for drug resistance. Treatment of drug-resistant tuberculosis is imperative, but requires staff training and supervision. Second-line drugs are, excepting the fluoroquinolones, less effective and more toxic than first-line drugs, and far more costly. Increased resources are necessary, but must not be diverted from existing resources for core tuberculosis control.

Conclusions

Forgetting is the key challenge in tuberculosis control. Political leaders forget the poor and disenfranchised, who are most likely to contract and die of tuberculosis. Health leaders forget simple, low-technology interventions and therefore neglect the core work of treatment observation, field supervision, and cohort monitoring and evaluation. Patients forget how sick they were and may stop medications when symptoms subside.

The hallmark of tuberculosis is persistence—the persistence of *M tuberculosis* for life in most infected people and persistence of reproducing bacilli during the initial weeks of treatment. This must be matched by persistence with basic tuberculosis control principles, not just in planning but in actual implementation. Innovation in tuberculosis control programs is crucial, and new technology can and should be appropriately used, but must accompany effective core public health practice.

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