Preventing the Untreatable: Why Drug-resistant Tuberculosis Must Be Prevented

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Summary

There were more than 9 million new cases of tuberculosis (TB) worldwide in 2009 (WHO, 2010). It takes at least six months of daily drug therapy to treat just one case of TB, thus the global TB burden represents more than 4 million person-years of treatment from the 2009 cases alone. While this represents an almost incomprehensible drain on public health resources, evidence of decreasing TB incidence over the last few years suggests that it is at least possible to impact this disease on a global scale. For more than a quarter million of these new TB cases, however, treatment will be unsuccessful due to the drug-resistant nature of their infections, and they will join the ranks of almost 2 million people who die of TB each year. Most countries outside of North America and Europe do not routinely test TB patients for drug resistance, nor do they have access to the correct drugs for drug-resistant TB; accordingly, fewer than 10% of the patients with drug-resistant TB worldwide receive appropriate treatment (WHO, 2011). While it is critical to build the global capacity to diagnose and treat drug-resistant TB patients appropriately, it is clear that for many low-income, high-burden countries, preventing the development of drug-resistant TB should be the primary means of tackling this problem.

Current realities

TB is a persistent infectious disease that has been a part of human history for thousands of years. Drug-resistant TB, however, is considered an emerging disease that has developed in the last few decades. While drug-sensitive TB is a treatable disease, the emergence of multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), and totally drug-resistant TB (TDR-TB) is "threatening to destabilize global TB control" (Sharma & Mohan, 2006) and has rapidly turned TB into a lethal disease again, even in high-income countries. TB in humans is caused primarily by the pathogen *Mycobacterium tuberculosis* (*Mtb*). Most strains of *Mtb* are sensitive to the critical antituberculous drugs, isoniazid (INH) and rifampin (RIF), which have been the foundation of effective "first-line" drug therapy for TB since the 1960s. MDR-TB is caused by *Mtb* strains that are resistant to INH and RIF and is either "acquired" when TB treatment is not completed correctly or it is directly transmitted from one person to another ("primary" MDR-TB).

MDR-TB has a significant impact on the clinical course and outcome of TB disease as none of the so-called "second-line" drugs used to treat MDR-TB are as effective as the first-line drugs, INH and RIF. Treating MDR-TB is also more complicated than treating drug-sensitive TB, as second-line TB drugs are costlier, often require intravenous administration, and are more toxic than first-line TB drugs. Furthermore, many countries do not have access to second-line drugs and an often-underappreciated aspect of MDR-TB is that even if the second-line drugs are available it can take two years or more to treat, resulting in social isolation, loss of employment, and long-term socioeconomic and psychological effects.

The World Health Organization (WHO) and the International Union Against TB and Lung Disease (IUATLD) began global drug-resistance TB surveillance in 1994. By 2002, MDR-TB had been found in all world regions. In 2006, a cluster of lethal TB cases (greater than 95% mortality), caused by MDR-TB strains resistant to both first-line *and* second-line drugs, was

reported in South Africa. These XDR-TB strains have since been found all over the world. Given that MDR-TB and XDR-TB are resistant to the drugs available in most developing countries, both are considered "virtually untreatable" in those regions. Consequently, patients with these diseases have either been isolated indefinitely or simply released into the community where they continue to transmit the disease.

Scientific opportunities and challenges

Acquired MDR-TB is prevented by ensuring appropriate and consistent treatment of drug-sensitive TB cases, and primary MDR-TB is prevented by identifying and treating/quarantining patients to avoid person-to-person transmission. If we know what needs to be done, why is this so difficult to achieve?

TB-treatment failures occur primarily because therapy requires daily ingestion of four different drugs for six months — a challenge for even the most self-sufficient and adherent patient. While initially the supply of first-line TB drugs was a significant hurdle for many countries, it appears that medication availability and cost no longer are major impediments to effective treatment of drug-sensitive TB in most parts of the world. Completing six months of TB treatment, however, requires more than drugs and supply chains; it requires complex social interactions between patient and care providers, and is almost impossible to maintain without significant social support for the patient. It has been demonstrated that the only reliable way to ensure effective TB therapy is through Directly Observed Therapy (DOT), a heavily supervised form of treatment in which patients are observed taking each and every dose of their medication. WHO reports show that a large proportion of TB patients are on DOT, but the truth on the ground contradicts such reports. It is clear from observations in Mexico, Africa, and Southeast Asia that very few countries are actually observing more than a small percentage of the daily medication events. Yet each country dutifully records a large proportion of its patients on DOT each year in reports to WHO. We will be able to minimize acquired drug resistance only when we are able and willing to acknowledge that DOT is not being implemented as reported; only with this acknowledgment will there be an impetus to develop new solutions, incentives, and appropriate social-support resources to ensure treatment adherence. Commitment to social services during TB treatment, together with creative operational solutions, is an area of opportunity that could bring in untapped funding as well as new expertise from the social sciences.

Regardless of how well TB treatment is managed, there will always be drug-resistant TB cases that can be directly transmitted as primary infections. It is critical that these cases be quickly identified and treated appropriately. This challenge is currently complicated by limitations in diagnostic technologies, availability and cost of drugs for treating drug-resistant TB, and severe social/adherence problems resulting from the minimum of 24 months of treatment needed to cure MDR-TB.

Until recently, MDR-TB diagnosis was a significant laboratory challenge. *Mtb* is a slow-growing organism requiring a sophisticated biosafety laboratory environment and eight to 12 weeks for culture and drug-sensitivity testing. Within the last three years, there have been major advances in the development of new molecular-based diagnostics that can detect drug-resistant TB in a matter of hours. While there is still some basic science needed to verify and validate these technologies, it is critical that funding bodies also recognize the need to start shifting from an almost exclusive focus on diagnostic innovation toward the broader aim of implementation and scale-up of existing technologies.

Regarding treatment, global TB organizations such as STOP TB and Green Light Committee have taken bold leadership roles in delivering and controlling low-cost second-line drugs for treating drug-resistant TB. Many nations are, however, moving too slowly to take advantage of

these opportunities and most countries are treating far fewer than 10% of the estimated number of MDR-TB cases.

Policy Issues

- *Acknowledging and characterizing the limitations of DOT*: This will require a transparent field evaluation of DOT worldwide to determine what is really happening on the ground and what level of treatment supervision actually is being conducted. Such an evaluation will need leadership buy-in from global TB control bodies, such as WHO and STOP TB, to ensure the national TB-control bodies are encouraged to report accurately.

- *DOT alternatives*: It is time for a paradigm shift. If DOT is not practical or feasible in most high-burden, low-income countries, alternatives must be elucidated. Many innovative treatment supervision models have been proposed (community involvement, incentives, and cell phone applications). An ideal first step is a world conference on alternatives to DOT. The purpose of this conference would be to provide the groundwork for new WHO recommendations for "Enhanced Adherence TB Treatment" guidelines instead of one-size fits-all DOT.

- *Social support for TB patients*: TB is a social disease. It is expensive and complicated to maintain the human networks necessary to support TB patients through their treatment. Global and national TB control and funding bodies need to acknowledge the social complexities of TB control and take some responsibility for the financial burden of this element of TB treatment. National and international TB organizations have shown great leadership in funding and maintaining new diagnostic laboratories and medication supply lines across the globe. The social programs supporting TB treatment require the same level of attention.

- *Diagnosis of drug-resistant TB — Technology*: Over the next five years, global TB funding and control organizations need to have an intense focus on development, implementation, and scale-up of the most promising rapid TB diagnostics.

- *Diagnosis of drug-resistant TB — National guidelines*: Within five years, rapid diagnosis of TB and drug-resistant TB will be cost effective and no longer require sophisticated laboratories. National TB programs worldwide need to start adapting their guidelines to shift from a strategy of using treatment failure to detect MDR-TB cases, to detecting drug-resistant TB cases early and rapidly using low-cost, next-generation diagnostics.

- *Treatment of drug-resistant TB*: Most national TB-control programs are not scaling up their drug-resistant treatment programs to keep pace with the treatment resources that are being made available through global TB programs, such as the Green Light Committee, STOP TB and U.S. President's Emergency Plan for AIDS Relief (PEPFAR). It is important for the national organizations crafting TB guidelines to develop into more nimble and adaptable bodies to take advantage of the rapidly evolving diagnostic and treatment landscape. It appears, in many cases, that conflicting government regulations and competing departmental priorities are obstructing progress. The global funding bodies should consider including legal and policy experts in existing TB program implementation teams to help smooth the way.

References

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*** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Prevention convened by the Institute on Science for Global Policy (ISGP) June 5–8, 2011, at the Estancia La Jolla Hotel, La Jolla, California.*

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Timothy Rodwell (see above). Dr. Rodwell initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Dr. Rodwell. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Rodwell, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- Tuberculosis (TB), in particular drug-resistant TB (DR-TB), continues to be a global public health issue of significant concern. However, more complete data is needed to adequately understand the depth of the problem and to pinpoint areas where increased attention is required. Thus, expanded research is needed to accurately determine the prevalence, incidence, and geographic distribution of all forms of TB.

- Current treatment options for DR-TB are limited and of unproven efficacy, especially when the disease is resistant to more than one first-line drug. Additional research on treatments for DR-TB and new guidelines for treatment regimens are needed to reduce TB mortality.

- While Directly Observed Therapy (DOT) and Directly Observed Therapy — Short Course (DOTS) have been heralded as successful strategies for TB control, current reported rates do not accurately reflect the true adherence rates in many countries. More data on this discrepancy, a complete evaluation of DOT(S) strategies, and a potential overhaul of the strategy are needed.

- Increasing drug completion adherence to drug-sensitive TB (i.e., non-drug-resistant TB or standard TB) regimens, including treatment completion and cure, will prevent many new cases of secondary DR-TB from developing. However, there is currently a gap in

existing TB control programs that should be filled by social support strategies. More social support programs are essential for this approach to succeed.

Current realities

Despite conflicting viewpoints on whether TB drug shortages exist throughout much of the world, it was generally agreed that significant strides have been made in acquiring drugs for drug-sensitive TB. It was further contended that most countries currently maintain adequate drug supplies for standard TB, but that drugs for treating all forms of drug-resistant TB (DR-TB) — including single drug-resistant TB (mono-DR-TB), multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB) — remain scarce.

DR-TB is a problem of escalating global public health significance. In addition to increased costs and time associated with treatment, DR-TB infection significantly increases the likelihood of mortality. There was strong consensus that there is a pressing need to halt the progression of DR-TB in all of its forms (e.g., mono-DR-TB, MDR-TB, and XDR-TB). It was argued that, presently, the best method for decreasing the incidence of DR-TB is to ensure treatment adherence/completion for drug-sensitive TB patients, thus significantly reducing the probability that they would develop resistant strains of the bacterium.

Although it was widely acknowledged that DR-TB is a significant public health dilemma, difficulties in adequately understanding the extent of global DR-TB prevalence and incidence were recognized. Currently, data do not accurately reflect the number of individuals affected by DR-TB or the geographical distribution of such infections. Consensus was reached that data on the current cases of DR-TB and the risk associated with emerging cases is presently inadequate.

It was also generally acknowledged that TB is a sociopolitical disease. Social support was seen as a critical element that often dictates the success of an individual's treatment regimen. Current research suggests that making more social support available to patients leads to increased treatment completion rates for all types of TB. Consequently, it was agreed that any proposals for programs to combat TB would need to incorporate major commitments for social support into their designs.

Following an extended discussion, general agreement was reached that adherence rates of DOT and/or DOTS, which are reported to the World Health Organization (WHO), do not accurately reflect the actual rates in-country.

Scientific opportunities and challenges

There was consensus that effective drugs and treatment protocols exist for drug-sensitive TB. It was equally clear that treating drug-sensitive TB until the patient is cured would significantly lessen the global burden of DR-TB by preventing the development of secondary drug resistance (i.e., resistance that develops via erratic and/or inappropriate drug therapies). However, many argued that even if drug-sensitive cure rates dramatically improved, substantial barriers to lowering DR-TB rates would remain. It was asserted that this is because curing drug-sensitive TB only tackles part of the problem: It does not take into account primary DR-TB infections (i.e., resistance that is spread from person to person).

Although drugs do exist for the treatment of most forms of DR-TB, skepticism was expressed regarding whether the right drug combinations have been clinically established (particularly for MDR-TB and XDR-TB) and whether current treatment protocols are universally accepted. It

was subsequently agreed that more data is required to address both the issue of drug combination efficacy and treatment guidelines for DR-TB.

It was acknowledged that significant improvements in TB diagnostics are on the horizon, and that rapid diagnostic tests will be available within the next five years. There was general consensus that these improved diagnostics are needed to address the present lack of accurate information related to the prevalence, incidence, and geographical distribution of DR-TB. Additionally, some discussion emerged regarding the challenges of sample quality and sample heterogeneity that are inherent in current TB testing procedures. While the question was raised whether sample heterogeneity could limit the validity of TB test results, it was generally viewed as not being a significant problem.

The social dimension of TB treatment was repeatedly highlighted as a major barrier to treatment adherence and increased inclusion of social support programs is required for more effective therapy. While there is a growing body of research on the utility and implementation of social interventions for individuals infected with TB, more attention to the effectiveness and practical role of social interventions is needed. Despite growing recognition of social barriers, the financial support for social programs remains too small.

The collective view was that more information is also needed to assess the extent of the problems found with DOT(S) implementation, uptake, and adherence. Some participants suggested that DOT(S) should be adapted to reflect a more realistic approach that would involve keeping the name but changing the protocol to be more consistent with what is feasible in a given country. This suggestion led to a discussion about what metrics should be considered for reorganizing DOT(S). It was repeatedly stated that the key indicator for any treatment method should be resolution of infection with continued negative status, rather than adherence to the method.

Questions were raised regarding the potential for a new TB vaccine and the efficacy of the current Bacille Calmette-Guérin (BCG) vaccine. The variable efficacy of the BCG vaccine was discussed, and it was contended that the principal gain from BCG vaccination is the prevention of TB meningitis in young children. A consensus emerged that a new vaccine for TB is desirable; however, it was also recognized that this is not a short-term solution given that vaccine development is a long and often arduous process.

Policy issues

The extent of the public health impact of TB was debated. It was recognized that while the true extent of the global TB burden remains unknown, approaches to communicating the degree of importance and the degree of uncertainty concerning how TB affects public health (i.e., TB risk), vary greatly. On one hand, some recommended a guarded assessment and a more judicious communication approach to avoid alarmism and panic. Others, however, argued that this tactic would downplay the fact that TB could become a future pandemic and that it would therefore discourage policy makers from acting in a timely fashion. No consensus was reached on the optimal way to move forward, but it was generally agreed these issues need urgent attention and clear decisions.

The opinion was expressed that current funding schemes are primarily targeted toward developing innovative, new diagnostics for TB, rather than implementing existing interventions already proven to be successful, including social support programs. The participants were in agreement that social programs would require increased political will to be more effectively implemented. Parallels were drawn between social approaches to HIV therapy and those that could be employed for TB. For example, it was proposed that lessons could be learned from

the United States President's Emergency Plan for AIDS Relief (PEPFAR), which only provides funding for implementation of proven existing interventions.

A significant portion of the discussion was focused on whether DOT(S) is effective in its current iteration and, if so, whether it needs to be replaced, renamed, or otherwise altered. It was agreed that the focus of any treatment should be on the resolution of infection via the completion of well-defined treatment protocols.

The discussion on the effectiveness of DOT(S) led to questions about why disparities exist between DOT(S) reporting rates and actual adherence observed within countries. A two-fold explanation was presented. First, it was asserted that the pressure for countries to conform to expected coverage rates is too strong, and therefore leads to misreporting. It was recommended that some flexibility should exist in the reporting benchmarks to allow for a more accurate assessment of the true treatment adherence rates. Second, it was suggested that confusion exists with respect to the definition of DOT(S), with some following the original WHO definition of DOT (i.e., strictly directly observed therapy) and others following the revised definition known as DOTS (i.e., directly observed therapy plus a series of other requirements). While it was agreed that a unified understanding of DOT versus DOTS is needed, it was also recognized that these terms are so ingrained in the treatment communities that it is a difficult problem to ameliorate. No firm solutions were presented.

In a continuation of the conversation on DOT(S), the role of WHO was extensively debated, primarily in relation to setting the guidelines for DOT(S) or other therapies. Agreement was reached that better data are needed before a strong case could be made that WHO must reassess DOT(S) protocols. However, it was also pointed out that a 2009 Cochrane Review suggested that the routine use of DOT(S) in low- and middle-income countries does not improve treatment outcomes. It was asserted that this study was largely ignored by WHO. Doubt was expressed as to WHO's ability to objectively consider contradictory data on DOT(S) effectiveness if the outcome would be unlikely to change accepted practices. The discussion concerning changes in DOT(S) protocol acknowledged that altering WHO practices would need to be driven by member states rather than the WHO Secretariat.

Forward-looking discussions considered the resource allocation implications of the proposals presented. Some participants asked what would be the contingency plan should the proposed policy recommendations fail to reduce the spread of DR-TB. This discussion was underscored by concern that only 10% of DR-TB patients worldwide are estimated to receive appropriate treatment, which leaves most infected individuals requiring therapy. Scaling up treatment to include more DR-TB infected individuals could be problematic if the recommended drugs are expensive and/or in short supply. While no consensus was reached as to how much the proposed recommendations in the policy position paper would prevent or eliminate DR-TB, support was given for several specific recommendations, including the need to increase social support programs and the need to identify and scale up programs to treat DR-TB.

Because foreign-born residents comprise approximately 50% of all U.S. TB cases, the topic of U.S. TB screening policies was discussed. Although some overseas screening does occur (based on risk from the country of origin), it was suggested that this policy could be improved by extending overseas screening requirements to additional countries.

Despite growing recognition that social barriers limit the effectiveness of protocols for TB treatment, the financial support for social programs has not caught up with the financial support for research. Without adequate funding for social programs, it was agreed that ensuring infected individuals are compliant with treatment will remain problematic.