SUPPLEMENT ARTICLE

Eliminating Tuberculosis and Tuberculosis–HIV Co-Disease in the 21st Century: Key Perspectives, Controversies, Unresolved Issues, and Needs

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The Millennium Development Goal for tuberculosis control is "to halt the spread of TB by 2015 and begin to reverse the worldwide incidence" [1]. The Stop TB Partnership targets include the following: (1) by 2015, reduce the global burden (prevalence and death rates) of tuberculosis by 50% relative to the global burden in 1990 (prevalence, <150/100 000 population; deaths, <15/100 000/y) and (2) by 2050, eliminate tuberculosis as a health threat (defined as a global tuberculosis incidence of <1 case/1 million population/y) [2, 3]. However, despite being declared a global emergency by the World Health Organization (WHO) in 1995 and ensuing major initiatives during the past 15 years [4], the global burden of tuberculosis, despite declining incidence, is higher today than at any other time in history.

Tuberculosis also remains one of the most important causes of death from an infectious disease [5]. The WHO figures indicate that 8 million new cases occurred during 2010, with 45 million tuberculosis-related deaths [6]. Since 2002, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) has invested $14 billion in 150 countries to support large-scale prevention, treatment, and care programs against AIDS, tuberculosis, and malaria—more than half in Africa. It is worrisome to note that despite this recent investment, only half of the estimated total tuberculosis caseload is detected in the WHO Africa region, implying that more than half of active tuberculosis cases remain undetected and remain a source for continued transmission of *Mycobacterium tuberculosis*. Despite nearly 20 years of WHO-directed and coordinated activity and >12 years of multidrug-resistant (MDR) tuberculosis–specific activity, the response to the drug-resistant tuberculosis epidemic seems to be ineffectual, with projected rapid increase in the global incidence of MDR tuberculosis.

The emergence and spread of MDR tuberculosis, extensively drug-resistant (XDR) tuberculosis, and, more recently, totally drug-resistant (TDR) tuberculosis poses a further threat [7], such that tuberculosis control does not seem to be within our grasp, with existing strategies failing to slow down the tuberculosis pandemic, particularly in sub-Saharan Africa where human immunodeficiency virus (HIV) is a major risk factor for tuberculosis. Currently, the number one cause of death for HIV-infected individuals in this region of the world is tuberculosis. According to WHO estimates, one-third of the world's population are infected with *M. tuberculosis*, forming a huge latent *M. tuberculosis* global reservoir [8]. This renders the prospect of ever eliminating *M. tuberculosis* from the human race almost impossible using current approaches. Thus, the focus for now should be on achieving global tuberculosis control.

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AIMS FOR REDUCING HIV TRANSMISSION AND COINFECTIONS

In June 2011, at a high-level meeting on AIDS at the Joint United Nations Programme on HIV/AIDS (UNAIDS), world leaders at the United Nations General Assembly set new HIV targets for 2015. Leaders committed to: (1) reduce sexual transmission of HIV; (2) halve the rate of HIV infection among persons who inject drugs; (3) eliminate new HIV infections among children; (4) increase the number of persons on life-saving treatment to 15 million; and (5) reduce by half the number of tuberculosis-related deaths in persons living with HIV. With nearly 7000 new HIV infections each day, the declaration calls for intensifying national HIV testing campaigns and urges countries to deploy new biomedical interventions as soon as they are validated, including earlier access to treatment as prevention [9].

Although the global number of new infections and deaths due to AIDS has dropped during the past several years, new HIV infections are still increasing in certain areas of the world, such as Eastern Europe and Central Asia. The increase in new HIV infections together with more successful deployment of antiretroviral therapy (ART) in other parts of the world has resulted in an increase in the number of persons living with HIV. When ART was launched in 2003, only 400 000 persons were receiving it; by the end of 2009, >5 million persons were receiving treatment [10]. Despite the success of stabilizing HIV infection globally, governments cannot be complacent: for every 2 individuals starting HIV treatment each year, 5 are newly infected. The stark reality is that multiple prevention modalities must be implemented to reduce the rates of new HIV infections because lifelong ART for all who are eligible for treatment is likely to be too costly to sustain for many national programs in low-income countries. HIV and *M. tuberculosis* coinfection is on the radar screen in terms of research and translational medicine. Other areas of *M. tuberculosis* coinfections, such as hepatitis B and/or C, are now emerging, particularly in Eastern Europe, and require attention.

Recent advances in several prevention modalities (vaccines, microbicides) and interventions (circumcision, behavior modification), together with advances in treatment [prevention of mother-to-child-transmission (PMTCT) and pre-exposure prophylaxis (PREP)], have brought new hope in the fight against HIV. Most notably were the HPTN-052 clinical trial results [11] which confirmed that early treatment is a potent intervention to dramatically reduce sexual transmission. Nevertheless, challenges remain regarding implementation of interventions on a population scale and the methods for assessing program effectiveness. Additional issues include gender inequality, stigma, gender-based abuse and violence, and the existence of laws and policies that adversely affect support programs aimed at persons living with and affected by HIV. Despite the challenges, increased efforts are needed to build and strengthen partnerships among various disease-specific foreign-funded programs within countries [12]. Funding that is leveraged through specific targets related to a single disease has resulted in the silo effect, which ultimately is not a sustainable model. An integrated approach to financing and care delivery will better serve the community by improving public health outcomes. Incentives should be attached to existing funding programs to ensure that healthcare funding works across multiple diseases. This will result in the development of a more holistic health system that will benefit a larger percentage of persons seeking care, not just individuals affected by a particular disease. Stronger linkages to treatment and supporting alternative treatment decisions need to be improved. Such an approach requires a shift in thinking not only by international funding agencies but also by national programs. Such a switch will ensure outside entities integrate their healthcare vision with the agenda that others bring to the table without stifling progress. Various models of integration have been suggested to improve care delivery, and the time is now for aligning and bringing tuberculosis and HIV management clinics closer to the patients at points of care. Despite the urgent calls to provide universal access to drugs for all tuberculosis and HIV-infected people, we are faced with the grim realities of present-day clinical care coupled with economic uncertainty.

CURRENT CONTROVERSIES AND PERSPECTIVES

A primary obstacle hindering progress toward achieving disease control seems to be the lack of creative and lateral thinking with unity of purpose. Historically, some widely held assumptions, dogma, and orthodoxy have prevailed, leading to polarization of thought, varying opinions, and continued debate within the scientific, medical, funding, and various other stakeholder communities [13]. The need for open debate is reflected by the needs surrounding all aspects of tuberculosis and HIV control strategies. This need has never been greater, especially in the current adverse global economic climate.

This journal supplement arises from the need to focus our attention on core problems and secure a broad spectrum of opinion from various geographical backgrounds. Key perspectives, controversies, unanswered questions, operational issues, challenges, and priority needs relate to a broad range of diagnostic, management, prevention, and surveillance issues regarding tuberculosis and HIV-infected and HIV-uninfected adults and children globally. The array of priorities spans development, evaluation, and implementation of new drugs, diagnostics, and vaccines to improve laboratory services; early and accurate diagnosis; development and validation of diagnostic testing algorithms; effective treatment at points of care; and improved surveillance, political governance, regulatory cohesiveness, commitment, and donor investments. Many

of these issues are covered in the 18 articles and 4 viewpoint articles appearing in this issue of the *Journal of Infectious Diseases.* These informational pieces are written by a wide variety of authors from several continents. Several articles infer that there has been some progress in drug and diagnostics development, but many challenges remain that will be more difficult to tackle and harder to overcome. These articles cover the state of the tuberculosis and tuberculosis-HIV epidemic and provide an opportunity for open and frank debate. Here we identify some of the key challenges and propose ways forward, including critical partnerships that need to be established to ensure necessary action is taken.

McNerney et al state that there is a general consensus that we need to detect early pulmonary disease and provide appropriate treatment in order to conquer tuberculosis . Diagnostic services play an important role in tuberculosis and tuberculosis-HIV care and ensuring good-quality laboratory services is essential to achieving rapid diagnosis that will lead to optimal patient care. The latest advances in diagnostics emphasize that, with limited finances, priority must be given to improved diagnostic tools that can be used to make diagnoses at the point of care, without referral to a laboratory or skilled technical personnel. Such tools will allow easier access to care for the most vulnerable populations. Nahid et al review technologies and platforms under current development or optimization and call for increased communication and coordination of clinical trials research activities among stakeholders to maximize the limited financial resources available.

Despite the investment in developing new point-of-care diagnostic devices that are aimed at meeting the needs of populations in resource-limited settings, there is a wide range of barriers, beyond cost, that need to be overcome in order for countries to adopt and use these assays. Implementing new diagnostic tests, providing guidance, and building laboratory capacity requires a partnership of international agencies, ministries of health, national tuberculosis programs and laboratories, clinicians, advocacy groups, and patients. Schito et al point out that many of these operational obstacles are based on lessons learned from the rollout of the Xpert MTB/RIF assay for rapid tuberculosis diagnosis, Pima™ for measuring CD4 T cells when initiating treatment, and the long-standing antibody-based lateral flow devices used to identify HIV-1 seroreactivity. They highlight the need for building laboratory capacity, monitoring assay quality, and modeling the impact and cost effectiveness of implementing rapid point-of-care diagnostics in a defined setting.

Palamountain et al review 8 barriers to implementing new diagnostics and provide a unique perspective from the supply-and-demand side for opportunities that highlight policy, capacity strengthening, and technology. In their viewpoint article, Cobelens et al present the need to reassess the WHO endorsement of new tuberculosis diagnostics and break the process down into 2 steps: technical policy recommendations followed by a programmatic assessment. The time between these 2 stages would be used to evaluate how the new diagnostic should be positioned within the diagnostic portfolio and assess the evidence for scale-up.

Children, who represent a neglected segment of the *M. tuberculosis*–infected population, are the most challenging to diagnose. In this issue, 2 articles present consensus statements from an expert panel that met on childhood tuberculosis diagnostics evaluation. In the first article, Graham et al, recognizing the pressing need for harmonized definitions and procedures in childhood tuberculosis diagnostics research, propose a standardized clinical case definition for classifying intrathoracic tuberculosis in children within tuberculosis diagnostics research studies. In the second article, Cuevas et al, building on the case definition proposed by Graham et al, discuss methodological issues in the conduct of childhood tuberculosis diagnostics research and present the Expert Panel's consensus recommendations on an alternative methodological approach to addressing these limitations as a step toward ensuring greater rigor and comparability of pediatric tuberculosis diagnostic studies. Getahun et al review the challenges of preventing, diagnosing, and treating childhood as well as maternal tuberculosis and argue that several low-cost interventions could have a high impact if they are adopted and integrated into existing maternal and child health services.

Although both HIV and *M. tuberculosis* are prone to acquire resistance to drug treatment regimens, the diagnosis of drug-resistant tuberculosis is more problematic and usually requires culturing to determine phenotypic susceptibility. Zumla et al review the main issues regarding drug-resistant tuberculosis and highlight the fact that the current tools are very poorly adapted to the constraints of resource-limited settings where the need is the greatest. The occurrence of MDR and XDR tuberculosis greatly complicates patient management within resource-poor national tuberculosis programs, in turn reducing treatment efficacy, increasing the cost of treatment, and raising the specter of a 21st century epidemic of untreatable tuberculosis. A serious question arises as to why, despite nearly 20 years of WHO-directed and coordinated activity and >12 years of MDR tuberculosis–specific activity, the global response to the drug-resistant tuberculosis epidemic has been so ineffectual.

Tuberculosis drugs, which are currently in clinical development, are reviewed by Lienhardt et al, who outline the challenges involved in identifying new drug combinations to be assessed in clinical trials. The authors point out the potential pharmacological interactions between drugs used for treating tuberculosis and HIV and raise a variety of important regulatory, postmarketing, and guideline issues. Phillips et al

suggest innovative multiarm, multistage clinical trial designs to overcome the drug combination bottleneck, which may lead to shortening the duration of evaluation of new drug regimens. Coxon et al compare target-based approaches that harness bioinformatic and computational methods with the conventional phenotypic-based approach for identifying new tuberculosis compounds to speed up the drug development pipeline. A common theme in all 3 articles is the need for increased collaboration not only among scientists but among all stakeholders.

Prison inmates are a frequently ignored population in which both HIV and *M. tuberculosis* are spread with minimal prevention and treatment intervention. Reid et al point out that inadequate prison health services can also drive tuberculosis drug resistance, HIV, and tuberculosis/HIV co-morbidities with sexually transmitted diseases. Lee el al review tuberculosis service delivery in prison systems supported by the Global Fund during the past 7 years and determine that promoting a more comprehensive package of tuberculosis care that is tailored for service delivery in prisons is needed and that there is minimal provision of MDR tuberculosis services in general.

In contrast to the issues of tuberculosis control in high-burden countries, Abubakar et al discuss the important issues for tuberculosis control in low-burden countries. They discuss the efficacy of the current BCG vaccine, preventative therapy, infection control measures, and cost-effectiveness of screening assays that may be used. The most cost-effective method for controlling an infectious disease such as tuberculosis on a global scale is a safe and effective vaccine that is based on improved understanding of an underlying protective mechanism. Axelsson-Robertson et al indicate that increased emphasis needs to be placed on discovering clinically relevant T-cell epitope responses in individuals protected from disease, assessing potential correlates of risk or protection, and identifying biologically and clinically relevant markers to gauge response to therapy. Brighenti and Andersson highlight the immunological differences between the immune response associated with the granuloma that is mounted locally compared with what is observed systemically. Uhlin et al review the current immunotherapies under development for adjunct treatment of drug-resistant tuberculosis. These therapies will improve treatment outcomes, reduce the duration of therapy, and modulate the host response to either enhance *M. tuberculosis* elimination or prevent immune-mediated pathological sequelae, such as immune reconstitution inflammatory syndrome. Zumla and Maeurer, in their viewpoint article, argue that there is an urgent need to re-think the immunology of *Mtb* infection since the biologically and clinically relevant *Mtb* target antigens that elicit protective immune responses may as yet be undiscovered. They present novel hypotheses and suggest feasible experimental designs to test them; the results of which may shed light on protective immune responses, which could in turn guide development of newer adjunct immunotherapies for DR-TB.

In a viewpoint article, Mudenda et al make a convincing case for an increased investment in research and routine autopsies, which have been declining during the past half century in Asian and sub-Saharan African countries. In addition to providing a more accurate cause of death determination and improving cause-specific mortality statistics, autopsies could provide a better understanding of the pathogenesis of tuberculosis and the protective immune mechanisms that operate in latent *M. tuberculosis* infection. Furthermore, autopsy studies on acute deaths in the community would allow for the study of background levels of subclinical tuberculosis disease, co-infection with *M. tuberculosis* and HIV, and other infectious and noncommunicable diseases not yet clinically manifested.

Funding and enhanced collaboration are the subjects of 2 articles. Kim et al outline the importance of enhanced communication, coordination, and collaboration across disciplines to accelerate the translation of fundamental scientific discoveries into clinically relevant technologies and interventions. In addition to the treatment, diagnosis, and prevention issues, they call for developing cohorts to evaluate the natural history of tuberculosis disease in the context of regional coinfections and comorbid conditions, as well as pedigreed samples collected from cohorts for the development of improved diagnostics and prognostic biomarkers. Akachi et al show that increased investment in national tuberculosis programs will successfully reduce the mortality rate and prevalence of tuberculosis. They present data on the performance of national tuberculosis programs from 22 high-burden countries and show that these investments reduced the global tuberculosis burden, providing new evidence for international and domestic funders to continue scaling up investments in tuberculosis control at a time when increased investment from both sources seems to be at risk. All articles highlight the dire need for increased governmental and funder investments. However, increased investment alone is not enough: funding must be appropriately targeted, especially to areas where the next infection will likely arise and areas where there has been gross investment neglect such as prisons. Lee et al illustrate that even in the presence of available funding, countries are failing to appropriately prioritize their funding requests from international agencies, with the prison sector, an important source of tuberculosis and MDR tuberculosis, remaining significantly underfunded.

PROSPECTS FOR ELIMINATING TUBERCULOSIS AND TUBERCULOSIS–HIV CO-DISEASE IN THE NEW MILLENIUM

MDR and XDR tuberculosis has now become entrenched in several areas of Eastern Europe, Asia, and sub-Saharan Africa

[6, 7]. Coincidentally, those same areas are experiencing high HIV prevalence rates. This now raises the specter of a 21st century epidemic of untreatable tuberculosis and HIV. Such an epidemic may drive the spread because patients coinfected with *M. tuberculosis* and HIV are less able to contain *M. tuberculosis* and because there is a lower predictive value of tuberculosis diagnostic tests for this group. The need to rethink current strategies for achieving disease control is required together with new bold steps to be taken through lateral thinking and new innovations. Essential steps for progressing toward disease control are to secure strong political and funder commitment for adequate and sustained funding; improve case detection rates and services at points of care; strengthen healthcare systems and laboratories through increased investments in human resources; empower communities; and promote basic science (improved drugs, diagnostics, and vaccines), translational, and operational research. Such steps require cross-sectional interactions that may seem obvious at first glance yet are difficult to achieve and maintain in reality. For instance, drug discovery and novel treatments modalities require surrogate biomarkers for response to therapy; the design of companion diagnostics for gauging vaccine uptake involve interface between vaccine development and diagnostics. These areas of research and development enjoy different funding strategies, and we need to identify better ways to increase the value of these funding programs by offering new and innovative productive interactions and cofinancing.

The building of key infrastructures (cohorts, biospecimen banks, biomarker discovery, modeling, and surveillance databases) to accelerate future research becomes important. There is a consensus that biobanking specimens will aid research and may accelerate development of new biomarkers and diagnostics. Although several sample repositories exist or are operationally active and collecting samples, the issue of how this might be financially supported in the long term has yet to be resolved. The cross-fertilizing nature of that endeavor is perhaps here most obvious: biobanks are not only dependent on excellent sample procurement, their value lies in the connection of detailed documentation and clinical follow-up of each individual case with the respective biological material.

The social and political factors that affect acceptance and implementation of new interventions need to be defined. Bridging the divide between research disciplines, from fundamental to implementation and basic discovery to technology development, is important. Achieving these huge goals with limited resources requires creativity, communication, and effective and equitable collaborative partnerships, along with leveraging of existing resources. One will have to carefully think through how community and program leaders, advisors and researchers, program implementers, healthcare professionals, program managers, advocates, educators, and government representatives interested in strengthening health systems through partnerships can work together and maintain coordination of all elements.

Furthermore, training and education initiatives that focus on building and enhancing partnerships are needed to scale up control efforts, and this requires partnerships with other health organizations, private providers, community-based organizations, affected communities, and academic institutions, among many other individuals and entities [12]. Close links among policy makers, researchers, community activists, and point-of-care management teams must be established with provision of a national framework to assess the effect of implementation of new technologies, including efficacy, health-system delivery, and scale-up. Financial commitment should be underpinned by planning that shows a clear understanding of how the financial resources are channeled within a country and how transparency and financial accountability are strictly achieved to ensure that resources reach where they are needed. Operational research is required to define how existing and newer tools could be used most efficiently within the resource limitations in particular settings. The latest WHO Report [6] states that in 2010, there were an estimated 8.8 million incident cases of tuberculosis, 1.1 million deaths from tuberculosis among HIV-negative people and an additional 0.35 million deaths from HIV-associated tuberculosis. The highest tuberculosis incidence rates occur in sub- Saharan African countries and these are associated with high local HIV rates. Since 2002, the availability of funding through the Global Health Initiatives (GHIs), the US President's Emergency Plan for AIDS Relief (PEPFAR) and the GFATM provided resources for the expansion of programme activities for tuberculosis and HIV/AIDS. With the global economic recession, scarcity of donor funding and cancellation of Round 11 by the Global Fund [14] every effort must be made by funders to ensure that gains being made by tuberculosis and HIV programmes are not lost.

Notes

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