STOP TB New Diagnostics Working Group
Strategic Plan 2006-2015

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1 Background

More than a century after its original development, the microscopic examination of sputum is still the only widely available diagnostic tool for identifying TB in most developing countries. However, under field conditions sputum smear microscopy shows a sensitivity of only 40-60%, partly due to the difficulty of maintaining well-equipped laboratories to perform it and the need for specialized training but mainly due to the inherent low sensitivity of the test. Poor sensitivity is exacerbated in the presence of HIV co-infection (falling as low as 20%) because HIV-associated TB is more commonly paucibacillary. Currently, only a small fraction (16%) of TB patients are reported with a laboratory-confirmed diagnosis, while others are either misdiagnosed as not having TB at all due to poor sensitivity of smear microscopy (AFB negative), are not diagnosed at all, because they do not have access to appropriate diagnostics tools or are not reported (AFB+ Figure 1).

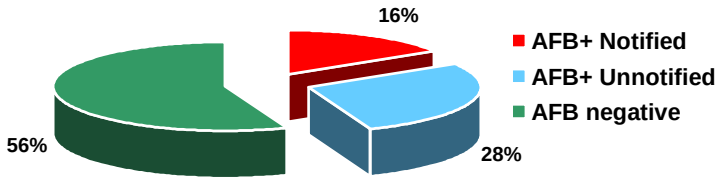

Figure 1: Breakdown of AFB-notified cases vs. total cases

The lack of appropriate diagnostic tools leads to many patients being diagnosed on the basis of clinical suspicion and (where available) chest radiography leading to both over and under-diagnosis. TB culture is more sensitive (close to 100%) but is only performed in reference centers, takes from 4 to 10 weeks for results and thus comes mostly too late to impact upon patient management and outcome.

New diagnostic tools for TB detection have been developed and introduced in developed countries. However, they have generally not been adopted in resource-limited, high-burden countries due to cost, complexity, lack of laboratory infrastructure or inadequate performance in endemic settings (e.g. failure to adequately discriminate between diseased patients and latently infected or vaccinated subjects). Novel technologies successfully introduced into developed countries require adaptation to match the needs of developing countries. The perception of companies involved in diagnostic tool development that this will not lead to an adequate return on investment has hampered subsequent introduction of such tools in high-burden regions.

The relatively poor performance of existing TB diagnostic tests leaves large numbers of patients undetected, erodes faith in public health services, impedes expansion of DOTS, leads to increased morbidity, and, most importantly, misses the opportunity to interrupt disease transmission.

The HIV pandemic has led to an increasing case load of TB in many places coupled with the reduced sensitivity of smear microscopy in TB-HIV co-infected individuals who commonly have smear-negative pulmonary and extrapulmonary disease. The dramatic surge of multi-drug resistant TB (MDR-TB), notably in Eastern Europe and hotspots in the Russian Federation and China, stretches the scant financial resources of local health systems beyond their capacities for the cost of second line drug treatment with no rapid risk stratification procedure available. Likewise, the absence of operationally convenient diagnostic tests for latent infection that accurately predict the risk of progression to active TB, especially in HIV-infected patients, constrains the implementation of effective and

rational preventive therapy strategies. Thus, the urgent need for a range of new diagnostic tools for various test indications is evident (Table 1).

Purpose	Test Indications
Case Detection	• **Detect pulmonary TB with high bacterial load (SS+)** • **Detect pulmonary TB with low bacterial load (SS -, Cx +)** • **Detect extra-pulmonary and pediatric TB**
Drug susceptibility testing	• **Detect MDR-TB for treatment** • **Detect MDR-TB for surveillance**
Latent TB Infection	• **Detect LTBI for surveillance** • **Detect LTBI and predict risk of progression for treatment**

Table 1: Diagnostic Tools needed for tuberculosis

2 Achievements 2001-2005, present situation (Table 2)

Since the creation of the New Diagnostics Working Group in 2001 a platform for focused development of the required diagnostic products has been established. Through TDR[1] and the Foundation for Innovative New Diagnostics (FIND) promising technologies have been screened and a series of new product developments initiated, supported, and/or subjected to field trials. Concurrently tools (such as the WHO/TDR TB specimen and strain banks) were developed to better assist researchers and enable such developments as well as to assist in validating their potential future public health impact (mathematical modeling).

Scope	Activities 2001-2005
technology screening	• TDR Bright Ideas Grant Programme • B&M Gates Foundation Grand Challenges • US National Institutes of Health • DFID TB Knowledge Programme • Industry survey of commercialized products for TB diagnosis and mapping of global distribution patterns
market research	• Publication of FIND/TDR TB Diagnostics Market analysis
development support	• Establishment of FIND • Expansion of TDR TB Specimen Bank to 6 new sites • Establishment of TDR Strain Bank • TDR/FIND sponsored comparative evaluation of DST methods and their cost-effectiveness in Peru • TDR sponsored smear microscopy methods review series

[1] UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)

Scope	Activities 2001-2005
	• Link and support STOP TB Laboratory Strengthening Subgroup to maximize availability and accessibility to new diagnostics
product development	• Feasibility and Development agreements with industrial partners for new diagnostics: phage detection, rapid culture, nucleic acid tests and lateral flow test
studies (evaluation and demonstration)	• Comparison of DST methods in Peru - completed • Laboratory evaluation of commercially available serology tests - completed • Diagnostic Evaluation Expert Panel (DEEP): established in 2004 to develop guidelines for conducting diagnostic trials - completed • Obstacles to and economic impact of TB diagnosis identified through TDR sponsored multi-country field trials - completed • WHO survey of TB laboratory services in Member States • The Royal Tropical Institute (KIT) and collaborators: antibody and antigen detection; microsystem technology, gas sensor/electronic nose and NAAT • London School of Hygiene and Tropical Medicine (LSHTM) and collaborators: o Evaluation of phage diagnostics (commercial and in-house) published. (Zambia). o Evaluations of in-house phage indirect DST undertaken. (Tanzania, Uganda, Argentina) o Publication of nucleic acid test evaluation. • FIND sponsored MGIT demonstration projects in 3 DOTS-plus project settings • FIND demonstration projects on improved TB case detection with rapid culture in HIV-endemic settings. • Wellcome Trust MODS operational evaluation, Peru • KIT/KEMRI
impact modeling	• TDR/Erasmus University -Mathematical modelling of potential impact of new tools in regional setting - completed.
regulatory aspects	• TDR review of regulatory policies, local distribution and procurement of diagnostics in 14 countries • TDR review of regulatory policies in WHO member states

Table 2: activities arising from Diagnostics Working Group 2001 to 2005

3 Strategic Vision 2006-2015

The vision of the Stop TB New Diagnostics Working Group is to develop and introduce cost-effective and appropriate new diagnostic tools that will contribute towards improved control of the global TB epidemic and improve the quality of patient care.

The ideal toolbox would contain diagnostic technologies, all of which perform equally well in HIV-infected subjects, to

1. improve TB case detection both through high sensitivity/specificity and improved accessibility – simple, accurate, inexpensive, same day, near-patient products would be the ultimate goal
2. rapidly and inexpensively identify drug resistant TB disease enabling timely effective patient treatment to reduce both individual morbidity and continuing transmission
3. reliably identify latent TB infection and define the risk of future progression to active disease enabling rational use of preventive therapy in appropriate subjects

4 Strategic Plan

The Strategic Plan of the Working Group addresses the needs at the different levels of the health care system sequentially, thus allowing rapid implementation of novel technologies where technical hurdles are less pronounced (ie regional reference centres) whilst development continues of more "perfect" solutions for introduction in settings closer to the patient (local microscopy centre or even health post). The plan aims to achieve the following three milestones:

1. By 2008 the Group plans to introduce an easy-to-use technology with accuracy similar to culture but capable of providing results in a few hours (or days) instead of weeks. This product will be implementable at the first referral level (district laboratories) and to some extent also in peripheral labs (microscopy centers).
2. By 2010 new tests for detection of active TB in a point-of-care (POC) setting, for example for use by rural health workers, will be available. Compared to smear microscopy, such tests will be more sensitive, much simpler and still as affordable. POC may be defined as i) instrument free device requiring minimal training or ii) hand held simplified instrument that requires minor training. Possible candidates may be based on lateral flow technologies, integrated, portable nucleic-acid test system or gas sensor technologies.
3. By 2012 a rapid diagnostic procedure capable of predicting the future progression of latent TB infection to active disease, in both HIV-infected and uninfected subjects, will be introduced.

The New Diagnostics WG and partners will assist progress towards these goals by means of the following strategic pillars:

- Advocacy and sponsorship of increased investment from the public and private sector in basic science that supports the development of diagnostic technologies.
- Continuous mapping of landscape for promising technologies and regular dialogue with diagnostic technology and test developers

- Facilitation of improved public and private sector stakeholder collaboration leading towards accelerated diagnostic tool development, evaluation, demonstration and market entry (test introduction and sustainable adoption).
- Targeted investment and management of product development in priority areas.
- Improving understanding, development and regulation of the diagnostics market in high burden countries aimed at encouraging application of new technologies to TB diagnostics
- Measuring the epidemiological and economic impact of new diagnostic tools in National TB Program settings.
- Assisting governments and public health agencies in developing countries to evaluate the utility and cost-effectiveness or local appropriateness of new diagnostics and develop effective implementation schemes that maximize patient accessibility.
- Liaison with agencies involved in strengthening laboratory capacity and implementation of laboratory quality assurance programmes.

4.1 Focus Areas

To meet these milestones progress must be achieved in all of the following focus areas: discovery biology and basic technology, product development, evaluation, demonstration and regulatory factors, each of which is discussed in detail in the following section.

4.1.1 Discovery Biology and Basic Technology

Tests either detect the host immunological response to *M. tuberculosis* or the organism itself. A variety of immunological assays (many of them in test strip format) are available on the open market, but none has been shown to have a diagnostic accuracy adequate for a systematic implementation. Furthermore, the impact of HIV-coinfection on results of these tests is mostly unknown. Better immunological targets are needed for the design of improved immunoassays with higher predictive value. Recent advances in gene sequencing, proteomics and expression analysis of *M. tuberculosis* and related strains provide a roadmap for further progress in this area. Continued research in this area and monitoring of the results will provide the required scientific basis for new antigen and antibody assays which may be converted into POC-suitable tools. Significant investment in basic science is needed to fulfil the potential of new diagnostics anticipated to have the greatest impact on TB control. Without such investment, most products in the development pipeline will lead to modest rather than revolutionary changes in TB diagnostics. The timing and level of such investment is critical if targets are to be met.

During the past five years, two diagnostic tests for the detection of latent TB have reached the market, both based on the detection and quantification of antigen triggered interferon-γ release from T-cells. However, neither of these procedures is able to forecast progression from the latent to the active disease state – this is thus an area in need of significant additional basic research to identify suitable markers of conversion since one third of the global population has latent infection and rationally targeted preventive therapy strategies are required.

Nucleic acid based tests show promise as tools for rapid and accurate detection of *M. tuberculosis* and related species which must be adequately differentiated. Different amplification procedures (such as PCR, TMA, LAMP) have been used successfully for this purpose, though they currently all suffer from unacceptable complexity of the overall workflow, high equipment cost and risk of cross-contamination, whilst sensitivity remains problematic. New system technologies must be found which allow complete integration of the entire workflow (including sample preparation), minimize reagent and equipment costs, rendering the entire procedure so robust that it can be used in settings like microscopy centers and eventually even in rural health posts.

4.1.2 Product Development

A wide range of suitable technologies is becoming available to address the diagnostic needs identified in the Strategic Vision of the New Diagnostics Working Group. Over 80 groups, including commercial, academic and public research institutions are engaged in diagnostics development. Technologies under development for improved case detection include rapid culture systems, phage detection, molecular-based methodologies, antigen and antibody detection, and detection of volatiles in sputum of TB patients. Rapid culture systems, phage

detection and molecular techniques are also being applied to rapid detection of MDR-TB. However, the development of large-scale manufactured and affordable industrial diagnostic products is presently hampered by several factors:

a) Until the recent launch of the TDR/WHO/FIND sponsored market report on TB Diagnostics, there was a significant lack of market data,

b) For this reason major diagnostic development companies have been reluctant to invest in TB product development, perceiving that the potential revenue which can be generated with these products in developed countries is low.

c) Promising product concepts are being developed in the academic environment and in smaller, start-up companies, but these groups will need additional funding and/or partnering with a major diagnostic company in order to complete the product development process.

d) Difficulty in gaining access to clinical patient samples and limited access to relevant study sites for product evaluation are major impediments for timely test development faced by most companies in the industrialized world

e) Distribution of diagnostics into remote areas, training and servicing is perceived to be expensive, difficult and hard to predict in its financial and organizational impact.

The Group will have to address all these hurdles in order to stimulate and drive the development of new diagnostic products.

Appropriate activities are: the provision of market data and further market insight, support in the product specification process, (co)funding for product development and studies, and facilitation of access to efficient distribution channels, as used by the Global Drug Facility.

4.1.3 Evaluation

All product developments are based on product specifications which ideally are contractually agreed with the development partner. During the (technical) evaluation phase product performance is evaluated against these specifications under relevant field conditions. The design and organization of these studies as well as access to relevant and reliable study sites is crucial to the success of this phase and an important area of engagement for the WG.

4.1.4 Demonstration

Demonstration projects will provide cost-effectiveness and impact data in disease endemic settings, and help to understand and define factors needed for successful and sustainable implementation. When developed in collaboration with local NTPs these projects generate an important familiarization effect and can usefully smooth the path to acceptance and future routine use. They differ from (technical) evaluation studies in the sense that they are larger in size and emphasize the impact of local factors and directly lead to implementation.

The understanding of cost-effectiveness and aspects of public health impact will be supported further by mathematical modelling activities. Initial estimates are important criteria for decision-making in the project selection and prioritization process, while assumptions will be challenged and verified as part of the demonstration projects.

4.1.5 Regulatory

The regulatory situation for TB diagnostics is characterized by huge between-country variation ranging from no regulation in few developing countries (although changing), through a relatively low level in Europe (self certified CE-mark, class III, other products) to one of the highest possible levels in the USA for NAAT products (PMA). Several regulatory agencies including many in Asia are presently reviewing their approach and introducing stricter guidelines for diagnostics. A high degree of fragmentation of regulatory requirements can easily turn into an impediment to industrial investment in TB diagnostics. Therefore the WG is continuously monitoring this dynamic environment and will contribute to a harmonized approach for at least most of the high endemic countries.

4.2 Objectives, Targets, Indicators

Objectives, targets and indicators are considered under the headings of Discovery, Development and Access.

4.2.1 Discovery

OBJECTIVE 1

Address existing knowledge gaps obstructing development of new diagnostic tools

Targets	Indicators (apply to all 3 target groups)
• **Sensitive, early detection of active disease** Discovery science to identify new markers (also in HIV-infected subjects) with improved discriminative power for active disease (may be antigenic, immunological, proteomic or other) Validation of candidate targets in suitable screening format (e.g. ELISA) with patient samples from target population(s) Exploration and further refinement of understanding of transmission dynamics and natural history to inform mathematical modeling of potential impact of new diagnostic tools • **Identification of LTBI at risk of progression** Discovery science to identify new markers (also in HIV-infected subjects) with improved discriminative power for predicting future progression to active disease (may be antigenic, immunological, proteomic or other) Evaluation of predictive value in identifying subjects at risk of progression of next generation of existing tools for detection of LTBI • **Simple, rapid identification of drug resistance** Discovery science to identify novel markers of drug resistance for first and second line drugs in cultured isolate Discovery science to improve detection of drug resistance direct from patient samples Validation of marker candidates in suitable screening format with patient samples from target population	• Number of studies received and financed through "Requests for Applications" • Number of agencies having announced related funding opportunities • Number of related peer-reviewed publications • Number of new promising technologies reported • Number of new diagnostic reagents/targets identified • Number of new promising technologies identified through landscape-mapping • Number of requests for reference material received by sample and strain banks • Number of publications associated with use of sample and strain banks • Number of target validation studies performed under the auspice of the Diagnostic Working Group • Number of new targets with contractually assured affordable and sustainable product access

4.2.2 Development

OBJECTIVE 2

Development and evaluation of a portfolio of new diagnostic tools and demonstration of impact

Targets	Indicators (apply to all 3 target groups)
For all three indications: (below) – Inclusion of related goals in research funding calls by major funding agencies – Public sector product development agreements with industry – Coordinated evaluation and demonstration projects • **Sensitive, early detection of active disease** Conceptualization and development initiation of simple rapid format tests for TB in sputum, serum, saliva or urine based on improved targets Introduction of least one product for the district laboratories by 2007 Introduction of at least one product for the peripheral laboratories by 2008 Introduction of at least one POC product for health centers by 2010 • **Identification of LTBI at risk of progression** Conceptualization and development initiation of test for risk of disease progression in a suitable platform based on best candidates Introduction of at least one product for point of care use by 2012 • **Simple, rapid identification of drug resistance** Conceptualization and development initiation of tests for drug resistance requiring equal or less infrastructure and training than current technologies Introduction of at least one product at first referral level by 2006 Introduction of at least one product at peripheral laboratory by 2008	• Number of agencies announcing relevant funding opportunities • Defined Customer Requirements and Product Specifications • Number of Product Development agreements with industrial partners • Number of successfully completed Development and Technical Evaluations according to Product Specifications • Number of clinical evaluation and demonstration sites developed and authorized • Number of evaluation projects initiated • Number of evaluation projects completed • Number of peer-reviewed publications reporting results from evaluation projects • Agreement on empiric design of Demonstration studies with selected NTPs • Number of Demonstration Studies initiated • Number of Demonstration Studies completed • Number of peer-reviewed publications reporting results from Demonstration Studies • Number of new targets with contractually assured affordable and sustainable product access

4.2.3 Access

OBJECTIVE 3

Implementation of new diagnostic tools and ensuring access

Targets	Indicators
• Definitive predictions of impact from the use of improved diagnostics on TB detection rate and transmission • Operational studies to demonstrate epidemiological and economic impact of new tools in high-burden settings • Accelerated registration of products with proven utility • National and international policy changes reflecting impact evidence on new diagnostics • Creation of demand through communication to stakeholders (NTPs, MOH, technical and funding agencies.) • Ensured access to proven technologies through inclusion in GDF or other procurement mechanisms	• Completion of mathematical model defining impact and cost-effectiveness • Number of countries with streamlined regulatory procedures for TB diagnostics • Number of market analysis updates • Number of new diagnostic tools included in TB policy recommendations of international technical agencies • Number of new diagnostic tools included in national TB policy recommendations • Number of NTPs in which new diagnostic tools are implemented at district level • Number of NTPs in which new diagnostic tools are implemented at local level • Number of NTPs in which new diagnostic tools are implemented at point of care

4.3 Activities, Timelines, Milestones

4.3.1 Discovery Biology and Basic Technology

The greatest impact on public health in the TB diagnostics area is expected from a highly accurate but field-usable testing device (such as a lateral-flow test strip). The most prominent roadblock for the development of suitable antigen or antibody assays is the lack of suitable immunological targets. In presently available serological tests, sensitivity is relatively high only in patients with smear-positive disease, but much lower in children, patients with extrapulmonary disease, HIV-infected individuals, and smear-negative cases, thus currently offering little additional benefit over sputum smear. These tests cannot reliably distinguish active tuberculosis disease from latent infection with *M. tuberculosis*; neither do they distinguish *M. tuberculosis* from other species of mycobacteria. During 2005, the Working Group in collaboration with TDR will complete an assessment of a wide range of commercially available serological rapid tests to provide a clear baseline for further improvements.

A fresh approach will be taken by FIND in 2005/06 to select more promising antigen combinations based on available research data and expert knowledge and opinion. It is anticipated that during 2006/07 an improved POC test (for blood, serum, urine or saliva) will be developed.

However, at this time it remains unclear whether any combination of the presently available range of antigens and antibodies will be specific and sensitive enough for the development of a truly satisfactory POC test which allows clear treatment decisions. To this end the Working Group plans to foster and finance additional research in this area building on recently developed knowledge from gene sequencing and expression profiling of the majority of members of the

mycobacteria family. It is anticipated that this information will facilitate the development of subsequent generations of improved POC-suitable test strips.

Research on predictive markers for the conversion of latent infection into active disease is still in its infancy. The Working Group estimates that basic research at academic sites will be needed for at least three or four more years until reasonable product development can be initiated. Because such products will also have quite a promising market in developed countries with low overall rates of TB burden, a reasonable drive for resource allocation in competent research centers can be assumed, which will be monitored and further strengthened by the Diagnostic Working Group.

Nucleic acid amplification tests (NAAT) have shown their ability to detect rapidly and reliably *M. tuberculosis* in sputum and other patient samples. The key challenge for improving the benefit from these technologies in the public health sector of developing countries is the lack of highly integrated solutions which are easy to operate and sufficiently affordable for implementation in public health programs. A user-friendly solution must both integrate the sample preparation process (which presently is still tedious) as well as the amplification and detection procedure. During 2005 and 2006 FIND will assess the technical feasibility of several promising system concepts, in order to select development partner(s) which can develop a highly integrated NAAT product for use at the First Referral Level (district lab) or at the Peripheral Level (presently microscopy center) until 2008. Although this will make NAAT available for broader use in developing countries for the first time, more miniaturization and simplification will be needed to make NAAT as widely useable as e.g. mobile phones.

4.3.2 Product Development

The Diagnostics Working Group will support product development both directly through product specific development partnerships and indirectly through the creation of a framework to stimulate and enable the planning of innovative diagnostic tool development.

The direct, product specific measures will financially and logistically support a portfolio of projects which respond to the specific needs of the different levels of the public health system in high burden countries (First Referral Level or district lab, Peripheral Lab or microscopy site, and Point of Care or rural health post). Different products will be needed for case detection, diagnosis of MDR-TB and latent infection. The essential targets for product introduction at the different levels of the health system are outlined in Figure 2.

Figure 3 illustrates in more detail the portfolio of presently active and planned projects together with their timelines for introduction.

The indirect measures comprising an enabling infrastructure are:

a. The release in 2005 of the first comprehensive market report with special emphasis on the public health markets in developing countries.

b. The detailed identification and description of customer requirements. These customer requirements are specific for the different segments of the public health system and serve as a basis for more detailed product specifications.

c. A further expansion and maintenance of the WHO/TDR TB specimen and strain bank to support product development with selected partners.
d. Clinical trial laboratory strengthening
e. Development of diagnostic trial design and monitoring tools
f. Generation of an inventory of clinical trial sites
g. Collation of regulatory and procurement policy information

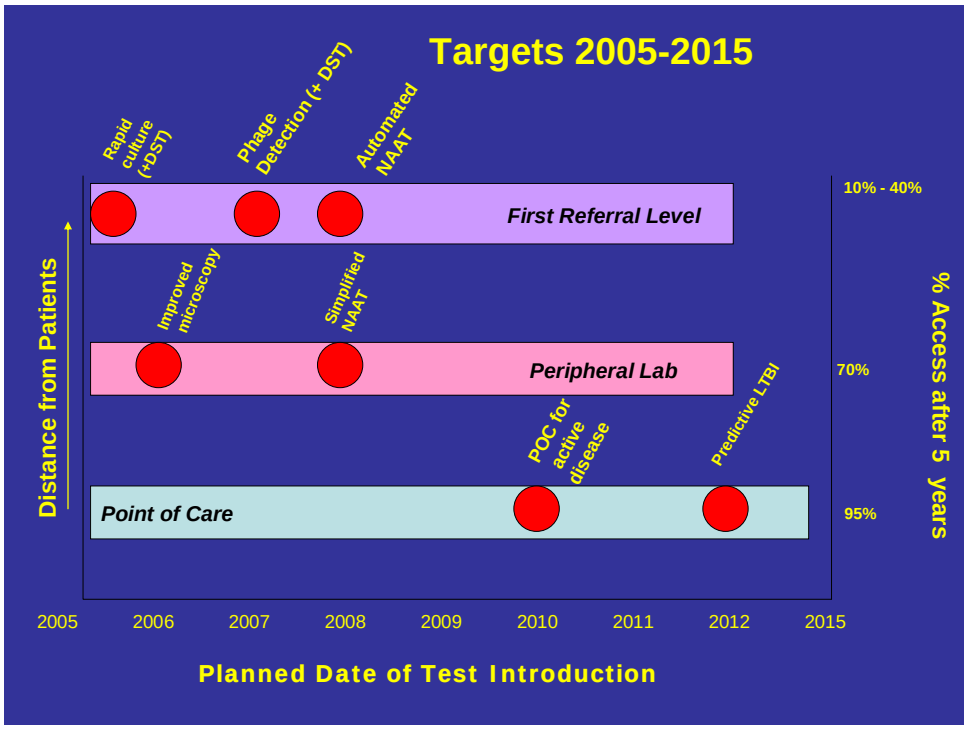

Figure 2: Targets for Test Introduction Leading to Sustainable Adoption: 2006-2015

Currently there are several promising TB diagnostic tests plugged into the research to demonstration continuum. These tests vary in their target population and the level of health system where they could be introduced (Figure 2). Tests that are anticipated to have the greatest impact on TB control and improved patient care should be readily accessible to patients, such as point of care tests. Other new tools may only be implemented at the peripheral laboratory level or referral laboratory due to their technical requirements. Such tests may potentially reach a smaller proportion of the population, but are still expected to have a positive and measurable impact on TB control. Furthermore, several of such tests are already commercially available and may be demonstrated and introduced into National TB Programs relatively rapidly, offering a short-term opportunity for improvement in TB diagnosis. Early implementation of such new technologies is needed to meet the urgent public health need. Demonstration projects and ultimate introduction of these tests will also require urgent public and private investment in laboratory strengthening and cost-effectiveness assessments.

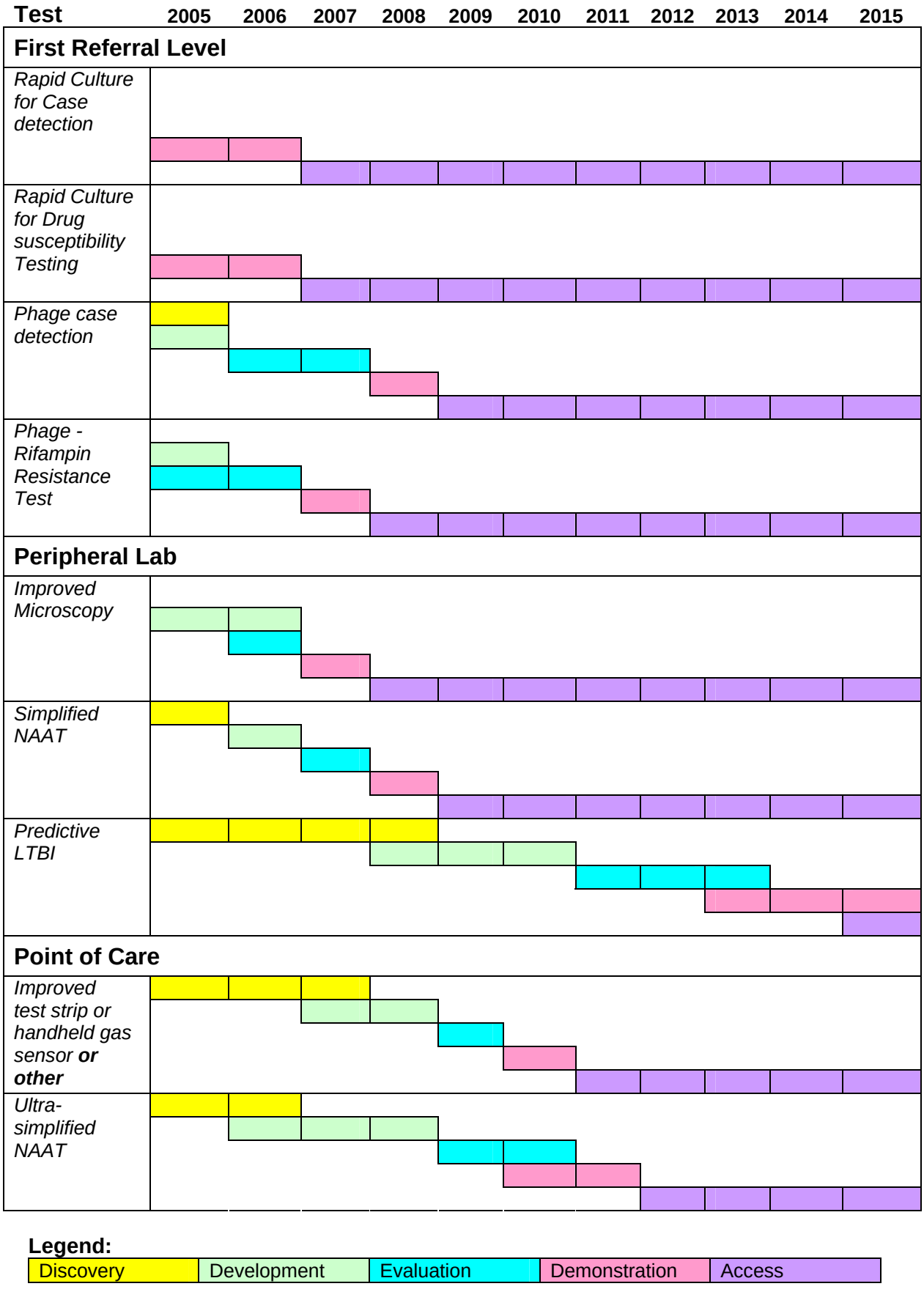

Figure 3: Portfolio of development projects

4.3.3 Evaluation

All products sponsored by or developed under the auspices of the Working Group will undergo a detailed technical evaluation, as outlined in Figure 3 at a product specific level. The provision of well characterized samples and bacterial strains from the WHO/TDR TB specimen bank and strain bank will be an important means to speed up this evaluation process, as will field studies performed in well-established, characterized and qualified research sites in high-burden countries, organized through the members of the Diagnostics Working Group.

4.3.4 Demonstration

All products which have successfully completed the development process and technical evaluation studies will subsequently be tested and further characterized in demonstration studies. The first of such studies (currently ongoing) involves a rapid culture method for case detection and detection of drug resistance, which is already in widespread use in the developed world, offering significant improvement in sensitivity over smear microscopy. However, greater cost and complexity will require substantial investment in laboratory infrastructure and human resources. Optimizing the translation of these technologies into improved TB control and patient care is the focus of demonstration projects underway in several African countries with high HIV-TB co-infection rates and in Eastern Europe for the management of MDR-TB. Improved microscopy, *e.g.*using bleach sedimentation, is another area in which demonstration projects will be initiated in the near future.

4.3.5 Regulatory

In recent years the Working Group has undertaken a comprehensive survey of the regulatory situation for TB diagnostics in high-burden countries, identified local stakeholders and gained insights into likely future trends in the regulatory environment. The Working Group will contribute to the harmonization of regulatory requirements by assembling a team of representatives from all affected stakeholders (regulatory bodies, manufacturers and public health agencies) and supporting studies that create confidence in a harmonized approach.

4.4 Monitoring and evaluation

Progress towards the overall goals of producing the diagnostic tools as envisaged above will be reviewed against the targets and timelines described at an annual meeting of the Working Group. Dedicated secretarial staff will monitor progress on a continuous basis and highlight bottlenecks and problems at the annual meeting of the full Working Group, or to appropriate individuals or sub-groups.

4.5 Risk Factors and Mitigation

4.5.1 Insufficient financial investment and timing of investment

Adequate investment early on is required to enable funding for discovery and of early stage technologies. Product specific development agreements require entering into financial commitments covering the entire planning phase of the project (until introduction) – otherwise attractive financial terms for the public health market cannot be achieved.

4.5.2 Technologies fail

Technologies can fail during the discovery phase, development phase and also as a result of evaluation or demonstration studies. Naturally, the risk decreases when projects reach a higher maturity phase. To offset the risk of technology failure the development portfolio comprises multiple options at each level of the development continuum, with the aim to introduce at least one customized solution for case detection at each level of the health system with a high degree of certainty. Likewise, the breadth of the portfolio for MDR-TB and conversion of latent TB will be risk-balanced, too.

4.5.3 Inadequate development of laboratory strengthening

Many of the new diagnostic technologies require improved laboratory capacity and development of laboratory infrastructure. Obtaining consistent high quality results requires training, continued education and the establishment of quality assurance and proficiency testing schemes to a degree which will vary according to the technology to be implemented. Collaboration with the DOTS Expansion Subgroup on Laboratory Strengthening will ensure the timely and appropriate strengthening of laboratory services to meet the requirements for implementation of new diagnostics.

4.5.4 Impaired access to new products

The introduction of improved diagnostic tools based on positive outcomes in Evaluation and Demonstration studies does not necessarily guarantee broad access and use. Several factors can contribute to reduced access including product or infrastructure costs which are too high, regulatory hurdles and lack of 'buy-in' or political will at the local or NTP level. Unreliable distribution and product support systems can prevent or dissuade product use. The Diagnostics Working Group has developed a range of means for dealing with such situations: contractually agreed affordable product pricing will be a prerequisite for funding in development partnerships, and regulatory hurdles will be addressed through the regulatory harmonization activities of the Working Group. Carefully selected Demonstration projects shall create buy-in, involving local stake holders in key countries in an early phase. Sustainability of product supply and product support will require the development of new logistic concepts, leveraging the experience the STOP TB Partnership has gained in the pharmaceutical sector with the Global Drug Facility.

4.5.5 Interrupted product supply

The Working Group is planning to make significant investments into discovery, product development, studies and supporting activities. The return for these investments must be a reliable and uninterrupted product supply at a steady quality level. Therefore development partners and manufacturers will be selected carefully and diligently through an appropriate pre-qualification process.

There is also the risk that manufacturers and suppliers involved in this process might change their business focus, sell-out to new owners with a different strategy or simply might default and collapse. The Working Group, through the Foundation for Innovative New Diagnostics (FIND), has developed an intellectual property strategy which assures access to the know-how of all sponsored products through a royalty–free license scheme which allows the transfer of the manufacturing process to more appropriate business partners if so required.

4.6 Modeling the predicted impact of novel diagnostics for detection of active TB

4.6.1 Objectives of proposed model

It is expected that new diagnostics will improve TB control by bringing improved accuracy to detection of active TB cases in all patient groups with tools that are widely accessible logistically, financially and technologically. A mathematical model is under development in order to test this hypothesis and generate predictions of the potential impact upon TB epidemiology of the envisaged introduction and anticipated performance of new diagnostic tools for detection of active disease. The model will be used to investigate the potential impact of a range of tools with varying sensitivity for detection of smear-positive and smear-negative disease and will take into account the predicted reach (or penetration) of each tool (e.g. district laboratory, local microscopy unit, POC) as well as performance compared to existing tools in both HIV-infected and uninfected subjects. The interaction between these predicted impacts and the anticipated epidemiological effects of the measures described in the strategic plans of the implementation working groups (DOTS expansion, TB/HIV and DOTS+) will also be investigated.

4.6.2 Model considerations

One of the largest anticipated benefits of newer, more sensitive diagnostic tests is in new prevention of "downstream" smear-positive cases through detection of cases whilst they are still smear-negative – interruption of future transmission potential through earlier, more

sensitive detection and treatment. However, this effect will be sensitive to some or all of the following:

- *The right patients getting tested*, which will depend upon

patient health-seeking behaviour, accessibility (or reach) of new tools and the proportion of future smear-positive patients who present for testing whilst still smear-negative

- *The natural history of disease*, specifically

both the rate at which smear-negative patients convert (or progress) to smear-positivity – this will be a key determinant though information is neither readily available nor easily investigated - and the proportion of prevalent smear-negative patients with symptoms sufficient to warrant investigation

- *Existing diagnostic algorithms*,

the sensitivity of which will determine the maximal incremental benefit possible from new tools – thus in regions where criteria for diagnosis of smear-negative disease are strict (and fewer smear-negative cases diagnosed) the additional impact of novel tools would be expected to be greater than in regions (such as SEARO) where clinical and radiographic "syndromic" diagnosis of smear-negative disease is common. If a POC diagnostic were ultimately available for use by rural community health workers without immediate recourse to radiography or nursing/medical evaluation the background sensitivity of case detection would be extremely low and the incremental benefit potentially large.

There are several important additional benefits which new diagnostic technologies could bring which may not be readily revealed by such a model:

- *Accurate* diagnosis – though radiography and clinical assessment can achieve detection sensitivity of 80% this is at the cost of poor specificity. Over-treatment of incorrectly diagnosed non-TB cases is costly both to health care systems (drug, human resource and infrastructure costs) and to individuals, their families and civil society, avoidably diverting scant resources. A sensitive diagnostic with improved specificity could considerably reduce over-treatment releasing resources for NTPs.

- *Convenient* diagnosis – a POC technology would reduce patient inconvenience (such as time off work) and patient cost, common impediments to diagnostic testing.

- *Improved cost-effectiveness* – whilst obviously dependent upon product cost, enhanced diagnostic accuracy and patient convenience should both contribute to improving cost-effectiveness, which should be further augmented by downstream effects upon averted future transmission resulting from earlier, more sensitive diagnosis.

4.7 Resource Needs

The funding required to support basic science and the development, evaluation, and demonstration of the proposed tests is US$ 497 million. Additional US$ 19 million are required for enabling and supporting infrastructure (reference material banks, clinical trial training and laboratory strengthening, pre-qualification of manufacturers, market analysis updates, regulatory harmonization, WG operations), amounting to a total budget need of US$ 516 million. Estimated total financing amongst all stakeholders US$ 80 million some of which may be shared costs with industry.

Funding gap thus estimated at US$ 436 million.

Activity	**Funding Needed**
1. Early-Stage Diagnostic Development and Research	***$206,000,000***
Discovery Science (to include POC, phage, predictive LTBI)	$75,000,000
Development (to include above plus simplified and automated NAAT, rapid culture and improved microscopy)	$131,000,000
2. Clinical Trials and enabling infrastructure	***$303,000,000***
Clinical trial training and laboratory strengthening	$3,000,000
Reference material banks	$3,000,000
Pre-qualification of manufacturers	$5,000,000
Market analysis updates	$1,000,000
Evaluation projects (all tools listed above)	$80,000,000
Demonstration projects (all tools listed above)	$211,000,000
3. Regulatory Approval and Registration	***$1,000,000***
Regulatory harmonization	$1,000,000
4. Working Group Operations	***$6,000,000***
Meetings, Secretariat, Coordination	3,000,000
Advocacy	$3,000,000
TOTAL	***$516,000,000***

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Budget proportion	0.11	0.12	0.12	0.12	0.11	0.10	0.10	0.09	0.07	0.07
Amount	56	61	63	60	57	53	50	45	35	36

Table 3: R&D costs for specific technologies