Tuberculosis: A Global Health Emergency

Approximately one-third of the world’s population—some 1.9 billion people—is infected with Mycobacterium tuberculosis, the bacterium that causes tuberculosis. In 1997, there were an estimated eight million new tuberculosis cases and almost two million deaths from tuberculosis (see Table 1). The global case fatality rate was 23 percent, but exceeded 50 percent in some African countries with high human immunodeficiency virus (HIV) rates. Among women of reproductive age, tuberculosis is a leading cause of death, surpassing all causes of maternal mortality.

Over 95 percent of new tuberculosis cases and deaths occur in developing countries (see Figure 1). The highest incidence and number of deaths occur in Asia and sub-Saharan Africa. Asia is the disease’s epicenter, containing nearly two-thirds of the world’s tuberculosis-infected population. Tuberculosis outbreaks also are occurring in Eastern Europe and the republics of the former Soviet Union, due in part to a reduced effectiveness of many health services. In this area, the number of notified tuberculosis cases rose by as much as 25 percent from 1994 to 1996. Demographic forces such as urbanization, increased travel, and migration of persons from high-incidence areas also are contributing to the spread of tuberculosis worldwide. The high incidence of HIV is a major factor in the tuberculosis epidemic in many regions, particularly Asia and Africa.

In the mid-1990s, the World Health Organization (WHO) and partners began a worldwide effort to promote the directly observed therapy, short-course (DOTS) strategy, a five-point package for tuberculosis control worldwide (see box on page 2). Where the DOTS strategy package has been fully implemented, tuberculosis case detection rates are high and nearly 80 percent of identified cases have been cured. Fully implementing the DOTS strategy remains a significant challenge, however.

This article reviews the epidemiology of tuberculosis, including the role of HIV in the epidemic, and the social and economic impact of tuberculosis, with a focus on the impact of tuberculosis on women. It also discusses current strategies and lessons learned from efforts to strengthen tuberculosis control activities.

What Is Tuberculosis?

Active tuberculosis disease most commonly affects the lungs (pulmonary tuberculosis) and causes a persistent cough (sometimes with bloody sputum), chest pain, exhaustion,
The DOTS Strategy Package

The DOTS (directly observed therapy, short-course) package consists of five critical components, all of which must be in place in order for DOTS programs to succeed:

- government commitment to sustained tuberculosis control;
- detection of infectious cases (mainly through passive case finding) using sputum-smear microscopy;
- a standardized, short-course chemotherapy (six to eight months), with direct observation of treatment for at least the first two months (see Figure 2);
- a reliable supply of anti-tuberculosis drugs; and
- information systems for monitoring and reporting of cases and outcomes.

Dual Crises: Tuberculosis and HIV

The worldwide tuberculosis epidemic is being accelerated by the HIV epidemic. Because HIV suppresses the body's immune system, HIV-infected persons are at increased risk of infection with tuberculosis, activation of a latent infection, and rapid progression of active disease. Persons with both tuberculosis and HIV infections are 30 to 100 times more likely to develop active tuberculosis than those infected only with tuberculosis.

Tuberculosis is the leading cause of death among persons with HIV infection, accounting for a third of AIDS-related deaths worldwide. In 1997, eight percent (640,000) of tuberculosis cases worldwide were associated with HIV infection. The prevalence of HIV and tuberculosis co-infection is especially high in Africa. In some African countries, more than 50 percent of tuberculosis patients are HIV infected.

The concurrence of the tuberculosis and HIV epidemics presents serious challenges to the prevention and control of both infections. The upsurge in tuberculosis cases worldwide, particularly in countries with a high prevalence of HIV, has overwhelmed tuberculosis control efforts and services.

The interaction between tuberculosis and HIV also complicates the overall management of tuberculosis. HIV-infected persons are less likely to react to a tuberculosis skin test, and chest x-ray results often are nonspecific due to the decline of the body's immune system. In addition, drug-related side effects such as rashes, dizziness, and headaches, which can complicate treatment and reduce patient compliance, are a particular concern in HIV-infected persons.

Tuberculosis Affects Families and Communities

In developing countries, active tuberculosis is primarily a disease of adults in their most productive years (between ages 15 to 59 years). Among women, up to 70 percent of deaths due to tuberculosis occur during childbearing years (ages 15 to 40 years). As a result, the disease can have a profound economic as well as health impact on families and their communities. As the adult wage earner and/or primary household manager becomes too ill to work and requires medical care, families suffer severe consequences.

Tuberculosis also impacts children. WHO estimated that in 1995 more than 180 million children under 15 years of age were infected with tuberculosis, and about 100,000 children die from the disease each year. Very young children, especially those under two years of age, face the highest risk of infection and are at particular risk of tubercular meningitis.

People with tuberculosis face discrimination and rejection in almost all cultures and regions. As a result, many people with tuberculosis, particularly women, deny their diagnosis and delay seeking treatment until the disease has progressed, which increases their risk of death.

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<thead>
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Table 1. Tuberculosis Burden by Region in 1997

night sweats, fever, and shortness of breath. The infection also can disseminate and infect other organs, including the reproductive tract and central nervous system. Active pulmonary tuberculosis is the only form of the disease that is infectious; the bacteria can be transmitted through airborne droplets when the affected person coughs, sneezes, or speaks.

A person with active pulmonary tuberculosis disease will infect an average of 10 to 15 people per year.

Most infected persons with healthy immune systems do not develop active tuberculosis. The risk of developing active disease is highest immediately after primary infection and among people with weak immune systems, (for example, people infected with HIV). Latent tuberculosis infection may persist throughout a person's lifetime without causing symptoms or being transmissible to others. In general, an infected person has a five- to ten-percent lifetime risk of developing active tuberculosis.

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as well as transmission of the disease to others. For example, in the Philippines, some tuberculosis patients choose to say that they have cancer because it is more socially acceptable than tuberculosis.5

Women and Tuberculosis

Worldwide, some 900 million women of reproductive age are infected with M. tuberculosis, and at least 2.5 million develop active disease each year. Tuberculosis is a leading cause of death among women of reproductive age, and accounts for nine percent of female deaths worldwide.16

While tuberculosis appears to be somewhat more common in men than in women, women with the disease often face more barriers to care, and therefore may experience more serious consequences of infection. In some regions, women may be more likely to die from active tuberculosis than men.17 The vulnerability of women with tuberculosis results from various factors, including lower awareness of tuberculosis, lack of financial independence, and/or greater constraints in accessing health care services.18,19

Tuberculosis in women also raises certain reproductive health concerns, including potential treatment effects during pregnancy and infertility from genital tuberculosis (see box on page 4).

The stigma of tuberculosis can be especially severe for women. Unmarried women with tuberculosis often encounter difficulties finding a partner, and married women can be at risk of abandonment. In Pakistan, for example, women who develop tuberculosis are more likely to be divorced or separated, or to be married to a man who takes a second wife, than women who do not have tuberculosis.20

Strategies for Tuberculosis Control

The primary tuberculosis control strategy recommended by the WHO Global Tuberculosis Program and the International Union Against Tuberculosis and Lung Disease is the detection and treatment of infectious (active) cases. Other interventions include childhood vaccination with the Bacille Calmette-Guérin (BCG) vaccine and preventive chemotherapy.21,22 The present global tuberculosis burden underscores the importance of providing sufficient resources to implement appropriate strategies as well as using available strategies more effectively.

Detection and treatment of infectious cases. Identification of cases and provision of prompt, effective treatment are the cornerstones of tuberculosis control. These measures interrupt the cycle of tuberculosis transmission and reduce the future burden of tuberculosis cases. In 1994, WHO endorsed these measures and made them part of the DOTS strategy package (see box on page 2).

When WHO launched the DOTS strategy globally, the goal was to detect 70 percent of all new active (smear-positive) tuberculosis cases and successfully treat 85 percent of these cases by the year 2000. Although programmatic and logistical difficulties have prevented full implementation in all countries, DOTS can be a very effective treatment strategy for controlling tuberculosis.5 Effective DOTS programs are cost-effective and result in
permanent cures of tuberculosis disease, reduced rates of transmission and relapse, and prevention of drug-resistant M. tuberculosis strains (see box on page 5). Fully implemented DOTS programs have recorded an average cure rate of nearly 80 percent (range: 70 to 95 percent) in such varied settings as China, Peru, Vietnam, and Bangladesh. 6

Effective use of the DOTS strategy worldwide remains a major challenge, however. Implementing DOTS is difficult in developing countries, especially in countries without well-organized health care infrastructures. To date, 102 of 212 countries reporting to WHO use the DOTS strategy to some extent (including 21 of the 22 highest-incidence countries), and at least 60 report implementing DOTS programs countrywide. In 1997, however, only 35 percent of the world’s population lived in areas where DOTS programs were working, and only 11 percent of the world’s total estimated cases beginning treatment during 1996 actually were cured under a DOTS program. 23 Lack of financial resources and leadership have been key barriers to DOTS implementation.

Although it is widely agreed that the DOTS strategy represents the essential basic minimum package, there is growing evidence and agreement that the DOTS package alone is not sufficient to control tuberculosis in developing countries, especially in countries with increasing HIV rates. A mid-1990s analysis of rates from 34 countries in sub-Saharan Africa with high HIV prevalence and excellent national tuberculosis programs showed that median tuberculosis case rates were increasing by ten percent per year—only five percent less than in countries with less effective programs. Even in countries with excellent programs and a low HIV prevalence, the median tuberculosis incidence rate still increased three percent each year. 24 These data suggest that additional interventions may be required to further reduce tuberculosis incidence, particularly among underserved and high-risk populations.

**BCG vaccination.** Since its discovery more than 75 years ago, the BCG vaccine has been administered to newborns to prevent tuberculosis infection. 25 Despite its widespread use, the efficacy of the BCG vaccine remains under debate. Most recent studies have shown that childhood vaccination does not prevent tuberculosis disease in adulthood, particularly in areas with concurrent HIV epidemics. 22 The vaccine appears to be effective in preventing leprosy and serious forms of tuberculosis in children, 26 however, and is an important component of many child health programs.

**Preventive chemotherapy.** Preventive therapy involves screening high-risk groups (such as contacts of active cases and HIV-infected persons) for latent tuberculosis infection and treating infected persons as a means of preventing active disease. Treatment generally involves administering various combinations of anti-tuberculosis drugs for six to twelve months. In developing countries, however, the BCG vaccine has been administered to newborns to prevent tuberculosis infection. 25 Despite its widespread use, the efficacy of the BCG vaccine remains under debate. Most recent studies have shown that childhood vaccination does not prevent tuberculosis disease in adulthood, particularly in areas with concurrent HIV epidemics. 22 The vaccine appears to be effective in preventing leprosy and serious forms of tuberculosis in children, 26 however, and is an important component of many child health programs.

Tuberculosis is a major threat to the health of women worldwide. Given that it generally affects women during their childbearing years, tuberculosis has a number of implications for their reproductive health. Listed below are selected issues that can affect the work of reproductive health providers whose clients may have tuberculosis.

- **Tuberculosis and pregnancy.** While limited data about the interaction of tuberculosis, pregnancy, and tuberculosis treatment are available, there is general agreement that the management of tuberculosis during pregnancy and the postpartum period is very similar to that of other patients. The use of isoniazid, rifampicin, and ethambutol in the DOTS regimen carries a minimal risk of fetal abnormalities or additional side effects. The treatment of multidrug-resistant tuberculosis (see box on page 5) and HIV-tuberculosis co-infection requires careful and expert clinical guidance. 14

- **Tuberculosis and contraception.** Rifampicin, a key component of tuberculosis treatment, can reduce the effectiveness of oral contraceptive pills. Contraceptive implants, injectables, and emergency contraceptive pills also may be affected. 27,28 In addition, rifampicin may reduce the effectiveness of anesthetics used for sterilization (female or male) or for other purposes. 29 Women who use oral contraceptives and require rifampicin should be advised to choose another appropriate contraceptive method. Women who are unable to find a suitable alternative to oral contraceptives should take a higher-dose ethinyl estradiol regimen (up to a maximum of 100 µg daily) with shortened pill-free intervals during and for four weeks after rifampicin use. 27

- **Tuberculosis and infertility.** When M. tuberculosis infects the reproductive tract, it can cause genital tuberculosis and subsequent infertility. Genital tuberculosis appears to be an uncommon disease, but its incidence is likely to increase as the tuberculosis epidemic progresses. 30,31 Currently, between five and ten percent of infertility cases in some countries may be linked to genital tuberculosis. 31,32 Diagnosis is difficult, and generally must be presumptive. Prompt treatment of genital tuberculosis (treatment is similar to that for pulmonary tuberculosis) is essential if a woman is to have a chance of retaining her fertility. Even with treatment, fertility rates after genital tuberculosis are low. Achieving a pregnancy only is likely if the infection has been detected at a very early stage, before irreversible tubal or endometrial damage has occurred. 33,34
countries, use of preventive therapy historically has been limited to young infants whose mothers have active tuberculosis and childhood contacts of known cases.35

The resurgence of tuberculosis in HIV-infected people has led experts to consider using preventive therapy as a strategy for tuberculosis control in developing areas with high HIV-prevalence.21,36 WHO and the International Union Against Tuberculosis and Lung Disease have recommended that preventive therapy be included in the care package for persons with concurrent HIV and tuberculosis infections, but they do not recommend this intervention as a control strategy.

The extent to which preventive therapy can reduce the long-term risk of developing active tuberculosis remains unclear. Furthermore, the feasibility of implementing preventive therapy programs in developing countries has been questioned.25,37 Issues that must be addressed include the timing and duration of chemoprophylaxis (six months, one year, or even lifelong regimens have been proposed), the effectiveness of drug regimens, and operational concerns such as methods of delivery and cost-effectiveness.

Developing Effective Tuberculosis Programs

As described above, successful tuberculosis control requires the identification of infectious cases and completion of appropriate treatment by all patients. Effective programs utilize community-based, regional, and national resources to increase tuberculosis awareness among their patients. The following program strategies are important for detecting infectious cases and encouraging effective treatment.

**Identify active cases.** Programs use various approaches to identifying active tuberculosis cases. Passive case finding is performed by diagnosing persons who present at health facilities with symptoms of tuberculosis. Active case finding (screening all persons in a community who may be infectious) is expensive and difficult to implement in low-resource settings.1 Diagnosis generally is performed using sputum-smear microscopy.

Sputum-smear microscopy is less expensive and more practical than other diagnostic tools such as bacterial culture, tuberculin skin test, and chest x-ray, although it is relatively insensitive. Two positive sputum smears generally are required to confirm the diagnosis of tuberculosis.7 Emerging diagnostic tools should help to facilitate this process (see box on page 6). Extending case finding to the community level can enhance program success, but may be difficult due to the need for trained providers to obtain, fix, and stain sputum smears, as well as trained microscopists to read the slides.

Once infectious cases have been identified, treatment must be offered. Patients generally are not hospitalized unless supervision of treatment cannot be guaranteed. Some national tuberculosis programs in Africa hospitalize

**Drug-Resistant Tuberculosis**

Resistance to anti-tuberculosis drugs is a worldwide problem and an increasing threat to tuberculosis control. Of particular concern is the rapid rise of multidrug-resistant tuberculosis (MDR-TB), which is defined as a minimum of resistance to isoniazid and rifampicin. MDR-TB has a case-fatality rate of about 70 percent.11 WHO has identified several “hot zones” where MDR-TB may affect up to 25 percent of all tuberculosis cases. The European region, particularly Eastern Europe, has the world’s highest prevalence of MDR-TB. Other hot zones include Delhi State in India, the Dominican Republic, Argentina, and Côte d’Ivoire.3

Because isoniazid and rifampicin are ineffective against MDR-TB, short-course chemotherapy is rendered useless. Patients with MDR-TB may need to be hospitalized or isolated to prevent transmission of primary drug resistance to others, further adding to the cost of treatment.38 Longer and more intensive treatment interventions—such as a “DOTS-Plus” strategy, which would involve observed treatment for up to two years—are being explored.39 There is concern, however, that increased treatment costs associated with a DOTS-Plus strategy could divert much-needed resources from established DOTS programs, many of which already face implementation challenges.
New Tools for Tuberculosis Prevention and Control

Technological advances in diagnostics, therapies, and vaccines are urgently needed. Faster field diagnostic methods with increased sensitivity are needed both to detect M. tuberculosis and to identify drug resistance. Ongoing research is exploring diagnostic technologies such as simple dipsticks that evaluate blood samples and manipulation of mycobacteria-specific bacteriophages (viruses that infect bacteria) to create culture-based tests.43

There also is a clear need for new anti-tuberculosis drugs and vaccines. Drugs that reduce the frequency and duration of treatment would have a tremendous impact on tuberculosis control by making it easier for both programs and patients to ensure complete treatment.22 Development of an effective vaccine is critical to controlling and ultimately eliminating tuberculosis. During the 1990s, investigators have made considerable progress and have developed numerous potential vaccine candidates representing a variety of approaches.
Bangladesh: A Successful Control Program

With over 260,000 new cases occurring in 1997, Bangladesh has one of the highest tuberculosis rates in the world. In 1984, the Bangladesh Rural Advancement Committee, a local nongovernmental organization, implemented an experimental tuberculosis-control program that relies mainly on community health workers. Local women are recruited from each village and trained to identify persons with chronic (more than four weeks) cough and to treat common illnesses. These community health workers collect sputum specimens and send them to a local laboratory for microscopy. Persons with positive sputum smears who agree to begin directly observed therapy are asked to sign a bond indicating that they will complete treatment and pay a deposit of 200 Taka (about US$5), which is forfeited if they default.

During the initial two months of therapy, the patients come to the community health worker's home daily to receive anti-tuberculosis drugs, which are provided free of charge by the government. During the remaining six months of therapy, the patients receive a week's supply of drugs at a time. At the completion of treatment, 100 Taka is returned to the patient; the remainder is given to the community health worker.

The program was expanded in 1992 and again in 1995, each time increasing its coverage to more thananas (subdistricts). A recent analysis demonstrated a cure rate of over 80 percent from 1992 through 1997, and a default rate of less than three percent. Important factors that led to the success of the program include the involvement and commitment of the community health workers and the community, a reliable supply of free drugs, availability of laboratory services, supportive management, and effective monitoring of treatment progress and outcomes.34,45

Lessons Learned and Conclusion

Tuberculosis is preventable and curable. Its control, however, requires an international public health effort. Experiences worldwide have shown that DOTS is an important tuberculosis control measure and can be effective when implemented intensively and widely, especially in high-incidence countries. Lessons learned from experiences with DOTS include:

- **Integrate tuberculosis services.** Education about tuberculosis and the importance of treatment compliance should be incorporated into other health services whenever possible. For example, collaboration with antenatal services and community-based HIV/AIDS services can provide an entry point for tuberculosis education. Health care workers in these settings have opportunities to identify infectious cases and encourage adherence to tuberculosis treatment.7,19,22

- **Establishment of community-based care.** Tuberculosis patients as well as their families and health care providers. Special efforts should be made to increase tuberculosis awareness among women and those at risk of HIV infection.18,22

- **Collaboration among health providers, community health workers, the community, and families is crucial to the success of any control program.**

- **Integration of tuberculosis services with other health services can increase opportunities for tuberculosis detection and treatment.**

For countries with dual epidemics of tuberculosis and HIV, programs may need to provide additional control services (such as evaluation of contacts of active cases and provision of preventive therapy to high-risk persons) to accelerate the decline of tuberculosis.22 The development of simple, inexpensive diagnostics, alternative treatment regimens (especially less expensive and shorter treatment regimens) and improved vaccines should be explored as ways to improve tuberculosis control efforts.

References
