

**An Imperfect Offering: Current Strategies for the
Control of Multidrug Resistant Tuberculosis in Severely
Resource-Limited Settings**

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I. INTRODUCTION

Known to medical science since antiquity, tuberculosis has proven itself an exceptionally hardy and adaptive adversary. While progress has been made to reduce the global incidence of drug-susceptible tuberculosis, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis during the past decade threatens to subvert recent advances in tuberculosis control. The incidence of MDR-TB and XDR-TB ought to command a rapid, coordinated response from multilateral and bilateral agencies, non-governmental organizations, and national governments, one that incorporates drug-resistant TB interventions within the broader context of national TB control strategies. Yet at a time when strong leadership and enlightened policy has the potential to radically alter the course of the epidemic, the global health apparatus has readily succumbed to a debilitating lethargy. Mired in the impolitic rhetoric of cost-efficacy, agencies have come to accept the emergence of MDR/XDR-TB as a regrettable, inevitable consequence of TB's global recrudescence in recent years. To contend that the current MDR/XDR-TB epidemic reflects entirely natural evolutionary processes of acquired resistance would be to ignore the profound historicity underlying its epidemiologic profile. An array of geopolitical, social, and economic factors has transmogrified an eminently treatable disease into an epidemiological nightmare.

The geography of the modern MDR/XDR-TB epidemic evinces the highly unnatural trajectory of the disease. It should come as no surprise that MDR/XDR-TB disproportionately afflicts destitute populations with no socioeconomic mobility living in states of subhuman privation. Tuberculosis—and by extension, drug-resistant tuberculosis—is by all accounts a disease of chronic poverty, one that is predicated upon the invidious socioeconomic stratification engendered by institutionalized wealth, power, and status differentials. Indeed, until Robert Koch's discovery of the tubercle bacillus in 1882, it was widely believed that susceptibility to tuberculosis was genetically determined and hereditarily transmitted, given the unmistakable association between poverty and illness "One has been accustomed until now to regard tuberculosis as the outcome of social misery," Koch wrote, "and to hope by relief of distress to diminish the disease. But in the future struggle against this dreadful plague of the human race one will no longer have to content with an indefinite something, but with an actual parasite" ¹. Since 1882 we have made tremendous strides in elaborating the etiology of tuberculosis, but have yet to redress the social immiseration that accounts for its differential morbidity and mortality. In this respect, MDR/XDR-TB is no different than any of the modern plagues that preceded it.

The "new tuberculosis", as several leaders in the field note, presents a unique set of challenges for practitioners in the twenty-first century. Specifically, the advent of HIV and the evolution of drug resistance have exacerbated problems of TB control. Ostensibly a theoretical risk to the general population, these cofactors are best understood as biosocial phenomena that are multiply more manifest in settings of severe poverty. The political economy of MDR/XDR-TB continues to foment drug resistance by erecting insurmountable barriers to quality healthcare for impoverished patients in high-burden countries. If we are to resocialize our conception of healthcare as a fundamental human

right, we must learn to expand prevailing models of cost-effectiveness to include the human cost of MDR/XDR-TB and other neglected diseases. New paradigms must include rubrics for an array of structural interventions that can best combat poverty and disease by revitalizing the public sector in overburdened, underdeveloped, or endemically corrupt nations. While public health will always be inextricably linked to a host of seemingly ancillary considerations—from agricultural development to educational reform to intellectual property rights—it is important to remember that the MDR/XDR-TB burden will not be alleviated through development alone. Supporting development projects to remediate chronic poverty cannot address the incidence of disease in the interim, and must be supplemented by immediate interventions to improve public health delivery.

This paper addresses the threat of MDR/XDR-TB on a global scale and presents a realistic assessment of the challenge. It is worth noting that the interventions outlined here are in many respects nonspecific to the MDR/XDR pandemic; they support a variety of vertical and horizontal programmes that will ultimately strengthen public health delivery in resource-limited settings in the long run. The recommendations I have included are deliberately general in regard to their prescriptive detail, for it is imprudent to assume that the MDR/XDR-TB epidemics in Indian villages and Russian penal colonies would command the same approach—the dynamics of MDR/XDR-TB transmission and control exhibit considerable variation from one region to the next. It is possible, however, to identify control strategies that have the potential to radically alter the course of the pandemic while simultaneously strengthening public health delivery at the community-level. Much debate currently centers around the efficacy of vertical interventions for TB control, ones that are primarily donor-driven and focus on a single disease. Many argue that vertical programmes promote a balkanized approach to public health delivery by missing opportunities to treat multiple issues in an integrated fashion. Proponents of horizontal programs argue that special priority must be given to the strengthening of preexisting health systems so that they may address a wide variety of issues in a self-sufficient manner. This paper argues that vertical programs—including those supported by public-private partnerships—can manage MDR/XDR-TB epidemics while simultaneously strengthening public health infrastructure.

II. THE GLOBAL SPREAD OF MDR/XDR TB

The World Health Organization estimates that *Mycobacterium tuberculosis* causes active disease in 9.15 million people across the globe, killing roughly 1.6 million of them.ⁱⁱ Roughly a third of the world's population carries the latent bacillus, which usually remains dormant in asymptomatic individuals.ⁱⁱⁱ The bacterium is astoundingly resilient, and is capable of acquiring resistance through mutation over a very short period of time.^{iv} In 1993, the WHO initiated a program of nearly unprecedented magnitude that sought to provide comprehensive TB care to some of the world's poorest populations; directly observed therapy, short course (DOTS) was an attempt to provide anti-TB treatment in the shortest possible time by creating uniform standards of treatment and care.^v While DOTS met with considerable success in some arenas—the WHO reports that treatment success in the 2004 DOTS cohort of 2 million patients was 84% on average—it was originally designed for settings and conditions in which resistance to first-line anti-TB

drugs was minimal.^{vi} Short-course chemotherapy is of limited utility for patients who are already infected with drug-resistant strains of *M. tuberculosis*.^{vii} In fact, in some instances, exclusive use of the DOTS approach was contributing to further resistance and preventable mortality.^{viii} Most MDR-TB patients are resistant to the two main first-line anti-TB drugs—isoniazid and rifampin—that form the backbone of short-course chemotherapy.^{ix} The total global burden of MDR-TB is estimated at almost 490,000 new cases per year, or roughly 5 percent of all TB cases; an estimated 120,000 of these patients die annually.^x MDR-TB outbreaks have been reported in institutional outbreaks throughout the United States, Europe, Asia, and Latin America, and have produced high fatality rates among immunosuppressed people, along with high rates of transmission among immunocompetent patients, caregivers, and family members.^{xi} The armamentarium with which to treat MDR-TB is nearly nonexistent, given that the last anti-TB drug was developed in 1960.^{xii} Only 10 percent of MDR-TB patients are receiving any treatment, and only about 3 percent are being treated according to WHO standards.^{xiii} Patients who develop MDR-TB or XDR-TB often require treatment for 18–24 months, sometimes hospitalization, and occasionally surgical resection of infected lung tissue.^{xiv}

A number of factors complicate WHO estimates of MDR-TB prevalence: first, there is a complete lack of data for many locations—only 22 of the 46 African nations have conducted drug-resistant surveys^{xv}—and second, there is a dearth of diagnostic laboratories capable of culturing TB and making an appropriate diagnosis in many resource-limited settings.^{xvi} Furthermore, countries identified as having the capability to conduct drug resistance surveys are more likely to have a well-functioning TB program, laboratory structure, and transport network and therefore lower rates of MDR-TB than countries that lack this infrastructure.^{xvii} Many experts agree that the 490,000 cases/yr approximation grossly underestimates the disease burden for these reasons.^{xviii} To complicate matters further, the methodology underlying drug-resistance surveys is seriously flawed: current survey methods include only smear-positive TB cases, yet not all MDR-TB cases are smear positive.^{xix} HIV-positive TB patients are more likely than other TB patients to be smear negative; this would significantly underestimate the MDR-TB burden in Africa, for instance, where HIV/TB co-infection is rampant.^{xx} There is no rigorous, randomized evidence for the standard of care for MDR-TB either.^{xxi}

While a significant number of new TB cases are being diagnosed as MDR-TB, most MDR-TB occurs in previously treated patients; roughly 60% of new MDR-TB cases in Eastern Europe are diagnosed in patients that have been previously treated for tuberculosis.^{xxii} Under proper conditions—assuming only quality-assured antibiotics are used in accordance with a prescribed treatment regimen—a patient with drug-susceptible TB will be cured^{xxiii}. In this regard, TB is an eminently treatable disease. The problem of drug-resistance arises when a patient is treated with an inadequate number of effective drugs for an inappropriate length of time, does not complete his or her treatment regimen, or has problems absorbing the drug itself—as is often the case with HIV/TB co-infection. Problematically, most programs continue to prescribe multiple cycles of first-line anti-TB therapy for patients that have some drug-resistance; with each iteration of this treatment, the number of drugs to which the patient becomes resistant increases.^{xxiv} Problems with

drug production, supply, and quality have been well-documented by TB experts as a central consideration in understanding the global disease burden. When faults in production or in the supply chain interrupt the availability of drugs, treatment regimens are adversely affected, which can often engender MDR-TB outbreaks. The other mechanism through which resistance is perpetuated is the direct transmission of drug-resistant strains, called primary or transmitted resistance; this latter mechanism has largely been neglected in the development of TB control programs.^{xxv} In most of the developing world, patients are admitted to large, overcrowded hospital wards with little or no ventilation, which also accelerates transmission^{xxvi}. Studies on the effect of improper ventilation on airborne contagions have shown that when a patient with infectious drug-resistant tuberculosis is admitted to such a hospital, up to 50% of the patients exposed on that ward can become infected within 24 hours; the rate of institutional transmission is much higher for prisons.^{xxvii} The coincidence of TB and HIV has accelerated drug resistance and contributed to the rapid transmission of HIV as healthcare institutions routinely house HIV positive patients with patients who have drug-resistant TB, creating opportunities for nosocomial transmission.^{xxviii} The malabsorption of first-line anti-TB drugs in immunocompromised AIDS patients results in suboptimal therapeutic blood levels that accelerate the acquisition of drug resistance.

Community-based treatment of MDR-TB or HIV/TB co-infection in people's homes and huts is the simplest way to reduce the probability of nosocomial transmission, considering most health care settings in the developing world utterly lack infection control facilities.^{xxix} But establishing community-based treatment outside a hospital currently is not feasible in some settings because the tradition and infrastructure for community care do not exist. Transmission control is highly expensive—the installation and maintenance of ventilation systems is prohibitively expensive for hospitals in resource-limited settings. In the past two decades, Partners in Health designed and implemented an effective transmission control program in Haiti that may serve as an instructive model for other resource-limited settings.^{xxx} Their model is a community-based treatment program through which few patients require hospitalization; when they do need to be hospitalized, there are admitted through a baseline triage to either a general medical ward, a TB pavilion, or basic isolation rooms based on smear results *and* HIV seropositivity. The general medical ward has natural ventilation and ultraviolet (UV) air disinfection; the TB ward has natural ventilation with more UV fixtures; the six isolation rooms are off a common corridor, with large exhaust fans built into the wall that draws air into the room from the corridor.^{xxxi} The installation of UV air disinfection in a TB/HIV ward in Lima has been shown to reduce nosocomial transmission by as much as 73%.^{xxxii} This approach—while far from perfect—could be highly effective if it is widely implemented in settings where no transmission control currently exists.^{xxxiii} Another promising new inhaled antibiotic called capreomycin may provide a new approach to contagion control; it is currently being developed by the Harvard-based nonprofit organization Medicine in Need (MEND).^{xxxiv}

More effort needs to be invested into new technologies that can effectively control the transmission of MDR/XDR-TB; without a vaccine and without early, accurate diagnosis

and treatment, the MDR/XDR-TB epidemic will be driven by transmission in the future.^{xxxv}

III. DIAGNOSIS OF MDR/XDR-TB

Active pulmonary tuberculosis is usually diagnosed using sputum smear microscopy, a decentralized service conducted at or near the point of care (POC). The test—developed in the 19th century—is an anachronism that is of limited use given the complexity of the modern TB epidemic.^{xxxvi} Two developments in the epidemiology of TB have rendered sputum microscopy largely ineffective: the increasing incidence of deadly HIV/TB co-infection—which is often smear-negative—and the rise of drug-resistant TB, which cannot be distinguished from drug-susceptible strains through microscopy alone.^{xxxvii} Thus, while sputum smear microscopy readily identifies the most infectious patients—those with the bacilli in their sputum—it does not identify drug-resistant cases. Drug-sensitivity testing (DST) and mycobacterial culture allow reliable diagnosis of drug-resistant strains, but they also require more resources than smear microscopy, including incubators, refrigeration, and elaborate biosafety containment facilities.^{xxxviii} New technologies are currently being developed that can overcome some of the basic limitations of culture systems.^{xxxix} But the utility of new technologies hinges upon a basic delivery infrastructure that ensures quality assured facilities, transport, and data management systems.^{xl}

The 2006 Global Plan to Stop TB stresses the importance of laboratory services in high-burden countries, stating that “every country should have a well-resourced and fully functioning national reference laboratory.”^{xli} It is absolutely essential that DST and culture services are included in any national TB control strategy.

The WHO’s Global Tuberculosis Control report for 2007 summarizes the dearth of laboratory capacity: “[national tuberculosis programs] in all WHO regions reported too few laboratories, weak quality control, and limited facilities to carry out culture and drug susceptibility testing. Facilities to diagnose and treat MDR and XDR-TB are not widely available.”^{xlii} To this end, the WHO created the Global Laboratory Initiative (GLI) to oversee laboratory capacity development and coordination. The GLI stipulates that in order to diagnose MDR-TB in the general population, countries will need one culture facility per 5 million people and one DST facility per 10 million people, although current global coverage falls far short of these mandates. Among nations with the heaviest burden of disease, the ratios are 1 culture laboratory per 7.8 million people and 1 DST laboratory per 14.2 million people.^{xliii}

The lack of a sufficient laboratory network in many underdeveloped countries requires the immediate attention of development experts. A functioning laboratory network coordinates the shipment of specimens from peripheral sites to central laboratories and reports results; while such networks are highly sophisticated throughout much of the developed world, developing nations still overwhelmingly rely upon on-site testing.^{xliv} The global TB laboratory network is a four-tiered system in which national public health officials determine the volume and quality of services provided and supra-national

laboratories provide quality assurance and technical assistance.^{xlv} The levels are as follows:

- Level IV Labs: These supra-national reference laboratories (SRLN) maintain the highest standards and are responsible for external quality control. There are 26 SRLNs.
- Level III Labs: These national reference laboratories are equipped to provide culture and DST services, but are often located in the national capital or other large cities.
- Level II Labs: These are mostly regional facilities and may or may not have the capacity to handle culture or DST testing, depending on the size of the district.
- Level I Labs: These are mostly clinic or district labs. They are limited to basic diagnostic tests like sputum microscopy.

While SRLNs pioneer TB research, assist in capacity building, and support their national subsidiaries, the more regional labs exhibit great variation in capacity. And while Level III laboratories handle the culture and DST needs of the domestic population, they frequently collaborate with Level IV laboratories on projects that are entirely funded by private sources; hence, not all countries are able to benefit from this collaboration.^{xlvi}

Third-party laboratories could be indispensable in providing critical in-country capacity. Many nations have untapped laboratory capacity in universities or non-governmental organizations (NGOs) that could conceivably diagnose and treat TB. These for-profit facilities often attract the most qualified administrators and technicians and are often extremely well-funded.^{xlvii} Any program that attempts to recruit third-party laboratories into a national TB control strategy must ensure that private laboratories adhere to the same standards of equitable access and quality assurance mandated by the GLI, and must be amenable to working closely with the national TB reference laboratory. Significant work remains to be done to determine the feasibility of public-private laboratory collaboration in resource-poor settings.

The Global Polio Lab Network (GPLN) is a centrally coordinated laboratory network that supports the polio eradication campaign: it is comprised of 7 supra-national reference laboratories, 15 regional laboratories, and 123 national laboratories that provide critical services for multiple countries.^{xlviii} The WHO is responsible for the accreditation of each laboratory and regulates quality assurance mechanisms across the board.^{xlix} By all measures, the GPLN is a success: it processes an estimated 80,000 samples annually, a fraction of the samples generated by the global TB community.^l The high incidence and prevalence of TB calls for a more decentralized laboratory structure than the GPLN, but nevertheless, the general systems developed to monitor polio—the sharing of capacity and funding along with the coordination of services—could inform the development of comprehensive MDR-TB laboratory networks in underdeveloped regions. TB laboratory directors need to have formal input in the implementation of TB strategy to ensure that the laboratory component is developed in tandem with the roll-out of other structural interventions.

There is a great need for skilled laboratory personnel that can mentor and train local laboratory staff. Fellowship programs modeled on the CDC's Epidemic Intelligence

Service—in which developing professionals are engaged with a network of peers and mentors—could prove useful in recruiting long-term in-country technical support. At present, there is a decided lack of pre-service training programs for laboratory technicians in underdeveloped regions. A survey conducted by Partners in Health on a laboratory capacity building project in Peru noted that

“The greatest impediment to improving the speed of laboratory improvements was the lack of a dedicated, on-site, experienced technical assistance provider that could work with laboratory management to build leadership capacity. Ultimately, a consultant from the United States was required and an experienced MDR-TB laboratory director from Eastern Europe was hired to lead the project.”^{li}

Anecdotal evidence from other case studies confirms the utter lack of human resources in high-burden countries.^{lii} Importing technicians from other countries is time-consuming, expensive, and unsustainable: native skilled workers must be recruited to strengthen and sustain local public health infrastructure.

The Peru study also noted that over 50% of the total turnaround time for TB samples is typically occupied by the referral process.^{liii} As samples and data flow from one institution to the next, it is imperative that laboratories streamline referral networks to expedite data collection and management. After a sample containing live bacilli is procured, it must be securely stored and transported to a culture facility—transport logistics often unnecessarily delay laboratory operations as collection and storage systems are determined largely on an ad hoc regional basis.^{liiv} It is absolutely essential that the costs associated with sample transportation are absorbed by the national TB program (NTP) so that the burden does not fall upon the—often impoverished—patient population. A study from Thailand revealed that a preponderance of TB suspects did not seek treatment because they had to pay for expensive tests—like x-rays—and could not afford them. Others cited the inconvenience of transportation and an overwhelming lack of confidence in the quality and efficacy of the public health care system; in the end, only 18 percent of patients were started on TB therapy within one month, and only 56% were started on therapy within two months.^{liv} Anecdotal evidence^{livi} from other high-burden countries affirms the obstacles patients face getting to health facilities and obtaining results within a reasonable time period.

Perhaps no other single step could radically improve treatment of MDR-TB than the institution of rapid point-of-care testing. Due to the remoteness of many high-burden areas and the complexity of treatment, drug-susceptibility diagnostics invariably lead to protracted delays in treatment that can augment the spread of MDR-TB.^{liivii} The rapid detection of resistant tuberculosis strains would allow patients to start the appropriate chemotherapy sooner, which is critical in high HIV settings where TB co-infection is endemic. The GLI is working to develop rapid molecular tests that identify *M. tuberculosis*—rather than other forms of *mycobacteria*—and probe for resistance to isoniazid and rifampin within 48 hours.^{liiviii} Scientists hope to develop a dip-stick test for TB—similar to the one for HIV—that uses sputum, urine, and/or blood to identify drug-resistant strains in smear-negative patients; this technology is actually within reach, but will require significant funding and political commitment in the next couple years.

^{lix}Ideally, point-of-care testing will detect disease during the patient’s initial visit and will assess the degree of drug-resistance, if any.

In sum, there must be an increase in sustainable funding from bilateral and multilateral donors to allow for the creation of a robust network of in-country laboratories with DST capabilities; this network must be subjected to rigorous assessment by supranational reference laboratories and must be fully integrated within the national TB program. Long-term technical assistance will allow for more laboratories to achieve DST and mycobacterial culture capacity, along with any future molecular tests for drug-resistant strains. Referral networks must be streamlined and standardized from one region to another, and the national TB program must absorb any cost associated with specimen transport and data delivery so that these costs do not fall upon the patient. Ideally, the excess laboratory capacity in wealthy nations could be used for mycobacterial culture and DST while laboratories are being built in high-burden nations, so that patients in resource-limited settings can obtain a reliable diagnosis regardless of their country’s laboratory capabilities. Finally, scientists and donors should heavily invest in the development of point of care testing for both drug-susceptible and drug-resistant tuberculosis, especially in settings where HIV-TB co-infection is prevalent.

Vertical programs to improve MDR/XDR-TB diagnostic capacity in resource-limited settings will necessarily strengthen the public health laboratory network in these regions. It is important to bear in mind that the implementation of a robust, coordinated laboratory network would improve health delivery on many fronts, including—but by all means not limited to—MDR/XDR-TB management. A self-sufficient laboratory network is a fundamental prerequisite for any integrated public health system. Moreover, a functioning laboratory network is of utmost importance to high-burden countries that seek to mobilize and maximize in-country capacity. While nongovernmental organizations have a valuable role to play in developing new approaches to treating disease, a successful laboratory network must be implemented and expanded through the public sector in high-burden countries to assure universal and sustained access.

IV. THE MDR-TB DRUG SUPPLY

MDR-TB treatment projects currently have two means of obtaining second-line drugs: they may procure quality-assured drugs through the WHO’s Green Light Committee (GLC) at concessionary prices, or they may obtain drugs of unknown quality through the open market.^{lx} All projects financed through the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) or UNITAID must procure second-line drugs through the GLC, which is currently experiencing a significant shortage of quality-assured drugs.^{lxi} The GLC itself is not responsible for drug procurement: it is responsible for ensuring that GLC-approved projects deliver quality-assured drugs in accordance with the WHO’s programmatic guidelines. The procurement of second-line drugs is the responsibility of the International Dispensary Association (IDA), which oversees second-line drug purchases, identifies suppliers for each medication, and solicits agreement with manufacturers for reduced prices for GLC-approved projects.^{lxii}

It is worth noting that the GLC Initiative has approved life-saving therapy for more than 40,000 patients since its establish in 2000, with 10,000 patients being approved for treatment each year.^{lxiii} The pilot program of the GLC—the initial phase of the initiative, characterized by the implementation of standardized protocols for drug procurement and data forecasting—is now over.^{lxiv} As countries deal with burgeoning MDR-TB epidemics, there will be a significant expansion of public-sector treatment programs, coupled with robust government- and donor-sponsored procurement of second-line TB drugs. This has the potential to greatly augment the supply of quality-assured drugs, provided that the demand for these drugs is accurately assessed in high-burden countries, though this is unlikely to occur under the current GLC approval system. The GLC pilot project approach is no longer practical or effective, and is too fragmented to achieve any sustainable scale-up. There is only one quality-assured supplier for each of the second-line drugs needed for GLC projects, and all approved projects must be obtained through a single procurement agency, the IDA.^{lxv} Recent manufacturing bottleneck demonstrates that a lack of supply depth threatens drug deliveries in no small way: two manufacturers in 2005 shut down their plants, halting the delivery of critical drugs for a considerable period of time.^{lxvi} As MDR-TB incidence rises and the number of GLC projects and patients increases, there will need to be more than one procurement agent for projects around the world.

The prequalification process for second-line drugs at the WHO is far too bureaucratic to keep pace with the need for rapid drug development. There are currently only two prequalified second-line anti-TB drugs, and only 17 products for TB in total—in contrast, there are 62 antiretroviral agents and 33 medicines prequalified for HIV/AIDS-related diseases.^{lxvii} A few factors may account for this discrepancy: developing HIV/AIDS drugs is far more lucrative for PhRMA agencies given the incidence of HIV/AIDS in the developed world, there is a high-volume HIV/AIDS drug market for suppliers, and the international commitment to fight HIV/AIDS has been far more robust for HIV/AIDS research than for TB. TB drug manufacturers in the United States should take advantage of the US Food and Drug Administration's accelerated approval mechanism, which was heavily utilized by HIV drug developers in the 1990s.^{lxviii} Drug suppliers have complained that the current prequalification program is too slow and bureaucratic, and that it lacks the translational power to encourage manufacturers to improve production standards to international levels. It appears that there is some truth to this complaint: while all GLC-approved second-line drugs have been approved by other Stringent National Regulatory Authorities (SNRAs)—like the FDA—only two of these products are WHO-prequalified.

Agencies that wish to avoid the hassle of WHO prequalification obtain second-line drugs from non-GLC approved projects under programmatic conditions that are often not up to par with WHO MDR-TB treatment guidelines. Despite the growth in GLC projects, they represent only a fraction—roughly 12,000—of the more than 400,000 reported MDR-TB cases each year.^{lxix} Hence, the vast majority of patients are seeking treatment from non-GLC approved projects and are receiving drugs that have yet to be quality assured. Treatment with substandard drugs will not cure patients and will ultimately amplify patterns of acquired resistance. Countries with the highest burden of MDR-TB are not be able to control outbreaks through GLC-approved projects alone, and are increasingly

turning to the open market for second-line drugs.^{lxx} Regulation and monitoring of drug quality within these markets is nonexistent or erratic at best, given that these markets are large, fragmented, and growing with alacrity.^{lxxi} Governments do not insist that their patients receive treatment with quality-assured second-line drugs, and there is even significant disagreement among regulators regarding what constitutes quality assurance. The three countries with the highest MDR-TB burden—India, China, and Russia—willingly treat patients with drugs of unknown quality; if this practice continues, it is the market for drugs of uncertain quality that will continue to grow in the future, and manufacturers will be less inclined to insist upon quality assurance.^{lxxii} Drugs of unknown quality will furthermore serve to only amplify patterns of resistance. Given the small number of patients being treated under the GLC, there is little financial incentive for manufacturers to seek WHO prequalification, given that this is a lengthy and arduous task. If the manufacturers of second-line TB drugs in high-burden countries could be incorporated into the prequalification program, the GLC could meet the shortfall of drugs while simultaneously assuring their quality. Public health authorities must provide attractive incentives to reward companies for bearing the costs associated with quality assurance—the Center for Global Development, the Clinton Foundation, and UNITAID are exploring avenues to incentivize companies to submit their drugs for WHO prequalification. There is reason to believe that manufacturers of second-line drugs in high-burden countries may become more amenable to working with the GLC in the future, given that profit-margin regulations and price caps in countries like India and China change regularly.^{lxxiii} Many Indian pharmaceutical companies are frustrated with the current price-control regime and are looking to sell their products internationally; those that sell quality-assured formulations of bioequivalent anti-TB drugs should be given the opportunity to do so.^{lxxiv}

Quality-enforcement mechanisms must be supplemented by accurate demand forecasting if we are to attenuate the chasm between drug supply and demand. The entry of a range of new suppliers into the market has balkanized efforts to assess demand, confounding attempts to translate estimated need into genuine demand.^{lxxv} In the case of malaria, the WHO's demand forecasts have historically been off by orders of magnitude: the WHO estimated that the 2005 demand for the drug Coartem was roughly 100 million doses, while the actual number turned out to be 55 million.^{lxxvi} Companies are less inclined to develop drugs if they must absorb all of the risks associated with incorrect forecasts; there must be some means of redistributing this risk so that it does not unduly burden suppliers and paralyze drug delivery.

Then there is the problematic dearth of new drugs to treat MDR-TB. As previously noted, the last new drug approved for TB was rifampin in the 1960s. Since then, only five new compounds are in Phase I or II clinical development, and two new formulations have progressed to Phase III development.^{lxxvii} Significant effort must be invested into the development of gentler, more affordable, and efficacious second-line treatment regimens that can radically shorten and simplify treatment. Ideal drug candidates would act against targets that are new to the TB drug arsenal to obliterate drug-resistant strains and persistent bacilli. They must also be effective for both HIV-positive and HIV-negative patients. While drug development efforts are indeed under way, it is important to bear in

mind that a typical drug takes at least 10-15 years to be developed from discovery to registration. A compound that has progressed to preclinical development has a mere 1 in 10 chance of being registered and made available to patients^{lxxviii}. The clinical trials for TB can be especially lengthy, so drugs for TB may exceed this average. There must be a focus on developing multidrug regimens, since cocktails of drugs with different mechanisms that are administered together have been proven to effectively manage drug-resistant TB strains. Stemming the tide of MDR-TB will require a minimum of three to four antibiotics immediately.^{lxxix} There must once again be significant financial incentives for drug development, considering that the burden of MDR-TB falls within impoverished countries with little or no production or development capabilities. With HIV, there is a large patient population in the developed world willing to pay upwards of \$17,000 USD a year for effective therapies—patients suffering from MDR-TB in low or middle income countries simply cannot afford to pay that amount. This disparity means that governments will ultimately be the ones responsible for ensuring access to curative and preventative deliverables.

Economic incentives for drug development may be classified as either push or pull mechanisms. Push mechanisms stimulate the supply or production side, while pull mechanisms stimulate the demand side. An attractive push mechanism is the development of a public-private partnership such as the TB Alliance that could consolidate R&D effort and facilitate information exchange among developers. Viable pull mechanisms include the use of advance market commitments, through which market demand—measured in price and units to be purchased—is guaranteed by a government or philanthropic organization in advance. Another equally viable pull mechanism is the institution of priority review voucher (PRV) that would grant a company priority review by the FDA for a drug in exchange for developing a new treatment for a neglected disease.^{lxxx}

There is little sense in denying that drug and vaccine development is technologically challenging, capital-intensive, and carries high risk. The total average development cost of a pharmaceutical drug over a ten-year period exceeds \$1 billion USD^{lxxxi}, and while commercial drugs generate significant profits to offset pharmaceutical companies' investments, the same does not hold true for anti-TB drugs. Hence, immediate vertical interventions will be necessary to remediate the quality and availability of second-line TB drugs. A mechanism needs to be implemented to make quality-assured second-line drugs readily available at reasonable prices to GLC-approved projects as well as to those programs that do not fall under the aegis of the GLC. Countries should be able to purchase second-line drugs however they choose, as long as these drugs are of superior quality. More than one procurement agent should be made available to countries participating in the GLC; this will allow for the scale-up of in-country capacity, which has been historically underutilized. Large countries within the GLC should be allowed to purchase second-line drugs from prequalified domestic manufacturers through a tiered approach, in which manufacturers who commit to completing the WHO process can sell their products under certain circumstances and rigorous testing. This tiered system already exists for first-line TB drugs, and encourages competition while lowering price. The WHO should also expedite its efforts to institute a reliable and transparent system

that can forecast drug demand by recruiting private industry experts, consulting firms, and NGOs that can translate estimated need into genuine demand. Above all, there must be a concerted global effort to develop at least three new anti-TB drugs that can be fast-tracked through the regulatory process. New therapies need to be developed that minimize drug-drug interactions in HIV/TB patients, who often experience significantly higher mortality shortly after co-infection.

V. CONCLUSION

There is little sense in denying that the treatment of drug-resistant TB is complex and expensive: national TB programs are ill-equipped to meet the challenge of MDR/XDR-TB, the requisite clinical and laboratory expertise is virtually nonexistent within the public sector, human resources for the actual delivery of care are scarce, and weak, overburdened, and underfinanced health systems in high-burden settings are unable to absorb scale-up costs. It would seem that the management of MDR/XDR-TB in resource-limited settings is a Pyrrhic victory at best, and a fool's errand at worst.

But questioning the cost-efficacy of treating MDR/XDR-TB presupposes that we can afford *not* to address the epidemic. In settings like South Africa and India, the prevalence of HIV and endemic TB—coupled with the widespread private availability of first and second-line anti-TB drugs—threatened to magnify the MDR-TB to an unprecedented scale.^{lxxxii} The collapse of centralized TB treatment in the former Soviet precipitated an MDR/XDR-TB catastrophe that brought the epidemic to the doorstep of Western Europe.^{lxxxiii} Responding promptly to an MDR-TB epidemic is far less costly than trying to retroactively manage a MDR-TB epidemic that has spiraled out of control.^{lxxxiv} Consider the MDR-TB epidemic in New York City prisons in the 1990s: by 1990, 4.3 million men and women were in prison—a 64% increase over a period of six years—following the government's "war on drugs", which committed thousands of petty traffickers to prison.^{lxxxv} Detention facilities were not prepared to meet this incredible burden, and prisoners lived in cramped quarters with little ventilation, crammed together with inmates that were infected with HIV and TB.^{lxxxvi} Unsurprisingly, this created the ideal climate for rampant MDR-TB infection and transmission, which went largely ignored until prison wardens, health professionals, and other "innocent" parties began to fall ill.^{lxxxvii} Then, the Occupational Safety and Health Administration intervened to contain institutional transmission, ordering caps on the number of inmates and upgrading detention facilities to improve ventilation.^{lxxxviii} These interventions eventually proved effective, but came at a heavy cost: more than \$1 billion was spent to rein in the epidemic.^{lxxxix} From a global MDR-TB perspective, this was a smaller-scale epidemic, but it still cost America an enormous sum in direct funds, productivity, and of course, human lives.

Avoiding an MDR/XDR-TB catastrophe requires a significant political and financial commitment—of near PEPFAR proportions—from wealthy nations. The PEPFAR experience could be instructive for global health experts looking to scale-up MDR-TB treatments in resource-limited settings. First, HIV/TB co-infection has been a priority of PEPFAR from its inception, and funding for HIV/TB programs increased from \$18.8 million in 2005 to \$169 million in 2008.^{xc} Many of the structural approaches that have

proven effective in the fight against global AIDS could inform TB care: expanding testing and treatment at the community level through home-based care, establishing accurate data forecasting methods and metrics to assess progress in drug treatment regimens, developing effective transport systems to allow diagnostics to reach central laboratories, developing a tiered and robust public health laboratory network, investing in increased surveillance to detect MDR/XDR-TB, and expediting the process of FDA approval of generic drugs. Unlike HIV and malaria, TB has no presidential initiative, and the WHO's Stop TB Plan fails to set the same universal access targets for TB that it has previously done for HIV/AIDS and malaria.^{xcii} Rather than arguing over which priority diseases warrant the greatest attention, it would be more productive to devise an integrated plan for universal access to treatment for HIV, TB, and other priority diseases. These projects must be implemented in tandem with one another, considering that there may never be a grassroots movement for TB—and other neglected diseases—like there has been for AIDS.

There is much debate as to whether the treatment of drug-susceptible TB is the best means of containing modern MDR-TB epidemics. Practitioners have argued that the first priority in addressing MDR TB is preventing its occurrence in the first place, which means that measures to control drug-susceptible TB should be granted precedence over measures to combat MDR/XDR-TB, specifically.^{xciii} While better treatment of drug-susceptible disease will decrease the likelihood of acquired resistance, the current MDR-TB epidemic is driven by transmission.^{xciii} Focusing *exclusively* on susceptible strains will be insufficient. MDR/XDR-TB need not compete with drug-susceptible TB for limited resources: vertical mechanisms to combat drug-resistant TB should be integrated within the general infrastructure for basic TB control. Analogously, the PEPFAR initiative coordinated its operations to address uncomplicated AIDS *and* HIV-TB co-infection, the latter of which features prominently in their current program.^{xciv} MDR-TB is by no means less infectious than drug-susceptible TB, as well-documented nosocomial and institutional outbreaks have evinced.^{xcv}

Ignoring the current MDR/XDR-TB epidemic is untenable from both a moral and public health perspective. National governments have yet to allocate adequate resource for MDR/XDR epidemics, and unless countries invest substantially in MDR control through the private sector, there is a likelihood that MDR/XDR strains could become the dominant form of tuberculosis.^{xcvi} Without significant investment in the development of new anti-TB drugs, tuberculosis management might return to the preantibiotic era. Treatment for drug-resistant TB must be incorporated within national TB control strategies and must garner significant funding from multilateral and bilateral agencies, NGOs, and ministries of health. There must be a greater push for vertically driven community-based models of primary care so that more patients can receive treatment at home and spend less time in congregate settings, where they may transmit drug-resistant strains to others. Large global health initiatives—like PEPFAR—and institutional donors for public health should incorporate MDR-TB treatment into existing programs, since MDR/XDR-TB is unlikely to garner sufficient attention in the developed world. High-burden countries like India, China, and Russia must take decisive steps to improve their public health systems—by promoting rational drug use and providing free care for

treatment of MDR/XDR-TB, for instance—if they seek to scale-up MDR-TB treatment to universal access.^{xvii} The extent of product development that took place in HIV/AIDS was made possible only by a significant vertical investment in biomedical research, partnerships in industry, and extensive coordination among multilateral and bilateral agencies—the biomedical, clinical, and operational demands of MDR/XDR-TB require an equally robust approach, one that commits substantial financial and human resources, enlists visionary investigators in clinical research, and fosters extensive cross-collaboration between industry and global organizations. Vertical programming for MDR/XDR-TB management can only strengthen public health infrastructure in countries where under-funded primary healthcare providers have scarce resources to respond to the most pressing needs of patients and communities.

ⁱ As quoted in Feldberg, 1995.

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