



Revised Strategic Plan of the Stop TB Partnership's Working Group on New Diagnostics

November 2007

Original documents:

Stop TB New Diagnostics Working Group Strategic plan 2006 – 2015

http://www.stoptb.org/wg/new_diagnostics/assets/documents/SP%20Stop%20TB%20Diagnostics%20WG%20-FINAL-Dec2005.pdf

The Global Plan To Stop TB, 2006-2015, January 2006, [WHO/HTM/STB/2006.35]

http://www.stoptb.org/globalplan/plan_main.asp

Index

	Page
1. Background	3
2. Current situation	
2.1 The disease	4
2.2 Funding	4
2.3 The tests	4
2.4 Diagnostics market survey	5
2.5 Impact on poverty	6
3. The WGND	6
4. Strategic vision	7
5. Priorities	
5.1 Scientific blue print for diagnostics development	7
5.2 Taking products currently in the pipeline forwards	8
5.3 Customer requirement documents	8
5.4 Addressing knowledge gaps	8
5.5 Early assessment of health service capacity to absorb new and modified tools	8
5.6 Issues related to pipe line stages (Value Chain)	8
5.7 Modelling predicted impact	11
5.8 Improving funding and environment for research	12
6. Achievements so far	12
7. WGND Objectives	13
8. WGND work plan	
8.1 General plan for sub group activities	14
8.2 Other activities to be undertaken by WGND	15
9. Subgroup work plan	16
9.1 Optimizing TB smear microscopy	
9.2. Culture-based diagnostics and resistance testing	
9.3. Nucleic-acid amplification techniques for diagnosis and resistance	
9.4. Diagnostics for Latent TB infection	
9.5. Point of Care Tests for TB	
9.6. Evidence Synthesis for TB diagnostics	
9.7. TB Diagnostics and Poverty	
9.8. TB Diagnostics and HIV	
10. Monitoring and evaluation	18
11. Risk factors and mitigation	18
12. Resource needs	19
Figure 1	20

1. Background

Considerable efforts are being made to improve the quality of and access to tuberculosis diagnostic services. The global case detection rate has increased from 28% in 2000 to 60% in 2005. Enormous efforts, too, are being directed towards the development of new diagnostic tools. There are more than 15 candidate technologies or products in the pipeline, some of them expected to be ready for introduction into public health delivery systems within two years.

It is estimated that approximately 50% of patients with tuberculosis are still not diagnosed or treated appropriately. In 2005, there were 1.6 million deaths due to tuberculosis. The problem is compounded by the increasing prevalence of multi drug resistant (MDR) and extensively drug resistant (XDR) tuberculosis and the close association between tuberculosis and HIV infection.

Sputum smear microscopy for acid fast bacilli remains the most widely used test to diagnose tuberculosis. Although the technique is inexpensive, specific and technically not exacting, it has several limitations including unacceptably low sensitivity in diagnosing tuberculosis and the inability to predict susceptibility to drugs used for treatment. Hence there is an urgent need for newer or improved methods for diagnosis to accelerate the fight against tuberculosis and to meet the target of elimination by 2050.

Significant progress has been made in this area, especially since the formation of the Stop TB Partnership (STP) and the STP's Working Group on New Diagnostics (WGND). The number of new products in the pipe line is increasing rapidly and the pipeline itself is fuller than ever before. Furthermore, the speed with which products progress from the stages of early development to the evaluation phase is increasing. The progress in some technological areas has been more rapid than that envisaged in the Global Plan to STOP TB 2006-2015. In other technological areas, however, it has been slower. It was therefore felt necessary to revise the strategic plan to include more recent developments with more precise targets and mile stones, and to reflect a more structured approach to new or modified diagnostics development, evaluation and introduction into public health systems while the overall aims and objectives remain the same. WGND activities also need to enter a new phase with emphasis on promoting efficiency and creating synergy between various stake holders.

2 Current situation

2.1 The disease

There were an estimated 8.8 million new TB cases in 2005, 7.4 million of which were in Asia and sub-Saharan Africa. Twenty two countries have been identified as having a high burden in terms of numbers of cases and together account for over 80% of global TB. The highest incidence rates are in the countries of sub-Saharan Africa where rates of over 500 per 100,000 population are observed. As against WHO 2005 target of 70% case detection, the actual detection rate was 60%. Prompt diagnosis requires fully operational laboratories. Despite efforts to expand access to microscopy, implement quality assurance and assemble reference laboratory networks there are too few laboratories, weak quality assurance systems, and limited facilities (if any) to carry out culture and drug susceptibility testing in many high burden countries.

The magnitude of drug resistant tuberculosis problem globally is not yet known. There are an estimated 400,000 MDR-TB cases emerging annually and XDR-TB has been reported in all world regions. Facilities to diagnose MDR and XDR-TB are almost nonexistent in high burden countries, and consequently these patient groups are underserved by current diagnostic services.

Three other special groups grossly underserved by existing diagnostic services are those with HIV infection, patients with extrapulmonary tuberculosis and children. There are particularly challenging issues in diagnosing tuberculosis in these groups.

An estimated one third of the population of the world has latent infection with *M. tuberculosis*. Tests are available that can identify such individuals but they are currently unable to determine the risk of progression to disease.

2.2 Funding

Funding for both diagnostic service delivery and for the development of new diagnostic tools is inadequate. Average annual per capita health budget in many high burden countries is less than US \$5. Only an extremely small proportion of this will be for TB diagnostics. Global funding for new TB tools has been estimated at US\$206 million, creating a funding gap of US\$6 billion over the next ten years according to estimates in The Global Plan to Stop TB 2006-2015. Of the US\$206 million invested, new diagnostics development received the least - 16.5 million - which is about 4% of the total investment for TB R & D.

2.3 The tests

No test is available that meets all requirements for TB diagnosis either in the performance parameters of the tests (sensitivity, specificity and predictive values) per se or in the

appropriateness for use in the high burden countries. The inadequacy of current technology results in complex diagnostic algorithms with repetitive testing often using multiple technologies. Consequences of this include additional cost, delay in diagnosis and drop out from treatment.

Testing priorities and test availability vary in different parts of the world. In high burden countries, the highest priority is to detect active TB cases. Sputum smear microscopy, the most used test in such settings detects only cases with large numbers of mycobacteria in the expectorate. Hence the sensitivity is low (40-60%) and particularly low for diagnosing tuberculosis associated with HIV infection, and disease in children. Smear microscopy may have little application at all in the diagnosis of extrapulmonary disease. Conventional TB culture is considerably more sensitive but should be performed only in centres with adequate biosafety facilities and takes about 4 to 10 weeks for the results and therefore may not impact much upon individual patient management and outcome.

In industrialized countries with low burdens of infection, diagnosis of any individual with active disease and latent infections are priorities. Molecular techniques, rapid culture and other more recently developed methods are used commonly in such countries, where the advanced laboratory infrastructure and stronger health systems exist. Routine application of these tests in many high burden countries is currently limited by constraints including cost, availability of personnel, safety, logistics, technical complexity, and generally weak health systems.

Limited access to tests for diagnosis, susceptibility testing and identifying latent infections add to the challenges faced by TB control programmes in high burden countries.

Inadequate testing capability has contributed to the emergence of drug resistant tuberculosis as a serious global public health concern.

2.4 Diagnostics market survey

TDR and FIND have jointly conducted the first ever global market survey for TB diagnostics and provided an overview of the current global market for TB diagnostics (<http://www.who.int/tdr/publications/publications/tbdi.htm>). Annually over US\$ 1 billion is spent world wide in TB diagnostics. This is twice as much as for TB drugs. Only one third of this is spent in the countries where 73% of the diagnostic testing takes place. About 83 million sputum smear microscopy tests are conducted in middle and low income countries per year.

2.5 Impact on poverty

The economic burden of seeking a TB diagnosis and treatment can be prohibitively high for patients and their households even where services are provided free of charge. Patients may spend 30 - 40% of their annual income on this. Costs include lost earnings, transport, childcare etc. and may involve the need to sell assets or borrow money with interest. These costs can tip families into, or exacerbate existing, poverty.

3. The WGND

The WGND was established in 2001 as a platform for focus on promoting development and adoption of new and modified diagnostic products. Since then, the WGND secretariat (UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)) and the Chair, Foundation for Innovative New Diagnostics (FIND) along with all the members of the WGND including international organizations, academia, NGOs and industry have contributed significantly to the advances in the field of TB diagnostics.

The mission of the WG is to advocate and implement research and/or operational activities in pursuit of the development and implementation of TB diagnostic tools and to collaborate with other elements of the Partnership so as to create synergy and add value to actions taken in pursuit of the aims of the Partnership.

To streamline and facilitate the WGND operations a core group has been established, with representation from major interest groups. To complement this, eight sub groups with specific tasks have also been created. Each subgroup has two joint co-ordinators who will develop work plans and targets for the sub group. The proposed structure is as shown in Fig 1. There are five subgroups with primary responsibility for advancing technology and the remaining three provide necessary information around specific issues that should guide tool development and implementation. These subgroups will work together to achieve WGND goals.

The role of the WGND is to coordinate and facilitate development, evaluation and implementation of new and modified diagnostics in a scientifically acceptable and timely manner by linking all stakeholders involved in the diagnostic development and evaluation pathway. New or modified diagnostics in this respect refer to all tests other than those which are currently being implemented in National Programmes of high burden countries. This document on strategic plan is developed to enable the WGND to be more proactive and to have an ordered model to anchor its activities.

4. Strategic vision

Taking into consideration the goals of the STOP TB Partnership and the specific diagnostic needs of national control programmes and patients in high burden settings and also the various aspects of development, evaluation and implementation of new tools, the following vision statement was adopted by the WGND.

The vision of the WGND is to develop and introduce cost-effective and appropriate new diagnostic tools that will contribute towards control of global TB epidemic and improve quality of patient care. The ideal toolbox, as envisaged by the WGND, will contain a portfolio of diagnostic technologies that will perform well in different categories of patients including those infected with HIV, extrapulmonary disease and children to

1. improve TB case detection through tests with better performance parameters and through improved accessibility.
2. rapidly identify drug resistant TB disease enabling timely and effective patient treatment to reduce both individual morbidity and continuing transmission
3. reliably identify latent infection and determine risk of progression to active disease allowing rational use of preventive therapy

Simple, accurate, affordable tests that can be performed at lower levels of the health care systems and produce results on the same day are the ultimate goal.

5. Priorities for the WGND

5.1 Scientific blue print for diagnostics development

From discovery to implementation, a diagnostic tool has to go through a chain of consecutive stages of development and evaluation. Every stage the tool crosses is a step closer to implementation and therefore the value of the tool increases with each stage. A clear roadmap of these stages (pipe line stages/value chain) must be defined for diagnostic test developers in academia and industry, so that there is a transparent understanding of the necessary steps required to achieve internationally recognized authorization for routine use.

Clear definitions of the stages, guidelines and criteria for tool evaluation and implementation can form the basis for a scientific blue print for diagnostic development.

This blue print which will act as best practice guidelines for diagnostics development, evaluation and implementation need to be developed as priority and made widely available. Such an approach would hasten and streamline tool development and enable accurate and realistic estimate of the future benefits of the test when applied under program conditions. It may also help regulatory authorities and end users while making choices.

5.2 Taking products currently in the pipeline forwards

There are several new/modified tools for tuberculosis diagnosis under various stages of development. An illustrative few of these are currently listed in the pipeline of the WGND. This pipe line needs to be expanded to include all possible candidates and their progress in the pipeline needs to be monitored continuously.

5.3 Customer requirement documents

For tool development it is essential to know the expected requirements at different levels of health care delivery in different settings and in different patient populations such as those infected with HIV, those with extrapulmonary disease and children. The requirements can also vary depending on the epidemiology of tuberculosis – high burden, high incidence of MDR/XDR tuberculosis - in the area. The WGND can contribute in this area by collating information to prepare such documents

5.4 Addressing knowledge gaps

Currently available evidence has to be reviewed to make recommendations for policy change and end use. This will also help in identifying research gaps. Role of tests within diagnostic algorithms need to be defined. WGND can contribute significantly to this requirement for scientific evidence for practice options

5.5 Early assessment of health service capacity to absorb new and modified tools

Early, and thereafter regular, assessments of the likely requirements for implementation of services based on any new technology are needed. These assessments should help guide resource priorities for test development.

5.6 Issues related to pipe line stages (Value Chain)

5.6.1. Discovery Biology

More basic upstream research is needed to identify candidate molecules and new technologies. Further research is needed for gene sequencing, proteomics, biomarker discovery and expression analysis of *M. tuberculosis* and related strains.

5.6.2. Development or modification of basic technology

Technologies under development for improved case detection include rapid culture systems, phage-based detection methods, molecular-based methodologies, antigen and antibody detection, and detection of volatiles in the breath or sputum of TB patients. Rapid

culture systems, phage-based detection and molecular techniques are also being applied to rapid detection of drug-resistant bacteria. Substantial research is required to adapt these for reliable use in resource poor settings and to address the infrastructure needs including long term maintenance, for biosafety.

Molecular tests (PCR, TMA, SDA, LAMP) can suffer from unacceptable levels of complexity in technology, high equipment costs and risk of cross-contamination and in addition, sensitivity remains modest and highly variable across settings. New systems must be found which allow complete integration of the entire workflow (including sample preparation) and minimize reagent and equipment costs thus, rendering the procedure so robust that it can be used safely in settings like microscopy centers and eventually even in rural health posts.

Modifications of the AFB smear microscopy technique can easily be deployed through existing facilities.

Currently available immunological assays do not have diagnostic accuracies adequate for systematic implementation especially in those with HIV-coinfection. There is also the potential for developing antigen detection assays. Utility of assays for detection and quantification of antigen specific interferon- γ release from T-cells need to be further explored in different settings.

Continued research is required to develop point of care (POC) -suitable tools based on molecular or immunological principles.

5.6.3. Translational research

Discoveries in basic science have to be developed into prototype diagnostic tests. To achieve this TB diagnostic expertise has to be coupled with basic sciences possibly through improved networking. Specimen banks, reference materials etc are required to support this stage. This concept is beginning to be accepted and funded

5.6.4. Technical Evaluation

The performance parameters like sensitivity and specificity of new tools are measured in the laboratory and in different patient groups. Impact on patient management and outcomes also need to be measured. The next important evaluation under field conditions is the weakest step at present, as there is little accepted methodology. 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. Important actions can include the sharing of reference materials, development of clinical trials site directory and GCP/ GCLP capacity building. A large bank of specimens (sputum, blood, sera, lymphocytes, urine etc) that could be

accessed readily by investigators who wish to conduct these basic evaluations of diagnostic tests are needed.

5.6.5. Large Scale Product Development and interesting the private sector in new TB diagnostics.

Development of large-scale manufactured and affordable industrial diagnostic products is presently hampered by several factors. In general, large scale use in the public sector is driven by national and international guidelines for tuberculosis management while the use in private sector is driven more by market forces. Both these aspects need to be addressed.

- Until the recent launch of the TDR/FIND sponsored market report on TB Diagnostics, there was a significant lack of market data.
 - Major diagnostics development companies may be reluctant to invest in TB product development, perceiving that the potential revenue which can be generated with these products in developed countries is low.
 - Promising product concepts are being developed in the academic environment and in smaller, start-up companies. These groups need additional funding and/or partnering with major diagnostic companies in order to complete product development processes.
 - Distribution of diagnostics into remote areas, training and servicing are perceived to be expensive and the financial and organizational impact hard to predict.
 - Detailed customer requirement documents for various levels and situations are lacking
- Appropriate activities include provision of market data and further market insight, establishment of public-private partnerships for developing diagnostics, support in 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.

5.6.6. Demonstration phase and operational research in high burden countries

Large scale projects are required to demonstrate cost-effectiveness and impact in disease endemic settings, and to define factors needed for successful and sustainable implementation. They differ from technical evaluation studies in the scale and emphasis on impact of local factors and directly lead to implementation. Critical aspects include defining how the test fits into the overall diagnostic testing algorithm, establishing quality assurance systems, training requirements and estimating true costs in the field. These aspects are critical to the ultimate utility and impact of tests.

When developed in collaboration with National TB Control Programmes, these projects lead to familiarization that can smooth the path to acceptance and future routine use. This

stage differs from retooling in that the product is still deployed by the research groups and not by the national programmes. The WGND can facilitate this stage by creating and sharing of evaluation tools and standardized methodology, in identification of sites, in collaboration and regular communication with national programmes and other STB Working Groups (DOTS Expansion, Laboratory Subgroup, TB/HIV etc), in funding, in facilitating training and establishing quality assurance systems, by advocacy and by addressing other logistics hurdles.

5.6.7. Regulatory issues

There is a huge inter-country variation ranging from no regulation at all to the very stringent. Several regulatory agencies are presently reviewing their approach and introducing stricter guidelines for diagnostics. Inconsistent regulatory requirements may act as an impediment to industrial investment in TB diagnostics.

There is a need to continuously monitor this dynamic environment and contribute to a harmonized approach especially in the high burden countries. It is also necessary to provide safe guards against poor quality tests. Defining indications and performance characteristics of currently available tests can aid in this.

5.6.8. Retooling

Tools which have completed their progression through the various stages of the pipeline and match customer requirements, are to be rapidly deployed, effectively used, and integrated into TB control programmes. Improving existing technologies such as methods of sputum collection and processing and/or deploying new tools are options for retooling. Empowering and capacity building within national/local research institutes and National TB Control Programmes is integral to the ultimate goal of sustainable tool introduction. Health systems research, health economic research, impact models, infrastructure development and quality assurance systems are required for this. Interaction between the WGND, the Retooling Task Force and the Lab Capacity Strengthening subgroup will be essential for effective retooling.

5.7 Modelling predicted impact

Understanding of the economic and public health impact will need to be supported further by health systems research and mathematical modelling. Initial estimates are important criteria for decision-making and prioritization process. Mathematical models can generate predictions of potential impact upon TB epidemiology of the envisaged introduction and anticipated performance of new diagnostic tools for detection of active disease taking into

account the predicted reach of each tool (e.g. district hospital laboratory, peripheral laboratory, primary health care clinics) and performance compared to existing tools. 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+) also need to be investigated. Several groups are currently working on different aspects of this issue. However, a model is only as good as the data and assumptions it is based on. Currently available models need to be critically reviewed and more quality data generated in areas identified, to feed the modellers

5.8 Improving funding and environment for research

Research, basic upstream research and operational field research in particular, have not received the funding required. Investment in TB research may be considered high risk from the business perspective since the potential returns for such investment can be low. There is also a need for advocating increased government spending especially on field research. By facilitating dialogue between research stake holders, scale and speed of diagnostic research can be improved.

6. Achievements so far

6.1. Recommendations for international policy change

STAG- TB 2007 (WHO) endorsed the recommendation for use of liquid culture and rapid species identification for culture and drug susceptibility testing to be integrated in a country specific comprehensive plan for laboratory capacity strengthening

STAG-TB 2007 (WHO) recommended revision of case definition based on sputum smear microscopy.

STAG-TB 2007 (WHO) recommended a reduction in the minimum number of sputum specimens examined in the investigation of pulmonary tuberculosis.

STAG-TB 2006 (WHO) recommends revised algorithm for diagnosis of smear negative tuberculosis.

6.2. Recommendation for policy change/ approval at national level

QuantiFERON TB Gold In Tube– FDA approved for tuberculosis screening 2007

6.3. Evidence reviews to change policies

Meta-analyses and systematic reviews published on different diagnostic tests

6.4. Examples of products in the pipeline (still to be updated)

Product	Purpose	Pipeline status
---------	---------	-----------------

6.5 Major funding for research (still to be updated)

7. Objectives of the WGND

The objectives are developed to attain the vision taking into account the needs in the focus areas

1. To develop a portfolio of tests with high performance characteristics for
 - Case Detection of pulmonary TB, extra-pulmonary TB and pediatric TB.
 - Drug susceptibility testing to detect MDR and XDR -TB
 - Monitoring response to treatment
 - Identifying latent TB infection with risk of progression
2. To make available in the portfolio tests that will perform well
 - in different categories of patients
 - at different levels of health delivery
 - in different epidemiological settings
3. To facilitate different stages of evaluation and documentation, in accordance with accepted quality standards and following established guidelines (e.g. DEEP) and reporting formats (e.g. STARD), of performance parameters, diagnostic value and impact.
4. To ensure access to newer tests and assist with implementation in National Control Programmes especially in high burden countries. Implementation of novel technologies may start where technical hurdles are less pronounced (i.e. regional reference centres) whilst development of appropriate technology for settings closer to patient continues.
5. As prerequisites to objectives 1, 2, 3 and 4,
 - a. To identify knowledge gaps obstructing development, evaluation and implementation of new or modified diagnostic tools
 - b. To prepare customer requirement documents for different clinical types of tuberculosis, different patient populations, different health delivery systems and different epidemiological settings
6. To develop a scientific blue print for TB diagnostics development, evaluation and implementation to provide guidance to scientists and investigators in academia, industry and public sector, in all aspects of development, evaluation and approval including regulatory approval.

8. WGND plan

8.1 General plan for sub group activities

1. Identify all candidate TB diagnostic tests and position them in the pipeline. Monitor and facilitate their progress. Although the WGND will describe the pipeline and progress of diagnostics in it, the ownership and onus for progress of the specific product remains with the respective developer.

By 2009 the Group plans to introduce at the first referral level an easy-to-use technology with accuracy similar to culture but capable of providing results in a few hours or days.

By 2010 new point-of-care (POC) tests for detection of active TB will be available.

Possible candidates may be based on lateral flow technologies, integrated, portable nucleic-acid test system or gas sensor technologies.

By 2012 a rapid diagnostic procedure capable of predicting progression of latent TB infection to active disease, in both HIV-infected and uninfected subjects, will be introduced.

2. Collate evidence and data on currently available diagnostic tests and for those in various stages of development and make recommendations
3. Develop clear criteria for describing the intended setting for candidate diagnostics tests including the expected level of the health system at which the test may be used, the opportunities for decentralisation of services using the test, its role in special settings such as high HIV prevalence areas or high MDR-TB or XDR-TB prevalence areas
4. Advocacy and sponsorship to increase investment from public and private sector in basic research that supports translational research and development of diagnostic technologies.
5. Identify priority areas requiring targeted investment and management of product development
6. Facilitate public - private stakeholder collaboration leading to accelerated diagnostic tool development, evaluation, demonstration and market entry
7. Assist governments and public health agencies in countries to evaluate utility, cost-effectiveness and local appropriateness of new diagnostics and develop effective implementation schemes that maximize patient accessibility

Details will be described under subgroup work plans

8.2 Other activities to be undertaken by WGND

8.2.1. Intensify collaborations within the WGND, with other WG of the STP and outside

<i>Activity</i>	<i>Indicator</i>	<i>Time line</i>
Establishment of Core Group		2007
Facilitating Core Group interaction	Teleconferences, meetings, email	Ongoing
Establishment of Sub-groups		2007
Promoting interaction with other WG	Representation of WGND in annual WG meetings, expert consultations and workshops around particular issues	Ongoing
Promoting WGND outside STB Partnership	Annual meeting of WGND during the Union's World Conference on Lung Health	
WGND documentation, website management	Evidence, data, comments, guidelines etc made available on the web	Ongoing

8.2.2. Develop a scientific blue print for TB diagnostics development and evaluation to provide guidance to scientists and investigators in academia, industry and public sector, in all aspects of development, evaluation and approval including regulatory approval
Through workshops and consultations this document will be readied for publication by 2009

8.2.3 Develop customer requirement documents for different situations and areas to assist in product development
Through consultations with stakeholders from different TB epidemiology areas and studies carried out in these areas, customer requirement documents for different health delivery levels and indications in these areas will be readied by 2009.

8.2.4. Predict by mathematic models the epidemiological and economic impact of new diagnostic tools in National TB Program settings, private and NGO sectors.
Plan for this activity is being prepared

Plan for the following will be prepared after the subgroups prepare the list of products in the pipeline

8.2.4. Facilitate integration of new tests into diagnostic algorithms and evaluating new algorithms and impact on patient out comes

8.2.5. Promote use of new technologies in high burden countries by development and regulation of TB diagnostics market

8.2.6. Liaise with STB retooling task force and lab capacity strengthening group to aid implementation including quality assurance programmes

9. Subgroup work plans

9.1 Optimizing TB smear microscopy (under preparation)

9.2. Culture-based diagnostics and resistance testing (under preparation)

9.3. Nucleic-acid amplification techniques for diagnosis and resistance (under preparation)

9.4. Diagnostics for Latent TB infection

A. Address knowledge gaps in tests for latent TB infection

Activities	Indicators	Time line
Review published literature on evaluation of IGRA in different parts of the world	Table indicating performance parameters	First - 2008 yearly update
Support and evaluate on publication, the ongoing studies examining use of IGRA in predicting development of disease.	Report with comments on the website	Website ready - 2008 Continuous update
Collate information on skin tests	Report with comments and suggestions	2008

B. Facilitate development and evaluation and document impact

The target is to have by 2012 a test to predict progression of LTBI to active disease

Activity	Indicator	Time line
Identify all tests for detecting LTBI and position them in the pipeline	Report on the pipeline status of tests	2008
Evaluate ESAT6/CFP10 in IGRAs or as a skin test reagent to identify LTBI and predict progression	• Numbers of studies	Yearly report

Cross-sectional studies on LTBI and risk factors.	ongoing, and focus • Numbers of new studies funded and focus • New collaborations facilitated • Summaries of final reports on these studies • Movement of tests along pipeline	
Longitudinal serial IGRA studies		
Use of IGRA as possible biomarkers of treatment response.		
Evaluation of tests for antibodies for prediction of risk of disease		
Antigen assays in serum or urine		

C. Facilitate implementation of new diagnostic tools and ensure access

This activity has to be done with other subgroups. There would be enormous market interest in a test that accurately predicts progression of LTBI to disease

Activities	Indicators	Time line
Contribute to identifying bottle necks		
Contribute toward customer requirement documents		

9. 5. Point of Care Tests for TB (under preparation)

9. 6. Evidence Synthesis for TB diagnostics (under preparation)

9. 7. TB Diagnostics and Poverty (under preparation)

9. 8. TB Diagnostics and HIV (under preparation)

10. 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 the annual meeting of the WGND.

11. Risk factors and mitigation

Insufficient financial investment and timing of investment

Adequate investment early on is required to enable funding for discovery mostly done in academic settings and of early stage technologies. Product specific development agreements requiring financial commitments covering the entire planning phase of the project (until introduction) is essential.

Technologies fail

Technologies can fail during the discovery phase, development phase and also at implementation. To offset the risk of technology failure the development portfolio of WGND comprises multiple options, with the aim to introduce at least one customized solution with a high degree of certainty

Inadequate development of laboratory strengthening

Many new diagnostic technologies require improved laboratory capacity and development of laboratory infrastructure and systems. 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. It is anticipated that collaboration with the DOTS Expansion Subgroup on Laboratory Strengthening and Retooling Task Force will ensure the timely and appropriate strengthening of laboratory services to meet the requirements for implementation of new diagnostics.

Impaired access to new products

The introduction of improved diagnostic tools 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. 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.

Interrupted product supply

The WGND is planning to make significant investments into discovery, product development 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 WGND, through 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.

12. Resource needs

(This section needs to be revised after finalising all parts of the plan)

The funding requested for 2006 to 2015 is US\$ 516 million (US\$ 497 million for basic science, development, evaluation and demonstration of tests and US\$19 million for infrastructure development including reference material banks, clinical trial training, laboratory strengthening, prequalification of manufacturers, market analyses updates, regulatory harmonisation, working group operations)

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

Figure 1 WGND Structure

