REVIEW

Tuberculosis: What We Don't Know Can, and Does, Hurt Us

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Mycobacterium tuberculosis has a penetrance of its host population that would be the envy of most human pathogens. About one-third of the human population would have a positive skin test for the infection and is thus thought to harbor the bacterium. Globally, 22 "high-burden" countries account for more than 80% of the active tuberculosis cases in the world, which shows the inequitable distribution of the disease. There is no effective vaccine against infection, and current drug therapies are fraught with problems, predominantly because of the protracted nature of the treatment and the increasing occurrence of drug resistance. Here we focus on the biology of the host-pathogen interaction and discuss new and evolving strategies for intervention.

Tuberculosis (TB) is a disease that, in the Western world, is held in check by effective public health systems that compensate for the relative shortcomings of current intervention strategies. However, because of the lack of vaccines and the need for new, faster-acting drugs, it is unclear how the disease can ever be controlled in the countries where it is truly endemic. In addition, as highly drug-resistant strains continue to evolve, we face the risk of losing control even in the industrialized world. Despite recent increases in research activity, we remain hampered by large gaps in our knowledge of the biology of this pathogen (Table 1). An increased appreciation of the bottlenecks in the life cycle of *Mycobacterium tuberculosis* (*Mtb*) should facilitate development of new intervention strategies that are applicable to those countries most in need.

The Life Cycle of *M. tuberculosis*

Infection with *Mtb* follows a pattern of events that have been established through animal models, as well as observations from human TB (*1*, *2*) (Fig. 1). The infectious bacilli are inhaled as droplet nuclei that have been exhaled into the atmosphere. These droplets are small enough to remain airborne for several hours. Estimations of the minimum infectious dose range from a single bacterium upward. Our understanding of the initial stages of infection in the lung is mainly through inference; it is generally believed that the bacteria are phagocytosed by alveolar macrophages, which then invade the subtending epithelial layer. This induces a localized inflammatory response that leads to recruitment of mononuclear cells from neighboring blood vessels, providing fresh host cells for the expanding bacterial population. These cells are the building blocks of the granuloma, which is the defining pathologic feature of this disease. Initially the granuloma is an amorphous mass of macrophages, monocytes, and neutrophils; however, the macrophages differentiate into several specialized cell types, including multinucleated giant cells, foamy macrophages, and epithelioid macrophages. With the development of an acquired immune response and the arrival of lymphocytes, the granuloma acquires a more organized, stratified structure. The macrophage-rich center becomes surrounded by a mantle of lymphocytes that may be enclosed within a fibrous cuff that marks the periphery of the structure.

The appearance of *Mtb*-specific lymphocytes about 2 to 3 weeks postinfection marks the end of the phase of rapid bacterial replication and the onset of a "containment" state that, in mice, is characterized by relatively stable bacterial numbers. At this time, the granuloma is extensively vascularized, and cells are actively recruited to the site of infection. In granulomas exhibiting the pathology associated with disease progression, the fibrous sheath becomes more marked, and the number of blood vessels that penetrate the structure diminishes. There is also an increase in the number of foamy macrophages, which may be responsible for the increase in caseous debris in the center of the granuloma (*3*). At these "late" stages, the caseous portion of the granuloma becomes hypoxic (*4*), a condition that can induce a state of nonreplicative persistence in *Mtb* in culture. Histology of infected tissues from immunocompetent patients with active TB reveals granulomas in all states of development from containment to active disease, which implies that the fate of each granuloma is determined locally, not systemically. Active granulomas exhibit extensive pathology, and, ultimately, the granuloma ruptures and spills thousands of viable, infectious bacilli into the airways (*5*), which results in the development of a productive cough that facilitates aerosol spread of infectious bacilli.

Recent observations in human TB patients indicate that neutrophil influx in late-stage disease may also contribute to the tissue damage and the dissemination of infectious bacteria into the air-

Table 1. Problems with prevention of and treatment for *Mtb* and shortcomings of current intervention strategies.

Global issue	Underlying regional problems
Failure to provide consistent infrastructure support for health care	- Inadequate public health sector in many regions - Variation in disease manifestations across individuals
Failure to develop effective diagnostic and disease status indicators (biomarkers)	- Inadequate testing for drug susceptibility and resistance - Reliance of current diagnostics mostly on the host immune response - Poor correlation of bacterial load in sputum with disease status or outcome - Lack of any indicators of lung pathology or health
Failure of bacillus Calmette-Guérin (BCG) vaccination to protect adult pulmonary TB	- Variability in host response to vaccination - Variability between BCG vaccine strains - Variability in bacterial strains causing infection - Variability in host genetics and/or the environment
Failure of chemotherapy to cure many patients with TB	- Length of therapy makes compliance difficult - Individual lesion types respond at different rates - Drug-tolerant bacteria develop subpopulations - New drug-resistant strains emerge frequently
Failure of target-based drug discovery programs	- Antibiotic killing involves complex biological processes - Genetic essentiality is not related to target vulnerability - Whole-cell screenings are not performed under conditions relevant to in vivo infection

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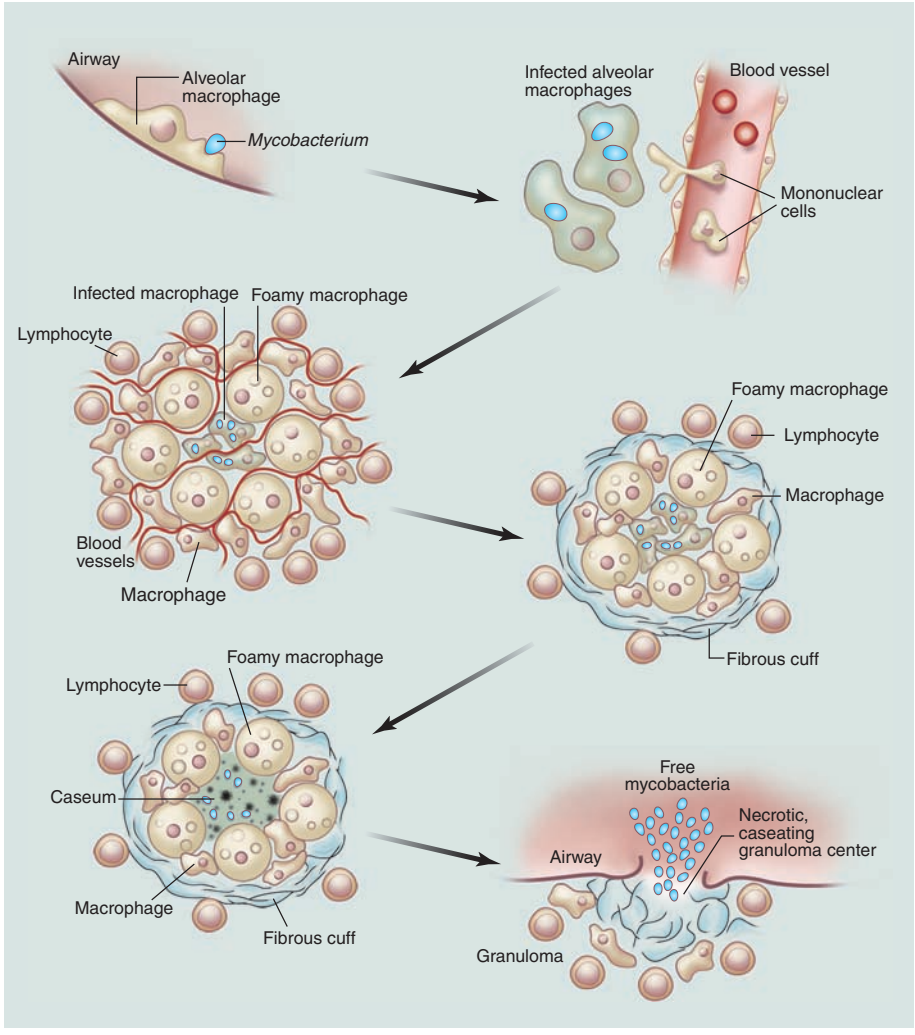

Fig. 1. The life cycle of *M. tuberculosis.* The infection is initiated when *Mtb* bacilli, present in exhaled droplets or nuclei, are inhaled and phagocytosed by resident alveolar macrophages. The resulting proinflammatory response triggers the infected cells to invade the subtending epithelium. This response also leads to the recruitment of monocytes from the circulation, as well as extensive neovascularization of the infection site. The macrophages in the granulomas differentiate to form epithelioid cells, multinucleate giant cells, and foam cells filled with lipid droplets. The granuloma can become further stratified by the formation of a fibrous cuff of extracellular matrix material that is laid down outside the macrophage layer. Lymphocytes appear to be restricted primarily to this peripheral area. Many of the granulomas persist in this balanced state, but progression toward disease is characterized by the loss of vascularization, increased necrosis, and the accumulation of caseum in the granuloma center. Ultimately, infectious bacilli are released into the airways when the granuloma cavitates and collapses into the lungs. [Adapted with permission from Macmillan Publishers Ltd. (*3*)]

ways (*6*). Modern imaging observations on human TB stress that the balance between containment and disease progression is complex and highly dynamic and appears to be a local phenomenon involving differential progression of individual granulomas within a single individual (*7*).

Immune Protection Through Vaccination

A preexisting, specific immune response against *Mtb*, acquired through vaccination or a chemotherapeutically resolved infection, has an impact on the course of TB (*8*) (Fig. 2). The immune host is not protected against infection, but progression to containment occurs earlier, and at a lower bacterial load. In most animal models, bacterial containment is achieved with 1/10th as many bacteria as would be found in the lungs of a naïve animal. At the human population level, this would make a substantial difference, because progression to disease is linked directly to bacterial load. If disease is determined at the level of the individual granuloma, then the presence of fewer granulomas may reduce the chance of developing active disease.

Although the contribution of antimicrobial effectors has been established in mice (*9*, *10*), the relative hierarchy of immune-mediated killing mechanisms in humans is unclear. However, from the increased susceptibility of HIV^+ humans, we infer that CD4 T cells are important in the control of human TB. Similarly, the use of tumor necrosis factor (TNF)–neutralizing agents for treatment of inflammatory diseases substantially increases the risk of TB, which suggests that the level of this cytokine is critical to the balance between disease control and pathology (*11*–*14*). From these data and studies of genetic mutations that predispose humans to TB (*15*), we infer that, similarly to mice, macrophage activation in humans is central to the control of infection.

BCG: It's Not for Everyone

Bacillus Calmette-Guérin (BCG) is the only approved vaccine against TB. It was developed though the serial in vitro passage of *M. bovis* until it became nonpathogenic. It is used in countries with endemic TB because it protects children against severe forms of disease, such as TB meningitis or disseminated infection. However, although effective against development of TB in some countries such as the United Kingdom (*16*), its efficacy has been questioned in several studies, most notably in India, where very limited (or no) protection has been reported (*17*). There are three main hypotheses as to why BCG works in some populations but not in others. First, BCG has become too attenuated through culture, and modern preparations of the vaccine are too benign to generate adequate protective immunity (*18*). Second, exposure of infants to environmental mycobacteria in countries like India could lead to tolerance (*19*–*21*) or, third, clearance of the BCG in some populations may occur before development of a protective immune response. Clearly, as we move forward with new vaccine constructs, it is vital that we better understand the limitations of BCG-induced protection, so that a new vaccine can be effective in those countries where it is most needed.

New anti-TB vaccination strategies can be divided into three broad categories. First, improving BCG by adding or overexpressing strongly immunogenic *Mtb* antigens, which would enhance and broaden the immune responses induced by the recombinant bacterium (*22*–*24*). Second, attenuating strains of *Mtb* through the deletion of genes for specific metabolic pathways required for survival or full virulence (*25*–*27*). And third, the use of prime-boost strategies that direct and amplify an initial "protective" immune response through subsequent inoculation with viral vectors encoding *Mtb* antigens or protein subunits (*28*–*33*).

However, if the protective immune response to these strains is subject to the same environ-

mental factors that limit the effectiveness of BCG in humans, then we have not progressed. This may, however, be circumvented through the prime-boost strategy of supplementing vaccination with BCG, or recombinant strains, with nonreplicating adenovirus or vaccinia virus strains encoding *Mtb* antigens (*28*–*33*), which could supplement existing BCG vaccination programs, although this too has met with mixed results (*30*, *32*).

Transition into the Field

So, given the limited efficacy of immune protection, where would vaccines be most useful in combating TB? Vaccination could play an important role in reducing transmission in areas that have a low incidence of HIV, particularly if there are multidrug resistant (MDR) strains of *Mtb* present. However, the impact of vaccination on populations with high incidence of HIV, such as sub-Saharan Africa, is open to question. Transmission of TB appears to be less efficient in HIV patients because a robust immune response is a major contributor to the pathology required for transmission (*34*–*36*). However, in areas where the coincidence of HIV and *Mtb* infections exceeds 80% of TB cases, this is unlikely to have a discernible impact. We have yet to see if these new modified vaccine strains will improve the protection afforded by BCG or will recapitulate the absence of efficacy of BCG vaccination among ethnic groups most at risk from the disease. The changing landscape of circulating hypervirulent strains, such as the immunosuppressive Beijing lineage, which may have emerged in response to BCG vaccination, also interjects some caution into extrapolation from results generated in the laboratory (*37*, *38*).

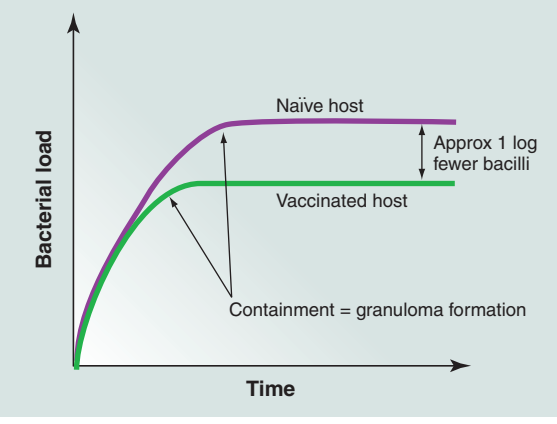

Fig. 2. The bacterial load in naïve and immune hosts. The course of *Mtb* infection in naïve and immune hosts follows a reproducible pattern in the mouse model. After infection, the bacteria replicate exponentially for a period of time until the host develops an acquired immune response, which limits bacterial replication. At this time, the infection makes a transition to a state of persistence or chronicity where the bacterial load is sustained at a relatively constant level. Transition into this persistent state occurs earlier in a vaccinated host or a host that has been infected and treated chemotherapeutically. In mice vaccinated with BCG, this transition occurs with a bacterial load that is about 1/10th that of a naïve host. The transition into persistence is marked by the development of a granuloma.

Chemotherapeutic Intervention

Current chemotherapeutic regimens require more than 6 months' treatment with multiple drugs. Such regimens are plagued with issues of patient noncompliance, inadequate health-care oversight, and the increasing proliferation of drug-resistant strains. The need for fast-acting, effective medications for use in resource-poor countries is immediate.

The balance of the physiological state(s) of the bacterial population inside the granuloma during the dynamic alterations in its structure is clearly central to persistence and progression to disease. Research involving bacterial strains defective in genes critical to various metabolic pathways has revealed different defects during the course of the infection cycle in mice. This implies, not surprisingly, that the bacterium regulates its metabolism differentially during the progression of disease (*7*). Such metabolic shifts could be driven by the availability of certain nutrients or carbon sources, the aerobic or hypoxic nature of the granuloma, or the level of stress induced by various infected host cells and the immune response. Because of the variability between granulomas within a single infected individual and their highly differentiated internal structure, granulomas offer an extremely diverse range of environments for *Mtb*.

In a contained lesion, the bacterial load appears relatively static, and it has been hypothesized that the bacteria are in a nonreplicative state of vegetative metabolism (*39*, *40*). However, more recent work monitoring bacterial replication via an unstable "clock" plasmid indicates that the bacterial population, even in apparently stable lesions, continues to undergo replication (*41*). It is unlikely that there is a simple binary distribution of bacteria between replicating and nonreplicating status, and even within a single granuloma, there are likely to be multiple local microenvironments supporting unique bacterial populations. The drugs that are currently in common usage preferentially target replicating organisms; therefore, a nonreplicative subpopulation of the bacteria present in the persistent or "latent" infection will show innate resistance to drugs. The innate resistance of nonreplicating *Mtb* may contribute substantially to the protracted treatment period required in current therapeutic regimens.

Bacterial Metabolism During Infection

Although the murine model for TB is imperfect, it has proven to be an extremely useful tool in probing some of the metabolic shifts required to sustain a bacterium transitioning from rich broth into an in vivo infection (*42*, *43*). One good example of a metabolic shift required to support infection is the realignment of the bacterium's lipid metabolism. Isocitrate lyase activity is required to sustain *Mtb* infection in the chronic phase of infection in the murine model (*44*). The enzyme appears to fulfill a detoxification function, controlling propionate levels when the bacterium uses specific carbon sources, such as cholesterol (*45*–*49*), which has been invoked as a nutrient during the persistent phase of infection (*46*, *50*).

Recent studies with the hypoxia indicator pimonidazole, coupled with direct measurements with an oxygen probe in lesions of primate and rabbit models, have confirmed previous speculation that the inner regions of a fully stratified granuloma have extremely low, but detectable, oxygen tension (*4*). This has implications for tissue pathology, but it may also affect the metabolic state of the bacterium, which up-regulates the DosR regulon to promote survival and reemergence into the growth state (*51*).

Drug Discovery Programs: Introduction of Realism at the Level of Screening

Drug discovery programs for the identification of novel targets, as well as new antimicrobials, are few and far between. The more traditional methods of target-based discovery and remodeling of recognized scaffolds have pretty much exhausted known possibilities. The search for anti-infectives, as a field, has placed an inappropriate emphasis on the need to demonstrate genetic "essentiality" for any target, which is based on the misplaced assumption that genetic knockouts can be phenotypically copied by small-molecule inhibitors of metabolic pathways. We need to shift our mind-set from the discovery of essential gene products to appreciating the subtle holistic interactions between pathways and gene products that are required for survival in the many different microenvironments of the host.

Increasingly sophisticated cell-based screens of *Mtb* in a variety of conditions that simulate the multiple microenvironments of the host are needed to identify those metabolic breakpoints that could feed new target-based development programs. From both the basic and the translational science aspects, understanding the adaptation of the organism and its points of vulnerability under various environmental conditions represents a logical pathway toward agents potent within the granuloma that may shorten therapy. Just as important is a better un-

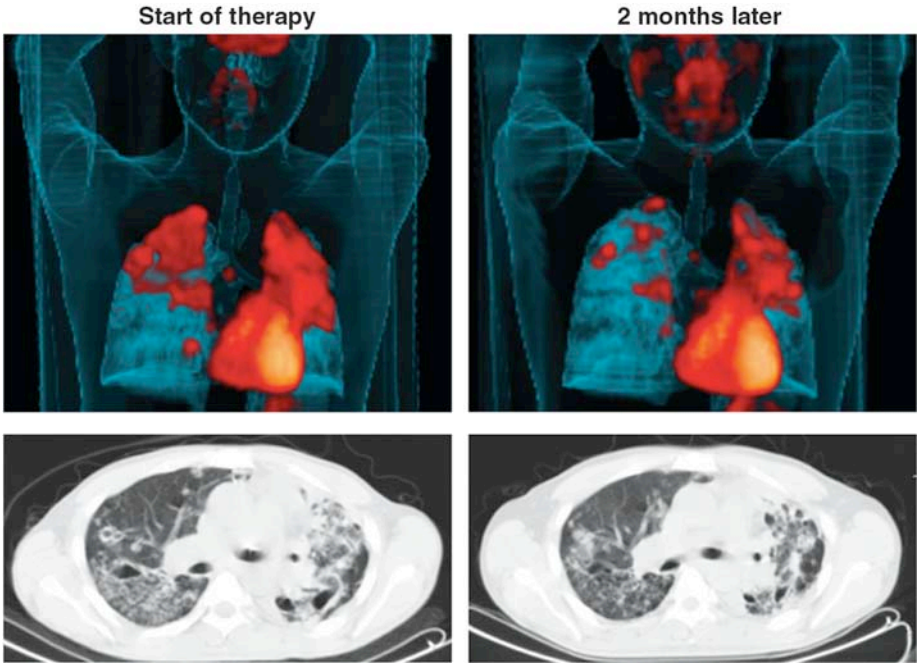

Fig. 3. Imaging disease progression in humans. 18-Fluorodeoxyglucose (FDG) PET and CAT scans from a patient with pulmonary TB: (**left**) at the time when therapy was initiated and (**right**) 2 months after treatment has begun. Below are two matched CAT slices from the area indicated by the plane on the left taken from the same scans. FDG is primarily a marker of increased tissue metabolism, such as inflammation, whereas CAT shows the structural abnormalities within this patient's lungs. Both sets of images illustrate the wide range of lesion types occupied by *Mtb* during infection that show differential kinetics of response to chemotherapy.

derstanding of the microenvironments experienced by the bacterium in the human host, so that these can be replicated in vitro. As one example, screening directly on *Mtb*-infected macrophages in differing states of activation would incorporate many of the host-mediated pressures responsible for inducing the different replicative and nonreplicative states of *Mtb* observed in the human host (*52*).

Missing Tools

As the field moves forward to evaluate new drugs and vaccines, we are clearly lacking some of the most basic tools for assessing efficacy. The mouse model fails to form granulomas that reproduce the tissue environments seen in humans. Accurate reproduction of these environments is likely to be important to both chemo- and immunotherapy. Rabbits and guinea pigs generate a tissue response that appears more comparable to that of humans, but it still requires validation in both human and primate infections (*4*, *53*–*56*). Rigorous studies comparing the disease in animal models to that of human disease are crucial to defining the validity of each model system.

The second critical shortcoming in our portfolio is the complete absence of any biomarkers for disease status (*57*). In mice, one can isolate tissues and count colony-forming units to determine the progression of disease in the context of bacterial replication, but we cannot do this in humans. There is no simple, noninvasive means of assaying whether an individual is containing his or her infection or progressing to active disease. The diagnostic tests in common usage today merely measure whether or not an individual has mounted an immune response to *Mtb*. Given that progression to disease is determined locally, at the level of the individual granuloma, it is unclear if we will ever be able to develop biomarkers for disease progression based on systemic readouts of immune status (*58*). Recent advances in positron emission tomography (PET)– and computerized axial tomography (CAT)–based imaging modalities have the potential to fill this gap (Fig. 3), but the relation between the observed pathology and bacterial burden has yet to be established. Because such imaging is not a practical method for diagnosing TB in the field, studies correlating comparable imaging data with immune responses or metabolites measurable in readily obtainable human samples (blood and/or urine) should be undertaken in an attempt to identify possible biomarkers of infection and disease. This is an extremely serious gap in moving new therapies into the field where, currently, impact becomes apparent only after many years.

Conclusions and the Cold Slap of Reality

The development of new drugs and vaccines is sorely needed, but they are not the complete answer. Tuberculosis is an infection that can be held in check by an effective public health system. Failure of the local health-care system can lead to the systematic selection and spread of drug-resistant strains, as recently observed in the KwaZulu-Natal province of South Africa, where extensively drug-resistant (XDR) strains resistant to as many as seven drugs are being observed (*59*–*61*). During the period leading up to the identification of these XDR strains, the health-care program in this region was in disarray, with only 18% of sputum-positive and 29% of hospitalized TB patients completing their treatment regimen. The coincidence of HIV was 80% in TB patients in this region, and there was no testing for drug-resistance conducted on the *Mtb* strains from patients. It is postulated that failed treatment regimens, in combination with the absence of drug-resistance testing, led to the selection and spread of these lethal strains.

The importance of an appropriately resourced, effectively managed public health system cannot be overstated. Even the best drugs or vaccines in the world will fail without an effective health-care infrastructure to administer and monitor their application. It is only through the combination of drugs, vaccines, and public health surveillance that we can hope to break the cycle of transmission, whereby each TB patient is responsible for one or more new cases of active disease.

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REVIEW

The Population Dynamics and Control of Tuberculosis

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More than 36 million patients have been successfully treated via the World Health Organization's strategy for tuberculosis (TB) control since 1995. Despite predictions of a decline in global incidence, the number of new cases continues to grow, approaching 10 million in 2010. Here we review the changing relationship between the causative agent, *Mycobacterium tuberculosis*, and its human host and examine a range of factors that could explain the persistence of TB. Although there are ways to reduce susceptibility to infection and disease, and a high-efficacy vaccine would boost TB prevention, early diagnosis and drug treatment to interrupt transmission remain the top priorities for control. Whatever the technology used, success depends critically on the social, institutional, and epidemiological context in which it is applied.

A century or more of social and economic progress, reinforced by the postwar discovery of efficacious drugs, had driven tuberculosis (TB) to low levels in the rich world of the 1980s. With no systematic evaluation of data from developing countries, no forewarning of the impending spread of HIV/AIDS or of the demise of the Soviet Union, and no coherent approach to control, TB was invisible to international donors and taken to be a fact of life in the most-affected parts of the world.

Four events put TB firmly on the global health agenda. First, the 1990 Global Burden of Disease Study (GBD 1990) identified TB as one of the top 10 causes of morbidity and mortality worldwide. TB became prominent in health statistics because untreated disease, with a case fatality rate of around 50%, cost millions of young adults decades of healthy life. Second, GBD 1990 and subsequent analyses began to measure the impact of the spread of HIV/AIDS and the health consequences of social and economic crisis in eastern Europe. Third, clinical and economic studies showed that combination drug treatment for TB was among the most effective and cost-effective of all health interventions. Fourth, in response to all these observations, the World Health Organization (WHO) launched a new control strategy, based on Directly Observed Treatment and Short-course drug therapy (DOTS).

In 2006 the Stop TB Strategy added new elements to DOTS, articulating the importance of managing drug-resistant and HIV-associated TB and of engaging the many different participants in health care. Twenty years on, systematic monitoring and evaluation have revealed both successes and failures of DOTS and the Stop TB Strategy. Among the successes, 36 million patients were treated worldwide between 1995 and 2008, and up to 8 million deaths were averted (*1*). WHO's target cure rate of 85% was exceeded in the 2007–2008 global cohort of 2.7 million new sputum smear-positive patients, and case detection in 2008 reached an estimated 61%, close to the 70% target. A combination of surveys, surveillance, and mathematical modeling suggests that targets of halving 1990 levels of prevalence and mortality by 2015 could be reached in four of six WHO regions. The exceptions are Africa (sub-Sahara) and Europe (former Soviet countries).

Worldwide, TB incidence per capita is falling at an estimated 1% per year. Although this slow rate of decline satisfies the Millennium Development Goal (MDG) for TB, which is to ensure that the incidence rate is falling by 2015, the world's population is growing at about 2% per year, so the total number of new TB cases is still rising (*1*). There are expected to be 9.8 million new cases in 2010, more than in any previous year in history. Eighty percent of these cases will be found in the 20 to 25 highest-burden countries, and more than one-third in India and China. A review of cases reported by 134 countries between 1998 and 2007 found that only 35 had per capita rates of decline exceeding 5% per year (*2*). These were countries with either small populations (<20 million) or high incomes [gross domestic product (GDP) > US$10,000 per capita]. Incidence rates were increasing in 41 countries, 19 in sub-Saharan Africa.

With MDG target year 2015 now in sight, we examine here a range of factors that affect TB burden and trends, and which could explain why drug treatment programs have had such little impact on TB transmission and case load.

TB Epidemiology and Control: The Standard Model

The expected effects of control are derived from the standard model of TB natural history in which the pathogen, *Mycobacterium tuberculosis*, is considered a single entity and the response to lung infection is represented by two dichotomies: fast (primary progression) or slow transition (via latency) from infection to infectious or noninfectious disease (Fig. 1) (*3*). This compartmentalization simplifies the natural history, makes epidemiological calculations easier, and facilitates the management of patients who can be placed in a few distinct categories. DOTS and the Stop TB

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