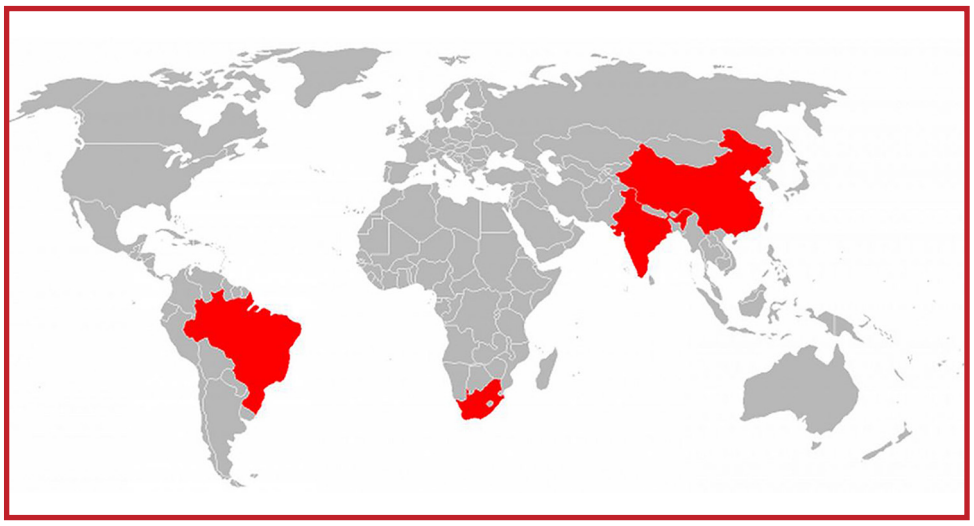

TB Diagnostics Market in Select High-Burden Countries: Current Market and Future Opportunities for Novel Diagnostics

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Centre international de TB McGill

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Publication supported by
UNITAID Secretariat
Chemin de Blandonnet 10 – BIBC III – 8th Floor
1214 Vernier
Switzerland
T +41 22 791 55 03
F +41 22 791 48 90
unitaid@who.int
www.unitaid.org

UNITAID is hosted and administered by the World Health Organization

This report was prepared by Carole Jefferson (consultant, Pennsylvania, USA), Claudia Denkinger (FIND, Geneva, Switzerland), Janet Ginnard (UNITAID, Geneva, Switzerland), Sandra Kik and Madhukar Pai (McGill International TB Centre, Montreal, Canada). Sources of funding include: Bill & Melinda Gates Foundation and UNITAID.

Graphics provided by J. Paciolla of ICA Design (Glen Rock, Pennsylvania, USA)

Acknowledgements: We would like to thank the entire TB Market Analysis Consortium, especially the in-country partners and National Tuberculosis Program staff in China, India, Brazil and South Africa for their contributions to the primary market analyses that are used in this report.

Cover photo credits: FIND (operator using Xpert); MSF (women at microscope); I. Moss/UNITAID (man in microscopy center)

Conflicts of interest statement: Madhukar Pai has no financial or industry conflicts to disclose. He serves as a consultant to the Bill & Melinda Gates Foundation, on the access advisory committee of TB Alliance, and on the scientific advisory committee of FIND. Claudia Denkinger is employed by FIND, a nonprofit organization that collaborates with industry partners, including Cepheid, Hain and BD, for the development, evaluation, and demonstration of new diagnostic tests for poverty-related diseases. Janet Ginnard is employed by UNITAID, an innovative financing mechanism that aims to increase access to critical health products. Carole Jefferson and Sandra Kik have no financial or industry conflicts to disclose.

CONTENTS

Abbreviations

ADA	adenosine deaminase
CRI	colorimetric redox indicator assay
CT	computerized axial tomography
DST	drug susceptibility testing
EPTB	extrapulmonary tuberculosis
HIV	human immunodeficiency virus
HRZE	isoniazid, rifampin, pyrazinamide and ethambutol
IGRA	interferon-gamma release assay
LED	light-emitting diode
LPA	line probe assay
LTBI	latent TB infection
MDR	multi-drug-resistant TB
MODS	microscopically observed drug susceptibility
MRI	magnetic resonance imaging
NAAT	nucleic acid amplification test
NRA	nitrate reductase assay
NTP	National TB Program
PaMZ	pretomanid, moxifloxicin, and pyrazinamide
PCR	polymerase chain reaction
PTB	pulmonary tuberculosis
SSM	sputum smear microscopy
TB	tuberculosis
TDR	WHO Special Programme for Research and Training in Tropical Diseases
TPP	target product profile
WHO	World Health Organization

Executive summary

Tuberculosis (TB) is a curable disease yet remains a global health problem with 9 million cases, including an estimated 550 000 in children, occurring in 2013. It is the second most common cause of death in adults from an infectious disease. An estimated 480 000 people developed drug-resistant TB. China, India and South Africa have the highest number of TB cases globally and, together with Brazil, account for 46% of all new cases. The majority of TB cases in high-burden countries are diagnosed by smear microscopy on a sputum specimen at peripheral microscopy centres. However, smear microscopy has low sensitivity and cannot detect extrapulmonary TB or drug-resistant TB. Thus there is a need for simpler, more rapid and more effective diagnostics that are designed for use in peripheral settings. In addition, universal drug-susceptibility testing (DST) – now included in the End TB Strategy – requires countries to scale-up DST capacity. New TB drugs are now on the market, and shorter, novel drug regimens are expected to be introduced by 2018. These regimens will require the use of diagnostics specifically designed for new regimens.

Test developers and manufacturers interested in entering the TB diagnostic market need data on current market size, both global and country-specific, on prioritized unmet diagnostic needs, and on estimated market opportunity associated with these needs. This report focuses on current and future markets in four high-burden, emerging economies – Brazil, China, India and South Africa. These four countries offer tremendous opportunities for new TB diagnostics, in part due to their national commitment to TB control in the face of high TB burdens, increased investments in new technologies, and growing economies. This report builds on a previous global market assessment by FIND and the World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases (TDR), published in 2006, and provides an updated snapshot of the TB testing landscape that has rapidly evolved in the past decade. WHO endorsed seven new TB diagnostic tools from 2007 to 2013, and there are several novel assays in the development pipeline. Thus, an updated analysis is warranted.

Based on a series of country-specific analyses of the served available market, the vast majority of TB diagnostics in Brazil and South Africa are used in the public sector, while India has a very significant private sector. In China, the majority of individuals with presumptive TB seek diagnosis in hospitals. There is a sizeable TB diagnostic market in the combined public and private (or hospital) sectors in these four countries. The more than 88 million tests performed during 2012-13 include the use of a variety of products to diagnose the disease and monitor the progress of treatment. China used the highest number of diagnostic tests (44.2 million), with India a close second (32.8 million), followed by South Africa (9.2 million) and Brazil (2.4 million). The served TB diagnostic market value of these four countries was estimated at US$ 480 million per year, with the market in China amounting to US$ 294 million; South Africa, US$ 98 million; India, US$ 71 million; and Brazil, US$ 17 million. The predominant diagnostic test across the four countries in 2012-13 was sputum smear microscopy, consisting of 54.9 million tests with a market value of US$ 87 million.

WHO has endorsed newer and more rapid diagnostic tests, including the Xpert® MTB/RIF assay that combines TB detection with rifampicin resistance testing. Over 10 million Xpert® MTB/RIF tests have been pro-

cured since the WHO endorsement of the product in 2010. While Xpert® MTB/RIF has shown much higher sensitivity than smears, and has significantly increased the detection of drug-resistant TB, the technology has limitations – including cost and the need for infrastructure (e.g. continuous power and temperature control) – and therefore cannot be widely used in most microscopy centres.

New diagnostic products are needed to combat the TB epidemic. The tests with highest priority are 1) a rapid sputum-based test for detecting pulmonary TB at the microscopy level; 2) a rapid non-sputum-based test for detecting all forms of TB; 3) a community-based triage test for use by first-contact health-care providers to identify persons who need further testing; and 4) a rapid drug susceptibility test for use at the microscopy level. All four tests are needed for use in decentralized peripheral settings rather than in reference or intermediate laboratories. If tests are to be successfully used in peripheral settings, they must take account of the lack both of infrastructure and of basic laboratory equipment and expertise. Target product profiles (TPPs) were developed for each of these high-priority tests. Today, no test on the market meets the key characteristics outlined in the product profiles, but novel tests will most likely be on the market within five years. Therefore, the potential available market in the year 2020 was estimated for these four priority products.

With key characteristics of the high-priority tests established, up-to-date estimates of potential market size can be used to engage developers in bringing needed diagnostics to market. While the analysis of the served available market acts as a baseline, the potential available market indicates future market opportunities in Brazil, China, India and South Africa for new diagnostics addressing each of the four product profiles.

The market potential varies according to the penetration of the test into decentralized settings and the patient populations or types of TB it detects. These variations are reflected in the different 2020 market opportunity scenarios for Brazil, China, India and South Africa outlined in this report. Each test has multiple scenarios. As a baseline, the sputum-based test for detecting pulmonary TB has an annual four-country market potential of 12 million tests with a market value of US$ 48–71 million, while the non-sputum-based test for detecting all forms of TB has an annual market potential of 16 million tests with a market value of US$ 65-97 million. The community-based triage test has the highest annual four-country market volume of 18 million tests but a lower market value of US$ 18-35 million due to its desired low price. The rapid drug susceptibility test has the most variability because of the different ways in which the test can be configured as well as how many and which drugs are included in the assay. If the test offers TB detection followed by drug susceptibility testing as a follow-up reflex test, it has an annual four-country market potential of 12 million tests for detection, valued at US$ 59 million, and an additional market for the follow-up drug susceptibility testing of 1.5 million tests valued at US$ 15 million.

The market potential for any of these tests may increase or decrease according to how well key TPP characteristics are met. For example, the market potential increases when the tests are expanded into more peripheral settings than microscopy centres or if the tests detect both pulmonary and extrapulmonary TB. Market opportunity can grow when volumes increase due to a focus on finding undiagnosed cases, especially in view of the number of persons with presumptive TB who need to be tested to find one TB case. Repeat testing for treatment monitoring will also enhance the market opportunity. The push towards universal DST will be a market driver as it is a key component of the End TB Strategy, but few people currently have access to DST. Additional opportunity also exists beyond these four countries. Another 18 high-burden countries contribute an additional 35% of the world's TB cases detected, with all other countries accounting for the remaining 19%. This represents an additional market opportunity that is likely to be at least double the estimates given here for these four countries.

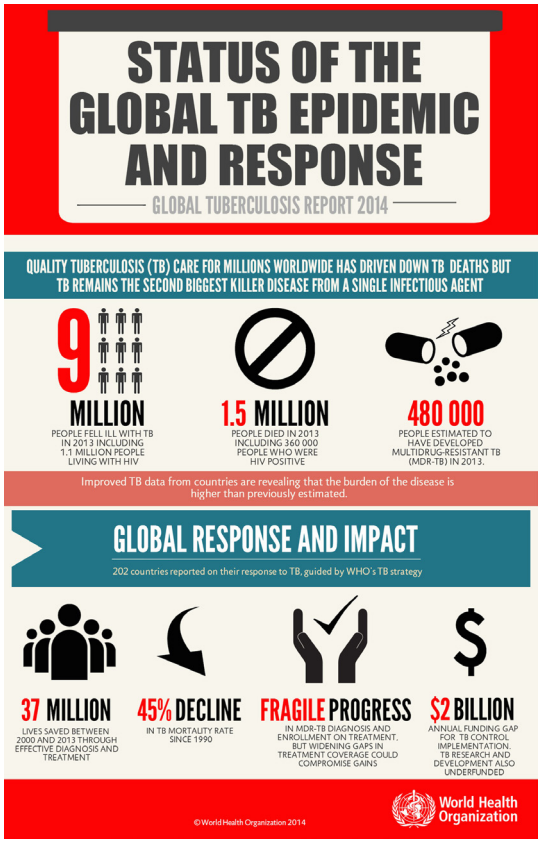
The market for TB diagnostics is evolving as new technology is introduced. Each of the four priority tests described has the potential to impact the market opportunity for the other three, as well as for current tests in the market. While there will be a market for each of these novel tests, there may be overlap in the intended target populations that benefit from the test. As a result, there could be competition between products that meet different product profiles, as well as competition between products that meet the same product profile. Overall, the competitive landscape and the way in which the TB diagnostics market

evolves depend on many factors, including when each test enters the market, what other tests are in use, the added value of each new test, and the roll-out of new TB drugs and regimens. It is very unlikely that one new diagnostic test will be sufficient or adopted for all initial diagnoses. Rather, countries are likely to adopt a mix of technologies on the basis of their patient population, drug resistance rates and use at different levels of the health-care system.

The market today consists of patients currently being served with existing diagnostic tests, albeit ones with limitations. Replacing smear microscopy and other initial diagnostic tests with an improved diagnostic, and introducing tools for universal DST, is a goal of many TB stakeholders, including countries, funders, and clinicians. Novel tests that meet these needs could have a significant market opportunity in the four profiled countries alone.

Introduction

Although typically curable, tuberculosis (TB) remains a global health problem. In 2013, 9 million people, including an estimated 550 000 children, had TB and 1.5 million people died. An estimated 480 000 people developed multi-drug-resistant TB (MDR TB).[1] Although progress has been made in increasing the TB cure rate, about one third of all TB cases are still either not being diagnosed or not being notified.



Source: WHO, Geneva
http://www.who.int/tb/features_archive/TB_Situation.jpg?ua=1

TB covers a spectrum of disease, ranging from latent infection to active disease. It is estimated that about one third of the world's population is infected with *Mycobacterium tuberculosis* but without symptoms of active disease (latent tuberculosis infection, or LTBI). Only about 10% of individuals with LTBI cannot contain the infection and develop active disease; this percentage is higher in patients with weak immune systems (as in the case of persons living with HIV).[2] Active disease is primarily a disease of the lungs (i.e. pulmonary TB) but it can affect any other organ of the body (i.e. extrapulmonary TB). A subset of TB infection and disease is due to drug-resistant strains of TB.

The majority of active pulmonary TB cases in high-burden countries are diagnosed by smear microscopy on a sputum specimen at peripheral microscopy centres.[3] However, smear microscopy has suboptimal sensitivity, particularly in certain patient populations such as children and HIV-infected individuals who often have difficulty providing a good-quality sputum sample and may have a low bacterial load.[4,5] In addition, drug resistance cannot be detected and extrapulmonary TB, which can account for 15–25% of all TB cases, is often missed by sputum smear microscopy.[6] The sensitivity of smear microscopy has also been shown to vary substantially from setting to setting, primarily because of variations in skills and time taken to evaluate a smear.[7]

Several new diagnostic tests have been endorsed by the World Health Organization (WHO) over the last eight years and have been introduced in many countries, thus improving those countries' diagnostic capabilities.

Table 1. TB diagnostic technologies endorsed by WHO

Year	Technology reviewed by WHO
2007	Commercial liquid culture and drug susceptibility testing (DST) tools, and rapid speciation strip tests
2008	Molecular LPAs for first-line anti-TB drug resistance detection
2010	LED microscopy
2010	Selected noncommercial DST methods (MODS, CRI, NRA)
2010	Xpert® MTB/RIF
2013	Policy update on Xpert® MTB/RIF with extension to childhood and extra-pulmonary TB

Source: UNITAD, Tuberculosis diagnostics technology and market landscape, 3rd edition. Additionally, WHO policies are available at http://www.who.int/tb/laboratory/policy_statements/en/.

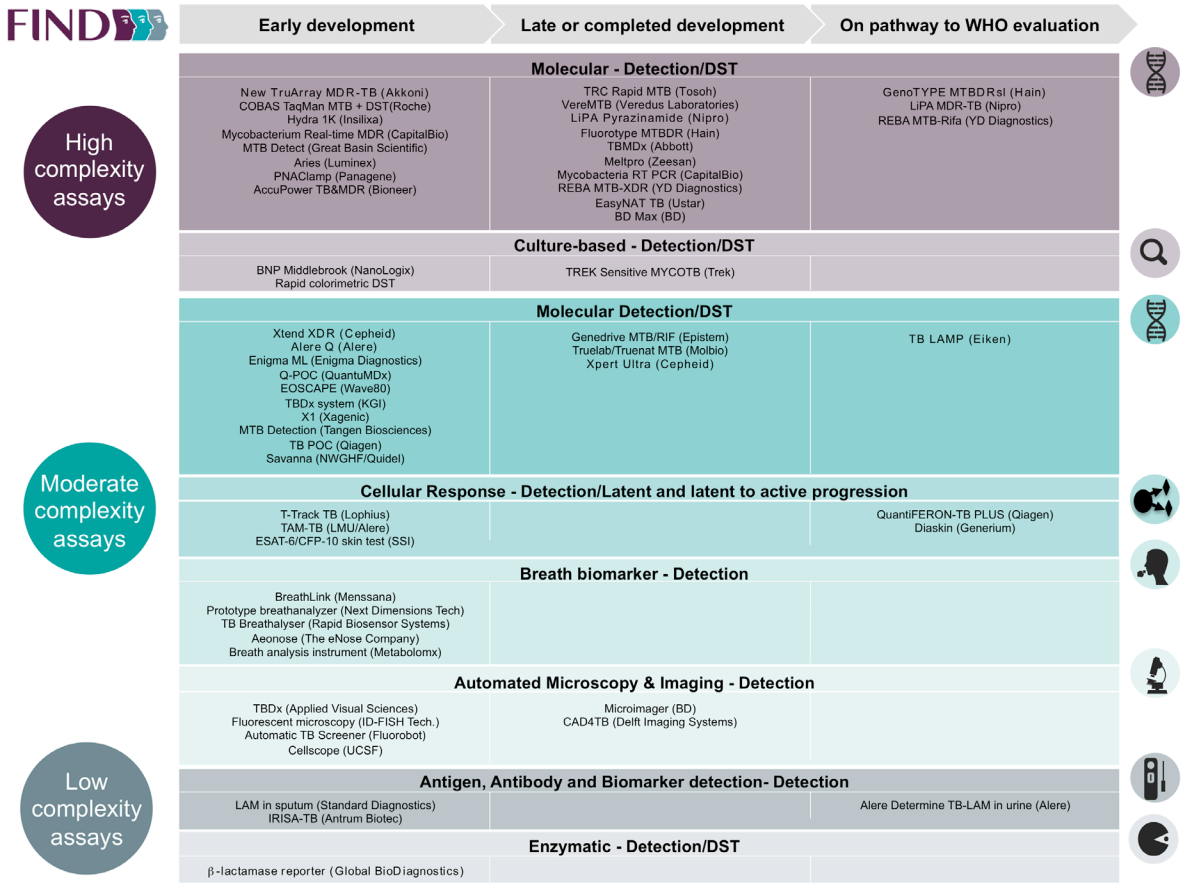
However, gaps persist between available technologies and diagnostic needs. Technologies such as liquid culture and line probe assays (LPAs), both endorsed by WHO, are increasingly used but remain more appropriate to reference laboratories and have limited impact on patient important outcomes.[8,9] A novel technology, the Xpert® MTB/RIF assay (Cepheid Inc., Sunnyvale, CA, USA), which was endorsed by WHO in 2010, yields rapid results, has greater accuracy in diagnosing active TB compared to sputum smear microscopy and can determine rifampin resistance. The assay is being adopted in many high-burden countries,[10,11,12] with over 10 million cartridges in over 100 countries procured at special concessional pricing.[13] The assay has increased the detection rates of rifampin resistant cases by five fold in some cases.[14] This demonstrates that new technology is being adopted, and is making a difference. However, Xpert® MTB/RIF also has limitations. The use of Xpert® MTB/RIF continues to be hampered by its high cost. In addition, the placement of Xpert® MTB/RIF in more peripheral settings is limited because of lack of needed infrastructure, such as a temperature-controlled environment and uninterrupted power supply (Appendix 4).[15] Additionally, health-care workers in these settings often have limited laboratory skills and lack basic laboratory equipment.[16] This means that Xpert® MTB/RIF cannot be deployed in the majority of microscopy centres. This creates a market opportunity for novel TB diagnostic tests.

The TB diagnostics gap

There remains an unmet need for simpler, more effective diagnostics that are designed for use in peripheral settings. Without the right diagnostic tools available near where patients seek care, 3 million people with TB are not diagnosed, early diagnosis is often not achieved and the WHO goal of TB elimination will not be reached.[17] Universal drug-susceptibility testing is another key component of the first pillar of WHO's End TB Strategy.[18] There are new TB drugs on the market (e.g. bedaquiline and delamanid) as well as new drugs and treatment regimens (e.g. PaMZ) in the pipeline (both first-line and second-line regimens). This creates a need for drug-susceptibility tests to be aligned with new regimens,[19] which enable regimen selection at the point of care and individualized therapy. The exact drugs and dosages in new regimens are not yet confirmed and will be determined by successful outcomes of ongoing clinical trials.[20]

New tests are needed at all levels of the health-care system, especially in peripheral settings such as microscopy centres, health posts and clinics. There is increasing interest in the TB diagnostic market by industry and, many products are in development. The growing pipeline of new TB diagnostics is shown in Figure 1, and described in detail in UNITAID's *Tuberculosis diagnostics technology and market landscape* report.[21]

Figure 1. Global TB diagnostic pipeline



Source: FIND, Geneva, 2015.

The focus on the TB diagnostics market occurs for a variety of reasons. Funders, including multinational donors, and high-burden countries are interested in improving access for patients in order to reduce diagnostic delays and curb TB transmission.[22] Clinicians and patients also need better and faster diagnostics to inform treatment decisions. Industry is interested in developing new, commercially viable products that fulfill unmet diagnostic needs.

The need for market information

On the basis of input from over 25 companies and test developers, the top questions focus on market size, market potential and which unmet diagnostic needs have the highest priority. Prior to entering the market, test developers need information to assess commercial viability and support the business decisions that direct product development.[23] A 2013 survey of over 90 industry stakeholders by FIND showed that 26% currently offered TB assays and 67% were planning to offer new or improved TB assays in the next five years. The survey found that decisions made by product developers on what assays to prioritize for development were informed by:

- time to return-on-investment
- global market size
- country-specific market size
- clear product requirements and user needs.

The first comprehensive market report on TB diagnostics by FIND and the WHO Special Programme for Research and Training in Tropical Diseases (TDR) dates back to 2006. It covered topics ranging from the disease manifestation, details about diagnostics in use and their current market, the need for improved diagnostics and what those markets might be.[24] The 2006 report showed a robust global market:

- Worldwide about US$ 1 billion was spent on TB diagnostics in 2004.
- One third of this amount, or US$ 326 million, was spent in low- and middle-income countries, where 73% of global testing occurred.
- Smear microscopy and chest X-ray were the most common tests (83 million and 47 million tests respectively) in low- and middle-income countries.
- Smear microscopy and chest X-ray eclipsed the use of more complex tests such as nucleic acid testing and culture.

However, the diagnostics landscape has changed significantly since 2006, due in part to WHO's endorsement of new technologies and their roll-out in countries, greater engagement of product developers, and major investments by funders and donors. In addition, while the 2006 report provided regional and global figures for the TB diagnostics market, test manufacturers would like country-specific data on current and potential markets, especially for countries with the highest burden of the disease and emerging economies.

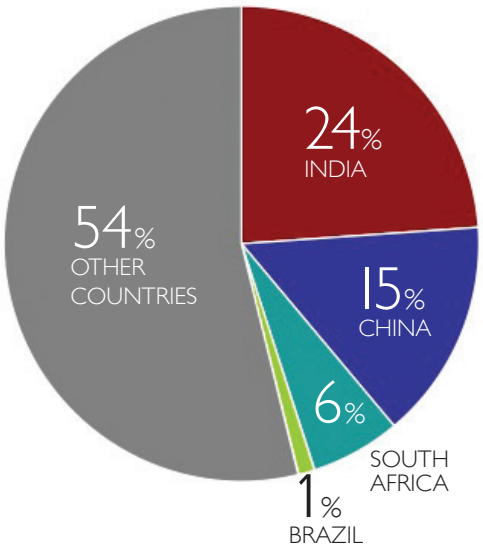
The commercial incentive for new diagnostics

A more recent assessment was done on the current state of TB diagnostics routinely in use in 2012–2013 in Brazil, China, India and South Africa. This assessment of the served available market was led by the McGill University, funded by the Bill & Melinda Gates Foundation, and done in collaboration with multiple partners, including the country's National TB Program (NTP), FIND and UNITAID. Details of the assessments can be found in the individual country publications.[25,26,27,28] A summary of the data from all four countries is presented in the next section of this report.

Together, Brazil, China, India and South Africa offer tremendous opportunities for new TB diagnostics, in part due to their national commitment to TB control in the face of high TB burdens, growing economies and increased investments in new technologies.[29] In November 2013, ministers of health from Brazil, China, India and South Africa issued a statement in Cape Town, South Africa, agreeing, among other things, to collaborate on improving systems to find and treat patients with TB.[30] China, India and South Africa have the highest number of TB cases globally and, together with Brazil, these countries accounted for 46% of all new active TB cases in 2012 (Figure 2). These countries alone have a combined population of almost 3 billion with a combined GDP of US$ 13 trillion.[31] They are large-scale purchasers and the public sectors are mainly government-funded, thus making them less reliant on donor funding. They have the potential to facilitate increased investments in new technologies and to introduce their use across different market

segments – i.e. the public sector and, in some countries, the hospital or private sectors. South Africa, in particular, has shown the ability to rapidly adopt new technology such as the Xpert® MTB/RIF assay and accounts for about 50% of the 10 million cartridges procured through 2010-2014. Companies from China and India have already launched in their respective counties new, domestic TB diagnostics, suggesting increased R&D at the country level.

Figure 2. Percent of New Active TB Cases in 2012 Showing Contribution of Brazil, China, India and South Africa to Global Total



Source: Global tuberculosis report. WHO. 2013

Priorities for new TB diagnostics

The TB community has expressed a need for a variety of different products and tools to combat the many aspects of TB disease in different patient populations.[32] A recent publication by Kik et al. outlined the priority-setting exercise for nine different test needs, including a rapid sputum-based TB diagnostic test with or without drug susceptibility testing (DST), a biomarker-based test, a triage or screening test, next generation DST, a treatment monitoring test, a diagnostic test for children and a predictive test for latent TB. By asking different stakeholder groups to rate relevant criteria – such as a test's impact on TB transmission and mortality, its perceived need, market potential, scalability and implementation at the point of care – the following tests emerged as top priorities for new product development over the next five years:[33]

- a rapid sputum-based test for detecting pulmonary TB at the microscopy level with or without rapid DST for selection of first-line regimen-based therapy (this was later separated into two different tests)
- a rapid non-sputum-based test for detecting all forms of TB at the microscopy level and at point of care
- a community-based triage test for use by first-contact health-care providers to identify persons who need further testing.

In addition to having a clearly defined list of diagnostics considered to be of high priority by the TB community, product developers need to understand the key characteristics for each diagnostic test in order to guide development decisions. Target product profiles (TPPs) were developed for each of the above priority diagnostics.[34] TPPs align the end-user needs with targets that test developers can use to design products. Key characteristics include, but are not limited to, how and where the test will be used and the intended

decision it should inform (e.g. treatment initiation, referral, follow-on testing), the type of specimen to use, operational conditions and accuracy of the test.

Reflecting the priorities defined above, four specific TPPs were developed (with the DST and the detection test at the microscopy level divided into two TPPs):

- a rapid sputum-based test for detecting pulmonary TB at the microscopy level
- a rapid non-sputum-based test for detecting all forms of TB at the microscopy level and at point of care
- a community-based triage test for use by first-contact health-care providers to identify persons who need further testing
- a rapid DST for use at peripheral centres.[35]

In April 2014, the Global Laboratory Initiative and the Stop TB Partnership's New Diagnostics Working Group convened a consensus meeting to agree on the proposed detailed TPPs for the identified high-priority diagnostics. The TB community stakeholders at the meeting included country representatives, researchers, clinicians, implementers and donors. The stakeholders reached consensus on the majority of the key characteristics of these four novel diagnostics, and the detailed TPPs are available in a WHO meeting report[36] and a subsequently published, with additional resources, in a special supplement in the *Journal of Infectious Diseases*.[37]

The 2012–2013 individual country market assessment shows that there is an ongoing and sizeable annual TB diagnostics market worth an estimated US$ 480 million in Brazil, China, India and South Africa combined.

With key characteristics of the high-priority tests being established, up-to-date estimates of potential market size can be used to attract developers and engage them in bringing needed new diagnostics to market. While the analysis of the served available market acts as a baseline, the section on the potential available market describes future market opportunities in Brazil, China, India and South Africa for new diagnostics that address each of the four TPPs.

Current served available market in Brazil, China, India and South Africa

The 2012–2013 individual country market assessment shows that there is an ongoing and sizeable annual TB diagnostics market worth an estimated US$ 480 million in Brazil, China, India and South Africa combined. This market covers a wide range of diagnostic products. A single person with TB may encounter multiple diagnostics, from initial diagnosis to treatment monitoring.

Methods

To help understand the current market, assessments were conducted to obtain the volume and cost of the TB diagnostic tests in use in both the public and the private sectors in each of the four countries. The data are based on the diagnostic tests being routinely used in the public and private or hospital sectors in 2012, except in India for which data are from 2013. Data collection covered tests for the diagnosis of latent and active TB, drug susceptibility and treatment follow-up. The types of tests included were:

- tuberculin skin tests
- interferon-gamma release assays (IGRAs)
- smear microscopy
- serological antibody-based tests
- culture
- identification or speciation tests
- nucleic acid amplification tests (NAATs) including line probe assay and Xpert® MTB/RIF
- phenotypic drug susceptibility tests
- adenosine deaminase (ADA) test.

Imaging tests (e.g. chest X-rays, CT/MRI), and tests such as histopathology were not included in this analysis, because they are used for a variety of conditions, and most countries do not have systems for capturing those test volumes.

Information on test volumes and total costs per test (i.e. cost-in-use) was collected from end-users, as reported or estimated by national TB programmes for the public sector (a bottom-up approach) For the private sector (in Brazil, India and South Africa) and the hospital sector (in China) data were collected through surveys of a selection of private laboratories and hospitals. Sales data on commercial tests were collected from producers and distributors of diagnostic tests (a top-down approach). Estimation and extrapolation were done when needed, usually on the basis of some form of primary data collection or extracted from published reports. The mix of data collection methods varied by country and can be found in the individual country publications.[38] The costs of tests done in the public sector included costs

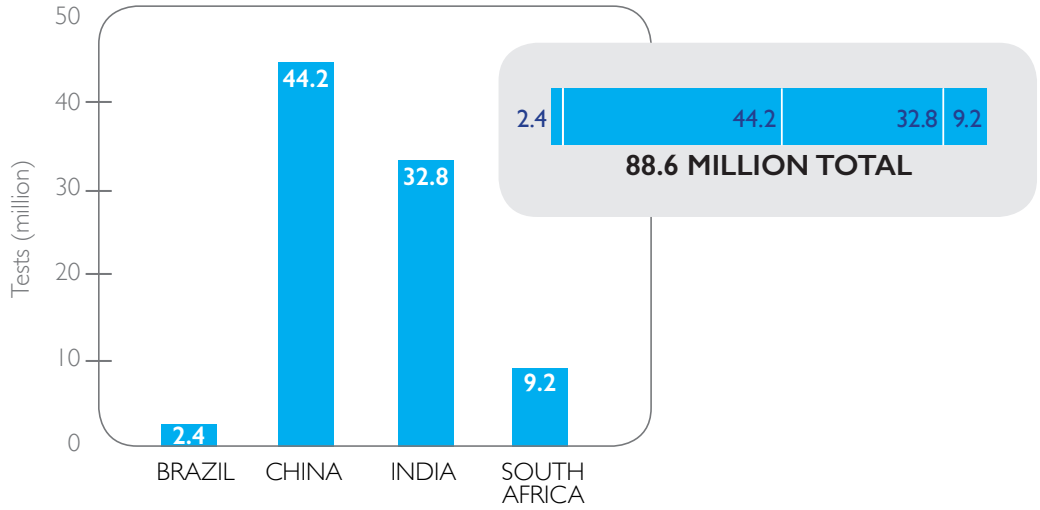
of reagents and consumables, instruments, labour and overheads. The overall market value for the combined public and private sectors was obtained by multiplying the overall test volumes of each test by the public sector costs per test. For example, the smear microscopy test volume in both sectors in South Africa was 4 994 000 tests. The total cost per test, including reagents and consumables, labour and laboratory overhead, was US$ 5.94, resulting in a smear microscopy market value of US$ 29.6 million. The total TB diagnostic market value for each country was the sum of the individual tests market value.

Results

A significant volume of TB testing is done (across all types of tests, for all indications) in these four countries, with over 88 million tests performed. China has the highest number of diagnostic tests (44.2 million), with India being second (32.8 million), followed by South Africa (9.2 million) and then Brazil (2.4 million) (Figure 3). The number of tests used in each country is a reflection of the population size, burden of disease, coverage of or access to testing, and diagnostic algorithms in place. The choice of tests mainly reflects diagnostic algorithms, and NTP budgets. Individual test volumes can be found in Table 2.

Figure 3. TB Test Volume in 2012* by Country

* India in 2013



Sum of all TB tests for all indications

The predominant diagnostic test across all four countries was sputum smear microscopy. Ziehl-Neelsen was the predominant (> 95%) smear method in the public sectors in Brazil and India. China used this method 88% of the time in both sectors combined, while South Africa always used the fluorescent method in the public sector. The 54.9 million smear tests include initial smears, typically two or three per person being evaluated for TB, and multiple smears for follow-up to monitor treatment in diagnosed TB patients. When considering the different tests typically carried out for diagnosis of active TB and treatment monitoring (smear, culture, NAAT, serology), the total test volumes are 71 million. Although the test volumes data were not attributed to specific tiers in the health-care system, the following assumptions can be made:

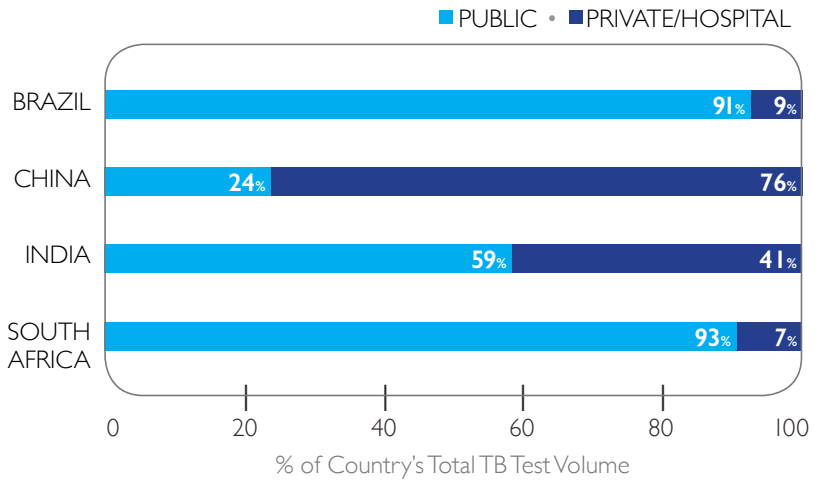
- 6 million tests were performed at the reference laboratory level (cultures, speciation, and LPA/PCR)
- 5 million tests were performed at the district level (Xpert® MTB/RIF and ELISA-based serological tests). This assumes that half of all serological tests are ELISA-based.
- 60 million tests were performed at the microscopy centre level (smears and rapid serological tests).

The test volume numbers represent actual tests performed rather than the number of people tested. The number of people with presumptive TB who received an initial diagnostic test was estimated to be 7.9 million in India, 6.2 million in China, 2.1 million in South Africa and 0.97 million in Brazil, for a total of 17.1 million people.

The analysis reflects each country's different market sectors (Figure 4). Over 90% of TB diagnostics in Brazil and South Africa are conducted by the public sector, while India has a very large private sector (i.e. outside of the Revised National TB Control Programme) where 41% of the tests are performed. China has both a public sector that is served by the Chinese Center for Disease Control and Prevention (China CDC) and a hospital sector that consists of designated TB hospitals and general (non-designated) hospitals where individuals with presumptive TB seek diagnosis. For the purposes of this report, we considered the hospital market in China to be a "private sector". The hospital sector in China accounts for 76% of the country's TB diagnostics volume. In countries with a large private or hospital market, it is typical for patients to move between sectors and to receive diagnostics in both.[39]

Figure 4. Share of TB Test Volume in 2012* by Sector

* India in 2013

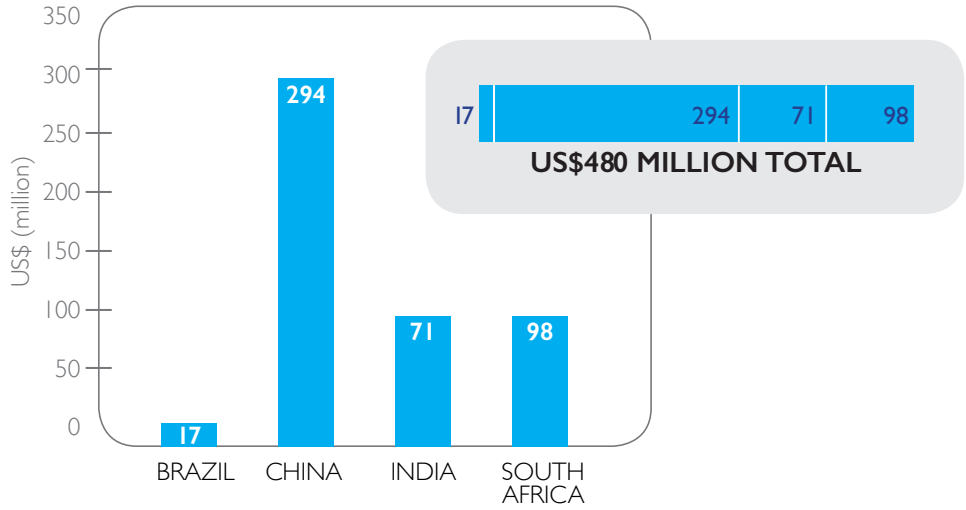


Based on all TB tests for all indications

The total combined (public and private) TB diagnostic market value in 2012 (2013 for India) was estimated at US$ 480 million, with China contributing US$ 294 million, South Africa US$ 98 million, India US$ 71 million and Brazil US$ 17 million (Figure 5). China has the highest market value, which is mainly a reflection of the higher test costs and larger volume of more expensive tests (e.g. IGRAs) that are being done in hospitals. India's market value is a mix of high volumes of low-cost tests (i.e. smears) in the public sector and an increasing volume of higher-priced tests in the private sector.

Figure 5. TB Test Value (US$) in 2012* by Country

* India in 2013



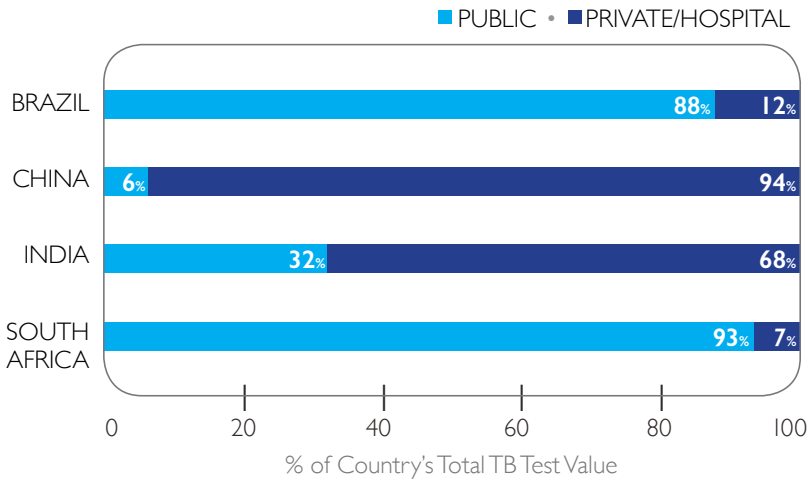
Based on the volume of all TB tests for all indications x total cost-in-use (e.g. reagents, instrument, labor and overhead)

Although Brazil has a significantly lower market size, due to the lower TB burden, it still spends only a slightly lower amount per TB case diagnosed (US$ 208) than do South Africa (US$ 280) and China (US$ 327), while India spends US$ 51.

In South Africa and Brazil the public sector value is substantially larger than the private sector (93% and 88% respectively) while the value of the private sector accounts for the majority of the diagnostic market value in India (68%) as does the hospital sector in China (94%) (Figure 6). The market estimates used the public costs for the overall market and therefore may underestimate the private market value (of particular importance in countries where a significant number of TB suspects seek an initial diagnosis in the private sector).

Figure 6. Share of TB Test Value in 2012* by Sector

* India in 2013



Based on all TB tests for all indications

Sputum smear microscopy, the predominant diagnostic test, has a market value of US$ 87 million in the four countries combined. When all tests typically performed for the diagnosis of active TB and treatment monitoring (smear, culture, NAAT and serology) are considered together, their combined market value is US$ 251 million.

Newer tests, especially NAATs, are expected to grow in importance, and thus in value, particularly in middle-income countries such as the four under review. As an example, from 2010 to 2014, these four countries acquired 6.7 million Xpert® MTB/RIF cartridges, with 5.6 million in South Africa and 1.1 million in the other three countries combined[40]. However, for now, sputum smear will remain a mainstay, especially in many low-income countries. It is important to note that, beyond these four countries, sputum smear microscopy is a sizeable market. For example, a previous market assessment that focused on the public sector alone in all 22 high-burden countries demonstrated that significant volume and value are added to the smear market when all high-burden countries are considered[41] (see side bar).

Sputum smear microscopy market in 22 high-burden countries

In the public sector alone of 22 high-burden countries, over 77 million smears, mostly using the direct Ziehl-Neelsen method, are performed annually (including 15.9 million tests for treatment follow-up) in 43 827 microscopy centres. This is from a recently published market assessment that examined smear microscopy in the public sector in high-burden countries. Sputum smear microscopy remains the predominant test for initial diagnosis in high-burden countries where about 80% of the global TB disease burden occurs. The public sector market volume in the 22 high-burden countries combined is 61.7 million smears performed for initial diagnosis on an estimated 31 million patients. Around 50% of the tests are carried out in Brazil, China, India and South Africa, which clearly represent an important market for new technologies. Initial smear tests have a market value of US$ 109 million. In addition, another 15.9 million smear tests are carried out for the monitoring of treatment outcomes. Several high-burden countries – notably Bangladesh, Cambodia, India, Indonesia, Nigeria, Pakistan, Philippines and Uganda – have a sizeable and even dominant private sector, which was not included in this assessment of all 22 high-burden countries. Therefore the actual market may in fact be larger than estimated.

Evolving markets

The TB diagnostics market is rapidly evolving as new technologies are introduced. The use of older technologies may be reduced when newer technologies are adopted. The impact of new technology on the market depends on how a country incorporates new tests into its diagnostic algorithm and how quickly the changes are implemented and funded. An example of rapid adaptation of a new technology is the nationwide scale-up of the Xpert® MTB/RIF assay in South Africa. In 2012, South Africa was in the process of scaling up Xpert® MTB/RIF as the initial diagnostic test instead of smear microscopy. In 2013, this transition was completed and, as a result, the total test volume in the public sector decreased by 12% from 8.5 million to 7.2 million. This change was due mainly to a reduction in smears (4.7 million in 2012 compared to 2.5 million in 2013) and some reduction in LPAs and culture. The reduction in overall test volume is in part due to a single Xpert® MTB/RIF test replacing the typical two or three smears per person. In that same period the use of the Xpert® MTB/RIF increased by 166% (1.9 million in 2013 compared to 0.8 million in 2012). As a result, South Africa's total market value for the public sector increased by 10%, from US$ 91 million to US$ 101 million. Brazil is also in process of adopting Xpert® MTB/RIF but its impact on the Brazilian market is not known at this time. In India, the private sector volume of Xpert® MTB/RIF was 26 620 in 2013, and this number increased by 175% in 2014,[42] again showing a rapidly evolving market.

Health care worker operating Xpert. Photo credit: FIND.

Serology (antibody-based) tests represent another recent example of changes in usage patterns. While serological tests were performed in significant numbers in the private sector in India in 2011, a recommendation against their use by WHO led India to implement a ban in 2012. It was estimated that 5.6 million serology tests were performed throughout India's private sector in 2011.[43] Their use reduced to 1.2 million tests in 2013, and further reductions have occurred in 2014. However, serology remains a popular test in the Chinese hospital sector with 7.9 million tests performed in 2012. Their use in Brazil and South Africa is limited.

In summary, there is a sizeable market in terms of volume and value that spans a broad range of TB diagnostic tests. This current assessment of the served available market is a useful baseline as the market evolves with increasing use of emerging technologies. Further change in the market is to be expected with the launch of new tests that are currently in development.

Table 2. Test volume and market value of public and private sectors combined

Test	Brazil (2012)		India (2013)		China (2012)		South Africa (2012)		Total	
Test	# (000)	Value US$ (000)	# (000)	Value US$ (000)	# (000)	Value US$ (000)	# (000)	Value US$ (000)	# (000)	Value US$ (000)
TST	725	4279	8942	10 000	1460	2581	1164	11 711	12 291	28 571
IGRA	Not routine	Na	170	7300	1885	139 313	12	475	2067	147 088
Serology	ND	ND	1244	12 800	7942	25 173	ND	ND	9186	37 973
SSM	1316	3748	21 134	17 800	27 489	35 669	4995	29 646	54 934	86 893
Culture (liquid + solid)	303	6892	502	5400	2415	27 772	1631	24 280	4851	64 244
ID/speciation	Na	Na	79	300	27	139	36	409	142	848
Xpert® MTB/RIF	21	381	194	2400	ND	ND	784	17 210	999	19 991
LPA	Not routine	Na	134	2400	124	10 801	362	10 941	620	24 142
PCR	0.6	28	379	12 300	261	4137	16	258	657	16 723
DST 1st (liquid + solid)	18	1832	8	200	-	-	38	1373	64	3405
DST 2nd (liquid + solid)	0.7	91	Na	Na	-	-	20	976	21	1067
DST 1st and 2nd (liquid + solid for China only)	-	-	-	-	907	47 069	-	-	907	47 069
ADA	Na	Na	Na	Na	1670	1476	108	522	1778	1998
Totals	2384	17 250	32 786	70 800	44 180	294 130	9165	97 800	88 516	479 980

#(000) = number of tests performed in thousands

Na = No data available, ND = not done, Not routine = not routinely done

TST = tuberculin skin test; IGRA = interferon gamma release assay; SSM = sputum smear microscopy; LPA = line probe assay; PCR = polymerase chain reaction; ADA = adenosine deaminase; DST 1st and 2nd = drug susceptibility test for first-line and second-line drugs.

Note: Some numbers for individual tests may vary slightly from previous publications due to rounding.

Future potential available market for new TB diagnostics in Brazil, China, India and South Africa

Need for market opportunity information on new high-priority tests

Test developers and manufacturers interested in entering the TB diagnostic market need information on new test characteristics and their market opportunity. TPPs were developed on four high-priority novel tests and the TB community reached consensus on most of the key characteristics outlined.

Currently, no test on the market meets all these key characteristics but novel tests will most likely become available within five years. The potential market in four high-burden countries with emerging economies (Brazil, China, India and South Africa) highlights a viable market for TB diagnostics. Up-to-date potential market size estimates, as well as clear product requirements, influence product development decisions and can assist developers to establish a solid business case for bringing needed diagnostics to the market.

Top four priorities for new TB diagnostic tests:

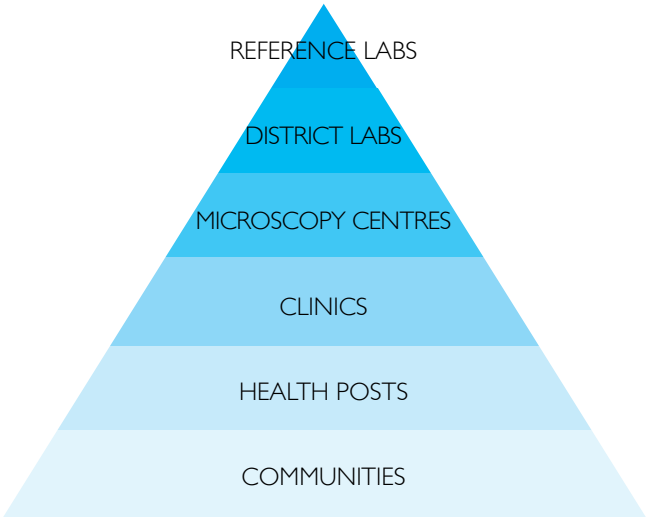
- rapid sputum-based test for detecting pulmonary TB (smear replacement)
- rapid non-sputum-based test for detecting all forms of TB at the microscopy level and point of care (biomarker test)
- community-based triage test to identify those who need further testing
- sputum-based rapid detection and drug susceptibility test for use at peripheral centres.

Levels of the health-care system

Health-care systems where TB diagnostic tests are used are often seen as having different "tiers" or levels, which can be represented by a pyramid. There are fewer, more centralized facilities (i.e. reference laboratories) at the top of the pyramid, and more decentralized facilities (i.e. microscopy centres, clinics and health posts) at the bottom, as represented by Figure 7. The lower tiers are where patients typically first seek care. The bulk of TB diagnostic testing occurs in microscopy centres.

Given essential differences between the various levels of the health-care system, a range of TB diagnostic tests is appropriate. For example, a more complex test requiring longer processing time or batched samples may be viable in centralized reference laboratories with improved infrastructure and high daily throughput. On the other hand, a simple rapid test with few resource requirements is essential for use in more decentralized settings. The choice of test and where it is performed can vary by country. The highest needs for novel tests identified in the prioritization exercise are those that can be used in lower health-care settings. Wherever testing occurs, it is of utmost importance to link the test results to clinical decision-making.

Figure 7. Levels of the Healthcare System for TB Diagnostic Testing



Infrastructure decreases at each lower level of the pyramid

Table 3. Definition of decentralized settings

Setting	Description
Microscopy centre	Current settings where smear microscopy is done by laboratory technicians
Clinics with laboratory	Setting with a basic laboratory facility where other tests are performed (e.g. HIV or malaria rapid tests) but currently not sputum smear microscopy or other TB tests. Tests are performed by laboratory technicians. It has a similar infrastructure to that of a microscopy center.
Health post	Setting where patients seek care but where no laboratory facility is present. It may also be known as a primary care clinic and is staffed by doctors, nurses or clinical officers.
Community	Setting within the community where patients live but not necessarily a setting for health care. It may also not be a fixed location as some community health-care workers move to various locations. Health-care workers perform testing in the community (e.g. tests for pregnancy, anaemia).

How target product profiles influence market opportunity

Each of the priority TPPs outlines the target population to be tested (i.e. adults or children), the goal of the test (i.e. diagnose pulmonary TB or extrapulmonary TB), the appropriate setting for use (i.e. the level of health-care system) and the test characteristics – all of which influence the potential market opportunity. The TPPs describe both optimal and minimal characteristics of the tests. All four of these new tests are to be used in decentralized peripheral settings, rather than in reference or intermediate laboratories, and to provide actionable results on the same day the test is performed. They are intended as tests that can be used at or near the point of care, and the goal is to help make treatment decisions in the same visit or the same day.

Certain operational characteristics – including infrastructure requirements such as temperature control, uninterrupted power supply and laboratory equipment – determine whether a test can be implemented in decentralized peripheral settings. The market potential increases when new tests can also be used in settings that are lower or more peripheral than microscopy centres (such as clinics, health posts or community care centres) as this should lead to improved access resulting in more patients being evaluated for TB.

Another factor that has an impact on the market potential is whether the test can be used solely for the diagnosis of pulmonary TB or for both pulmonary and extrapulmonary TB. If the test can detect only pulmonary TB, the market will be smaller than if the test can be used to detect both pulmonary and extrapulmonary TB.

Children with TB are currently drastically under-diagnosed. Diagnosing pulmonary TB in children is a challenge as they often cannot produce sputum and children frequently have extrapulmonary TB. A test to detect TB (both pulmonary and extrapulmonary) in children is likely to require an easily accessible specimen other than sputum. If a test can be used to detect TB in children in addition to adults, its market size increases regardless of where in the health-care tiers the test is implemented.

New regimens for TB treatment are being studied, and the outcomes will reflect which drugs should be included in a novel DST assay. The convergence of test development with regimen development is necessary in order to protect new drugs and drug regimens from rapidly resulting in resistance development (particularly when only three drugs are being used). The current first-line regimen includes isoniazid, rifampin, pyrazinamide and ethambutol (HRZE). An alternative regimen evaluated for first-line therapy includes pretomanid, moxifloxicin, and pyrazinamide (PaMZ), is being explored and most other considered new regimens include fluoroquinolones and pyrazinamide. How well any novel DST test is aligned with new treatment regimens will impact its market potential.

Patients in a MDR-TB ward. Photo credit: FIND.

Methodology for assessing the potential available market for new TB diagnostics in Brazil, China, India and South Africa

It is assumed that at least some of these novel tests will become available in the next five years. For this reason the future market opportunity in Brazil, China, India and South Africa was estimated for the year 2020. The initial step was to determine the potential available market for 2012 – 2013 using country-specific data, and then to apply each country's population growth rate (increasing) and TB prevalence rate of change (declining) to calculate the market opportunity in 2020. The market potential was determined using 2012 data that are readily available from WHO reports, data from the country's national TB programme and from the assessment of the served TB diagnostic market. The calculations took into account the number of prevalent and notified cases, the percentage of pulmonary TB and extrapulmonary TB, the estimated number of paediatric cases, and the ratio of people tested in order to detect one TB case. As new tests may alter the diagnostic algorithm, the potential market was determined on the basis of the number of people tested rather than the number of existing tests done.

The market opportunity volume (number of tests) was assessed separately for each of the four novel tests and takes into account how many patients might be tested in total, assuming one test per patient. The range of the market value (in US$) is based on the projected volume of each test multiplied by the lowest and highest price points contained in the product profiles (see Appendix). The exception is the TB detection + DST test as no consensus was reached on its price points and therefore prices from affordability studies were used. The prices used in all market potential estimates are all considered to be ex-works and do not include shipping, import/customs duties, or operational costs. This varies from the current served market value that did include other costs making up the total cost-in-use. The market potential for each novel test was estimated for different scenarios according to where the test would be implemented, its intended target population or the type of TB it detects, using the optimal and minimal criteria outlined in the TPP. For more details on the methods used, refer to the Appendix and to a recent supplement in the *Journal of Infectious Diseases*.[44]

Potential available market in 2020 in Brazil, China, India and South Africa for new TB diagnostics consistent with target product profiles

Adoption and scale-up of new technology can occur rapidly, as seen in South Africa with the implementation of Xpert® MTB/RIF. Despite this, primary data show that smear microscopy is still the mainstay of diagnosis in most countries other than South Africa. This means that there is a viable market opportunity for novel tests to replace existing diagnostic technologies. In Brazil, China, India and South Africa combined, the number of people in 2012 with presumptive tuberculosis receiving an initial diagnostic test was 31.6 million across all sectors (public, private and hospital). This is only 63% of individuals who should have been tested in order to find all TB cases in these countries.

The 2020 annual potential market in four high-burden countries (Brazil, China, India and South Africa) was calculated for each of the four high-priority tests based on the TPPs in the WHO consensus report.[45]

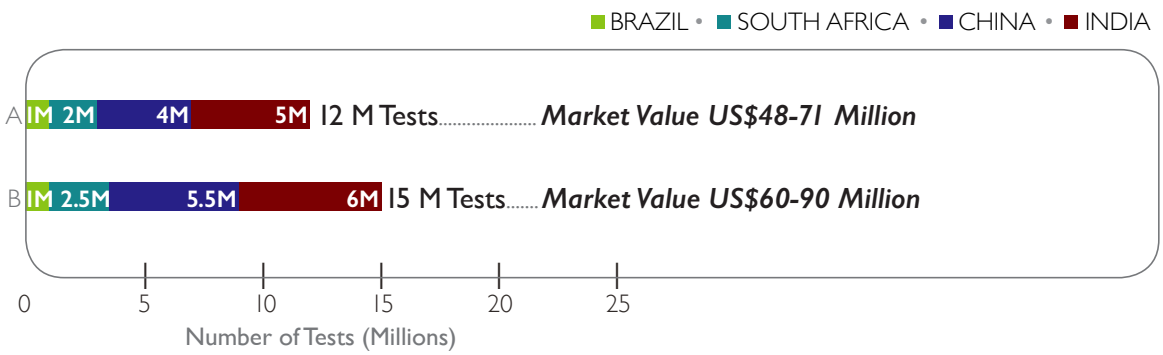
1. Sputum-based test for TB detection ("smear replacement test")

Based on the WHO consensus report, this product profile is for a rapid, easy-to-perform, sputum-based test with increased sensitivity for the detection of pulmonary TB, replacing the initial sputum smear microscopy in peripheral settings such as microscopy centres. The goal of the test is to diagnose pulmonary TB and support the initiation of TB treatment on the same day. The target population is all patients being evaluated for pulmonary TB who are able to produce sputum. The aim is to replace with a single test the 2 – 3 initial sputum smears that are currently performed per patient. The test result would ideally be available in under 20 minutes, but in any case no longer than 2 hours, at a price of US$ 4 – 6. Because this test is intended to replace sputum smear microscopy, it could leverage the infrastructure, supply chain and quality control systems in place in those settings.

Annualized four-country potential available market (Figure 8) based on a price range of US$ 4–6 per test:

- If the test is used for initial diagnosis only, the potential four-country market volume in 2020 would be 11.9 million tests with an annual market value of US$ 48 – 71 million.
- If the test were able to monitor therapy, the market opportunity would increase to 15 million tests with an annual market value of US$ 60 – 90 million. This assumes two additional tests conducted on each diagnosed TB patient.

Figure 8. Sputum-based Smear Replacement Test
Potential Market Volume in Tests with Corresponding Market Value in 2020



A) Smear replacement test at microscopy centre for initial diagnosis only

B) Smear replacement test at microscopy centre for initial diagnosis plus treatment monitoring

Market value range determined at US$4 & US$6 per test (as per ex-works price in TPP)

A base case of 12 million tests annually at the price of US$ 4 per test, projected over a seven-year product life cycle, results in a cumulative market value in the four countries combined of US$ 336 million.

The potential market for a smear replacement test in these four countries depends on the current technology being used for initial diagnosis. For example, in 2013 South Africa completed the rollout of Xpert® MTB/RIF as the initial diagnostic test, while smears continue to be performed for treatment monitoring. Consequently, for a new initial diagnostic test to be considered for use in South Africa, it would have to replace or be used in conjunction with the Xpert® MTB/RIF test.

2. Rapid, non-sputum-based TB detection test ("biomarker test")

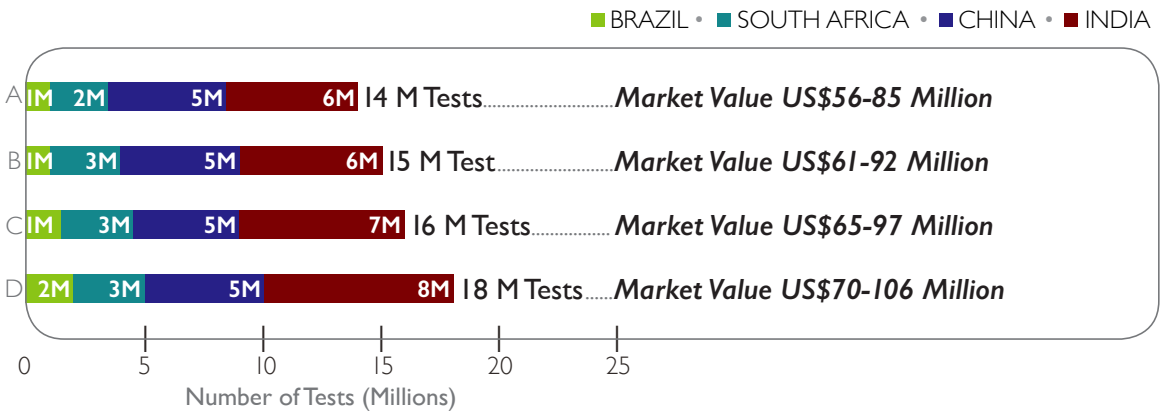
Based on the WHO consensus report, this product profile is for a rapid, easy-to-perform diagnostic using an easily accessible (non-sputum) sample that can accurately diagnose all forms of TB. It would most likely be a biomarker-based test. The goal of the test is to diagnose pulmonary TB – and, ideally, extrapulmonary TB – and to support the initiation of TB treatment regimens on the same day. The target population is all adults and children who are being evaluated for TB using non-sputum samples. At a minimum, this test would be used in peripheral microscopy centres, replacing the initial diagnostic test (e.g. smear microscopy or Xpert® MTB/RIF), and in health-care clinics that have an existing laboratory where sputum smears might not currently be performed. Health-care workers with limited training should be able to perform the test and interpret the result. Due to its ease of use, the test would ideally be implemented more peripherally in health posts and clinics without attached laboratories. The test result would ideally be available in under 20 minutes, but in any case no longer than 2 hours, at a price of US$ 4–6.

The annualized four-country potential available market (Figure 9) based on a price range of US$ 4–6 per test would be as follows:

- If the test is used only for pulmonary TB (adult and paediatric) and at microscopy centres and clinics with a laboratory, the potential four-country market volume in 2020 would be 14.1 million tests with an annual market value of US$ 56 – 85 million.
- If the same test can be utilized in microscopy centres, clinics and health posts, the potential market would increase to 15.4 million tests with an annual market value of US$ 61 – 92 million.

- Adding the ability to detect extrapulmonary TB, with use only in microscopy centres and clinics with a laboratory, would increase the test volume to 16.1 million tests and the annual market value to US$ 65 – 97 million.
- The largest market opportunity for this test is when it can be used for both pulmonary and extrapulmonary TB, as well as for all forms of paediatric TB, and is implemented at microscopy centres, clinics and health posts. This would result in 17.6 million tests per year in the four countries combined, with an annual market value of US$ 70 – 106 million.

Figure 9. Non-sputum-based Biomarker Test Potential Market Volume in Tests with Corresponding Market Value in 2020



A) Biomarker test for PTB and paediatric TB at microscopy centres and clinics

B) Biomarker test for PTB and paediatric TB at microscopy centres, clinics and health posts

C) Biomarker test for PTB, EPTB and paediatric TB at microscopy centres and clinics

D) Biomarker test for PTB, EPTB and paediatric TB at microscopy centres, clinics and health posts

PTB = Pulmonary TB
EPTB = Extrapulmonary TB

Market value range determined at US$4 & US$6 per test (as per ex-works price in TPP)

A base case of 16 million tests annually at the price of US$ 4 per test, projected over a seven-year product life cycle, results in a cumulative market value in the four countries combined of US$ 448 million.

The simpler the test, the more likely it is to be implemented at health posts, microscopy centres and clinics, thus increasing access. With use in these peripheral tiers of the health system, this test should increase the number of patients with presumptive TB who are tested. This should result in an increase of the number of TB cases being diagnosed, especially if the test is able to detect extrapulmonary TB and pulmonary TB in those patients unable to produce sputum.

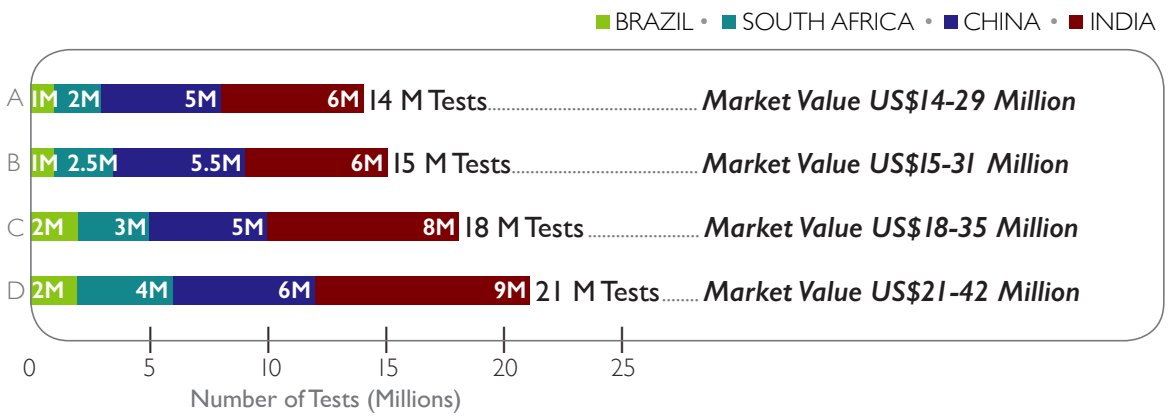
3. Community-based triage test to rule out TB ("triage test")

Based on the WHO consensus report, this product profile is for a simple, low-cost test for use by first-contact providers in the community to rule out TB in persons with presumptive TB. The goal of the test is either to rule out TB or to refer patients for additional/confirmatory testing. A positive triage test would direct patients to further evaluation with a confirmatory test (for pulmonary TB) or additional work-up (for extrapulmonary TB). The target population of this test is all adults and children with symptoms of, or risk factors for, active pulmonary TB and ideally extrapulmonary TB. It would be implemented at microscopy centres, primary care clinics, health posts and ideally at the community level. The time-to-result ideally would be less than 5 minutes but it would be acceptable up to 30 minutes, with a desired price of US$ 1 – 2.

The annualized four-country potential available market (Figure 10) based on a price of US$ 1 and US$ 2 per test would be as follows:

- If the triage test can be used only for pulmonary TB (using sputum specimens) with implementation at the health post and above, the 2020 potential four-country market volume is 14.3 million tests with an annual market value of US$ 14 – 29 million.
- If the same test can also be implemented at the lowest level of health care (community care), the market value increases to 15.4 million tests with an annual market value of US$ 15 – 31 million.
- If the test is able to detect both pulmonary and extrapulmonary TB (using non-sputum specimens), with implementation at the health post and above, the market opportunity increases to 17.6 million tests with an annual market value of US$ 18 – 35 million.
- The largest market opportunity for this test is attained if it can triage pulmonary TB, extrapulmonary TB and all forms of paediatric TB, with implementation down to the level of community care. This would result in a potential market of 21.1 million tests in the four countries combined, with an annual market value of US$ 21 – 42 million.

Figure 10. Triage Test
Potential Market Volume in Tests with Corresponding Market Value in 2020



A) Triage test for PTB testing (sputum-based) at microscopy centres, clinics and health posts

B) Triage test for PTB testing (sputum-based) at microscopy centres, clinics, health posts plus in the community

C) Triage test for PTB, EPTB and paediatric TB (non-sputum-based) at microscopy centres, clinics and health posts

D) Triage test for PTB, EPTB, paediatric TB (non-sputum-based) at microscopy centres, clinics, health posts plus in the community

PTB = Pulmonary TB
EPTB = Extrapulmonary TB

Market value range determined at US$1 & US$2 per test (as per ex-works price in TPP)

A base case of 18 million tests annually at the price of US$ 1 per test, projected over a seven-year product life cycle, results in a cumulative market value in the four countries combined of US$ 126 million.

This test should be simple enough for broad use in the lower levels of a health-care system. As the majority of patients screened for TB do not have the disease, triaging patients with this test would reduce the number of more expensive confirmatory tests performed. Although targeted for use in the lower levels of the health-care system, it could also be used at the same level of care as the confirmatory testing – especially in settings with a large volume of patients.

4. Next-generation drug susceptibility test at microscopy centres ("detection + DST")

Based on the WHO consensus report, this product profile is for a sputum-based test using a single platform that can detect both TB and resistance against current first-line regimens. The goal of the test is to inform the choice between first-line regimens (HRZE, which will likely be in use for the foreseeable future), as well as alternative regimens under investigation (such as PaMZ or other fluoroquinolone-based regimens). The test is not necessarily intended to provide individual drug treatment information tailored to a specific patient. The target population for the test is patients who are being evaluated for TB, with a special focus on those at high risk of drug-resistant TB. The test is used in peripheral microscopy centres rather than in intermediate or reference laboratories. The time-to-result should ideally be less than 20 minutes but would be acceptable up to 2 hours. Consensus on price points was not reached when this product profile was developed and will depend greatly on the number of drugs tested. Consequently the price points for the rapid detection + DST test use assumptions from affordability studies.[46]

The product profile suggested that a new DST should ideally include testing for rifampin, moxifloxacin, pyrazinamide and isoniazid, reflecting the perceived importance of the drugs in regimens under development at the time of the consultation (HRZE or PaMZ) and the prevalence of resistance. The importance of detecting resistance against the individual drugs was ranked as follows: first is rifampin, then a fluoroquinolone (at least moxifloxacin), and then pyrazinamide and/or isoniazid. This acknowledges that targeting isoniazid is a priority need that is based on current regimens, while targeting pyrazinamide is a priority need for future regimens. Additional drugs could be incorporated into the test. The exact drugs to include in a new test may appear like a moving target as the medicine landscape develops but the suggested priorities are in the TPP. It is acknowledged that this presents a challenge for test developers.

Without a consensus by TB stakeholders on the preferred option, this test could be designed in multiple ways:

- TB detection and DST testing could be done together (detection plus DST upfront in one test assay).
- TB detection could initially be done alone, followed by DST if TB is detected.
- TB detection could be combined with rifampin testing, followed by additional DST if TB is detected and rifampin resistance is found.

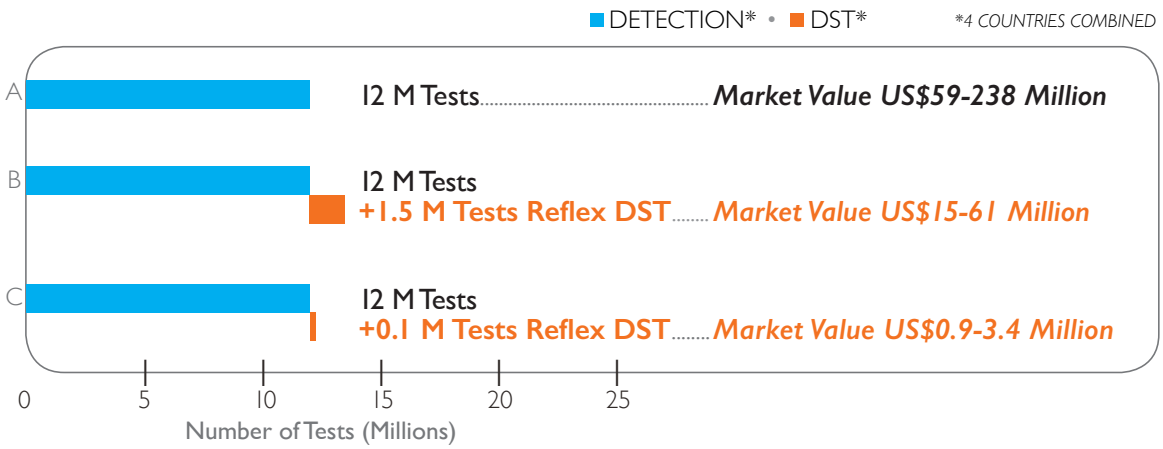
The annualized four-country potential available market (Figure 11) would be as follows:

The different test configurations will greatly affect the market potential of any of the follow-up drug resistance tests. Therefore each configuration is estimated separately. The potential market for all options assumes that the initial test would be used on all patients in the target population, resulting in a potential market volume for the detection component equal to that for the rapid sputum-based test. However, the market value is higher because of the added value of DST with each test.

- The first option is one that combines TB detection and DST in a single test assay.
  - ❏ For this test configuration, the 2020 potential four-country market is estimated to be 11.9 million tests. The market value will depend on the price point set by how many different drugs are tested. This results in a market value that ranges from US$ 59 million to US$ 238 million annually, based on a price of US$ 5 and US$ 20 per test.
- The second option is one where DST follows the initial TB detection test if TB is detected.
  - ❏ For this test configuration, the estimated annual four-country potential market volume for the TB detection test is the same 11.9 million tests as above with an annual market value of US$ 59 million (assuming a price of US$ 5 per test). The potential market volume for the follow-up (reflex) DST is 1.5 million tests. The annual market value of the reflex DST is from US$ 15 million up to US$ 61 million on the basis of prices of US$ 10 and US$ 40 per DST. The DST price point will depend on how many different drugs are included in the assay.
- The third option is where the initial TB detection test is combined with testing for rifampin resistance, followed by additional DST if both TB is detected and RIF resistance is found.
  - ❏ For this test configuration, the four-country market potential for TB detection combined with rifampin testing is the same 11.9 million tests with an annual market value of US$ 59 million (assuming a price of US$ 5 per test). The annual potential market volume for the follow-up (reflex) DST is 0.09 million tests, with an annual market value of US$ 0.9 – 3.4 million based on a price of US$ 10 and US$ 40 per DST. The reflex DST price point will depend on how many different drugs are included in the assay. Additionally, the market size for the follow-up DST depends on the prevalence of country-specific rifampin resistance.

Both option 2 and option 3 assumed increased sensitivity of 95% for the detection of pulmonary TB prior to the DST reflex test.

Figure 11. Detection and Drug Susceptibility Test (DST) Potential Market Volume in Tests with Corresponding Market Value in 2020



A) Sputum-based TB detection plus DST all in one test

B) Sputum-based TB detection alone followed by DST if TB is detected

C) Sputum-based TB detection plus RIF test followed by additional DST if RIF resistance is found

RIF = Rifampin

Market value based on ex-works prices. Lower values include at least one drug while highest value likely includes > 3 drugs. Exact drugs to be included are not yet confirmed.

A base case of (using the second design option) 12 million detection tests annually at the price of US$ 5 per test, projected over a seven-year product life cycle, results in a cumulative market value in the four countries combined of US$ 420 million. For the 1.5 million DST follow-up tests, the total four-country market value would be US$ 140 million over the same seven-year product cycle.

For the first option, if the prevalence of drug-resistant TB were low, consideration should be given to whether countries would adopt a higher-priced test for all patients or whether it would be only used selectively for high-risk patients.

This product profile describes the most competitive product versus Xpert® MTB/RIF since it offers DST. This is especially important for those countries with a high MDR rate. The new test could compete with or replace Xpert® MTB/RIF if there is added value to the country's public or private sector that Xpert® MTB/RIF does not offer (e.g. the ability to implement at lower levels of care, lower price or ability to test for susceptibility to additional drugs). Given the right characteristics, this test can also replace smear microscopy.

Opportunities beyond the four countries

This approach to estimating the market opportunity can be applied to countries other than Brazil, China, India and South Africa. These four countries account for only 46% of the new TB cases detected, which means there is an additional market opportunity that could double the estimates given here. A recently published market assessment for a smear replacement test in the 22 high-burden countries indicated a market opportunity in the public sector alone of 31 million tests with an annual value of US$ 154 million (see side bar).

Additional opportunity exists beyond these four countries. Another 18 high-burden countries contribute to an additional 35% of the world's TB cases and all other countries account for the remaining 19% of TB cases detected. This represents an additional market opportunity that is likely to be at least double the estimates given here for these four countries.

Children with TB remain under-diagnosed. The total global paediatric market is thought to be up to 1 million children,[47] which is much higher than current WHO estimates. A test that is appropriate for children could be a better option for those coping with today's diagnostics (0.3 million) and – more significantly – for those not currently diagnosed.

With the endorsement of the universal DST goal in the End TB Strategy, there is now a growing impetus to offer DST to all persons with TB right at the time of diagnosis. If implemented, this strategy will greatly increase the need for DST technologies in all high-burden countries, and a product that combines detection with DST may be more desirable from the NTP perspective.

Another way to view additional market opportunity is to consider the approximately 3 million individuals globally who developed TB and were not reached by national systems or not diagnosed or notified as having TB. A common estimate is that 7–10 people need to be evaluated in order to find one TB case. Therefore it is estimated that at least another 21–30 million people would need diagnostic testing for TB in order to find these additional 3 million cases.

Xpert® MTB/RIF, with instruments in over 100 countries and more than 10 million cartridges sold during 2010 – 2014, shows that markets for new TB diagnostics do exist. To illustrate that market opportunities still exist alongside the roll-out of Xpert® MTB/RIF, in a single year in the 22 high-burden countries, smear microscopy was carried out on an estimated 31 million patients for the purpose of initial diagnosis.[48]

Smear market replacement for 22 high-burden countries

Sputum smear microscopy remains the predominant test for initial diagnosis in the 22 high-burden countries. A recently published market assessment looked at smear microscopy in the public sector in the high-burden countries and assessed what the market potential for a smear replacement test would be. The public sector market volume in the 22 high-burden countries combined is 61.7 million smears carried out on an estimated 31 million patients for the purpose of initial diagnosis. If a replacement test, in this case a molecular test priced at US$ 5, were performed once on each patient, it would result in a market of almost 31 million tests with a value of US$ 154 million annually. Several high-burden countries – notably Bangladesh, Cambodia, India, Indonesia, Nigeria, Pakistan, Philippines and Uganda – have sizeable and even dominant private sectors that were not taken into consideration in this estimation due to lack of data; therefore the actual market may in fact be higher than estimated.

Market penetration of new TB diagnostics

The potential available market reflects future opportunity and does not attempt to address the market penetration rates or market shares of different tests. The share of market opportunity and speed of market penetration that any given product can expect depends on the competitive landscape and how well the product fits the product profile (on the range from minimal to optimal) and on the interplay of the key characteristics. Competition for the same potential market occurs when different products are introduced matching the same product profile. Other factors affecting market penetration in each country include the TB epidemiology, economics, funding available for NTPs, product integration into national diagnostic algorithms and its subsequent implementation by the national TB control programme. How broadly any of these four novel tests are used will depend on how well the product meets the TB community needs and priorities, as reflected in WHO endorsement and national policies.

In order to be utilized as an initial diagnostic by the national TB programme or the private sector, a new test must bring added value beyond that provided by the tests currently in use, such as smear and in some cases Xpert® MTB/RIF. This typically involves trade-offs between variables such as price, performance, ease of use, reduced training, and the ability to detect extrapulmonary TB and pulmonary TB in those patients unable to produce sputum. Countries may decide to incorporate new tests in a variety of ways such as throughout the entire network or in situations where smear, Xpert® MTB/RIF or other new novel tests are not suitable.

When considering replacing an existing technology with a different test, cost is often a determining factor. Even with a lower price, the costs of switching tests are still taken into account, whether in terms of training, infrastructure, proficiency testing programmes, quality assurance, policy updates or other switching costs. Conversely, South Africa has shown that switching costs do not have to be a deterrent to adopting new technology when it is shown that the advantages outweigh the costs. Minimizing of switching costs could be an advantage for any given technology or product.

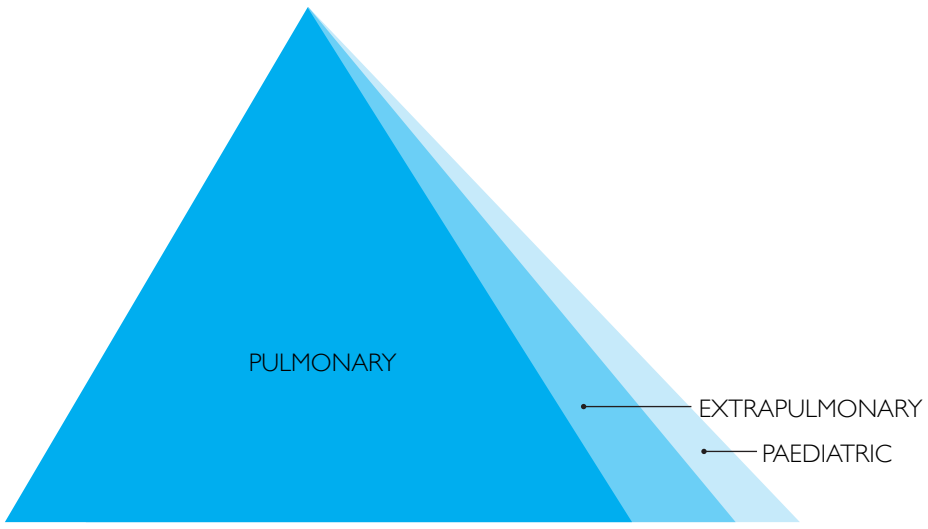
A new test must provide additional value to the TB programme, clinicians and patients. This added value could include faster results, more accuracy, greater sensitivity, simpler to perform, ability to test a wider patient population, or a lower price or cost-in-use. Additional value may be derived from a single characteristic or a combination of characteristics. Another consideration is a diagnostic platform technology that can perform a variety of tests (e.g. viral load) may be more acceptable to a health system than a technology that can only do a TB diagnostic test. By 2020, it is expect many NTPs will have digitized their systems and any technology that can easily link to the system will be more desirable.

TB drug and regimen landscape is changing. The availability of new TB drugs and regimens will highlight the need for interdependency of diagnostics and treatments. Drug susceptibility tests will be needed to direct patients toward appropriate therapy and to monitor any emergence of drug resistance. At this time, the exact drugs in new regimens have not been confirmed. Progress of any new drug or regimen can be found on the TB Alliance website (http://www.tballiance.org/).

Impact of novel tests on the overall market

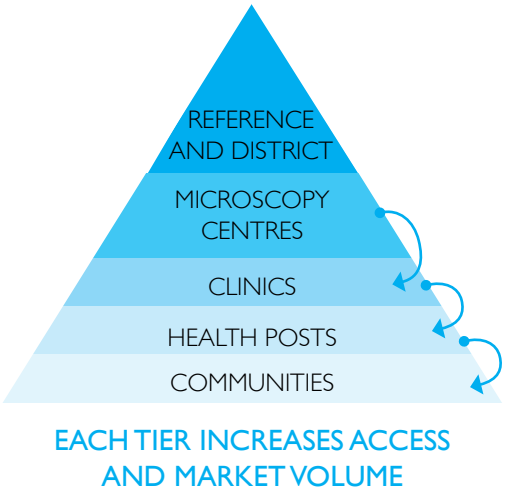
Novel tests will have an impact on the overall TB diagnostic market. Universal DST for patients will be a major market driver in the future. The DST market will expand as new TB drug regimens create a priority for new DSTs aligned with new treatments. Many people with presumptive TB are not served by the current array of diagnostic tests. Market opportunity can expand when volumes increase as a result of improved access and of a focus on finding undiagnosed cases, especially in view of the number of people who need to be tested to find one TB case. Markets can expand horizontally as new patient populations are tested or can expand vertically as test implementation moves into additional lower or more peripheral settings. Figure 12 illustrates the increased market size as additional patient groups, such as children with presumptive TB and individuals with presumptive extrapulmonary TB, are included in the intended target population. Figure 13 illustrates the market growth impact of increasing access by using the test in more of the lower levels of the health-care system. It is generally accepted that, in order to improve access, a diagnostic test needs to be carried out closer to the patient care.

Figure 12. Market Expands When Additional Types of TB Can Be Detected By a Test*



* Illustrative only

Figure 13. Market Expands as Suitability for Use in More Decentralized Settings Increases Access*



* Illustrative only

The overall market can expand with the introduction of a new technology that fits any of the four product profiles. The potential market for any new test is increased either by replacing an existing test, by adding the new test but not replacing any existing test (e.g. addressing a new market), or by making the test available to patients who did not previously have access to appropriate diagnostics (e.g. testing people not served by existing technologies). It is also possible for the overall market value to expand, even if the overall market volume might decrease (e.g. the 2–3 initial smears per patient are replaced by one new diagnostic test per patient). It is also likely that a patient may receive more than one diagnostic test, such as a triage test, then a confirmatory test, a DST and then tests to monitor therapy.

Interaction of new novel tests

Each new novel test can have an impact on the market opportunity for the other three. Competition may occur between products with different profiles when the target patient populations overlap (e.g. between a sputum-based smear replacement test and a broadly-used non-sputum-based biomarker test). Conversely, high uptake of one test could increase the potential market for others (e.g. a triage test increases the number of people who need a confirmatory test).

The target populations and the location where the test can be implemented are not uniquely different for each of the four potential new tests. Table 4 shows for each test the overlap of the optimal target populations or type of TB detected, while Table 5 shows where the tests will be utilized optimally.

Table 4. Target Population or Type of TB Each Test Ideally Could Diagnose

Target Product Profile	PTB	EPTB	Paediatric TB	MDR-TB
Sputum-based Smear Replacement Test	•			
Non-sputum-based Biomarker Test	•	•	•	
Triage Test*	•	•	•	
Sputum-based Detection + DST	•			•

PTB = Pulmonary TB
EPTB = Extrapulmonary TB

* Triage test used with confirmatory test as needed

Table 5. Decentralized Settings Where Each Test Would Ideally Be Used

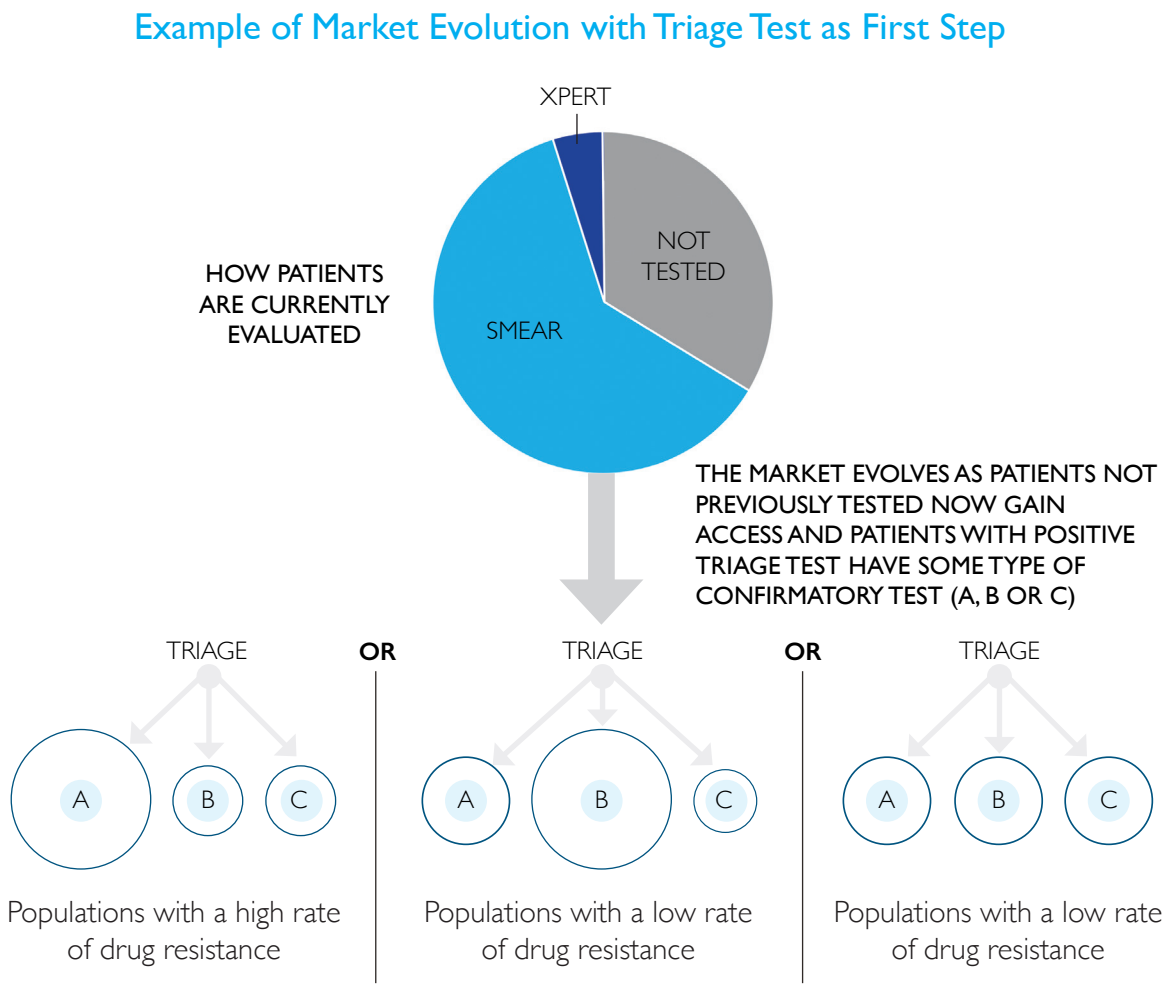
Target Product Profile	Microscopy Centers	Health Clinics	Health Posts	Community
Sputum-based Smear Replacement Test	•			
Non-sputum-based Biomarker Test	•	•	•	
Triage Test	•	•	•	•
Sputum-based Detection + DST	•			

There are no data on the exact impact and interaction that these novel tests will have but two examples serve to illustrate possible interactions.

Example 1. Illustrative of one possible scenario

In this scenario, the new triage test is established as the first step in the diagnostic algorithm. The existing market may evolve into one in which the triage test is followed by one of three different confirmatory tests. Given that 7 – 10 people are evaluated for TB to find one case, a low-cost triage test allows for the cost-efficient adoption of more expensive confirmatory tests.[49] The decision as to which confirmatory test to use may be based on patient populations or the type of TB one is trying to detect (pulmonary, extrapulmonary, paediatric or drug resistant). Figure 14 illustrates different potential scenarios of the use of various confirmatory tests on the basis of local epidemiology. If the patient population has a high rate of MDR, the detection + DST test may be the predominant confirmatory test. Contrarily, if the patient population has a low MDR rate but a high rate of patients unable to produce sputum, the non-sputum biomarker test may be the predominant confirmatory test.

Figure 14. Possible Scenario Where Multiple Tests Will Exist in Future Market*



Different Possible Confirmatory Tests:

A) Confirmatory sputum-based test that includes DST for people at high risk MDR

B) Confirmatory test that is non-sputum-based for patients unable to produce sputum

C) Confirmatory sputum-based test for pulmonary TB without DST

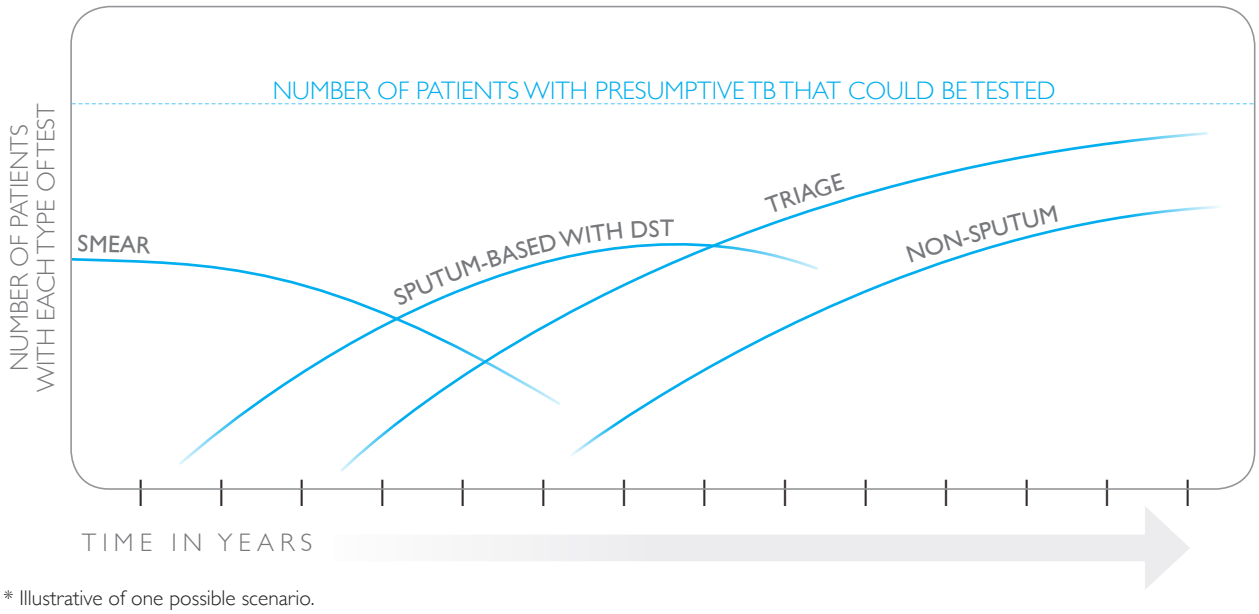
DST= Drug Susceptibility Test
MDR= Multi-Drug Resistant TB

* Illustrative only

Example 2. Illustrative of one possible scenario

This illustrative example focuses more on how the market may evolve depending, in part, on product introduction timelines. There may be an advantage for the first test that is introduced, but the one with most added benefits will have the biggest impact in the long term. Figure 15 illustrates one possible scenario in which the market evolves over time with different tests being introduced at different times. It shows that smears may decrease as a sputum-based test with DST is introduced. If a test offers faster results and improved sensitivity, replacement of smear would be a viable consideration for TB programmes. If a non-sputum test is then introduced later, it could be used selectively (extrapulmonary TB, paediatrics) or, as illustrated, it could replace a sputum-based test due to ease-of-use benefits, performance and lower price. Introduction of a triage test may then affect the market size of the other novel tests that could now be utilized as confirmatory tests. Obviously, market introduction could occur in a different order, causing the market to evolve differently.

Figure 15. Evolving Market Over Time Based on Test*



* Illustrative of one possible scenario.

Evolution of the market

The mix of new tests and existing tests will vary by country. As new products endorsed by WHO enter the market, they will be adopted and used in diagnostic algorithms. This will cause the market to evolve. Overall, however, the way in which the TB diagnostics market evolves will depend on the competitive landscape and other factors such as:

- when each test enters the market
- what other tests are in use
- the added value that each new test brings, and how it priced
- how quickly country policies and algorithms are revised.

It is very unlikely that one new diagnostic test will be adopted for all initial diagnosis and monitoring. Countries are likely to adopt a mix of technologies, based on patient populations, MDR rates and levels of the health-care system. While diagnostic testing will move closer to the patient, there will continue to be diagnostic testing at all levels of the health-care system and not just in peripheral settings. This diversity

of different needs is the reason why four unique product profiles were developed. Whether the adoption of new tests occurs aggressively, as in South Africa, or in more specific situations or patient populations, as in many other countries, the opportunity remains for one or more different new tests to enter the market.

Market drivers exist that are not directly related to these specific novel diagnostics. They include:

- improvements to overall health-care access, quality and delivery, including economic growth that leads to overall higher expenditure on health
- increasing use of digitized systems and eHealth
- increasing health-care expenditures driving demand for diagnostics
- increasing competition among manufacturers with improved products and customer support
- increasing collaboration between the public and private sectors, and expansion of concessional pricing agreements to cover private sectors in high-burden countries.

Limitations and uncertainty of market potential estimates

The limitations of the market estimates for Brazil, China, India and South Africa should be taken into consideration. These estimates apply only to four countries; they are not global estimates, nor even estimates for all high-burden countries. There is additional market opportunity outside these four countries that was not included in these estimates.

In the calculation of the market potential estimates, the assumption that has the most influence on market size is the number of people with presumptive TB who are tested in order to identify one TB case. Country-specific data were available for pulmonary TB and were applied to extrapulmonary TB and childhood TB for each country. Additionally, this ratio (7 – 10 persons tested to identify one case) was kept constant through to 2020, although it might be expected to increase over time as prevalence decreases. As an example to demonstrate the effect of the ratio, for all four countries the potential market for the sputum-based smear replacement test was recalculated using both a lower ratio of five persons tested to identify one case and a higher ratio of 15 tested per case identified. As a result, the original market size of 12 million tests for a sputum smear replacement test expanded to a range from 7.7 million to 23 million, and the market value at the US$ 4 price point ranged from US$ 31 million to US$ 93 million.

There is always uncertainty in price points for products under development. The price points used reflect those discussed during TPP development and are not intended to imply a commitment by donors or countries to buy at these prices. It is important to note that the prices outlined for each of the tests in the product profile are considered ex-works, which means they represent the manufacturers' selling price and do not include shipping, import or local taxes, distribution or other fees. Nor do these prices include running costs such as laboratory staff, building space or utilities (if needed). Volume discounts and negotiated prices are also not reflected. This varies from the current served market value that did include, on the basis of best available information, other costs making up the total cost-in-use.

There are limited data on the increased number of individuals who can be tested as the diagnostic test is implemented at the lower levels of the health-care system. The increase in the potential available market when implementing the test at these levels assumed a 10% increase in the number of tests implemented in each health-care level lower than microscopy centres. This was based on a study showing that 25% of the population of Africa had access only to health-care facilities with no infrastructure, while 47% had access to facilities with minimal infrastructure.[50]

How broadly these four new potential tests will be used depends in part on how well the product fits the TPP with regard to the minimal-to-optimal range of characteristics and the interplay of the key characteristics. The market opportunity may be lower if the product does not meet all the TPP characteristics, especially with regard to price and operational parameters.

Furthermore, there are market opportunities outside of the four TPPs, including, for example, a highly predictive test for latent TB infection. The potential market for latent TB tests was not covered because it was not one of the high priority tests at this time. As interest in detecting latent TB infections increases, particularly in high- and middle-income countries with low TB incidence, the future market potential for these types of diagnostic tests should be assessed.

Many developments are ongoing to improve chest X-rays (e.g. digital chest X-rays, computer-aided diagnosis [CAD] software for interpretation of results). This market was outside the scope of this report both for the current market and future market potential.

Conclusion

In conclusion, the market today consists of patients currently being served with existing diagnostic tests, albeit ones with a variety of limitations. Smear remains the mainstay of initial diagnosis in three of the four countries despite its low sensitivity in children, people living with HIV and people with extrapulmonary TB. The scale-up of Xpert® MTB/RIF in over 100 countries demonstrates that new technologies are indeed being rolled out and that up-front DST does indeed identify many more patients as having MDR-TB. Improved diagnostics, including options to replace or complement smear microscopy, is a goal of many TB stakeholders – including countries, funders, clinicians and patients. The development and implementation of novel DST tests aligned with the launch of new TB drug regimens has the potential to improve patient outcomes. All of this reflects a significant market opportunity in these four countries alone.

Country summaries

South Africa

Population: 52 million in 2012; 54 million in 2020
GDP in 2013: US$ 350.6 billion

TB prevalent cases: 450 000 in 2012; 426 660 in 2013
TB prevalence rate of change (2009–2012): -1.12%
Estimated number of individuals with presumptive TB (including PTB, EPTB and paediatric TB) in the whole country: 3 150 000 in 2012; 2 986 623 in 2020
Cost per TB case spend in the country on TB diagnostics in 2012: US$ 280

Public laboratory network[51]: 240 smear microscopy laboratories, 18 regional laboratories with culture, DST and line probe assay capabilities, and 1 central reference laboratory.

Public versus private: tests 93% public, 7% private; value 93% public, 7% private.

Served market (2012): Test volume and market value of combined public and private sectors

Test	Units (000)	Value US$ (000)
TST	1164	11 711
IGRA	12	475
Serology	ND	ND
SSM	4995	29 646
Culture (liquid + solid)	1631	24 280
Identification/speciation	36	409
Xpert® MTB/RIF	784	17 210
LPA	362	10 941
PCR	16	258
DST 1st (liquid + solid)	38	1373
DST 2nd (liquid + solid)	20	976
ADA	108	522
Totals	9165	97 800

Na = No data available; ND = not done; Not routine = not routinely done; TST = tuberculin skin test; IGRA = interferon gamma release assay; SSM = sputum smear microscopy; LPA = line probe assay; PCR = polymerase chain reaction; ADA = adenosine deaminase; DST 1st and 2nd = drug susceptibility test for first-line and second-line drugs.

Potential market for four novel tests in 2012 and 2020, South Africa

	2012			2020		
1. Sputum-based test for TB detection	**Number of tests (million)**	**Value at price US$ 4**	**Value at price US$ 6**	**Number of tests (million)**	**Value at price US$ 4**	**Value at price US$ 6**
Initial diagnosis only	2.1	US$ 8.4 M	US$ 12.7 M	2.0	US$ 8.0 M	US$ 12.0 M
Initial diagnosis plus treatment monitoring	2.6	US$ 10.6 M	US$ 15.9 M	2.5	US$ 10.0 M	US$ 15.1 M

	2012			2020		
2. Rapid, non-sputum-based TB detection test	**Number of tests (million)**	**Value at price US$ 4**	**Value at price US$ 6**	**Number of tests (million)**	**Value at price US$ 4**	**Value at price US$ 6**
For only PTB at microscopy centres and clinics	2.6	US$ 10.5 M	US$ 15.8 M	2.5	US$ 10.0 M	US$ 15.0 M
For only PTB at microscopy centres and clinics plus health posts	2.9	US$ 11.5 M	US$ 17.2 M	2.7	US$ 10.9 M	US$ 16.4 M
For PTB and EPTB at microscopy centres and clinics	3.1	US$ 12.3 M	US$ 18.4 M	2.9	US$ 11.6 M	US$ 17.4 M
For PTB and EPTB at microscopy centres and clinics plus health posts	3.3	US$ 13.4 M	US$ 20.1 M	3.2	US$ 12.7 M	US$ 19.0 M

	2012			2020		
3. Community-based triage test to rule out TB	**Number of tests (million)**	**Value at price US$ 1**	**Value at price US$ 2**	**Number of tests (million)**	**Value at price US$ 1**	**Value at price US$ 2**
For PTB (sputum-based test) at microscopy centres, clinics and health posts	2.5	US$ 2.5 M	US$ 5.0 M	2.4	US$ 2.4 M	US$ 4.8 M
For PTB (sputum-based test) at microscopy centres, clinics and health posts plus at community level	2.7	US$ 2.7 M	US$ 5.4 M	2.6	US$ 2.6 M	US$ 5.2 M
For PTB and EPTB (non-sputum-based test) at microscopy centres, clinics and health posts	3.3	US$ 3.3 M	US$ 6.6 M	3.2	US$ 3.2 M	US$ 6.3 M
For PTB and EPTB (non-sputum-based test) at microscopy centres, clinics and health posts plus at community level	4.0	US$ 4.0 M	US$ 8.0 M	3.8	US$ 3.8 M	US$ 7.6 M

4. Next generation test for DST at microscopy centres	2012			2020		
Option 1: Detection and DST all at once	**Number of tests (000)**	**Value at price US$ 5**	**Value at price US$ 20**	**Number of tests (000)**	**Value at price US$ 5**	**Value at price US$ 20**
	2117	US$ 10.6 M	US$ 42.3 M	2006	US$ 10.0 M	US$ 40.1 M
Option 2: Detection and DST reflex	**2012**			**2020**		
Detection test = Same as Option 1 units and value at price US$ 5	**Number of tests (000)**	**Value at price US$ 5**		**Number of tests (000)**	**Value at price US$ 5**	
	2117	US$ 10.6 M		2006	US$ 10,0 M	
DST reflex test	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**
	266	US$ 2.7 M	US$ 10.6 M	2519	US$ 2.5 M	US$ 10.1 M
Option 3: Detection + RIF, then DST reflex when RIF resistant	**2012**			**2020**		
Detection + RIF test = Same as Option 1 units and value at price US$ 5	**Number of tests (000)**	**Value at price US$ 5**		**Number of tests (000)**	**Value at price US$ 5**	
	2117	US$ 10.6 M		2006	US$ 10.0 M	
DST reflex test	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**
	10	US$ 0.1 M	US$ 0.4 M	9	US$ 0.09 M	US$ 0.4 M

PTB = pulmonary TB; EPTB = extrapulmonary TB; DST = drug susceptibility test; RIF = rifampin.

India

Population: 1237 million in 2012; 1353 million in 2020
GDP in 2013: US$ 1.877 trillion

TB prevalent cases: 2.8 million in 2012; 2.6 million in 2013

TB prevalence rate of change (2009–2012): -7.78%
Estimated number of individuals with presumptive TB: (including PTB, EPTB and paediatric TB) in the whole country: 25 200 000 in 2012; 14 660 721 in 2020
Cost per TB case spend in the country on TB diagnostics in 2012: US$ 51

Public laboratory network[6]: 13 098 smear microscopy laboratories, 70 laboratories with culture capabilities and 38 with DST capabilities.

Public versus private: tests 59% public, 41% private; value 33% public, 67% private.

Served market (2013): Test volume and market value of combined public and private sectors

Test	Units (000)	Value US$ (million)
TST	8942	10.0
IGRA	170	7.3
Serology	1244	12.8
SSM	21 134	17 .8
Culture (liquid + solid)	502	5.3
Id/speciation	79	0.3
Xpert® MTB/RIF	194	2.4
LPA	134	2.4
PCR	379	12.3
DST 1st (liquid + solid)	8	0.2
DST 2nd (liquid + solid)	Na	Na
ADA	Na	Na
Totals	32 786	70.8

Na = No data available; ND = not done; Not routine = not routinely done; TST = tuberculin skin test; IGRA = interferon gamma release assay; SSM = sputum smear microscopy; LPA = line probe assay; PCR = polymerase chain reaction; ADA = adenosine deaminase; DST 1st and 2nd = drug susceptibility test for first-line and second-line drugs.

Potential market for four novel tests in 2012 and 2020

	2012			2020		
1. Sputum-based test for TB detection	Number of tests (million)	Value at price US$ 4	Value at price US$ 6	Number of tests (million)	Value at price US$ 4	Value at price US$ 6
Initial diagnosis only	7.9	US$ 31.5 M	US$ 47.2 M	4.6	US$ 18.3 M	US$ 27.5 M
Initial diagnosis plus treatment monitoring	10.0	US$ 39.9 M	US$ 59.9 M	5.8	US$ 23.2 M	US$ 34.9 M

	2012			2020		
2. Rapid, non-sputum-based TB detection test	**Number of tests (million)**	**Value at price US$ 4**	**Value at price US$ 6**	**Number of tests (million)**	**Value at price US$ 4**	**Value at price US$ 6**
For only PTB at microscopy centres and clinics	9.6	US$ 38.4 M	US$ 57.6 M	5.6	US$ 22.3 M	US$ 33.5 M
For only PTB at microscopy centres and clinics plus health posts	10.5	US$ 41.9 M	US$ 62.8 M	6.1	US$ 24.4 M	US$ 36.5 M
For PTB and EPTB at microscopy centres and clinics	12.0	US$ 48.0 M	US$ 72.0 M	7.0	US$ 27.9 M	US$ 41.9 M
For PTB and EPTB at microscopy centres and clinics plus health posts	13.1	US$ 52.4 M	US$ 78.5 M	7.6	US$ 30.5 M	US$ 45.7 M

	2012			2020		
3. Community-based triage test to rule out TB	**Number of tests (million)**	**Value at price US$ 1**	**Value at price US$ 2**	**Number of tests (million)**	**Value at price US$ 1**	**Value at price US$ 2**
For PTB (sputum-based test) at microscopy centres, clinics and health posts	9.4	US$ 9.4 M	US$ 18.8 M	5.5	US$ 5.5 M	US$ 11.0 M
For PTB (sputum-based test) at microscopy centres, clinics and health posts plus at community level	10.2	US$ 10.2 M	US$ 20.4 M	6.0	US$ 6.0 M	US$ 12.0 M
For PTB and EPTB (non-sputum-based test) at microscopy centres, clinics and health posts	13.1	US$ 13.1 M	US$ 26.2 M	7.6	US$ 7.6 M	US$ 15.2 M
For PTB and EPTB (non-sputum-based test)at microscopy centres, clinics and health posts plus at community level	15.7	US$15.7 M	US$ 31.4 M	9.1	US$ 9.1 M	US$ 18.2 M

4. Next generation test for DST at microscopy centres	2012			2020		
Option 1: Detection and DST all at once	**Number of tests (000)**	**Value at price US$ 5**	**Value at price US$ 20**	**Number of tests (000)**	**Value at price US$ 5**	**Value at price US$ 20**
	7867	US$ 39.3 M	US$ 157.3 M	4577	US$ 22.9 M	US$ 91.5 M
Option 2: Detection and DST reflex	**2012**			**2020**		
Detection test = Same as Option 1 units and value at price US$ 5	**Number of tests (000)**	**Value at price US$ 5**		**Number of tests (000)**	**Value at price US$ 5**	
	7867	US$ 39.3 M		4577	US$ 22.9 M	
DST reflex test	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**
	1059	US$ 10.6 M	US$ 42.3 M	616	US$ 6.2 M	US$ 24.6 M
Option 3: Detection + RIF, then DST reflex when RIF-resistant	**2012**			**2020**		
Detection + RIF test = Same as Option 1 units and value at price US$ 5	**Number of tests (000)**	**Value at price US$ 5**		**Number of tests (000)**	**Value at price US$ 5**	
	7867	US$ 39.3 M		4577	US$ 22.9 M	
DST reflex test	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**
	72	US$ 0.7 M	US$ 2.9 M	42	US$ 0.4 M	US$ 1.7 M

PTB = pulmonary TB; EPTB = extrapulmonary TB; DST = drug susceptibility test; RIF = rifampin.

China

Population: 1351 million in 2012; 1337 million in 2020
GDP in 2013: US$ 9.240 trillion

TB prevalent cases: 1.4 million in 2012 and 1.3 million in 2013
TB prevalence rate of change (2009 – 2012): -4.52%
Estimated number of individuals with presumptive TB (including PTB, EPTB and paediatric TB) in the whole country: 9 800 000 in 2012; 6 738 496 in 2020
Cost per TB case spend in the country on TB diagnostics in 2012: US$ 327

Laboratory network: Of the 3490 TB laboratories/dispensaries, 3320 perform smear, 1014 culture and 190 DST. There are estimated to be at least 34 provincial and 345 prefectural designated TB hospitals performing TB diagnostics.

Public versus private: tests 24% public (CDC), 76% private (hospital); value 6% public (CDC), 94% private (hospital).

Served market (2013): Test volume and market value of combined public and private sectors

Test	Units (000)	Value US$ (000)
TST	1460	2581
IGRA	1885	139 313
Serology	7942	25 173
SSM	27 489	35 669
Culture (liquid + solid)	2415	27 772
Id/speciation	27	139
Xpert® MTB/RIF	ND	ND
LPA	124	10 801
PCR	261	4137
DST 1st and 2nd (liquid + solid)	907	47 069
ADA	1670	1476
Totals	44 180	294 130

Na = No data available; ND = not done; Not routine = not routinely done; TST = tuberculin skin test; IGRA = interferon gamma release assay; SSM = sputum smear microscopy; LPA = line probe assay; PCR = polymerase chain reaction; ADA = adenosine deaminase; DST 1st and 2nd = drug susceptibility test for first-line and second-line drugs.

Potential market for four novel tests in 2012 and 2020

	2012			2020		
1. Sputum-based test for TB detection	Number of tests (million)	Value at price US$ 4	Value at price US$ 6	Number of tests (million)	Value at price US$ 4	Value at price US$ 6
Initial diagnosis only	6.2	US$ 24.7 M	US$ 37.0 M	4.2	US$ 17.0 M	US$ 25.5 M
Initial diagnosis plus treatment monitoring	7.9	US$ 31.7 M	US$ 47.6 M	5.5	US$ 21.8 M	US$ 32.7 M

2. Rapid, non-sputum-based TB detection test	2012			2020		
	Number of tests (million)	Value at price US$ 4	Value at price US$ 6	Number of tests (million)	Value at price US$ 4	Value at price US$ 6
For only PTB at microscopy centres and clinics	6.9	US$ 27.5 M	US$ 41.3 M	4.7	US$ 18.9 M	US$ 28.4
For only PTB at microscopy centres and clinics plus health posts	7.5	US$ 30.0 M	US$ 45.0 M	5.2	US$ 20.7 M	US$ 31.0 M
For PTB and EPTB at microscopy centres and clinics	6.9	US$ 27.7 M	US$ 41.6 M	4.8	US$ 19.1 M	US$ 28.6 M
For PTB and EPTB at microscopy centres and clinics plus health posts	7.6	US$ 30.3 M	US$ 45.4 M	5.2	US$ 20.8 M	US$ 31.2 M

3. Community-based triage test to rule out TB	2012			2020		
	Number of tests (million)	Value at price US$ 1	Value at price US$ 2	Number of tests (million)	Value at price US$ 1	Value at price US$ 2
For PTB (sputum-based test) at microscopy centres, clinics and health posts	7.4	US$ 7.4 M	US$ 14.8 M	5.1	US$ 5.1 M	US$ 10.2 M
For PTB (sputum-based test) at microscopy centres, clinics and health posts plus at community level	8.0	US$ 8.0 M	US$ 16.0 M	5.5	US$ 5.5 M	US$ 11.0 M
For PTB and EPTB (non-sputum-based test)at microscopy centres, clinics and health posts	7.6	US$ 7.6 M	US$ 15.2 M	5.2	US$ 5.2 M	US$ 10.4 M
For PTB and EPTB (non-sputum-based test)at microscopy centres, clinics and health posts plus at community level	9.1	US$ 9.1 M	US$ 18.2 M	6.2	US$ 6.2 M	US$ 12.4 M

4. Next generation test for DST at microscopy centres	2012			2020		
Option 1: Detection and DST all at once	Number of tests (000)	Value at price US$ 5	Value at price US$ 20	Number of tests (000)	Value at price US$ 5	Value at price US$ 20
	6174	US$ 30.9 M	US$ 123.5 M	4245	US$ 21.2 M	US$ 84.9 M
Option 2: Detection and DST reflex	2012			2020		
Detection test = Same as Option 1 units and value at price US$ 5	Number of tests (000)	Value at price US$ 5		Number of tests (000)	Value at price US$ 5	
	6174	US$ 30.9 M		4245	US$ 21.2 M	
DST reflex test	Number of tests (000)	Value at price US$ 10	Value at price US$ 40	Number of tests (000)	Value at price US$ 10	Value at price US$ 40
	882	US$ 8.8 M	US$ 35.3 M	606	US$ 6.1 M	US$ 24.3 M
Option 3: Detection + RIF, then DST reflex when RIF-resistant	2012			2020		
Detection + RIF test = Same as Option 1 units and value at price US$ 5	Number of tests (000)	Value at price US$ 5		Number of tests (000)	Value at price US$ 5	
	6175	US$ 30.9 M		4245	US$ 21.2 M	
DST reflex test	Number of tests (000)	Value at price US$ 10	Value at price US$ 40	Number of tests (000)	Value at price US$ 10	Value at price US$ 40
	65	US$ 0.6 M	US$ 2.6 M	45	US$ 0.4 M	US$ 1.8 M

PTB = pulmonary TB; EPTB = extrapulmonary TB; DST = drug susceptibility test; RIF = rifampin.

Brazil

Population: 199 million in 2012; 117 million in 2020
GDP in 2013: US$ 2.246 trillion

TB prevalent cases: 120 000 in 2012; 110 000 in 2013
TB prevalence rate of change (2009 – 2012): + 0.6%
Estimated number of individuals with presumptive TB: 1 400 100 in 2012; 1 523 843 in 2020
Cost per TB case spend in the country on TB diagnostics in 2012: US$ 208

Laboratory network[25]: approximately 4000 local public and private laboratories performing mainly smear microscopy, 26 state laboratories with culture and DST capabilities, and 1 Federal District reference laboratory; 220 laboratories perform culture and 35 laboratories perform DST.

Public versus private: tests 91% public, 9% private; value 88% public, 12% private.

Served market (2012): Test volume and market value of combined public and private sectors

Test	Units (000)	Value US$ (000)
TST	725	4279
IGRA	Not routine	Na
Serology	ND	ND
SSM	1316	3748
Culture (liquid + solid)	303	6892
Id/speciation	Na	Na
Xpert® MTB/RIF	21	381
LPA	Not routine	Na
PCR	0.6	28
DST 1st (liquid + solid)	18	1832
DST 2nd (liquid + solid)	0.7	91
ADA	Na	Na
Totals	2384	17 250

Na = No data available; ND = not done; Not routine = not routinely done; TST = tuberculin skin test; IGRA = interferon gamma release assay; SSM = sputum smear microscopy; LPA = line probe assay; PCR = polymerase chain reaction; ADA = adenosine deaminase; DST 1st and 2nd = drug susceptibility test for first-line and second-line drugs.

Potential market for four novel tests in 2012 and 2020

	2012			2020		
1. Sputum-based test for TB detection	Number of tests (million)	Value at price US$ 4	Value at price US$ 6	Number of tests (million)	Value at price US$ 4	Value at price US$ 6
Initial diagnosis only	1.0	US$ 3.9 M	US$ 5.8 M	1.1	US$ 4.2 M	US$ 6.3 M
Initial diagnosis plus treatment monitoring	1.1	US$ 4.4 M	US$ 6 .6 M	1.2	US$ 4.8 M	US$ 7.1 M

2. Rapid, non-sputum-based TB detection test	2012			2020		
	Number of tests (million)	Value at price US$ 4	Value at price US$ 6	Number of tests (million)	Value at price US$ 4	Value at price US$ 6
For only PTB at microscopy centres and clinics	1.2	US$ 4 .7 M	US$ 7.0 M	1.3	US$ 5.1 M	US$ 7.7 M
For only PTB at microscopy centres and clinics plus health posts	1.3	US$ 5.1 M	US$ 7.7 M	1.4	US$ 5.6 M	US$ 8.4 M
For PTB and EPTB at microscopy centres and clinics	1.4	US$ 5.5 M	US$ 8.2 M	1.5	US$ 5.9 M	US$ 8.9 M
For PTB and EPTB at microscopy centres and clinics plus health posts	1.5	US$ 6.0 M	US$ 8.9 M	1.6	US$ 6.5 M	US$ 9.7 M

3. Community-based triage test to rule out TB	2012			2020		
	Number of tests (000)	Value at price US$ 1	Value at price US$ 2	Number of tests (million)	Value at price US$ 1	Value at price US$ 2
For PTB (sputum-based test) at microscopy centres, clinics and health posts	1.2	US$ 1.2 M	US$ 2.4 M	1.3	US$ 1.3 M	US$ 2.5 M
For PTB (sputum-based test) at microscopy centres, clinics and health posts plus at community level	1.3	US$ 1.3 M	US$ 2.6 M	1.4	US$ 1.4 M	US$ 2.8 M
For PTB and EPTB (non-sputum-based test) at microscopy centres, clinics and health posts	1 .5	US$ 1. M	US$ 3.0 M	1.6	US$ 1.6 M	US$ 3.2 M
For PTB and EPTB(non-sputum-based test) at microscopy centres, clinics and health posts plus at community level	1.8	US$ 1.8 M	US$ 3.6 M	1.9	US$ 1.9 M	US$ 3.8 M

4. Next generation test for DST at microscopy centres	2012			2020		
Option 1: Detection and DST all at once	**Number of tests (000)**	**Value at price US$ 5**	**Value at price US$ 20**	**Number of tests (000)**	**Value at price US$ 5**	**Value at price US$ 20**
	965	US$ 4.8 M	US$ 19.3 M	1051	US$ 5.2 M	US$ 21.0 M
Option 2: Detection and DST reflex	**2012**			**2020**		
Detection test = Same as Option 1 units and value at price US$ 5	**Number of tests (000)**	**Value at price US$ 5**		**Number of tests (000)**	**Value at price US$ 5**	
	965	US$ 4.8 M		1051	US$ 5.2 M	
DST reflex test	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**
	64	US$ 0.6 M	US$ 2.6 M	70	US$ 0.7 M	US$ 2.8 M
Option 3: Detection + RIF, then DST reflex when RIF-resistant	**2012**			**2020**		
Detection + RIF test = Same as Option 1 units and value at price US$ 5	**Number of tests (000)**	**Value at price US$ 5**		**Number of tests (000)**	**Value at price US$ 5**	
	965	US$ 4.8 M		1051	US$ 5.2 M	
DST reflex test	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**	**Number of tests (000)**	**Value at price US$ 10**	**Value at price US$ 40**
	2	US$ 0.02 M	US$ 0.08 M	2	US$ 0.02 M	US$ 0.08 M

PTB = pulmonary TB; EPTB = extrapulmonary TB; DST = drug susceptibility test; RIF = rifampin.

Appendices

Appendix 1 – Additional details on how potential available market was derived

Method summary:

1. Estimated the percentage of TB patients with pulmonary TB, extrapulmonary TB and childhood TB for each country.
2. Calculated the number of cases for each of the above using WHO estimated prevalence data for each country.
3. To determine the number of individuals tested to find one TB case (often called "suspect-to-case" ratio), applied country-specific pulmonary TB ratios.
    - Since non-pulmonary TB data were not available, the pulmonary TB ratio was applied to all cases.
    - Increased the numbers of people tested when the test was implemented at lower or more peripheral settings than at a microscopy centre:
        - 10% increase in volume when implemented at health-care clinics with laboratories compared to implementation at microscopy centres only
        - 20% increase in volume when implemented at health posts compared to implementation at microscopy centres only
        - 30% increase in volume when implemented at community level compared to implementation at microscopy centres only.
4. Applied each country's population growth rate and TB prevalence rate of change over the last three years to calculate the market opportunity in 2020.

Key variables and assumptions per country

Variable or assumption	South Africa		Brazil		China		India		Total#		Source
	2012	2020	2012	2020	2012	2020	2012	2020	2012	2020	
Prevalent TB cases	450 000	426 660	120 000	130 606	1 400 000	962 642	2 800,000	1 628 969	4 770 000	3 148 878	2012: WHO report 2013 2020: estimated based on population size in 2020 according to World Bank and estimated TB prevalence rate (using country-specific 3-year average decline in TB prevalence rate)
Percentage of all prevalent TB patients that have PTB	76%	Same as 2012	78%	Same as 2012	98%	Same as 2012	72%	Same as 2012	80%	Same as 2012	WHO report 2013
Percentage of all prevalent TB patients that have EPTB	14%	Same as 2012	14%	Same as 2012	0.75%	Same as 2012	20%	Same as 2012	14%	Same as 2012	WHO report 2013: % of notified TB cases with EPTB
Percentage of all prevalent TB patients that are children with TB (unable to provide sputum)	10%	Same as 2012	8%	Same as 2012	1%	Same as 2012	8%	Same as 2012	6%	Same as 2012	Calculation: notified smear-positive TB cases among children assumed to represent 5% of all children with TB (personal communication A. Mandelakas & B. Kampmann) and 85% of children with TB assumed to be unable to produce sputum.
Number of individuals with presumptive TB needed to test to find one TB case (suspect-to-case ratio)	7	Same as 2012	15	Same as 2012	7	Same as 2012	9	Same as 2012	8.3#	8.6#	Country-specific ratios obtained from NTPs or data from NTPs
Estimated number of individuals with presumptive PTB	2 393 650	2 986 623	1 400 100	1 523 843	9 596 671	6 598 687	18 177 579	10 575 255	31 568 000	21 684 408	Calculation: (number of prevalent PTB cases in 2012 multiplied by the suspect-to-case ratio)
Number of individuals with presumptive PTB: suspects tested in 2012 (in microscopy centres)	2 116 667 (88% of PTB suspects)	88% of PTB suspects	965 544 (69% of PTB suspects)	69% of PTB suspects	6 173 936 (64% of PTB suspects)	64% of PTB suspects	7 867 194 (43% of PTB suspects)	43% of PTB suspects	17 123 341 (54% of PTB suspects)	54% of PTB suspects	Number of individuals tested with smear and/or Xpert in each country (data provided by NTPs)
Number of individuals with presumptive PTB not tested in 2012	276 983	12% of PTB suspects	434 556	31% of PTB suspects	3 422 735	36% of PTB suspects	10 310 385	57% of PTB suspects	14 444 659	46% of PTB suspects	Calculation: (number of prevalent PTB cases in 2012 multiplied by suspect-to-case ratio) – (TB suspects tested in the public and private sectors in 2012)

Number of individuals with presumptive EPTB (assumed all not tested in 2012)	441 000	418 127	252 000	274 272	73 500	50 539	5 040 000	2 932 144	5 806 500	3 675 082	Calculation: number of EPTB cases in 2012 multiplied by suspect-to-case ratio
Number of children with presumptive TB (unable to provide sputum; therefore assumed not tested in 2012)	315 350	298 994	147 900	160 972	129 829	89 271	1 982 421	1 153 322	2 575 500	1 702 559	Calculation: number of children with TB, unable to provide sputum in 2012 multiplied by suspect-to-case ratio
Total number of individuals with presumptive TB (PTB, EPTB and children combined) in the country	3 150 000	2 986 623	1 800 000	1 959 087	9 800 000	6 738 496	25 200000	14 660 721	39 950 000	26 344 927	Calculation: sum of number of individuals with presumptive PTB, EPTB and children with presumptive TB (unable to provide sputum)

# weighted averages.
TB = tuberculosis; PTB = pulmonary tuberculosis; EPTB = extrapulmonary tuberculosis; NTP = national tuberculosis programmes.
Source: Reprinted with permission from Kik SV, Denkinger CM, Jefferson C, Ginnard J, Pai M. Potential market for novel tuberculosis diagnostics: worth the investment. J Infect Dis. 2015;211(Suppl 2):S58–66.

Appendix 2 – Target Product Profiles (TPP) for four high-priority novel TB diagnostics

TPP for a sputum-based smear replacement test for TB detection

Characteristic	Optimal requirements	Minimal requirements
Scope		
Goal	To develop a sputum-based test for detecting pulmonary TB at the microscopy-centre level of the health-care system to support the initiation of TB therapy during the same clinical encounter or the same day	
Target Population	Target groups are all patients suspected of having pulmonary TB who are able to produce sputum, in countries with a medium prevalence to a high prevalence of TB as defined by WHO [a]	
Target user of the test [b]	Health-care workers with a minimum amount of training (that is, with skills that are similar to or less demanding than those needed for performing smear microscopy)	
Setting (level of the health-care system)	Microscopy-centre level (primary health-care centres with attached peripheral laboratories) or higher levels of the health-care system	
PERFORMANCE CHARACTERISTICS		
Diagnostic sensitivity [b]	Sensitivity should be > 95% for a single test when compared with culture (for smear-negative cases it should be > 68%; for smear-positive it should be 99%)	Sensitivity should be > 80% for a single test when compared with culture (for smear-negative cases it should be > 60%; for smear-positive it should be 99%)
Diagnostic specificity [b]	> 98% specificity when compared with culture	
Possibility of using test for treatment monitoring	Yes: a test that is able to replace microscopy and also be used to monitor treatment is more likely to be adopted and more likely to completely replace smear microscopy	No
OPERATIONAL CHARACTERISTICS		
Manual preparation of samples (steps needed after obtaining sample)	No steps or 1 step; precise volume control and precise timing should not be required	A maximum of 2 steps; precise volume control and precise timing should not be required
Reagent integration	All reagents should be contained in a single device	A maximum of 2 external reagents should be required; these should be part of test kit
Data export (connectivity and interoperability)	Integrated ability for all data to be exported (including data on use of the device, error rates and rates of invalid tests, and personalized, protected results) over a USB port and network	Integrated ability for all data to be exported (including data on use of the device, error rates and rates of invalid tests, and non-personalized results) over a USB port
Time to result [b]	< 20 minutes	< 2 hours
Power requirements	Battery operated with recharging capability and a circuit protector	
Maintenance and calibration [b]	Preventative maintenance and calibration should not be needed until after 2 years or 5 000 samples; only simple tools and minimal expertise should be required; an alert to indicate when maintenance is needed should be included; the device should be able to be calibrated remotely or no calibration should be required	Preventative maintenance should not be needed until after 1 year or 1 000 samples; only simple tools and minimal expertise should be required; an alert to indicate when maintenance is needed should be included; the device should be able to be calibrated remotely, should calibrate itself or no calibration should be required
Operating temperature and humidity level	Between +5 °C and +50 °C with 90% humidity	Between +5 °C and +40 °C with 70% humidity
Reagent kit – storage, stability and stability during transport	2 years at 0 °C to +50 °C with 90% humidity; should be able to tolerate stress during transport (72 hours at +50 °C); no cold chain should be required	12 months at 0 °C to +40 °C with 70% humidity; should be able to tolerate stress during transport (72 hours at +50 °C); no cold chain should be required
Internal quality control	Full internal process controls are necessary, including controls for sample processing and amplification (for NAAT)	
PRICING		
Price of individual test [b] (costs of reagent only; after scale-up; ex-works (manufacturing costs only, excluding shipping))	< US$ 4 for detecting TB	< US$ 6 for detecting TB
Capital costs for instrument [b]	< US$ 500 per module	< US$ 1400 per module

Abbreviations: NAAT, nucleic acid amplification test;

[a] High-prevalence countries are those with >40 cases per 100 000 population; medium-prevalence countries are those with 20–40 cases per 100 000 population; and low-prevalence countries are those with <20 cases per 100 000 population (19).

[b] These characteristics were considered to be the most important, and specific consensus was asked for and reached through a Delphi survey.

Source: Adapted from High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland: meeting report. Geneva: World Health Organization; 2014

TPP for a rapid non-sputum-based biomarker test for TB detection

Characteristic	Optimal requirements	Minimal requirements
SCOPE		
Goal	To develop a rapid biomarker-based test that can diagnose pulmonary TB and optimally also extrapulmonary TB using non-sputum samples (for example, urine, blood, oral mucosal transudates, saliva, exhaled air) for the purpose of initiating TB treatment during the same clinical encounter or on the same day	
Target Population	Target groups are adults and children including those who are HIV- positive and suspected of having active pulmonary TB or extrapulmonary TB in countries with a medium prevalence to a high prevalence of TB as defined by WHO [a]	
Target user of the test [b]	Health-care workers with a minimum of training	Trained microscopy technicians
Setting (level of the health-care system)	Health posts without attached laboratories (that is, levels below microscopy centres) or higher levels of the health-care system	Primary health-care clinics with attached laboratories; peripheral microscopy centres or higher levels of the health-care system
PERFORMANCE CHARACTERISTICS		
Diagnostic sensitivity for pulmonary TB in adults [b]	Sensitivity should be ≥ 98% for smear-positive culture-positive pulmonary TB, and ≥ 68% for smear-negative culture-positive pulmonary TB in adults (that is, sensitivity should be similar to that of the Xpert MTB/RIF assay) Overall pooled sensitivity should be ≥ 80% in adults with HIV infection	Overall sensitivity should be ≥ 65% but should be > 98% among patients with smear-positive culture- positive pulmonary TB (that is, sensitivity should be similar to that of smear microscopy) Overall pooled sensitivity should be better than the sensitivity of smear microscopy in adults with HIV infection
Diagnostic sensitivity for extrapulmonary TB in adults [b]	Ideally, sensitivity should be ≥ 80% for all forms of microbiologically confirmed extrapulmonary TB [c,d]	Diagnosis of extrapulmonary TB is an important need, and a test that can diagnose extrapulmonary TB in addition to pulmonary TB will have significant benefits for individual patients; additionally, it is likely to be better accepted in the community of care providers. No lower range of sensitivity was defined
Diagnostic sensitivity in children [b]	Sensitivity for childhood intrathoracic TB should be ≥ 66% for microbiologically confirmed TB (that is, similar to the sensitivity of the Xpert MTB/RIF assay) [e]	Diagnosis of childhood TB is an important need, and a test that improves the diagnosis of TB in children will have significant benefits for individual patients; additionally, it is likely to be better accepted in the community of care providers. No lower range of sensitivity was defined
Diagnostic specificity [b]	At least as specific as the Xpert MTB/RIF assay for detecting pulmonary TB, extrapulmonary TB and childhood TB (that is, the test should have 98% specificity when compared against a microbiological reference standard); the test should distinguish between active TB and latent or past infection	
OPERATIONAL CHARACTERISTICS		
Sample type	Not invasive or minimally invasive, non-sputum samples (such as, urine, blood, oral transudates, saliva, exhaled air)	
Manual preparation of samples (steps needed after obtaining sample)	Sample preparation should be integrated or manual preparation should not be required	A limited number of steps only; precise measuring should not be needed for any step (such as precise measuring of volumes or time)
Time to result [b]	< 20 minutes including time spent preparing the sample	< 1 hour including time spent preparing the sample
Instrument and power requirements	No instrument needed	Small, portable or hand-held instrument (weighing < 1 kg) that can operate on battery or solar power in places where power supplies may be interrupted
Maintenance and calibration [b]	Disposable, no maintenance required	Preventative maintenance should not be needed until after 1 year or > 1 000 samples; only simple tools and minimal expertise should be required; an alert to indicate when maintenance is needed should be included; the instrument should be able to be calibrated remotely or no calibration should be needed
Operating temperature and humidity level	Between +5 °C and +50 °C with 90% humidity	Between +5 °C and +40 °C with 70% humidity
Result capturing, documentation, data display	An instrument-free test with the ability to save results using a separate, attachable reader	The test menu must be simple to navigate; the instrument should have an integrated LCD screen, simple keypad or touch screen, and the ability to save results using either the instrument or a separate reader

Internal quality control	Internal controls should be included for processing the sample and detecting TB	Internal control included only for processing the sample
PRICING		
Price of individual test [b] (costs of reagents and consumables only; after scale-up; ex-works (manufacturing costs only, excluding shipping))	< US$ 4	< US$ 6

Abbreviations: HIV, human immunodeficiency virus; LCD, liquid crystal display.

[a] High-prevalence countries are those with > 40 cases per 100 000 population; medium-prevalence countries are those with 20–40 cases per 100 000 population; and low-prevalence countries are those with < 20 cases per 100 000 population (19).

[b] These characteristics were considered to be the most important, and specific consensus was asked for and reached through a Delphi survey.

[c] The sensitivity for detecting extrapulmonary TB should also be tested against a composite reference standard that includes culture with or without a nucleic acid amplification test, histology, smear microscopy, biochemical testing, presenting signs, and response to treatment with anti-TB therapy, depending on site of infection. Xpert MTB/RIF testing has an estimated sensitivity for diagnosing TB of 84% for lymph node aspirates or other tissue samples, and 55% sensitivity for samples of cerebrospinal fluid, when compared with a composite reference standard, but Xpert MTB/RIF testing requires invasive samples (17).

[d] Xpert MTB/RIF has an estimated sensitivity for microbiologically confirmed TB of 85% for detecting TB in lymph node aspirates or other tissue samples, 80% for cerebrospinal fluid, and 44% for pleural fluid but testing requires invasive samples (from aspiration, biopsy, lumbar puncture or thoracentesis).

[e] The test's sensitivity in children should be evaluated against a composite reference standard as defined by an international panel of experts (6).

Source: Adapted from High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland: meeting report. Geneva: World Health Organization; 2014

TPP for a community-based triage/referral test for identification of TB suspects

Characteristic	Optimal requirements	Minimal requirements
Scope		
Goal	To develop a test that can be used during a patient's first encounter with the health-care system to identify patients with any symptoms of or risk factors for active TB, including patients coinfected with HIV, those who do not have TB and those who need referral for further confirmatory testing	To develop a test that can be used during a patient's first encounter with the health-care system to identify patients with any symptoms of or risk factors for active pulmonary TB, including patients coinfected with HIV, those who do not have TB and those who need referral for further confirmatory testing
Target Population	Adults and children with signs and symptoms of active TB at any site in countries with a medium prevalence to a high prevalence of TB as defined by WHO [a]	Adults and children with signs and symptoms of active pulmonary TB in countries with a medium prevalence to a high prevalence of TB as defined to a high prevalence of TB as defined by WHO [a]
Target user of the test [b]	Community health workers and informal providers who have had a minimum of training	Health workers trained to the level of auxiliary nurses
Setting (level of the health-care system)	Community level or village level or higher levels of the health-care system	Health posts and primary-care clinics or higher levels of the health-care system
PERFORMANCE CHARACTERISTICS		
Diagnostic sensitivity [b]	Overall sensitivity should be > 95% when compared with the confirmatory compared with the confirmatory test for pulmonary TB [c] no lower range of sensitivity was defined for extrapulmonary TB [d]	Overall sensitivity should be > 90% when compared with the confirmatory compared with the confirmatory test for pulmonary TB [c]
Diagnostic specificity [b]	Specificity should be > 80% compared with the confirmatory test	Specificity should be > 70% compared with the confirmatory test
OPERATIONAL CHARACTERISTICS		
Sample type	Non-sputum samples (such as urine, oral mucosal transudates, saliva, exhaled air or blood from a finger- stick	Sputum; non-sputum samples are preferred (such as urine, oral mucosal transudates, saliva, exhaled air, or blood from a finger-stick; imaging technology
Manual preparation of samples (steps needed after obtaining sample)	Sample preparation should be integrated or manual preparation should not be required (excluding waste disposal); precise timing and measuring should not be required	2 steps (excluding waste disposal); precise timing and measuring should not be required
Time to result [b]	< 5 minutes	< 30 minutes
Instrument and power requirements	None	Small, portable or hand-held device (weighing < 1 kg); should have an option for battery power or solar power
Maintenance and calibration [b]	Disposable; no maintenance required	Preventative maintenance should not be needed until after 1 year or 1 000 samples; only simple tools and minimal expertise should be required; an alert to indicate when maintenance is needed should be included; the device should be able to be calibrated remotely, should calibrate itself, or no calibration
Operating temperature and humidity level	Between +5 °C and +50 °C with 90% humidity	Between +5 °C and +40 °C with 70% humidity
Result capturing, documentation and data display	An instrument-free test with visual readout and with the ability to save results using a separate, attachable reader	The test menu must be simple to navigate; the instrument should have an integrated LCD screen, a simple keypad or touch screen, and the ability to save results using either the instrument or a separate reader
Internal quality control	Internal controls should be included for processing the sample and detecting TB	Internal control included only for processing the sample
PRICING		
Price of individual test[b] (costs of reagents and consumables only; after scale-up; ex-works (manufacturing costs only, excluding shipping))	< US$ 1	< US$ 2

Abbreviations: HIV, human immunodeficiency virus; LCD, liquid crystal display.

[a] High-prevalence countries are those with > 40 cases per 100 000 population; medium-prevalence countries are those with 20–40 cases per 100 000 population; and low-prevalence countries are those with < 20 cases per 100 000 population (19).

[b] These characteristics were considered to be the most important, and specific consensus was asked for and reached through a Delphi survey.

[c] The performance characteristics of the triage test need to match those of the confirmatory test that will be used.

[d] The sensitivity of the triage test should be compared with the sensitivity of a composite reference standard (that includes culture with or without a nucleic acid amplification test, histology, smear microscopy, biochemical testing, presenting signs and response to treatment with anti-TB therapy, depending on site of infection) to account for the fact that the test may detect cases of early TB or extrapulmonary TB in cases in which a standard microbiological reference standard might not perform well.

Source: Adapted from High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland: meeting report. Geneva: World Health Organization; 2014

TPP for drug susceptibility tests (DSTs) at microscopy centres

Characteristic	Optimal requirements	Minimal requirements
Scope		
Goal	To develop a test to diagnose TB disease and detect drug resistance to inform decision-making about optimal current and likely future first-line therapy (HRZE, REMox or PaMZ), and possibly to detect resistance to additional second-line anti-TB agents and determine whether there is a need for further testing	
Target Population	Target groups are all patients suspected of having TB, with a special focus on those at high risk of morbidity and mortality from drug-resistant TB, such as people living with HIV, and those at high risk of having MDR-TB (for example, household contacts of patients diagnosed with MDR-TB, and persons with a history of TB, especially those for whom first-line therapy has failed) in countries with a medium prevalence to a high prevalence of TB as defined by WHO [a]	
Target user of the test [b]	1. RIF 2. FQs (including MOX) 3. INH and PZA (equally important) 4. AGs and CAP Ordered by preference. Optimally, all anti-TB agents would be included, but as a minimum at least RIF should be included	
Lowest setting of implementation (level of the health-care system)	Microscopy centre level or higher levels of the health-care system	
PERFORMANCE CHARACTERISTICS		
Diagnostic sensitivity compared against genetic sequencing as the reference standard [b]	Sensitivity should be > 98% for detecting targeted SNPs for resistance to RIF, FQs, PZA, INH, and AGs and CAP when compared with genetic sequencing	Sensitivity should be > 98% for detecting targeted SNPs for resistance to RIF, and 95% for detecting SNPs for resistance to FQs, PZA, INH, and AGs and CAP when compared with genetic sequencing
Diagnostic sensitivity compared against phenotypic DST as the reference standard	Sensitivity should be > 95% for detecting resistance to RIF, FQs, PZA, INH, and AGs and CAP when compared with the recommended reference phenotypic culture DST for a specific anti-TB agent	Sensitivity should be > 95% for detecting resistance to RIF and >90% for detecting resistance to FQs, PZA, INH, and AGs when compared with the recommended reference phenotypic culture DST for a specific anti-TB agent
Diagnostic specificity compared against genetic sequencing as the reference standard [b]	Specificity should be ≥ 98% for any anti-TB agent for which the test is able to identify resistance when compared against genetic sequencing as the reference standard The positive predictive value (PPV) of a resistance call will depend on the underlying prevalence of resistance in the population tested: if the prevalence is < 3% then very high specificity (that is, ≥ 99.7%) must be achieved to obtain a PPV of > 90%; if the prevalence of resistance is ≥ 20% (for example, by testing only high-risk patients), a specificity of >97% is sufficient to achieve a PPV of > 90%	
Diagnostic specificity compared against phenotypic DST as the reference standard	Targeted sequencing for the mutations included in the test that indicate resistance against any anti-TB agent should exceed 98% when compared against the phenotypic reference standard recommended for each anti-TB agent.	
OPERATIONAL CHARACTERISTICS		
Maintenance and calibration [b]	Preventative maintenance should not be needed until after 2 years or > 5 000 samples; an alert to indicate when maintenance is needed should be included; the instrument should be able to be calibrated remotely or should not require any calibration	Preventative maintenance should not be needed until after 1 year or 1 000 samples; an alert to indicate when maintenance is needed should be included; the instrument should be able to be calibrated remotely or should not require any calibration
Time to result [b]	< 30 minutes	< 2 hours
Data analysis	Data analysis should be integrated (there should be no requirement for a PC); exported data should be capable of being analyzed on a separate or networked PC	
Data export (connectivity and interoperability)	Integrated ability for all data to be exported (including data on use of the device, error rates and rates of invalid tests, and personalized, protected results) over a USB port and network	Integrated ability for all data to be exported (including data on use of the device, error rates and rates of invalid tests, and non-personalized) over a USB port
Operating temperature and humidity level	Between +5 °C and +50 °C with 90% humidity	Between +5 °C and +40 °C with 70% humidity

Reagent kit – storage, stability and stability during transport	2 years at +5 °C to +50 °C with 90% humidity; no cold chain should be required; should be able to tolerate stress during transport for a minimum of 72 hours at 0 °C to +50 °C	18 months at +5 °C to +40 °C with 70% humidity; no cold chain should be required; should be able to tolerate stress during transport for a minimum of 72 hours at 0 °C to +40 °C
Internal quality control	Full controls are necessary, including controls for sample processing, amplification and detection of TB	
PRICING		
Price of individual test [b,c] (reagent and consumables only; after scale-up; ex-works (manufacturing costs only, excluding shipping))	Optimal price: < US$ 10 Meeting participants emphasized the critical need for the price to be kept within an affordable range. A price higher than currently available technologies (for example, molecular testing for simultaneous detection of TB and resistance to RIF or for resistance to RIF and INH both cost approximately US$ 10 per test) would be justified only if the new tests add substantial value in terms of improved performance, greater suitability for decentralization, and the number of anti-TB agents for which resistance can be detected. The market size for reflex testing will also need to be taken into account. Consensus was not reached on the minimal requirement (that is, the highest acceptable price point)	
Capital costs for instrument [b]	US$ 1400 per module (for a test combining detection and DST)	US$ 1400 per module for DST only

Abbreviations: NAAT, nucleic acid amplification test.

[a] High-prevalence countries are those with >40 cases per 100 000 population; medium-prevalence countries are those with 20–40 cases per 100000 population; and low-prevalence countries are those with <20 cases per 100000 population (19).

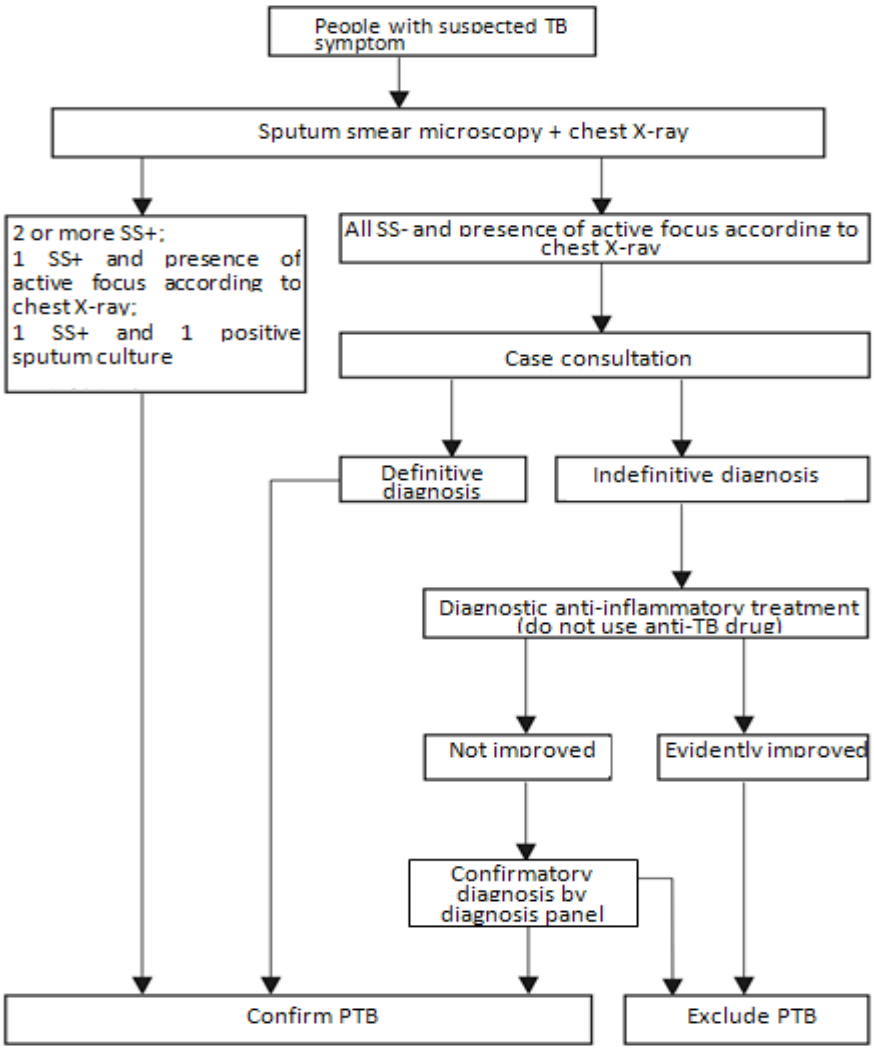
[b] These characteristics were considered to be the most important, and specific consensus was asked for and reached through a Delphi survey.

Source: Adapted from High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland: meeting report. Geneva: World Health Organization; 2014

Appendix 3 – Country diagnostic algorithms

China

Recommended diagnostic algorithm for individuals (>15 years) with symptoms presumptive of pulmonary tuberculosis in China

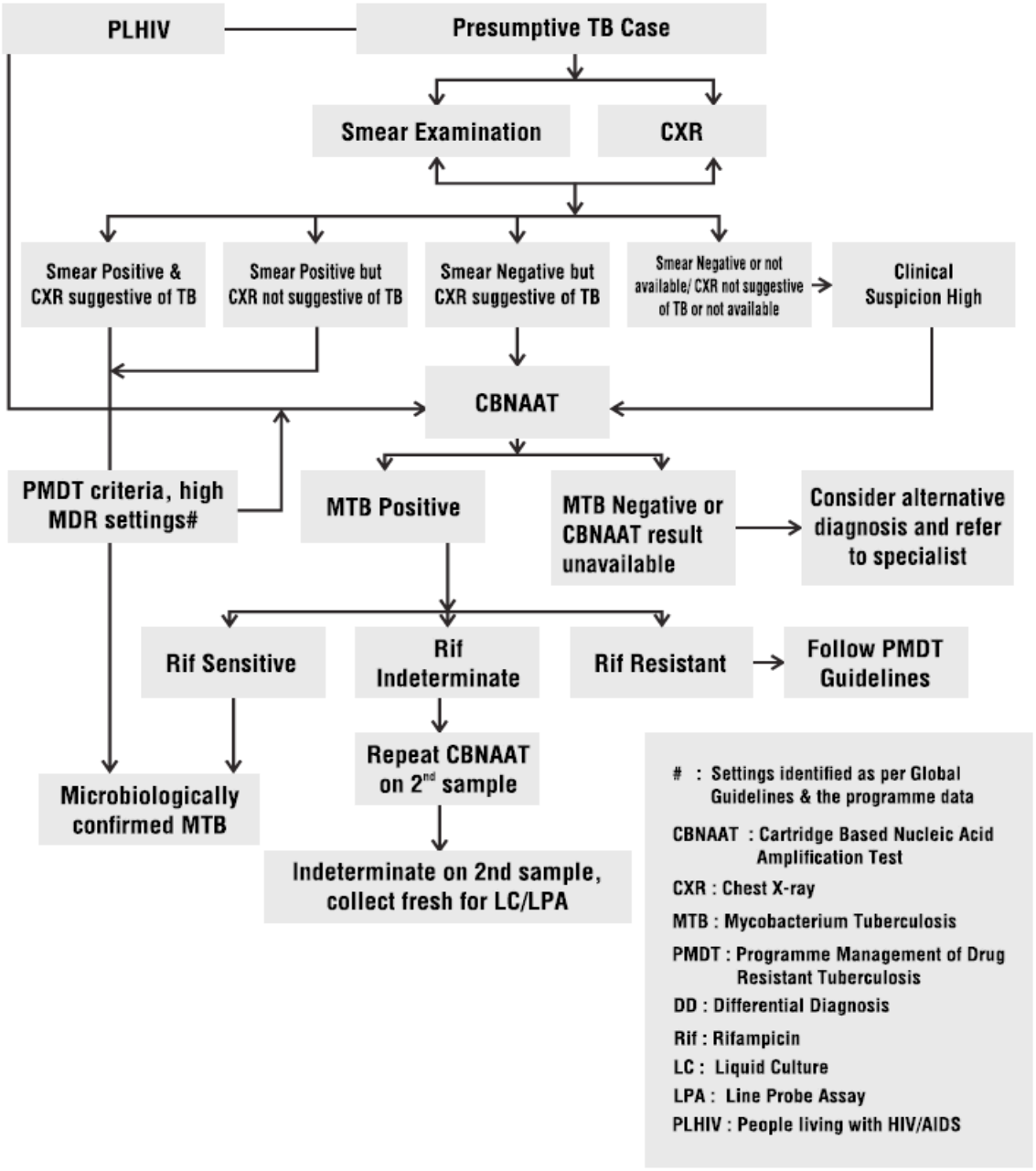


Flowchart on examination and diagnosis of PTB patients with the age ≥15

Source: Guidelines for Implementing the National Tuberculosis Control Program in China, Department of Disease Control, MOH; Department of Medical Administration, MOH; Chinese Center for Disease Control and Prevention, http://www.docin.com/p-609654057.html&key=%E8%82%BA%E7%97%A8%E6%80%8E%E4%B9%88%E6%B2%BB.

India

Revised diagnostic algorithm for diagnosis of TB including DST, liquid culture testing and CBNAAT.

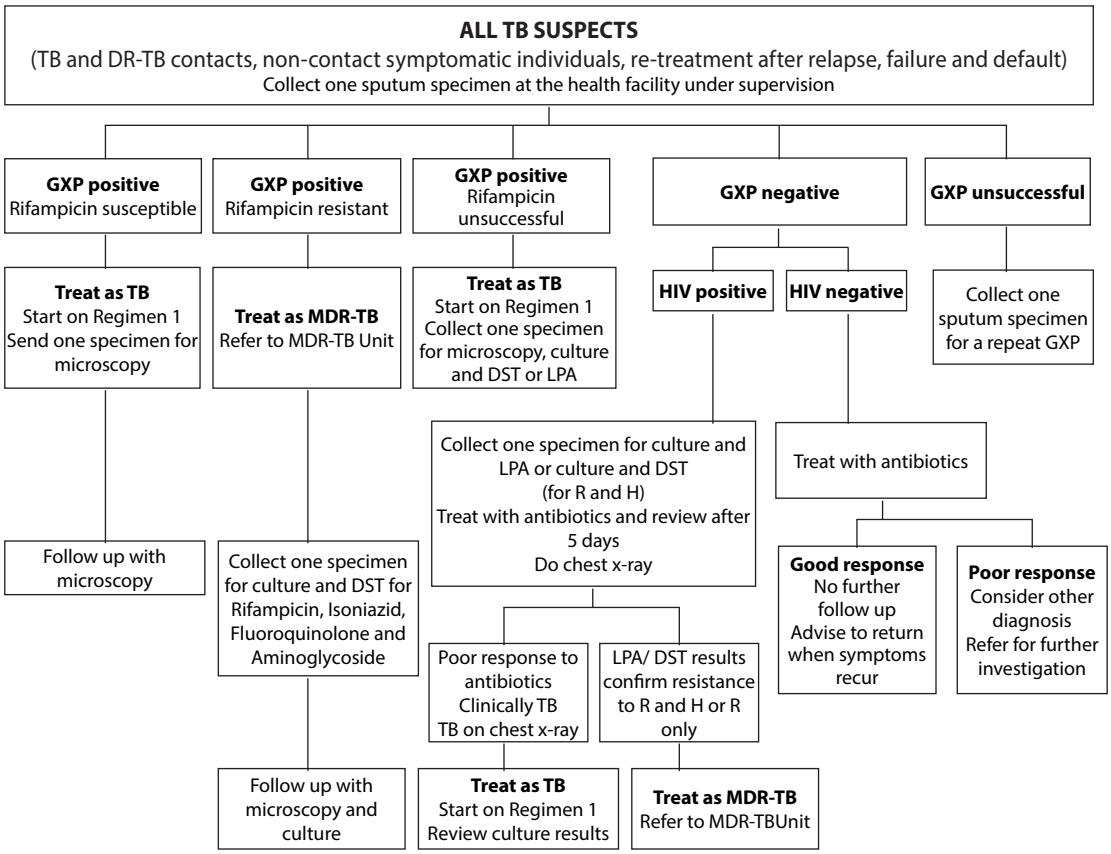


CBNAAT=cartridge based nucleic acid amplification test, CXR=chest X-ray, MTB=mycobacterium tuberculosis, PMDT = programmatic management of drug-resistant TB, DD=differential diagnosis, Rif=rifampicin, LC=liquid culture, LPA=line probe assay, PLHIV=people living with HIV/AIDS

Source: Revised National TB Control Programme, Ministry of Health and Family Welfare, Delhi. http://www.tbcindia.nic.in/

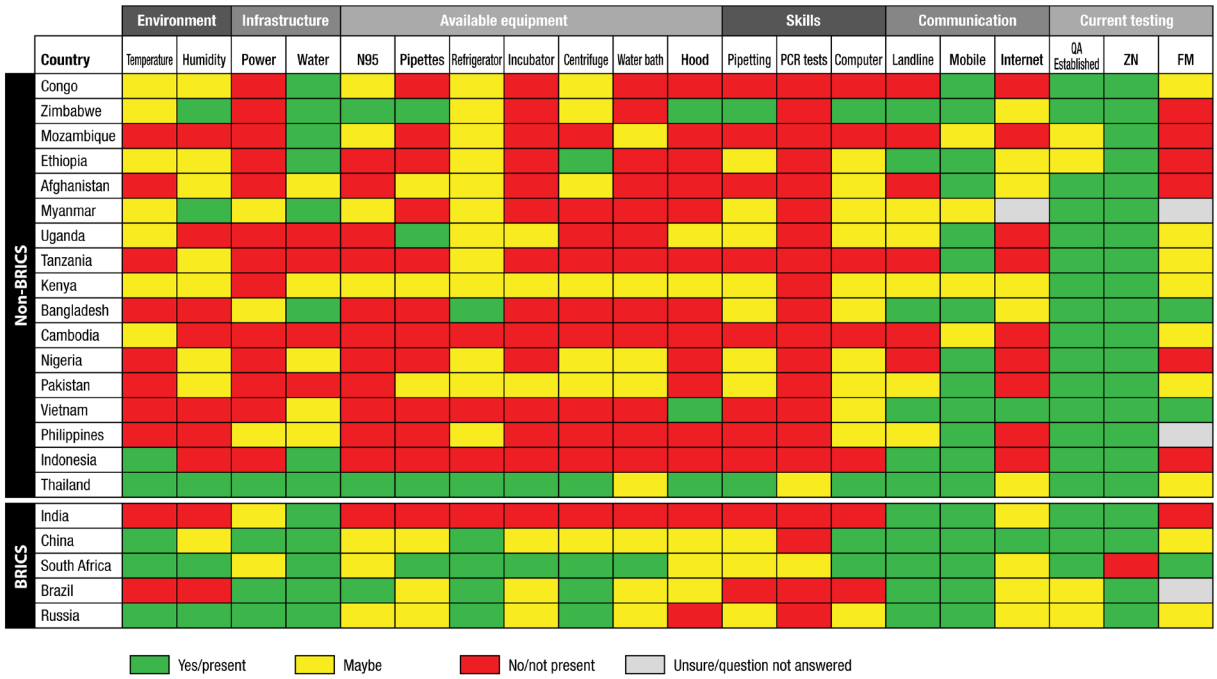
South Africa

GeneXpert (new) testing algorithm in place during 2012 in South Africa in the public sector



Source: National Tuberculosis Management Guidelines 2014, Republic of South Africa Department of Health, http://www.hst.org.za/publications/national-tuberculosis-management-guidelines-2014.

Appendix 4 – Characteristics of peripheral microscopy centres in 22 high-burden countries



Questions related to environmental conditions (Is temperature or humidity not a concern?), infrastructure (Is a stable power supply, clean water supply and room security present?), presence of equipment (gloves, N95 respirator, micropipettes, refrigerator, incubator, centrifuge, hot water bath or biosafety hood) and skills (to operate a micropipette or computer or perform a PCR test) and the presence of means of communication (landline, mobile or internet). Additional questions asked about whether quality assurance (QA) measures and waste management were established or whether stock of testing supplies was always replenished in time. In addition we asked about which diagnostic tests were currently used. Countries are sorted by increasing purchasing power parity. BRICS countries are Brazil, Russia, India, China and South Africa.

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