CH. 11. Tuberculosis and the Ethics of Global Health Care

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"Tuberculosis is really not a medical disease.
We know how to diagnose it,
we know how to treat it and
we know how to prevent it.
It's a socio-economic problem"

Dr. E. Hershfield,
Director of TB Control, Manitoba
(North-South Institute 1997:6)

Nota Bene

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Introduction

Even relatively privileged anthropologists who are not engaged in some sort of applied work, but who live along side the poor while conducting their research can not escape the realization that many--often most--of the subjects of their research are people who are chronically afflicted with illness. It is, therefore, quite astonishing to read many contemporary ethnographic accounts which continue to focus on segmented aspects of research; economic development, gender, religion or a plethora of other popular topics are often appraised without any acknowledgment of widespread chronic illness and death which form the context of daily life. There is an ethical dimension to such silences that is rarely explored and to Which Whittaker alludes when she notes that:

> Equally serious in the eyes of some anthropologists are the silences that many anthropologists maintain in their ethnographies on crucial matters such as the hardships caused by the infringements of western development, accompanying governmental or corporate oppressions and other tough issues that confront the communities they study. Problems such as these in anthropology are not uncommon in medical and health development... (Whittaker, 2005:516)

This chapter is offered as an attempt to dissolve some of the rhetoric of safety which we detect in the discourse of risk and protection which surrounds Multiple Drug Resistant Tuberculosis (MDRTB) and Extensively Drug Resistant Tuberculosis (XDTB) and its control via the anticipated imposition of containment measures, including quarantine and sanitary cordons. Such measures, in our estimation, may be promoted as a way of protecting humanity without due care taken to prevent an explosion of high death rates among the global poor who will bear the brunt of any attempt to segregate infection. The discourse of risk containment, which characterizes quarantine, rationalizes the isolation of one part of humanity from the rest as an ethical dilemma whereby the 'greater good' is the protection of the many at the expense of the few (those quarantined). This may simply be a classic ideological move, however, in which the protection of the privileged (the few) at the expense of the poor (the many) is neatly rationalized via notions of objectivity associated with a spurious kind of population triage based on the manipulation of inadequate data and very questionable assumptions. It is a conflation of risk with responsibility. It is our contention that this not only abrogates all social responsibilities but that—at least in the cases of MDRTB and XDTB—will not ultimately protect those who live within the boundaries of privilege anyway. The most robust response to resistant TB in the interest of all parties is to treat the most vulnerable and the poor, first.

Treatment, as we have discovered with HIV-AIDS, is a form of prevention and inseparable from it.

Tuberculosis: the pathogenic context

Tuberculosis (TB) has been infecting humans for thousands of years; it has been the epidemic scourge of sedentary populations since the domestication of animals in the Levant around 7,000 years ago. TB probably troubled earlier humans with occasional infections arising from the butchering and skinning of some kinds of animals they hunted; but without prolonged close proximity to the herd animals (mainly ungulates) associated with settled village life, it was not a persistent danger to mobile hunting populations prior to domestication. The microbe Mycobacterium tuberculosis causes the symptoms we associate with TB. Like many bacteria (and antibiotics) TB has evolved from soil bacteria and it is closely related to the common animal pathogen *M. bovis*.

TB infections have been identified in mummified remains dating from 2000 to 4000 BCE (Bloom and Murray 1992). It was often called the "white plague" (in contrast to the black buboes symptomatic of the Bubonic plague) and reached an apex in the 17th and 18th centuries, during which time approximately 20% of adults in endemic regions eventually succumbed to the disease. Between 1850 and 1950, an estimated one billion people worldwide died of TB (Iseman 1994). Far from improving, it has recently been estimated that a staggering one third of the world's adult population is probably infected with TB (Gandy and Zumla 2003a).

It is possible for TB to infect virtually any part of the body and it is not restricted to the lungs, although they constitute its primary mode of infection (via respiration) and so pulmonary tuberculosis represents the most common set of symptoms. However, the brain, skeleton, skin and genitals are not uncommonly affected and infection of the lymph nodes (historically known as "scrofula") has always been common. By far the most commonly reported form of TB infection, however, is pulmonary tuberculosis, with 85% of reported cases being infections of the lungs (Gandy and Zumla 2003a). Indeed, it has often been said that, "the principal risk factor for acquiring TB infection is breathing" (Bloom and Murray 1992:1058).

To critically assess the ethical dimensions of TB it is important to understand the basic elements of the infection, which begins with the arrival of the tubercle bacillus in the lungs[i]. The body's first immune response in the form of an attack by alveolar macrophages begins with an attempt to engulf the intruding bacteria. This is followed by a symbiotic phase, in which the

numbers of the bacteria and macrophages grows rapidly, forming a cluster within the infected tissue. Next, the body initiates what is termed a "delayed hypersensitivity reaction" in order to kill the infected macrophage cells. During this stage toxins emitted by the bacteria induce lesions, which may be hidden in the lungs or seen as a glandular swelling in the neck, armpits or groin. The body reacts to these toxic clusters of TB bacteria by surrounding them with a thick waxy coating. Eventually new macrophages arrive to destroy any bacteria escaping from these toxic clusters, thus successfully (though alas only temporarily) containing the disease in encapsulated lesions that may harden (calcify) over time, scarring the lungs or other tissues. The disease may persist in this latent state for months, years or even sometimes decades, until an increase in stresses on the immune system eventually allows the lesion to break down and release millions of bacteria directly back into the blood and lymph systems. This happens as a paroxysm, which can quickly lead to death. The secondary stressors of the immune system, which re-open the infection sites, are often the result of other infections, and so TB is often found in particularly lethal associations with other diseases; especially with HIV in recent history. This is the culminating stage of the disease, which is often fatal because the massive new influx of TB bacilli into an already compromised immune system simply overwhelms the body's defenses. Importantly, this is also the point at which TB is most highly infective, as the bacteria in the lungs are then spread through coughing, sneezing, spitting, or just talking. Along with breathlessness and coughing, additional symptoms during the infective stage often include fever, general feelings of malaise, loss of weight, anaemia, metabolic disruptions and psychological disturbances (Gandy and Zumla 2003a, 10). TB generally kills people who die of tuberculosis in association with a plethora of other illnesses. So, while TB precipitates death, it is but one agent in a multi-causal chain of stresses and infections.

Importantly, the progression of the disease from initial infection to full-blown tuberculosis is not a given. It is actually not uncommon for the disease to progress no further than the fourth stage, and for a person to live the rest of their life with a dormant infection. In fact, in an otherwise healthy adult, the chance of a TB infection progressing to actual tuberculosis disease is only 5-10% over an entire lifetime (Koehler 1994). Of course, the key words are 'otherwise healthy adult'. Malnourishment, chronic viral infections, co-infection (especially with HIV), and a host of other factors including psychological stressors, all dramatically increase the likelihood of a TB infection leading to death. Poor people are most likely to live under these additional stressors

and so TB is far more often a fatal disease among the disadvantaged than any other group, no matter what the infection rate may be. In epidemiological terms, what is called "the case fatality rate" is far worse for the poor even if prevalence and incidence rates are the same as those experienced by more advantaged parts of a population.

The highly differentiated case fatality rate associated with poverty has tremendous consequences for ethical concerns, particularly because one of the main ways in which public health officials anticipate dealing with resistant forms of TB is simply to expand the standard practices developed for dealing with it—and chief among these are the invocation of involuntary procedures, especially quarantine. The isolation that sanitary cordons (barriers at the ward, sanitarium, or household level) and the imposition of quarantine (public geographical isolation at the level of neighborhoods, ghettos, cities, etc) strives to achieve, greatly impacts the poor. Without major supports, containment projects are likely to increase their poverty which in turn magnifies the very stresses which make TB lethal in the first place. So, while quarantines may be rationalized as a protection of the wider society and intended to limit the numbers of persons infected with a disease, in the instance of TB (and many other infections) they actually have the capacity—indeed, the likelihood—to greatly increase mortality among those quarantined. We will return to this issue throughout the paper, and in the conclusion. However, as a harbinger it deserves early mention because with highly drug resistant forms of TB the image of an untreatable disease has developed, which further risks the lives of those who may become defined as beyond hope, and in the context of public health triage measures, this would mean the withdrawal of supports from quarantined populations and catastrophic numbers of deaths.

Control and Quarantine in the history of TB.

The intractable nature of TB in the era before antibiotics led to isolation, often in the countryside, and the creation of sanatoria, first in Europe, then later in North America. It also led to the enactment of "Tuberculosis Control Laws" in many jurisdictions, many of which remain in force[ii]. For example, except for Idaho and Maryland, all states in the U.S. have laws which allow for the forcible isolation of tuberculosis patients, either at home or at a state facility. In addition, twenty-three states maintain laws which can require involuntary treatment of those diagnosed with TB (Gostin, 1993). In Canada there is a *Federal Quarantine Act* which deals with infectious diseases and movement into and out of the country and at the provincial and territorial levels,

quarantine falls under the control of communicable diseases in general (Ries, 2005).

It is possible that the segregation of individuals with active TB in quarantined locations away from the rest of the population contributed to the drop in TB rates prior to the introduction of effective antibiotics. But, this has never been convincingly proven; a likely alternative explanation is that the bacterium co-evolved with its hosts to a less virulent form, thus increasingly its survival potential. However, Pasteur's invention of heating cow's milk in order to kill the bacillus did demonstrably lower TB rates by reducing the transfer of *M. bovis* to humans (Bloom and Murray 1992).

The third major innovation in TB control prior to the antibiotic age was the development of the *Bacille Calmete-Guerin* (BCG) vaccine, which is the most widely used form of vaccine in the world. It is the only TB vaccine available, and is annually delivered to approximately 90% of all newborns globally through the Expanded Programme on Immunization, or EPI (WHO 2002). Unfortunately, there is a great deal of controversy as to whether the BCG vaccine actually works, and if it does work, how well it actually protects people against TB. There seems to be a broad consensus that neonatal vaccination is not particularly effective against adult tuberculosis, and so there has been keen interest in recent years in the development of new TB vaccines (WHO 2002). There are two approaches to developing new vaccines: 1) development of a vaccine that would prevent primary infection and disease following exposure (the goal of the BCG vaccine) and, 2) the development of a vaccine that would prevent progression from the latent stage to TB disease in those already infected (WHO 2002). The latter could help control epidemics and reduce mortality by restricting transmission, though not infection in the first instance: it would help those infected now.

Given the severely debilitating and often lethal symptoms of TB, it was a major medical breakthrough when antibiotics were found that proved highly effective against the bacillus. Although the tuberculosis bacterium is resistant to traditional antibiotics such as penicillin or sulfa; in 1945 *streptomycin* (discovered by a soil biologist) was first used effectively against TB (Iseman 1994). However, the use of *streptomycin* alone was unsuccessful in curing most cases of tuberculosis infection, and researchers realized that this was due to mutational variations that conferred resistance on at least some of the bacilli. In classic Darwinian fashion, the selective pressure of the antibiotic left alive only resistant bacteria, and without competition from the

bacteria killed by the antibiotic, remaining drug-resistant strains quickly took over the host tissues. The results of this relapse were often worse than the primary infection. The solution to this problem turned out to be *isoniazid*, another antibiotic that is effective against tuberculosis. By combining *streptomycin* and *isoniazid* to treat TB, lifetime cures were achieved without inducing drug resistance. Iseman (1994) explains why this is so:

> Random bacterial mutations that conferred resistance to individual drugs occurred infrequently during microbial replication, approximately once in 10^5-10^8 [bacteria]. These mutations were unlinked; therefore, the probability of a microbe spontaneously developing resistance to two drugs was the product of the individual risks or 1 in 10^5 x 1 in 10^6 = 1 in 10^{11}. Because the number of bacilli in a patient, even with extensive disease, rarely exceeds 10^9, it was highly improbable that multiresistant mutants would occur spontaneously. Thus, when isoniazid and streptomycin were given together, the isoniazid killed the mutants resistant to streptomycin and vice versa, ultimately eliminating the bacteria from the body (1994: 2428-2429).

This form of combination drug therapy was a major medical breakthrough, and it was certainly heralded as such. Along with *rifampicin, pyrazinamide* and *ethambutol, streptomycin* and *isoniazid* became the five major anti-TB drugs that promised to "close the book" on tuberculosis (Garrett 1994:33, Long and Avendano 2000). Indeed, international infectious disease experts were so optimistic, they declared that tuberculosis was to be eradicated as a public health problem by the year 2000 (Waaler 2002:745).

Resistance grows: The Creation of Multi-Drug Resistant Tuberculosis

Unfortunately, such confidence in the triumph of biomedical science over tuberculosis was premature. The early findings of drug resistance resulting from monotherapy (treatment with only one antibiotic) presaged the growing realization in the World Health Organization (WHO) in the late 1980s and early 1990s that multiple drug resistance in tuberculosis was also becoming a serious a problem.

> Clinical TB drug resistance develops as a result of spontaneous genetic mutations in *M. tuberculosis*, which are selected if antituberculosis drugs are used inconsistently or inappropriately, e.g. if monotherapy is applied. In patients with drug-resistant tuberculosis, additional drug resistance may develop if a prescribed multidrug regimen includes the drugs these patients are already resistant to. In this situation, some of these patients may end up effectively

receiving monotherapy (WHO 2004).

In this way, a patient's TB that is resistant to one antibiotic may become resistant to several other antibiotics through inappropriate prescription. Patients may also play a role in the creation of MDR-TB by discontinuing their treatment before the bacteria have been completely eradicated from the body. Tuberculosis treatment is particularly challenging in this respect, as patients may be required to complete "up to a year of medication adherence in the absence of detectable symptoms" (Barrett et al. 1998:261).

Drug resistance in TB occurs in similar patterns throughout the world. About 85% of all resistant cases are made up of monoresistant H/S, double resistant HS, triple resistant HSR and quadruple resistant HSRE[iii] (WHO 2004). The pathway of drug resistance suggested is resistance to either H or S, leading to double resistant HS, leading to triple resistant HSR, leading to quadruple resistant HSRE. The WHO is careful to note that Aother pathways can and do exist, but states that "their contribution to the drug resistance problem is relatively minor" (WHO 2004:94). The basic inference is that "monoresistance to H or to S is the foundation for the acquisition of additional drug resistance" (WHO 2004:94).

There are also characteristic differences in resistance patterns between those individuals who have been previously treated for TB (acquired resistance) and those who were initially infected with a drug-resistant strain (primary resistance). The prevalence of acquired resistance is significantly higher than the prevalence of primary resistance worldwide. Among individuals with drug resistant TB, the "proportions of monoresistance are lower in patients having re-treatment [than in those with primary resistance], whereas double resistance remains essentially unchanged. Triple and quadruple resistance are higher [in acquired resistance cases] by about the same proportion as monoresistance is lower" (WHO 2004:94). These patterns are due to amplification caused by re-treatment, "i.e. the selective pressures of treatment create double resistance from mainly monoresistant H [or] S cases. The absence of a significant change in double resistance proportions can be explained by selective pressure, leading to an increase in triple and quadruple drug resistance modes thus balancing the inflow from the monoresistance mode" (WHO 2004:94).

These reports are deeply disturbing in two ways. The fact that acquired resistance is more prevalent than primary resistance leads to the conclusion that drug resistance in TB is predominantly being created by current treatment methods, rather than being the product of

mutations in so-called "wild" strains of TB. In addition, the fact that monoresistance is being proportionally replaced by triple and quadruple resistance through re-treatment means that current treatment programs are not only creating resistance, they are amplifying existing resistance manifold times. There are now strains of TB that are resistant to all known antibiotics and this renders the populations in which they have appeared, a potential target for the imposition of containment measures, beginning with sanitary cordons and ending with quarantine. It is a very frightening thought that *our own medicine* has created and amplified drug resistance in tuberculosis to the point that "the current manageable pandemic of TB has the potential to become an unmanageable MDR-TB pandemic" (Blanc and Uplekar 2003:103). Of course, there would be an attempt to "manage" a global MDR-TB epidemic and to understand what that "management" entail we might well begin by examining the situation prior to the advent of any known treatment. To this we can add a number of very salient contemporary elements including, especially, the development of vast slums in a world which is now predominantly urban.

What would it look like if MDR-TB was to become the dominant strain of the disease? Quite simply, the world would be catapulted back to the situation of the 1930's, when the nature of the disease was understood, but there were no effective treatments. This is not an exaggeration: "the case fatality rate for TB resistant to two or more major antibiotics (multidrug resistance) is 40 to 60%, equivalent to untreated TB" (Iseman and Madsen 1989, as cited in Bloom and Murray 1992). This includes strains of MDR-TB which are still susceptible to some antibiotics; if a strain which is universally resistant becomes dominant, the mortality rate would be even higher. It would be highest among the urban poor...which is where the majority of the world's poorest inhabitants now dwell.

As terrifying as the thought of untreatable TB is, there are mixed opinions as to how seriously its potential to become pandemic should be treated. One widely held view is based on the fact that Amost drug-resistant cases [of TB] have historically involved failed treatment in individuals (Iseman 1994:2429). According to this line of reasoning, person-to-person transmission of drug-resistant TB has generally been rare "presumably because the metabolic compromises made by the microbes to enable drug resistance have made them modestly less virulent. And, in the normal host B whose immune system has a 90% chance of containing a

tuberculosis infection for a lifetime B even a small reduction in pathogenic capacity would make transmission of drug-resistant disease quite uncommon" (Iseman 1994:2429). While it is true that acquired resistance is more common than primary resistance, there is a vast leap of faith in the assumption that this is because drug-resistant tuberculosis bacilli are somehow less "hardy" than the "wild" non-resistant type—indeed, the metaphorical use of the term "wild" presumes this, but there is no evidence for it. We simply do not know that this is the case, and to assert it is utterly irresponsible science.

Other researchers working in areas like Haiti, which are deeply affected by MDRTB, notably the medical anthropologist James Farmer, argue, "pulmonary MDRTB appears to be as easily transmitted as are drug-susceptible strains" (Farmer 1999:246). Some of the confusion may arise from the fact that many of the early studies of MDT-TB included individuals who were co-infected with HIV, which tends to increase the probability of systemic TB rather than just the pulmonary form of the disease (Farmer 1999). In general, existing data from microbiology "do not show drug-resistant strains to be universally either more or less virulent than susceptible strains of the same organism. Certain organisms may become debilitated and require an extremely susceptible host, whereas others may have an enhanced capability of infecting humans and causing serious disease" (Cohen 1992:1053).

While it is certainly true that there have been more reported cases of acquired resistance than primary infected with MDR-TB, there are explanations for this fact that do not rely on the highly dubious claim that drug resistance is inversely related to infectivity. It is far more likely that MDR-TB infections are more frequent in people with other infections, making it a systemic rather than primarily a pulmonary disease competing with other pathogens in a weakening host who may die from any of a number of infections. It seems likely that there is a combination of two other factors at work here: 1) Treatment-induced MDR-TB is more likely to be reported than acquired MDR-TB, due to the simple fact that a person must be receiving medical care in order to acquire drug resistance; while there is no such guarantee that a person with primary MDR-TB infection will ever come to the attention of medical researchers. 2) Since drug resistance in tuberculosis is a fairly recent evolutionary development, and it is still evolving today, there is a very real possibility that along with MDR-TB being equally infective as drug-susceptible TB and spreading at a comparable rate, it is actually being created at even higher

rates. In other words, it is now replacing TB.

The most frightening possibility for the spread of drug resistance stems from the amazing ability of bacteria to transfer genes among themselves. Bacteria of the same class, and sometimes even bacteria of different classes, have the ability to pass plasmids containing DNA back and forth between individuals (Garrett 1994). This "gene transfer" can allow a relatively harmless bacterium normally found in the gut, such as *E. coli,* to pass antibiotic resistance on to much more dangerous bacteria such as *M. tuberculosis*. Thus the general misuse of antibiotics, not just in the treatment of TB, can contribute to the increase in MDR-TB. This can happen in any hospital, agribusiness farm, or laboratory where antibiotics, people and pathogens mix. Among the most likely sites, therefore, are large institutions in the so-called "developed" world.

Extensively Drug Resistant Tuberculosis: XDR-TB

XDR-TB is defined by the World Health Organization (WHO) Global Task Force as resistance to at least rifampin and isoniazid, plus resistance to the fluoroquinolones and to at least one of the injectable drugs (capreomycin, kanamycin and amikacin). Although there are other second-line drugs, the fluoroquinolones and injectable agents are both the most potent and easily tolerated drugs and consequently without them, treatment of XDR-TB, if it is even diagnosed before death, is extremely difficult to accomplish. XDR-TB is extremely difficult to cure, and virtually impossible to treat in settings of poverty, since the few remaining classes of drugs are very not very potent, highly toxic, and very expensive. It is an extremely frightening development, thus far poorly covered by the press and not well investigated by the corporate medical research community—probably because there is little anticipated profit which could flow from it. It now appears, however, that XDR-TB, while not very well understood, probably exists as a small number of cases wherever MDR-TB has evolved, and so is also widespread, though as yet represents only a small percentage of those initially assessed as harboring MDR-TB. Poor TB control practices, high HIV prevalence, and hospital acquired (nosocomial) transmission have probably played major roles in its development. So, XDR-TB has emerged in the poorest places in the world, and is growing there, relatively hidden from view.

The Global Context of Resistant TB Today

The World Health Organization (WHO) began to pay serious attention to tuberculosis in 1991, when it first established global targets for TB control, and by 1993, it had declared the TB epidemic a global emergency (Kumaresan and Harries 2004). In 1997, the WHO published the first global report on anti-tuberculosis drug resistance in the world from the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. The second report was published in 2000, and the most recent global data are in the third report, published 2004. The following overview of MDR-TB in the world today describes trends and data from the 2004 report except where otherwise referenced.

As has already been stated, approximately 1/3 of the global population is infected with the TB bacillus, and of those some are undoubtedly actually XDR-TB cases. Of these 2 billion people, about 8 million develop active tuberculosis every year and 2 million die (Blanc and Uplekar 2003). There are 425 thousand new MDR-TB cases every year, concentrated in the former Soviet Union as well as a few provinces in China (WHO 2005). Israel and Ecuador are two of the other MDR-TB 'hot spots' identified by the WHO. Other areas of the world have lower prevalence of MDR-TB, but there is no region that is completely free of drug-resistance. It is important to understand that the WHO data are only as good as the detection networks in place to recognize the existence of a pathogen. In the case of a pathogen like MDR-TB detection only takes place when the person seeks medical attention in the first place, or where a research project has taken MDR-TB as its subject and has obtained meaningful samples. MDR-TB by its very nature is difficult to detect and can only be known in most instances when treatment for TB has failed and the patient seeks further treatment; XDR-TB is generally seen where there are research protocols in place to detect MDR-TB. Thus, the measures of both forms of resistant TB do not indicate the absence of the disease, only the absence of its detection following failed treatment for TB, or MDR-TB in the case of XDR-TB.

Worldwide, the measure prevalence of resistance to at least one anti-tuberculosis drug (any resistance) ranges from null measures (0%) in a few Western European countries to 57% in Kazakhstan, with the median at 10%. The prevalence of multi-drug resistance ranges from 0% in eight countries to 14% in Kazakhstan and Israel, with the median at 1%. The main problem with the global statistics stems from the simple fact that they depend on reporting—which

depends in turn surveillance associated with people actually receiving treatment. So, very poor areas of the world which are known to have high HIV rates and likely numerous co-infections may still report extremely low prevalence and incidence rates of TB, though the population almost certainly has high infection rates which are simply undetected. As well, in some areas the densest concentrations of both diseases are to be found in prison systems (Eastern Europe, China and Russia for example) and are under-reported because the imprisonment rates themselves are either unreported or systematically underestimated, and prisoners are often untreated populations where imprisonment is a *de facto* death sentance.

The Global scenario

Worldwide there are 10 areas that are known to have a high or very high measured prevalence of MDR-TB (defined as more than 6.5% of total TB cases), though as we have suggested, there are almost certain more. These are set out in Table 1 below (adapted from WHO 2004).

Table 1: Countries/settings with MDR-TB prevalence higher than 6.5%, 1999–2002

Setting	**Survey Year**	**MDR-TB Prevalence (%)**
Ecuador	2002	6.6
Henan	2001	7.8
Latvia	2000	9.3
Lithuania	2001	9.4
Lianoning	2002	10.4
Estonia	2000	12.2
Uzbekistan	2000	13.2
Tomsk Oblast	2002	13.7
Israel	2001	14.2
Kazakhstan	2000	14.2

The table details the relative prevalence of MDR-TB around the world, but as in our

discussion, it simply does not give a full picture of the problem. The absolute number of cases in a country is also a factor in determining the scope of MDR-TB, and those further predicate XDR-TB. Thus, in many countries with relatively few TB cases, a high prevalence of MDR-TB does not reflect a high absolute number of cases. Conversely, a low prevalence of MDR-TB in a high-burden setting, such as South Africa or some provinces in China, could actually reflect a large number of MDR-TB cases. A comparison of South Africa and Kazahkstan illustrates this point: in South Africa, the prevalence of MDR-TB is around 3%, while in Kazakhstan it is almost 15%. These numbers seem to indicate that MDR-TB is a much larger problem in Kazahkstan than in South Africa, yet the extremely high prevalence of all cases of TB in South Africa (and a recently reported outbreak of XDR-TB) means that both countries almost certainly have about the same absolute number of MDR-TB cases: that is, about 3000 diagnosed each year. This is the highest absolute number of MDR-TB cases in the world, followed by three provinces in China (Hubei, Henan and Liaoning). The countries with the fewest absolute number of MDR-TB cases are Luxembourg, Andorra, Malta, Iceland, Slovenia, New Zealand and Scotland.

The data indicating increases in the prevalence of MDR-TB are deeply disturbing. An increase in prevalence of any resistance reflects an environment that favours the acquisition of additional drug resistance, thus leading to future increases in MDR-TB and ultimately XDR-TB. Equally unsettling are the large gaps in the worldwide surveillance of all resistant forms of TB that still exist. This all points to a particularly difficult scenario for planning because the available data strongly suggest that those places that are least surveyed probably have the largest problems. This assumption is also based on the fact that a country's inability to carry out MDR-TB surveillance is likely to indicate a lack of capacity in TB control services in the first place. Therefore, un-surveyed areas are likely to have worse TB control in general than surveyed areas and they could easily generated an epidemic long before it is actually discovered to be one. This problem is made far worse when people working in a region as researchers have some idea of the toll that disease is taking on the people, but do not report it because they are there, ostensibly, to study something else. This most certainly includes, among others, anthropologists.

The Hyper-Dynamic Duo: The Special Case of HIV Co-Infection

Despite the growing prevalence of MDR-TB and XDR-TB in many areas of the world, drug resistance in tuberculosis is apparently not yet epidemic. However, the emergence of HIV has created a dreadful synergy with TB, since "the impaired [immune] defenses associated with HIV disease facilitate the transmission of MDR-TB" (Iseman 1994:2429). Indeed, "the HIV pandemic has made a dramatic impact on TB in regions where TB and HIV infections are co-prevalent" (Blanc and Uplekar 2003:101). In regions such as Africa, South America and Asia where a large proportion of the population is already infected with tuberculosis, "TB has emerged as the most common HIV-related disease" (Blanc and Uplekar 2003:101). This is due to the fact that latent TB infections are increasingly able to progress to active tuberculosis as HIV compromises the body's immune system. While only 5 to 10 percent of TB-infected individuals "develop tuberculosis disease at some point during their *lifetime* … for HIV positive individuals infected with tuberculosis, the chances are 7 percent to 10 percent *every year*" (Koehler 1994:33).

There is some controversy over whether or not HIV is a specific risk factor for resistant TB. While the WHO (2004) asserts, "HIV-infected TB patients are not more likely to develop drug resistance than HIV-negative TB patients," other studies have found that "HIV infection is associated with increased rates of resistance to antituberculosis drugs" (Gordin et al. 1996). It is possible that Gordin et al.'s study was influenced by its location in New York City, and that HIV and MDR-TB were associated in this study because MDR-TB was actually the dominant strain of TB among those infected with HIV. It is also plausible that the population infected with HIV and the population being infected with MDR-TB overlapped because they were acquiring both infections from the same sources, namely others whose co-infection of HIV allowed their MDR-TB to progress to active disease.

In any case, the real issue is not whether HIV causes drug resistance in tuberculosis. A far greater problem is the certainty that HIV co-infection greatly increases the probability that latent TB infections will progress to active disease, which has implications for broadcasting the disease in rapid transmission as well as for the earlier death of the host. Since TB is only infectious in the active stage of the disease, the total number of infectious cases of TB worldwide has been greatly increased by the HIV pandemic. In the best case scenario, a case

of TB is treatable, and the patient, whether co-infected with HIV or not, may be cured. However, MDR-TB is *in the best case* scenario only curable 60% of the time (WHO 2004) and as we have indicated, XDR-TB is rarely treatable, at any time. Therefore the fact that "the HIV epidemic threatens to promote wholesale transmission of MDR-TB" has grave implications for the future mortality, especially in populations of the global poor (Iseman 1994:2429).

DOTS-Plus: The Possibility for Bringing MDR-TB Under Control—at least for awhile

If resistant forms of TB are not checked in its advance, it is widely agreed that the results will be disastrous for humanity. Given that "the cure rates among patients harbouring multi-drug-resistant [strains of TB] range from 6% to 59%" (WHO 2004), allowing MDR-TB to become the dominant strain of the disease will return global TB case fatality rates to the levels of the pre-antibiotic era. The rapid emergence of XDR-TB would be even worse. Unfortunately, current medical practices are not just allowing resistant TB to spread; they are actively promoting its development.

The directly observed therapy, short-course (DOTS) strategy, promoted by the WHO since 1993, is composed of five elements that are necessary for global TB control:

> [1] Political commitment;
>
> [2] Case detection using sputum smear microscopy among persons seeking care for prolonged cough;
>
> [3] Standardized short-course chemotherapy under proper case-management conditions, including directly observed treatment;
>
> [4] Regular, uninterrupted drug supply;
>
> [5] Standardized recording and reporting system that allows assessment of individual patients as well as overall programme performance
>
> (WHO 2004).

The aim of the DOTS strategy is to detect and cure cases of TB while trying to minimize the development of further drug resistance. This is widely thought of as "the most cost-effective way of arresting the spread of the disease" (Blanc and Uplekar 2003:96). In order to reduce the creation of new cases of MDR-TB, ensuring that patients are able to complete their courses of medication is the most important aspect of the DOTS strategy.

Surveillance is also very important to identify and treat existing MDR-TB. The WHO (2004) suggests, "immediate action must be taken to increase the coverage of drug resistance surveillance in the former Soviet Union." It will also be important to "begin to gather data on the crossover of HIV and MDR" in this region (WHO 2004). More than data-gathering is needed however: "of the highest priority is the proper implementation or expansion of DOTS and DOTS-Plus both to control MDR in areas of known high prevalence and to avoid an epidemic of potentially catastrophic proportions that could destabilize TB control" (WHO 2004).

There is disagreement among researchers as to the best method for bringing restant forms of TB under control. Some feel that it is important to have control measures for drug-susceptible TB well in place before attempting to deal with MDR-TB and XDR-TB, since "an immediate response to MDR-TB without improving the treatment of drug-susceptible cases would result in the creation of more drug-resistant organisms and could make the containment of MDR-TB unattainable" (Blanc and Uplekar 2003:103). An opposing opinion is held by Farmer (1999) who argues that treating drug-susceptible TB while ignoring resistant TB will only lead to an increase in the transmission of primary multi-drug resistance. He cites the example of an HIV ward in a hospital in Spain, which, by treating drug-susceptible TB while failing to diagnose and treat MDR-TB, actually increased the prevalence of MDR-TB in the ward to 65% of all TB cases in less than 5 years (Farmer 1999). Clearly, ignoring resistant forms of TB is not an option, even in the short term. If TB is being replaced by MDR-TB, and perhaps XDR-TB, then only treating the first form will simply abet the evolution of the latter forms—it's a simple evolutionary equation.

The second-line anti-tuberculosis drugs include *kanamycin, amikacin, capreomycin, cycloserine, ethionamide,* the quinolones (*ofloxacin, ciprofloxacin, sparfloxacin and levofloxacin), para-amonisalicylic acid (PAS)* and *clofazimine* (Long and Avendano 2000). They are "more expensive, more toxic, and less effective" than the standard anti-TB drugs, and so there is little reason to take them unless one is infected with MDR-TB or (Farmer and Walton 2003:167) or XDR-TB. For those who do have a drug-resistant strain of the disease, however, these drugs are the only hope for a cure. Until recently, the international health community, including the WHO, told people in developing countries that these second-line

drugs were not part of their treatment plan. The argument was that DOTS, using first-line drugs, "should be the sole TB treatment strategy in the Western hemisphere's poorest countries" (Farmer and Walton 2003:168). The logic behind this argument was partially based on the need for coordinated global efforts to control the tuberculosis epidemic, but of far greater importance was the perceived cost-effectiveness of the DOTS strategy. Second-line TB drugs have become linked in the consciousness of researchers and policy makers with extremely high prices (e.g. Blanc and Uplekar 2003), when in fact there have been no studies of the relative costs of treatment with first- or second-line drugs (Farmer and Walton 2003) and if one takes into account the costs which accrue from transmission and spread, there are no good cost effectiveness estimates whatsoever. Most second-line drugs are no longer under patent, and so they are subject to great variations in price dependent upon demand and public pressure. Farmer and Walton (2003) report that advocacy in Peru led to a drop in price from $US 10,000 to $US 600 per patient for second-line drugs, while treatment of drug-susceptible TB in New York City costs more than $US 20,000 per patient. It is important to be highly skeptical of claims about the relative cost effectiveness of (not) treating MDR-TB. Farmer has been instrumental in developing the concept of DOTS-Plus, "a DOTS-based strategy that relies on drug susceptibility testing and second-line drugs in order to bring patients with MDR-TB to cure" (Farmer and Walton 2003:176). The WHO has realized (belatedly) the necessity of treating MDR-TB, and has called for the use of DOTS-Plus expansion in Eastern Europe as well as test sites in South American "MDR-TB hot spots" (WHO 2004, Farmer and Walton 2003). Parsimoniousness with drugs is a good way to increase resistance in TB, since "in the choice of a treatment regimen, one must not aim to keep drugs in reserve. That is the way to lose one battle after another" (Long and Avendano 2000:119).

TB and resistant forms of TB as an Ethical Issue

Much of this paper thus far has been a discussion of the threat resistant forms of TB pose to global tuberculosis control and how existing policies and treatment projects may actually contribute to the evolution of resistance. If hioghly resistant forms of TB are allowed to become dominant strains of the disease worldwide, it will certainly change things drastically for those of us who live in affluent nations. However, for the 2 million people who now die every year from tuberculosis, to say nothing of the millions more whose health and wellbeing

are severely compromised by the disease, even 'treatable' TB is already terrifyingly deadly. Today, "the majority of those who die of TB die not of drug-resistant disease, but of lack of access to any effective antituberculous therapy" (Farmer and Walton 2003:164). In a resistant TB era, the lack of access to which Farmer and Walton refer will become increasingly widespread, so it will be social and economic variables associated with the stressors of life, which will continue to most affect morbidity and mortality from the disease. There is ample evidence that those stressors are now at work around the globe.

Despite the nearly miraculous advances in medicine over the past 50 years, to say nothing of the existence of powerful antibiotics, which are effective against all but the most highly resistant strains of resistant TB, "there is more tuberculosis in the world today than ever before" (Waaler 2002:745). Researchers and experts have cited many different reasons for the persistence of appallingly high rates of TB, most notably the HIV epidemic and the increasing prevalence of resistant forms of TB. However, as Waaler (2002:745) notes, "there seems to be general agreement that even the non-HIV/AIDS related incidence, prevalence and mortality are much higher than the availability of efficient diagnostic methods and cheap and efficient drugs should make reasonable, acceptable and achievable."

The main reason for the increase in Tuberculosis is simply the ever-increasing gap between the worlds's rich and its poor, understood both in terms of countries and individuals. Blanc and Upkelar (2003:106) have recently noted that TB and poverty are closely linked—we would prefer top say that they are intimately linked. The probability of becoming infected with the disease, of developing clinical disease and of then spreading it, are all associated with malnutrition, crowding and poor sanitation – factors nearly always associated with poverty. A vicious cycle is thereby established. Poor people are malnourished and live in crowded, unhygienic conditions, where TB flourishes; the poor receive inadequate health care in which TB is not diagnosed rapidly; treatment, if received at all, is often inconsistent or partial. Resultant ill health and death then worsen poverty, amplifying the cycle. This is a way that "social forces, ranging from political violence to racism, come to be embodied as individual pathology" (Farmer 1999:13).

The patterns of TB prevalence along economic lines are both revealing, and quite shocking. Some 95% of tuberculosis cases and 98% of TB deaths occur in the

poorest regions of the world (WHO 2004). Much of this burden of illness can be attributed to international financial relationships, in that "the 'debt trade' has been a major factor in perpetuating and intensifying poverty and ill health. Cuts and under financing of public health spending associated with the structural adjustment programs mandated by the World Bank, have resulted in severe deterioration in health-care delivery programs, especially in Africa (Benatar 2003:224).

Within wealthy and developed nations, there is also a contrast in TB outcomes between the rich and the poor. Benatar (2003:226) points out that "both absolute and relative wealth affect health. Among the developed countries it is not the richest societies that have the best health but rather those with the smallest differential between rich and poor." In the United States, a country that is extremely stratified along both economic and racial lines, "poverty and racism increase the likelihood that one will become infected … [and] progress to active disease" (Farmer 1999:13). Among those that have active infections, "poverty and racism [further] increase the likelihood of dire outcomes among the sick by restricting access to effective therapy or rendering it less effective if patients are malnourished or addicted" (Farmer 1999:14).

Thus, while the TB epidemic is being discussed at the international level as being're-emergent', some researchers now argue that "only from a highly particular point of view can it be seen as … a 'reemerging' disease" (Farmer 1999:185). Tuberculosis was considered 'conquered' when it was no longer a problem for wealthy and powerful individuals in wealthy and powerful countries. It is now considered re-emergent as drug resistance and HIV co-infection have started to make it a perceived threat to the wealthy once again. For the global poor in many parts of the world, tuberculosis has just remained "the leading cause of young adult deaths" (Farmer 1999:185) and is now a worsening problem of plague proportions. That is not 're-emergence': it is expansion.

Heifets and Iseman (2003:707) argue that "current concepts of morality and responsibility as well as the availability of potent modern technology compel us to take action on this crisis". How, then, can ethical concepts be usefully inserted into discussions about tuberculosis?

Fundamental to any discussion of an ethics of TB is the conflict between traditional medical ethics and a form of public health ethics. Traditional medical ethics focuses on individual autonomy and human dignity, while public health ethics focuses on the protection and promotion of health in communities (Verma et al. 2004). Specific to TB, a central ethical concern is "balancing the patient's rights and autonomy with the protection of the public's health" (Verma et al. 2004:5). This may be too confining a way of understanding the discourse on risk. MDR-TB and XDR-TB will change this discourse to one, which pits populations against one another rather than individuals against groups. Privileging the perspectives of the wealthy over the poor and rather circuitously enveloping the ethical discussion within the parameters of individual vs. group dilemmas are conflating estimates about the risk of contagion. This does not bode well for useful policy development in the arena of containment—it will not contain the disease, but it will coercively and unequally distribute death in massive disproportion.

TB control that requires quarantine/coercion. DOTS

> "Coercion and detainment can be a morally acceptable strategy to fight the spread of tuberculosis, but these measures need to be placed into a much broader context than that of their short-term potential effectiveness. TB should be de-stigmatized by full acknowledgment that we all share the blame for its perpetuation." (Doyal 2001:208).

One commentary on the ethical aspects of TB control states that "if individuals are required to sacrifice their autonomy for the good of the community, then it is the community's responsibility to attend to the individuals health requirements and to support and facilitate the discharge of the individual's obligations" (Verma et al 2005:5). This statement of ethical obligation has fascinating legal and policy ramifications (Ries, 2005). Clearly it is a responsibility for a community, whether that is defined as a local group, a country, or an international organization, to attempt to improve the health of an individual that has been deprived of their autonomy. 'The discharge of the individual's obligations', however, is a more complicated matter. It is a challenge to determine the extent of the community's responsibility for the obligations of individuals. For example, if the individual has dependents, what are the

community's obligations insofar as feeding, housing, or educating those dependents? If the individual's income is put at risk by the required treatment, what responsibility does the community have to ensure the continuation of that livelihood once the treatment is completed? The ethical conclusion seems to be that requiring an individual to undergo treatment for the sake of 'public health' must not result in that individual's or their dependents' situation worsening as a consequence of undergoing the treatment. By including the social context of individuals within the framework, it *de facto* becomes a discussion of groups and group rights. The exact meaning of this will of course vary from situation to situation, and the logistics seem formidable. This should not, however, deter the planners of TB interventions from considering the ethical implications of TB control measures as they pertain to groups.

One of the groups upon which control measures like quarantine have a disproportionate impact is health care workers. Regarding the specific impact of quarantine, an editorial in the *Canadian Journal of Nursing*, concludes regarding the recent SARS epidemic in Toronto that:

> The procedure of quarantine, from its beginnings, seems to have been imposed from the outside, as a law or interdict, and resulted in, or at the very least represented, segregation, social and psychological isolation, stigma, reduced social status, and the potential powerlessness of those affected (Wynn and Peter, 2003:207)

Although tuberculosis certainly raises ethical dimensions that go beyond individual rights, discussions of the ethics of TB control usually stop here. This may be due to the culture of ethics in medicine that values individual rights over group rights. More specifically, we note that "our notion seems to be that individuals have rights; groups have responsibilities to individuals, and it is rarely the reverse" (Stephenson 2001:14). However, TB can also be understood on a larger scale as "a human rights issue, raising important questions about equity regarding who suffers the most from disease, and the global imbalance with regard to disease burden as well as reciprocal social obligation to alleviate suffering" (Verma et al 2004:5).

Benatar's (2003) concepts of meso- and macro-level ethics are especially useful in expanding this discussion. Benatar describes the expansion of medical ethics

beyond the dyadic doctor-patient relationship, and moves it into the multi-faceted and interdisciplinary realm of human rights. Meso-level ethics is roughly analogous to public health ethics, and is the arena of responsibility that health professionals have for public health and the common good. Macro-level ethics is much more holistic and considers the "ecological security, international relations and the interdependence of all forms of life" (Benatar 2003:232). Individuals are conceived as autonomous but always connected: "sharing equal rights with all other citizens of the world, in a relationship of interdependence" (Benatar 2003:232). Tuberculosis control can be linked to all dimensions of ethics, from the individual care at the micro-level, to the public health programs of the meso-level, to the WHO's global TB control program at the macro-level. The implication of Benatar's holistic ethical premises is clearly to treat individuals and groups under the same ethic of global care. Bluntly, to protect ourselves, we must protect others.

Ethics at the macro-level must take into account the global disparities between individuals and groups. "An intercultural medical ethics will of necessity have to move beyond the dimension of individual entitlement and rights and towards some way of addressing the rights of groups of people who are disadvantaged." (Stephenson, 2001:14) This is difficult under current ethical frameworks, in which medical ethics are viewed "as a moral arbiter based on hard logic and absolute categories … these represent ideologically loaded core assumptions representing a Western post-industrial world view: the individual, consent, choice, worth and goodness (as opposed to evil) and control" (Stephenson 2001:5). In such an individuated conception of ethics, "notions of group rights, as well as more environmental notions of cause of all forms of pathology (including crime) become either unthinkable or even anathema" (Stephenson 2001:5). From the standard ethical standpoint, the appalling rates of tuberculosis among the global poor are viewed, at best, as a public health problem rather than an ethical problem. At worst, forms of resistant TB are being constructed as the product of 'noncompliance' on the part of patients. Nobody discusses the failure to comply with the provision of treatments on the part of international corporate bodies.

The challenge is to re-conceptualize ethics so that the interconnections between the lifestyle of the wealthy elites of the world and the misery and ill-health of the global poor are clearly laid out. As Farmer and Walton (2003:176) state, "*global health equity* must become a central component of wise policy in the coming years." One method of accomplishing this is by thinking less in terms of human rights and more in terms of human duties, particularly those humans fortunate enough to live in the wealthy countries of the world. As one scholar puts it, "the achievement of a global civil society will require acknowledging and promoting the idea of human duties as an essential component of human rights" (Benatar 2003:232).

One difficult area in this re-configuring of medical ethics is the use of antibiotics themselves. The way that our medical culture uses antibiotics guarantees that microbes will develop drug resistance - and "one is given to wonder at the ultimate wisdom of this … and the role that individual rights ascendant over collective responsibilities may play in ever trying to remove so-called 'modern medicine' from this nasty evolutionary *cul de sac*." (Stephenson 2001:12). It is a sticky and probably unanswerable ethical question as to whether or not one can withhold antibiotics from an individual for 'the common good', because after all, what is the community but a collection of individuals?

In terms of tuberculosis, it is possible to at least partially evade this dilemma by focusing on the fact that the global burden of TB could be very much alleviated by reducing or eliminating malnutrition and elevating people out of poverty. Although there is probably no effect on initial infection, malnutrition has been shown to interfere with cell-mediated immunity and so increase the likelihood that a latent infection will progress to active disease (Cegielski and McMurray 2004). Therefore there are more pressing ethical issues that must be dealt with before tackling the question of who should get access to which antibiotics. However, the issue is not going to just go away, and it is a question that will have to be dealt with at some point in discussions of tuberculosis control. Researchers and policy makers will have to be extremely careful that any new anti-tuberculosis drugs created in the future are not withheld from those in developing nations for reasons of 'cost effectiveness'. Clearly, however, the best

possible intervention would be a combination of vaccine development and poverty reduction…especially a reallocation of nutritional resources.

Conclusion

We have tried to show that the current spread and future threat of drug-resistant tuberculosis is an ethical issue that is framed by a discourse of risk which has constrained ethical discussions and limited our view of both obligation and viable treatment and prevention alternatives. Many policy writers continue to invoke the protection of the greatest numbers (as if that can be predicted) even while advocating for a humane approach to mandatory quarantine. For example, in discussing the impact of quarantine on the poor, Booker (1996:99) states, "It would be wrong to compound the problems that these people [the poor] already face, but we cannot wait to address the problems of the spread of tuberculosis until all of the medical, educational, and economic injustices of the country are remedied" In contrast, we suggest that the best way to protect all human beings from a rapidly expanding infectious disease which will return our species to the pre-antibiotic era is for the efforts of governments, health organizations, and researchers to be directed towards improving the basic quality of life for the global poor. The idea that they will actually attempt to avoid meaningful treatment if it becomes available is largely a paranoid fantasy created by narrowly cost counting, xenophobic think tanks associated with the neo-liberal world view. We hope that we have been convincing in our arguments that the most effective control for all forms of resistant TB is improving sanitation, housing, and medical access, rather than simply increasing the use of antibiotics. Even if readers remain unconvinced, however, the issue may become a moot point soon enough, as we enter the post-antimicrobial era of antibiotics and enter a period of resurgent pandemics. The problem is certainly a "macro" issue and so its solution must engage a "macro" form of ethics. There are some research efforts underway to find new anti-tuberculosis drugs, but "the pharmaceutical industry cannot be expected to provide a limitless supply of new antimicrobial agents for resistant organisms" (Cohen 1992:1054). Indeed, the wisdom of doing so may be deeply flawed. Bacteria have been evolving forms of resistance to limit competition for food resources among

themselves for billions of years and humanity has at times briefly harnessed some elements of that competition to serve its own ends. But such an engagement is only temporary and provides us with an illusion of control (Stephenson, 1997). Emphatically, we are not going to beat them at their own game. Instead, "as antimicrobial resistance increases, health efforts need to be focused on preventing transmission and infection rather than on treating infection once it has occurred" (Cohen 1992:1055). This shift in perspective is overdue and it is also a simple necessity for survival. "Today, the concept of an untreatable bacterial disease is foreign to most physicians in the developed world." (Cohen 1992:1050). One area where physicians—and the rest of us—can glimpse some of the most salient characteristics of resistant TB forms is to be found in prisons, around the world, where it now rages. Yet these crucibles of the disease are well beyond our inspection in most instances. Aside from the ethical issue of sentencing people to incarceration in places where they will be exposed to greatly elevate rates of potentially fatal diseases, prisons are almost certainly at the epicenter of global drug resistance, as well as infection (Benatar 2003:223). They are, in essence, the kind of quarantined populations that we are warning against creating, writ large. For we must ask, how are prisons so very different from the sentence we now impose, and may continue to impose with a rationale of quarantine protection, on the global poor?

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i Gandy and Zumla (2003a) provide a detailed description of the infectious process of the TB bacillus, which we summarize here.

[ii] The infectious nature of tuberculosis was not realized until the early 18th century, at which time the Decree of Lucca in Italy "required physicians to notify the General Sanitary Council of the names of patients with phthisis and to destroy their belongings after death" (Bloom and Murray 1992:1056). The formal proof of TB's infectiousness did not occur until 1865, when Jean Antoine Villemin (a French physician) transferred pus from infected humans and cattle to rabbits, which subsequently developed TB. This breakthrough in human knowledge of the disease was entirely ignored, however, and it is Heinrich Hermann Robert Koch (a German physician) who is generally given credit for isolating the bacillus (along with Anthrax) in 1882. His work with culture filtrates was later used in the development of the tuberculin skin test, which is still the principal way of establishing TB infection (Bloom and Murray 1992.).

iii Here, H stands for isoniazid; S for streptomycin; R for rifampicin; and E for ethambutol. These are standard abbreviations.

NB. All footnotes will be eliminated in the published version; information will either be incorporated into the text, or forgone.