SUPPLEMENT ARTICLE

Tuberculosis Diagnostics in 2015: Landscape, Priorities, Needs, and Prospects

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In 2015, tuberculosis remains a major global health problem, and drug-resistant tuberculosis is a growing threat. Although tuberculosis diagnosis in many countries is still reliant on older tools, new diagnostics are changing the landscape. Stimulated, in part, by the success and roll out of Xpert MTB/RIF, there is now considerable interest in new technologies. The landscape looks promising, with a robust pipeline of new tools, particularly molecular diagnostics, and well over 50 companies actively engaged in product development. However, new diagnostics are yet to reach scale, and there needs to be greater convergence between diagnostics development and development of shorter-duration tuberculosis drug regimens. Another concern is the relative absence of non–sputum-based diagnostics in the pipeline for children and of biomarker tests for triage, cure, and progression of latent *Mycobacterium tuberculosis* infection. Several initiatives, described in this supplement, have been launched to further stimulate product development and policy, including assessment of needs and priorities, development of target product profiles, compilation of data on resistance-associated mutations, and assessment of market size and potential for new diagnostics. Advocacy is needed to increase funding for tuberculosis research and development, and governments in high-burden countries must invest more in tuberculosis control to meet post-2015 targets for care, control, and prevention.

Keywords. tuberculosis; diagnostics; pipeline; unmet needs; market potential.

While much progress has been made with tuberculosis control, the World Health Organization (WHO) estimates that 9 million people developed tuberculosis in 2013 and that 1.5 million died, including 360 000 people who were infected with human immunodeficiency virus (HIV; Figure 1) [1]. Rapid, accurate diagnosis is critical for timely initiation of antituberculosis treatment, but many people with tuberculosis (or tuberculosis symptoms) do not have access to adequate initial diagnosis. In 2013, >3 million cases were missed by the health system, either because they were not diagnosed or were not notified to national tuberculosis programs [1].

Access to adequate diagnosis is particularly poor for patients with multidrug-resistant (MDR) tuberculosis and in cases of childhood tuberculosis. Globally, in 2013, the WHO estimated that 480 000 people developed MDR tuberculosis [1]. However, only 136 000 MDR tuberculosis cases were detected, with second-line treatment initiated for 97 000. Also, in 2013, an estimated 535 000 children developed tuberculosis, but the true case burden of childhood tuberculosis is likely higher. A model-based estimate suggests that the number was closer to 1 million children in 2010 [2]. Childhood tuberculosis is very difficult to diagnose, and most conventional tuberculosis tests perform poorly in this high-risk population.

In 2014, the WHO and partners announced a post-2015 tuberculosis strategy and accompanying targets with the goal of ending the global tuberculosis epidemic [3]. This ambitious strategy aims to reduce the tuberculosis incidence by 90% by 2035 (compared with the 2015 incidence). Early diagnosis of tuberculosis, including universal drug-susceptibility testing (DST), and systematic screening (active case finding) of contacts and high-risk groups are key components of this new strategy. Discovery, development, and rapid uptake of new

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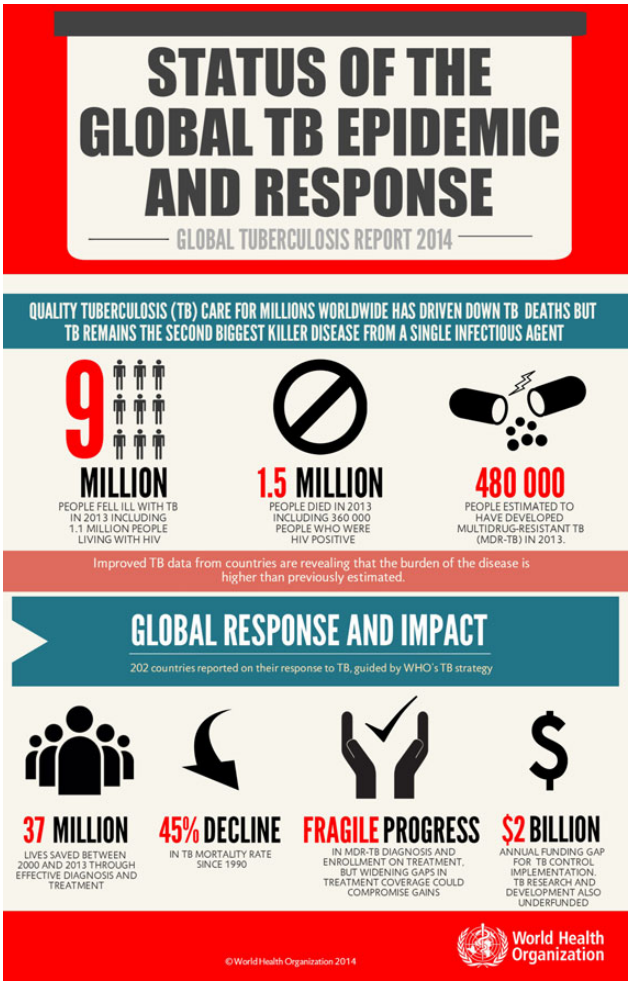

Figure 1. Status of the tuberculosis problem in 2014. The graphic is reproduced with permission from the World Health Organization (http://www.who.int/tb/features_archive/globaltb_report2014/en/).

tools, interventions, and strategies are also highlighted as important components [3].

LANDSCAPE AND PIPELINE OF TUBERCULOSIS DIAGNOSTIC TECHNOLOGIES

Although tuberculosis diagnosis in 2014 is still reliant on older tools such as smear microscopy and culture, new diagnostics are changing the tuberculosis diagnostics landscape. Worldwide, the ongoing roll out of Xpert MTB/RIF (Cepheid, Sunnyvale, California) continues to be the most important, measurable shift in the tuberculosis diagnostics landscape. According to the WHO, as of 30 September 2014, 3553 GeneXpert instruments (comprising >17 000 modules) and 8.8 million Xpert MTB/RIF cartridges had been procured by the public sector in 110 of 145 countries eligible for concessional pricing [4]. The Xpert technology is significantly more sensitive than sputum smear microscopy and can also rapidly detect rifampicin resistance with high accuracy [5].

Stimulated, in part, by the success and roll out of Xpert MTB/RIF, there is now considerable interest in new tuberculosis diagnostics. The 2014 UNITAID TB Diagnostics Technology and Market Landscape report summarized the technologies that have been endorsed by the WHO and described the pipeline of novel tools that are on or likely to enter the market [6]. As described in the UNITAID report and summarized by stakeholders such as the Foundation for Innovative New Diagnostics, the landscape looks promising, with a robust pipeline of new tools and well over 50 companies actively engaged in product development. Figure 2 shows the pipeline of tools and the expected complexity of the products under development.

In the short term, the most impressive trend is the expansion of the range of molecular technologies that could potentially replace smear microscopy [6]. As shown in Figure 3, new molecular products on the market (or in the pipeline) will compete with the Xpert technology, and some may be deployable in peripheral microscopy centers, where millions of patients are tested. This level of decentralized deployment is feasible but challenging with the Xpert technology because of technical and infrastructure issues [7–10].

In addition to rapid case detection, newer molecular tools will have the capacity to identify drug-resistance mutations and thereby help countries reach the post-2015 target of universal DST for all patients with tuberculosis, at the time of detection. With the impending introduction of new tuberculosis drug regimens (described below), this is of great significance. New drug regimens will require companion diagnostics to ensure rapid completion of the so-called test and treat approach. While newer molecular diagnostics are ideally suited to serve the role of companion diagnostics to new drug regimens, a major hurdle is the lack of high-quality validation studies of newer molecular tests. Several assays are now on the market with virtually no validation trials published on their accuracy and performance. This suggests the need for ensuring global and country-level systems for rapid validation of new tools, to ensure that such evidence is translated into policies.

In the medium term, the need for a biomarker-based, low-cost, non–sputum-based test remains an important priority for tuberculosis diagnostics at the primary care level, where the majority of people first seek care [6]. Although biomarker discovery is an active area and several potential products (eg, antigen or antibody detection tests, volatile organic compound analysis, and enzymatic detection) are under development, no test under development is likely to be on the market with policy endorsements within the next 3–5 years [11].

In the longer term, a breakthrough in biomarker discovery is necessary to identify those with latent *Mycobacterium tuberculosis* infection who are at the highest risk of progressing to tuberculosis, so that the vast pool of latently infected individuals can be successfully reduced [6]. Since molecular tests are usually not helpful for treatment monitoring, a biomarker-based test

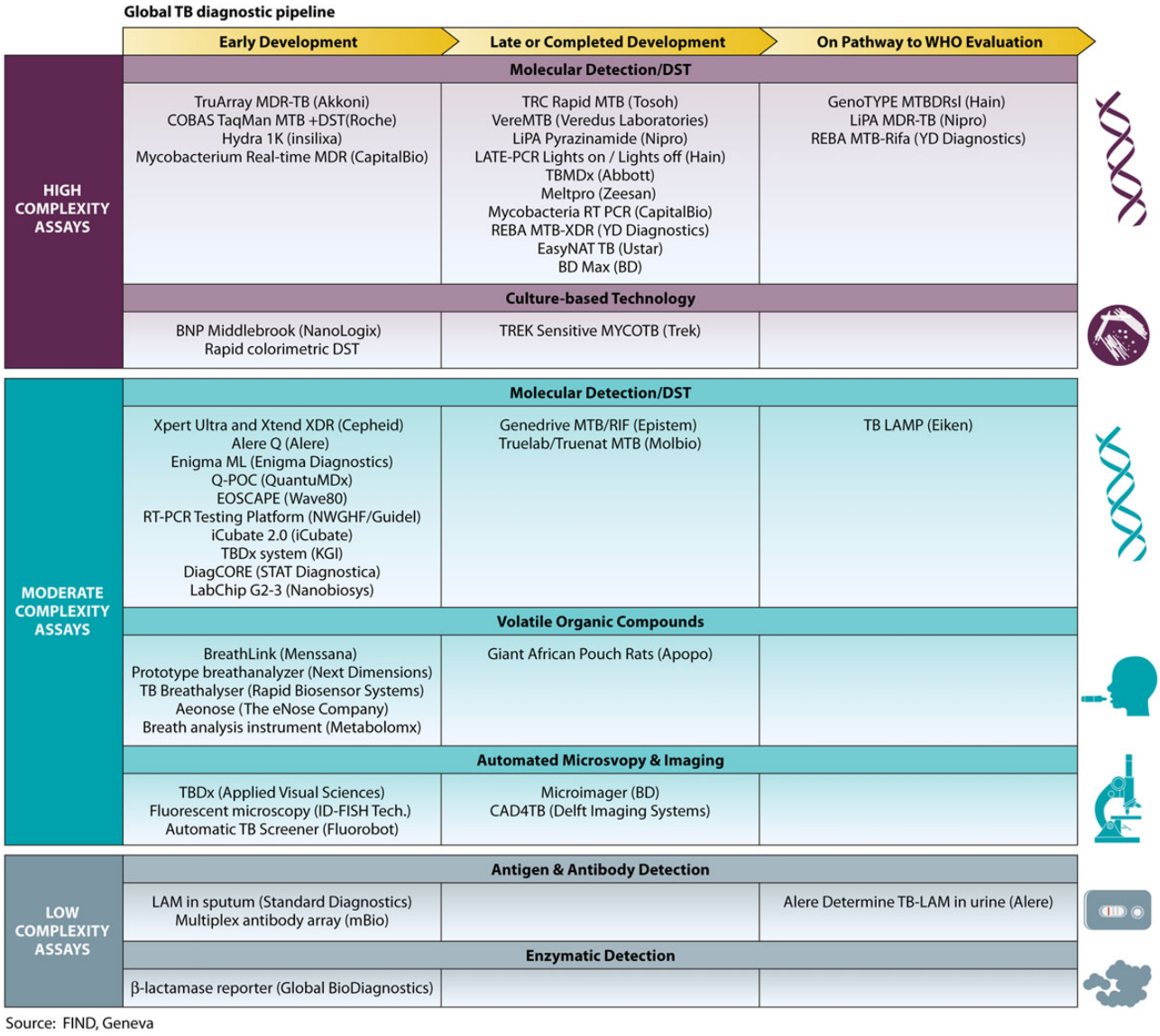

Figure 2. Current tuberculosis diagnostics pipeline listing the development phases and the types of technologies in development or evaluation. Complexity categorization was based on criteria that are used for similar diagnostics by the US Food and Drug Administration. Early development refers to prototype development after the proof-of-concept stage. Late-stage development refers to turning the prototype into a design-locked, manufacturable product. The graphic is reproduced with permission from the Foundation for Innovative New Diagnostics.

for cure will also be enormously helpful. The pipeline for such tests is currently weak, with few companies working on biomarker discovery to support research and development of such products. However, governmental and nongovernment organizations continue to fund the search for new biomarkers useful to meet the diagnostic, prognostic, and treatment monitoring needs.

NEEDS AND PRIORITIES

The ongoing roll out of Xpert MTB/RIF has had a positive influence on the tuberculosis diagnostics landscape, has attracted new investments and product developers, and has created a robust pipeline of technologies [6]. It has also ploughed the way for wider access to molecular tests and universal DST and prepared the ground for the next wave of innovative technologies. Lessons learned from Xpert implementation will be invaluable for scaling up next-generation technologies [9, 10].

However, the Xpert technology was not designed to reach lower tiers of the healthcare system or to meet all needs (eg, it cannot detect latent *M. tuberculosis* infection or resistance against multiple drugs). Despite initiatives to reduce the price, high cost continues to be a hurdle for underfunded national tuberculosis programs [12]. A recent survey of 22 countries with a

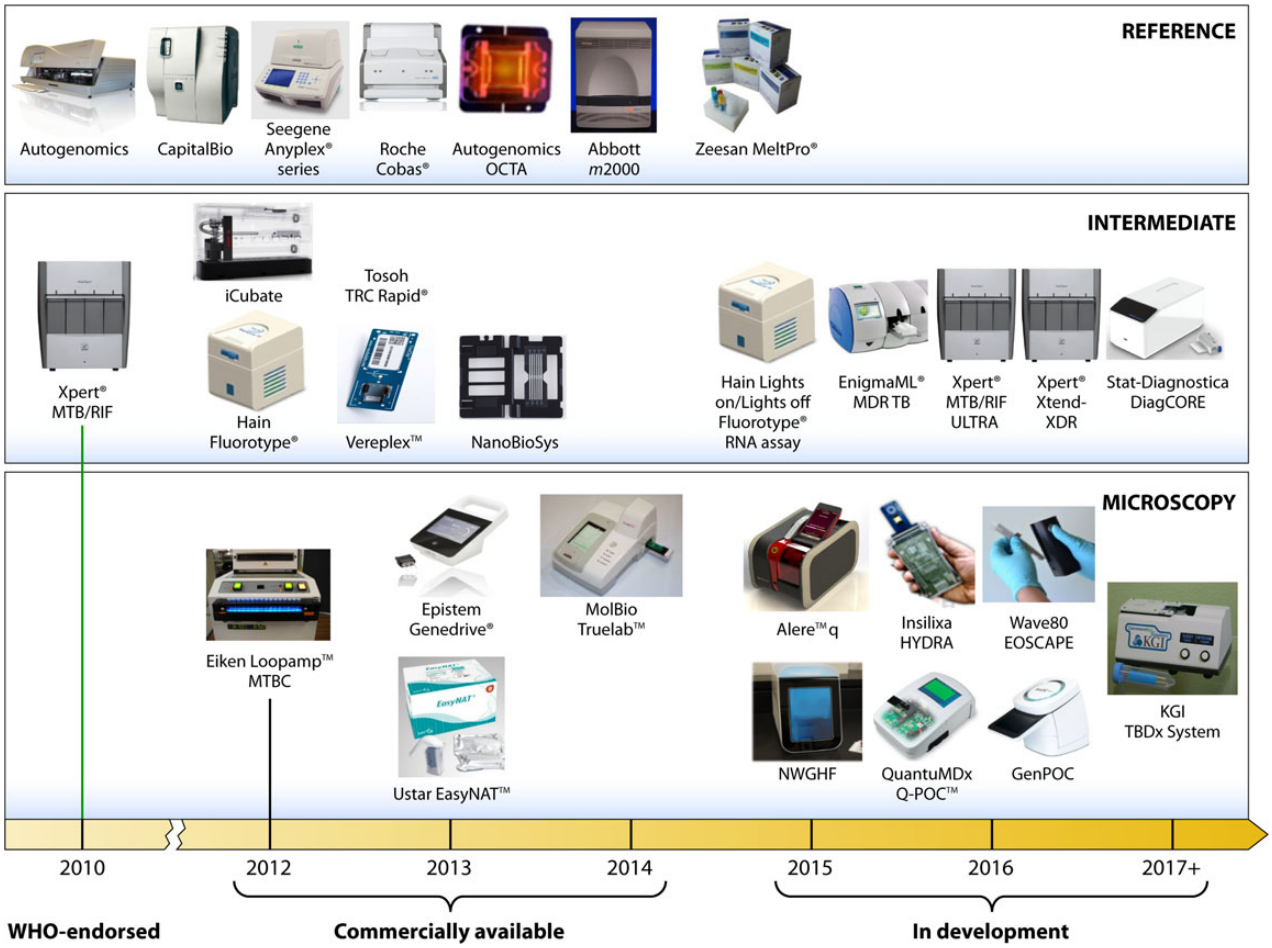

Figure 3. Pipeline of molecular diagnostics for tuberculosis, by level of deployment (ie, reference, intermediate, and peripheral microscopy laboratories). The graphic is reproduced with permission from the UNITAID (http://unitaid.org/images/marketdynamics/publications/UNITAID_TB_Diagnostics_Landscape_3rd-edition.pdf).

high tuberculosis burden (HBCs) showed that, while a majority (86%) of these countries have a policy or algorithm for use of Xpert technology, current implementation is mostly donor funded, largely dependent on testing in centralized laboratories, and primarily involves patients with presumed drug-resistance or HIV infection [13]. The survey used the ratio of smear volumes for initial diagnosis to the number of Xpert cartridges procured during a roughly similar period as an approximate index of Xpert market penetration in the public sector. The ratio in South Africa was 1.6, significantly lower than most other HBCs, where approximately 40–70 smears were performed for each Xpert cartridge [13]. This suggests that wide-scale implementation of Xpert technology has mostly occurred in South Africa, while other HBCs continue to rely heavily on smear microscopy.

A recent published study of various stakeholders helped establish the most important unmet needs and identify tools that are of highest importance. Kik et al conducted a priority-setting exercise to identify the highest priority tests for target product profile (TPP) development and investment in research and development [14]. For each of the potential TPPs, 10 criteria were used to set priorities, including prioritization by key stakeholders (eg, managers of national tuberculosis programs), potential impact of the test on tuberculosis transmission, morbidity and mortality, market potential, and implementation and scalability of the test. On the basis of this analysis, the following were identified as the highest priorities: (1) a point-of-care sputum-based test as a replacement for smear microscopy (ie, a smear-replacement test); (2) a point-of-care, non–sputum-based test capable of detecting all forms of tuberculosis via the identification of characteristic biomarkers or biosignatures (ie, a non–sputum based biomarker test); (3) a point-of-care triage test, which should be a simple, low-cost test for use by first-contact healthcare providers as a test for ruling out tuberculosis (ie, a triage test); and (4) rapid DST at microscopy centers (ie, a rapid DST).

Given the variety of unmet needs [14] and the diversity of sites where testing can occur [15], it is important for product developers to have access to (1) a clearly identified list of diagnostics that are considered high priority by the tuberculosis community; (2) well-developed, detailed TPPs for priority diagnostics, based on a consensus-building process; and (3) up-to-date market size estimations for the priority TPPs [16, 17]. These issues are addressed in subsequent articles in this supplement. The article by Denkinger et al [18, 19] describes the final TPPs that have been developed for the highest priority tests and reviewed in a consensus meeting hosted by the WHO and partners, while the articles by Kik et al [20] and Pantoja et al [21] describe the potential future market for new assays the and affordability of new tests by countries, respectively.

ALIGNMENT OF DIAGNOSTICS WITH NOVEL TUBERCULOSIS TREATMENT REGIMENS

In a recent analysis, Wells et al outlined the need for a better alignment (or convergence) between new tuberculosis diagnostics with the likely tuberculosis treatment landscape in the next 3–4 years [22]. Because of promising results in phase 2 trials, the Global Alliance for TB Drug Development and partners have launched the Shortening Treatment by Advancing Novel Drugs trial of the PaMZ drug regimen, which contains pretomanid (previously called PA-824), moxifloxacin, and pyrazinamide. If the trial is successful, by 2018, this could reduce the duration of tuberculosis therapy to 4 months [23].

For the PaMZ regimen to be implemented successfully, it is important to ensure that existing molecular diagnostics are more widely used and to develop next-generation molecular assays that can detect resistance to markers that are aligned with novel regimens such as PaMZ. This means that product developers will need better data about the molecular mechanisms of resistance. Efforts are underway (described elsewhere in this supplement by Solomon et al [24]) to develop a database of mutations associated with drug resistance and to develop strain collections to enable assessment of new diagnostic assays.

There are other new drugs, such as bedaquiline and delamanid, that have already received partial regulatory approval for use in treating MDR tuberculosis [25]. Linezolid, although not approved for MDR tuberculosis, is already being used in the field [26]. Phenotypic resistance tests for these drugs have not been established, and careful monitoring needs to take place before critical concentrations are selected on the basis of clinical data. Even though these may be new drugs to treat tuberculosis, the mechanisms of action are either similar to those of existing drugs (as is the case between bedaquiline and clofazimine), background resistance already exists (as in the case of linezolid), or they are in the same class of drugs (eg, nitroimidazoles). Thus, it will be important to monitor for drug resistance during treatment. This will be especially important for treatment of extensively drug-resistant (XDR) tuberculosis, since the number of effective drugs available is much smaller. With such limited choices, the likelihood of treating patients with XDR or pre-XDR tuberculosis with a suboptimal regimen becomes much higher. As a result, this also increases the chance of developing resistance to the remaining active drug(s), thus reducing the effectiveness of new compounds in our toolbox.

Also, as part of prelaunch activities, it is important for countries to establish sample collection and transport systems, laboratory information management systems, mechanisms for external quality assurance for molecular and DST tools, and information and communication technologies for rapid reporting of results, case notification and linkages to care, and supply chain and logistics management [27]. Greater use of existing tests (like Xpert technology, liquid cultures, and line probe assays) and drug regimens will enable national tuberculosis programs to develop and fine-tune these systems and then transition to newer drug regimens and companion diagnostics by 2018.

ONGOING EFFORTS TO IMPROVE CHILDHOOD TUBERCULOSIS DIAGNOSIS

Although identifying tuberculosis cases continues to be a challenge in adults, active tuberculosis in several special populations, including pediatric patients, is more difficult to diagnose because of extrapulmonary involvement, paucibacillary aspects, or nonspecific presentation. In low-income and middle-income countries, difficulties arise towing to the similarity of symptoms to other common diseases, including bacterial pneumonia and viral infections, and to comorbid conditions, such as malnutrition. As a result, tuberculosis treatment is often performed empirically, which leads to underdiagnosis or, in some cases, to overdiagnosis and subsequent inappropriate prescription of drugs to patients without infection. Underdiagnosis leads to increased morbidity and mortality due to tuberculosis. Overdiagnosis results higher treatment costs to tuberculosis programs and potentially contributes to the development of drug resistance due to poor adherence. This is further complicated by the fact that the time to symptom resolution in young children treated for tuberculosis requires >2 months in the majority of cases [28]. As a result, symptom-based diagnosis may not resolve when these patients are receiving tuberculosis treatment and may suggest MDR tuberculosis. Additional clinical evaluations would be needed to determine the etiology or whether to consider switching to a drug-resistant tuberculosis regimen.

Despite the need for better diagnostics, funding for pediatric diagnostics is woefully inadequate compared with that for adult diagnostics, which itself continues to lag behind funding for HIV diagnostics. Unfortunately, diagnosis and treatment is not a priority for many funding organizations since pediatric

tuberculosis has a limited impact on disease at the population level. Therefore, control of tuberculosis in children is considered to be of limited programmatic value. The original directly observed treatment, short-course strategy was heavily focused on identifying infectious cases by use of sputum smears, and this led to national tuberculosis programs placing greater emphasis on adults.

Despite these challenges, interest in diagnosing and treating tuberculosis in children has gained momentum over the past few years. This includes standardizing case definitions of tuberculosis in children [29], developing and manufacturing first-line tuberculosis drugs in appropriate child-friendly formulations (through the Global Drug Facility), and inclusion of children in clinical trials [30]. This last point is significant because disease end points, pathogenesis, and drug metabolism is different in children and infants, compared with adults [30]. Several funding institutions have recently supported research initiatives to identify new biomarkers that could be used to diagnose tuberculosis in children. These biomarkers include a combination of biological measurements at the protein or genomic level that reflect an interaction between the host and the pathogen [31, 32].

As the results of these investments become available, a greater need will be placed on further evaluating potential biomarkers, using a set of well-characterized and highly pedigreed samples. Unfortunately, standard sets of samples from children exposed to and suspected of having tuberculosis are not widely available. Although many private collections exist, standardized definitions, collection, processing, and storage of samples have not been adopted. Consequently, evaluations of potential diagnostic biomarkers may be discrepant despite the use of existing pediatric samples. Moreover, additional challenges in documenting tuberculosis exposures with clinical symptoms consistent with infection and lack of funding have hampered current efforts to store these samples in biorepositories. In addition, low sample volumes typically obtained from children and infants prevent wide dissemination of material to large numbers of investigators. Finally, there is a need not only for well-defined samples from children with tuberculosis, but of samples from children in tuberculosis-endemic areas who have clinical signs consistent with tuberculosis but are free of the disease. This is most critical because the performance of a biomarker will need to be able to differentiate *M. tuberculosis* infection from a number of other conditions that typically present with similar clinical signs in tuberculosis-endemic areas.

MARKET FOR NEW TECHNOLOGIES

Product developers need information on market size and potential, to make investment decisions [17]. A recent series of studies have tried to quantify the current served available market value of tuberculosis diagnostics. A survey of 22 HBCs showed that they performed 77.6 million sputum smears in >42 000 microscopy centers annually, with a cost of $137 million [33]. Of these, 61% were performed in the BRICS countries. A detailed analysis of what Brazil spent on tuberculosis diagnosis showed that, during 2012, an estimated 2.4 million tuberculosis diagnostic tests were conducted, resulting in an estimated overall market value of $17.2 million [34]. The public sector accounted for 91% of the test volume and 88% of the market value. Smear microscopy was the most commonly used test (1.3 million tests [55%]), with an estimated cost of $3.7 million. A total of 302 761 cultures were performed, representing 13% of the test volume and 40% ($6.9 million) of the market value. On average, $208 was spent on tuberculosis diagnostics for every Brazilian patient with notified tuberculosis during 2012 [34].

Another analysis estimated the expenditure on tuberculosis diagnosis in South Africa during 2012–2013 [35]. This study showed that South Africa has a sizeable tuberculosis diagnostic market in terms of volume and value. In 2012, during Xpert scale-up, the public and private sectors performed 9.2 million tuberculosis diagnostic tests, with an estimated total cost of $98 million. The public sector accounted for 93% of the overall test volume and value, with microscopy and culture accounting for the majority of tests performed. In 2013, the public sector market value increased to $101 million (a 10% increase over 2012). While Xpert volumes increased by 166%, total tuberculosis test volumes decreased by 12%, compared with 2012 values [35]. Similar analyses are being completed for China and India.

On the basis of these analyses, Kik et al [20] made projections about the potential available market for the 4 priority TPPs that have been developed. They found that, of the 4 TPPs, the greatest potential available market in terms of value would be for a sputum-based tuberculosis detection and DST upfront test. A test that can be deployed at lower levels of the healthcare system and used for detecting (or ruling out) all forms of tuberculosis, such as a biomarker test or a triage test, would have the largest potential market volume.

The publication of technology and market landscape reports, TPPs, and market size estimates are all intended to stimulate increased investments in the area of tuberculosis diagnostics. While the overall trend is positive (as seen in the number of products and companies), tuberculosis research and development as a whole continues to be severely underfunded.

FUNDING FOR TUBERCULOSIS RESEARCH AND DEVELOPMENT AND FOR PRODUCT EVALUATION

A 2014 annual research and development funding report by Treatment Action Group, showed that the world invested only one third of the required $2 billion needed every year for new

drugs, diagnostics, and vaccines to fight the global tuberculosis epidemic effectively [11]. In 2013, $676.6 million was spent on tuberculosis research. Of the $9.8 billion in funding required for tuberculosis research during 2011–2015, as estimated by The Global Plan to Stop TB, only 20% of this amount has been mustered at the end of 2013. The Treatment Action Group report registered a significant funding shortfall across every category of tuberculosis research: basic science, diagnostics, drugs, vaccines, and operational research. The report also showed that, during 2013, research and development spending by pharmaceutical companies for tuberculosis was among the lowest recorded levels. These funding trends have great consequences for biomarker and basic research work that is critically important for novel tuberculosis tests and biomarkers for childhood and extrapulmonary tuberculosis, markers for treatment monitoring, and markers for predicting progression from latent *M. tuberculosis* infection to tuberculosis. In addition to increasing funding for research and development, donors, governments, and private industry must find a way to increase funding for product evaluation. Otherwise, we may see a plethora of new tools with few data to support or refute their incorporation into policy.

CONCLUSIONS

In 2015, the tuberculosis diagnostics landscape looks promising, with a robust pipeline and several companies actively engaged. However, new diagnostics have yet to reach scale, and there needs to be greater alignment between diagnostics and novel tuberculosis drug regimens. While the pipeline is robust for molecular tools, the pipeline is less robust for other products, especially biomarker-based tests for cure, triage, and predicting progression of latent *M. tuberculosis* infection. Several initiatives, described in this supplement, are ongoing to stimulate product development and policy, including assessment of needs and priorities, development of TPPs, compilation of data on resistance-associated mutations, and assessment of market potential for new diagnostics. If these initiatives are complemented with increased advocacy for funding for tuberculosis research and development with greater engagement of countries in evaluation of new tools, and if governments in HBCs actively scale-up new diagnostics and drug regimens, it will help make the post-2015 vision of a tuberculosis-free world a reality.

Notes

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