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Sharing the spotlight in Durban: A report from IAS TB2016 at AIDS2016

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ABSTRACT

Tuberculosis (TB) is now recognized as the number one cause of death worldwide due to a single infectious pathogen and is the cause of death in one-third of people living with HIV worldwide. An inaugural pre-conference focused on TB (TB2016) was held at the International AIDS Society Conference AIDS2016. This report focuses on key messages from the TB2016 conference that are important for the medical, public health, activist, and scientific communities.

Introduction

The 2016 International AIDS Society (IAS) Conference in Durban, South Africa attracted over 18,000 delegates from over 183 countries. In recognition of greater awareness and action needed in combating global tuberculosis infection (TB), and in particular, TB and HIV coinfection, an inaugural IAS preconference “TB2016” was conducted over two days prior to AIDS2016. Worldwide, we have achieved a 2% annual reduction in TB incidence, when the annual incidence must fall by 20% between the years 2015 and 2050 to achieve the TB Global Plan elimination goal [1]. TB2016 brought together over 1000 clinicians, public health officials, ministers of health, nongovernmental organizations, and activists to discuss new scientific TB findings, devise a roadmap for TB research, and strategies for boosting partnerships with civil society, political systems, and funding for the global fight against TB with the ultimate goal of TB elimination [2]. This report highlights select messages and presentations from TB2016. The authors are exclusively responsible for this report. This report is not endorsed by IAS.

Out of the shadow

The conference opened with highlights on the global burden of tuberculosis infection and on the intersections of the HIV and tuberculosis pandemics by South African Minister of Health Dr. Aaron Motsoaledi. A major theme from TB2016 was that it is time for TB to step out of the shadow and into the spotlight to receive its due attention as a global public health threat. TB is the number one cause of death worldwide due to infection. Each day 4400 people die from tuberculosis. Over 9 million cases of active TB disease occur annually, and 3 million of these cases go undiagnosed [3]. Furthermore, TB causes greater than one-third of the deaths each year in HIV-infected individuals [3]. Dr. Motsoaledi cautioned, "We will not end AIDS without ending TB. We will either succeed or fail together, and so working alone is not an option"[2]. This important message was echoed throughout the entire IAS AIDS 2016 conference.

A paradigm shift: ending tuberculosis

As has been the case for HIV, there has been a paradigm shift from the goal of controlling TB to ending TB. The UNAIDS 90-90-90 HIV treatment targets to end the AIDS epidemic by 2030 consist of the following: 1) 90% of all people living with HIV (PLHIV) will know their HIV status; 2) 90% of those diagnosed with HIV infection will received sustained antiretroviral therapy; and 3) 90% of those receiving antiretroviral therapy will have viral sup-

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pression [4]. Dr. Motsoaledi, also chair of the Stop TB Partnership Board, called to our attention the Stop TB Partnership (hosted within United Nations Offices for Project Services, UNOPS) Global Plan to End TB 2016–2020 [5]. The 90-(90)–90 people-centered global targets for tuberculosis, with the ultimate goal of ending TB as a global health problem, consist of the following:1) reach 90% of all people who need TB treatment, including 2) 90% of people in key populations, and 3) achieve at least 90% treatment success [5].

Dr. Eric Goosby, United Nations special envoy on tuberculosis, identified barriers to achieving these goals and charged us to evaluate the "TB cascade of care" and learn lessons from the "HIV cascade of care." We need to identify and overcome barriers to TB diagnosis, entry into care, and retention in care. Dr. Goosby noted that overcoming these barriers will require adequate political will and funding models of care that treat multiple diseases, including HIV, TB, and chronic medical conditions like diabetes mellitus, hypertension, and chronic lung diseases. To test and treat all, the global community needs universal health coverage, a concept that has not been universally embraced.

With the current public health systems, diagnostics, and drugs, we have been unable to end tuberculosis, and current predictions suggest that we will be unable to do so for >100 years. Under our current systems and tools, the world has seen an alarming escalation of multi-drug resistant (MDR) and extensively drug resistant (XDR) TB. Only two new drugs approved for tuberculosis treatment have entered the market in half a century, and access to these drugs has been very limited worldwide. The only available vaccine was developed nearly a century ago and only shows moderate efficacy in reducing severe TB cases in children. To face such challenges and urgent needs, Jose Luis Castro, president of the International Union against Tuberculosis and Lung Diseases (IUTLD) noted that we do not need yet another "call for action." Clearly the action that is being taken is not working. We need a "call for change" —a paradigm shift. However, if the paradigm shift does not spread beyond the few engaged in studying and treating tuberculosis, the impact will be minimal. The spotlight must be visible to all.

Activism and engagement

How do we shine the spotlight? One of the many ways is through activism. The world has witnessed the enormous role that HIV activists have played in the fight to end HIV/AIDS. Where are the TB activists? They were present at TB2016. Many of the TB activists for HIV. South Africa's Thokozile Phiri from Facilitators for Community Transformation reminded us of the importance of engaging traditional, community, and religious leaders. She asked why we cannot perform TB self –testing in an effort to expand TB testing and for wider engagement with communities to expand testing. A perfect illustration of engaging civil society and religious leaders was lived out in Durban on the following day when Minister Motsoaledi launched a National TB Coalition partnering with government, civil society organizations, and religious organizations at a local church [2]. Minister Motsoaledi called upon churches, mosques, synagogues and other places of worship to get involved:

"Today, we again summon the nation, communities, religious groups, men, women and the youth to participate in this groundbreaking TB testing campaign. As we do so, we must remind one another that to have tuberculosis is not a shame. We must allay the fears of those who contract the disease that they will be shunned, excluded and made to suffer in silence away from everybody else. We must stand firm against prejudice, stigma and exclusion" [6].

Parliamentarians from 18 African nations participated in the conference and launched the African TB caucus. Select representatives presented their plans and ideas on how to raise TB awareness in their respective countries, in addition to increasing funding for TB programs and research.

Dr. Lucica Ditiu, executive director of the Stop TB Partnership, spoke about the importance of engaging "key populations" and asking for their advice on how to design better strategies to reach their communities for testing and treatment. Examples of "key populations" affected by tuberculosis include: prisoners, migrants and refugees, miners, health care workers, people living with HIV, sex workers and victims of sex trafficking.

Mike Frick, TB/HIV senior project officer from Treatment Action Group (TAG), called the audience to use human rights 1) to resolve ethical dilemmas in TB prevention, diagnosis, treatment and care; 2) change the way TB is culturally perceived; 3)galvanize advocacy; 4) resolve inequities that drive the TB epidemic. Additionally, human rights principles should strengthen publicly funded research, partnership with private enterprises and diffusion of scientific knowledge and applications to those affected by tuberculosis. Governments were called to adequately fund and regulate TB science and research, engage the public, create distribution systems through which science and technology can reach affected communities, and develop national plans for accountability in reaching goals.

The science of TB: another paradigm shift?

The meeting of public health officials, clinicians, activists, politicians, and scientists under one roof demonstrated how critical it is that these key stakeholders do meet and communicate. Clifton Barry, Ph.D. from the US National Institute of Health explained to the audience that the seemingly slow progress that has been made on TB diagnostic, treatment, and prevention fields has certainly been not due to a lack of effort. TB is an ancient pathogen that has evolved over time to successfully evade human immune responses. TB infection poses complex immunologic challenges—along the spectrum from latency to active disease.

TB immunology challenges

One of the key themes of this conference is our incomplete understanding of the human immune response to *Mycobacterium tuberculosis* (MTB). Dr. Barry began his talk by showing three studies with negative findings in terms of improving TB treatment that were published in the New England Journal of Medicine (NEJM) [7–9] and an apt quotation from Drs. Digby Warner and Valerie Mizrahi published in the same issue as these studies, "As these trials have confirmed, our understanding of the science underlying positive clinical outcomes remains rudimentary. It's time to go back to the basics." [10]

The speakers in the TB Immunology section emphasized the clinical paradigms that exist with the current technologies that are being used for diagnosis and treatment of active TB infection. In particular, Dr. Barry spoke to the challenges of determining whether or not TB infection is completely cleared after treatment. Although mycobacterial cultures of respiratory samples may be negative after two months of therapy, bacilli may still be present that exist in various microenvironments [11]. By studying resected pulmonary TB lesions, researchers have been able to better able to understand the immunologic spectrum of TB lesions, penetration of drugs into these lesions, and development of drug resistance of TB populations within the lesions [12]. Depending on the environment, some bacilli may be more vulnerable to propagating drug resistance and result in persistence after therapy; calling for better markers of sterilizing immunity and clearance of all bacilli. When designing new TB treatment regimens, attention should be persis-

Table 1
Seven new approaches to TB vaccine development.

1) Target adolescents and adults first
2) Vaccination that aims to prevent infection
3) Aerosol and combination vaccines
4) CMV-TB vaccines
5) Induce unconventional immunity [37]
6) Better targeting of conventional T cells, including potential use of "immunodominant" antigens that show variation [38]
7) Learn about success early in product development

Source: Dr. Willem Hanekom, Bill and Melinda Gates Foundation, TB2016 presentation

tent pathology with consideration of lesion- penetration data for drug combinations.

Furthermore, the distinction between latent TB infection (LTBI) and active TB infection can be challenging and current laboratory tests cannot definitely determine the state of immunologic control of the bacilli and whether or not there is an active infection. Dr. Barry highlighted a recent report in Nature Medicine that used

2-deoxy-2-[18F]fluoro-d-glucose positron emission and computed tomography to identify pulmonary abnormalities that suggests subclinical, active disease in HIV positive patients, who are otherwise thought to have latent tuberculosis infection (LTBI) [13]. Patients with these lesions may be more likely to progress to clinical disease. These results challenge the current two option paradigm of active versus latent disease and suggest that better biomarkers are needed to identify when recurrence (after treatment) or reactivation (after exposure) may occur.

TB vaccine challenges and updates

Unfortunately, we have not yet witnessed the development of a protective TB vaccine for the prevention of TB infection or disease. Dr. David Russell from Cornell University noted that one of the reasons for this failure may be that we have allowed ourselves to be locked into an inaccurate immunologic paradigm of protection. Currently we define disease protection by the development of "control" of infection and failure by "loss of control." This paradigm has largely been shaped from loss of control experiments in knock-out mice. Dr. Russell purported this paradigm has generated a "circular argument for those immune correlates used to assess experimental vaccine efficacy human vaccine trials." Furthermore, because we cannot do human challenge studies, vaccine candidate success has been measured by the induction of peripheral immune correlates such as cytokine production, immune recognition and T-cell subset markers. However, the current immune correlate paradigm has failed to predict TB vaccine efficacy in humans, as evidenced by the negative study of the MVA85A vaccine in 2013. Dr. Russell asked, "What if disease progression is medicated by an expansion of permissive host cells and NOT by a loss of control?" His group has developed *Mycobacterium tuberculosis* reporter strains to probe the impact of vaccination at sites of infection [14]. They are studying TB infection in mice and exploring the phenotype of the phagocytes infected with TB in the mouse lung. They are also collaborating with others to study a similar model in non-human primates and also in resected lung tissue from humans. His group's long-term goal is "to develop a strategy to reduce the incidence or induction of permissive host cells and expand controller cell populations."

Dr. Willem Hanekom from the Bill and Melinda Gates foundation continued by posing two major questions regarding TB vaccines: 1) Can we control tuberculosis without an effective vaccine? 2) How will we know if any of the TB vaccines currently in trials, or yet to be developed, work? Dr. Hanekom answered the first question with a "No!" and introduced seven novel approaches to TB vaccine development (Table 1). He showed mathematical modeling work from Gwenan Knight that to achieve 2050 TB elimination goals, TB vaccine development should focus on vaccines targeted at adolescents and adults [15]. Adults and adolescents are more likely to transmit TB than children and will halt the chain of transmission. Even a vaccine with moderate efficacy in adults could have a major impact on ending tuberculosis [15]. One of the major challenges in TB vaccine development is lack of a correlate of protection. The current TB vaccines have been designed to induce conventional T cell responses. Dr. Hanekom suggested that we need to learn more about interactions of T cells in the lungs and better define the features of protective T cell immunity to TB [16]. Interestingly, it was noted that some people with repeated exposures to tuberculosis never acquire TB infection. One explanation that has been proposed is alterations in glycosylation patterns of antibodies that are associated with resistance to TB infection (Galit Alter, unpublished data). Finally, Dr. Hanekom noted that the TB vaccine field would benefit greatly from human challenge models whereby we might be able to detect vaccine efficacy in earlier stages of vaccine development, prior to the conduct of large clinical trials.

Dr. Mark Hatherhill from the South African Tuberculosis Vaccine Institute discussed the challenges in study design and assessment of TB vaccine efficacy for TB vaccines designed to prevent infection and those designed to prevent active disease among persons already latently infected. Ideally we would develop a vaccine that prevents both. However, it might be possible that a vaccine would not prevent infection but might prevent the development of active disease. Such a vaccine would still be beneficial in halting transmission of TB. However, there is a challenge in demonstrating protective immunity in this case, since our current diagnostic technology relies upon detection of latent infection, and we do not have diagnostic tests that predict who will go on to develop active disease. A vaccine that prevents infection would likely need to target infants before TB exposure. Additionally, if interferon gamma release assay (IGRA) technology will be used to determine if the vaccinated individuals develop TB infection, then these vaccines will need to avoid the peptides that are used in IGRA tests. Finally, the endpoint of study (i.e. development of TB disease), age of the study population, and incidence of TB disease in the study population will influence the sample size needed for the study. A study of adults already infected with TB would likely require the smallest sample size; however, it might be the most difficult to demonstrate vaccine efficacy in this population.

LTBI updates

It is estimated that one third of the world's population has been infected with tuberculosis. Therefore, treatment of latent tuberculosis infection (LTBI) is an important part of eliminating TB worldwide. The WHO recommendations for LTBI therapy are aimed predominantly at low TB incidence settings, therefore, more practical and effective treatment programs are needed to address the many diverse populations infected with TB requiring LTBI therapy.

Dr. Tom Sumner from the London School of Hygiene and Tropical Medicine reviewed the efficacy of INH versus rifamycin containing LTBI programs. He demonstrated that in high transmission settings, a rifamycin with INH was as effective as INH alone in an

HIV positive population [17] and that the shorter duration of rifamycin containing programs likely led to greater adherence. Furthermore, rifamycin-containing programs were more likely to sterilize the TB infection than INH therapy and therefore, prevent future reactivation [18]. Since the majority of TB disease following preventive therapy is due to new infections (as opposed to reactivation) in high incidence settings, the role of preventive therapy needs to be further evaluated in these situations.

In addition to needing more effective, shorter LTBI therapy programs for all populations, there is also a need for effective programs in special settings, such as after exposure to MDR-TB, during pregnancy and post-partum periods and in HIV positive individuals. Dr. Timothy Sterling from Vanderbilt University reported several new clinical trials that are underway to evaluation new LTBI programs in these settings. Some of these trials include a trial of 12 weeks of INH and rifapentine in pregnant and postpartum women; other trials are investigating 6 months of levofloxacin (in one study) or delamanid (in another study) in people exposed to MDR-TB. Additional trials are studying periodic, recurrent treatment of INH and rifapentine in HIV positive individuals living in high incidence settings. Another way to improve compliance, drug levels and possibly efficacy is to reformulate current medications into long-activing injectable forms of the drug. This has been very effective for anti-psychotic medications, for several hormones and is looking very promising for HIV antiretroviral medications. Dr. Susan Swindells from the University of Nebraska discussed the possibility of reformulation TB drugs into long activing injectable forms for treatment of LTBI or active TB disease. Early studies in animals models are encouraging, but current TB drugs may prove a challenge for reformulation, calling for the development of novel anti-TB targets that are able to be reformulated into long acting agents.

TB transmission

Dr. Robin Wood from the University of Capetown presented the concept of aerobiology and discussed the use of this discipline to measure airborne transmission of disease. Dr. Wood's research group has used atmospheric CO2 levels as an inexpensive measure of rebreathed air. Indoor CO2 concentrations are often 4000 ppm, ten-fold higher than outside air. In fact, modern building codes can result in significant rebreathing of air. Quantification of shared air measurements were presented, with a significant increase during winter months in South Africa when windows are mostly closed. Using modern bioaerosol technologies, they measured amounts of viable TB up to 1000 fold higher than old studies from the 1950's had reported. Highly sophisticated aerosol technologies were developed including particle size spectrometry, laser spectrometry, CO2, temperature and humidity monitors. This ability to detect TB in aerosols might be applicable to new methods for diagnosis of TB, and even TB screening of populations in enclosed spaces. The presentation concluded with the statement that the TB epidemic in high-burden settings was the result of high volumes of exchanged air and prevalence of infectious cases.

A shining example of multi-faceted HIV and TB interventions, including TB infection control measures and the direct application of the aerobiology, was outlined in Dr. Gerald Friedland's update on the MDR and XRR-TB epidemic in Tugela Ferry, South Africa (oral presentation and abstract number 8). We learned how this epidemic of drug resistant TB among predominantly HIV infected patients with very high mortality and nosocomial transmission [19] was stabilized and reversed. The TB infection control measures included strengthening inpatient and outpatient airborne infection control policies, strengthening TB directly observed therapy short-course (DOTS) program, integrating TB and HIV prevention and treatment services, and reducing reliance on inpatient care. Focus was placed on decentralized care, with patient-centered community based early case detection and treatment interventions for both HIV and TB. The strengthening of airborne infection control included emphasizing natural ventilation through opening windows and utilization of mixer fans, identifying and separating MDR/XDR-TB suspects, employing cough officers, providing N95 respirators to personnel, providing surgical masks for patients, and establishing an institutional culture of good infection control practices. Environmental assessments showed that air changes per hour (ACH) in the hospital wards increased from <1 ACH with windows closed and mechanical ventilation off to 15 ACH with windows closed and mechanical ventilation on to 60 ACH with windows open and mixer fans on. Patients who received decentralized care to community based HIV/MDR-TB treatment were demonstrated to have good adherence rates and good treatment outcomes. In addition they were found to have lower mortality and default rates than historical controls from a centralized treatment program [20].

TB diagnostics, biomarkers, and precision medicine updates

Moving toward a precision medicine approach for TB therapy was a common theme of the conference. The search is on for which diagnostics will aid in determining the tailored treatment and monitoring of treatment success. Understanding the "phenotypes" of TB infection, including types of lung lesions, may assist in directing therapy and duration of therapy.

Dr. Gerhard Walzl from Stellenbosch University presented the development of a blood RNA signature for tuberculosis disease risk in patients with LTBI. The signature was derived by following a cohort of South African adolescents infected with MTB. It was tested in his cohort and also in a cohort from the Gambia [21]. The authors of this study demonstrated that the relative risk of developing TB disease using their signature was between 6 and 14 [21]. Dr. Walzl discussed the Correlate of Risk Targeted Intervention Study (CORTIS) which will evaluate this gene signature in large cohort. The study aims to screen over 10,000 people to identify 1500 HIV-negative persons who test positive for this gene signature and HIV-uninfected 1700 person who test negative for the gene signature. They then plan to provide targeted, short-course preventive therapy (isoniazid and rifapentine for 12 weeks) to patients who test positive for the gene signature with the highest risk of TB disease. Aims of this study include testing whether the preventive therapy reduces the rate of incident TB disease compared to the standard of care in a high TB burden country among HIV-negative persons (active surveillance). They will also test whether this gene signature differentiates persons with prevalent or incident TB disease from persons without TB disease [22].

For those who have already undergone active TB treatment, can we predict who has achieved a sterilizing cure? Dr. Walzl shared data that has subsequently been published in Nature Medicine regarding the use of positron emission tomography and computerized tomography (PET-CT) to evaluate response to treatment of active tuberculosis. Ninety nine HIV-negative, non-diabetic adults with active pulmonary tuberculosis were recruited at diagnosis and followed during their treatment course with PET-CT at diagnosis, one month and six months after TB treatment was initiated. GeneXpert MTB-Rif testing was repeated at six months after therapy. In addition, mRNA detection assays for MTB were performed at the six month time point. Interestingly, many patients who had the clinical outcome of cure with culture conversion had ongoing inflammation on PET-CT and presence of MTB mRNA and DNA in respiratory samples at 6 months after treatment. The authors suggest that apparently curative treatment for TB may not eradicate all of the MTB bacteria in most patients, that there is an important role for the immune system in maintaining a disease free state in

these patients, and that better markers of treatment response are needed for the successful development of shortened TB treatment strategies [23]. Dr. Walzl noted that a study is being planned to see if PET-CT can be used to predict those who have less severe burden of pulmonary TB and can be cured with 4 months of therapy, rather than 6 months [24].

The African European Tuberculosis Consortium (AETBC) utilized multiplex cytokine arrays to study patients presenting with symptoms of active TB to primary health clinics in multiple African countries. They report identifying a seven-marker host serum protein biosignature for the diagnosis of TB disease [25]. A point-of-care test using a lateral flow assay will be tested to confirm these findings in the Screen TB project. This study will focus on high TB prevalence areas with difficult access to efficient TB diagnostic services and laboratories [26].

TB drug pipeline update

The session on TB Drug Discovery began with Dr. Stuart Cole from École Polytechnique Fédérale de Lausanne. Dr. Cole is recognized for his earlier seminal research on sequencing the *M. tuberculosis* genome in 1998 while at the Pasteur Institute. Using the genome data to develop new drugs has proved more challenging than anticipated. Screening compounds for selected targets of TB metabolism have yielded few compounds. Many targets which may look promising are "promiscuous", which means that multiple drugs can inhibit them. A consortium of research institutions called MM4TB (More Medicines for TB) has been assembled, to pool resources and talent. While the pipeline is considered insufficiently robust, a candidate benzothiazinone (PBTZ169) has shown promise in vitro. This compound shows activity against all strains of *Mycobacterium tuberculosis*, including MDR and XDR isolates, with MIC's of 1–10 ng/mL. Synthesis is simplified in a one pot system, using 4 reagents. PBTZ169 demonstrated excellent activity in mice and guinea pigs, with an excellent profile. Phase 1 clinical trials in humans were completed in Moscow, and Phase 2 trials are expected to commence November 2016.

Repurposing of established antibiotics for TB therapy was the topic of Dr. von Groote-Bidlingmaier's talk, from Stellenbosch University, South Africa. Carbapenems have high intrinsic resistance to the beta-lactamases of *M. tuberculosis*, but only anecdotal clinical studies have been performed. Their group tested early bactericidal activity (EBA) of carbapenems in smear-positive TB patients for 14 days. Meropenem was compared with traditional isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE) treatment, administered to arms with 15 subjects each. The arms were matched by age, sex, HIV status, BMI and mean log CFU/ml of initial sputum cultures. EBA activity of meropenem was very similar to HRZE, with minimal side effects. They recently published these preliminary results in a letter to the editor in the New England Journal of Medicine [27].

Additional details about the TB treatment pipeline can be found in the TAG 2016 Pipeline Report Tuberculosis Edition at http://www.pipelinereport.org/2016/tb-treatment.

TB drug resistance updates

Dr. Gunar Günter gave a report from the frontlines of Katatura State Hospital in Namibia, where he treats many patients with drug-resistant tuberculosis. He reminded us that the success rates for MDR-TB treatment are not improving. In some places, mortality rates of patients co-infected with HIV and MDR-TB are similar to those of the TB pre-chemotherapy era [28]. A recent systematic review and meta-analysis evaluating 30 studies of MDR-TB and HIV coinfected patients found an overall treatment success rate of 57% (95% CI 46–68%) for adults with MDR-TB and mortality rate of 38% (29–48%) [29]. We did learn that higher treatment success rates (71–86%) can be achieved when resources are available and individually tailored treatment regimens are used [30-33]. However, in many parts of the world, resources are lacking for costly drugs, drug monitoring, and individually tailored regimens.

Dr. Sebastien Gagneux of the Swiss Tropical and Public Health Institute explained how compensatory mutations and epistasis between antibiotic resistance mutations increases the fitness of MDR-TB from [34, 35]. Disconcertingly, "optimal" combinations of drug resistance mutations are "selected" in clinical settings. Dr. Alexander Pym from the KwaZulu-Natal Research Institute for Global Health outlined the evolution of TB drug resistance in KwaZulu-Natal, South Africa based on whole genome sequencing and dating analysis of isolates [36]. Dr. Pym and colleagues noted that mutations conferring INH and streptomycin resistance in the TB clone responsible for the XDR-TB Tugela Ferry outbreak were acquired 50 years prior to outbreak and that mutations leading to the emergence of MDR and XDR strains in *rpoB, pncA, rrs,* and *gyrA* genes occurred 10 years prior to the outbreak [36]. In the majority of cases, INH resistance was the initial resistance mutation to be acquired, which would not be detected by current rapid molecular diagnostics employed in many countries that only assess rifampin resistance. Such a history of the evolution of MDR and XDR-TB in South Africa begs that follow up questions as to what is currently evolving in many parts of the world. What might we expect to see fifty years from now? Most importantly, how can we prevent the development and spread of further TB drug resistance?

Implications and conclusions

The conference concluded with a session by Dr. Trevor Mundel of the Bill and Melinda Gates Foundation discussing the challenges to fighting TB in the 21st century. As has been outlined in this report, the challenges are many. The workers are too few and are underfunded. The closing session of TB2016 called for answers to key scientific questions and innovation across the TB research spectrum. Nonetheless, as has been highlighted in the field of HIV research at AIDS2016, the harnessing of human scientific ingenuity, funding, and advocacy can advance science and clinical care in tremendous ways. We need to learn from and draw in our colleagues from the HIV field. Advocacy for adequate funding, open minds for paradigm shifts, and willingness to work together across the spectrum of bench to the bedside to public health program implementation is critical. With the current tools and models of care, we are only achieving an annual 2% decline in TB incidence per 100,000 persons globally. In order to achieve the TB Global Plan elimination goal of <1 million cases per year worldwide, we will need major new tools and implementation procedures to reach an annual 20% decline in TB incidence per 100,000 persons globally. Thus, we do need a call for change, a call for action, and a call to shine the light on this human rights, public health, and scientific challenge that continues to plague the modern world in 2016—TB.

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