SUPPLEMENT ARTICLE

Translating the Tuberculosis Research Agenda: Much Accomplished, but Much More to Be Done

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Despite the availability of effective diagnostics and curative treatment regimens for tuberculosis, millions of people die each year of this disease. The steady global increase in the number of tuberculosis cases caused by multidrug-resistant and extensively drug-resistant strains of *Mycobacterium tuberculosis* are of major concern, especially in light of the thin tuberculosis drug pipeline. New tuberculosis drugs are undergoing clinical evaluation, and renewed hope comes from fresh approaches to improve treatment outcomes using a range of adjunct host-directed cellular and repurposed drug therapies. Current efforts in developing second-generation and new rapid point-of-care diagnostic assays take advantage of recent genetic and molecular advances. Slow progress in the development of prophylactic and therapeutic vaccines requires increased funding for basic as well as translational research. Although major challenges remain, these can be overcome by cementing our resolve, raising advocacy, bolstering global funder investments, and leveraging more effective collaborations through equitable public–private partnerships.

Keywords. tuberculosis; research; drug resistance; new treatment regimens; resource-limited settings.

This supplement provides an update on the status of *Mycobacterium tuberculosis* (*Mtb*) research for drugs, vaccines, and diagnostics, and the intersection of these disciplines to better understand tuberculosis disease pathogenesis. Interest remains high in using cellular therapy and harnessing regulatory networks to either suppress *Mtb* growth or alleviate pathology due to host–pathogen interactions. In addition, epidemiological disease modeling, diagnostic impact assessment, the search for novel biomarkers, and regulatory challenges are highlighted separately. Advances in pediatrics include updates to the National Institutes of Health case definitions and a roadmap to meet the diagnostic needs.

Global collaborative efforts for tuberculosis biomarker research and a central curated tuberculosis drug resistance database are 2 programs for which international collaboration has been successful and can provide much-needed resources to meet future challenges. Over the past few years, the tuberculosis research community has made significant advancements, but many challenges including improved diagnostic tools, better-tolerated drug regimens of shorter duration, and a safe, effective prophylactic vaccine still remain elusive. We must resolve to address these deficiencies with adequate funding from global stakeholders, smarter and better-coordinated collaborative efforts, and increased advocacy for equal access to affordable and cost-effective life-saving medicines and diagnostics.

Drug resistance to first-line drugs is problematic, but it is particularly concerning in pediatric populations due to a lack of diagnostic tools and standardized case definitions. Moreover, pediatric-friendly drug formulations are often not available, and treatment is lengthy with accompanying toxic side effects. Furthermore, if not completely cured, drug-resistant tuberculosis can reactivate and be transmissible later in life. There is general consensus that the lack of adherence to the current regimen is the primary driver of resistance and is the

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rationale for developing new drug regimens. Although trials for new drug regimens are beginning, regulatory approval will not be available for many years, and past experience has indicated that adult registration precedes therapeutic pediatric trials. Thus, the potential for host-directed therapies to reduce the length of treatment or the toxic side effects must move forward to address adherence in general, but is especially important for pediatric patients.

Tuberculosis is a disease of estimates; the true burden is unknown because many who are infected live in countries that lack resources to diagnose and provide healthcare. Autopsy studies from Africa paint a grim picture of a substantial undiagnosed burden of tuberculosis and multidrug-resistant (MDR) tuberculosis [1, 2]. The 2014 World Health Organization (WHO) annual tuberculosis report has revised the global tuberculosis estimates of new cases and deaths upward and, as more proactive screening takes place with newer diagnostics, the numbers are anticipated to rise. Thus, a more accurate picture of the true burden of disease and drug resistance will emerge as new easier-to-use, more accurate, and affordable diagnostics designed to perform with minimal infrastructure are scaled up [3] and molecular surveillance methods expand to include additional low- and middle-income countries. It has been estimated, based on immunological tests, that approximately one-third of the world's population is latently infected with *Mtb* [4]. On average, there is a 12% age-weighted lifetime risk of this asymptomatic group going on to develop active disease at some point in their lifetime in settings of low exogenous reinfection [5]. In 2013, the WHO estimated that 9 million people developed clinical tuberculosis disease and, from the pool of active disease, it is estimated that 5% of these patients harbor an MDR strain [6] requiring longer, more toxic treatment regimens. More concerning is the 9% of MDR patients who acquire or develop extensively drug-resistant (XDR) tuberculosis [6], as this severely complicates treatment. It is critical that MDR patients are monitored for pre-XDR to help curb the rising trend. Increasingly, reports from India and South Africa are emerging of nearly untreatable tuberculosis disease [7, 8]. Although all tuberculosis infections are transmitted, the majority of XDR tuberculosis cases occur as a result of drug resistance mutations that are transmitted rather than mutations that emerge under the selection pressure of inadequate drug treatment. Recent data suggest that, in places like KwaZulu-Natal, the majority of XDR tuberculosis cases may be transmitted rather than acquired [9]. Over the coming years, these estimates will change and likely increase unless a concerted effort to thwart the development and transmission of drug-resistant tuberculosis is deployed.

DETERMINING DRUG RESISTANCE IN THE FIELD

With the introduction of rifampicin and isoniazid in the 1950s, tuberculosis was a treatable and curable disease by the 1960s. Despite the availability of drugs over the past several decades, >4000 people died of tuberculosis every day in 2013 (equivalent to 11 commercial jet liners crashing) [6]. Key issues include inadequate diagnostic tools to identify who is truly infected, empiric treatment due to poor healthcare systems, and laboratory services in many high-burden countries (HBCs). According to the WHO, 3 million tuberculosis-infected people were either not diagnosed or not reported to national tuberculosis programs in 2013 [6] and likely lost to follow-up. Globally, only 8.5% of new bacteriologically confirmed tuberculosis cases and 17% of those previously treated for tuberculosis were tested for drug resistance in 2013 [6]. Recently, new insights were observed for *Mtb* rifampicin resistance through a series of compensatory mutations in other parts of the RNA polymerase outside the *rpoB* locus [10–12]. It has been suggested that even if drug pressure is removed, drug-resistant tuberculosis is unlikely to disappear due to these types of compensatory epistatic mechanisms that incur very little to no fitness cost to the bacteria. If true, the epistatic interactions between the strain genetic background, drug resistance–conferring mutations, and compensatory mutations may play a role in defining evolutionary trajectories toward multidrug resistance [13]. Moreover, programmatic challenges (eg, drug stockouts, improper drug storage, counterfeit drugs, poor adherence due to long treatment regimens and toxicity, hospitalization requirement to treat MDR tuberculosis) contribute to promote drug resistance. In addition, a better understanding of the complexity of *Mtb* infection in the lung, including different metabolic states of bacteria and phenotypic heterogeneity of bacterial population within or between lesions needs, to be taken into account [14, 15]. Thus, multiple components including bacterial biology, host tissue response to tuberculosis infection, and operational issues have complex interactions that shape the development of drug resistance for *Mtb* (Figure 1).

A number of advances over the years, such as WHO's endorsement of the GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, California) [16] and the accelerated conditional regulatory approval of 2 new tuberculosis drugs, bedaquiline (Sirtiro) and delamanid (Deltyba), have raised hopes that better tools and new drug regimens will lead to higher cure and lower relapse rates. The largest rollout of GeneXpert MTB/RIF occurred over the past 5 years in South Africa. Recently, a WHO policy update, based on a systematic review of the literature, was published [17]. Those results demonstrated that GeneXpert MTB/RIF should be used rather than conventional microscopy, culture, and drug susceptibility testing (DST) as the initial diagnostic test to diagnose pulmonary tuberculosis and rifampicin resistance in adults and children suspected of having MDR tuberculosis or human immunodeficiency virus (HIV)–associated tuberculosis. For the first time, a conditional recommendation was given to use GeneXpert MTB/RIF as an add-on test to smear microscopy in locations where MDR

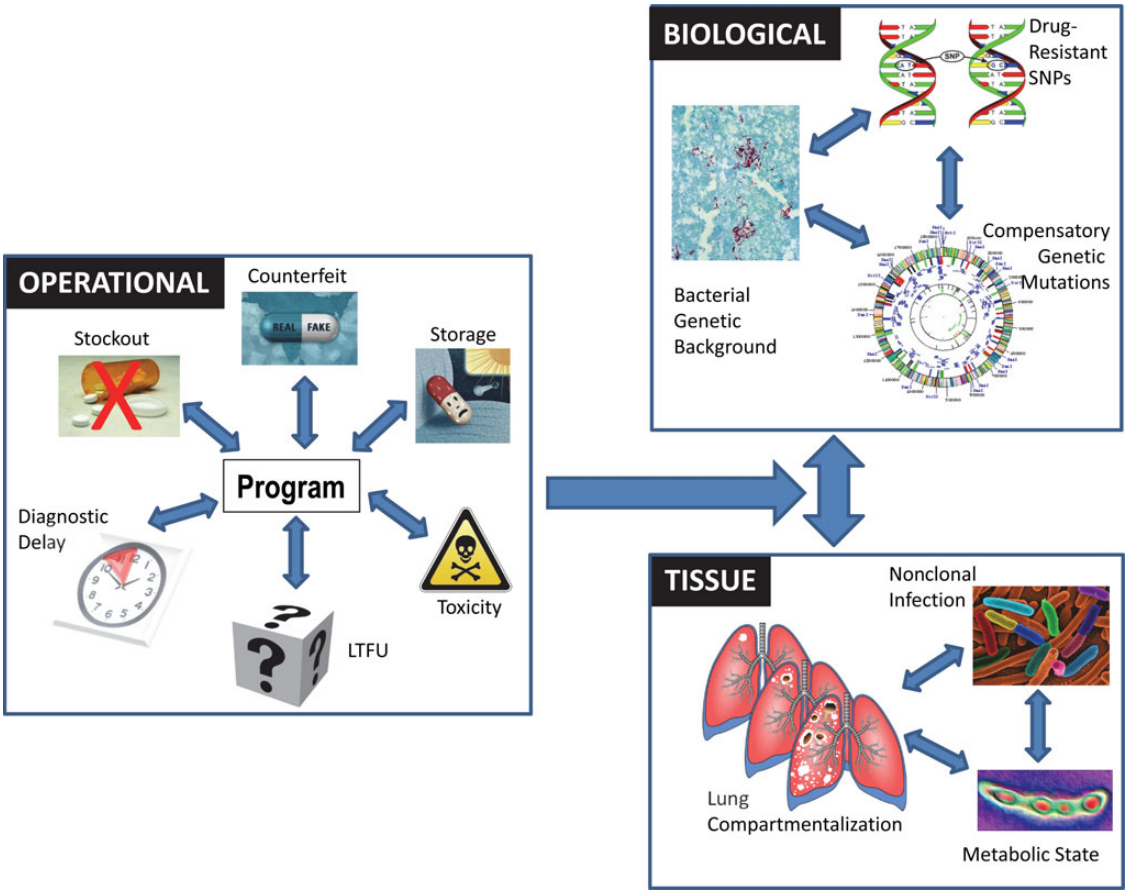

Figure 1. Drivers of *Mycobacterium tuberculosis* drug resistance. Interplay between biological forces of the bacteria and complex compensatory genetic mechanisms with host tissue and population dynamics can drive drug resistance. However, additional operational and programmatic issues conspire to accelerate and promote its establishment in a community. Abbreviations: LTFU, loss to follow up; SNP, single-nucleotide polymorphism.

tuberculosis or HIV are of less concern and especially for testing smear-negative patients who are clinically suspected of having active disease. Interestingly, an affordability and cost-effectiveness analysis of using GeneXpert MTB/RIF to diagnose tuberculosis could not be performed because of the wide variation in methodologies used, underlying assumptions, and the intended use. In addition, because treatment is empiric in many tuberculosis-endemic areas, the introduction of a diagnostic does not typically increase case notifications, nor does it improve outcome measures such as morbidity and mortality [18, 19]. For these studies, we need to take into consideration the disease state (latent, active, chronic) and the population behavioral dynamics in context with the healthcare system. In addition, alternative metrics need to be developed to capture more qualitative measures of success such as how a diagnostic test impacts community drug resistance, number of MDR patients inappropriately started on first-line treatment, and the negative impact of empiric treatment for individuals prescribed lengthy and toxic drug regimens when they do not have tuberculosis.

Recently, a series of technical, performance, and operational criteria have been released through a WHO consultation process that identified 4 high-priority diagnostic target product profiles. Specifically, this includes a community-based triage test, a non-sputum-based biomarker assay, a sputum-based assay that detects tuberculosis at the microscopy center, and a next-generation drug susceptibility test that also can be performed at a microscopy center [20]. These target product profiles provide developers a blueprint of what the field requires in regard to diagnostic performance and operational characteristics. A less-than-perfect test, if correctly implemented, can still impact the incidence [21] and reduce the spread of drug-resistant tuberculosis [22]. However, a quick result does not necessarily translate to better patient outcomes as coverage is less than perfect, only a proportion of those diagnosed are initiated on treatment, and the continuum of care is strife with inefficiencies and bureaucracy. Poor healthcare systems need to be strengthened, which goes beyond building physical infrastructure, and must include changes in policy, investments in

information technology, and political will. Political commitment is needed to ensure that healthcare and laboratory support are included as a line item in national budgets and that there are national strategic programs that monitor and evaluate health systems with defined metrics. Moreover, regulatory efforts to ensure quality diagnostics need to be adopted in many HBCs. This will level the playing field and set rules that are more transparent for diagnostic manufacturers.

DIRE NEED TO ADVANCE NEW DRUG REGIMENS

A number of phase 3 clinical trials (Ofloxacine-Containing, Short-Course Regimen for the Treatment of Pulmonary Tuberculosis, High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis, Rapid Evaluation of Moxifloxacin in Tuberculosis) substituting fluoroquinolone drugs into new first-line drug regimens have recently been completed [23–25]. Unfortunately, these trials failed to meet their primary objective of treatment shortening. Although bedaquiline and delamanid are conditionally approved by regulatory agencies, these drugs have limited availability in the field even with compassionate use agreements in place. Moreover, the use of these new drugs needs to meet clinical monitoring criteria outlined by the WHO that are difficult to comply with in many HBCs. Nevertheless, for many patients with XDR tuberculosis, these new drugs, in combination with other WHO class 5 drugs, are the only options available.

Despite the introduction of new drugs, new regimens have yet to be adopted due to regulatory hurdles, funding shortfalls, business retraction of pharmaceutical investment due to low return on investment, and bureaucratic rationale. More concerning is that the drug pipeline has fragmented with essentially no new drug classes in phase 1 clinical trials [26] and that several tuberculosis drug developers have left the field, putting more strain on already limited resources. Several drug candidates are in preclinical development, but the required preclinical toxicology, pharmacology, and regulatory work has been delayed, in part because of a lack of resources. Although this issue is a common concern for antimicrobial resistance in general, the current prospect of untreatable tuberculosis must be addressed by incentivizing drug companies, removing regulatory barriers where appropriate, increasing global funding for tuberculosis research and surveillance, and allocating resources to support drug development and clinical trials. Current global investment in tuberculosis research shows a shortfall of US$2 billion of the estimated US$8 billion per year needed to combat the world's leading curable infectious disease.

The TB Alliance initiated a phase 3 trial of pretomanid, moxifloxacin, and pyrazinamide (STAND) in 2014 and recently launched another phase 3 trial (NixTB) of bedaquiline, pretomanid, and linazolid. Although new drug regimens are a key goal, it is important to note that the correct dose of drug, especially in combination with other tuberculosis drugs, is difficult to determine. Even for older and repurposed drugs, the dose range for toxicity, pharmacokinetic (PK)/pharmacodynamic (PD) parameters, and tolerability are not well characterized. For some drugs such as rifampicin, we may have been underdosing for nearly half a century [27]. The concentration used today was chosen 40 years ago based on cost of the drug rather than on PK findings. Results from the multiple arm, multiple stage study suggest that a dose of 35 mg/kg can improve treatment outcomes for drug-sensitive tuberculosis [28]. Correct dosage for repurposed drugs such as clofazimine is not known, especially for salvage tuberculosis therapy, and the potential resistance mechanism being similar to bedaquiline needs to be better understood before it is widely implemented. New drug development tools, supported by regulatory authorities, to better inform tuberculosis drug development are needed. Recently, the European Medicines Agency issued a Qualification Opinion on the in vitro hollow-fiber model for tuberculosis (HFS-TB) [29], and language on the HFS-TB system has been included in the updated US Food and Drug Administration (FDA) Guidance on Tuberculosis Drug Development. This important drug development tool can be used by developers to understand PK/PD relationships and to inform dose selection for early clinical studies.

The release of new drugs without sufficient guidance with regard to dosage, timing, or length of treatment, and in the absence of new drug regimens, may undermine the effectiveness of these new treatment options in the future. Reports of clinical tuberculosis isolates resistant to potentially new chemical entities such as linezolid [30] are emerging, and care must be taken not to undermine their future effectiveness. This requires a significant coordination and investment in research into mechanisms and markers of drug resistance and associated diagnostics to ensure that additional resistance mutations in *Mtb* are not seeded and established among circulating strains.

The rationale for multidrug combinations is well established and has proven to reduce the development of acquired drug resistance if the patient adheres to the treatment regimen. However, some drugs have a low barrier for inducing resistance. Examples of this are the fluoroquinolones, which have been shown to promote higher mutation rates in *Mtb* [31]. It is conceivable that including multiple drugs that lower the barrier to resistance may have a contrary effect of exacerbating and ultimately contributing to drug resistance. Utilizing new tools and animal models that are vetted and endorsed by regulatory agencies will promote a clear path for pharmaceutical companies and reduce the uncertainty and the associated risk in advancing new drug regimens. Additional resources and incentives should be made available for pharmaceutical companies to more effectively work together to develop new drug regimens and diagnostics. These and other

advances are being addressed by the Critical Path to New TB Drug Regimens (CPTR). The CPTR Consortia provide an environment for stakeholders (funders, pharmaceutical industry, in-vitro diagnostics developers, governments, nongovernmental organizations, clinicians, scientists, policy makers, regulatory authorities, etc) to work together in a secure and collaborative atmosphere where the rules of engagement are well delineated.

BALANCING INSPIRATION WITH REALISTIC GOALS

Although tuberculosis cases are falling globally, the global pace of a yearly 1.5% reduction is too slow and will not meet the tuberculosis end target by 2035 [6]. Of concern are the numbers of new drug-resistant cases (3.5%), which remain unchanged globally, and that MDR tuberculosis epidemics in some countries may undermine the current elimination strategy. To begin reversing the spread of drug-resistant tuberculosis, much more needs to be done to promote infection control procedures, initiate contact tracing, and actively use DST in retreatment cases. The low coverage of DST in many countries remains one of the main constraints limiting the detection and proper treatment of MDR and XDR tuberculosis among people diagnosed with tuberculosis. A total of 29.8% (24.3%–35.3%) of patients with MDR tuberculosis have resistance to a fluoroquinolone or a second-line injectable agent [6]. These patients are in danger of developing the most difficult-to-treat XDR tuberculosis and would in many circumstances be eligible to receive regimens containing new tuberculosis drugs if those options are available.

Recently, the WHO drafted new global indicators, milestones, and targets for the post-2015 tuberculosis strategy [32]. Although this is a bold move needed to reduce tuberculosis deaths by 95% and the incidence by 90%, additional tools, including a new effective prophylactic vaccine, must be developed and implemented by 2025. However, with no known correlate of protection and in the absence of a successful vaccine candidate, a roadmap with allocated funding has not been well articulated. A more effective vaccine is a critical tool missing in the prevention toolbox, which would more cost-effectively control the tuberculosis epidemic. The experience of other fields, such as HIV, stresses this point, even though 37 FDA-approved drugs are available (http://aidsinfo.nih.gov/education-materials/fact-sheets/21/58/fda-approved-hiv-medicines) and the treatment-as-prevention concept has gathered momentum [33]. Nevertheless, workers in the HIV field have known that they cannot treat themselves out of the HIV epidemic without significantly more resources [34], and the tuberculosis field should take heed. As a first step, a global initiative working on tuberculosis vaccines, the Global Tuberculosis Vaccine Partnership, is being established to mobilize and optimize use of globally available funds to more effectively manage the vaccine pipeline.

Chronic shortfalls in funding are hampering progress on all fronts, from basic research to patient care. To make advances, biomarker and vaccine research must be given a higher priority to support more basic high-risk research and clear paths to advance to clinical trials. Better tools to identify active tuberculosis cases in all populations (especially in pediatric and HIV-infected), using different samples, with limited healthcare resources must be prioritized. In addition, better tools are needed to identify latent tuberculosis, predict when latently infected patients are in danger of progressing to active disease, and monitor patients during treatment to confirm cure and minimize relapse. The fact that inflammatory responses could also be harmful has been recently appreciated in tuberculosis [35]. Yet, pivotal work published in 2014 provided evidence that bacterial proliferation (with subsequent increase in mutational rates) and inflammation are closely linked: Patients with advanced tuberculosis disease (culture positive and comparatively more disease involvement) exhibited increased type I interferon levels along with low interleukin 1 (IL-1) levels. Balancing proinflammatory signals in patients with tuberculosis by tipping the balance to IL-1 showed in a preclinical model that bacterial load is decreased, lung damage limited, and survival increased [36]. The study also shed light on possible adverse effects of second-line drugs as they may interfere with prostaglandin E2 production [37], a key mediator in the balance between IL-1 and type I interferon responses. These and other reports suggest that host-directed therapies, in addition to the standard drug treatment regimens, may be able to alter the clinical course of tuberculosis; well-designed clinical trials are needed [38].

CONCLUSIONS

The goal of "zero" tuberculosis deaths will remain aspirational without a clear roadmap and targeted funding. A fresh look at what can be realistically achieved with the current level of funding needs to be taken. A back-to-basics approach, putting increased emphasis on a better understanding of the fundamentals of the immune response to tuberculosis, has been the approach of some funders. This has led many researchers to concentrate on areas such as host–pathogen interactions within granulomas, the mucosal immune system, and innate responses to identify key tuberculosis molecules associated with nonprogression, as well as biomarkers to better predict disease progression or monitoring treatment outcome. A safe and effective tuberculosis vaccine is >10 years away, as a candidate has not advanced beyond phase 2 efficacy trials. However, without a correlate of protection, hitting the target of a safe and effective tuberculosis vaccine candidate by 2025 is unlikely.

Finally, integrating health services for patients needs to be a priority. Tuberculosis disease and treatment involves families, not individuals, and funding needs to support wellness centers

with a wide variety of tools at their disposal rather than specific disease treatment. Tuberculosis rarely occurs in isolation and is often associated with other underlying diseases, both infectious, such as HIV and pneumonia, and noncommunicable, such as hyperlipidemia and hypertension [39]. We are just now starting to scratch the surface of the interaction with metabolic diseases such as diabetes [40]. Malnutrition and poverty contribute to diagnostic and treatment complications and will require an integrated effort to address underlying issues, including harmful economic systems, conflict, environmental factors (such as drought and climate change), and population growth [41].

Notes

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