

**Tuberculosis:
Ancient Foe, Modern Scourge**

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Abbreviations used in this paper:

BCG, bacillus Calmette-Guérin;
CDC, Centers for Disease Control and Prevention;
DOTS, directly observed therapy, short-course;
ELISA, enzyme-linked immunosorbent assay;
ELISPOT, ex-vivo enzyme-linked immunospot;
EMB, ethambutol;
FIND, Foundation for Innovative New Diagnostics;
INH, isoniazid;
IOM, Institute of Medicine;
LTBI, latent tuberculosis infection;
MDR, multidrug-resistant;
NCET, National Coalition for the Elimination of Tuberculosis;
PEPFAR, President's Emergency Plan for AIDS Relief;
PHS, Public Health Service;
PPD, purified protein derivative;
PZA, pyrazinamide;
RIF, rifampin;
RPT, rifapentine;
RVCT, report of verified case of tuberculosis;
SM, streptomycin;
TBESC, Tuberculosis Epidemiologic Trials Consortium;
TBTC, Tuberculosis Trials Consortium;
USAID (United States Agency for International Development);
WHO, World Health Organization

I. Introduction

Tuberculosis and humans have had a long relationship with each other. The relationship has not been a friendly one. Evidence of the disease has been found in Egyptian mummies (Cave, 1939; Zimmerman, 1979) and pre-Colombian mummies in northern Chile (Salo et al., 1994; Arriaza et al., 1995). For centuries, tuberculosis has been a major killer of humans (Dubos and Dubos, 1952). As recently as the 1940s, TB was so common among U.S. healthcare workers that urban medical schools routinely admitted six extra students every year, expecting to lose that many to TB (Rosenthal, 1992). The devastation wreaked by TB stimulated research that led to several medical breakthroughs during the 19th and 20th centuries (Rieder, 1998; Young and Robertson, 1998). The breakthroughs include:

- Identification of the bacillus *Mycobacterium tuberculosis* as the causative agent of TB in 1882 was a key element in the formulation of Robert Koch's principles for the study of microbial infection.
- Calmette and Guérin were pioneers in the field of vaccination with the development in 1921 of bacillus Calmette-Guérin (BCG), an attenuated form of the bovine tubercle bacillus that is still used today in TB vaccines.
- The first randomized, controlled trial in medicine, begun in 1947, tested the effectiveness of streptomycin in treating TB.
- Selman Waksman was awarded the Nobel Prize in 1952 for discovering streptomycin (in 1943) and showing that it inhibited the growth of the tubercle bacillus. Waksman also coined the word "antibiotic."

The control of infectious disease, including TB, is regarded as one of the 10 great public health achievements in the United States in the 20th century (CDC, 1999). Indeed, after 1945, our success in treating infectious diseases, including TB, was so remarkable that in 1969 the Surgeon General of the United States testified to Congress that it was "time to close the book on infectious diseases" (Bloom and Murray, 1992).

However, with the important exception of smallpox, we have not closed the book on infectious diseases. In fact, infectious diseases—not cancer or chronic diseases such as cardiovascular disease—cause the largest number of deaths worldwide. TB is estimated to kill 2 million persons each year, making it a leading cause of adult death in the world (Bloom and Murray, 1992; Raviglione et al., 1995; Dye et al., 1999; Corbett et al., 2003). The resurgence of TB in the U.S. between 1985 and 1992 (CDC, 2003a) was a reminder that while TB is an ancient malady, it is very much a contemporary problem as well—even in industrialized societies and even though we know its cause, how to prevent it, how to treat it, and how to cure it.

A reasonable person might well ask, "If we know the cause of TB, how to prevent it, etc., then what's the deal? Why not just take care of the problem?" Are we unwilling or unable to use the tools that science has given us? Do we need new and better tools? In other words, what more—if anything—do we need to know and do in order to tackle the

global TB epidemic and prevent the resurgence of TB in the U.S. and other industrialized countries?

More than 50 years ago, the microbiologist René Dubos said this about TB (Dubos and Dubos, 1952):

“Tuberculosis is a social disease, and presents problems that transcend the conventional medical approach...Its understanding demands that the impact of social and economic factors on the individual be considered as much as the mechanism by which tubercle bacilli cause damage to the human body.”

In other words, the tubercle bacillus grows in the “social soil” we give it (Draus, 2004, p. 3). If our goal is to control the global TB epidemic, then understanding the social soil in which TB thrives will be just as important as understanding the TB germ itself and how it interacts with the human organism.

This paper will describe (1) the cause, diagnosis, and treatment of TB; (2) the epidemiology of TB in the U.S. and around the world; (3) the biology of TB and what we need to know about the biology of the tubercle bacillus and the disease it causes in order to develop tools that will enable us to respond more effectively to the global epidemic; and (4) the policies that support the control and prevention of TB in the U.S. and around the world. The reader should see the following papers for recent reviews of the global epidemic (Frieden et al., 2003), the epidemiology of TB in the U.S. and around the world (Iademarco and Castro, 2003), and the need to develop and use new tools (Paluzzi and Kim, 2003). For comprehensive books about TB see Reichman and Hershfield (2000) and Iseman (2000).

II. Tuberculosis as a Disease

Cause of Tuberculosis Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*, also known as the tubercle bacillus or TB germ. The disease can affect any part of the body—except, as a public health nurse once said, hair and teeth—but in 85% of cases, it affects the lungs. The disease is transmitted from one person to another when a person with active pulmonary (in the lungs) TB coughs, speaks, or sings and exhales droplets of moisture containing live TB germs. As the water in these droplets evaporates, microscopic “droplet nuclei” form; the droplets can be inhaled into the deepest recesses of the lungs of another person. Transmission typically requires extended indoor contact with a person with active pulmonary TB, as TB germs are killed by the ultraviolet light in sunlight. (To learn more about the material described in this section, see *Core Curriculum on Tuberculosis: What the Clinician Should Know*; CDC, 2000a).

The consequences of exposure to TB germs are summarized in Figure 1.

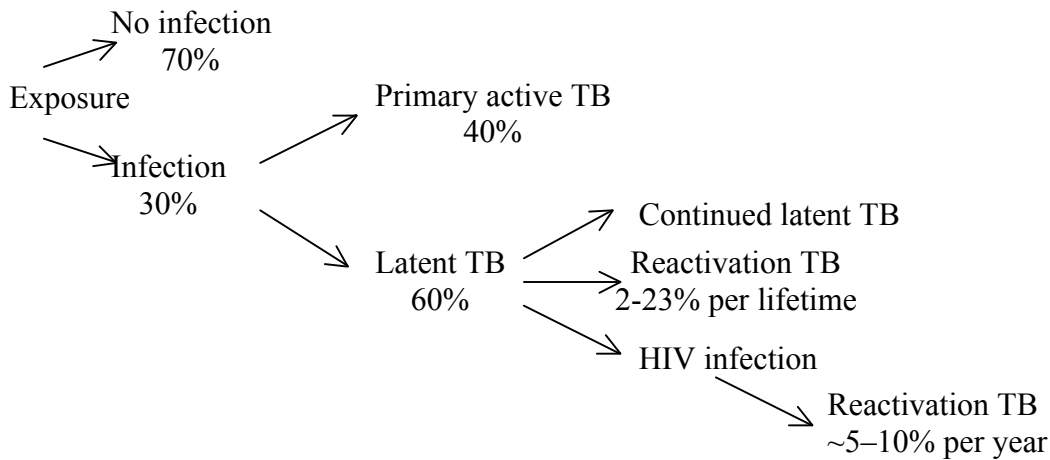


Fig. 1. Outcomes associated with exposure to *Mycobacterium tuberculosis* (after Fig. 1, Parrish et al., 1998)

Only 30% of exposed individuals are infected, and only about 40% of infected individuals develop primary active TB. Most (60%) infected individuals develop a latent TB infection (LTBI). A person with LTBI has no symptoms and cannot infect others despite having living TB germs in his/her body. LTBI can progress (reactivate) to active TB, especially if the immune system is compromised, e.g., by HIV infection. Drug treatment can cure active TB and reduce the chance of progressing from LTBI to active TB.

Response to a Case of Active TB A person with active TB is sick—and knows it. Symptoms typically include fever, chills, night sweats, appetite and weight loss, and easy fatigability. If the person has pulmonary TB, the symptoms will likely include having a prolonged, productive cough; chest pain; and hemoptysis (production of sputum containing blood). In order to determine whether a person with these symptoms had active TB, a medical evaluation is performed. Such an evaluation includes a Mantoux tuberculin skin test (intracutaneous injection of PPD (purified protein derivative, which is prepared by ammonium sulfate precipitation of tuberculin, a sterile filtrate of cultured *M. tuberculosis*; Davis, 2000), a chest X-ray, collection of sputum for microscopic inspection for tubercle bacilli, culturing of sputum to determine whether the TB germ is present and, where appropriate, culturing the bacteria to determine their pattern of susceptibility to TB drugs. Genotyping (DNA fingerprinting) is often performed to identify the particular strain of the TB germ growing in the patient.

The “gold standard” of TB diagnosis is identification of the TB germ after culturing it and growing sufficient quantities for analysis. However, culturing the TB germ is expensive and slow (weeks) and requires technical facilities that are often unavailable in developing countries. Thus, diagnosis is often based on a test for “acid-

fast” bacteria in a sputum smear (made by smearing sputum on a microscope slide). The requirements for this test are a compound light microscope, a few reagents, and skilled personnel who can perform the test and identify acid-fast bacteria in the stained smear.

Contact Investigation The report of a case of active TB in the U.S. (and other low-burden countries) launches a contact investigation, the objective of which is to identify persons who may have been infected by the index case (the first case identified in a given locale at a given time).

A contact investigation begins with an interview in which the healthcare worker ask the patient to identify his/her “contacts,” i.e., persons with whom the patient has spent time and thus whom the patient may have infected (or who may have infected the patient). Beginning with those persons with whom the patient has had the most contact—i.e., family members, co-workers—public healthcare workers track down the contacts and counsel them about their possible infection.

Contacts are encouraged to have a tuberculin skin test. Some contacts will test negative, others positive. Individuals with recent contact may have to be re-tested after several weeks. Individuals who have a positive skin test are candidates for follow-up tests—chest X-ray, etc.—to determine whether they have active tuberculosis. All individuals with a positive skin test are further evaluated for appropriate therapy, whether for latent infection or active disease.

The traditional “shoe leather” approach to contact investigations—described above—has recently been aided by the tools of molecular epidemiology (Small et al., 1994; Murray and Nardell, 2002).

In 2003, the contact investigation scenario played out in the U.S. more than 14,871 times (the number of reported cases of active TB; CDC, 2004a). It requires a robust infrastructure that has:

- Healthcare workers with appropriate technical training and, increasingly, with cross-cultural training to work with foreign-born patients,
- A network of laboratories with the technical staff and equipment needed to deliver timely, accurate results,
- An information management system that enables timely reporting of cases, the management of individual cases and contact investigations, and the evaluation of program performance, and
- Educational and training materials for healthcare providers, patients, and the community at large.

Treatment New recommended treatment regimens for active TB were published in 2003 (American Thoracic Society et al., 2003). The recommendations include eight regimens for tuberculosis caused by drug-susceptible organisms, with additional recommendations for special situations, e.g., patients with HIV infection, children, pregnancy, and hepatic disease. The preferred regimen for treating active TB is combination drug therapy for six

months, with four drugs—isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin (SM)—given for an eight-week initial phase and two drugs—INH and RIF—given for a 16-week continuation phase. The drugs used in the regimen are adjusted when the results of drug-susceptibility tests are known.

Patient compliance with this treatment can be a problem for several reasons: the regimen requires the patient to take many pills for a long time; the drugs may cause side effects; and the patient usually begins to feel much better after taking the drugs for a few weeks. However, failure to complete the regimen can lead to a relapse and the emergence of drug-resistant organisms. Thus, TB healthcare workers need to develop an acknowledged, patient-centered treatment plan to ensure the completion of therapy. This approach typically involves 6–9 months of directly observed therapy in which an outreach worker watches as the patient takes each and every dose of medication.

The most commonly used regimen for LTBI involves one drug (INH) taken for 6–9 months (CDC, 2000a).

The treatment of a case of active TB has both a medical objective (it cures the patient) and a public health objective (it stops transmission of the disease within the community). The treatment of a case of LTBI also has both a medical objective (it reduces the patient’s chances of ever developing active TB) and public health objective (by preventing future cases of active TB and thus the possibility of transmitting the disease to others).

Summary Two keys to successful TB control are: (1) the prompt diagnosis and treatment of cases of active TB; and (2) the use of contact investigations to identify and treat persons infected with the tubercle bacillus. The successful use of these strategies, together with the implementation of infection control measures in congregate settings in which transmission can occur—hospitals, long-term care facilities, homeless shelters, and prisons and jails—will reduce the incidence of TB in a community.

III. TB in the United States

Definitions Active TB is a reportable disease in the U.S. and leads to a “Report of a Verified Case of Tuberculosis (RVCT),” which is submitted to the Division of TB Elimination (Center for HIV, STD, and TB Prevention, CDC). Each year the CDC publishes an extensive summary of TB epidemiology in the U.S. during the previous year (CDC, 2003a). The two parameters of most interest for our discussion are “number of cases” (based on RVCTs; also known as the “incidence”) and “rate” (the number of reported cases per 100,000 population; also known as the incidence rate).

Decline and resurgence National reporting of incident TB cases in the U.S. was fully implemented in 1953, when the number of cases was 84,304 and the rate was 53.0 (Iademarco and Castro, 2003). In the years after 1953 (and surely in the years before 1953, though the records are not as complete for the earlier period), the incidence and

rate of TB declined steadily in the U.S. (Institute of Medicine, 2000; CDC, 2004a). In 1959, the following words appeared in a report from a conference organized by the Public Health Service (PHS) and the National Tuberculosis Association (now the American Lung Association) at Arden House in Harriman, NY (United States Public Health Service, 1960):

“Tuberculosis can be extinguished as a public health problem...If the opportunity to end tuberculosis is not seized now, it may be lost indefinitely.”

The conference had been organized to advise the PHS on how to use available resources to accelerate the decline of tuberculosis in the U.S. The conferees had every reason to forecast the demise of TB in the U.S. They were buoyed by the evident success of the (then) new combination drug therapy, rapidly declining TB morbidity and mortality, and robust categorical (i.e., targeted) federal funding for TB prevention and control activity. In fact, the incidence and rate of TB continued to decline at a rate of 5% to 6% per year for most of the next 26 years and reached a low of 22,201 cases and a rate of 9.3 in 1985.

However, in the mid-1980s, the trend toward elimination was reversed and the nation experienced a resurgence of tuberculosis for several years, with a 20% increase in reported cases between 1985 and 1992 (26,673 cases; rate, 10.5). In 1992, a series of front-page articles in the *New York Times* heralded the re-emergence of TB as a threat to the public's health in the U.S. Dr. Lee Reichman—then President of the American Lung Association and currently the Executive Director of the New Jersey Medical School National Tuberculosis Center—said of our failure to prevent and cure TB, “We should be ashamed.” (Specter, 1992).

The Arden conferees did not foresee events that would make their declaration appear, in hindsight, to be prophetic indeed. The U.S. did not seize the opportunity it had in 1959 to extinguish TB as a public health problem. By the early 1970s, federal policymakers, convinced by years of steady decline in incidence that TB had become a “disease of the past,” no longer gave states funds targeted for TB control but gave them instead “block grants” and let the states decide how to spend the money. Given the steady decline in TB rates for many years and given the competing demands for funding for other public health problems, states began to provide less money for TB control. The result was a slow but steady deterioration of the public health infrastructure needed to prevent and control TB, including the closing of chest clinics in cities across the nation.

The Arden conferees and federal and state policymakers did not anticipate the emergence of HIV/AIDS, increased rates of immigration, and a host of socioeconomic problems—including increases in homelessness, injection drug use, and rates of incarceration—that would create fertile soil for the re-emergence of tuberculosis as a serious public health threat in the U.S. in the 1980s. Or, as Paul Draus (2004, pp. 55–56) puts it:

“When the fuels accumulated (poverty and inequality), the winds picked up (AIDS, homelessness, immigration), and the fire crews withdrew (cutting of public health and social welfare programs), TB was fanned into a flame...”

Causes of the Resurgence of TB in the U.S. Experts have identified five factors that led to the resurgence of TB in the U.S. (Bloom and Murray, 1992; Iademarco and Castro, 2003). The first factor was the deterioration of the infrastructure necessary for TB control and prevention. Thus, when TB began to re-emerge in the U.S. in the mid-1980s, the nation was ill prepared to respond (Brudney and Dobkins, 1991).

The second factor was the emergence of HIV/AIDS, which weakens the immune system and makes persons particularly susceptible to *M. tuberculosis* (Selwyn et al., 1989; Daley et al., 1998; Small and Fujiwara, 2001; Corbett et al., 2003). HIV-seropositive individuals who are newly infected with *M. tuberculosis* are more likely to progress rapidly to active TB; and HIV-seropositive individuals with LTBI are more likely to progress from LTBI to active TB. Moreover, because the clinical manifestations of TB are unusual in HIV-seropositive individuals, there may be delays in diagnosis and thus increased opportunity for transmission to others (CDC, 2000a; de Jong et al., 2004).

The third factor was the immigration to the U.S. of persons from countries with high TB burdens. In 1986, when the CDC first began recording “country of origin” of TB cases, 22% of all reported cases were among foreign-born persons. The proportion of cases among foreign-born persons rose steadily after 1986 and surpassed 50% in 2002 (CDC, 2003a). The countries of birth for the largest number of immigrants are Mexico (25% of all foreign-born cases), Philippines (11%), Vietnam (8%), India (7%), and China (5%).

The fourth factor was the transmission of TB in congregate settings such as homeless shelters, long-term care facilities, jails/prisons, and hospitals. Social problems—and structural violence—in the U.S. contributed to large increases in the populations of homeless shelters and jails/prisons in the 1980s, leading to crowding in these facilities. In addition, inadequate infection control practices in all these congregate settings led to increased transmission of TB.

The fifth factor was the occurrence of drug- and multidrug-resistant (MDR) strains of *M. tuberculosis*. (Multidrug-resistant organisms are, by definition, resistant to both INH and RIF.) Persons with MDR TB may remain infectious for a longer period of time, especially if their drug resistance is not diagnosed in a timely manner, and will thus transmit their infection to more people. Moreover, drug-resistant TB may require up to 24 months of treatment with second-line drugs. These drugs are less effective, more expensive, and have greater side effects than first-line drugs used to treat drug-susceptible TB.

Responses to the Resurgence At the same time that TB was resurging in the U.S., the CDC’s Division of TB Elimination was preparing “A Strategic Plan for the Elimination of Tuberculosis in the United States.” The optimistic goal of the plan was to eliminate

TB in the U.S., defined as less than 1 case per 1 million population. This report was finally published in 1989 (CDC, 1989), by which time the historic decline in TB rates had reversed. Nevertheless, the plan was timely in that it provided a strong rationale for increased federal funding for TB control. Substantial increases in funding were needed to rebuild the infrastructure that had been allowed to crumble during the nearly 10-year period when categorical funding for TB control was zero. The nation lacked the trained professionals, laboratories, and organizational capacity it needed to respond swiftly to the emerging epidemic.

Federal funds to the CDC for TB control activities increased 3.7-fold between 1990 and 1994 (in real dollars, adjusted to 1990 \$). Since 1994, federal funding has been steady in actual dollars but has decreased 27% in adjusted dollars (National Coalition for the Elimination of Tuberculosis, 2004).

The increase in funding has enabled the CDC and state and city public health departments across the nation to regain control of TB. Since 1993, the number of cases and the rate of TB have decreased every year to new historic lows of 14,871 cases and a rate of 5.1 (CDC, 2004a). Several other consequences of increased funding include the following (CDC, 2003a): (1) The proportion of cases treated by DOT increased from 21.7% in 1993 to 52.5% in 1999; (2) The proportion of patients receiving the recommended four-drug regimen increased from 40.9% in 1993 to 80.2% in 2002. (3) From 1993 to 2002, the number of cases resistant to INH decreased from 1,565 to 851, and the number of cases resistant to both INH and RIF decreased from 485 to 136. (4) The proportion of reported TB cases with HIV test results increased from 30% in 1993 to 49% in 2001. All of these indicators suggest that the infusion of federal funding has revitalized TB control in the U.S. (Frieden et al., 1995; McKenna et al., 1998).

TB control and prevention in the U.S. in recent years has also been guided by several other documents, including the following: *Ending Neglect: The Elimination of Tuberculosis in the United States*, a report from the Institute of Medicine (2000); “CDC's Response to Ending Neglect: The Elimination of Tuberculosis in the United States” (CDC, 2003b); and “Federal Tuberculosis Task Force Plan in Response to the Institute of Medicine Report, *Ending Neglect: The Elimination of Tuberculosis in the United States*” (Federal Tuberculosis Task Force, 2003).

Persisting Problems The 14,871 reported cases of tuberculosis in 2003 were only the tip of an iceberg. Ten million to fifteen million persons in the U.S. have LTBI. They have been infected with the TB germ but have no symptoms and cannot spread the disease to others; however, a substantial proportion of them will eventually develop active TB unless they are treated. Some populations are at higher risk, e.g., individuals who are co-infected with both the TB germ and HIV. If left untreated, persons with LTBI represent more than one million future cases of TB.

Because the probability of progressing from LTBI to active disease can be reduced 90% by chemotherapy, the CDC recommends treating persons with LTBI (CDC, 2000b). However, because it is inefficient to screen populations in which the incidence

of LTBI is low, the CDC and the Institute of Medicine recommend a strategy of *targeted testing*, in which only populations at high-risk for LTBI are tested. Such high-risk groups, which are defined epidemiologically, include persons who were recently infected with TB; homeless persons; inmates of prisons and jails; persons with HIV/AIDS; and recent immigrants and refugees from countries with high TB burdens (CDC, 2000b). Some TB control programs, universities, and colleges now use a “risk assessment questionnaire” to determine which persons should be given a TB skin test—instead of requiring that everyone, e.g., all new students, be tested (Gounder et al., 2003; Koppaka et al., 2003). Such targeted testing uses limited resources more efficiently.

The CDC also recommends targeted testing of a high-risk population, e.g., persons at a homeless shelter, *only* if a plan is in place to provide treatment for those persons who have a positive TB skin test and who will benefit from treatment for LTBI (CDC, 2000b). In the absence of such a treatment plan, there is no obvious reason to perform the tests.

In offering treatment to a person with LTBI, a healthcare provider is asking someone who is not sick—has no signs or symptoms of TB and cannot spread the disease to others—to embark on a treatment regimen that lasts (typically) 9 months, may cause side effects, and will only reduce, not eliminate, the chance of ever developing active TB. As you might imagine, many persons decline such treatment.

Nevertheless, targeted testing and treatment of LTBI can be an effective means for speeding the decline of TB in the U.S. Regrettably, recent budget reductions have reduced the ability of the CDC to support these activities (National Coalition for the Elimination of Tuberculosis, 2004).

A second persisting problem facing TB control in the U.S. is the ethnic disparity in the incidence of TB. Black, non-Hispanic persons continue to have a disproportionate share of TB cases in the U.S. The rate of tuberculosis in blacks in 2002 was 12.6 cases per 100,000 population, compared to 1.5 cases per 100,000 population in white, non-Hispanic persons, resulting in a black:white ratio of 8.4 (CDC, 2003a). The proportion of TB cases in African Americans is even greater if only TB cases occurring in U.S.-born persons are examined. In 2002, there were 7,296 cases reported in U.S.-born persons, 48% of all TB cases in the U.S. Of those cases in U.S.-born persons, 3,387 occurred in black, non-Hispanic persons, representing 47% of all U.S.-born cases.

Although rates of TB in both blacks and whites have declined substantially over the past decade, the disparity remains. It is a legacy of poverty, racism, and poor access to healthcare. To close the gap, increased efforts must be made to eliminate TB in African Americans in the U.S. In the process of eliminating this disparity, we may be able to develop strategies we can use to address other racial and ethnic health disparities.

Efforts to address this disparity began with a focus on seven southeastern states: Alabama, Arkansas, Georgia, Louisiana, Mississippi South Carolina, and Tennessee. TB rates in these states have been consistently above the national average; more than half of

the TB cases in these states occur in blacks. Improved understanding of racial disparities for TB in these states will provide essential information that can guide efforts to reduce the disproportionate impact of TB on blacks. However, the disparity in TB rates in African Americans is a national, not a regional, problem. Thus, the Division of TB Elimination is also working with partners in other parts of country on projects to address the disparity.

Preventing and controlling TB in foreign-born persons is another persistent problem, because additional resources are needed to work with this population. For example, in Minnesota, where 76% of the TB cases are in foreign-born persons, the current caseload of active TB cases includes persons from 25 countries of origin, representing 20 different languages spoken. Serving such a diverse population poses formidable challenges to local health departments and clinicians, especially in rural areas of Minnesota, where more than 20% of Minnesota's TB cases occur. The challenges include providing not only interpreter services but also healthcare workers with cross-cultural training who can work effectively with patients and their families and with community-based organizations that address the medical and other needs of immigrant and refugees.

Summary The incidence and incidence rate of TB in the U.S. have declined for the past 11 years. This success has been made possible by increased federal funding, which reinvigorated the public health infrastructure that supports TB control and prevention. Once again TB is retreating into segments of U.S. society—e.g., ethnic minorities and immigrants—that are more difficult to reach and treat. In addition, the pool of persons with LTBI, if left untreated, will continue to generate new cases of active TB. Given the increase in the proportion of cases in the U.S. among foreign-born persons, the U.S. can reduce its TB burden by engaging in global TB control.

IV. The Global TB Epidemic

The TB “mini-epidemic” in the U.S. (and other industrialized nations) in the 1980s and 1990s pales in comparison to the raging global TB epidemic. The WHO estimates that there were 8.8 million new cases of TB in 2002 (incidence rate = 141) and 1.8 million deaths due to TB (WHO, 2004a). Nearly one-third of the world's population—two billion persons—are infected with the tubercle bacillus (they have LTBI; Corbett et al., 2003). In 1993, to heighten public and political awareness of the epidemic, the WHO declared TB to be a global health emergency.

Fuelled by HIV/AIDS and poverty, the global TB epidemic is growing, not shrinking. Its scope and scale—and the human suffering it causes—are beyond imagination. Thus, while it was the TB epidemic in the U.S. that roused U.S. policymakers, it is the global epidemic that has their attention now. And it is the global epidemic that drives scientists and physicians in their search for new drugs, vaccines, and diagnostic tools to fight the disease. It is the global epidemic that drives public health workers in their search for better ways to use existing tools and to exploit new ones.

The largest number of cases are in Southeast Asia, with India alone accounting for

20% of all cases in 2002 (WHO, 2004b). However, the incidence rate in sub-Saharan Africa, 350 cases per 100,000, is higher than that in Southeast Asia (Fig. 2). The estimated TB incidence rate is much higher in several countries in sub-Saharan Africa: Botswana (657), Lesotho (726), Namibia (751), Swaziland (1,067), Zambia (668), and Zimbabwe (683). Twenty-two high burden countries account for 80% of TB incidence (Fig. 3; WHO, 2004b).

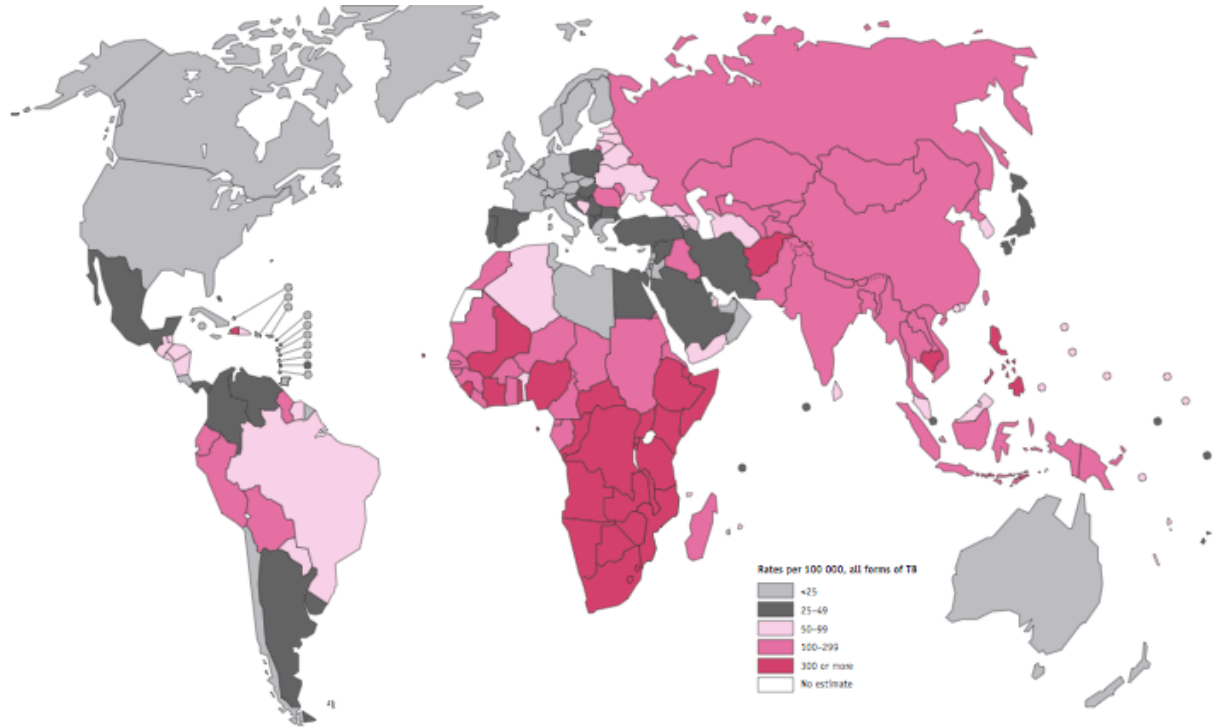


Figure 2. Estimated TB incidence rates, 2002 (WHO, 2004b).

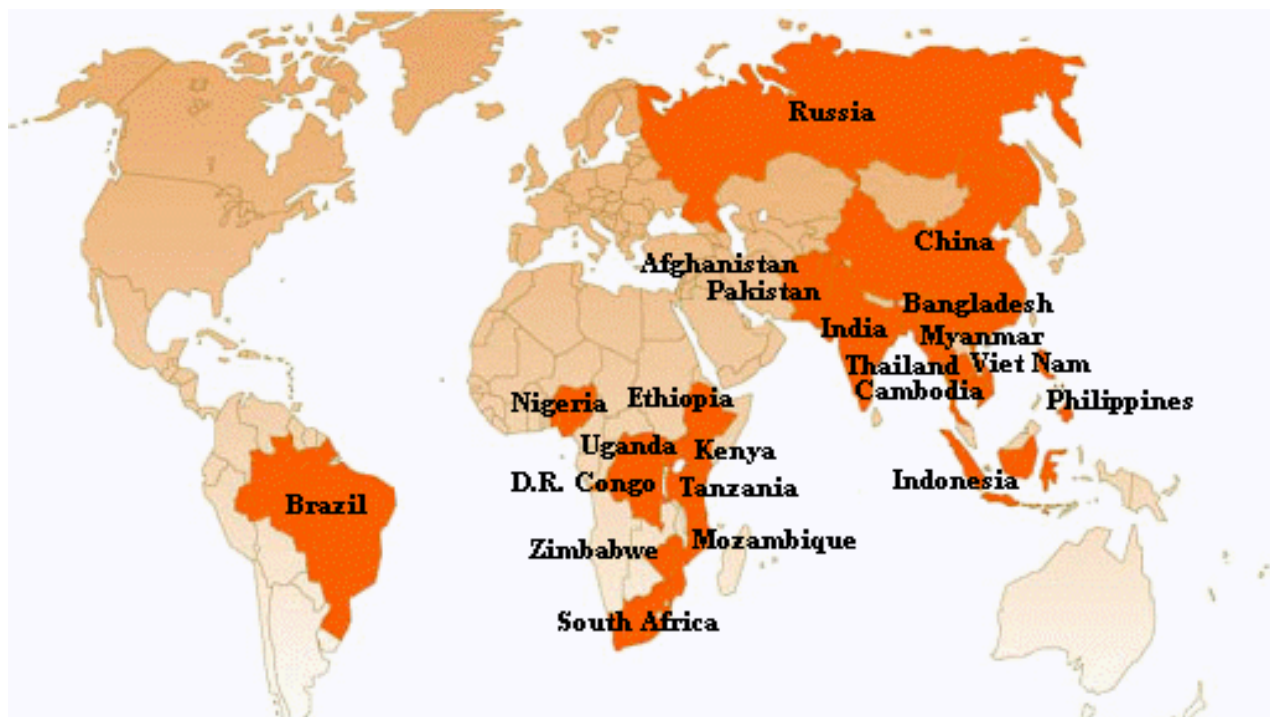


Figure 3. The 22 High-Burden Countries (Stop TB Partnership, 2004).

The DOTS Strategy In 1991, the World Health Assembly (WHO, 1991) established the following global targets for TB control by the year 2000: to detect at least 70% of all infectious (sputum-smear-positive) cases and to cure at least 85% of those detected.

The WHO-recommended strategy for reaching the detection and cure targets is DOTS—Directly Observed Therapy Shortcourse. DOTS has also functioned as a “brand name” and marketing tool for WHO (when printed in lower case letters and upside-down, “dots” reads as “stop,” as in “stop TB”).

The DOTS strategy has five points, or elements (WHO, 2004c):

- Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services,
- Standardized treatment regimen of six to eight months for at least all sputum smear- positive cases, with directly observed therapy (DOT) for at least the initial two months,
- A regular, uninterrupted supply of all essential anti-TB drugs,
- A standardized recording and reporting system that allows assessment of treatment results for each patient and of the TB control program performance overall, and
- Political commitment.

The last element—political commitment—is crucial, for without government commitment, the first four elements of the strategy will not work. Political commitment is needed to build and maintain a public health infrastructure, which, in the case of TB, means a trained workforce that can perform sputum-smear microscopy, deliver drugs to patients, and keep records and prepare reports. Infrastructure also includes tools—for example, light microscopes—needed to perform these tasks.

The DOTS strategy has been enormously successful in some settings, for example Peru (Suarez et al., 2001). However, by the end of 2001, only 15 countries had met the targets for detection and cure; the only high-burden country to have reached the targets was Vietnam (WHO, 2003a). Thus, in 2001, the date for reaching the detection and cure targets was re-set from 2002 to December, 2005. Now it appears that the goals will not be met by 2005 either (Sharma, 2004). WHO Director-General, Lee Jong-wook, announced in March 2004 at the Stop TB Partners’ Forum in Delhi, India, that while treatment is successful in 82% of cases, only 37% of smear-positive cases were detected in 2002. He added, “Although this reflects a big advance over last decade, it also means that a tremendous effort is needed for the coming twenty-one months.” (Lee, 2004; WHO, 2004b).

The DOTS strategy has its detractors. For example, Médecin Sans Frontières (MSF) points out that the DOTS strategy overemphasizes patients with smear-positive TB and thus pays too little attention to patients with smear-negative pulmonary TB and to patients with extrapulmonary TB (Sharma, 2004). Moreover, some countries have adopted the DOTS strategy in principle but only partially in practice (Elzinga et al., 2004). Nevertheless, the approach of the WHO and others involved in global TB control has not been to scrap the DOTS strategy but rather to identify constraints that have limited and continue to limit the effectiveness of the strategy (Elzinga et al., 2004).

Co-epidemics of TB and HIV/AIDS The global TB epidemic is being fuelled by the HIV/AIDS epidemic (Bloom and Murray, 1992; Corbett et al., 2003). The prevalence of HIV in adult (15 to 49 years old) cases of TB in 2000 was estimated to be 11%. Nine percent of all new TB cases in adults in 2000 were attributable to HIV, and 12% of deaths from TB were attributable to HIV (Corbett et al., 2003). The co-incidence of TB and HIV is highest in several countries in sub-Saharan Africa, where more than 50% of cases of TB in adults (15 to 49 years old) are co-infected with HIV (Fig. 3). The National Intelligence Council predicted in 2002 that the incidence of HIV/AIDS will increase significantly in the next few years in the following populous, strategically important countries: Nigeria, Ethiopia, India, China, and Russia (National Intelligence Council, 2002). Such a rise in the incidence in the prevalence of HIV/AIDS will fuel a rise in the incidence of TB, just as it has elsewhere.

The devastating effect of HIV/AIDS on the immune system is well known. Not so well known, however, is that TB and HIV interact synergistically (de Jong et al., 2004), “each increasing the pathogenicity of the other” (Sanduzzi et al., 2001). Persons infected with HIV progress more rapidly to active TB following infection with *M. tuberculosis*, and persons with LTBI are more likely to progress to active TB if they are also infected with HIV (Parrish et al., 1998). At the same time, *M. tuberculosis* increases the production of HIV virions (Sanduzzi et al., 2001). The two diseases have, as a result, been called “the cursed duet” (Sanduzzi et al., 2001). Moreover, due to drug-drug interactions between rifamycins and some antiretroviral drugs, some TB treatment regimens are not recommended for patients co-infected with HIV (American Thoracic Society, 2003).

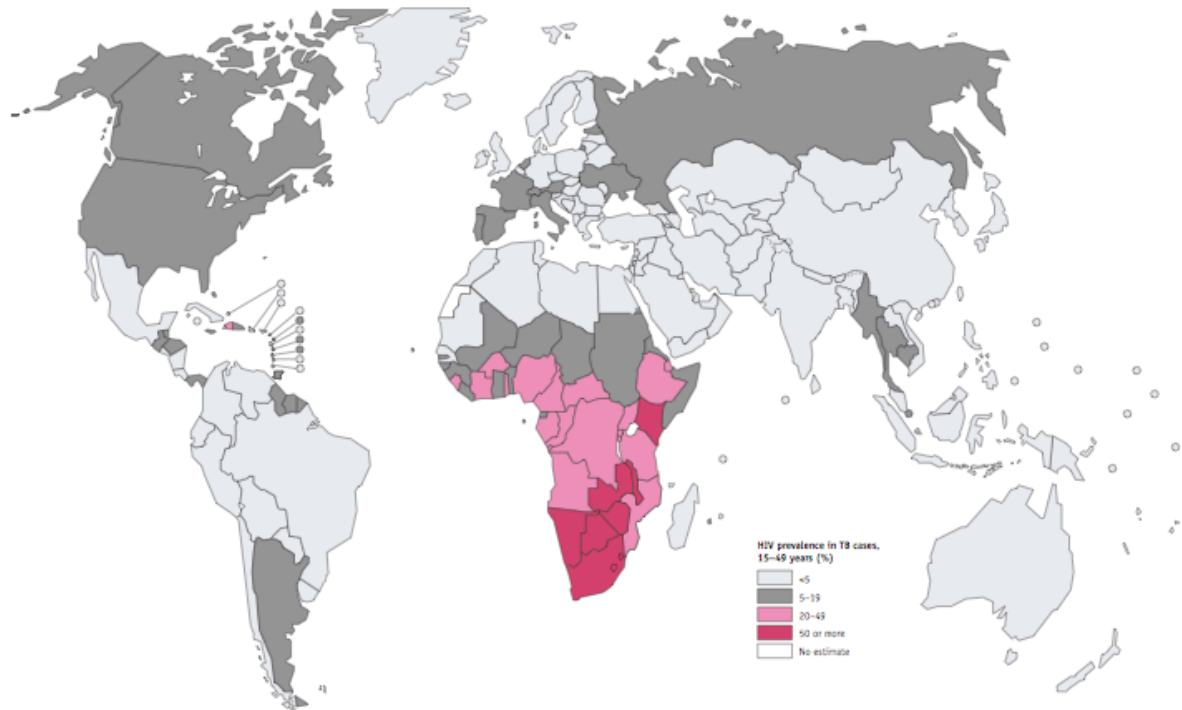


Figure 3. HIV Prevalence in TB Cases, 2002. The highest prevalence is in sub-Saharan Africa, where more than 50% of cases of TB in adults (15 to 49 years old) are HIV-positive (WHO, 2004b).

A recent analysis of the interactions between TB and HIV/AIDS control programs stated, “For many years efforts to tackle TB and HIV have been largely separate despite overlapping epidemiology.” (Anderson and Maher, 2001). This separation has resulted not only in inefficiencies in healthcare delivery in settings that can ill afford such inefficiencies but has also caused healthcare providers to miss opportunities to prolong life, relieve suffering, and simultaneously address both the TB and HIV epidemics. However, policymakers have finally begun to address this grievous, wasteful situation with evidence-based solutions.

For example, because TB is a major cause of morbidity and mortality in patients with HIV, it seems reasonable to promote HIV counseling and testing of all TB patients. Moreover, established DOTS programs could provide integrated treatment for both TB and HIV/AIDS (Friedland et al., 2004). Christopher Dye and his colleagues have used mathematical modeling to suggest that antiretroviral drugs can be effective tools in TB control by enhancing the treatment of TB (Williams and Dye, 2003).

Multidrug-resistant TB Drug resistance can be *primary* or *secondary*. Primary drug resistance occurs when a person is initially infected with tubercle bacilli that are drug-resistant; secondary drug resistance emerges during treatment. The causes of secondary drug resistance are numerous. They include failure of the healthcare provider to prescribe an appropriate treatment regimen (Mahmoudi and Iseman, 1993); failure of the patient to take *all* medications (i.e., to comply with the treatment regimen); and poor

quality of the drugs (low bioavailability).

The new TB treatment guidelines place the responsibility for patient compliance squarely on the shoulders of the healthcare provider (American Thoracic Society et al., 2003). Thus, the existence of drug-resistance, whether primary or secondary, is a red flag for a dysfunctional healthcare system. The dysfunction may lie with individual providers and/or with the system as a whole (Reichman and Tanne, 2002). Of course, the genetic mutations that express themselves as drug resistance occur spontaneously, but it is we humans who establish the conditions that select for drug resistance.

Tubercle bacilli can be resistant to any one of the many anti-TB drugs (*monoresistance*) or to more than one. However, in the world of TB control, the term “*multidrug-resistance*” is reserved for organisms that are resistant to at least INH and RIF, the two most effective anti-TB drugs (CDC, 2000a). *Superstrains* are resistant to at least three of the four first-line drugs.

Christopher Dye and colleagues estimated that 273,000 new cases of MDR TB occurred in 2000 (Dye et al., 2002). The report “Anti-Tuberculosis Drug Resistance in the World” estimated an incidence of 300,000 new cases each year (WHO, 2004d), 79% of them being superstrains. The WHO report was based on surveillance data from 77 settings and represented only one-fifth of the global total of smear-positive TB cases. According to leader of the WHO study, Dr. Mohamed Abdel Aziz, “The true burden is unknown. The more we survey, the more multi-drug-resistant TB we find” (McNeil, 2004). In other words, the drug-resistance problem may be much bigger than the estimates.

MDR TB was present in all 77 settings and countries, but its prevalence ranged from 0% in some Western European countries to 57.1% in Kazakhstan, one of the global hotspots of MDR TB. “The former Soviet Union is the MDR-TB capital of the world—incidence is 10 times that elsewhere,” said Stop TB’s Paul Nunn (Brown, 2004; see also Reichman and Tanne, 2002, and Cox et al., 2004). The prevalence is also high in the Chinese provinces of Henan and Liaoning; Ecuador; and Israel (presumably among immigrants from the former Soviet Union).

MDR TB is a serious problem for TB control not only because its presence is an indicator of a dysfunctional healthcare system. “Treating normal TB costs less than US\$10 a month, but for MDR-TB that figure is between \$500 and \$6000,” said Dr. Mario Raviglione, the Director of Stop TB (Brown, 2004). Moreover, the results of drug-susceptibility studies of tubercle bacilli isolated from patients may not be available for two to three months in underdeveloped countries. During that time, the patient may be given drugs to which the bacilli are resistant; such patients will continue to be sick and infectious. Even worse, if the prescribed regimen contains only one drug to which the bacilli are susceptible, the situation is ripe for the emergence of resistance to that drug as well. This is the so-called amplifier effect, which “amplifies” the resistance of the bacilli to yet another drug. Finally, second-line drugs are much more toxic and less effective than first-line drugs; thus, they must be administered for much longer than six

months—18–24 months (CDC, 2000a).

Christopher Dye and colleagues (2002) recommended a three-part response to MDR TB:

- widespread implementation of SCC [shortcourse chemotherapy] as the cornerstone of good tuberculosis control,
- improved resistance testing and surveillance, and
- the careful introduction of second-line drugs after a sound evaluation of cost, effectiveness, and feasibility.

The first recommendation, in effect, endorses the DOTS strategy. Effective use of the DOTS strategy is the best available method to prevent the emergence of secondary drug resistance. The second recommendation, however, underscores the fact that diagnosis by sputum-smear-microscopy—an element of the DOTS strategy—is an incomplete diagnosis in a setting in which MDR TB is present. A complete diagnosis in such settings must include drug-susceptibility testing, and the results of such tests must be made available as soon as possible.

The third recommendation translates a proper diagnosis into an appropriate treatment regimen. Despite the difficulty in treating MDR TB, several studies have shown that it can be done, even in resource-poor settings (Farmer et al., 1999; Farmer et al., 2000; Tahaoglu et al., 2001; Suarez et al., 2002; Mukherjee et al., 2004). A key element in addressing the epidemic of MDR TB is the WHO's DOTS-Plus initiative, which builds on the five elements of the DOTS strategy but also takes into account specific issues, such as the use of second-line anti-TB drug (WHO, 2004e).

To ensure that second-line drugs are used properly and to make these expensive drugs available in poor-resource settings, the WHO formed The Greenlight Committee. This committee functions as a technical review panel that receives applications from countries seeking to buy second-line drugs. If the committee can be assured that an applicant country will use the second-line drugs without generating resistance to yet more drugs, the committee validates the proposal and sends it on to the “Working Group on DOTS-Plus for MDR-TB,” a body established by the WHO and its international partners. The Working Group has negotiated with the pharmaceutical industry to provide second-line drugs at low cost for projects approved by the Greenlight Committee (see also Gupta et al., 2001).

Public-private Partnerships and the Global Epidemic Numerous public-private partnerships were formed during the latter half of the 1990s to overcome the failures of the global health system (Buse and Walt, 2000a, b; Buse and Waxman, 2001). The partnerships were formed to share the risks, costs, and benefits associated with the research and application of new vaccines, drugs, diagnostic tools, etc. Several such partnerships have recently been formed in response to the global TB epidemic, but only one of them, The Stop TB Partnership (Stop TB), will be described here. Other partnerships will be described in a subsequent section.

Stop TB is a network of about 300 country partners; international organizations; public and private donors; governmental and non-governmental organizations; and academic institutions. WHO is the lead agency and also houses the secretariat of Stop TB. Other members of the partnership include the American Lung Association, Open Society Institute, Partners in Health, USAID, and The World Bank.

The goal of Stop TB is “to accelerate social and political action to stop the unnecessary spread of tuberculosis around the world” (WHO, 2004f). Its activities have included the following:

- Organizing the Ministerial Conference on TB & Sustainable Development in Amsterdam, The Netherlands, in March 2000, which brought ministers of health, finance, and development planning from 20 high-burden countries together with representatives of UN agencies, donor countries, and technical agencies,
- Publishing The Global Plan to Stop Tuberculosis (2001),
- Organizing international forums in 2001 (Washington, D.C.) and 2004 (New Delhi),
- Supporting six working groups to expand DOTS; respond to emergencies, (TB/HIV co-epidemics, DOTS-Plus for MDR TB); and develop new tools (drugs, diagnostics, and vaccines),
- Housing the Global Drug Facility, which reviews proposals for technical soundness and provides grants for buying high-quality anti-TB drugs, and
- Maintaining an extensive Image Library.

Of Stop TB, Lee Reichman said this: “Stop TB is, to my mind at least, an acknowledgement by all partners that global TB is indeed a global emergency and that the mobilization of the numerous partners’ efforts has a very good chance of bringing about, first, recognition and, then, solutions of the problem.” (Lee Reichman, personal communication). An independent external evaluation of the Stop TB Partnership concluded that the “partnership has scored some major achievements in only three years.” (Institute for Health Sector Development, 2003)

Intersection of TB in the U.S. with the Global Epidemic That the global epidemic is linked to TB in the U.S. is clear in the rising proportion of reported cases of TB in the U.S. among foreign-born persons. This proportion has increased steadily in recent years, from 27% of all cases in 1992 to 53% of all cases in 2003. In 2002, for the first time since birth country was added to the case report form in 1986, the proportion of total cases occurring in foreign-born persons exceeded 50%. In 22 states in 2002, more than half of the reported tuberculosis cases were among foreign-born persons. In seven states—California, Colorado, Hawaii, Idaho, Massachusetts, Minnesota, and New Hampshire—more than 70% of the cases occurred among foreign-born persons. Moreover, the case rate among foreign-born persons is at least eight times higher than among U.S.-born persons. Given the scale of global migration and international travel in the 21st century, tuberculosis will not be eliminated in the U.S. until the incidence of

tuberculosis is reduced elsewhere in the world

V. The Biology of Tuberculosis—Basic and Applied

Tried and True (sort of) Methods We have known the cause of TB since 1882, when Dr. Robert Koch announced to the world the results of experiments that had led him and his colleagues to identify *Mycobacterium tuberculosis* as the culprit (Koch, 1994). Koch reported his results in an evening lecture to the Physiological Society of Berlin on March 24 of that year. (March 24 is observed each year as World TB Day.) In the preceding years, Koch and his colleagues had developed methods for growing the tubercle bacillus and had refined a method for staining the bacillus for microscopic observation. The gold standard for the diagnosis of active pulmonary TB is, to this day, based on these two methods developed in Koch's laboratory more than 120 years ago. Another diagnostic test, the tuberculin skin test was described in 1909 (von Pirquet, 1909). The BCG vaccine was first administered to humans in 1921 (Fine, 2000).

It was many years before scientists found a cure for TB, but they did. In 1944, soil microbiologist Selman Waxman and his colleagues at Rutgers University announced they had discovered an antibiotic that could kill the TB germ. That drug, streptomycin, soon performed miraculous cures TB patients who were deathly ill. Other such "miracles" followed, and by the early 1950s, scientists had discovered several other anti-TB drugs. Four such drugs, when taken in combination for 6–8 months, can cure tuberculosis (Davis, 2000; CDC, 2000a).

The Emergence of Drug Resistance However, soon after clinicians began using streptomycin, they found that while some patients were cured, other patients got well for a while and then relapsed (Fujiwara et al., 2000). Similar results followed the introduction of other anti-TB drugs when they were used in a single-drug regimen (monotherapy). What these disappointed clinicians (and their patients, no doubt) were seeing was the emergence of secondary drug resistance of the tubercle bacillus—even when patients were compliant with the treatment regimen. How could resistance emerge under these conditions?

The answer to this question can be found in two numbers: (1) the probability of spontaneous mutations in the genes whose products are the targets of anti-TB drugs and (2) the number of tubercle bacilli in a patient's body. For example, if the probability of the occurrence of a mutation that expresses itself as resistance to INH is 1×10^{-6} , and if the number of tubercle bacilli in a tuberculous cavity is $1 \times 10^8 - 1 \times 10^9$, then each round of replication of the bacilli in the cavity will produce, on average, 100–1,000 organisms that are resistant to INH. If we assume that these resistant organisms are otherwise "fit," then they would be selected for in the presence of INH. Similar calculations can be made for other anti-TB drugs. Thus, if a patient with drug-susceptible TB is given monotherapy, we would predict the emergence of secondary drug resistance—just as clinicians observed in the 1940s and 1950s (Tiruvilualma and Reichman, 2002).

However, if a patient with drug-susceptible TB is placed on four-drug combination therapy, the probability of developing drug resistance is extremely low.

This is because the bacilli in such a patient would have to undergo four mutations—one each in the four genes whose products are the targets of the four drugs—in order to be able to grow in the presence of the four drugs. The number of such “quadruple mutants” emerging in a typical lung cavity is approximately $(1 \times 10^{-6})^4 \times (1 \times 10^8 \text{ to } 1 \times 10^9) = 1 \times 10^{-16} \text{ to } 1 \times 10^{-17}$, a very low number, indeed. Hence, the recommendation that patients be treated with a four-drug regimen.

The logic that leads to the conclusion that monotherapy will likely result in drug-resistant TB also leads to the conclusion that a single drug should never be added to a failing multidrug regimen. That such a regimen is failing—i.e., the patient is not getting better—suggests that the patient is infected with organisms that are resistant to all the drugs the patient is receiving. Adding a single drug to such a regimen is the equivalent of administering monotherapy to a patient with drug-susceptible TB. And the results will be the same: the generation of drug resistance and treatment failure (Mahmoudi and Iseman, 1993).

Prescribed monotherapy can be intentional—as it was in the 1940s and 1950s and can be even today, out of ignorance. It can also occur when the quality of the drugs is poor, when drugs are available intermittently during treatment, or when a patient takes some, but not all, of the prescribed medications. Fixed-dose combinations—pills that contain multiple anti-TB drugs in a single preparation, e.g., the product Rifater, which contains INH, RIF, and PZA—can be used to reduce nonadherence to prescribed therapy (Iseman, 2000).

Wanted: New Tools Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Disease (and thus the top federal AIDS scientist), said in 1992 at the peak of TB resurgence in the U.S. that TB might become as serious a health threat as AIDS unless a major new research effort was begun (Altman, 1992). In that same year, *Science* magazine published a lead article about this “reemergent killer” in the U.S. (Bloom and Murray, 1992). The paper described the context for the reemergence of TB, identified the major scientific problems that needed to be addressed in order to combat the disease, and estimated the economic cost of failure to address the problem.

Basic and applied research about TB had ground nearly to a halt from 1970 to 1990, because little funding was available to support such research. Also, few young scientists had been trained to study TB. The result was not only little progress in understanding the disease but also a crumbling of the scientific infrastructure needed to do TB research.

However, since 1990 a renaissance in basic research about TB has been made possible by substantial increases in NIH funding. Between 1990 and 2003, NIH funding for TB-related research increased 23.5-fold, from \$3.7 million to \$86.9 million (in constant, 1990\$; the actual figure in 2003 was \$122.4 million) (Institute of Medicine, 2000; personal communication, NIH Budget Office, 2004). Over the past decade, we have seen a renaissance in basic research about *M. tuberculosis*; the cell and molecular biology of TB; and the application of such basic research to the development of new and

better diagnostic tests, anti-TB drugs, and TB vaccines. Investments in basic research are usually for the long term, but we are already beginning to harvest the fruits of the labor of cell and molecular biologists.

The IOM report identified the following as high priority areas for research:

- diagnostic methods to identify persons with LTBI,
- methods to identify those infected persons at highest risk for progressing from LTBI to active disease,
- new tools to prevent or treat TB, including vaccines and drugs, and
- behavioral and social science studies of how to improve patient adherence to treatment regimens.

(These priorities are also reflected in the working groups established by Stop TB). The IOM report also recommended that at least some of the research should occur in the international arena and involve collaboration among the CDC, NIH, USAID, and international partners.

The Underlying Science Before we can develop new tools, we need to know much more about the basic biology of *M. tuberculosis*. A big step toward understanding TB was the sequencing of the genome of *M. tuberculosis* (Cole et al., 1998). For example, genomic analysis revealed two new families of proteins and also genes that code for enzymes involved in the synthesis of polyketides, which act as toxins responsible for the virulence of other species in the genus *Mycobacterium* (George et al., 1999). Genomic analysis also identified potential protein targets for the development of vaccines and potential sites of variation in antigens at the surface of the bacterium (Ginsberg, 2000; Andersen, 2001). Renewed interest in TB has also led to the application of a multidisciplinary approach—microbial pathogenesis, also known as cellular microbiology—to the study of the disease (Glickman and Jacobs, 2001).

Example: the use of comparative genomics. Comparative genomics involves the comparison of genomic sequences of different species or different strains of the organism. Comparative genomics has been used to study the evolution of *M. tuberculosis* (Brosch et al., 2002; Tsolaki et al., 2004); identify virulence factors and the immune response to infection (Fleischmann et al., 2002); identify new drug targets (Barry et al., 2000; Cole, 2002); and develop new diagnostics and vaccines (Cole, 2002). For a review of the application of comparative genomics to the study of TB, see the paper by Mostowy and Behr (2002).

Example: the biology of latency. *M. tuberculosis* can live for decades in the human body in the form of an asymptomatic infection referred to as LTBI, only to re-emerge and cause active TB (Parrish et al., 1998). Where does the organism reside—which organs, cells, and intracellular compartments—in a person with LTBI? How does it elude the defense mechanisms that usually kill invasive microorganisms, both intra- and extracellularly (Russell et al., 2002; Fratti et al., 2003)? How does the interaction of *M. tuberculosis* with the immune system during LTBI result in an apparent stand-off

between the bacillus and the host organism (Chan and Flynn, 2004)? What molecular adaptations enable the organism to survive within the host organism? Might some of these adaptations suggest new targets for anti-TB drugs?

Example: molecular epidemiology. When confronted with a new case of active TB, public health officials must perform a contact investigation. The purposes of such an investigation are (1) to identify other individuals who have had close contact with the infected person; (2) test these contacts in order to determine whether they too are infected; and (3) where appropriate, offer them treatment. In this way, an outbreak can be limited.

For decades, contact investigations have been based on a patient's response to a set of standard questions: Who do you live with? Work with? Socialize with? The answers to these questions provide TB controllers with the names of persons who will then be skin-tested for TB infection. This approach has its limitations, however, primarily because individuals may not identify all their contacts. Contact tracing by this traditional "shoe-leather" approach is especially difficult when it involves mobile populations such as the homeless, who move from shelter to shelter, county to county, or even state to state. The tool of DNA fingerprinting (molecular genotyping) is now helping TB controllers identify links between TB cases, even when they are widely separated in time and/or place.

Just as the DNA molecules of individual humans differ from each other in slight but detectable ways, the DNA molecules in different strains of the TB germ can be distinguished through DNA fingerprinting. Thus, if two individuals are infected with TB germs that have identical DNA fingerprints, one can tentatively conclude that the two individuals are linked to each other in a chain of transmission. In other words, TB controllers can use molecular epidemiology to study the pattern of TB transmission within their communities.

DNA fingerprinting was crucial in identifying a cluster of related cases of TB in rural Alabama (Dobbs et al., 2001). TB germs from 25 cases in 10 counties in Alabama were found to have identical DNA fingerprints. Subsequent follow-up interviews showed the cases could be linked to each other via facilities in three counties: a correctional facility and two homeless shelters. Thus, the use of molecular epidemiology revealed a statewide TB outbreak that health officials had not previously recognized. Molecular genotyping has also been used to determine whether recent TB cases in a community were the result of ongoing transmission or were instead the result of the reactivation of a remote infection (Small et al., 1994; Geng et al., 2002; Maguire et al., 2002; Weis et al., 2002); to identify high-risk groups for targeted testing (Herández-Garduño et al., 2002); and to study the transmission of strains across international borders (Quitugua et al., 2002).

The genotyping techniques being used to study TB include restriction fragment length polymorphism (van Embden et al., 1997), spacer oligotyping (spoligotyping; Kamerbeek et al., 1997), variable number tandem repeat typing (VNTR; Frothingham

and Meeker-O'Connell, 1998), and VNTR using mycobacterial interspersed repetitive units (MIRUs; Mazars et al., 2001).

Several reviews of the methods of molecular epidemiology and their application to TB have been published recently (Burgos and Pym, 2002; Murray and Nardell, 2002; Barnes and Cave, 2003; Kanduma et al., 2003). See also the November 2002 issue of *Emerging Infectious Diseases* (http://www.cdc.gov/ncidod/EID/vol8no11/contents_v8n11.htm).

Given the evident power of genotyping in TB control, the CDC would like to determine the molecular genotype of every sample of TB germs isolated from cases in the U.S. The power of such *universal genotyping* was shown recently in a TB outbreak in Kansas, where Kansas health officials identified clusters of cases that would have been hard to link through standard contact investigations. They found the use of genotyping particularly useful in working with homeless communities, where contact investigations traditionally are difficult to pursue due to the anonymity of the population. Universal genotyping drew attention back to active cases that had no apparent epidemiological link with each other. Then, as a result of more intensified investigations, further cases were not only linked but led to new cases being diagnosed early in the disease process. Even more significant was the fact that the genotyping results yielded indisputable evidence of case-to-case transmission among homeless persons. As a result, the shelters that house the homeless have become far more willing to partner with public health efforts to control and eliminate tuberculosis in their population.

New and Better Diagnostic Tools We need new tools to diagnose TB. On that point there is widespread agreement (Institute of Medicine, 2000; Perkins, 2000; Drobniewski et al., 2003). The IOM report (Recommendation 5.2) states, “To advance the development of diagnostic tests and drugs for both latent infection and active disease, action plans should be developed and implemented. The CDC should then exploit its expertise in population-based research to evaluate and define the role of promising products” (Institute of Medicine, 2000). One of the six working groups established by the Global Partnership to Stop TB is focused on the development of new diagnostic tools.

The commonly used diagnostic methods—tried but not always true— include the microscopic identification of acid-fast bacilli in sputum smears, the tuberculin skin test, and various methods for culturing bacteria. The limitations of these methods include inadequate sensitivity; logistical problems, e.g., the use of the tuberculin skin test requires two clinic visits; inadequate specificity (inability of the tuberculin skin test to distinguish among LTBI, active TB, vaccination with BCG, and infection with mycobacteria other than tuberculosis); and the long time required to culture the slow-growing *M. tuberculosis* (Drobniewski et al., 2003; Schluger, 2003). The last is especially an impediment in the diagnosis of drug-resistant TB (Garcia de Viedma, 2003; Drobniewski et al., 2004).

More rapid detection of TB infection and of drug-resistance is being made possible by advances in molecular biology. Some new diagnostic tests are based on the recognition and amplification of mycobacterial DNA sequences (Garcia de Viedma,

2003; Huggett et al., 2003). Others use specific mycobacteriophage to detect the presence of viable *M. tuberculosis* (Wilson et al., 1997; Albert et al., 2001; Kisa et al., 2003).

A new diagnostic test for tuberculosis infection that has several advantages over the currently used, nearly century-old tuberculin skin test has been developed by scientists at the CDC, in collaboration with the private sector. The QuantiFERON®-TB test, uses an ELISA (enzyme-linked immunosorbent assay) to measure the amount of interferon-g released by white blood cells in response to PPD (Mazurek et al, 2001; CDC, 2003c; Cellestis, 2003). This test is based on whole blood, requires only one clinic visit, and does not cause the booster phenomenon seen when skin testing is used (CDC, 2000a). Another test under development is an ELISPOT (ex-vivo enzyme-linked immunospot) assay based on antigens ESAT-6 and CFP-10, which are not expressed in *M. bovis* BCG and most environmental Mycobacteria (Lalvani et al., 2001; Chapman et al., 2002).

While these new tests show great promise, the consensus among TB experts remains that we need to continue to support basic and applied research to improve existing diagnostic tools and develop new ones. In May 2003, the World Health Assembly launched the Foundation for Innovative New Diagnostics (FIND), a public-private partnership of academic and industry groups—including the United Nations Development Program, World Bank, WHO, and Bill & Melinda Gates Foundation—that will identify new technologies for diagnosing infectious diseases and then shepherd them through the research and development pipeline (WHO, 2003b; Foundation for Innovative New Diagnostics, 2004). In doing so, FIND aims to develop a model that will address market forces that currently inhibit the development and marketing of such technologies. FIND will base its model on TB.

New Drugs, More Effective Drug Regimens The first anti-TB drug, streptomycin, was licensed in 1952 (Brown, 1992). Although more than a dozen other anti-TB drugs and their derivatives have been developed since then (Davidson and Le, 1992), there has been relatively little progress for the past 30 years (Global Alliance for TB Drug Development, 2000, 2001), and no new class of TB drugs has been introduced since 1966 (Reichman and Fanning, 2001).

We need new TB drugs that can be used to shorten treatment regimens. In the most commonly used regimen for active TB, patients take four drugs—INH, RIF, PZA, and ETH for eight weeks and then INH and RIF for an additional 18 weeks (American Thoracic Society et al., 2003). A widely used treatment regimen for LTBI involves taking one drug (INH) for nine months (CDC, 2000b). The length of these regimens is a factor in patient nonadherence to treatment regimens. Moreover, several anti-TB drugs have unpleasant, even toxic, side effects, including nausea, hearing loss, and hepatitis (CDC, 2000a). Another reason why we need new anti-TB drugs is the growing problem of multidrug-resistant TB. Thus, the development of new anti-TB drugs is a high priority (Institute of Medicine, 2000; Global Alliance for TB Drug Development, 2000, 2001; O'Brien and Nunn, 2001; Orme, 2001), a priority reflected in the development of several

collaborations, including:

Global Alliance for TB Drug Development. The Global Alliance for TB Drug Development is a nonprofit public-private partnership whose mission is to ensure equitable access to a faster TB cure and whose goal is to register a new anti-TB drug by 2010 (<http://www.tballiance.org>). The Alliance is a “virtual research and development (R&D) organization that outsources R&D projects to public or private partners.” After identifying bottlenecks in the TB drug development process—from the identification of drug targets to the marketing of a new drug—the Alliance provides funding to move the development process along (Global Alliance for TB Drug Development, 2000). The Alliance recently licensed the drug PA-824 and related nitroimidazole compounds for development. The Alliance has also published an economic analysis of TB drug development, to convince for-profit entities that the development of TB drugs can be profitable (Global Alliance for TB Drug Development, 2001).

Tuberculosis Trials Consortium (TBTC). A crucial element in the development of new tools will be population-based research, i.e., clinical trials, that asks whether the tools do what they were designed to do. For example, how long must a new anti-TB drug be administered in order to cure active TB? With respect to treatment regimens, how can we improve patient and provider compliance? Does a new TB vaccine confer any better protection than the existing BCG vaccine?

The CDC is mandated by the U.S. Public Health Service to conduct TB therapy trials. Thus, for more than 35 years, the CDC has been responsible for conducting clinical trials to evaluate new drug regimens for preventing and treating TB. Ongoing clinical trials are being done by the Tuberculosis Trials Consortium (CDC, 2004b), a consortium of 28 academic clinical centers and Veterans Administration Centers in the U.S., Brazil, Canada, South Africa, Spain, and Uganda. Consortium members work closely with local public health departments to recruit and manage patients enrolled in the clinical trials. Thus, the consortium not only does research but also sustains scientific infrastructure at sites around the country.

In a short time, the TBTC has become the world’s premier research institution conducting such clinical trials country (Tuberculosis Trials Consortium, 2001). The recent addition of sites outside the U.S. and Canada will enable the TBTC to engage in global TB control efforts by broadening the applicability of its findings and by training foreign investigators in the highest caliber clinical research.

The new treatment guidelines for tuberculosis incorporated the results of several studies done by the TBTC (American Thoracic Society et al., 2003). These include the importance of obtaining sputum samples to identify persons at high risk for relapse or failure; shortened regimens for patients identified as being at low-risk for relapse or failure; and treatment in special situations, i.e., HIV co-infection. Selected HIV-negative patients can now be effectively cured with a regimen consisting of only 56 DOT visits; this represents a 22% reduction in doses and a significant cost advantage. The TBTC’s newest project, Study 27, is evaluating the use of moxifloxacin (a fluoroquinolone) to

decrease the infectious period and thus potentially shorten or simplify the treatment of disease (O'Brien, 2003).

One of the TBTC's other new projects is Study 26, a Phase III clinical trial that will compare the effectiveness and tolerability of two regimens for treating LTBI. In one regimen in the trial, patients will take INH—currently the most commonly used treatment for latent tuberculosis infection—daily for nine months, self-supervised. Patients treated with the other regimen will take a combination of INH and rifapentine (RFP) once weekly for three months, administered under direct observation. If the RFP/INH combination is found to be as good as, or better than, INH alone, the duration of treatment of LTBI could be reduced from nine months to three months and from 270 doses to 12 doses. Because adherence to or completion of the treatment regimen for LTBI is recognized to be the most challenging aspect of this intervention, the newer, shorter, entirely supervised regimen can be expected to overcome this challenge and to be especially effective in highly vulnerable populations, such as children and persons living with HIV infection.

A New and Better Vaccine It is far better to prevent TB than to treat it. Prevention is cheaper (Sawert, 2000; Marks et al., 2003), and it avoids the terrible human cost of disease. Moreover, vaccines have been effective tools for preventing and controlling many other infectious diseases.

The only TB vaccine currently available is BCG, an attenuated strain of *M. bovis*. Though it has been used since 1921, its effectiveness is still controversial (Fine, 2000). There is a lack of consistency in its protection, and it induces a positive skin test for TB, thus complicating the diagnosis of TB, especially LTBI. Meta-analysis of data from 14 prospective trials and separately from 12 case-control studies found that in children BCG vaccination significantly reduces the risk of active TB cases and deaths and protects from serious forms of pediatric TB, i.e., meningeal and disseminated (miliary) TB (Colditz et al., 1994). However, the vaccine's efficacy in reducing the risk of pulmonary TB has varied considerably in clinical trials, with some trials showing that the vaccine actually *increases* the risk of pulmonary TB (Colditz, 1994; Fine, 2000).

Recent evidence suggests that differences in the efficacy of BCG among trials are likely the result of several factors, including exposure of persons to environmental mycobacteria (mycobacteria other than tuberculosis), genetic variability in the human populations studied, and genetic variation in the bacterial strains used to produce the BCG vaccine (Fine, 2000). This genetic variation has evolved during the 70+ years that BCG has been growing in laboratories around the world (Behr et al., 1999; Young and Robertson, 1999; Andersen, 2001; Black et al., 2002). Thus, development of a better TB vaccine is a high priority (CDC, 1998; Institute of Medicine, 2000; Ginsberg, 2000; Andersen 2001; Ginsberg, 2002; Wang and Xing, 2002; Britton and Palendira, 2003; McMurray, 2003).

The list of potential vaccines includes live attenuated vaccines, subunit vaccines, and naked DNA vaccines (for reviews, see Brandt and Orme, 2002; Sacksteder and Nacy,

2002; von Reyn and Vuola, 2002; Young and Stewart, 2002). One of the most promising candidates is a live attenuated recombinant BCG (rBCG30) vaccine, which has been modified to overexpress antigen 85 protein (Horwitz et al., 2000; Aeras Global TB Vaccine Foundation, 2004; Filmore, 2004). Aeras began Phase I clinical trials of this vaccine early in 2004.

Another promising candidate vaccine is a subunit vaccine (it uses no live organism) containing a recombinant fusion protein of antigenic domains from *M. tuberculosis* combined with adjuvants (Filmore, 2004). This vaccine has been approved by the FDA for Phase I clinical study in the U.S.; the trial will be conducted by Corixa Corporation and GlaxoSmithKline (GlaxoSmithKline, 2004). According to Anthony Fauci, the Director of the National Institute of Allergy and Infectious Diseases, “This is the first new TB vaccine to be tested in our country in more than 60 years.” (National Institute of Allergy and Infectious Diseases, 2004).

In the meantime, although vaccination with BCG does not provide 100% protection, BCG remains a useful tool in preventing TB (Colditz et al., 1994; Aronson et al., 2004; Dye, 2004).

Behavioral and Social Science Research New tools—whether they be new drugs, new drug regimens, or a vaccine—can work only if people actually use them properly. Behavioral and social science research seeks to understand the barriers that prevent proper use. Much of this research is done by the Tuberculosis Epidemiologic Studies Consortium (TBESC), which conducts epidemiologic, behavioral, economic, laboratory and operational research (CDC, 2004c). The consortium’s studies provide data for more effective and efficient TB control that will ultimately lead to reduce the incidence of TB in the U.S. and around the world.

The TBESC, established in 2001 by the CDC's Division of Tuberculosis Elimination consists of 22 sites, 20 in the US and two in Canada. Each TBESC site is a collaboration between a local and state health department, academic institution(s), or for-profit and non-profit organizations. These collaborations bring together two exceptionally talented groups—TB controllers and academic scientists—whose training and experience complement each other. The work of the TBESC addresses significant questions in TB control and prevention while building local capacities for epidemiologic research in participating state and metropolitan TB control programs and academic institutions.

The Consortium's research includes studies with the following objectives:

- Identify and overcome barriers to treatment adherence for latent TB infection and TB disease among African Americans,
- Improve surveillance to identify missed opportunities for preventing tuberculosis in foreign-born persons,
- Assess the TB knowledge, attitudes, beliefs, and practices among private providers serving foreign-born populations at risk for tuberculosis,

- Develop culturally appropriate TB educational materials for leaders and staff of Hispanic service organizations,
- Develop a national genotyping registry for a molecular epidemiologic analysis of multidrug-resistant strains of the TB germ, and
- Develop strategies for building capacity for tuberculosis control in low-incidence areas of the U.S.

Summary Substantial increases in funding to the CDC and NIH since 1990 have stimulated progress in our understanding of TB and our ability to translate what we have learned into the practical work of preventing, treating, and curing TB. Public-private partnerships—sometimes involving the CDC and NIH—are playing a critical role in these endeavors. We can only hope that the new diagnostic tools, drugs, and vaccines will fulfill their early promise.

VI. Education, Advocacy, and Policy

Introduction In his Nobel lecture, Robert Koch (1905) underscored the importance of “instructing the people on the danger of tuberculosis.” Such instruction is needed today as much as it was in 1905, because people today are surprised to learn that TB still exists in the U.S and that humanity is facing a global TB epidemic as devastating as the HIV/AIDS epidemic. They believe that TB, like smallpox, is a disease of the past. But TB is not a disease of the past—not in the U.S, not anywhere in the world.

There is a good reason why TB has become invisible to most Americans: the U.S. is experiencing an all-time low in the number of new cases. However, now is not the time for complacency. Instead we should be taking steps to ensure that our success in reducing the incidence of TB in the U.S. does not lead to another cycle of neglect like the one we experienced in the 1970s and 1980s. The U.S. should also be working with international partners in the global arena.

Because TB is a public health problem, addressing the problem necessarily requires public activities. Such activities are most likely to occur when both the public and policymakers know about TB. The importance of public education as the basis for such public activities was identified by the Committee for the Study of the Future of Public Health (Institute of Medicine, 1988):

“In a free society, public activities ultimately rest on public understanding and support, not on the technical judgment of experts. Expertise is made effective only when it is combined with sufficient public support, a connection acted upon effectively by the early leaders of public health.”

In other words, education of the public ultimately leads to the implementation of policies, i.e., the activities of government. Two crucial intervening steps between education and the implementation of policies are (1) accumulating evidence and then articulating arguments for developing policies, and (2) advocacy for the adoption of particular policies. In this section of the paper, these four steps—education, articulation of

proposed policies, advocacy, and implementation of policies—will be described as they apply in the U.S. to domestic TB control and the role of the U.S. in addressing the global epidemic.

Education Education—of healthcare providers, the general public, and policymakers—is the linchpin of TB control and prevention (CDC, 1989; Institute of Medicine, 2000). A revised “National Strategic Plan for TB Training and Education, 2004–2008” provides a blueprint for a TB training and education for the next five years (Francis J. Curry National Tuberculosis Center, 2004).

Educating healthcare providers. “Think TB!” is an imperative of TB educators in the U.S. As the incidence of TB declines in the U.S., doctors and nurses in low-incidence regions see so few TB cases that they sometimes fail to diagnose a case of active TB in a timely manner. For example, when a sick woman reported to a hospital emergency room in Alabama in August 2002, she was diagnosed as having sinusitis and was sent home with a cough suppressant, an antibiotic, and an anti-inflammatory drug (Waddell et al., 2003). When she returned to the emergency room in November 2002—this time with a four-month cough, fever, and chills—she was diagnosed with bronchitis and was sent for breathing treatment with a bronchodilator. Six weeks later, in early 2003, she reported to an emergency room in Texas, where she was given a presumptive diagnosis of influenza. Finally, two weeks later, when she reported again to the same emergency room in Texas, she was diagnosed with pulmonary TB. By then, she had exposed members of her family (including eight grandchildren), healthcare workers, and others to TB germs and infected many of them.

Scenarios like this can be avoided when providers suspect and diagnose TB early. In other words, public and private healthcare providers must “Think TB” when they see a patient who has symptoms consistent with a diagnosis of TB. Before they can “Think TB,” providers must be educated about TB.

Such education and training is an ongoing process, and it occurs in several ways and venues and involves many partners. National leadership in this area is provided by the CDC’s Division of TB Elimination, through its Communications, Education, and Behavioral Studies Branch. The branch has produced numerous publications—pamphlets, brochures, booklets, books, movies, online training courses—about TB. The branch also sponsors the TB Education and Training Network; organizes the TB Behavioral and Social Sciences Research Forum; and works with three national model centers (Newark, NJ; New York, NY; San Francisco, CA). The model centers produce training materials and offer short courses and workshops.

Materials also been produced by state and city health departments. Many of these materials are available through the TB Education and Training Resource Guide (CDC, 2004d). Another rich source of information about TB is the internet (Kato-Maeda and Small, 2001; Abu-Amero, 2002). Web resources include on-line journals as well as web sites maintained by foundations, governments, and private organizations.

Educating the general public. The “public” has access to many, if not all, of the resources described above. In addition, the CDC and others have produced brochures, web pages, etc. for patients and the general public.

Print media have played an important role in keeping the U.S. and global TB epidemics before the American public. In fact, it was a series of front-page articles in the *New York Times* in 1992 that led to the development of a first-year seminar about TB at Franklin & Marshall College. Recent articles in periodicals as diverse as *New Scientist* (Lee, 2002) and *Mother Jones* (Patterson, 2003) continue to remind their readers of the scale of the global epidemic. College students are learning about TB at not only Franklin & Marshall College but at other institutions, e.g., Valdosta State University (Turco and Byrd, 2001) and San Jose State University (Kerr and Elwell, 2002).

Developing Policy The federal responsibility for TB control resides within the Division of Tuberculosis Elimination, a division of the National Center for HIV, STD, and TB Prevention within the CDC. The Division of Tuberculosis Elimination—in collaboration with the National Center for Infectious Diseases, the Public Health Practice Program Office, and the National Institute of Occupational Safety and Health—is, in effect, the U.S. national TB program. It is charged with providing leadership and resources to control, prevent, and eventually eliminate TB in the U.S.

Dozens of other federal agencies and private organizations also assist in developing and/or implementing policies that support TB control. Among the most prominent of the private organizations have been the American Lung Association, the National TB Controllers Association, and the International Union Against Lung Disease/North American Region (and others that will be identified in the next section on Advocacy).

Four documents have been central to the development of federal TB control policies: “A Strategic Plan for the Elimination of Tuberculosis in the United States” (CDC, 1989); *Ending Neglect: The Elimination of Tuberculosis in the United States*, a report from the Institute of Medicine (Institute of Medicine, 2000); “CDC's Response to *Ending Neglect: The Elimination of Tuberculosis in the United States*” (CDC, 2003b); and “Federal Tuberculosis Task Force Plan in Response to the Institute of Medicine Report, *Ending Neglect: The Elimination of Tuberculosis in the United States* (Federal Tuberculosis Task Force, 2003). These documents, along with many others—addressing issues such as TB control among farm workers and in prisons and jails; infection control; and MDR TB—have provided epidemiologic evidence to support specific TB control and prevention policies.

Advocacy Much of the money for TB control and prevention, both domestic and global, is public money appropriated by the U.S. Congress. Thus, advocates for TB control and prevention must do two things well: (1) convince Congress that TB is a serious public health problem and (2) show Congress how increased federal funding will be used to alleviate the problem.

In *Tuberculosis Elimination: An Advocate's Guide* (American Lung Association, 2004), advocacy is defined in this way:

“Advocacy is a catchall word for a set of skills used to create a shift in public opinion and to mobilize the necessary resources and forces to support an issue, policy or constituency.”

The IOM report (Institute of Medicine, 2000) acknowledged the importance of advocacy when it identified “mobilizing support for elimination” as a crucial step in eliminating TB in the U.S. The report linked social mobilization, particularly advocacy, to the generation of political will to eliminate TB. (For further discussion of the importance of advocacy for TB control, see Klautdt, 2000).

The IOM report singled out one organization, the National Coalition for the Elimination of Tuberculosis (NCET), as having played a key role in advocacy for TB control and prevention. Founded in 1991, NCET is a coalition of individuals and more than 50 national, state and local public health, medical professional, health care, and service organizations. Leadership is provided by the American Lung Association and the American Thoracic Society. In Fall 2003, NCET sponsored a workshop on the topic of TB advocacy and released its advocate's guide; and in 2004, NCET published its second white paper on TB: *TB Elimination: The Federal Funding Gap* (National Coalition for the Elimination of Tuberculosis, 2004). This paper is being used in lobbying efforts to increase federal funding for domestic and global TB control. NCET also works with the National Tuberculosis Controllers Association to organize a “Day on the Hill,” in which TB controllers lobby their representatives and senators for increased funding for TB control and prevention.

Two other organizations that advocate for TB control and prevention are RESULTS, Inc. (<<http://www.results.org/>>), and Princeton Project 55 (<<http://www.project55.org/>>). RESULTS is a “nonprofit grassroots advocacy organization, committed to creating the political will to end hunger and the worst aspects of poverty.” It has chapters in more than 100 communities in the U.S. One of its 11 major initiatives, “World Health/Diseases of Poverty,” is about the global TB epidemic.

Princeton Project 55 is a “nonprofit organization established by members of the Class of 1955 at Princeton University to mobilize alumni and students, and others who share our concerns, to provide civic leadership and to develop and implement solutions to systemic problems that affect the public interest.” In its Tuberculosis Initiative, Project 55 has not only engaged in old-fashioned lobbying in Washington but has also published editorials in national newspapers, hosted two conferences, and placed undergraduate students and recent graduates in internships with organizations involved in TB education, outreach, and diagnostic and drug development.

Policymakers' Response to TB Resurgence in the U.S. During the 1990s, policymakers in Washington, D.C., approved substantial increases in federal funding for TB control and prevention (primarily to the CDC) and for basic research about TB (primarily to the NIH). These increases—and many of the projects made possible by the increased

funding—were described in detail in earlier sections of this paper. TB advocates have clearly succeeded in their efforts, at least with respect to TB in the U.S. The new challenge for TB advocates will be to sustain the increased funding levels when TB is, once again, waning in the U.S.

Policymakers' Response to the Global TB Epidemic: Why Should the U.S. Care about the Global TB Epidemic? The IOM report recommended that the U.S. continue to play a significant role in global TB control, arguing that the U.S. has a moral obligation to provide technical advice and other resources in order to help countries and organizations address the epidemic. However, because the incidence of TB in the U.S. is much lower than it is in many countries, one might well ask why the U.S. should care at all about the global TB epidemic (Kassalow, 2001). We should care for at least two reasons.

First, we should care out of self-interest. In 2002, for the first time in history, more than half (51%) of the reported TB cases were among foreign-born persons (CDC, 2003a). Given the scale of immigration and international travel, it should be no surprise that experts have concluded, “Tuberculosis will not be eliminated in the United States until the worldwide epidemic is brought under control” (Institute of Medicine, 2000). Moreover, as long as the global epidemic continues, U.S. workers whose occupations bring them into contact with persons with active TB—e.g., healthcare workers, immigrant and refugee workers, corrections officers—will continue to be infected by the tubercle bacillus.

Global disease prevention should be at the center of the national security agenda U.S., according to The National Intelligence Council (2000). The Council reached this conclusion not only because diseases such as TB can be transmitted to U.S. citizens but also because they weaken the global economy. More than 70% of the nearly 15 million people sick with TB are in the most productive years of their lives (Stop TB Partnership, 2001). To the extent that countries with high TB burdens are U.S. trading partners, their economic decline poses a national security threat to the U.S. Indeed, the potential economic impact of the TB epidemic was reflected in the title of Stop TB’s ministerial conference in Amsterdam: “Tuberculosis and Sustainable Development.”

A second reason the U.S. should care about the global TB epidemic is that the U.S., with its considerable monetary and technical resources, has a moral obligation to help the disadvantaged of the world. (Of course, other developed countries share this obligation.) In *Infections and Inequalities* and *Pathologies of Power* and elsewhere, Dr. Paul Farmer has argued eloquently for improving health services for the disadvantaged among us (Farmer, 1999; Farmer, 2003). Moreover, the prevention and treatment of TB are among the most cost-effective of any healthcare intervention, especially in low-income countries (World Bank, 1993). Thus, support for TB programs should be among the highest priority for any government, including that of the U.S. (Enarson, 2000; Farmer, 2001).

The U.S. does not need to “go it alone” in the fight against the global TB epidemic. The emergence of a host of multilateral, public-private partnerships to fight

TB and other diseases has made it possible for governments to partner with private for-profit organizations, academic institutions, foundations, and other non-governmental organizations. Examples of such partnerships include the Global Alliance for TB Drug Development; The Global Fund to Fight AIDS, Tuberculosis and Malaria; and the Aeras Global TB Vaccine Foundation.

Strategic choices by the CDC. Given its technical expertise, the CDC's Division of Tuberculosis Elimination plays a crucial role in the U.S. response to the global epidemic. However, given the enormity of the global epidemic, the Division must make difficult decisions about how best to use its limited resources outside the U.S. Thus, the Division collaborates with other U.S. and international organizations to leverage international development resources to provide technical support for global tuberculosis control. The Division's partners include USAID; the Tuberculosis Coalition for Technical Assistance; the Global AIDS Program; and the Global Fund for AIDS, Tuberculosis, and Malaria. The President's Emergency Plan for AIDS Relief (PEPFAR) should become another valuable partner in countries where TB and HIV are co-epidemic.

Guided by a strategic plan, the Division of Tuberculosis Elimination provides technical support to 16 countries. These countries include Mexico, the Philippines, and Vietnam (the largest numbers of foreign-born TB cases in the U.S. occur in persons who come from these three countries (CDC, 2003a); an expansion of DOTS coverage in Brazil, India, and Russia; a focus on MDR TB in the Baltic States, Peru, and Russia; and an emphasis on TB/HIV in Botswana and other countries with a mission in the Global AIDS Program (CDC, 2003b; Agerton, 2003).

By supporting TB control efforts in these countries, the CDC is also learning how to control and prevent TB in special situations. In Latvia, for example, in a project also supported in part by funds from USAID, the CDC and the Latvian government have established a training center to help other countries cope with MDR TB. In Botswana, where about 80% of TB cases are also infected with the virus that causes AIDS, the CDC is not only helping local health officials cope with co-epidemics of TB and HIV but is also learning more about the dynamics of TB infection in a population with a high prevalence of HIV infection. Thus, the answers to questions being asked in countries like Latvia and Botswana will have important implications for TB control and prevention throughout the world, including the United States.

Example: the CDC and U.S.-Mexico binational tuberculosis control. Immigrants from Mexico contribute substantially to U.S. tuberculosis morbidity (CDC, 2003a). Of the 7,659 reported cases among foreign-born persons in the U.S. in 2002, 1,889 (25%) were from Mexico. Most (70%) of these cases occurred in the four states that border Mexico—Arizona (103 cases), California (812 cases), New Mexico (13 cases), and Texas (381 cases). Although these four border states account for a significant proportion of the Mexico-born cases, the number/percentage of Mexico-born cases reported by other states appears to be increasing. For example, for the five-year period of 1998–2002, seven other states reported that at least 15% of their cases were Mexico-born: Colorado, Idaho, Kansas, Nebraska, Nevada, Oregon, and Wyoming. Thus, there appears to be a growing

trend of Mexico-born migration and settlement in communities beyond the four border states.

Nevertheless, TB continues to be a particularly significant problem along the U.S.-Mexico border. The 2,000-mile border region includes four states in the U.S., six states in Mexico; 44 counties, 14 pairs of sister cities, and 12 million inhabitants (United States-Mexico Border Health Commission, 2004). More than 1 million persons cross the border each year (CDC, 2004e).

The incidence of TB among border communities is higher than national rates in both Mexico and the United States and for their respective states overall (CDC, 2001). The counties along the border are among the poorest economically in the U.S. According to the MMWR of January 19, 2001, “about one-third of the U.S. border families live at or below the poverty line, compared with national average of 11%...and 10 of 24 counties evaluated along the border are medically underserved and of low socioeconomic status” (CDC, 2001; United States-Mexico Border Health Commission, 2004).

Thus, several factors make TB control along the U.S.-Mexico border urgent, difficult, and expensive: the higher incidence of the disease; the low socioeconomic status of much of the population; linguistic and cultural barriers; and the extra effort required to ensure that patients, especially those who cross the border, complete treatment.

If TB control programs in the U.S. and Mexico do not combine their resources and work together, they will limit their effectiveness in managing TB in the migratory population along their common border. Thus, a regional strategy to combat active TB disease along the border is essential. Since 1991, the CDC has funded several projects that have improved the coordination of and communication about TB control activities in this region (CDC, 2004e). Bi-national TB control projects in several adjoining jurisdictions along the U.S.-Mexico border of Arizona, California, and Texas are responsible for control activities on both sides of the border, including case management, contact investigations, and provision of laboratory services for diagnosis and case management. These projects focus on persons with TB who cross the border frequently.

Additional projects include CureTB and TB*Net*. CureTB, operated by the San Diego County TB control program, is a joint U.S.-Mexico referral system designed to improve the continuity of care for patients with active TB and their contacts who are at high risk. TB*Net*, operated by the Migrant Clinicians Network and based in Austin, Texas, issues a portable medical record to its patients; the record helps the patient gain access to medical services for TB disease or infection.

In March 2003, the CDC and the Mexico National TB program established the *United States-Mexico Binational TB Referral and Case Management Project* (Advisory Council for the Elimination of Tuberculosis, 2003). The project is the result of three years of planning by representatives of the U.S., Mexico, and other key stakeholders. The goals of the project are to coordinate the referral of patients between the health

systems of both countries and to ensure continuity of care and completion of TB treatment for patients who migrate between the U.S. and Mexico. This effort will improve our understanding of migrating TB patients, ensure that patients receive continuous care, and allow the completion of six-month treatment regimens necessary to cure TB. As a result, MDR TB can be prevented.

The symbol of this new program is the *Binational Health Card*. This card contains a unique identification number to track patients, the location where the card was issued, treatment initiation date, date of last dose of TB treatment, treatment regimen, DOT or non-DOT administration of treatment, and toll-free telephone numbers in Mexico and the U.S. The card links to secure databases in Mexico and the U.S. for providers to access clinical information by telephone and manage the patient's care. Through the card, the new initiative will, for the first time, integrate the efforts of CureTB and TBNet and link their referral services directly with a similar effort by the Mexico National TB Program.

Global Fund for AIDS, Tuberculosis, and Malaria. Since its creation in January 2002, this public-private partnership has become the world's largest financier of programs to fight these three diseases. As of May 2004, the Fund had collected \$2,477 million from donors, most of it from countries and foundations: 55% from EU nations, 25% from the U.S., and 20% from "other" (Aidspace, 2004a). As of July 31, 2003, the Bill and Melinda Gates Foundation had contributed \$100 million (Global Fund to Fight AIDS, Tuberculosis, and Malaria, 2003). The Fund announced its fourth round of proposals in January 2004. In three previous rounds, the Fund committed US\$ 2.1 billion over two years to 224 programs in over 120 countries to combat the three diseases. TB-related projects have received 16% of the funds (Global Fund to Fight AIDS, Tuberculosis, and Malaria, 2004). The Fund is managed by an international board; the current chair is U.S. Secretary of Health and Human Services Tommy Thompson.

The Global Fund makes grants, but it does not provide technical assistance to help countries prepare proposals or implement them. However, some countries that need funds have limited resources to develop a proposal and therefore must seek help and advice from TB experts from outside their country. The CDC has provided technical expertise to at least one country (Ethiopia), and Aidspace has published several guides to help countries find such technical assistance (Aidspace, 2004b).

A technical panel at the Global Fund reviews each proposal for its soundness, to ensure that the funds will be used properly. The panel also judges the robustness of the country-wide partnership ("country-coordinating mechanism") that submitted the grant proposal and that will oversee its implementation, should it be funded. Dr. Richard Feachem, the Executive Director of the Global Fund, provided this rationale for the Fund's faith in the country-coordinating mechanism: "There is no country with which I am familiar where the public infrastructure alone can mount an adequate response to HIV/AIDS, tuberculosis, or malaria. It just cannot be done. In all countries we need to mobilize and empower the non-government actors alongside the government actors, alongside with the public infrastructure" (Feachem, 2002).

While it may be too early to provide a definitive evaluation of the Fund's performance, the U.S. General Accounting Office (2003) gave the fund a favorable review after its first year. The G.A.O. and others have also identified challenges the Fund is facing, in particular the performance of the country-coordinating mechanisms and a lack of funds (Tan et al., 2003). Nevertheless, the Global Fund appears to be the best international strategy we have for tackling these three diseases.

The President's Emergency Plan for AIDS Relief (PEPFAR). PEPFAR will be the first large-scale effort by the U.S. government to treat people living with HIV/AIDS. President Bush announced this ambitious initiative to fight AIDS, tuberculosis, and malaria in Africa and the Caribbean in his 2003 State of the Union Address (Bush, 2003):

Today, on the continent of Africa, nearly 30 million people have the AIDS virus—including 3 million children under the age 15. There are whole countries in Africa where more than one-third of the adult population carries the infection. More than 4 million require immediate drug treatment. Yet across that continent, only 50,000 AIDS victims—only 50,000—are receiving the medicine they need.

Because the AIDS diagnosis is considered a death sentence, many do not seek treatment. Almost all who do are turned away. A doctor in rural South Africa describes his frustration. He says, "We have no medicines. Many hospitals tell people, you've got AIDS, we can't help you. Go home and die." In an age of miraculous medicines, no person should have to hear those words.

AIDS can be prevented. Anti-retroviral drugs can extend life for many years. And the cost of those drugs has dropped from \$12,000 a year to under \$300 a year—which places a tremendous possibility within our grasp. Ladies and gentlemen, seldom has history offered a greater opportunity to do so much for so many.

We have confronted, and will continue to confront, HIV/AIDS in our own country. And to meet a severe and urgent crisis abroad, tonight I propose the Emergency Plan for AIDS Relief—a work of mercy beyond all current international efforts to help the people of Africa. This comprehensive plan will prevent 7 million new AIDS infections, treat at least 2 million people with life-extending drugs, and provide humane care for millions of people suffering from AIDS, and for children orphaned by AIDS.

I ask the Congress to commit \$15 billion over the next five years, including nearly \$10 billion in new money, to turn the tide against AIDS in the most afflicted nations of Africa and the Caribbean.

This nation can lead the world in sparing innocent people from a plague of nature. And this nation is leading the world in confronting and defeating the man-made evil of international terrorism.

The funds will be dispersed as follows: \$9 billion to 12 nations in Africa and 2 in the Caribbean, through bilateral arrangements; \$5 billion to approximately 100 other nations with which the U.S. has bilateral HIV/AIDS programs; and \$1 billion to the Global Fund (Tobias, 2004).

Response to the President's announcement was swift and often very favorable. The initiative was described as "a serious response to AIDS" (New York Times, 2003); "as welcome as it was surprising" (Intelligencer Journal, 2003); as "a tremendous breakthrough" by health economist Jeffrey Sachs (Kaiser, 2003); "encouraging, even historic" by Paul Zeitz, the Executive Director of the Global AIDS Alliance (Zeitz, 2003); and a "welcome sign" by Dr. Helene Gayle of the Bill and Melinda Gates Foundation (Gayle, 2003). When the U.S. Senate voted to approve the bill on May 16, 2003, the legislation was described as a "legislative trophy" that President Bush could carry with him to his upcoming meetings with world leaders (Stolberg, 2003).

However, PEPFAR has its detractors. Several critics have said that PEPFAR provides too little funding to the Global Fund but instead funds new, bilateral programs in 14 nations and two (Clinton, 2003; Kaiser, 2003; Kim, 2003; New York Times, 2003). As a result, PEPFAR may provide little assistance to other countries where the AIDS virus is spreading rapidly, including China, India, and Russia. In addition, RESULTS, Inc., and the Open Society Institute (2004) challenged Mr. Tobias to work with other donors to address the TB/HIV coepidemics, by "better integrating TB and HIV/AIDS efforts through expanding TB programs to reach all those HIV patients with TB and linking TB programs to HIV/AIDS voluntary counseling and testing."

In bypassing the Global Fund, which already has a funding mechanism in place, PEPFAR delayed funding. Indeed, Randall Tobias, President Bush's new AIDS coordinator, did not announce the first round of funding until February 2004 (Tobias, 2004).

Much of the funding for infectious disease control flows through USAID, but much of the PEPFAR funds will be channeled instead through a new account, the Millennium Challenge Account, "which requires poor nations to meet criteria of good government to receive aid" (Becker, 2003). Critics have questioned the wisdom of adding yet another agency to the groups already giving federal funds to disease control projects overseas. It is worth noting that both USAID and Mr. Tobias's office are in the State Department, not in the Department of Health & Human Services.

Summary Advocates for TB control and prevention should be proud of their accomplishments in the past 15 years. Their efforts have put TB on the national political agenda and have resulted in substantial increases in funding to the CDC and NIH for TB-related activities. Their efforts have also succeeded in increasing U.S. support of global TB control.

VII. Conclusion

The resurgence of TB in the U.S. in the 1980s could have been avoided, because we had the tools and the knowledge to prevent, treat, and cure TB. However, HIV/AIDS and powerful social forces converged at a time when federal funding for TB control was woefully inadequate. Increases in funding targeted for TB have resulted in steady

declines in the incidence of TB in the U.S. since 1992—and this has been accomplished without developing any new tools. The U.S. experience in the past 15 years thus provides a graphic example of what Dr. Lin Yan of WHO’s Beijing office meant when he said, “TB is not a technical problem, but a political commitment and monetary problem. The only problem is how to control resources and increase funding.” (Dorgan, 2001)

The global epidemic dwarfs the one in the U.S.: Whereas 26,673 cases of active TB were reported in the U.S. in 1992 at the peak of the resurgence, nearly 25,000 new cases of TB occur *every day* globally. Responding to the global epidemic will require political commitment in all countries—donors and recipients alike—and increases in funding. Increased funding, together with *existing* tools, is already having an impact on TB control and prevention in many settings. However, we could do a much better job if we had better tools to diagnose, treat, and prevent TB. In particular, a better vaccine would be almost a miracle.

The “medicalization” of TB—and of HIV/AIDS, malaria, etc.—will alleviate but not solve the underlying problems of poverty: inadequate housing, poor nutrition, and substandard healthcare. Surely we must address the medical needs of suffering men, women, and children, but we should also help them build strong, stable societies. Such societies will not only meet the needs of their members but will, some have argued, increase global security as well (Horton, 2001).

With TB waning once again in the U.S., policymakers will be tempted to decrease funding for TB control, just as they did in the 1970s. Lee Reichman has called this pattern “the U-shaped curve of concern” (Reichman, 1991):

“First, evaluation indicators of a public health program show improvement leading to diminishment of compelling need. Then resources providing fuel and direction for the program are removed. Finally, the incidence of the disease “controlled” begins to rise in proportion to the diminished resources.”

Thus, the challenge now facing TB advocates in the U.S. is to convince policymakers in Washington to continue to provide the resources for TB-related activities, not only the U.S. but around the world. The technical expertise in the U.S. in public health, medicine, and basic science should be seen as a global resource. We need to sustain this expertise and deploy it for the benefit of humankind.

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