FIND

STRATEGY FOR TUBERCULOSIS

(AND LOWER RESPIRATORY TRACT INFECTIONS)

2015-2020

ABOUT FIND

FIND was founded in 2003 to bridge existing development gaps for essential diagnostics by initiating and coordinating research and development (R&D) projects in collaboration with the international research community, the public sector, and the *in vitro* diagnostics industry. Today, FIND is a leading partner across the value chain of diagnostics development and delivery. We have programmes in Tuberculosis and Acute Febrile Respiratory Infections, Malaria and Acute Febrile Syndrome, Hepatitis C, and Neglected

Tropical Diseases. We also have mini-portfolios in areas affecting reproductive and child health: HIV; sexually transmitted infections; and infections and nutritional deficiencies in children under five years old. At FIND, we envision a world where diagnostics guide the path to health for all people. We aim to turn complex diagnostic challenges into simple solutions to transform lives and overcome diseases of poverty. To do this we focus on four strategic goals throughout all the disease areas in which we work:

■ Catalyse development:

Identify needed diagnostic solutions and remove barriers to their development.

■ Guide use & policy:

Lead products through the clinical trials pathway to global policy on use and market entry.

■ Accelerate access:

Support uptake and appropriate use of diagnostics to achieve health impact.

■ Shape the agenda:

Improve understanding of the value of diagnostics and strengthen commitment to their funding and use.

FIND's Vision

A world where diagnosis guides the way to health for all people

FIND's Mission

Turning complex diagnostic challenges into simple solutions to overcome diseases of poverty and transform lives

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ABOUT TUBERCULOSIS

In 2012, there were an estimated 8.6 million Tuberculosis (TB) cases and 1.3 million deaths worldwide, the majority of which were likely preventable with existing treatments. Major gains have been made in the fight against TB over the past decades. In its "Global Tuberculosis Report 2013" the World Health Organization (WHO) confirms that the world is on track to meet the targets of the 2015 UN Millennium Development Goals and is reversing TB incidence. Similarly, all regions except for Africa and Eastern Europe are on track to achieve reducing the mortality rate by 50%. However, to accelerate the fight against TB and move towards elimination of the disease, two major challenges must be urgently addressed:

• Each year an estimated three million patients, i.e. about one-third of all TB cases, do not receive diagnosis and treatment.

• The rise of drug resistance is creating a public health crisis. WHO estimates that in 2012, 450,000 people fell ill with multidrug-resistant TB (MDR-TB). While in the same year the number of patients detected worldwide with rapid drug susceptibility tests (DST) increased by more than 40% to 94,000, three out of four MDR-TB cases still remain undiagnosed.

FIND is working to improve diagnosis of TB and identification of drug resistance to increase adequate treatment for individual patients, disease control at the population level and prevent the spread of drug resistance. In 2010, FIND and the global health care community made an important advance in the fight to control TB through diagnosis with the introduction of Xpert MTB/RIF (Xpert) – a tool that transformed DST to enable rapid detection of TB and resistance to rifampicin, the key component in the established first-line treatment regimen. Xpert replaced a test that used to take 120 days at a reference-level laboratory to now allow test results to be available in 90 minutes at lower levels of care. Thanks to rapid policy endorsement and major commitments by the global community and donors like The Global Fund, the test was rolled out to over 120 countries in less than two

years. However, critical gaps in TB diagnosis remain. Despite the success of Xpert, its scope remains limited by its cost and infrastructure requirements, demonstrating that new diagnostic tools do not necessarily reach everyone eligible for testing or increase the overall number of TB cases diagnosed if implemented within established care settings.

We advocate for innovative tests that improve performance characteristics and can be deployed at all levels of the health care system, including at the community level. With new, wide-ranging tests we can reach the three million people who have TB but are currently undiagnosed. When such tests are combined with the appropriate implementation strategies and linkage to treatment, the result is a comprehensive diagnostic solution that will broaden access to early testing, minimize diagnostic delay, result in a treatment decision at the first medical encounter and interrupt TB transmission. Novel tests are also needed to enable rapid DST and treatment monitoring to detect insufficient treatment sooner. This is critical to prevent the further development and spread of drug resistance and to protect new regimens and drugs entering the market, e.g. PaMZ and Bedaquiline. In addition to innovative tests, new testing strategies are necessary to find TB cases and further curb the epidemic, as merely testing symptomatic patients will have limited impact.

Lastly, FIND's work in implementing new diagnostic tools has highlighted significant shortcomings in the health care systems in many low- and middle-income countries that limit the impact of diagnostic tests, further demonstrating the need for more comprehensive diagnostic solutions. To increase the impact of diagnostic tools we must improve supply chain management, quality assurance of laboratories (particularly at peripheral sites), training of health care workers and referral of specimens for more intensive testing, like second-line DST.

FIND will advocate to highlight the vital role of diagnostics in controlling the spread of TB and raise awareness of the funding challenges for research and development in the area of TB.

PAST AND CURRENT ACTIVITIES

2014 marks the 11 year anniversary of FIND's work and partnerships to develop new diagnostic tools and support their implementation in low-resource settings. Through FIND's TB programme, we have introduced six new technologies for diagnosis of TB and rapid detection of drug resistance, including Xpert, which was endorsed by the WHO in 2010 and is now used in more than 120 countries. And FIND is actively engaged in shaping the future of diagnostic test development through specifying target product profiles (TPPs) with key stakeholders. These recent developments have reinvigorated public and private sector support in the fight against TB. In addition, FIND has helped shape the process for policy on use as a WHO partner for clinical trials and enabled rapid uptake of new technologies in countries.
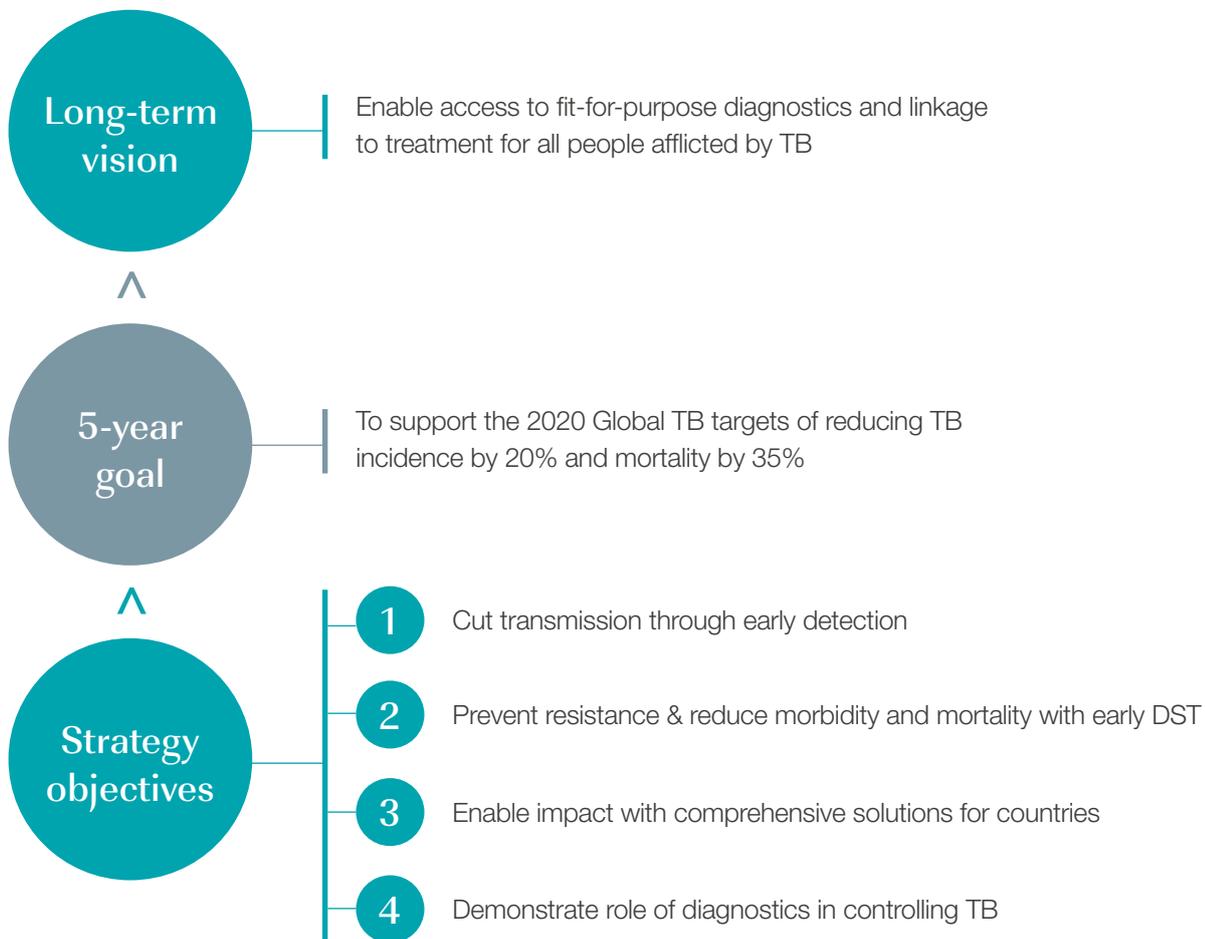
FIND is also working to accelerate the adoption of new diagnostic tools. Our work in laboratory strengthening promotes local ownership and builds capacity. We work in partnership with ministries of health to develop locally appropriate solutions based on international best practices. In the past five years, FIND has trained close to 4,400 health care workers and worked with over 360 laboratories in 39 countries. Through the work of FIND and our partners, an estimated 300,000 lives per year have been saved. In India alone, 90% of all MDR-TB cases reported in 2012 by the country were diagnosed through FIND supported tools and programmes.

GOALS AND OBJECTIVES OF THE FIND TB PROGRAMME

TB is one of the top three infectious disease pandemics that overwhelmingly affects patients in low-resource settings. FIND has been engaged in the fight against TB since 2003. The vision of the FIND TB programme for the future is to enable access to fit-for-purpose diagnostics and linkage to treatment for all people afflicted by TB. We support the 2020 Global TB targets of reducing the number of people suffering or dying from TB by 20% and 35%, respectively. We will do this by focusing on the following objectives:

- Cut transmission through early detection

- Provide correct treatment through early DST to prevent antimicrobial resistance and decrease morbidity and mortality

- Enable impact through comprehensive, country-specific solutions

- Demonstrate the vital role of diagnostics in controlling the TB epidemic

Addressing challenges to meet global goals of TB programme

Long-term vision — Enable access to fit-for-purpose diagnostics and linkage to treatment for all people afflicted by TB

5-year goal — To support the 2020 Global TB targets of reducing TB incidence by 20% and mortality by 35%

Strategy objectives

1 Cut transmission through early detection

2 Prevent resistance & reduce morbidity and mortality with early DST

3 Enable impact with comprehensive solutions for countries

4 Demonstrate role of diagnostics in controlling TB

GLOBAL DIAGNOSTIC NEEDS IN TUBERCULOSIS AND CURRENT LANDSCAPE

In order to achieve the objectives of our TB strategy and enable global goals, FIND is addressing a variety of needs ranging from development to delivery of diagnostics.

Regarding the development needs described in detail in the following section (lettered A – E), we have identified the overarching need for better fit-for-purpose tests. At lower levels of the health care system, performance of current diagnostic tests is highly variable depending on operator expertise (i.e. smear), quality assurance and maintenance of the device (e.g. Xpert). Simpler, more robust and easy-to-use tests are required to maintain the desired performance characteristics in routine clinical settings and particularly at the lower levels of care.

SIMPLER, MORE ROBUST
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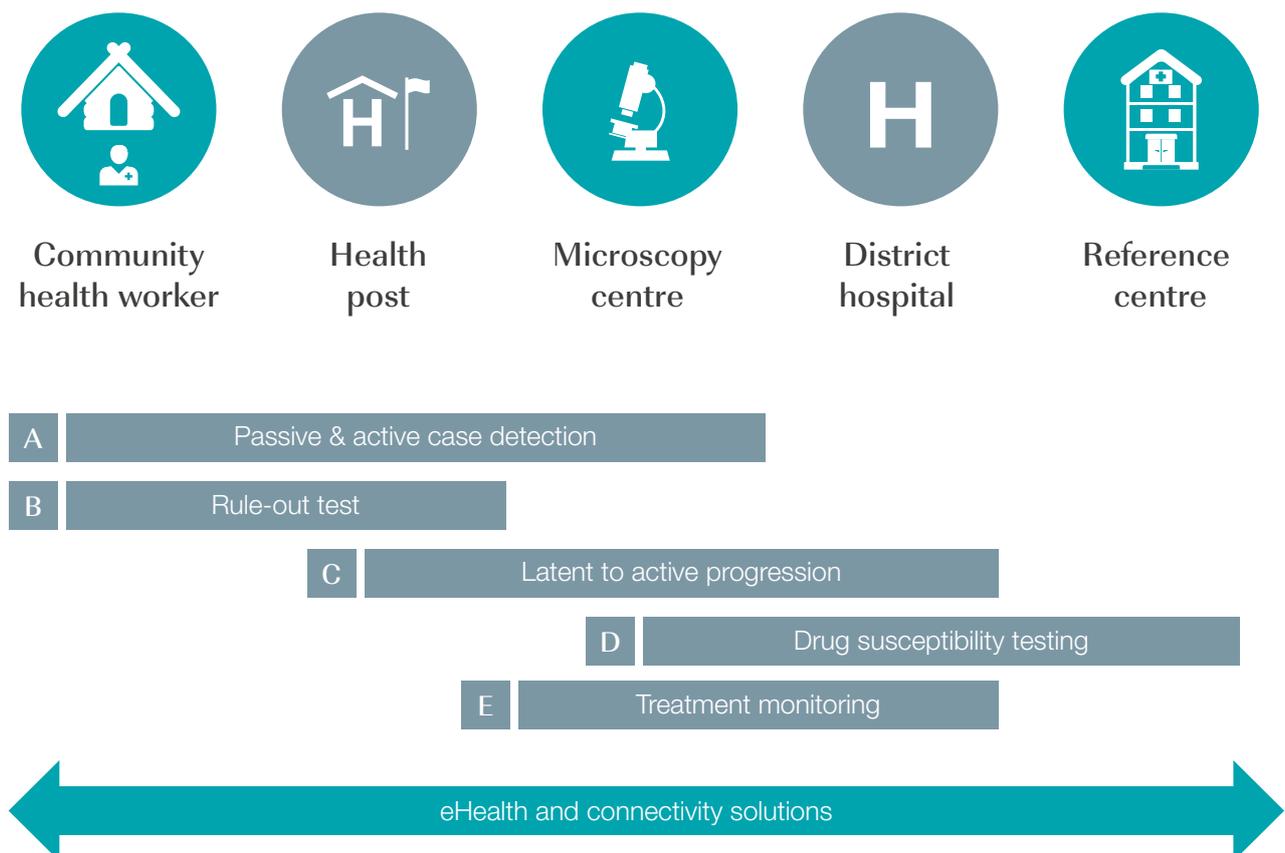TO EFFECTIVELY FIGHT
TUBERCULOSIS.

Cutting transmission through early detection

Reducing TB transmission through earlier diagnosis requires innovative, user-friendly tools that can be used at the lower levels of the health system, as well as improved strategies to increase access to existing tools. New tools that are needed include:

A. Better tests for passive and active case detection: The performance characteristics of rapid tools for TB detection are still not as effective as culture tests, e.g. the 90% sensitivity of Xpert compared to culture. With more sensitive tests, patients with TB can be identified upon first presentation to the health care system at lower levels of care and patients with paucibacillary disease can be detected, e.g. HIV patients and children. More sensitive tests would also enable active case finding, enabling the detection of a large amount of patients who do not have symptoms of TB early in their active disease. These more sensitive tests will eliminate treatment delay due to missed diagnosis and reduce morbidity, mortality and transmission through early treatment.

Summary of needed diagnostic tools for TB across the health care system

| Community health worker | Health post | Microscopy centre | District hospital | Reference centre |

- **A** — Passive & active case detection
- **B** — Rule-out test
- **C** — Latent to active progression
- **D** — Drug susceptibility testing
- **E** — Treatment monitoring

eHealth and connectivity solutions

B. Rule-out/triage test: A highly sensitive test with reasonable specificity, combined with a confirmatory test, would also be of tremendous value by reaching more patients and reducing the cost of the diagnostic algorithm. In the short term, a positive triage test would most likely lead to a molecular test, ideally with DST, or more invasive testing if extrapulmonary TB is suspected.

C. Test for latent TB progression to active TB: A substantial amount of active TB cases develop from latent TB, rather than progressing directly to active TB upon first infection. A test that can predict which patients will progress from latent TB infection (LTBI) to active TB would guide preventive therapy, contribute to an incidence reduction and help achieve the WHO's goal of pre-eliminating TB by 2035.

FIND is also working to better **understand if and how existing tools could be used as part of innovative strategies to improve TB control**. For example, chest X-rays could be evaluated for active case finding or as a triage tool to reduce the number of costly confirmatory tests needed. **Operational research** and policy guidance to shape novel strategies are needed to improve the implementation of existing tools and develop new approaches.

> Tests that can rapidly detect drug resistance and inform treatment choices are vital to prevent development of future resistance and to decrease transmission, morbidity and mortality.

Selecting correct treatment through early DST to prevent antimicrobial resistance

Preventing the spread of antimicrobial resistance also requires innovative tests, including:

D. Rapid drug susceptibility tests: Tests that can rapidly detect drug resistance and inform treatment choices are vital to prevent development of future resistance and to decrease transmission, morbidity and mortality. Molecular tests such as Xpert MTB/RIF, combined with sequencing in the longer term, show the highest promise for rapid detection, but further work is needed to understand the correlation of mutations with phenotypic testing and patient outcomes. At lower levels of the health care system, testing should inform first-line regimen selection (currently HRZE only but possibly PaMZ in the near future), while at higher levels of care, treatment decisions for individualized therapy should be supported by DST.

E. Test for treatment monitoring/Test of cure: Tests that assess patient response to therapy and cure can result in management changes, e.g. adherence counselling, changes in duration of therapy or additional resistance testing, and thus can further aid the appropriate management of patients and prevent the development of microbial resistance. Currently, there is no test of cure, and the most commonly used test for treatment monitoring (smear microscopy) is limited in its sensitivity and its ability to differentiate between live and dead bacteria or between Mycobacterium tuberculosis (MTB) and non-tuberculous mycobacteria (NTM).

State of technology development to meet needs for new tests

	Technology Approach	Stage	Details
A **Better tests for passive & active case detection**	Decentralized molecular test	Late	Multiple platforms in the pipeline (e.g., Molbio, Epistem, Alere), many combined with DST
	Sputum-free RDT	Early	No suitable biomarkers yet, but work ongoing
B **Rule-out test**	Beta-lactamase	Mid	Development ongoing
	Multiple other tests on blood, urine, breath	Early	Biomarker work ongoing (as above for detection test); easier to meet goal of rule-out test (imperfect specificity)
C **Latent to active prediction tests**	Research focused on immune activation markers	Early	No suitable biomarkers yet, but work ongoing
D **Centralized and decentralized DST**	Decentralized molecular test	Mid	Multiple platforms in development for centralized and decentralized DST (see above)
	Centralized molecular test	Mid	Database work to correlate mutations with phenotypic DST and outcomes ongoing; multiple platforms under development
E **Rx monitoring & test of cure**	Molecular or biomarker	Early	No suitable biomarkers yet, but work ongoing and molecular solutions explored as well

Syndromic approach to lower respiratory tract infections

• Why is it necessary to combine a syndromic approach with diagnostics for TB?

Studies have shown that many opportunities of diagnosing patients with TB are missed on their first visit to health care providers. This can in part be explained by the fact that TB programmes are not well integrated into the public health system and are often only utilized by patients once a work-up or treatment trial for other more common diseases like bacterial pneumonia has been unsuccessful. A syndromic approach might also substantially reduce antibiotic overtreatment, for example by differentiating viral from bacterial etiologies.

• What is the right approach?

A syndromic approach should take place in stages. Initially the pathogen class is identified, either viral or bacterial. While some biomarkers like procalcitonin are available for this, further research is necessary to evaluate their usefulness in TB endemic settings and potentially improve upon them. In addition to biomarkers for pathogen detection, markers of severity are needed, particularly in children. Together, pathogen and severity markers could significantly improve clinical decision making in low-resource settings. Optimally the pathogen would be identified along with markers of resistance; however, this requires large and likely different panels according to region and seasons and will be difficult to achieve on affordable platforms that are adequate for use in low-resource settings in the near future.

• How will we accomplish the work?

Given the potential for significant impact and the strong overlap with needs in other FIND disease programmes, e.g. malaria and acute febrile syndrome as well as neglected tropical diseases, syndromic tests to differentiate between different pathogen classes are a clear priority for us. However, given the current knowledge gaps, we will work on promoting the discovery of biomarkers through our biorepository and drive field evaluation, as well as development of tests targeting suitable biomarkers in partnership with our colleagues in the malaria and acute febrile syndrome programme at FIND.

Enabling impact through comprehensive, country-specific solutions

Increased use of diagnostics has exposed a number of gaps and bottlenecks that erode the impact of new and existing tests. Most low- and middle-income countries face the problem of linking diagnosis to treatment, for example 20% of TB patients with a positive Xpert test never make it to treatment. There are various reasons to account for this, ranging from poor transport systems for samples and results, to poor referral systems and patients lost to follow-up. There is limited access to treatment for drug-resistant TB and not enough trained health care workers are available in chronically weak health and laboratory systems. Moreover, capacity, technical knowledge and crosscutting tools to develop and ensure effective implementation of country specific roll-out plans for new diagnostic solutions are often lacking, e.g. standard operating procedures, quality assurance programmes.
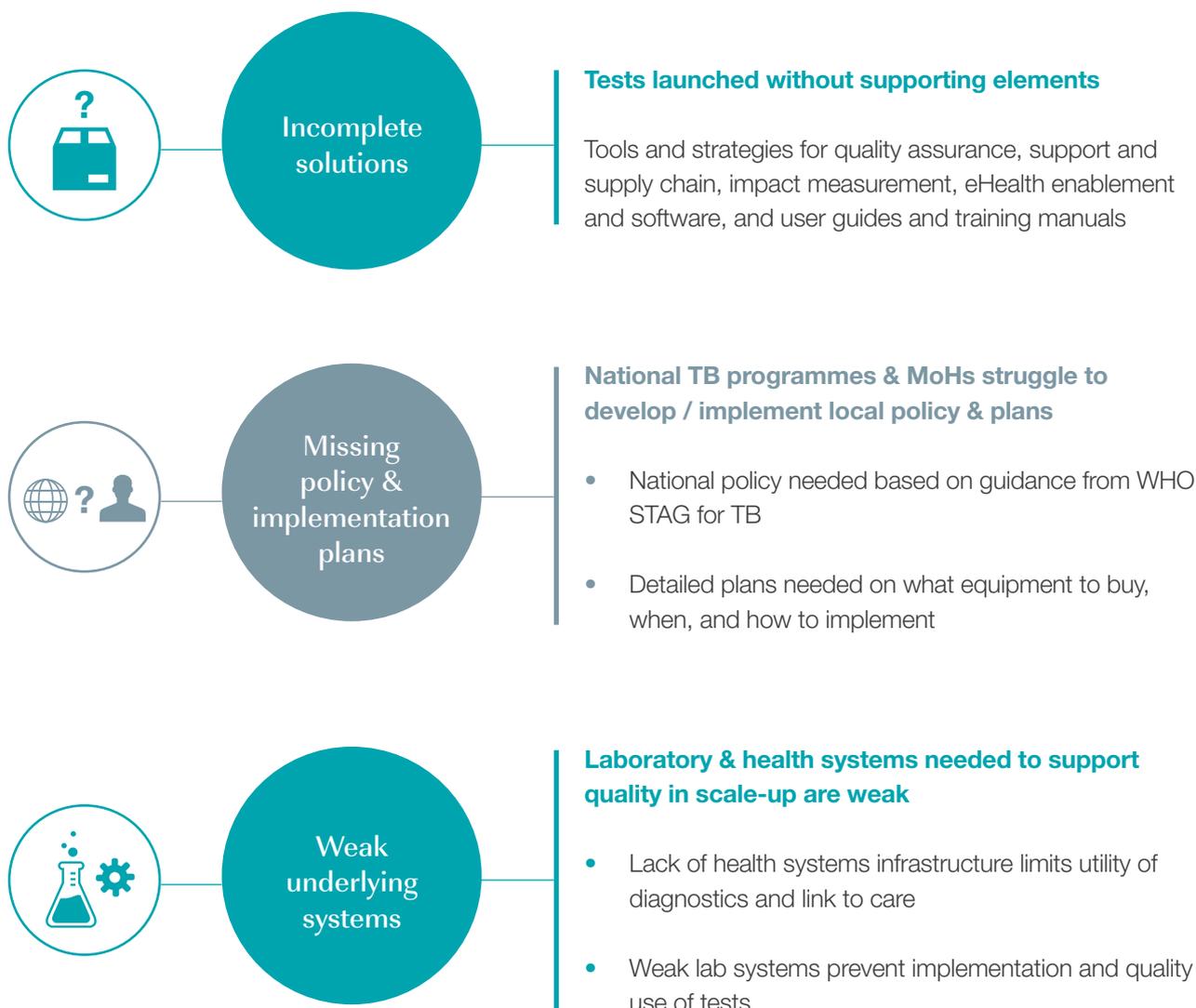
While many groups are active in large-scale implementation projects, provide technical assistance and work to build diagnostic capacity in lower- and middle-income countries, there is often limited coordination of these efforts on a national or regional/provincial level. There is also minimal focus on connecting improved diagnostic use and laboratory strengthening with the broader health system.

These efforts often focus on individual components of diagnostics implementation, rather than taking a comprehensive approach that would ensure a more long lasting impact through country-owned implementation.

FIND advocates for further strengthening of implementation capacity for diagnostics at the country level and should include the following:

- Improved monitoring and better systems to link diagnosis to care, e.g. via eHealth solutions

- Comprehensive support to ministries of health to support the development and execution of evidence-based guidelines and implementation plans that include a focus on quality assurance, training, monitoring and evaluation, maintenance and supply chain management

- Improved tools, strategies and quality management systems

- Efforts to integrate TB diagnosis into the health care system with a focus on co-morbidities and syndromic approaches

Challenges to maximizing the impact of TB diagnosis

Incomplete solutions

Tests launched without supporting elements

Tools and strategies for quality assurance, support and supply chain, impact measurement, eHealth enablement and software, and user guides and training manuals

Missing policy & implementation plans

National TB programmes & MoHs struggle to develop / implement local policy & plans

- National policy needed based on guidance from WHO STAG for TB

- Detailed plans needed on what equipment to buy, when, and how to implement

Weak underlying systems

Laboratory & health systems needed to support quality in scale-up are weak

- Lack of health systems infrastructure limits utility of diagnostics and link to care

- Weak lab systems prevent implementation and quality use of tests

Demonstrating the role of diagnostics in controlling the TB epidemic

To address any of the needs defined above, FIND is committed to developing and implementing diagnostics. A first step to achieving this is demonstrating the value of diagnostics for TB control through data collection, impact measurement and modelling. This should provide a foundation for expanded advocacy efforts to increase knowledge and commitment to diagnostics.

FIND'S TB MANDATE FOR 2015-2020
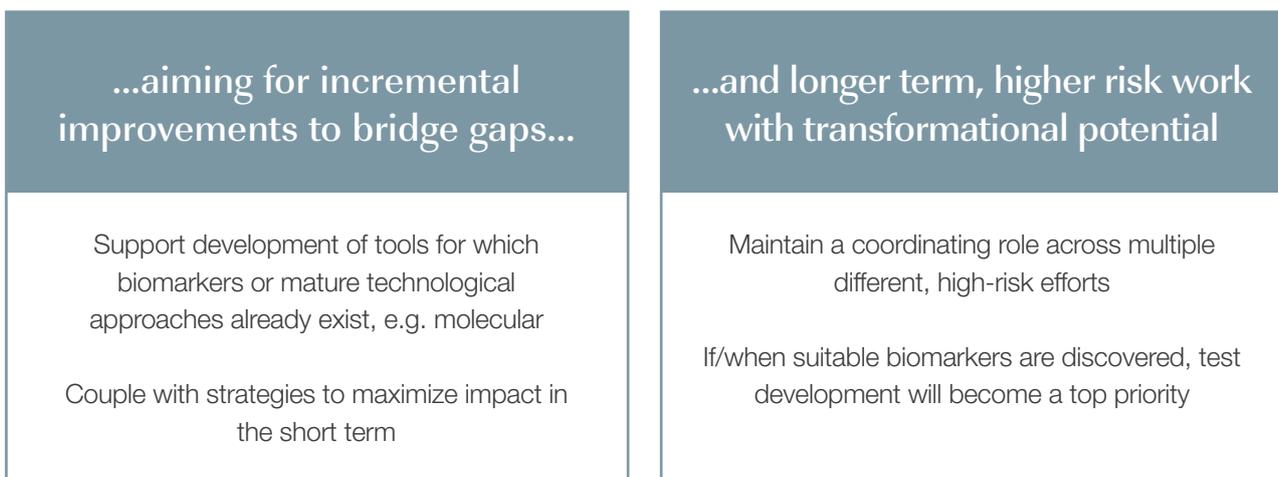
Priorities in development

Given the broad range of potential interventions for FIND in the area of TB, we have prioritized our development activities to maximize our influence based on two criteria: the impact of the new solution both on individuals and overall public health; and the likelihood of FIND's success given technical feasibility, fit with FIND capabilities, availability of funding, etc.

Our prioritization reflects a two-tiered approach. We will capitalize on existing technologies and use innovative implementation strategies to facilitate incremental improvements that can be delivered in the short term, while laying the groundwork for transformational technologies to be developed in the middle to longer term.

A two-pronged approach to prioritization of needs for innovative tests

Given that tools to address the most critical needs in TB diagnosis are in the early stages of development , i.e. biomarker discovery, etc.

...we will take a two pronged approach to prioritization

...aiming for incremental improvements to bridge gaps...	...and longer term, higher risk work with transformational potential
Support development of tools for which biomarkers or mature technological approaches already exist, e.g. molecular Couple with strategies to maximize impact in the short term	Maintain a coordinating role across multiple different, high-risk efforts If/when suitable biomarkers are discovered, test development will become a top priority

In the area of development, FIND's top priority is **an improved test for passive case detection**: that would replace smear-microscopy; potentially reach lower levels of the health care system; have increased sensitivity to support the diagnosis of patients with paucibacillary disease, for example HIV patients or children; and provide a rapid turnaround time to produce an actionable result at the time of the first visit, i.e at the point-of-care (POC). Given the state of technology, we believe that molecular solutions offer the best chance to have an impact in the near term, and we will pursue them most aggressively. While a sputum-free rapid test that can be done on easily accessible samples, such as blood or urine, would be the ideal smear-replacement test, particularly for the diagnosis of TB in patients with sputum-scarce TB (e.g. children or HIV-positive patients), no suitable biomarker is currently available. Therefore, FIND will contribute to long-term research by supporting academic groups in biomarker discovery, in part through collaboration with the Bill and Melinda Gates Foundation (BMGF). Once suitable biomarkers become available, supporting development will be our top priority. A sputum-free rapid test would also best meet needs for **active case detection**.

FIND's experience has shown that DST is paramount to prevent the further spread of drug resistance. **Decentralized solutions** to inform regimen selection and **centralized solutions** to inform individualized therapy, coupled with improved sample transportation and logistics, can improve access to DST. Given current technological approaches, both are feasible in the relatively near term. The ideal decentralized DST test would be combined with the molecular detection test described above and is a top priority for FIND. For centralized solutions, we will play a supporting and coordinating role to ensure that the tests under development meet the needs of low- and middle-income countries. We will also focus on sequencing to support surveillance. This will inform regimen selection in the absence of testing each individual with DST and will also provide important information to select targets for molecular DST for centralized and decentralized solutions.

One promising FIND innovation that is in development is a **rule-out test** or triage test. A positive rule-out test suggests that the patient is at high risk of having TB and should get tested with a confirmatory molecular TB detection test, ideally with DST. In addition, a triage test on a non-sputum sample could identify patients with extrapulmonary TB and facilitate referral for further invasive testing. In these algorithms, a rule-out test has the potential to decrease costs and increase the number of patients tested.

We will also address the need for tests to **detect latent TB infection** and predict progression to active TB, which offer an opportunity to curb transmission. However, no biomarker has been identified to date, and tests would have to be user-friendly and affordable in order to be administered frequently enough to prevent the progression that typically happens less than two years after a new latent infection.
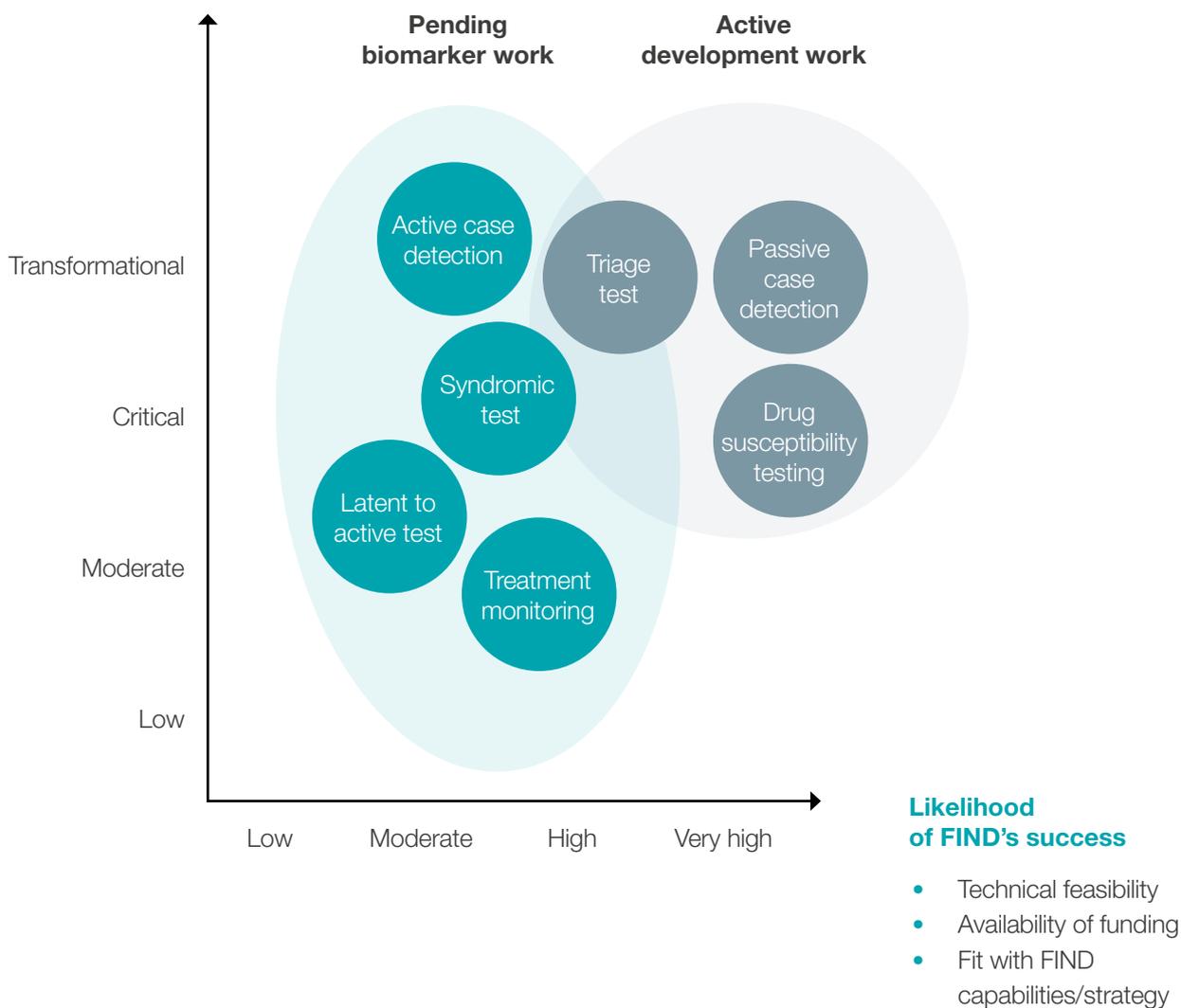
We will also engage in the development of **treatment monitoring tests**, which have the ability to improve patient important outcomes but are unlikely to have a substantial impact on the overall transmission of TB. There is active biomarker research ongoing to support development of treatment monitoring tests, and FIND is scouting possible biomarker options to consider their evaluation with samples from our biorepository and in the field.

One promising FIND innovation in development is a rule-out test that has the potential to decrease costs and increase the number of patients tested.

Prioritization of needs to be addressed with new tests via development and policy work

Impact

- Public health impact
- Individual impact

Pending biomarker work / Active development work

- Active case detection
- Triage test
- Passive case detection
- Syndromic test
- Drug susceptibility testing
- Latent to active test
- Treatment monitoring

Impact axis: Transformational, Critical, Moderate, Low

Likelihood of FIND's success axis: Low, Moderate, High, Very high

Likelihood of FIND's success

- Technical feasibility
- Availability of funding
- Fit with FIND capabilities/strategy

Key

- Core FIND focus
- FIND supports/coordinates

THROUGH THE WORK OF
FIND AND OUR PARTNERS,
AN ESTIMATED 300,000
LIVES PER YEAR HAVE
BEEN SAVED.

Enabling interventions

In addition to focusing on the previously mentioned development priorities, FIND will also support objectives for TB through a set of enabling activities. These supporting activities are further presented in detail in our Access strategy.

Development and policy enablement

Our immediate highest priority will be to promote an **improved understanding of how diagnostic tests are currently used and how innovative strategies can identify more TB patients and increase access to treatment**. In parallel, we will focus on evaluating new and improved tests that will revolutionize the fight against TB. Through **our close collaboration with WHO**, we will plan the appropriate **large-scale demonstration studies** as well as the **impact and cost-effectiveness modelling** to generate the **evidence for global policy and guidance of use**. We will **conduct**

the studies in-country, and once the WHO policy is generated, we will help build country capacity to translate WHO guidance into rapid scale-up of testing within public programmes.

A key component in supporting test development is the availability of samples and strains for early proof-of-principle studies. One of our most comprehensive resources, the **FIND TB Specimen Bank** was founded in 2006 to support the development of TB diagnostic technologies. Since then, about 150,000 aliquots have been entered into the bank. The FIND collection currently counts over 60,000 aliquots in the form of sputum, serum, EDTA plasma, P800 plasma and urine. Over the next years, FIND will expand its biorepository to include samples to support the assessments of DST tools and treatment monitoring tools. In addition, we will develop panels that allow early limits of detection, inclusivity and exclusivity evaluations.

eHealth solutions

Throughout all of FIND's development work, we place a high priority on ensuring that tests are compatible with eHealth solutions and accompanied by supporting connectivity tools. These eHealth solutions will allow for safe, efficient and appropriate collection, storage and transmission of valuable diagnostic data, with potential impact beyond the care of the individual patient to include health systems management (e.g. surveillance, stock management) and device management.

FIND's priorities for enabling interventions

Catalyse development

- Maintain a publically available specimen bank and expand to changing needs with new test development

Guide use & policy

- Operational research, evaluation and demonstration studies to determine how to best use new & existing tools

Accelerate access

- Support countries in development and execution of national guidelines and implementation plans
- Develop and implement comprehensive packages of tools for: QA, training, M&E, maintenance, eHealth
- Facilitate integration of TB care w/ co-morbid diseases
- Provide structured mentoring for quality management systems and laboratory strengthening

Shape the agenda

- Strengthen impact assessment, modelling, and cost effectiveness measurement & communicate impact

Implementation enablement

FIND's initial implementation efforts were focused on maximizing the impact of current tools and promoting integration with other tests. As innovative tests are developed, we will support their integration into country disease control programmes in accordance with global policy recommendations and guidance.

We will work with local and international implementing and funding partners to provide harmonized, comprehensive support to ministries of health to **facilitate development and execution of evidence-based national guidelines and implementation plans**. FIND will ensure that these plans are aligned with national laboratory and disease control plans. As countries put these plans into practice, we will help them identify gaps and deploy experts to solve problems and develop local capacity. Through this implementation support, we will also work to ensure increased **integration between TB programmes and those for control of co-morbid diseases**. We will mentor and train local health care partners to **strengthen higher quality management systems in laboratories**.

FIND will ensure that all tests are part of a "packaged solution" that includes clear guidance on use, training materials, maintenance and support, quality assurance, impact measurement and linkage to care and surveillance. We **will develop and deploy comprehensive tools that can be part of this packaged solution**, e.g. quality assurance tools, eHealth software, etc.

We will also reinforce our focus **on monitoring and evaluation, and impact assessment**. We will support the development and implementation of **eHealth solutions** to strengthen results reporting, supply chain management, and conduct quality assurance. In partnership with countries, we will collect evidence and conduct **operational research** to refine implementation in various settings and for different patient groups.

Through our evidence-based research, FIND will show the tangible impact of improved TB diagnostics in terms of lives saved and future cases prevented and advocate for the increased prioritization of diagnostics.

Interaction in upstream and downstream activities

FIND acts as a bridge throughout the value chain from product development to guidance of use and in-country implementation, which enables us to provide valuable feedback and insight at every level of the diagnostic pathway. In all our TB work, we will transfer our expertise and experience gained through test implementation to directly inform new test development and guidance of use on a global and national scale. Similarly, we will support implementation efforts by passing on the lessons learned in the development process to country programmes to ensure maximum impact.
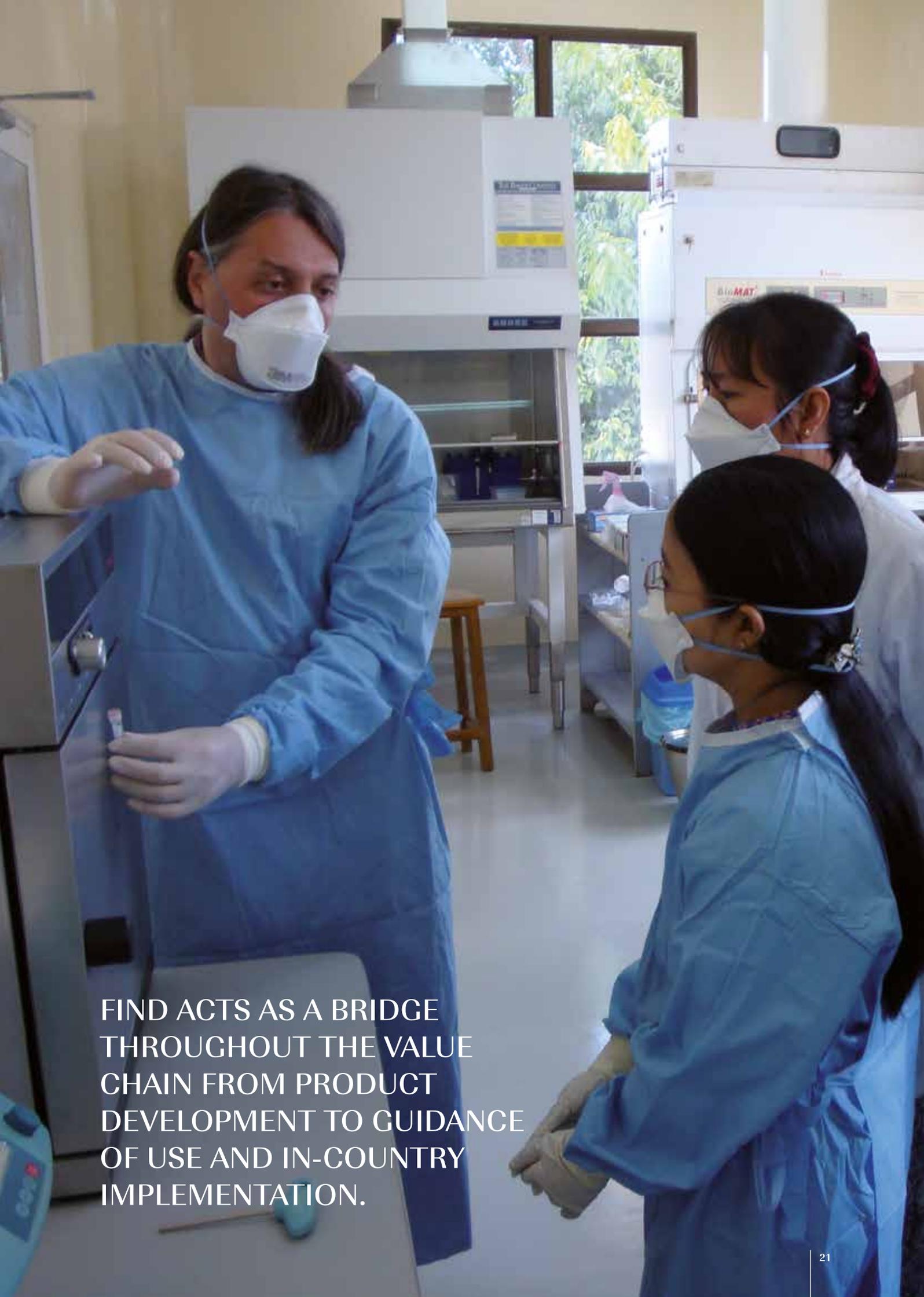
FIND ACTS AS A BRIDGE
THROUGHOUT THE VALUE
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FIND'S IMPACT IN THE FIGHT AGAINST TB

Expected impact and 2020 targets

Intervention	Direct indicators by 2020	Patient important outcomes and population level indicators
Support development of decentralized molecular or biomarker test (ideally with DST and for implementation as a screening test) Support development of centralized DST test	• >2 highly sensitive tests for detection endorsed by WHO and introduced at the level of the microscopy centre and rolled out in 5 – 10 low- to middle-income countries (LMIC) • 2 tests for molecular DST endorsed by WHO and introduced at the decentralized level to support regimen selection and rolled out in 5 – 10 LMIC • >2 tests for molecular DST introduced at the centralized level for at least all category 1+2 drugs and rolled out in 5 – 10 LMIC • All tests are eHealth enabled	**Patient important outcomes:** • Reduction in TB-associated mortality • Reduction in time to diagnosis of drug resistant TB (DR-TB) **Population level indicators:** • Increase in case notification rates • Incidence reduction • DR-TB incidence reduction
Support development of rule-out/triage test	• 2-3 rule-out/triage tests developed and assessed in trials and endorsed by WHO • All tests are eHealth enabled	
Support development and evaluation of tests for syndromic approach	• 2 sensitive tests for differentiation between bacterial and viral pathogens developed and in clinical studies • All tests are eHealth enabled	**Patient important outcomes:** • Reduction in time to diagnosis of TB **Population level indicators:** • Number of TB clinics integrated into primary health care system • Reduction in antibiotic use

Support development of treatment monitoring test	• 2 treatment monitoring tests developed and in clinical studies • All tests are eHealth enabled	**Patient important outcomes:** • Reduction in time to diagnosis of DR-TB **Population level indicators:** • DR-TB incidence reduction • Decreased failure rates
Develop innovative strategies to improve detection and increase impact through operation research/studies	• 3 pragmatic trials undertaken with innovative strategies; Novel testing approaches endorsed by WHO • >3 modelling studies and/or operational research projects conducted	**Patient important outcomes:** • Reduction in TB-associated mortality **Population level indicators:** • Increase in case notification rates • Incidence reduction

In addition to these development targets, we will expand our impact through enabling work in endemic-countries. **Our overall goal is to support improved country implementation of both new and existing tools through different project targets**. We will increase access to diagnosis, ensure linkage to treatment and measure progress based on patient and programme level outcomes, e.g. reduction in time to diagnosis and in time from diagnosis to treatment, increased case detection, programme efficiency, and overall health outcomes. Further detail on our in-country work is provided in the Access strategy.

EXPANDING OUR PARTNERSHIPS

FIND will catalyse the development of new innovative tests through our partnerships in academia and industry. There are a number of developers with tests already in progress, and we will engage with them to communicate the diagnostic needs for TB, e.g. with target product profiles. Our work on other diseases has shown us that many of these developers have limited resources throughout the various phases of product development to product realization. We will meet these needs and ensure the development of fit-for-purpose products for low- and middle-income countries.

We will continue to expand our biorepository for samples and strains to enable early proof-of-principle and validation studies. We will grow our sample and strain collection to support diagnostic development by partnering with groups that perform clinical studies, such as the TB Alliance. Since FIND does not conduct biomarker discovery work, we will support our academic partners by providing specimens from our bank. We will also promote ongoing, collective discussions as to the state of discovery and the implications of potential advances to maintain a link between this work and the realities of country programmes.

We will continue to partner closely with the WHO as a Collaborating Centre to support the implementation and achievement of the WHO's strategic objectives. In addition, we will expand existing partnerships with other international agencies that complement our work in countries, e.g. Centers for Disease Control and Prevention.

To guide policy and use we will conduct clinical trials in collaboration with the TB Clinical Diagnostics Research Consortium, partners within the European & Developing Countries Clinical Trials Partnership and others. We will bring researchers together and **foster collaborations** in various aspects of our work by joining forces with the Stop TB Partnership's New Diagnostics Working Group (NDWG), the Critical Path to Tuberculosis Drug Regimens (CPTR) and academic groups.

We will **accelerate access to diagnostics** by working with a range of partners including ministries of health, the WHO Global Laboratory Initiative (GLI), technical and funding agencies (Centers for Disease Control and Prevention, USAID, UNITAID, The Global Fund), regional bodies such as African Society for Laboratory Medicine (ASLM), and other international and local implementing partners, including MSF. As a key shift in our approach to partnerships, FIND will expand collaborations with the private sector, e.g. large multi-national companies, for both implementation and laboratory strengthening. In this perspective, we will expand our implementation work with partners such as CHAI and PSI, to also ensure access to high quality diagnostic tools within the private sector.

FIND is a WHO Collaborating Centre in Tuberculosis Laboratory Strengthening and TB Diagnostic Technology Evaluation.

Expanding our partnerships across the value chain

Catalyse development	Guide use & policy	Accelerate access	Shape the agenda

Academia

Industry

PATH

WHO/WHO GLI/NDWG

Country government and ministries of health

Private partnerships	Private partnerships

TB CDRC

Partner within EDCTP

Clinton Health Access Initiative

Médecins Sans Frontières

Centers for Disease Control and Prevention

ASLM

McGill	McGill

KNCV

Partners in Health

The Union

Project Hope/ AMREF/others

Treatment Action Group

In addition to the previously mentioned partners, we will collaborate with AERAS, TB Alliance and other product development partnerships working in vaccine and drug development to leverage synergies within a joint approach to new tool development, specimen collection and impact measurement.

We will also partner with non-governmental organizations, advocacy groups and others to disseminate information on shaping the diagnostics agenda. We will develop close partnerships with potential funders. In addition to traditional donors, endemic country governments and venture capital firms will be critical for guiding funding flows to the most promising products.

THE NEXT STEPS

Although substantial gains have been made in the fight against TB over the past decades, significant hurdles remain. The disease continues to take an estimated 1.3 million lives per year and causes untold human and economic burden on low- and middle-income countries. The threat of drug resistance continues to grow, and if left unaddressed will not only undermine the progress we have made, but could also spread the burden of TB to countries where it does not currently have a significant prevalence.

Funding for TB research and development is much lower than needed – a 2013 report from the Treatment Action Group showed a US$ 1.39 billion shortfall between actual funding for TB research and development and the targets set by the Stop TB Partnership. For diagnostics, R&D investment in 2012 was only US$ 42.4 million – less than 15% of the global target of US$ 340 million set by the Stop TB Partnership.

Meeting global targets for TB control will require dramatically increased financial and political commitment globally and more specifically with respect to diagnostics. These investments in the fight against TB are critical to meeting global goals, ensuring health equity and eliminating this devastating disease.
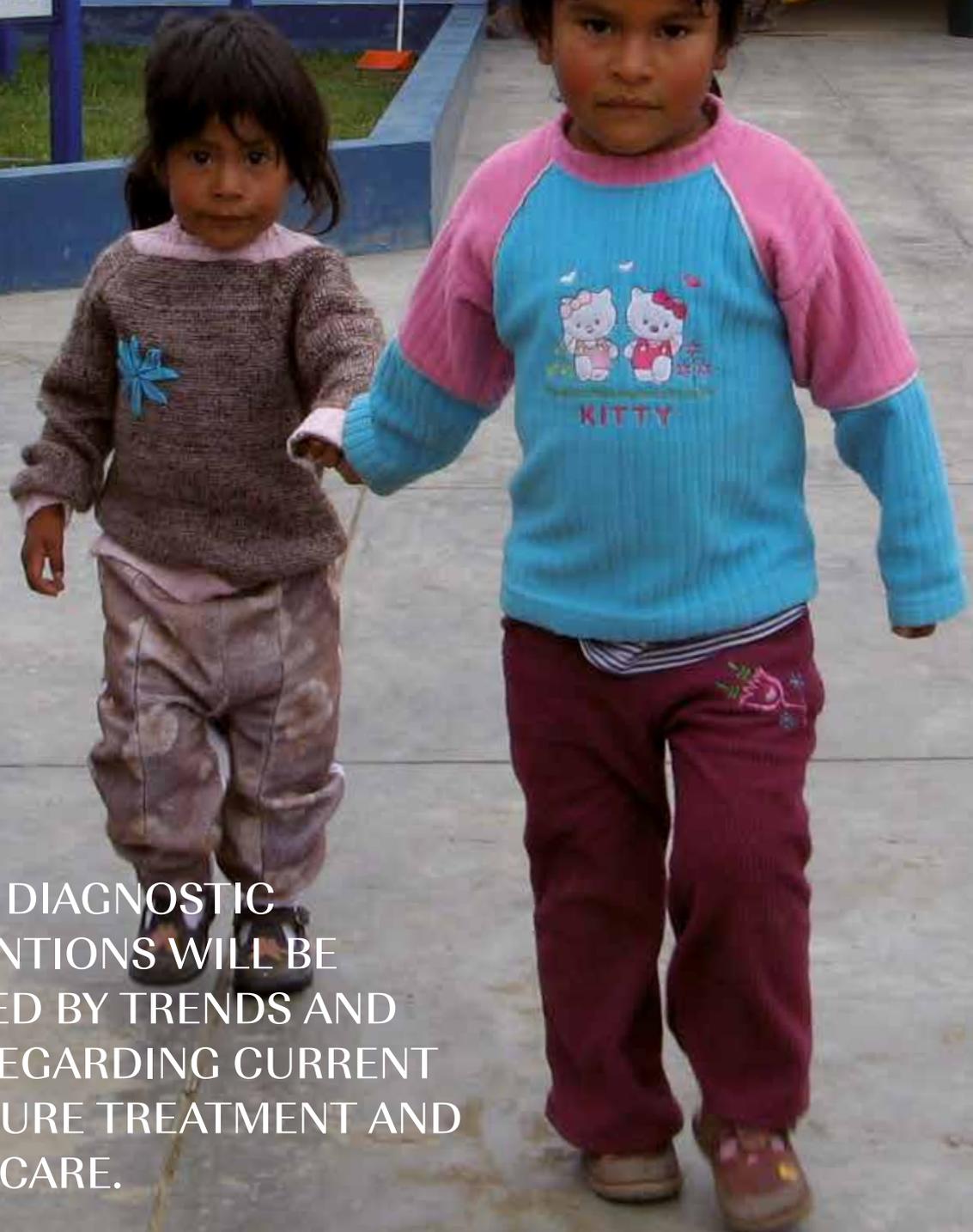
ALL OUR DIAGNOSTIC
INTERVENTIONS WILL BE
INFORMED BY TRENDS AND
NEEDS REGARDING CURRENT
AND FUTURE TREATMENT AND
PATIENT CARE.

APPENDIX A: ADDITIONAL TABLES

FIND's role and preconditions for successful outcomes

Intervention	FIND's role	Preconditions
Support development and evaluation of: • Rule-out test • Smear-replacement test (biomarker or molecular) • DST • Tests for a syndromic approach to lower respiratory tract infections	• Scout technology • Proof-of-principle evaluations on samples • Develop TPPs • Match-make on TPPs • Support development • Gather knowledge on molecular targets of resistance (support database development) • Provide specimens for early feasibility studies • Provide platform for clinical evaluation • Facilitate path to endorsement by WHO	• Continued donor support • Biomarker for detection, rule-out or identification of latent that progresses to active TB is identified • Detection of biomarkers on POC platforms possible • Molecular targets of resistance are identified • Platforms for DST testing can be developed for use at microscopy centre • Improved biomarker for differentiation between bacterial and viral pathogens identified • Syndromic approach can be sufficiently standardized across different epidemiological settings • Appropriate partnerships with donors, agencies, ministries of health (MOH), academia and industry for evaluation and demonstration studies
Development and implementation of comprehensive diagnostics implementation package	• Conduct studies to enhance the understanding of the current diagnostic ecosystem to improve use of existing tests • Translate global guidance into country level implementation and development of guidelines and tools • Help MOHs identify gaps (e.g. connected care), coordinate solutions and deploy experts for technical assistance • Support development or update of national strategic implementation plans • Develop quality assurance tools and guidance	• Continued donor support for implementation of diagnostics in low-income countries • WHO endorses new TB diagnostic tests • MOHs committed to TB diagnostic implementation • Appropriate partnerships with donors, agencies, MOHs, academia and industry

Development and implementation of eHealth solutions	• Develop solutions with partners that allow for collection of different types of diagnostic data to an aggregator • Facilitate the use of relevant data by third party eHealth applications.	• Diagnostic providers willing to support a common aggregator • Countries willing to adopt eHealth solutions
Develop models for integrated implementation with co-morbid diseases	• Conduct demonstration studies on cross-cutting platform technologies for TB and co-morbid conditions (e.g. HIV) • Develop and disseminate guidance and tools for integrated implementation	• Cross-cutting platform technologies available • Integrated diagnosis would lead to better patient management and health system efficiency • WHO endorsement; MOHs willing to implement • Established links with other national programmes
Evaluate impact of different diagnostic solutions through modelling and/or operational research	• Work with partners to conduct modelling studies of different diagnostic strategies • Embed operational research in implementation programmes	• Appropriate partnerships for modelling studies and operational research • Country capacity and approval for operational research

STRATEGY FOR TUBERCULOSIS

(AND LOWER RESPIRATORY TRACT INFECTIONS)

2015-2020