# TUBERCULOSIS CONTROL: CHALLENGES OF AN ANCIENT AND ONGOING EPIDEMIC

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Tuberculosis (TB) has been with us for thousands of years. From the ancient Egyptians, whose mummies still harbor its nucleic acid, to the Romantic Age writers, who thought it begot genius, our forebears struggled with—and against—TB. For most of that history, control of TB was hampered by a misunderstanding of its most basic features. Despite Hippocrates' apt description of the disease as marked by fevers, sweats, sputa, and wasting, he believed it to be a hereditary condition. While Osler knew its origins well, he had few tools, beyond diagnostic acumen, with which to challenge it. Trudeau, the father of the sanatorium movement in America, eventually succumbed to the disease himself—his "rest therapy" failing even its greatest proponent.

In contrast, the last century played witness to a dramatic expansion of the armamentarium against TB. By the 1960s, so many of the components essential to fighting, even eradicating, an infectious disease were in place: tools of diagnosis, therapeutics, even primary and secondary prevention. Yet today this treatable, preventable disease kills nearly 2 million people on our planet each year. Clearly, the paradigm of "microbes and medicines" has proven inadequate in the control effort. How did the public health approach fail, and how is it being redirected? To ultimately control and eliminate this disease, we will need to understand the last century's outstanding successes as well as its abject failures in the fight against TB.

## ANTIOBIOTIC ERA

The Bacille Calmette-Guerin (BCG), an attenuated strain of *Mycobacterium bovis* introduced as a TB vaccine in the 1920s, was quickly embraced in many areas. Early observational trials of nursing students and exposed schoolchildren in Europe, along with some of the later controlled trials in places such as India and Africa, confirmed the initial claims of efficacy, particularly for meningitis and miliary disease in high-prevalence areas.[1] The U.S. trials of BCG showed conflicting results: while it was demonstrated to be protective in Native Americans on reservations, it was without efficacy in children in Georgia.[2] Ultimately, a new solution made the question of BCG efficacy in the U.S. essentially moot: antimycobacterial agents.

In the early decades of the 20th century, the first pharmacologic agents used, unsuccessfully, against TB were compounds such as gold and calcium (the latter, it was hypothesized, would inhibit TB, based on the observation that healed tuberculous lesions are calcified). Later, in the 1930s, the new sulfa drugs were tested, but also found to be of no benefit. It was the discovery of streptomycin by soil biologist Selman Waksman in 1944 that truly offered a magic bullet for TB. Waksman, a Ukrainian immigrant working in New Jersey with fungal products that he termed "antibiotics," found one with activity against *Mycobacterium tuberculosis* and relatively low toxicity in animals.[3] In 1948 came the results of a British trial that has since served as a model for drug study design: a randomized, controlled trial, it demonstrated a clear benefit, though not complete efficacy, of streptomycin over no treatment.[4] Waksman went on to win the Nobel Prize in Medicine for his work with streptomycin in 1952.

Contemporaneous with Waksman's search for biological agents, scientists were investigating chemical compounds with activity against TB. The compound para-aminosalicylic acid (PAS) was found to inhibit TB growth, but its use was limited to some degree by its toxicity.[5] Three separate pharmaceutical companies are credited with the simultaneous recognition of isonicotinic acid hydrazide or isoniazid (INH) in 1952.[6] Its effects were unprecedented: when given orally to patients who had failed other therapies, fevers resolved, coughs ceased, appetites returned, and radiographs cleared, without significant toxicity. The companies soon learned that their discovery had been described by chemists in 1912 and thus could not be patented, thereby greatly limiting its price.

Within a year, INH was generally available. Its effect on TB control was remarkable: rest therapy was abandoned and sanatoria closed precipitously, including Trudeau's at Saranac Lake, New York, in 1954. In Madras, India, a rigorous study of sanatorium vs. home therapy was published in 1959.[7] It demonstrated that treatment at home, with frequent clinic visits, was as effective as that afforded in an institutional setting, where rest, nutrition, and nursing care were more readily had. Patients the world over could now be safely treated at home, at a considerable savings to the public.

The earliest studies of antimycobacterial monotherapy led to a concerning observation: decreasing therapeutic efficacy over time. Researchers hypothesized that this apparent drug resistance might be averted by using two or more agents at once, and set out to investigate such combination therapy. The first study examined the combination of streptomycin and PAS, concluding that the combination was more efficacious than either drug alone and better prevented the development of resistance.[8] Later, when INH was introduced and combinations were studied, triple therapy with streptomycin and PAS for 24 months became the standard, providing high cure rates with low drug resistance.[9]

New agents introduced in the 1960s and 70s led to further improvements in combination regimens. Ethambutol, better tolerated than PAS, came to replace that agent, reducing the length of treatment to 18 months.[10] When this regimen was augmented by the addition of rifampin, length of treatment could be further reduced to nine months.[11] And the combination of INH, rifampin, and pyrazinamide was shown in multiple studies to achieve cure in just six months. While rifampin and pyrazinamide were less potent against actively dividing organisms than the bactericidal INH, they shortened the duration of therapy in part because of their superior sterilizing activity, or ability to kill the semidormant mycobacteria responsible for relapse.[12] Later investigations demonstrated that intermittent regimens achieved therapeutic drug levels and were equivalent to daily administration.[13]

## SECONDARY PREVENTION

In 1954, soon after the introduction of INH, New York pediatrician Edith Lincoln proposed a novel use for the drug. Lincoln had observed the remarkable effect of INH in her patients, including those with primary TB, who appeared to be protected from progression to chronic disease.[14] She hypothesized that the drug might benefit even those with only positive tuberculin skin tests, in the absence of pulmonary disease. She took her idea to the United States Public Health Service (USPHS), which conducted a series of placebo-controlled trials involving 70,000 people.[15] The results were impressive, supporting what became known then as INH prophylaxis and later as treatment of latent TB infection. Overall, more than 50% of the expected cases of TB were prevented, with greater benefits in the young and the more recently infected. There seemed to be no significant side effects.

Prophylactic INH was broadly recommended by the American Thoracic Society (ATS) in 1967.[16] Expectations were high: the ATS anticipated a reduction in TB morbidity of 50% to 75% with widespread use. That would not come to fruition. In 1970, two cafeteria workers in the U.S. Capitol Building were found to have active TB. A tuberculin testing campaign was undertaken and several thousand workers who tested positive were started on INH. Within months, 19 had developed hepatitis and two had died of fulminant liver failure.[17] Why this side effect had not emerged in the large-scale trials in the 1950s was initially unclear.

The ultimate analysis demonstrated associations including alcohol, polypharmacy, and age, leading to the recommendation of an age limit of 35 for INH prophylaxis. Over time, that limitation was reconsidered and revised in light of emerging evidence about INH safety, including the preventability and reversibility of hepatic toxicity with close clinical monitoring. Today, the ATS endorses targeted tuberculin testing and nine-month INH treatment of individuals at high risk of developing TB, regardless of age.[18]

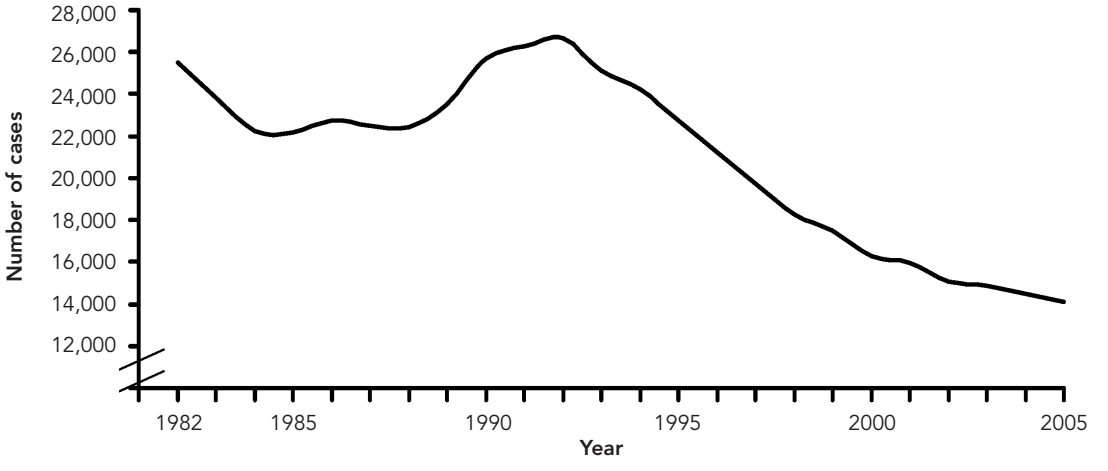
## FALTERED CONQUEST

The availability of effective antibiotic therapy heralded an age of optimism. In 1960, the USPHS announced its goal of "approach to zero tuberculosis." Four years later, Waksman published his memoirs under the title *The Conquest of Tuberculosis*. The nearly 6% per year decline in U.S. TB incidence over the 30 years following the introduction of INH reinforced this sentiment.[19] In 1985, however, a surprising trend became apparent: U.S. TB incidence was increasing (Figure 1). Soon, the same was recognized in other developed nations and, more strikingly, in the developing world: in sub-Saharan Africa, the annual increase in TB incidence was a staggering 500%.[20]

There is no doubt that the human immunodeficiency virus (HIV) epidemic played a substantial role in the resurgence of TB worldwide. The shared risk factors, including poverty, drug use, and homelessness, promoted co-infection with TB and HIV. By the mid-1990s, 10% to 15% of TB patients in the U.S. and more than 30% of TB patients in Africa were also infected with HIV.[21] HIV depresses the very components of the host immune system most important in the response to TB, namely cell-mediated immunity and stimulatory cytokines such as interferon-gamma. Indeed, whereas an HIV-negative individual has an estimated 10% lifetime risk of reactivation of latent TB, an HIV-positive person's risk of reactivation was found to be increased dramatically, on the order of 10% per year.[22]

HIV infection was also shown to increase the risk of progression to active disease after newly acquired

**Figure 1. Reported TB cases, United States, 1982–2005[a]**




[a]As of March 29, 2006

Source: Centers for Disease Control and Prevention (US). Reported tuberculosis in the United States, 2005. Atlanta: Department of Health and Human Services, CDC; 2006.

TB = tuberculosis

infection.[23] Recognizing this deadly combination could be a challenge: HIV might induce anergy to tuberculin skin testing, and atypical presentations of active disease were common, from pulmonary disease with unusual chest radiographic findings to extra-pulmonary TB.[24] By 1999, TB was responsible for 30% of deaths in HIV patients globally.

In the U.S., ongoing migration from high-prevalence countries also affected TB rates, due to importation of active or latent disease. From 1986 through 1992, TB among the foreign-born accounted for 60% of the increase in the total number of cases, with Asian and Hispanic people having the greatest impact.[25] Furthermore, the contribution of cases among the foreign-born to the U.S. total climbed steadily (Figure 2). By 2000, the case rate among the foreign-born was at least seven times that of U.S.-born people.[26] The rates among refugees were particularly concerning: during the late 1990s in one county in Georgia, refugees were found to represent nearly 20% of all cases among the foreign-born, despite making up only 10% of that group.[27]

Drug resistance also played a significant part in the resurgence of TB, both in the U.S. (Figure 3) and abroad. Despite the cautionary observations of single-drug resistance seen in the early studies of antimycobacterial monotherapy, the emergence and transmission of multidrug-resistant TB (MDR-TB) in the 1980s were, in a sense, man-made. Suboptimal therapy, including erratic ingestion, insufficient number of drugs, and inadequate treatment length, led to the selection of strains resistant to both INH and rifampin, and at times to additional first-line agents. By 1991, 7% of TB isolates from naïve patients and 30% from previously treated patients were MDR in New York City—not surprising given the adherence rate of just 50% during that era.[28,29] The problem was not limited to New York City: 2.2% of all cases nationwide were MDR-TB in the mid-1990s.[30] In the developing world, the 1990s also witnessed the increasing threat of MDR-TB, with new case prevalence as high as 14% in areas of Eastern Europe.[31]

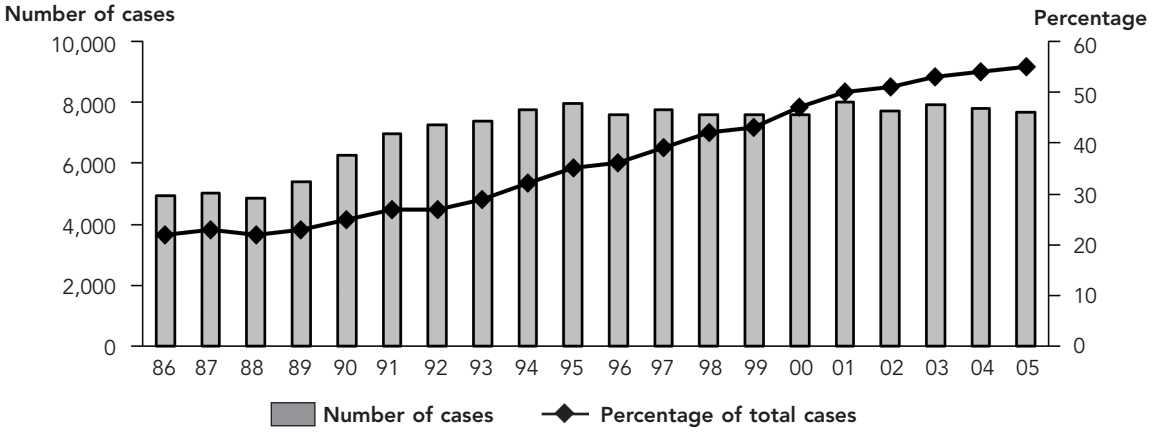
But perhaps the most appalling factor was the neglect of TB as a public health priority. As rates fell, complacency rose; for instance, in 1972, categorical federal funding for TB control was terminated.[19] The subsequent crumbling of infrastructure disproportionately affected the marginalized members of society most dependent on public funds: the poor, the homeless, and the incarcerated. It also contributed to nosocomial TB transmission, both between patients and from patients to health-care workers, bringing the issue directly into the view of the medical community.[32]

## MODERN APPROACHES

### United States

Directly observed therapy (DOT) took its inspiration, in some sense, from the sanatorium model: close con-

**Figure 2. Trends in TB cases in foreign-born people, United States, 1986–2005[a]**




[a]As of March 29, 2006

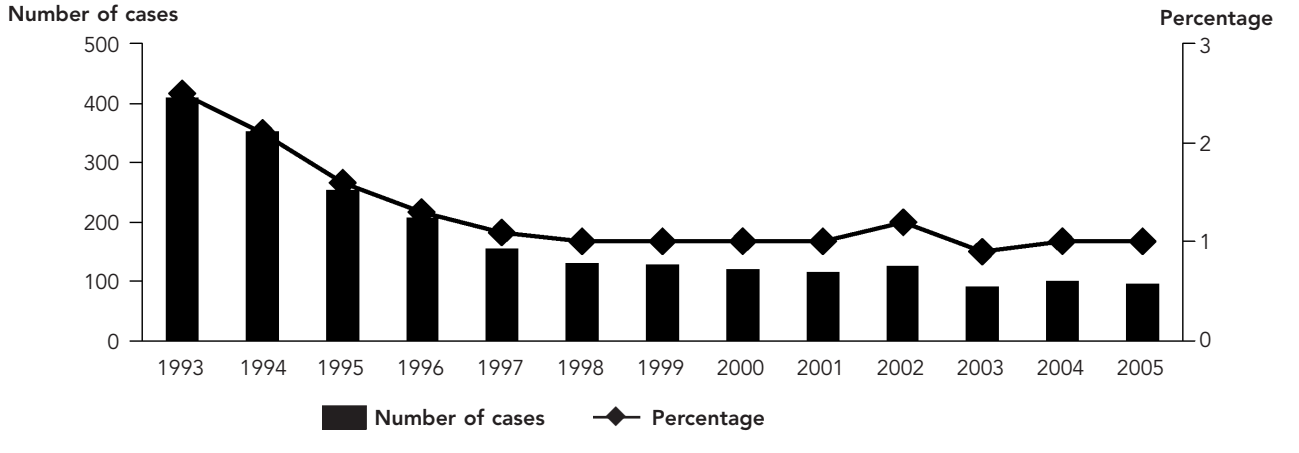
Source: Centers for Disease Control and Prevention (US). Reported tuberculosis in the United States, 2005. Atlanta: Department of Health and Human Services, CDC; 2006.

TB = tuberculosis

tact with the patient throughout the treatment process to ensure completion of a full treatment regimen. Baltimore was one of the first cities to adopt the DOT model in the early 1980s and its experience is compelling.[33] Using a community-based approach, the Health Department provided therapy at a location convenient to the patient: home, place of employment, school, or institutional setting, such as a jail or nursing facility.

From 1981 to 1992, during a national upsurge in TB, in a city troubled by poverty and a growing HIV epidemic, a 50% reduction in TB rates was achieved. Furthermore, the MDR-TB that so plagued other urban

**Figure 3. Primary[a] MDR-TB,[b] United States, 1993–2005[c]**




[a]Based on initial isolates from people with no prior history of tuberculosis

[b]MDR-TB is defined as resistance to at least isoniazid and rifampin.

[c]As of March 29, 2006

Source: Centers for Disease Control and Prevention (US). Reported tuberculosis in the United States, 2005. Atlanta: Department of Health and Human Services, CDC; 2006.

MDR-TB = multidrug-resistant tuberculosis

centers was averted: less than 1% of isolates from patients managed with DOT in Baltimore were drug-resistant. DOT has subsequently become the standard nationally, contributing to the falling incidence of TB in the U.S. since the mid-1990s (Figure 1).

In 1992, the CDC released its "National Action Plan to Combat Multidrug-Resistant Tuberculosis," and significant efforts have since been made to address the issue of drug resistance. The initiation phase, or first two months, of TB therapy now generally includes four drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) in recognition of the high baseline prevalence of single-drug resistance.[34] Drug susceptibility testing has become routine, aiding both clinical care and epidemiological surveillance. Formal screening and infection control programs have been initiated in institutional settings including prisons and hospitals, in recognition of the risk of MDR-TB transmission at such facilities. And while randomized controlled trials on MDR-TB treatment regimens are lacking, the emphasis on management of MDR-TB in consultation with or by referral to specialized centers has led to improved outcomes, with long-term success rates now at 75%.[35]

The experience in California over the past decade is exemplary: the number of MDR-TB cases decreased 33%, while the proportion of MDR-TB of all TB cases held steady at 1.4%.[36] The fact that more than 80% of those MDR-TB cases occurred in the foreign-born suggests new tactics will be necessary to eliminate MDR-TB in the U.S.

Indeed, renewed efforts have been made to address TB control in the foreign-born. TB screening is required for foreign-born people applying for permanent legal status; approximately 800,000 applicants were screened annually as of 1998.[37] This figure includes those currently in the U.S. on nonimmigrant visas who want to adjust their status, who are screened in the U.S. with tuberculin skin testing and chest radiography (if skin test is positive), and immigrants and refugees applying from abroad, who are screened overseas with chest radiography and sputum smear microscopy (if chest radiograph is abnormal) by physicians designated by the U.S. consul. Both groups are referred to local health departments in the U.S. for further evaluation if active or latent disease is identified by screening; overseas applicants with smear-positive TB must be treated before departure for the U.S.

While this system appears to identify most applicants with active TB, improvements are needed. Overall, fewer than 15% of those referred from overseas for evaluation in the U.S. are found to have active disease, suggesting that more specific screening tools would be beneficial.[38] In addition, immigrants and refugees with TB may be lost to follow-up after arriving in the U.S., if they fail to seek further evaluation. A study of immigrants and refugees arriving in San Francisco in the early 1990s highlights these issues.[39] Nearly 20% of those referred to the health department by overseas physicians failed to report for evaluation, and only 7% of those who did report were found to have active TB. Refugee status was an independent predictor of failure to seek further evaluation, which is particularly concerning given the documented higher prevalence of TB in refugee groups. Another shortcoming is that the program does not address the large number of undocumented foreign-born people entering and residing in the U.S., for whom no formal screening exists.[37]

Several other approaches to TB control among the foreign-born have been implemented. Contact tracing is one means of identifying new cases of both active and latent disease. Contact tracing of foreign-born cases has been found to yield higher numbers of TB-infected contacts than does contact tracing of U.S.-born cases.[40] Obstacles include language and cultural barriers, high background prevalence of tuberculin skin test positivity among close contacts, concern on the part of patients and contacts regarding legal residence status, high mobility within the U.S. among some contacts (i.e., migrant workers), and return of contacts to country of origin.[37] Despite these challenges, contact tracing of foreign-born cases may be more cost-effective than other control approaches.[41]

Partnerships with local community-based organizations and community leaders may also facilitate control efforts; one public health department found it had better than expected completion rates for treatment of latent TB among refugees when case manager cultural mediators were involved.[42] And as control of TB among the foreign-born will ultimately depend on the success of TB control abroad, the CDC strategy also includes support of foreign TB control programs.

**Developing nations**

In the developing world, efforts have been made to reduce the cost of DOT while maintaining its efficacy. DOT, short-course (DOTS) is the World Health Organization (WHO) program introduced in the 1990s.[43] It emphasizes the diagnosis and treatment of sputum smear-positive TB, given the higher mortality and increased infectiousness of such cases. DOTS combines supervised swallowing for at least the first two months of treatment with political commitment, microscopy services, drug supplies, and monitoring (Figure 4).

Treatment regimens vary, but four drug regimens for the first two months are standard, given the risk of drug resistance, and are generally followed by two

**Figure 4. The expanded framework of the DOTS strategy**

**Sustained political commitment**
to increase human and financial resources and make tuberculosis (TB) control a nationwide activity that is integral to the national health system.

**Access to quality-assured TB sputum microscopy**
for case detection among people presenting with, or found through screening to have, symptoms of TB (most importantly, prolonged cough). Special attention is necessary for case detection among people infected with human immunodeficiency virus and other high-risk groups, e.g., people in institutions.

**Standardized short-course chemotherapy to all cases of TB under proper case-management conditions, including direct observation of treatment**
proper case management conditions imply technically sound and socially supportive treatment services.

**Uninterrupted supply of quality-assured drugs**
with reliable drug procurement and distribution systems.

**Recording and reporting system enabling outcome assessment**
of each and every patient and assessment of the overall program performance.

Source: World Health Organization. An expanded DOTS framework for effective tuberculosis control. Geneva: World Health Organization; 2002. WHO/CDS/TB/2002.297.

DOTS = directly observed therapy short-course

drug combinations for another four to six months.[44] Daily administration is preferred, particularly for the first two months, and fixed-dose drug combinations, thought to reduce prescription errors and increase patient adherence, are encouraged. By 2004, the strategy had been adopted by 183 nations, including the 22 nations with the highest TB incidence.[45]

While DOTS has been credited with preventing the emergence of resistance, it has little effect on current cases of MDR-TB, which until recently were considered too costly to treat in developing countries.[46] However, as the experience in Peru through 1999 demonstrates, MDR-TB can be treated successfully in a resource-poor setting, when individualized regimens that include second-line drugs are used.[47] This community-based outpatient approach yielded likely cure in more than 80% of patients who received at least four months of therapy, despite TB resistance to a median of six drugs.

WHO's response to MDR-TB is DOTS-Plus, a program now in the developmental stage, setting global policy for the management of MDR-TB.[48] One significant obstacle will be funding for the more expensive second-line drugs needed to treat MDR-TB, an issue that is being addressed in novel ways via agreements with the pharmaceutical industry.[49] The recent recognition of extensively drug-resistant TB (XDR-TB), resistant to INH, rifampin, any fluoroquinolone, and at least one of three injectable second-line drugs, makes the implementation and expansion of DOTS-Plus imperative (Figure 5).[50]

There is also concern that DOTS alone may be insufficient to control TB in areas with high HIV prevalence. Indeed, some regions of Africa have escalating rates of TB despite the implementation of DOTS. Clearly, expanding the availability of antiretroviral therapy is imperative. In addition, a more multifaceted approach to TB control itself has been advocated for such areas, addressing such measures as contact tracing and prevention of reactivation of latent disease.[51] There is now substantial evidence that INH therapy reduces the incidence of active TB in HIV-infected people.[52] However, in the developing world, this therapy has proven logistically difficult to implement, in part because tuberculin skin testing and screening chest radiography require multiday and often multisite commitments on the part of the patient. Several recent studies (in Thailand and South Africa) have addressed these issues, demonstrating that in HIV patients without active TB, the use of INH therapy in the absence of pretreatment screening for latent TB is both feasible and beneficial.[53,54]

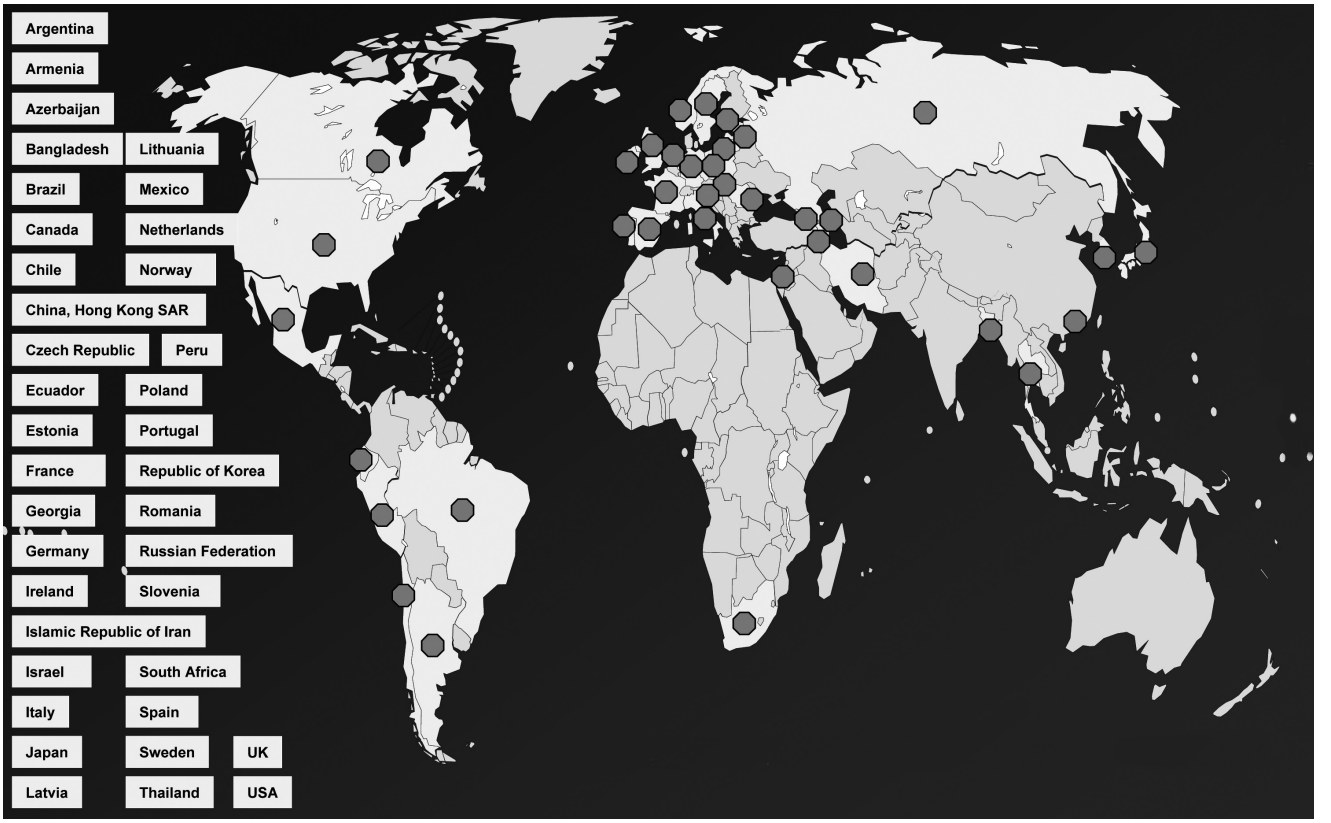
## NOVEL TOOLS

### Diagnostics

Today, TB is a 21st century disease, yet one that is being fought, for the most part, with 19th and 20th century tools. With the resurgence in TB, there has been renewed interest in updating that technology. Some of the greatest advances have been in the realm of diagnostics. In the last decade, molecular epidemiology has been increasingly used to understand TB transmission. By differentiating among various TB genotypes, DNA fingerprinting has contributed to outbreak investigations, allowing investigators to distinguish between related and sporadic cases.[55] It has also been used in suspected cases of laboratory cross-contamination of culture specimens, averting misdiagnosis of uninfected people, which is estimated to occur with a frequency of 1.5%.[56] In population-based studies, DNA fingerprinting has identified clustering of cases not previously recognized as linkages or recent transmissions, demonstrating the shortcomings of traditional contact tracing and enhancing control efforts.[57]

Another important advance in diagnostics is that of nucleic acid amplification, introduced in the mid-1990s. Sputum smear microscopy and culture have been the mainstays of TB diagnosis since Koch's dis-

**Figure 5. Countries with extensively drug-resistant tuberculosis[a]**




[a]As of May 2007

Source: World Health Organization. Extensively drug-resistant tuberculosis: what, where, how, and action steps [cited 2007 Jun 4]. Available from: URL: http://www.who.int/tb/xdr/xdrmap_1may_en.pdf (Reproduced with permission).

covery of *Mycobacterium tuberculosis* in the 19th century. Yet they are imperfect techniques. The sensitivity of routine sputum smear microscopy is as low as 50%, and its specificity is affected by the local prevalence of non-tuberculous mycobacteria. Culture is the gold standard, but it is slow and requires laboratory services that may be unavailable in remote areas.

Nucleic acid amplification techniques offer several advantages. The sensitivity is higher than that of smear microscopy, reaching 90% overall and 60% for smear-negative samples in pulmonary disease.[58,59] Because the tests detect DNA or RNA sequences unique to *Mycobacterium tuberculosis,* their specificity approaches 100%. And the results are available rapidly, when treatment decisions are being made. Thus, nucleic acid amplification tests may be useful, in certain clinical settings, for distinguishing tuberculous from non-tuberculous infections, and identifying cases of smear-negative TB weeks in advance of culture. The role in the developing world is not yet clear; while experimental use in South Africa has demonstrated its utility, cost will likely be prohibitive for some time.[60]

The diagnosis of latent TB infection has, until recently, been limited to tuberculin skin testing. Skin testing, which relies on the delayed type hypersensitivity reaction, has several disadvantages: it requires a 48- to 72-hour return visit, its interpretation is prone to subjectivity, and it is not specific for TB, as the purified protein derivative (PPD) used to stimulate a response includes antigens common to many mycobacteria, including BCG. Newer in vitro tests based on the production of interferon-gamma in response to TB infection address these deficiencies.

In the QuantiFERON-TB Gold assay, available since 2004, blood is incubated with TB-specific antigens, after which interferon-gamma levels are measured.[61] While the lack of a confirmatory standard for latent TB infection limits evaluation, studies suggest that

the QuantiFERON technique is comparable to the tuberculin skin test.[62] Agreement between the two tests tends to be high, and the QuantiFERON appears to better discriminate between TB and non-tuberculous mycobacteria, including BCG. A similar diagnostic test not yet approved by the Food and Drug Adminstration, T-SPOT.TB, may have a higher sensitivity than QuantiFERON for detecting latent disease in immunosuppressed patients.[63] Further research will be needed to assess the cost-effectiveness of these novel assays.

**Therapeutics**

TB therapeutics is another area of active development. New agents are being sought to shorten the total duration or lower the dosing frequency of regimens for drug-sensitive strains, to offer therapeutic options for MDR-TB, and to better treat latent TB. Fluoroquinolones such as moxifloxacin are under study, and may prove capable of shortening treatment duration.[64] Long-acting rifamycins, such as rifapentine, offer the possibility of once-weekly administration for active disease.[65] Oxazolidinones including linezolid have been found to have in vitro activity against TB, and recent evidence suggests that linezolid is highly active against MDR-TB.[66]

One novel agent with great promise is a diarylquinoline (referred to as R20791), which targets the proton pump of adenosine triphosphate (ATP) synthase.[67] Studied thus far in mice, its bactericidal activity exceeds that of INH and rifampin, and it appears capable of converting cultures after two months of therapy. Another new drug that has been studied in vitro and in a murine model, PA-824, is a nitroimidazole with potentially broad applications.[68] It is active in acute disease, against MDR-TB, and under conditions that simulate latent infection.

**Prevention and collaboration**

In the area of TB prevention, a major focus has been on developing a better TB vaccine. Several approaches have been employed. Some groups are working on improving, rather than replacing, the existing BCG vaccine.[69] One candidate has a second copy of a gene that codes for a secretory protein (antigen 85b), and thus produces more protein than the parent BCG, leading to a more vigorous immune response. Another candidate has been modified to include a *Listeria* gene that stimulates a CD8 T-cell response, thought to be lacking with the current BCG vaccine.

Other vaccines in development are novel ones not based on BCG, such as attenuated *Mycobacteria tuberculosis* and subunit vaccines comprised of either protein or DNA.[70] One subunit vaccine in clinical trials in the United Kingdom and Africa is MVA85A, which consists of a modified vaccinia virus designed to express a subunit of antigen 85.[71] Phase I studies showed that while the vaccine induced high levels of antigen-specific T-cells in BCG-naïve volunteers, levels were up to 30 times greater in volunteers who had previously received BCG. Use of this vaccine as a booster for BCG may therefore prove to be the best strategy.

Perhaps the most effective innovation to come from the response to the resurgence of TB will be that of collaboration. This endeavor has crossed not only regional and national borders, but also organizational ones: public-private initiatives to promote, fund, and deliver TB control measures on a global scale. The Stop TB Partnership came out of a 1998 meeting on the TB epidemic; today, it is housed in the WHO and comprises a network of more than 120 organizations, from governmental to philanthropic, local to international, which share the goal of eliminating TB. It is charged with the expansion of DOTS, the introduction of DOTS-Plus, and the development of new drugs, diagnostics, and vaccines.

In 2000, Stop TB organized a meeting on drug development in Cape Town, South Africa, that led to the founding of the Global Alliance for TB Drug Development. This not-for-profit enterprise, with stakeholders ranging from academia and industry to foundations and governmental agencies, was designed to accelerate development of and promote equitable access to new, more effective TB drugs. Its first drug, the nitroimidazole PA-824, is now in phase I trials; the developer, Chiron Corporation, has agreed to make the drug available royalty-free in endemic countries.[72] Stop TB now has similar partnerships underway for diagnostic tools (Foundation for Innovative New Diagnostics) and vaccines (Initiative for Vaccine Research).

Another public-private entity is the Global Fund, launched in 2001 with the support of the United Nations (UN) and the G8 countries to provide funding of large-scale public health initiatives to combat acquired immunodeficiency syndrome (AIDS), TB, and malaria. Partners include major development agencies such as the World Bank and the WHO, as well as governmental, private-sector, and community representatives. Thus far, more than $500 million has been committed to TB projects throughout the world through the Global Fund.

## CONCLUSIONS

The UN Millennium Development Goals aim to halt and begin to reverse the TB incidence by 2015, and to halve the TB prevalence and mortality rates between

1990 and 2015. To achieve these goals, the WHO set targets in 1991 to be met by 2000: detection of 70% of all new sputum smear-positive cases arising each year, and successful treatment of 85% of these new cases. When those targets were not met by 2000, the target year was changed to 2005.[73] Since then, improvements have been made: in 2004, the global detection rate of new sputum smear-positive cases reached 53% and treatment success was at 82%.[74] In many regions, TB incidence has stabilized or declined; global prevalence is falling at about 5% per year. Yet global TB incidence increased from 1990 through 2003, and there has been no significant fall in the mortality rate. Indeed, based on the larger global population, more people died from TB in 2003 than in 1990.

These trends suggest that the global TB incidence will increase further in the next decade, fueled in great part by failures to control TB in Africa and, to a lesser extent, in Eastern Europe. To avoid that prophecy, much work will need to be done. It is clear that targeted therapies including antibiotics and vaccines will be crucial to the effort, and ongoing work to expand the armamentarium is to be commended. Yet it is equally clear that the mere existence of such therapies will not be sufficient.

A reduction in the world TB burden will require an increased dedication of resources to address both sensitive and drug-resistant TB in a sustained manner, a willingness to expand access to HIV therapy widely, and a readiness to adapt global solutions to local needs and circumstances. A lesser commitment, as history has shown, is no commitment at all.

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