ELSEVIER

Social Science & Medicine 61 (2005) 847–859

SOCIAL SCIENCE & MEDICINE

www.elsevier.com/locate/socscimed

Limited good and limited vision: multidrug-resistant tuberculosis and global health policy

Jim Yong Kim*, Aaron Shakow, Kedar Mate, Chris Vanderwarker, Rajesh Gupta, Paul Farmer

Harvard Medical School, 641, Huntington Avenue, Boston, MA 02115, USA

Available online 17 May 2005

Abstract

Almost a third of the world's population is infected with *Mycobacterium tuberculosis,* the organism that causes tuberculosis disease. Most of those infected never fall ill, but individuals who do can recover if they have access to effective therapies. This paper discusses certain ethical and ethnographic issues raised by cases in which patients are infected with *M. tuberculosis* strains resistant to at least the two most powerful drugs on which therapy is usually based. In most poor countries, people with such multidrug-resistant tuberculosis (MDR-TB) were, until very recently, considered "untreatable." In addition to being consigned to a permanent state of ill health, they were also at risk of transmitting their resistant strain to others. In this paper we discuss the logic of "cost-effectiveness," which international health policy-makers utilized to make the case that treatment of MDR-TB is not feasible in resource poor settings. These analyses, which have held sway in public health policy for many years, are flawed, we argue, because they ignore and conceal the social determinants of access to health services and often rely on assumptions rather than evidence. We propose that policies based solely on analyses of cost-effectiveness of specific interventions for individual settings can be short-sighted and, because they do not pay sufficient attention to the social, political, economic, epidemiological and pathophysiological factors influencing the production of health, will ultimately hinder progress toward effective global TB control.

Keywords: Tuberculosis; Health policy; Cost-effectiveness; Poverty

Introduction

Five years into the third millennium and several decades into the so-called "post-antibiotic era," infectious diseases are still the leading cause of adult mortality globally (WHO, 2003c). Against those who echo the United States Surgeon General's 1969 claim that "it's time to close the book on infectious diseases" (Garrett, 1989), the terrible mortality from tuberculosis (TB), which is almost always curable with antibiotics delivered appropriately, serves as a standing rebuke. To the community of specialists, the statistics are by now numbingly familiar. Almost one-third of the world is infected with *Mycobacterium tuberculosis*, the organism that causes TB (Kochi, 1991). During 2002, approximately 8.3 million people became sick with TB and 1.8 million died from this illness (Corbett et al., 2003). Yet less than half of all TB cases worldwide are properly diagnosed, and fewer than 60% of those are cured (WHO, 2003a). Where the human immunodeficiency

*Corresponding author. Tel.: +41 22 791 3910; fax: +41 22 791 4846.

E-mail address: Kimj@who.int (J. Yong Kim).

0277-9536/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.socscimed.2004.08.046

virus (HIV) has established itself, the news is even worse: in sub-Saharan Africa, from 1990 to 1999, TB incidence escalated by almost 250%. An estimated one-third of AIDS deaths are due to TB (WHO, 1999a, b).

Grim epidemiologic profiles in the developing world coexist with half a century of breathtaking medical and scientific innovation. Indeed, the successive revolutions of antibiotic therapy, bioengineering, and genomics have spawned an especially bitter paradox: the regions most desperately in need of the results of innovation are precisely the places in which they are unavailable. Two hundred years ago, TB ravaged affluent countries and poor alike (Cegielski et al., 2002); today, rates of TB have become telling indicators of a society's wealth or poverty. At present, 98% of deaths from tuberculosis worldwide are in developing countries (Dye, Scheele, Dolin, Pathania, & Raviglione, 1999). While the poorest sectors of society are at greatest risk, anyone living in a TB endemic region can be affected. Indeed, a significant proportion of those infected are literate, have considerable education, and earn good incomes (Commission on Marcoeconmics and Health, 2002). Just as poverty increases the individual risk of contracting and developing TB, so too, the disease catastrophically undermines the earning power of individuals and communities (STOP TB, 2000).

Tuberculosis is, in every sense, both a cause and a result of poverty. The very definition of health as "more than the absence of disease" (WHO, 1946) means, of course, that the poor are precisely those who will never enjoy health in settings in which common, treatable diseases remain untreated. Tuberculosis is perhaps the most striking case in point. As one of the world's most common infections, *M. tuberculosis* does not cause active disease in all who are infected. Among that fraction of the infected who do fall ill, however, the majority live in poverty (WHO, 2002). Many studies have attempted to reveal how poverty and social inequalities determine, through myriad mechanisms, who will fall ill from TB and who will not (Farmer, Kim, Mitnick, & Timperi, 1999a; Farmer, Kononets, Borisov, et al., 1999b). These same inequalities determine, even more directly, who among the sick will have access to effective TB treatment. Over the past few decades, almost all TB deaths have been concentrated—now almost exclusively—among the world's poor. What this differential indicates, here too, is that health is more than the absence of disease. Tuberculosis is not simply a matter of infection; it is a reflection of patterned resource distribution. Understanding social inequalities, and even social theory, is central to understanding the persistence and re-emergence of TB, topics that we and others have explored in depth (Farmer, 1999a, b; Rubel & Garro, 1992). Here, however, we will focus on one of the newest and most telling chapters of the TB story: the emergence of bacterial strains resistant to the most powerful and effective treatments now available.

In many of the regions where TB is already common, inadequate therapy has allowed mutant *M. tuberculosis* organisms to develop and spread a reservoir of bacteria that resist the medications of first resort (WHO/IUATLD, 1997, 2000). The present-day legacy of these poor therapeutic practices comes in the form of cases that cannot be cured by the standard TB treatment. This treatment is based on "short-course" chemotherapy (SCC) which consists of 6 months of therapy using four first-line anti-TB drugs). Where multidrug-resistant tuberculosis (MDR-TB) (defined as TB resistant to at least isoniazid and rifampicin, the two cornerstone drugs of SCC) is already prevalent, such regimens—even when properly administered—are often inadequate (Espinal et al., 2000). Indeed, SCC can even worsen the problem by facilitating the "amplification" of drug resistance, which occurs when a patient's treatment regimen is clinically ineffective, allowing bacterial strains to survive, mutate, and, through the process of natural selection, "acquire" resistance to other drugs in the regimen (Furin, Becerra, Shin, Kim, Bayona, & Farmer, 2000; Coninx et al., 1999). Since a little more than a dozen effective antituberculous agents are presently in use (i.e. first- and second-line anti-TB drugs), the emergence of "superbugs," strains resistant to all known drugs, is a real threat (Harvard Medical School, 1999). In an increasingly integrated world, these lethal TB strains do not stay at home in their MDR-TB "hot spots," but travel within their human hosts via air, land, and sea (Kenyon, Valway, Ihle, Oronato, & Castro, 1996; Lambregts-van Weezenbeek, Jansen, Nagelkerke, van Klingeren, & Veen, 1998; Codina, Vidal, Martin-Casabona, Miravitlles, & Martin, 1999).

Controlling drug-resistant tuberculosis: a brief history

In discussions of TB control in resource poor settings it is often observed that the global crisis of TB is nothing new. Twenty-five hundred years ago Hippocrates described it as the most widespread disease of his time—and, he claimed, a disease that was almost always fatal.[1] At the height of the Roman Empire his successor Galen saw treatment of the disease to be so often useless that he allegedly warned colleagues against visiting patients in late stages of the disease, because their inevitable death might damage the reputation of the physician.[2]

[1] *Of the Epidemics*, I, 2.

[2] "Introductio seu medicus," in *Opera Omnia*, ed. C.G. Kühn, Hildesheim: Georg Olms Verlagsbuchhandlung, 1965 [1827]: 744–5.

Such chilling advice from the popularizer of the Hippocratic Oath would seem to highlight profound changes in medical ethics in the age of antibiotics. Yet, until recently, the clinical approach to MDR-TB in poor countries contained disturbing echoes of Galen's clinical strategy for TB. Although several studies demonstrated treatment success in the industrialized world (Telzak et al., 1995; Geerligs, van Altena, Lange, van Soolingen, & van der Werf, 2000; Flament-Saillour, Robert, Jarlier, & Grosset, 1999; Narita, Alonso, Lauzardo, Hollender, Pitchenik, & Ashkin, 2001; Viskum & Kok-Jensen, 1997), MDR-TB was considered "incurable" elsewhere (Murray, 1994). The rise of antituberculous drug resistance presented TB control programs with an apparent zero-sum game: many worried that the treatment for MDR-TB was so expensive that it would draw resources away from basic TB control (WHO, 1997a, b; Enarson, Rider, Arnadottir, & Trebucq, 2000; Coker, 2002).

Developed by the International Union Against Tuberculosis and Lung Disease (IUATLD) in the 1970s and then adopted by the World Health Organization in the early 1990s, the "DOTS (Directly Observed Treatment-Short Course) strategy" is a highly effective approach based on five simple principles: sputum smear tests for active pulmonary TB disease; a 6-month course of inexpensive antituberculous drugs; direct observation of treatment (DOT) to ensure that all medications are properly taken; a record-keeping system to monitor treatment outcomes; and, political commitment for the treatment of all patients (WHO, 2003b). The emergence of the DOTS strategy is a capsule history of the double-edged antibiotic miracle. Only months after Selman Waksman's discovery of streptomycin during World War II, physicians discovered, to their distress, that when used alone, the drug rapidly lost its efficacy against the TB bacillus in a significant number of cases. In effect, their patients' illness became, once again, incurable (Ryan, 1993). These early experiences with the first effective antituberculous agent led to an understanding that *M. tuberculosis* was able to acquire resistance to a single agent and that drug-resistant strains could then be transmitted to others. As a result, TB treatment came to consist of a combination of drugs to ensure that *M. tuberculosis* organisms are eradicated from the body without acquisition of resistance to any single drug. Several years went by before intensive research and development of other antituberculous drugs paved the way for the British Medical Research Council's (BMRC) groundbreaking demonstrations of "combination therapy" (Medical Research Council, 1950).

The problem was that some early antituberculous drugs, such as para-aminosalicylic acid (PAS) and cycloserine, were relatively weak and toxic, necessitating long courses (18–24 months) of therapy and aggressive management of side effects. Moreover, some of the drugs were difficult to produce, and as proprietary ("patented") substances, they were prohibitively expensive for most individuals and state-run public health programs (Ryan, 1993) It was not until the clinical demonstration of isoniazid's efficacy in 1952, and that of rifampin a decade later, that effective ambulatory TB treatment truly became feasible. For patients and doctors alike, these two drugs were a dream come true. They could be taken orally, in contrast to the injectable streptomycin. They killed the tubercle bacillus effectively enough to be used in well-tolerated concentrations. In combination with a third and fourth drug (i.e., ethambutol or pyrazinamide), combination chemotherapy based on isoniazid and rifampin reduced duration of treatment to a matter of mere months and proved to be feasible in resource-poor settings (Rouillon, 1991; Enarson, 1995; Fox, Ellaed, & Mitchison, 1999). Because side effects were rare, patients did not require constant monitoring in a hospital or sanitarium setting.

For TB control programs in developing countries, where hospital infrastructure was limited or nonexistent, SCC was a major breakthrough. The benefits of isoniazid to supervised ambulatory care programs in poor settings were recognized early (Tuberculosis Chemotherapy Centre, 1959). As defined in the 1978 Alma Ata Declaration on primary health care, TB treatment seemed to some to fit neatly into more decentralized public health models advocated by many multilateral funders supporting primary health care in resource-poor settings (Pio, 1983).

However, the very ease of the new isoniazid- and rifampin-based regimens proved a dangerous liberty. With patients removed from direct, inpatient supervision, it was difficult to ensure that drugs were being taken properly. Rates of treatment completion are significantly lower without direct observation (Fox, 1993). The full dimensions of this hazard, however, did not become clear in the United States until the late 1980s. In a series from Harlem Hospital, for example, only 11% of patients could be shown to have completed their therapy (Brudney & Dobkin, 1991). Unsurprisingly, New York became the epicenter of the most celebrated epidemic of MDR-TB (Frieden, Sterling, Pablos-Mendez, Kilburn, Cauthen, & Dooley, 1993).

From the very start, drug resistance was clearly a "biosocial" phenomenon. New York's public hospitals had been increasingly starved for TB resources since Congress ceased direct funding of tuberculosis control in 1972, and outpatient supervision of poor TB patients had suffered greatly (Reichman, 2001). In 1986, the Centers for Disease Control discouraged routine drug-susceptibility testing of all isolates on the grounds that it was no longer cost-effective (Garret, 1994). At the same time, the advent of HIV created a large pool of people for whom the dangers of ineffective treatment were magnified. Among injection drug users the danger was

particularly acute: they were significantly more likely to contract both HIV and TB (Stop TB, 2001). They were shuttled in and out of prisons, hospitals, and shelters, and without proper clinical oversight, they were unlikely to take their medications regularly. This combination of social and biological processes was the perfect recipe for MDR-TB.

The disease first became epidemic in the crowded prisons of New York, where the recently declared "War on Drugs" had led to a sharp rise in prison censuses (Reichman, 2001; Farmer, 1999b). With rifampin and isoniazid rendered clinically ineffective, MDR-TB patients, when treated, had to endure 2-year courses of treatment with older medications like PAS and cycloserine. Not only did this imply long hospitalization in many cases, but because the drugs no longer had lucrative markets, their manufacture by an industry in the full flush of the bioengineering revolution had largely ceased. It took government intervention by the FDA in 1992—under pressure from Congress—to convince a small firm to become the sole US manufacturer of a special form of PAS. At that scale, the drug did not come cheap (US FDA, 1992). Also, extraordinarily expensive measures to control the disease, like the use of negative airflow rooms and complete isolation of patients were required. In total, although involving fewer than 1 000 cases annually, the New York epidemic was stemmed at an estimated cost of $1 billion (Frieden, Fujiwara, Washko, & Hamburg, 1995; Garrett, 1994). In the aftermath of the New York epidemic, US public health authorities recognized the importance of DOT, which became one of the guiding principles of national TB control programs (NTPs) (Bayer & Wilkinson, 1995).

At around the same time, the WHO was embarking on a much-needed campaign to expand TB treatment worldwide. Their strategy was shaped by two policy developments. In 1993, the World Bank published *Investing in Health,* which heralded the emergence of the World Bank as one of the most influential bodies in international health. In this document, the Bank—which had taken on the responsibility for guiding economic policy reforms in the developing world after the debt defaults of the 1980s—aggressively promoted decentralization of public health systems in poor countries, using its leverage as a funder to discourage hospital-based care (World Bank, 1993). As the Bank emerged as the world's largest financer of NTPs in poor countries (in part, due to the Bank's ranking of TB control as one of the most cost-effective health interventions), its "recommendations" were taken very seriously in developing countries.

Meanwhile, the WHO had begun to see the fruits of its essential-drugs program, which sought to institute a basic pharmacopoeia for developing countries. The idea of the essential-drugs plan was to assist national health authorities by limiting pharmaceutical purchases, centralizing quality control and clinical management guidelines, introducing economies of scale, and encouraging generic production. Indicated for the treatment of what was, and still is, one of the leading causes of adult death worldwide, streptomycin, rifampin, isoniazid, pyrazinamide, and ethambutol were early entries on the WHO Model List of Essential Drugs (WHO, 2003c). As generic production increased, the price of first-line TB drugs fell rapidly: by the mid 1990s, SCC cost as little as $13 (WHO, 1997b). The DOTS strategy was at the nexus of these disparate developments. And one of the first countries to adopt DOTS was the Republic of Peru.

Peru in the early 1990s was in economic and political turmoil. Its health indicators reflected the prevailing disorder. After a debt default and a dose of fiscal "shock therapy," the state-run health services were particularly hard-hit. Faced with armed insurrection by Maoist rebels in the Andean provinces and withering opposition by activists in several poor urban communities, the Health Ministry of President Alberto Fujimori consented to one of the popular movement's most vehement demands: effective TB treatment for all citizens, free of charge. Tuberculosis was rife within the poor neighborhoods of Lima, and a survey conducted in the 1980s suggested that cure rates were less than 50%, with more than four in ten Peruvian patients abandoning treatment in mid-course (Hopewell, Sanchez-Hernandez, Baron, & Ganter, 1984).

Over the next several years, the WHO and the Peruvian government succeeded in what is still one of the more remarkable public health achievements in the developing world. By the second half of the 1990s, the Peruvian NTP had instituted a network of community health centers that afforded near universal coverage in the country's poorest shantytowns and most remote rural provinces. As the WHO expanded its global campaign to universalize implementation of DOTS, it held up Peru as the model of what could be accomplished through a combination of political will and sensible program management, calling it "the country with the most successful DOTS strategy" in the world (WHO, 1999a, b; Suarez et al., 2002).

At the time, clinical and epidemiologic data on drug resistance in developing countries was scarce. In the absence of evidence to the contrary, the architects of the DOTS strategy claimed that full implementation of DOTS would prevent the emergence of new resistant *M. tuberculosis* strains, rendering MDR-TB a tragic but isolated problem. As data accumulated, however, such hopeful assumptions proved to be flawed. The first global anti-TB drug resistance surveillance (DRS) project, conducted jointly by the WHO and the IUATLD, showed drug-resistant strains to be ubiquitous worldwide, with significant concentrations of MDR-TB in Eastern Europe, south and Southeast Asia, and Latin America (WHO/IUATLD, 1997). One of the

"hot spots" of this man-made emerging infectious disease was Peru, whose history of poorly implemented TB control continued to haunt it. What happened to DOTS programs in areas where MDR-TB was already established? As of 1996, more than one-fifth of all TB patients in Peru were infected with strains resistant to at least one drug. Would DOTS, which is based on precisely the two drugs to which all patients with MDR-TB are by definition, resistant, be able to remove the threat of MDR-TB, as had been claimed?

At the time, the answer seemed unclear to leaders in global TB control. In fact, since MDR-TB cases were not officially being treated in resource-poor settings like Peru, it was extremely difficult to even raise such questions. Hemmed in by budget constraints, the country's state-run TB control program focused entirely on drug-susceptible disease. Scarce "treatment" for MDR-TB was available only in the private sector. Within the national TB program, a retreatment regimen for patients failing the initial treatment was one that added a single new drug to the standard DOTS SCC regimen. Yet, it had long been agreed that addition of a single drug to a failing TB treatment regimen can be disastrous and lead to the development of further drug resistance (Iseman, 1993). This policy was raised to international prominence when the retreatment regimens were recommended by the WHO itself (WHO, 1997a, b). When poor patients failed these retreatment regimens, they were either offered another course of the exact same drugs, an often ineffective mixture of random drugs, or nothing at all.

But MDR-TB did not go away, and soon there were hundreds of cases within the crowded slums of northern Lima. When members of our team associated with the non-governmental organization (NGO) Partners In Health (PIH) began a small project to treat "chronic" TB patients in one such shantytown district, the dangers of repeated courses of short course chemotherapy soon became clear. Patients suffering from pulmonary MDR-TB, we discovered, were readily transmitting their disease to close contacts (Becerra et al., 2000). Because these "primary" MDR-TB cases do not respond to the two most powerful drugs in the standardized DOTS cocktail, further treatment with repeated regimens of first-line drugs risked "amplifying" their drug-resistance patterns. Patients who survived ineffective short-course chemotherapy often emerged with TB bacilli that were resistant to even more antituberculous drugs. Some of these patients, our team discovered, realized that they were receiving ineffective therapy and sought to secure "second-line" TB drugs not included in the standard short course regimen. But since these drugs were expensive and usually taken in unsupervised settings, they often received incomplete or improperly administered doses. Their infecting strains then became resistant to even more drugs, and were transmitted in this amplified form to family members, colleagues and neighbors.

Through these various mechanisms, patients developed disease due to strains with many different drug resistance patterns. At that point, it became clear to PIH staff that each individual's sputum sample would have to be tested for resistance to second-line, as well as first-line TB drugs prior to initiation of therapy. Susceptibility testing for resistance to second-line drugs, however, was a lengthy and complicated process and not available in Peru at the time. Thus it was clear that any effective solution would have to be transnational.

After uncovering the MDR-TB outbreak in northern Lima in 1996, PIH modified its decade-long experience with community-based TB treatment in rural Haiti to the conditions of an urban shantytown (Farmer, Robin, Ramilus, & Kim, 1991). Aided by institutional contacts and funded by private donations, the Lima-based team initiated treatment for a cohort of approximately 50 patients. In contrast to the standardized DOTS regimen, these patients received chemotherapy tailored to their individual infecting strain: their sputum samples were sent to the US for drug-susceptibility testing in order to ensure that the drugs they were taking would fight the bacteria effectively. For the entire course of treatment each patient was assigned a trained outreach worker who visited his or her home daily to verify that they were taking the medicines properly. Not only did this ensure adherence to the regimen, but it prevented the nosocomial transmission that can take place within hospitals and clinics. The outreach workers, themselves residents of the shantytown, also provided psychological and social support—including, in some instances, nutritional and monetary supplements (Sweetland, Acha, & Guerra, 2002). Home-based care also facilitated identification and screening of contacts and family members at risk for primary MDR-TB and moreover, cost a fraction of inpatient treatment. The challenge was significant, since community-based care of MDR-TB had never been conducted in a resource-poor setting, except on a very small scale in Haiti (Farmer, 1997). Community health workers were trained to gather basic clinical, epidemiological and even ethnographic data, and to recognize common adverse reactions to chemotherapy, in order to bring them to the attention of clinical staff for proper management.

The call for universal treatment of MDR-TB in resource-poor settings was met at first with a great deal of skepticism in the international health community. Several objections were raised. First, the complexities of clinical care for MDR-TB made its implementation in a disrupted, impoverished location such as northern Lima impossible. It was assumed that patient compliance with drug regimens could not be ensured, raising the prospect of exacerbated second-line drug resistance. Second, some argued on the basis of extant data from the US

and Europe, the cost of treatment regimens for MDR-TB was so ruinously high that the limited resources available to the international TB community could not sustain both it and crucial expansion of DOTS-based programs—which was, after all, the best way of preventing the emergence of new drug-resistant disease. Third, the combination of expensive laboratory infrastructure for drug susceptibility testing, expensive second-line drugs, and intensive management by expensive, highly trained clinical personnel put it financially out of reach. Fourth, some argued management of MDR-TB, even if clinically successful, was not cost-effective relative to a DOTS-only implementation strategy because, they claimed, the burden of MDR-TB would decrease (through spontaneous self-cure, the minimal cure rates provided by SCC and death) such that the problem would disappear. Fifth, many were concerned that promotion of treatment of MDR-TB would lead to chaos in treatment. Many countries, it was argued, could not properly manage their drug-susceptible cases for 6 months so proper management of MDR-TB cases over 12–24 months would be impossible. In reality, most countries were purchasing and using second-line drugs under a range of treatment schemes. Finally, some critics argued that drug-resistant strains were less virulent or less infectious than drug-susceptible ones; even if untreated, they would not spread much beyond their narrow zones of incidence. Thus, much was at stake for Partners In Health in Lima as the success or failure of its community-based MDR-TB treatment had implications throughout the world's poorest settings.

The policy debate

In April of 1998, at the suggestion of Howard Hiatt (a former Dean of the Harvard School of Public Health), Partners In Health, Harvard Medical School, and the WHO convened a meeting of international TB experts to discuss the prospects of treating MDR-TB in settings of poverty (Farmer & Kim, 1998). At this meeting, preliminary data from the Lima project—showing good clinical outcomes in nearly 85% of the allegedly "untreatable" patients with MDR-TB—swayed some who had argued, often vehemently, that MDR-TB was "incurable" or "untreatable" in resource-poor settings. Most notably, the director of the Global TB Program of WHO and several key staff acknowledged the importance of MDR-TB and commenced efforts to work with PIH to develop models for its management.

Certain other leaders in international TB control, however, were dismissive and even openly hostile. The idea of rethinking policies that in effect condemned poor patients suffering from MDR-TB to death and their families and communities to infection with highly drug-resistant strains was controversial. On several occasions, when PIH staff members proposed such a reorientation they were told that it was "immoral" to treat MDR-TB in poor settings because doing so would mean that patients with drug-sensitive disease would not be treated. Especially in the early stages of this debate, PIH staff responded both in public fora and in print. Their counter-argument had six facets:

(1) Historically, attention to MDR-TB has actually brought more attention to the global problem of TB and increased funding (Klaudt, 2000). The goal of the TB community should focus on using the threat of MDR-TB to dramatically increase overall funding for TB, rather than seeing TB funding as a zero-sum game.
(2) Great care must be taken in arguing that it is ever "immoral" to treat sick, poor patients (the same logic, we noted, was stalling efforts to treat AIDS in Africa).
(3) The price of treating MDR-TB was artificially high as a result of an entirely tractable market failure and prices of drugs could be lowered with appropriate, relatively simple interventions. (Farmer & Kim, 1998).
(4) Repeated cycles of short-course chemotherapy, which was the recommendation for poor countries at the time for patients failing treatment, are neither effective nor benign, since they lead to exacerbation of the problem through the phenomenon of amplification. (Furin et al., 2000).
(5) The rise of explosive epidemics of MDR-TB in Russian prisons (Farmer, 1999c), and also the rising tide of HIV-associated TB in many areas of the world, required dramatically scaled-up responses to these diseases.
(6) The virulence and transmissibility of MDR-TB was still not well understood and there was evidence that drug-resistant strains of *M. tuberculosis* could be just as difficult to control as drug-sensitive ones (Gupta , Raviglion, & Espinal, 2002b).
(7) Responding promptly to MDR-TB would be much more "cost-effective" than waiting until it was a much larger and more expensive problem to solve (Gupta et al., 2001a; Gupta, Raviglione, & Espinal, 2001b).

The theory of limited good revisited

Some of these arguments were based on our own experience, others were based on published data and some were based on data that has since been published by our group and others. As we will describe below, many of these arguments have been addressed and a

consensus within the global TB community today is growing rapidly.

While we were clearly participants in this debate as physicians and managers of health programs in developing countries, we were also "observers". As ethnographers, we searched for ways of understanding more fully the positions of our critics and interlocutors, but this was complicated because of our role as advocates for patients who were demanding treatment. In the past, we had studied the experiences and explanatory frameworks of people sick with TB; now we were seeking to "study up," as Laura Nader had suggested years ago (Nader, 1972). The fates of many were in the hands of policy makers who were working from assumptions quite different from our own. Studying the logic of international public health was, we found, fraught with peril. We have hesitated more than once in writing of the debates discussed here. Yet we concluded that our version of this particular story must be told. Short-sighted policies that inadvertently lead to non-treatment of the destitute sick are the result of a convergence of factors. Many of the most important factors were not in the control of the global health policy makers with whom we were debating. Because these policies are still so important, we have attempted here a critical ethnography of one such policy related to MDR-TB. We also regard this exercise as a contribution to the sociology of knowledge, with the caveat that policies such as the ones we critiqued are often based on scarce evidence (Farmer, 2002).

In our search of the anthropological literature for a theoretical hook on which we might hang our ethnography of the global TB policy community, we revisited George Foster's formulation, the "image of limited good" (Foster, 1965). Foster's project, surprisingly, was much like our own—to seek to understand and then change uninspired (and sometimes self-destructive) worldviews that lead to poor outcomes. Foster's notion of limited good was developed through work he did in the Mexican community of Tzintzuntzan beginning in the 1940s. Development and aid specialists had asked him to help them answer a question: with the growth in the Mexican economy, and the many opportunities that were emerging, why weren't the people of "traditional" Mexican communities more "entrepreneurial" in taking advantage of these avenues for lifting themselves out of poverty? Foster observed that

> Broad areas of peasant behavior are patterned in such fashion as to suggest that peasants view their social, economic, and natural universes—their total environment—as one in which all of the desired things in life such as land, wealth, health, friendship and love, manliness and honor, respect and status, power and influence, security and safety, *exist in finite quantity* and *are always in short supply,* as far as the peasant is concerned (Foster, 1965).

In Foster's model, several factors conspire to explain the ostensible lack of peasant interest in his or her own "development" and economic advancement. Foster's model suggests that poor peasant communities approximate closed socioeconomic and natural systems in which goods are traded within the community (Foster, 1965). A natural consequence of this closed system is that the sum of the resources present must remain constant and non-expanding. To the peasants in such communities, all resources are "finite." Further, these limited resources are "insufficient to satisfy each member with all of the things, the 'good,' that he wants" (Foster, 1972). While these conditions might suggest possible violent struggles over the scant resources available, Foster found that instead of promoting an acquisitive desire among the impoverished, the lack of adequate resources lead to a communal understanding that all were involved in a zero-sum game in which one peasant's gain was another's loss.

This zero-sum game provided significant disincentives, both ritual (fiestas and other exorbitant social functions), and informal (gossip, backbiting and vicious jealousy) that helped to return 'limited good' societies to equilibrium and status quo; individuals were constantly being shepherded toward adaptive but not very entrepreneurial behaviors. Foster also found that the peasants he studied, though aware that there are possibly unlimited resources beyond the community, view such resources as generally inaccessible and rarely secured, unless by luck or some stroke of good fortune.

George Foster returned frequently to the community of Tzintzuntzan. On his website, he describes his last trip, which occurred in the summer of 2000. He notes that the "image of limited good" has not prevented several of the young people from the village from traveling on a regular basis to Alaska to work on fishing boats and return with $20,000 in cash after 6 months of labor. Other indicators of dramatic change included improvements in access to electricity (14% of homes in 1945 to over 95% in 2000), televisions in almost every home, gas stoves, cars and many other modern conveniences. Foster writes, "while I see traces in the behavior of some of my age mates [he was over 80 when he wrote this], Limited Good is no longer a brake on progress" (Foster, web site).

The "image of limited good" as anthropological theory has been debated for years and while still taught in many anthropology courses, it is not used very often to describe the behavior of people in developing countries, in part because so many poor communities are deeply enmeshed in transnational social webs: they are not closed societies in any meaningful way. Some

have lumped the idea with other "essentializing" discourses that paint with a broad brush and that do not capture the resistance, conflict and unequal power relations that exist within all communities and across national borders. But as we attempted to understand the behavior of policy makers within the global TB control community, the specific characteristics that Foster ascribes to the image of limited good seemed to be instructive—in a perverse sense. But there was one striking difference between the Mexican peasants who endured scarcity and the policy makers we studied. While policy makers certainly provided no evidence that the "image of limited good" characterized their own lives, they seemed to insist that it was the most important principle in shaping policies for global TB control.

Foster has argued that in peasant societies "people share a cognitive orientation in which they perceive their socioeconomic and natural environments to constitute a closed system." In addition, he writes, peasants feel that "resources…are insufficient to satisfy each member with all of…the 'good' that he wants" and that "they also know that there is more 'good,' perhaps in unlimited quantities beyond the boundaries of their system, hence not available to them" (Foster, 1972, p. 58). Similar notions were evident among TB policy makers who argued that treatment of MDR-TB siphons resources away from DOTS expansion or treating drug-susceptible TB. In the mid-1990s, the US government donated a negligible sum of money for global TB control. New York city had just spent $1 billion to respond to a relatively modest epidemic of MDR-TB in the early 90s but as of 1995, not a single dollar was allocated for TB control in the very settings that were the countries of origin of most TB patients in the urban United States.

After decades of slim pickings, TB policy makers were accustomed to setting modest goals. The treatment of MDR-TB in resource-poor countries did not figure in the list of objectives advanced by international standard-setting bodies. Rather than focusing more energy on rich country governments that were ignoring the global TB pandemic including MDR-TB, some critiqued our team for raising the issue of MDR-TB when even DOTS expansion elicited little interest in the funding community. These critics expressed fear that our interventions would make TB control seem "expensive" and thus push TB treatment off the list of "cost-effective interventions" that would be recommended to poor governments by the World Bank and other funders. And the World Bank's policy recommendations—"austerity measures"—were often conditions for credit and political support.

We have written elsewhere about the impact of neoliberal economic reforms and the burden of debt repayments on poor country health budgets (Kim, Millen, Irwin, & Gershman, 2000). During the period of structural adjustment that spanned the 70s through the 90s, the primary goal of first world governments and the multilateral lending institutions was to ensure that poor countries paid back their debt. The pressure placed on poor country governments, which did not always prioritize the health of their own poor people, led to reductions in already paltry health care budgets in many of the poorest countries in the world (Kim et al., 2000). Rather than first arguing for debt relief and the restoration of health care budgets as a condition for canceling debt, many health policy makers, including those in the TB world, simply looked to cost-effectiveness analyses to help them find and recommend the most favorable interventions within the context of "limited" and in many cases shrinking resources. Recently, several influential economists, including Jeffrey Sachs, have argued for comprehensive debt relief linked to increasing resources for health (Sachs, 2002). This is welcome but it is important to note that this initiative, which could have been driven much earlier by those most intimately aware of the devastating impact of defunding poor country health care systems, was not. Many international health experts seemed to regard pernicious economic policies as a force majeure well beyond their sphere of influence.

Foster also noted that in peasant societies, many felt that "one person's gain with respect to any 'good' must by necessity be another's loss" and that as a result, "people in Limited Good societies opt for an egalitarian, shared-poverty, equilibrium, status quo style of life, in which no one can be permitted major progress with respect to any 'good'" (Foster, 1972, p. 58). Tuberculosis policy makers applied similar notions to poor people because of what they felt was at stake. Attention to MDR-TB would cause the limited number of resources to be misspent on expensive interventions that helped only a few when they could be spent more wisely on far less expensive interventions that could help so many more. While some of these same leaders had been creative in developing interventions like DOTS, MDR-TB, because of its cost and complexity, was simply something to be avoided and used only as a scare tactic to push poor country governments to adopt DOTS. PIH attempted to respond to these arguments and, at the same time, to push for more adequate funding for global health emergencies. But one of the key interventions was to address a third problem: the exorbitant prices at which second-line antituberculous drugs were sold.

Challenging the assumptions: questioning drug pricing

One of the most influential arguments advanced by those who argued against treating MDR-TB in poor communities was the high cost of medicines. Capreomycin, the most important parenteral agent used in the treatment of MDR-TB, cost USD $30 for a single day's doses in 1996, the year we began treating patients in

northern Lima. The same drug could be found for USD $8 in Europe. Differences between the highest and lowest market prices for second-line anti-TB drugs were also significant (Farmer, 1999a). While increased demand for first-line anti-TB drugs had worked to lower prices of first-line drugs by upwards of 40% even after prices had reached very low levels, a perceived lack of demand for second-line drugs kept prices high.

With very little effort, we soon discovered that almost all of the drugs required for the treatment of MDR-TB were off-patent, many for decades (Farmer, 1999a). Why, then, were these medications so expensive? Before 1999, the WHO and most other TB experts had declared that treating MDR-TB was not cost-effective and had advised developing countries to avoid purchasing anything but first-line drugs. Therefore, market forces were never brought to bear on the prices of these most generic drugs. After consensus was reached, a new WHO working group understood that they needed to lure the international generic drug industry into the manufacture of second-line drugs. On consultation with several experts on both TB drugs and drug procurement, a meeting was called in order to bring all potential purchasers (national tuberculosis programs in regions with a heavy burden of MDR-TB, TB-focused NGOs) together to create a pooled-procurement mechanism that would effectively create a market for second-line drugs. It was decided that the involvement of Nobel Prize recipients Doctors Without Borders (MSF) and the International Dispensary Association (IDA), a well-known Dutch non-profit generic drug manufacturing and procurement agency, would be critical.

The Working Group called a meeting in Geneva in July 1999, but at the last minute the venue was changed to Cambridge, MA and hosted by PIH and Harvard Medical School and jointly sponsored by WHO. The initial list of invitees was limited to 15 people who would actually offer expertise or be interested in purchasing drugs. In the end, however, representatives from 30 organizations or national TB control programs attended with the number of participants reaching 60. At this meeting, both MSF and IDA pledged to begin working on procuring second-line drugs. It was also agreed that the group should submit a proposal to place seven of the most important second-line anti-TB drugs on the WHO Model List of Essential Drugs (EDL). The meeting concluded that the Working Group should organize a pooled-procurement mechanism to increase the availability of these second-line drugs at low cost. Medicines procured through this pooled-purchasing mechanism would only be made available to countries and organizations that complied with treatment guidelines established by a technical committee of the Working Group (WHO, 2000a, b, c).

In August of 1999, the Program in Infectious Disease and Social Change of Harvard Medical School and the Communicable Diseases Cluster of the WHO submitted an application to include the seven second-line anti-TB drugs to the WHO's Model List of Essential Drugs. These drugs, the application read, would only be used, "in settings with established DOTS programs and in WHO-approved DOTS-Plus treatment regimens." Including these drugs on the WHO's EDL would help ensure tighter control of second-line drugs as it would give national TB programs the power to regulate the distribution of these drugs. Irrational prescription of second-line drugs was an acknowledged reality and prohibitive pricing is one reason why this practice was not more widespread. In November 1999, after intense debate, all seven of the drugs were included in the "reserve antimicrobial" section of the WHO's Model List of Essential Drugs (WHO, 2003c). By February of 2000, MSF had agreed to procure all the drugs and provide them to approved programs at cost. Eli Lilly and Company, WHO and MSF began negotiations for agreement on supply of capreomycin and cycloserine. This combination of events led to dramatically lower prices. Overall, the price reductions for the most expensive drugs have hovered in the 95% range in comparison with the prices PIH was paying in 1996 (Gupta, 2000). Simultaneously, a "Green Light Committee" was created to help develop programmes that would use these drugs under the right conditions (Gupta et al., 2002a).

The impact of this novel approach has been significant (Gupta, 2002). Several projects are now established across the globe looking at how best to manage MDR-TB. Preliminary data have fully supported our claims in terms of cure rates (WHO, 2004), feasibility (Suarez et al., 2002), fitness (Cohen, Sommers, & Murray, 2003), and patients adhering to treatment (Nathanson et al., 2004). In addition, although we have been critical of narrow cost-effectiveness analyses that unnecessarily limit options for the poor, recent studies have argued that MDR-TB treatment is indeed cost-effective (Suarez, et al., 2002; WHO, 2004). Clearly, the debate over MDR-TB has shifted from a question of whether to treat patients to a search for the best ways to treat them. Indeed, the Green Light Committee model is now being studied for its relevance for its relevance to efforts to control HIV and malaria (Gupta, Irwin, Raviglione, & Kim, 2004; Attaran et al., 2004).

Conclusion

Why would such an argument as that documented above be of interest to anthropologists and other social scientists? In our view, the struggle over the treatment of MDR-TB, HIV, and drug-resistant malaria is in many ways the most important debate of our times. In the coming year, more than 6 million adults will die from

HIV, TB and malaria alone (WHO, 2002). But because the patients are poor and the treatments expensive, the logic of "cost-effectiveness" had stalled innovation in treatment and control of HIV and drug-resistant strains of TB and malaria. MDR-TB is an airborne disease, and the biosocial events fueling the emergence and spread of this disease finally forced policy makers to abandon notions of limited good and to seek new methods and new resources. With the release of a WHO/IUATLD-sponsored study showing MDR-TB outbreaks in each of 35 countries surveyed, and extensive transnational transmission of highly-resistant strains, it became clear to most observers that the dilemma of MDR-TB would have to be addressed. Of particular concern were settings like South Africa and India, where HIV and endemic tuberculosis, along with widespread private availability of first and second-line antituberculous medications in the private sector, threatened to magnify the MDR-TB problem to an unprecedented degree. In the former Soviet Union, the collapse of cumbersome centralized state TB treatment had created what has been, by any measure, a human catastrophe (Farmer et al., 1999b). This latter disaster, as many observers did not fail to point out, was on Western Europe's doorstep.

More importantly, the world has witnessed unprecedented international awareness of public health problems, as the linked catastrophes of TB and HIV have drawn public attention well beyond the community of public-health professionals. Precise strategies are still a matter of debate, but the prospects for significant financial commitment to improve health services in resource-poor settings are more real now than ever before in human history. Epidemics such as TB and HIV, we are realizing, are the worst in many centuries. Along with its newfound commitment to fighting them, the global community is also arriving at an understanding that we must build a secure base of knowledge and experience in the clinical, operational and political aspects of these interventions. Although cost effectiveness analyses will be important tools for policy makers, equity and improved access to care for the poor are not to be dismissed—nor are the social inequalities that serve to form these epidemics.

Historically, public health specialists have enjoined their colleagues to "keep it simple," with standardized, easy-to-implement and inexpensive interventions suitable for resource-limited settings. The world is now poised to move beyond minimalism and think about the full range of tools and interventions that will be necessary to meet the most pressing global health challenges. Simplicity and efficiency are indeed essential to any public health endeavor. But a desire to maximize efficacy and resources should not obscure the clinical, epidemiologic, and social reality: controlling HIV, MDR-TB and other health problems that afflict the poor world are complex projects. In addressing them, we have no choice—unless we begin doing whatever it takes to address these epidemics in all their social complexity, we will be complicit in the greatest natural disaster in human history. Botswana has lost almost 30 years of life expectancy in a decade due to the co-epidemic of TB and HIV (USAID, 2002), the Russian prisons are exploding with MDR-TB and now HIV (Harvard Medical School/Open Society Institute, 1999), and India and China are sitting on top of explosive epidemics of both TB and HIV (Corbett et al., 2003). How we respond to these challenges, quite simply, will determine how history judges our generation.

Emile Durkheim once observed that the mercantile class was an exception to his general rule that no professional activity could be without its own ethics. "This moral anarchy," he wrote, "has been claimed…as a right of economic life. It is said that for normal usage there is no need of regulation." But from where, he went on to ask, "could it derive such a privilege? Clearly, if there has been self-delusion to this degree among the classical economists it is because the economic functions were studied as if they were an end in themselves, without considering what further reaction they might have on the whole social order (Durkheim, 1957)."

In confronting the modern plagues we would argue that global health policy makers should not use economic tools like cost-effectiveness analysis to exempt themselves from considering what effects their actions will have "on the whole social order." Rather than assume a fixed universe of limited resources that makes only the simplest and least expensive interventions possible in poor countries, we must search for a more appropriate share of rapidly expanding global resources just like the new generation of fishermen in Tzintzuntzan. Any barriers that currently exist to comprehensive global TB control, either in the minds of policy makers or in the "real world," must be brought down. With the creation of the Global Fund to Fight AIDS, TB and Malaria and President Bush's Emergency Plan for AIDS Relief, we are witnessing the beginnings of just such a movement.

Treatment of MDR-TB is simply one small example of how the rich, often arbitrarily, construct barriers to health for the poor. If we are to tackle problems like HIV in sub-Saharan Africa, we must move quickly from theories of limited good to theories and actions that are based on an understanding of the scale and importance of the problem. Such theories and actions, we are convinced, will not only be more effective, they will have the added benefit of serving both justice and simple human decency.

References

Attaran, A., Barnes, K. I., Curtis, C., d'Alessandro, U., Fanello, C. I., Galinski, M. R., Kokwaro, G., Looareesuwan, S., Makanga, M., Mutabingwa, T. K., Talisuna, A., Trape, J. F., & Watkins, W. M. (2004). WHO, the Global Fund, and medical malpractice in malaria treatment. *Lancet*, *363*, 237–240.

Bayer, R., & Wilkinson, D. (1995). Directly observed therapy for tuberculosis: history of an idea. *Lancet*, *345*(8964), 1545–1548.

Becerra, M. C., Freeman, J., Bayona, J., Shin, S. S., Kim, J. Y., Furin, J. J., Werner, B., Sloutsky, A., Timperi, R., Wilson, M. E., Pagano, M., & Farmer, P. E. (2000). Using treatment failure under effective directly observed short-course chemotherapy programs to identify patients with multidrug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*, *4*(2), 108–114.

Brudney, K., & Dobkin, J. (1991). Resurgent tuberculosis in New York city: human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. *American Review of Respiratory Disease*, *144*(4), 745–749.

Cegielski, J. P., Chin, D. P., Espinal, M. A., Frieden, T. R., Rodriquez Cruz, R., Talbot, E. A., Weil, D. E., Zaleskis, R., & Raviglione, M. C. (2002). The global tuberculosis situation. Progress and problems in the 20th century, prospects for the 21st century. *Infectious Disease Clinics of North America*, *16*(1), 1–58.

Codina, G., Vidal, R., Martin-Casabona, N., Miravitlles, M., & Martin, C. (1999). Multidrug-resistant tuberculosis caused by W-related strains in three immunocompetent foreign-born patients. *International Journal of Tuberculosis and Lung Disease*, *3*(1), 82–84.

Cohen, T., Sommers, B., & Murray, M. (2003). The effect of drug resistance on the fitness of Mycobacterium tuberculosis. *Lancet Infectious Disease*, *3*(1), 13–21.

Coker, R. (2002). Should tuberculosis programmes invest in second-line treatments for multidrug-resistant tuberculosis (MDR-TB)? *International Journal of Tuberculosis and Lung Disease*, *6*(8), 649–650.

Commission on Macroeconomics and Health. (2002). *Macroeconomics and health: investing in health for economic development*. Geneva: World Health Organization.

Coninx, R., Mathieu, C., Debacker, M., Mirzoev, F., Ismaelov, A., de Haller, R., & Meddings, D. R. (1999). First-line tuberculosis therapy and drug-resistant *Mycobacterium tuberculois* in prisons. *Lancet*, *353*, 969–973.

Corbett, E., Watt, C. J., Walker, N., Maher, D., Williams, B. G., Raviglione, M. C., & Dye, C. (2003). The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Archives of Internal Medicine*, *163*, 1009–1021.

Durkheim, E. (1957). *Professional ethics and civic morals* (p. 15). London: Routledge.

Dye, C., Scheele, S., Dolin, P., Pathania, V., & Raviglione, M. C. (1999). Global burden of tuberculosis estimated incidence, prevalence, and mortality by country. *JAMA*, *282*, 677–686.

Enarson, D. A. (1995). The international union against tuberculosis and lung disease model national tuberculosis programme. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, *76*, 95–99.

Enarson, D. A., Rieder, H. L., Arnadottir, T., & Trebucq, A. (2000). *Management of tuberculosis: a guide for low income countries*. Paris: International Union Against Tuberculosis and Lung Disease.

Espinal, M. A., Kim, J. S., Suarez, P. G., Kam, K. M., Khomenko, A. G., Migliori, G. B., Baéz, J., Kochi, A., Dye, C., & Raviglione, M. C. (2000). Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *JAMA*, *283*(19), 2537–2545.

Farmer, P. E. (1997). Social scientists and the new tuberculosis. *Social Science & Medicine*, *44*(3), 347–358.

Farmer, P. (1999a). *Infections and inequalities: the modern plagues*. Berkeley: University of California Press.

Farmer, P. E. (1999b). Cruel and unusual: drug resistant tuberculosis as punishment. In V. Stern, & R. Jones (Eds.), *Sentenced to die? The problem of TB in prisons in East and Central Europe and Central Asia* (pp. 70–88). London: International Centre for Prison Studies.

Farmer, P. E. (1999c). TB superbugs: the coming plague on all our houses. *Natural History*, *108*(3), 46–53.

Farmer, P. E. (2002). Social medicine and the challenge of biosocial research. In G. Plehn (Ed.), *Innovative structures in basic research: ringberg-symposium, 4–7 October 2000* (pp. 55–73). München: Generalverwaltung der Max-Planck-Gesellschaft, Referat Presse- und Öffentlichkeitsarbeit.

Farmer, P. E., & Kim, J. Y. (1998). Community-based approaches to the control of multidrug-resistant tuberculosis: introducing "DOTS-plus". *British Medical Journal*, *317*, 671–674.

Farmer, P. E., Kim, J. Y., Mitnick, C., & Timperi, R. (1999a). Responding to outbreaks of multidrug-resistant tuberculosis, introducing "DOTS-Plus". In L. B. Reichman, & E. S. Hershfield (Eds.), *Tuberculosis: a comprehensive international approach*, (2nd ed.) (pp. 447–469). New York: Marcel Dekker Inc.

Farmer, P. E., Kononets, A. S., Borisov, S. E., et al. (1999b). Recrudescent tuberculosis in the Russian Federation. In: Harvard Medical School and Open Society Institute (Eds.), *The global impact of drug-resistant tuberculosis* (pp. 39–83). Boston: Program in Infectious Disease and Social Change, Harvard Medical School.

Farmer, P. E., Robin, S., Ramilus, S. L., & Kim, J. Y. (1991). Tuberculosis, poverty, and "compliance": lessons from rural Haiti. *Seminars in Respiratory Infections*, *6*(4), 254–260.

Flament-Saillour, M., Robert, J., Jarlier, V., & Grosset, J. (1999). Outcome of mutidrug resistant tuberculosis in France: a nationwide case control study. *American Journal of Respiratory and Critical Care Medicine*, *160*(2), 587–593.

Foster, G. M. Changes in Tzintzuntzan: 1988–2000. http://hearstmuseum.berkeley.edu/exhibitions/tzin/43.html

Foster, G. M. (1965). Peasant society and the image of limited good. *American Anthropologist*, *67*, 293–293.

Foster, G. M. (1972). A second look at limited good. *Anthropological Quarterly*, *45*, 57–64.

Fox, W. (1993). Compliance of patients and physicians: experience and lessons from tuberculosis I. *British Medical Journal*, *287*, 33–35.

Fox, W., Ellaed, G. A., & Mitchison, D. A. (1999). Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units. 1946–1986, with relevant subsequent publications. *International Journal of Tuberculosis and Lung Disease*, *10*(Suppl 2), S231–279.

Frieden, T. R., Sterling, T., Pablos-Mendez, A., Kilburn, J. O., Cauthen, G. M., & Dooley, S. W. (1993). The emergence of drug-resistant tuberculosis in New York City. *New England Journal of Medicine*, *328*(8), 521–526.

Frieden, T., Fujiwara, E., Washko, R., & Hamburg, M. A. (1995). Tuberculosis in New York City: turning the tide. *New England Journal of Medicine*, *333*(4), 229–233.

Furin, J. J., Becerra, M. C., Shin, S. S., Kim, J. Y., Bayona, J., & Farmer, P. E. (2000). Effect of administering short-course standardized, regimens in individuals infected with drug-resistant *Mycobacterium tuberculosis* strains. *European Journal of Clinical Microbiology & Infectious Diseases*, *19*(2), 132–136.

Garrett, L. (1989). Emerging viruses, growing concerns. *Newsday* May 30.

Garrett, L. (1994). *The coming plague: newly emerging diseases in a world out of balance*. New York: Farrar, Straus, and Giroux.

Geerligs, W. A., van Altena, R., Lange, W. C. M., van Soolingen, D., & van der Werf, T. S. (2000). Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands. *International Journal of Tuberculosis and Lung Disease*, *4*(8), 758–764.

Gupta, R., Kim, J. Y., Espinal, M. A., Caudron, J. M., Pecoul, B., Farmer, P. E., & Raviglione, M. C. (2001a). Responding to market failures in tuberculosis control. *Science*, *293*, 1048–1051.

Gupta, R., Raviglione, M. C., & Espinal, M. A. (2001b). Should tuberculosis programmes invest in second-line treatments for multidrug-resistant tuberculosis (MDR-TB)? *International Journal of Tuberculosis and Lung Disease*, *5*(12), 1078–1079.

Gupta, R., Cegielski, J. P., Espinal, M. A., Henkens, M., Kim, J. Y., Lambregts-Van Weezenbeek, C. S., Lee, J. W., Raviglione, M. C., Suarez, P. G., & Varaine, F. (2002a). Increasing transparency in partnerships for health—introducing the green light committee. *Tropical Medicine and International Health*, *7*(11), 970–976.

Gupta, R., Raviglione, M. C., & Espinal, M. A. (2002b). Evidence and uncertainties. *International Journal of Tuberculosis and Lung Disease*, *6*(8), 651–653.

Gupta, R., Irwin, A., Raviglione, M. C., & Kim, J. Y. (2004). Scaling up treatment for HIV/AIDS: lessons learned from multidrug-resistant tuberculosis. *Lancet*, *363*, 322–324.

Harvard Medical School/ Open Society Institute. (1999). *Global impact of drug-resistant tuberculosis*. Cambridge: Cambridge University Press.

Hippocrates, Of the Epidemics I, 1.2; Airs Waters and Places IV and VII; Aphorisms V, 9.

Hopewell, P. C., Sanchez-Hernandez, M., Baron, R. B., & Ganter, B. (1984). Operational evaluation of treatment for tuberculosis: results of a 'standard' 12-month regimen in Peru. *American Review of Respiratory Disease*, *129*(3), 439–443.

Iseman, M. D. (1993). Treatment of multidrug-resistant tuberculosis. *New England Journal of Medicine*, *329*, 784–791.

Kenyon, T. A., Valway, S. E., Ihle, W. W., Oronato, I. M., & Castro, K. G. (1996). Transmission of multidrug resistant *Mycobacterium tuberculosis* during a long airplane flight. *New England Journal of Medicine*, *334*(15), 933–998.

Klaudt, K. (2000). The political causes, solutions of the current tuberculosis epidemic. In J. Whitman (Ed.), *The politics of emerging and resurgent infectious diseases*. Basingstoke: Macmillan Press.

Kim, J., Millen, J., Irwin, A., & Gershman, J. (Eds.). (2000). *Dying for growth: global inequality and the health of the poor*. Monroe, Maine: Common Courage Press.

Kochi, A. (1991). The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercle*, *72*, 1–6.

Lambregts van Weezenbeek, C. S., Jansen, H. M., Nagelkerke, N. J., van Klingeren, B., & Veen, J. (1998). Nationwide surveillance of drug-resistant tuberculosis in the Netherlands: rates, risk factors and treatment outcomes. *International Journal of Tuberculosis and Lung Disease*, *2*(4), 296–302.

Medical Research Council (1950). A Medical Research Council investigation: treatment of pulmonary tuberculosis with streptomycin and para-aminosalicylic acid. *British Medical Journal*, *2*, 1073–1085.

Murray, J. F. (1994). Tuberculose multirésistante. *Rev Pneumol Clin*, *50*(5), 260–267.

Nader, L. (1972). Up the anthropologist: perspectives gained from studying up. In D. Hymes (Ed.), *Reinventing anthropology*. New York: Pantheon Books.

Narita, M., Alonso, P., Lauzardo, M., Hollender, E. S., Pitchenik, A. E., & Ashkin, D. (2001). Treatment experience of multidrug-resistant tuberculosis in Florida, 1994–1997. *Chest*, *120*, 343–348.

Nathanson, E., Gupta, R., Espinal, M. A., et al. (2004) Adverse events in the treatment of multidrug-resistant tuberculosis: preliminary results from the DOTS-Plus initiative. *International Journal of Tuberculosis and Lung Disease*, in press.

Pio, A. (1983). The future of the fight against tuberculosis in the world. *Z Erkr Atmungsorgane*, *161*(1), 96–99.

Reichman, L. (2001). *Time bomb*. New York: McGraw Hill.

Rouillon, A. (1991). The mutual assistance programme of the IUATLD. Development, contribution and significance. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, *66*, 159–172.

Rubel, A., & Garro, L. (1992). Social and cultural factors in the successful control of tuberculosis. *Public Health Reports*, *107*, 626–636.

Ryan, F. (1993). *The forgotten plague: how the battle against tuberculosis was won— and lost*. Boston: Little, Brown.

Sachs, J. (2002). Resolving the debt crisis of low income countries. *Brookings Papers on Economic Activity*, *1*, 257–286.

Stop TB Partnership. (2000). *The economic impact of tuberculosis*. Geneva: WHO.

Stop TB Partnership. (2001). *The global plan to stop TB*. Geneva: WHO.

Suarez, P. G., Floyd, K., Portocarrero, J., Alarcon, E., Rapiti, E., Ramos, G., Bonilla, C., Sabogal, I., Aranda, I., Dye, C.,

Raviglione, M., & Espinal, M. A. (2002). Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet*, *359*(9322), 1980–1989.

Sweetland, A., Acha, J., & Guerra, D. (2002). Enhancing adherence: the role of group psychotherapy in the treatment of MDR-TB in urban Peru. In A. Cohen, A. Kleinman, & B. Saraceno (Eds.), *World mental health casebook* (pp. 51–79). New York: Kluwer Academic/Plenum Publishers.

Telzak, E. E., Sepkowitz, K., Alpert, P., Mannheimer, S., Medard, F., el-Sadr, W., Blum, S., Gagliardi, A., Salomon, N., & Turett, G. (1995). Multidrug-resistant tuberculosis in patients without HIV infection. *New England Journal of Medicine*, *333*, 907–911.

Tuberculosis Chemotherapy Centre, Madras. (1959). A concurrent comparison of home and sanitorium treatment of pulmonary tuberculosis in South India. *Bulletin of the World Health Organization*, *21*, 51–144.

United States Food & Drug Administration. (1992). *The Pink Sheet*, February 19.

United States Agency for International Development. (2002). Recent HIV seroprevalence levels by country: July 2002.

Viskum, K., & Kok-Jensen, A. (1997). Multidrug-resistant tuberculosis in Denmark. *International Journal of Tuberculosis and Lung Disease*, *1*, 299–301.

World Bank. (1993). *Investing in health*. Washington, DC: World Bank.

World Health Organization. (1946). Constitution of World Health Organization. adopted and signed on 22 July 1946 by the representatives of 61 States (*Official Record of World Health Organization*, *2*, 100).

World Health Organization. (1997a). *Guidelines for the management of drug-resistant tuberculosis*. Geneva: WHO, WHO/TB/96.210.

World Health Organization. (1997b). *Treatment of tuberculosis: guidelines for national programmes* (2nd ed.). Geneva: WHO, WHO/TB/97.227.

World Health Organization. (1999a). *Global tuberculosis control. WHO report 1999*. Geneva: WHO, WHO/TB/99.259.

World Health Organization. (1999b). *Report on infectious diseases: removing obstacles to healthy development*. Geneva: WHO.

World Health Organization. (2000a). *Procurement of second-line anti-tuberculosis drugs for DOTS-PLUS pilot projects, Cambridge, 5–6 July 1999*. Geneva: WHO, WHO/CDS/TB/2000.276

World Health Organization. (2000b). *Tuberculosis and sustainable development: report from the ministerial conference in Amsterdam*. Geneva: WHO, WHO/CDS/STB/2000.6.

World Health Organization. (2000c). *WHO expert committee on malaria, twentieth report*. WHO Technical Report Series 892. Geneva: WHO.

World Health Organization. (2002). *Report on infectious diseases: scaling up the response to infectious disease: a way out of poverty*. Geneva: WHO, WHO/CDS/2002.7.

World Health Organization. (2003a). *Global tuberculosis control: surveillance, planning, and financing.* Geneva: WHO, WHO/CDS/TB/2003.316.

World Health Organization. (2003b). *Treatment of tuberculosis: guidelines for national programmes* (3rd ed.). Geneva: WHO, WHO/CDS/STB/2003.313.

World Health Organization. (2003c). *Model list of essential medicines* (13th ed.). Geneva: WHO.

World Health Organization. (2004). Report of the meeting of the working group on DOTS-plus for MDR-TB. 24–25 October 2003, in press.

World Health Organization, International Union Against Tuberculosis and Lung Disease. (1997). *Anti-tuberculosis drug resistance in the world: the WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance 1994–1997*. Geneva: WHO, WHO/TB/97.229.

World Health Organization, International Union Against Tuberculosis and Lung Disease. (2000). *Anti-tuberculosis drug resistance in the world No.2, prevalence and trends*. Geneva: WHO, WHO/CDS/TB/2000.278.

Further reading

Claudii Galeni Opera omnia ed. C.G. Kühn, Leipzig, 1821–1833: XIX, 419 (repr. Hildesheim: Olms, 1964–1965).

Suarez, P. G., Watt, C. J., Alarcon, E., Portocarrero, J., Zavala, D., Canales, R., Luelmo, F., Espinal, M. A., & Dye, C. (2001). The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *Journal of Infectious Diseases*, *184*(4), 473–478.