FIND
foundation
for innovative new diagnostics

2012 Activity Report

Our vision is of a world where everyone has equitable and timely access to high quality and affordable diagnosis.

Our mission is to drive the development and early implementation of innovative diagnostic tests that have a high impact on patient care and disease control in low-resource settings.

2012 Activity Report


NEELAM

Table of contents

Leadership message

Mark Kessel, Chair of the Board
Catharina Boehme, Chief Executive Officer

Mark Kessel

Dr. Catharina Boehme

In 2013, FIND and its partners will have completed a decade of developing and delivering diagnostics for diseases afflicting resource constrained countries. When FIND was officially launched in May 2003, the importance of diagnostics for reducing transmission of infectious diseases and improving disease control was beginning to be recognised. For over 100 years, light microscopy had been the primary tool for diagnosing Tuberculosis in the public health sector in developing countries, and R&D funding for more accurate and reliable tools for use in this sector was noticeably absent. Since then, it has become more evident that better diagnostics, and not only for TB, result in improved disease management and patient outcomes. Increased commitment to development in this area is starting to have an impact, but diagnostics still represent less than 5% of the total R&D funding for neglected diseases. Nonetheless, much progress has been made since 2003, with FIND playing a large and exciting part in this.

Through our TB programme, we developed and introduced six new technologies that are revolutionizing the detection and treatment of TB and multidrug-resistant (MDR) strains. According to recent estimates, scale-up of these new tools in endemic countries is saving 300,000 lives per year. By building laboratory capacity, we're accelerating access to these new tools and enabling speedy diagnosis of

TB and MDR-TB. We have established more than 80 local laboratories and trained over 2000 laboratory professionals.

Our malaria programme continues to work to ensure that a consistently high quality of rapid diagnostic tests is maintained. Through this multi-partner programme, which forms the basis for UN procurement, use of substandard products has decreased from 76% to 17%. An improved blood transfer device that allows for safe collection and transfer of blood from a finger-prick reached 52 million patients in 2012.

For sleeping sickness, we are making major contributions toward reaching the 2020 disease elimination targets by developing three new critical tests: the first ever rapid test for sleeping sickness, now being used to screen populations at risk; a fluorescence microscopy method for confirmation; and a next-generation molecular test for surveillance.

To accelerate the effective development and quality assurance of diagnostics for TB, malaria and neglected diseases, our clinical reference materials and a clinical trial platform are being made more widely available to stakeholders.

These accomplishments would not have been possible without the dedication of our core team of 60 professionals, working with over 200 partners across 61 countries.

From an organizational perspective, 2012 was a year of change: After having steered FIND through an economically challenging period, Philippe Jacon announced that effective January 1, 2013 he would pursue other opportunities within industry. Prior to retiring from his position as Chair of the Board, Gerald Möller brought the expertise of three new members to FIND's Board of Directors: Daniel Camus, Detlev Ganten and Ilona Kickbusch. Marcel Tanner joined us as Chair of the Scientific Advisory Board. We welcome these new members, all of whom have crucial roles to play in FIND's governance and strategic positioning.

The diagnostics landscape today is dynamic, providing a number of exciting opportunities for the future. We have played an active role in shaping that landscape and in the process have learned a lot. We aim to apply this knowledge to our strategic review to ensure that we are optimally positioned to address the significant diagnostic needs of the global community in the years ahead.

In closing, we would like to thank our donors for their continued support and commitment to FIND and its partners towards improving world health.

Current governance

Board of Directors

Mark Kessel,
In-coming Chair,
Partner, Symphony Capital LLC
and Of Counsel,
Shearman & Sterling LLP

Ilona Kickbusch,
PhD, Director, Global Health
Programme, Graduate Institute
of International and Development
Studies, Geneva

Gerald H. Moeller,
MD, PhD, Vice Chair,
Chair on several boards, among
them Brahms AG, Bionostics Inc,
Febit AG, and 4sigma

Bernard Mach,
MD, PhD, Founder and Chair
of NovImmune

Daniel Camus,
PhD, Chief Financial Officer,
the Global Fund to Fight AIDS,
Tuberculosis and Malaria

Gene Walther
MBA, Deputy Director,
Diagnostics at Bill & Melinda
Gates Foundation

Professor Detlev Ganten,
MD, PhD, Chair of the Foundation
Board of the Charité Foundation,
Berlin

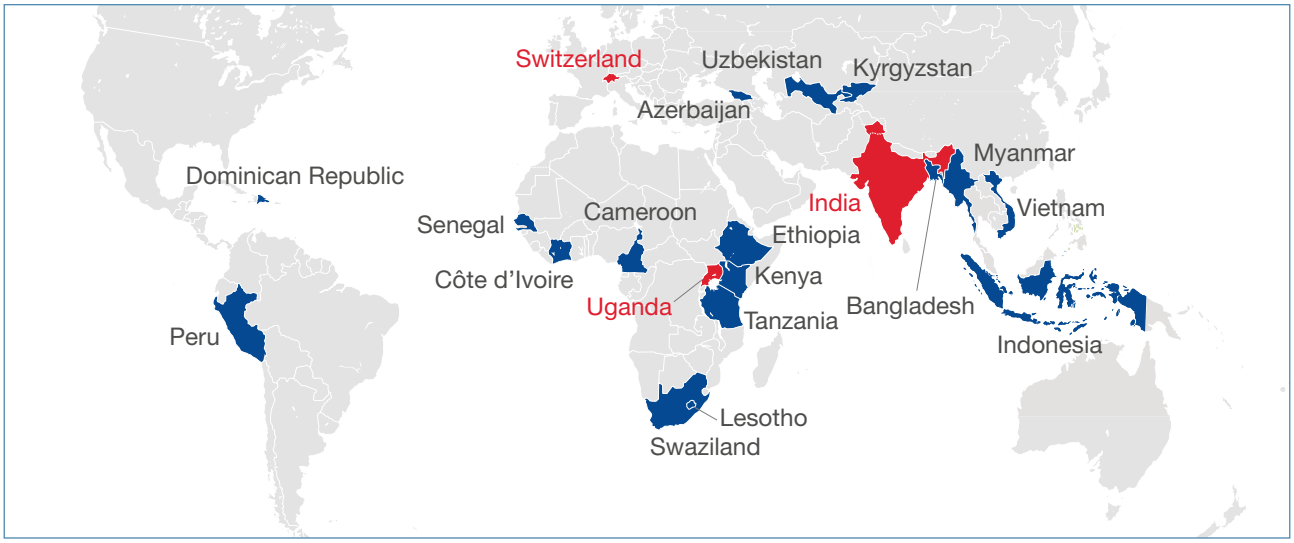
Catharina Boehme
MD (ex officio)

Scientific Advisory Board

Prof. Marcel Tanner, PhD, MPH, Chair
Cliff Barry, PhD
Prof. Dr. Frank Bier

Partnering to deliver improved diagnostics

60 people operating in 25 countries and 200 partners in 61 countries



FIND Geneva

Catharina Boehme, Chief Executive Officer

Heidi Albert, Senior Technical Officer, CDC CoAg
Audrey Albertini, Scientific Officer – Malaria
Alexandra Amann, Human Resources Assistant
David Bell, Head, Malaria/Acute Febrile Syndrome
Jessica Bennett, Project Coordinator, CDC CoAg
Sylvain Bieler, Project Manager
Tamara Biéler, Accounting Assistant
Christophe Broggi, Chief Financial Officer
Nora Champouillon, Senior Logistics Officer
Louisa Chaubert, Accounting Manager
Diana Choa, Executive Assistant to the CEO & Board of Directors
Christiane Elfman, Receptionist / Administrative Assistant
Françoise Fichet, Receptionist / Administrative Assistant
Rossana Gambin, Manager, Human Resources & Administration
Iveth Gonzalez Jimenez, Scientific Officer
Beatrice Gordis, Communications Officer
Christen Gray, Biostatistics and Data Manager
Sandy Haldimann, Scientific Team Administrator – EXPAND-TB
Heidi Hopkins, Medical Officer
Sandra Incardona, Technical Officer – Malaria
Kekeletso Kao, Senior Project Manager – EXPAND -TB
Gerd Michel, Senior Technology Officer
Joseph Ndung'u, Head, HAT & Other Neglected Diseases
Pamela Nabeta, Medical Officer
Juan Daniel Orozco, Senior Implementation Officer
Mark Perkins, Chief Scientific Officer
Catherine Pilet, Accounting Assistant
Sharon Saacks, Senior Operating Officer and Quality Manager
Jérôme St-Denis, Senior Advocacy and Resource Mobilization Officer
Eloise Valli, Technical Officer, Clinical Team
Julie Vercruysse, Scientific Team Administrator – Malaria
Thomas Verges, Logistics Officer – EXPAND -TB
Miranga Wijegoonewardena, Accountant, Reconciliations & Financial Analysis
Hanna Yirga, Scientific Team Administrator – HAT & OND
Knut Feldmann, Senior Project Manager – EXPAND -TB
Cameron Peters, Organizational Strategy
Cameron Stocks, Social Media
Ranald Sutherland, Technology and Business Development
Tatiana Titova, Website
Alessandra Varga, Communications

FIND India

C.N. Paramasivan, Head of TB Programme, FIND India & South East Asia
Vollepore Balasangameshwara, Senior Programme Manager and Technology Officer
Jacques Debayle, Senior Project Manager
Kumar Johri Satyender, Finance Officer
Kumar Kapoor Vinod, HR Officer
Prabakaran Loganathan, Senior Microbiologist (Trg.) (ICEIT)
Shaily Luthra, Senior Administrative Assistant
Ramesh Mahadevan, Logistics Officer
Neeraj Raizada, Medical Officer
Tarak G Shah, Medical Officer
Pooja Srivastava, Biomedical Engineer
Rahul Thakur, Medical Officer

FIND Uganda

Ajay Kumar Thirumala, Project Manager and Technology Officer
Caroline Asiimwe, Coordinator-Malaria Diagnostics Implementation Project
Daniel Kyabayinze, Medical Officer
George Lukyamuzi, Scientific Officer
Jean Nsekera, Office Manager
Barnabas Nyesiga, Assistant Scientific Officer


Achievements in 2012

Over the past year, FIND is proud to report exciting progress. The following achievements merit particular mention for each of our disease areas.

Tuberculosis

For tuberculosis, Xpert® MTB/RIF has experienced a major uptake globally with 1.9 million cartridges procured in the public sector of 80 low- and middle-income countries. Country data have confirmed significant increases in case detection and reductions in time to treatment and misdiagnoses for TB and MDR-TB. An additional 200 lab technicians and healthcare workers were trained and on-site mentoring was provided to more than 80 laboratories in 25 countries. As a result, 27 additional laboratories are now operational for routine testing and case reporting. Our targets for MDR-TB detection were exceeded by 10%.

Based on clinical trial data provided by FIND and partners, WHO approved the use of LPA for second-line drugs as a rule-in test for XDR-TB where LPA capacity is available. This rapid test will allow for more efficient infection control, resulting in programmatic management of drug-resistant TB.

Malaria

A highly sensitive, near-field molecular test for malaria (LAMP) was released into the market, a low-pricing agreement was established and the first 20,000 units were ordered. Development of a high-throughput test, based on the same platform and intended as an elimination and surveillance tool, is currently underway.

As part of our rapid diagnostic kits for malaria, an estimated 50 million units of our improved blood transfer device have been sold. The device is designed to minimize user errors and infection risk for health workers.

Our global Quality Assurance Programme for rapid diagnostic tests for malaria has seen a 50% increase in 2012. Results were used by all leading global health procurement agencies to inform purchasing decisions, and to screen production lots before dispersal to the field.

Sleeping sickness

The first ever RDT for sleeping sickness or human African trypanosomiasis screening was launched in December 2012. This represents a major step forward towards the elimination of this disease and a practical step towards realizing the intentions of the London Declaration. LED-based fluorescence microscopy was endorsed for use in routine confirmation of HAT in the Democratic Republic of Congo, improving sensitivity of conventional microscopy for parasite detection. The Ministry of Health of Uganda has shown political commitment by indicating support for the inclusion of the HAT LAMP test in the national disease programme's diagnostic algorithm for elimination of both forms of HAT.

Highlights of 2012

- Following a successful six-year collaboration with WHO to develop simple and effective diagnostic tests for sleeping sickness, a new Memorandum of Understanding was signed with the aim to facilitate access to rapid tests for the surveillance and identification of the disease.

- Becton Dickinson and FIND announced a new collaboration to promote access to early and accurate diagnosis of multidrug-resistant tuberculosis among HIV-infected patients and other vulnerable populations in India.



- Two years after its launch, the RapidSMS reporting project in Uganda – a health monitoring system based on text messaging – was rolled-out on a national level, enabling real-time data reporting from remote rural areas and providing more accurate epidemiological data on malaria, as well as information on other diseases in the country, to the Ministry of Health.

- A joint study by FIND and partners in southern Zambia demonstrated the positive impact of FIND's approach to high quality training and instructions in the accurate implementation of malaria RDTs.

- The Bill & Melinda Gates Foundation, the United States President's Emergency Plan for AIDS Relief (PEPFAR), the United States Agency for International Development (USAID) and UNITAID announced a buy-down agreement to reduce the cost of Xpert cartridges by 40% in 145 high-burden countries.

- The new malaria diagnostic strategy, designed to provide the tools for the effective control and eventual elimination of malaria, was released.

- FIND and the TB Alliance announced a new partnership to increase efforts to coordinate the development of novel tools to fight TB, including drug-resistant TB, and identify emerging drug resistance trends globally.

- A paper by FIND research partners on the successful use of the LAMP DNA test to detect sleeping sickness parasites is one of the PLOS Neglected Tropical Diseases Top Ten Research Articles.

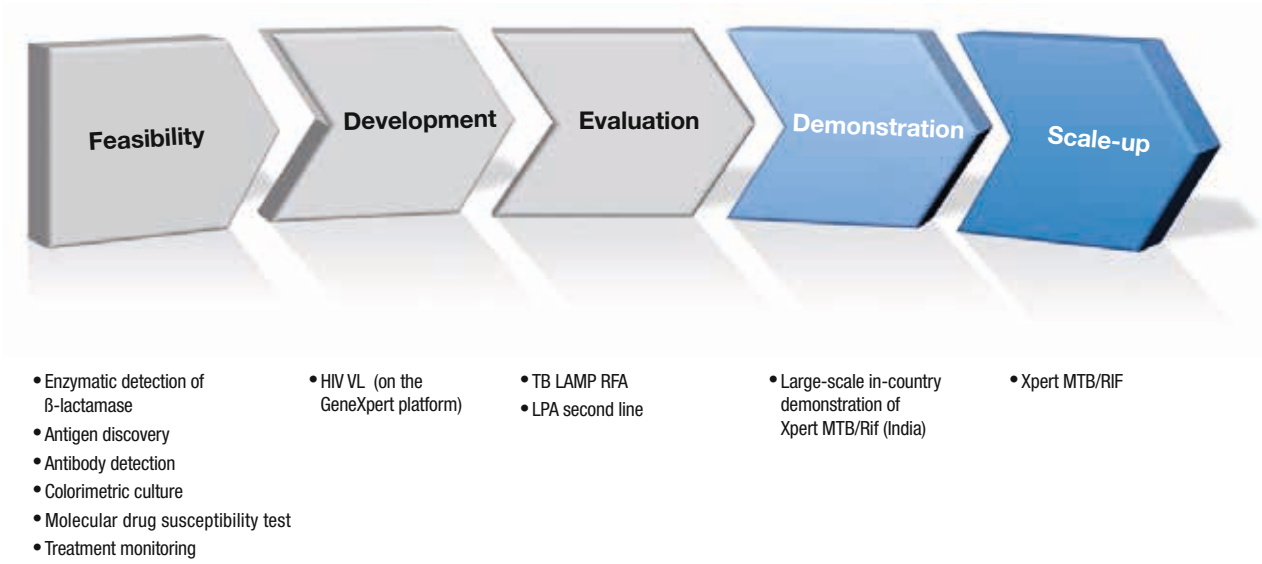
- Ministries of health have been emphasizing capacity-building within Africa, and FIND's Malaria & AFS programme, in close collaboration with partners, developed capacity for the collection, preparation and interpretation of placental samples in eastern Uganda. The study results were published this month and the work was present at the annual meeting of the American Society for Tropical Medicine & Hygiene.

- FIND and Standard Diagnostics, Inc. of the Republic of Korea, announced the launch of the first rapid test to screen for sleeping sickness at a workshop in Kinshasa, Democratic Republic of the Congo.

- The Minister of Health of the Democratic Republic of the Congo informed FIND that based on the encouraging results of a one-year evaluation study, the DRC is endorsing the use of Acridine Orange fluorescence microscopy in routine diagnosis of sleeping sickness.

Tuberculosis

Status of technologies and projects in FIND's portfolio as at year end 2012



Overview

The global burden of TB remains enormous. In 2011, there were an estimated 8.7 million new cases and 1.4 million people died from TB. Control of this disease depends on the rapid identification and treatment of active cases. Though progress has been made toward improving the fraction of all cases detected and notified to national programmes, most patients have faced considerable delays in diagnosis because of the paucity of diagnostic tools available. Between 2007 and 2012, FIND and partners completed development of 6 new diagnostic products for TB which received regulatory approval, 5 of which have been endorsed by WHO for use in national disease control programmes.

These innovative products have been implemented in national health programmes, with over 6 million tests a year performed in developing countries. The co-developed Xpert MTB/RIF assay was the subject of considerable roll-out activities in 2012. By the end of the year, cumulatively 1.9 million cartridges had been shipped to the public sector in 80 low and middle-income countries. One consequence in terms of public health has been that strategic planning at national levels now has to ensure that this product is included in TB algorithms to maximize its contribution to a rational use of resources, rapid case detection and treatment of patients. Strong uptake of Xpert MTB/RIF through appropriate algorithms should result in a measurable reduction in transmission rates over time. Xpert MTB/RIF has also established a new and much more stringent benchmark, changing expectations for for the performance of new technologies in development and ultimately the quality of life for TB patients.

FIND and partners accelerated the EXPAND-TB programme, with 65 laboratories in 24 countries by the year's end, diagnosing 24,870 MDR-TB cases in 2012 (10% more cases than anticipated). These patients received appropriate and timely treatment, thus interrupting transmission and preventing


further spread of drug resistance. Training in liquid culture and DST, rapid speciation, line probe assay and Xpert MTB/RIF was provided to 138 laboratory staff, managers, physicians and nurses in 2012. MDR-TB case detection targets were exceeded in 2012. In fact, today in India more than 80% of MDR-TB cases are identified under EXPAND-TB using LPA alone.

Despite this success, timely and accurate diagnosis at the periphery of the health care system – at microscopy centres and in primary care settings – remains elusive for many patients. The rapid expansion of MDR-TB and XDR-TB, together with the planned introduction of new drugs and new drug combination therapies, are events that also need to be addressed by the development of new diagnostic solutions. In order to interrupt transmission, both the speed and completeness of case detection must improve, as must early initiation of appropriate treatment. These changes will not be possible without further improving the range and performance of diagnostic tests and making them available closer to where patients first seek care. One of our primary goals in TB therefore continues to be to bring accurate testing to primary care or first referral settings, and to expand the menu of drug resistance testing to support the ongoing development of novel regimens.

FIND and partners are developing point of care triage tools to identify patients in primary care settings for referral for definitive testing. For many national TB control programmes, widespread implementation of molecular tests for all symptomatic TB suspects would be unaffordable, despite its cost-effectiveness. One of the most effective ways to decrease the cost per case detected is to increase the likelihood that patients referred for molecular testing actually have TB through triage testing (by eliminating tests for patients that definitely don't have TB). There are currently no proven effective methods to do this. Triage testing (rather than definitive diagnostic testing) would ease performance requirements around specificity, and moderate the implementation challenge of ensuring accompanying TB treatment at the primary care level.

The development of diagnostics, unlike drugs or vaccines, is critically dependent upon the availability of clinical materials and study populations in TB-endemic countries at all phases of development. Over the last 5 years, FIND conducted 20 early phase and 6 demonstration phase TB studies at more than 50 trial sites in more than 30 countries, and enrolled over 100,000 study participants. In addition, we collected 120,000 specimen aliquots from 6,000 participants in 6 countries. We also managed to significantly increase quality standards in our trials and continuously adapt trial design and outputs to the steadily increasing expectations of the international public health community. Together with our partner sites, we have optimized study processes and timelines. With adequate funding, we now require less than 1 year from design lock to CE marking and 2 years to WHO submission. Building on what has become one of FIND's key strengths – conducting clinical trials for diagnostics – FIND provides support to R&D teams and test developers. This helps to accelerate TB biomarker discovery, facilitate the entry of new commercial groups into the field of TB diagnostics development and offers a rapid clinical pathway towards global policy approval.

The emergence of drug resistance, in its many forms, poses a significant threat to global TB control efforts. Currently, few patients in disease-endemic countries have access to testing and treatment for drug resistant TB. The inability to rapidly detect drug resistance has long been a blind-spot in the implementation of existing regimens, and is likely to plague future regimens if efforts are not made to develop diagnostics

that could accompany these regimens. During the past two decades, the molecular basis of resistance to the major drugs used to treat TB has been mapped, and several PCR-based assays for resistance to drugs relevant to current treatment regimens have been commercially developed. FIND initiated new projects in 2012 to identify technical approaches that could be used for near-patient testing of resistance to TB drugs, to develop reagents and feasibility data around them, and to create a plan for phased development of assays on existing or emerging technology platforms.

FIND also initiated two interesting new projects in 2012 that are intended to enhance applicability – and therefore maximize the impact – of future TB diagnostic technologies. We are developing a kit that can be used with any existing or new molecular TB test to monitor therapy in routine care or as part of new drug assessment; and we will be testing mobile health (m-health) approaches to provide accurate and timely reporting of results to patients as part of our clinical trials.

Upstream projects in 2012

Feasibility / exploration projects

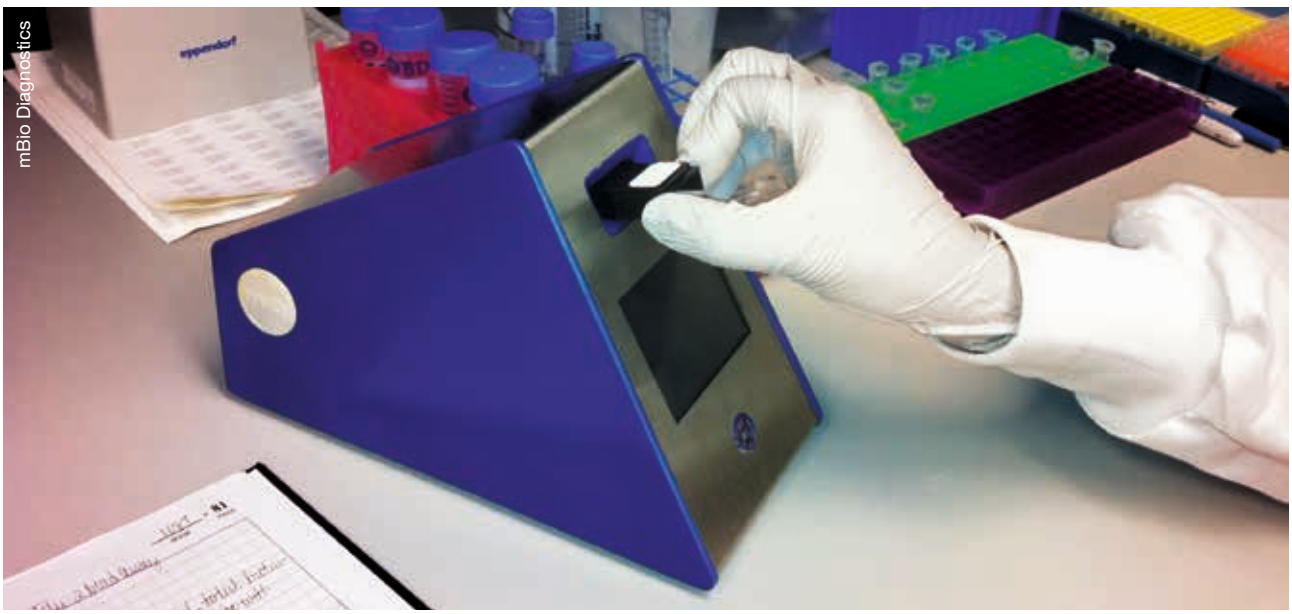
Enzymatic detection, *M. tuberculosis* ß lactamase reporter assay

FIND has continued to collaborate with Global BioDiagnostics (GBD) and partners (Stanford University and University of Texas A&M) to support the development of a novel point of care test for the rapid diagnosis of TB infection. The assay is based on the reaction of endogenous bacterial β-lactamase to detect M. *tuberculosis* in sputum, upon generation of a fluorescent signal. By end of 2012, GBD had secured funding from Wellcome Trust for a 2-year Strategic Translation Award, based on promising data on fresh samples collected in Lima, Peru (through FIND) and in Houston, USA. FIND developed a Target Product Profile for the assay and will continue to provide specimens for reagent development in order to undertake a feasibility study as soon as a prototype from GBD is ready for field trials. FIND will also assess the possibility of having an alternative instrument-free approach based on a colorimetric reaction as a follow-on in the future.

Antibody detection (serology POC test for detection of active TB)

The project seeks to identify an antigen set that will enable detection of active TB in a point-of-care assay with high sensitivity to be used as a triage test. Laboratory testing on a Luminex multiplex platform as a reference has identified 57 potentially discriminatory proteins. These proteins are currently being assessed in the field in Peru and Vietnam using the multiplex planar array platform of mBio Diagnostics.

The first phase of these validation studies was completed successfully by the end of 2012. Early results indicate high concordance between the two platforms to show that the results from the mBio assay can be used for clinical trials in the field for further protein down-selection.


mBio Diagnostics

Solid culture MDR/XDR-TB colour test

The aim of this project is to examine the feasibility of using a low-cost thin layer agar direct culture method to detect TB and screen for isoniazid, rifampicin, and fluoroquinolone resistance using sputum samples. This colour test has been packaged into a complete, simple and inexpensive research-only kit format that could be suitable for basic regional laboratories that currently provide only sputum microscopy. Preliminary work in Peru has accomplished a proof of concept using stored MTBC isolates. A prospective multicentre feasibility study in Romania was carried out and highlighted areas of optimization in comparison with reference-standard methods. If molecular methods prove unsuitable for expanded drug resistance testing, the colour test may be a feasible back-up method.

Molecular and phenotypic DST

The project started in late 2012 and seeks to identify technical approaches that could be used for near-patient testing of resistance to the TB drugs pyrazinamide, fluoroquinolones and aminoglycosides, and for developing reagents and feasibility data. The main project components are the design and development of genotypic drug susceptibility testing chemistries that are adaptable to a variety of instrumentation platforms, and the evaluation of new phenotypic drug susceptibility testing options.

Activities scheduled for 2013 include the development of consensus Target Product Profiles, a landscape analysis of relevant phenotypic approaches, and feasibility studies of at least two molecular approaches.

Molecular treatment monitoring

This new project aims to develop and validate a platform-independent kit for use in combination with any existing or new molecular TB test, to monitor therapy in routine care or as part of new drug assessment. The kit will be optimized with regard to ease-of-use, robustness and cost. Available approaches to monitoring TB patients to assess their response to therapy remain sub-optimal.

Partners in Italy (Dr. Daniela Cirillo and team) and US (Dr. David Alland and team) have developed an innovative approach for selective DNA amplification from viable bacilli in clinical specimens and are working on optimizing the protocol using Xpert MTB/RIF. Further proof of principle data will be reviewed in 2013.

A partnership to accelerate TB diagnosis and treatment

FIND and the Global Alliance for TB Drug Development signed a partnership agreement in October to increase efforts to coordinate the development of complementary novel tools to fight TB, including drug-resistant TB, and identify emerging drug resistance trends around the globe.

"By coordinating drug and diagnostic development efforts, we can optimize TB diagnosis and treatment for the millions in need and get patients on the proper course of treatment as quickly as possible. This need is particularly critical with a new generation of improved TB treatments on the horizon" said Dr. Mel Spigelman, President and Chief Executive Officer at TB Alliance.

Currently, few drug-resistant patients in lower-income countries are correctly diagnosed. Drug-resistant TB is often "found" by determining a patient's reaction to first-line treatment, which means that by the time they are identified as having drug-resistant TB, months have passed, and patients have become even more resistant than they were prior to their latest therapy. By developing a new arsenal of diagnostics that complement drug regimens in development, health care providers will be able to modernize their approach to TB management and treat patients with drugs to which they will respond right from the start.

The collaboration will initially focus on resistance to fluoroquinolone and pyrazinamide, two drugs used in current treatments that are also critical in new treatment regimens under development.

Manual isothermal NAAT for TB (LAMP)

Additional TB LAMP evaluation studies were conducted after protocol changes, which included an improved training programme for users and increased input volume, were begun towards end 2011 and completed in 2012. All data was submitted to the WHO Expert Group, which declined to make any recommendations either for or against use by public sector programmes of the assay and requested instead that more studies be undertaken by third parties. The cost effectiveness of the TB-LAMP assay at its current price was also questioned.

An action plan for independent studies has been agreed for 2013, including an assessment to see how the technology can be made less operator-dependent and assay costs reduced. It is expected that a new data package will be available for presentation to the WHO Expert Group by end March 2014.

Line probe assay (LPA) for resistance to second-line drugs

This molecular LPA is designed to rapidly detect extensively drug-resistant tuberculosis (XDR-TB) in laboratories that have established LPA for MDR-TB screening. Mutations associated with resistance to a number of second-line drugs, including fluoroquinolones and certain injectable drugs, can be detected. Performance data on the test was presented to a WHO Expert Group in September 2010, but a recommendation was deferred until additional data in support of direct testing was available for review. Further studies were undertaken and data from these studies, as well as additional data from an independent 5-site study were presented to the WHO Expert Group in March 2012. The Expert Group concluded that the assay can be used as a rule-in test for XDR-TB where LPA capacity is available, but that it cannot be used as a replacement test for conventional phenotypic DST.

Automated NAAT for TB (Xpert MTB/RIF)

The major event in 2012 was an agreed buy-down of the Xpert MTB/RIF cartridge ex-works price from $16.86 to $9.98, effective as of August 2012.This was co-funded by USAID, PEPFAR, UNITAID and the Bill & Melinda Gates Foundation: the Cepheid-FIND supply agreement was altered accordingly.

In 2011, FIND and Cepheid had entered into a new agreement to develop and implement a remote calibration kit consisting of a standard cartridge containing calibration chemistries and associated software, allow the operator to self-calibrate the modules. This removes the need to send the modules back to a central geographical point with all the import/export costs and related concerns. Field trials in Europe, North, Africa and Asia were successfully concluded by end of September 2012. The data demonstrated that the product met specifications, no hardware or software bugs were found and it was formally released in November 2012.

FIND is now working to further expand the utility of the test by working on processing methods for extrapulmonary specimens.

Automated NAAT for HIV Viral Load (Xpert VL)

FIND engaged with Cepheid to rapidly develop a qualitative HIV diagnostic assay (for use with at-risk newborns) and a quantitative HIV viral load assay that can be run on the same platform as the Xpert MTB/RIF assay. A main achievement in 2012 was to move from a mix of external and on-board reagents to having all reagents (liquids and beads) included in the cartridge for the viral load assay.

The quantitative software is currently under testing. The manufacturing line was established and validated, and cartridge manufacturing for the Alpha trials started in late November. A separate product using the same cartridge and reagents is being developed for a qualitative HIV-1 test based on whole blood capillary or dried blood spot samples. Alpha trials of the prototype assay in 2013 are expected to lead to the launch of a CE-marked product in mid-2014.

Innovative technology matched by affordability

FIND has demonstrated it can pioneer innovative diagnostic tools, but uptake in low-resource settings, where they are most often needed, has to overcome weaknesses in technological or infrastructure capacity and offer an affordable pricing structure. Already in 2004, we recognized the potential of the GeneXpert system for revolutionizing the diagnosis of TB and eventually signed a partnership agreement with Cepheid, the manufacturer of the Xpert technology, for the development of a test designed specifically for the detection of TB in developing countries. In 2010, the WHO endorsed the Xpert MTB/RIF for use in low-resource settings as the initial diagnostic test in cases of suspected MDR-TB or TB/HIV co-infection.

FIND established a successful pricing agreement that brought the test to as low as $9.98 at market maturity with higher volumes. In a drive to further expand adoption of the Xpert MTB/RIF test, the Bill & Melinda Gates Foundation, the United States President's Emergency Plan for AIDS Relief (PEPFAR), the United States Agency for International Development (USAID) and UNITAID elected to fund a buy-down agreement to make FIND-negotiated prices of Xpert available in 145 high-burden countries at an earlier time point, before the market was fully mature.

GeneXpert is a fully automated diagnostic system that, with the Xpert MTB/Rif cartridge, can detect TB and resistance to rifampicin in less than two hours. The faster the diagnosis, the faster patients can be put on the appropriate treatment regimen including second-line drugs in case of resistance. Simple sample processing and minimal bio-safety and training requirements make it possible for highly accurate molecular testing to be used outside conventional laboratories and in rural settings in high-burden countries.

Early implementation

Expanding Access to New Diagnostics for TB – 24,870 patients diagnosed with MDR-TB in 2012

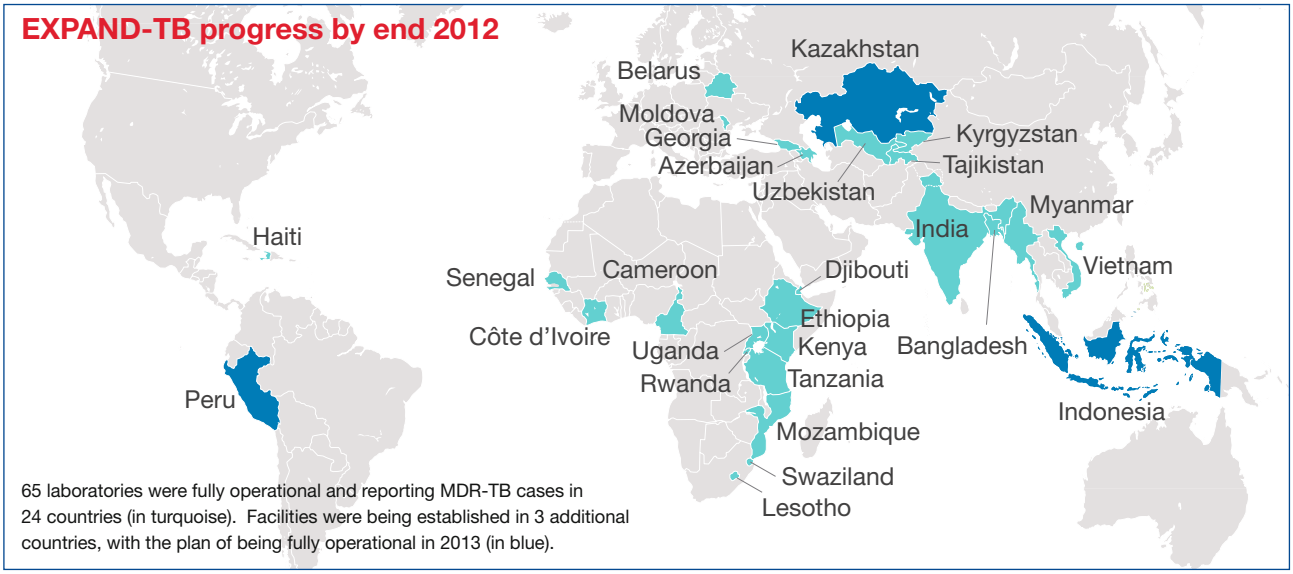
The EXPAND-TB (Expanding Access to New Diagnostics for TB) Project, initiated in 2009, aims to accelerate access to diagnostics for patients at risk of multidrug-resistant tuberculosis (MDR-TB). The 6-year project focuses on establishing or strengthening 99 central or regional reference laboratories in 27 TB and/or MDR-TB high-burden countries. Other collaborating partners include: the World Health Organization, the Stop TB Partnership's Global Laboratory Initiative (GLI) and Global Drug Facility (GDF). FIND is the implementing agency for EXPAND-TB and has been coordinating project activities within the partnership and ensuring capacity building to support appropriate transfer and use of our co-developed technologies.

EXPAND-TB diagnosed 25,000 patients with MDR-TB in 2012, exceeding annual targets for case reporting by 10%. These patients received appropriate and timely treatment, contributing to interrupting transmission and preventing further spread of drug resistance.

There was also unprecedented progress in 2012 in the following areas: 65 laboratories were fully operational and reporting MDR-TB cases by the end of the year in 24 countries. Training on liquid culture and DST, rapid speciation, line probe assay and Xpert MTB/RIF was provided to 138 laboratory staff, managers, physicians and nurses in 2012. 131 laboratory orders were shipped to the actively reporting countries for a total amount of USD 10 million.

The project having reached maturity after four years of implementation and trouble-shooting efforts contributed to these results. Projections based on the acceleration experienced in the past year show that targets set for the next two years will be achieved. Decentralizing the management structure and bringing it closer to the sites has also been a significant contributing factor to this improvement, resulting in overall cost-effectiveness of the project. The partners have initiated discussions around the transitioning strategy of the project and will initially pilot it at a few sites. The experience from the pilot run will be used as a model for implementation across all 27 countries during the last year of the project, ensuring a smooth transition back to the local Ministries of Health and partners where applicable.

EXPAND-TB progress by end 2012



65 laboratories were fully operational and reporting MDR-TB cases in 24 countries (in turquoise). Facilities were being established in 3 additional countries, with the plan of being fully operational in 2013 (in blue).

Building global capacity for diagnostic testing

This project is designed to strengthen laboratory capacity for diagnostic testing of TB, malaria and HIV. With several partners, FIND has implemented a set of activities focused on strengthening the quality of laboratory services, supporting the introduction of new rapid diagnostic tools and increasing laboratory human resources capacity.

Initiated in 2010, the project's scope and geographic spread has been steadily expanding. From an initial 3 countries, FIND is now working in 9 countries, namely Botswana, Dominican Republic, Ethiopia, Haiti, India, Lesotho, Tanzania, South Africa, and Vietnam, with activities in a further four countries planned in the new grant period starting in October 2013.

India fights TB with effective new tools and improved infrastructure

It took several months before Nadya, who had been coughing and losing weight, made it to the New Delhi TB centre to be tested. She was lucky not to have a more severe form of the disease, so was treated as an out-patient. She was able to live with and continue to take care of her family. Nadya is likely to make a complete recovery. For Laxmi, however, things were not so simple. Her test revealed she had multidrug-resistant (MDR) TB and would require a more complicated therapeutic drug regimen. Being able to distinguish rapidly between the various forms of TB that have emerged in recent decades can make all the difference between full recovery or continued decline and even death.

The Xpert MTB/RIF diagnostic test reduces from weeks to hours the time it takes to detect TB bacteria and to determine if they are resistant to rifampicin, the most widely used anti-TB drug. With the ability to start appropriate treatment immediately, there is every chance the patient will fully recover. The emergence in recent years of drug resistant TB – more life-threatening and more difficult to treat – presents the Indian Ministry of Health with major challenges for control of a disease which every year kills more than 300,000 people in the country. Since 2012, new diagnostic tests for TB, co-developed by FIND and its partners, such as liquid culture and DST, rapid speciation and line probe assay have become the current gold standards for diagnosing the disease and MDR-TB. However, using these tests requires a significant upgrade in laboratory infrastructure.

FIND's programme in India, as part of EXPAND-TB, includes training laboratory staff, providing guidelines and developing quality assured processes, thus contributing to the successful setup and correct use of these improved technologies.

Since the introduction of the new diagnostic tools and DOTS – directly observed treatment – doctors are witnessing tangible improvements. Dr J.N. Banavaliker, Director of the Rajan Babu Institute for Pulmonary Medicine and Tuberculosis in Delhi, says *"We now see far fewer patients in an advanced stage of TB with little chances of survival."*

Main project areas are laboratory quality management systems strengthening, support to the introduction of new FIND co-developed diagnostic technologies for TB, as well as development and introduction of electronic tools to assist with quality assurance activities.

Other activities vary according to specific country needs and include:

- Development and implementation of training courses covering implementation of Xpert MTB/RIF, TB Laboratory Management; laboratory safety, waste management and equipment maintenance; and the Strengthening Laboratory Management towards Accreditation (SLMTA) programme in Spanish.
- Support to the national roll out of Xpert MTB/RIF through provision of in-country technical support to implementation planning, development and evaluation of External Quality Assurance (EQA) systems, standard operating procedures and comprehensive Xpert MTB/RIF training materials, and by conducting training for clinicians.
- In-country capacity-building for quality assurance of HIV RDTs
- Supporting in-country engineers to become qualified biosafety cabinet certifiers, including support, mentorship and procurement of specialised certification equipment.

Synergies with other FIND downstream activities, notably EXPAND-TB programme, were taken advantage of wherever possible, including joint technical assistance and in-country support, and use of training materials and tools developed in this project for other programmes.

Laboratory preparedness to improve access in China

FIND supported a TB Control Project in China to validate and demonstrate the operational feasibility, cost-effectiveness, and impact of five new TB diagnostic technologies. FIND's involvement in this project terminated at end 2012.

By then, the diagnostic technologies had been validated and recommendations were submitted to China's Ministry of Health: that the use of LED microscopy be scaled-up in laboratories at township, county, city, and provincial levels that process more than 25 smear samples a day; and that line probe assay and the GeneChip microarray technology be rolled out in city-level labs for MDR-TB identification in high-risk suspects where qualified laboratory infrastructure and staff are present.

In addition, both TB LAMP and Xpert MTB/RIF were shown to perform well compared to solid culture. Results also suggested that Xpert can significantly reduce the turn-around time of TB identification and is cost-effective when compared to the combined cost of traditional culture and identification. The cost of this technology is significantly lower than traditional DST for detection of rifampicin resistance. Based on this project's findings, the validated diagnostics have now been adopted by some provinces in China to improve local TB diagnostic capability.

FIND/J. Debayle

Clinical trial capacity and reference materials

In 2012, FIND conducted studies for TB at 28 trial sites in 7 countries, including 21 new trial sites, and enrolled approximately 61,750 participants. The high increase in new trial sites in 2012 is due largely to an implementation trial across India at 18 sites enrolling roughly 6,000 people per month. The most heavily used trial sites are located in India, Peru, South Africa, and Vietnam. Use of our updated data entry and data management tool has been adopted by all disease areas as well as for the large-scale implementation trial across India. It has provided a means of data entry which requires no specialized installation and very little training per site.

TB reference materials

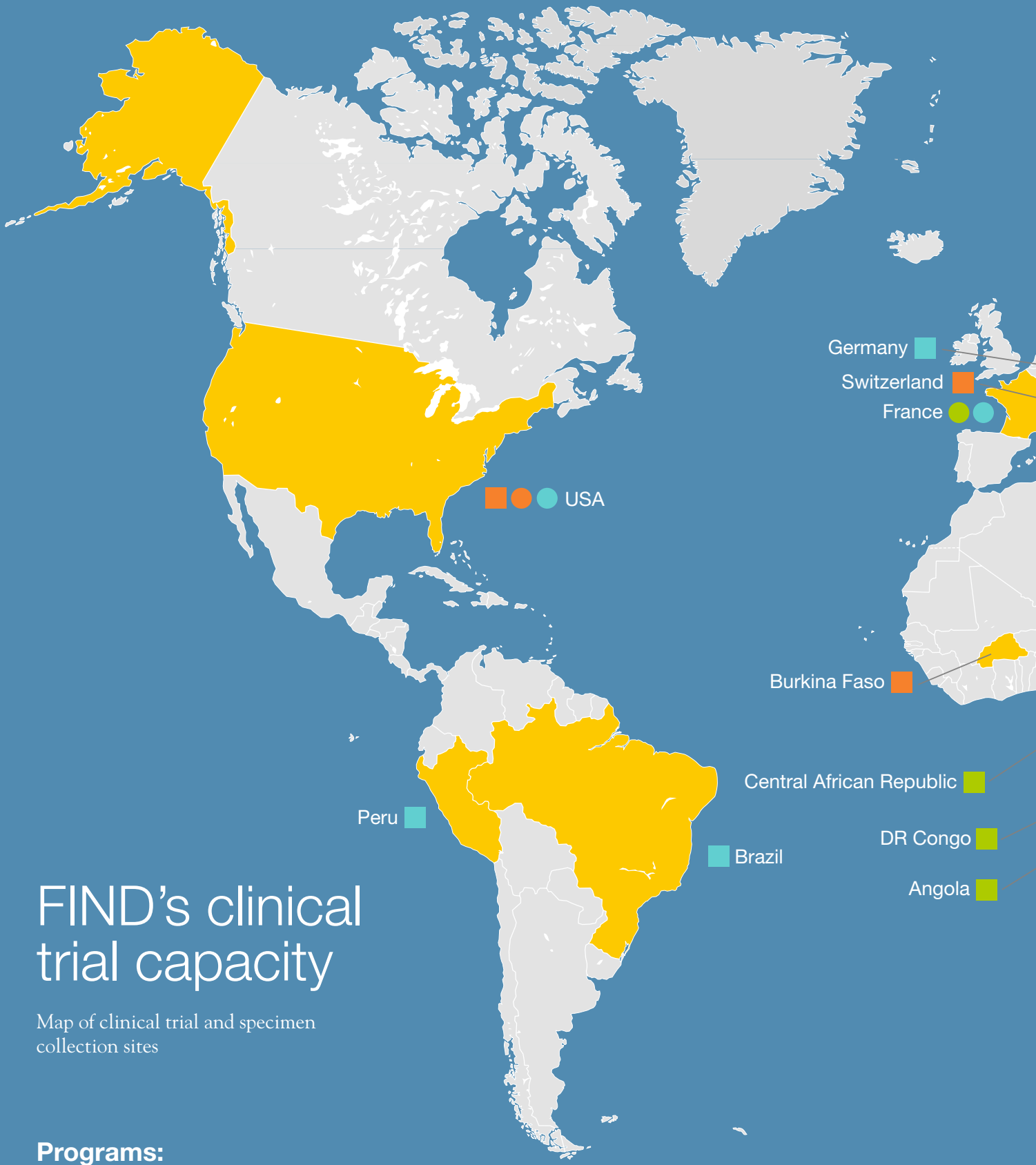
Access to reference clinical materials collected in TB-endemic countries has always been a critical bottleneck in the development and evaluation of new diagnostics for TB. To overcome this problem, FIND established a central repository in Thailand in early 2007 and started specimen collection activities at several of its collaborating sites. Collections include well characterized urine, serum, plasma and sputum specimens from TB suspects enrolled at participating clinics. The repository currently holds over 68,000 aliquots from approximately 4500 patients from Africa, Asia and South America. Aliquots are frozen on site and maintained at -70 °C. Each sample is linked to detailed clinical and microbiological information and a final diagnosis is assigned according to a standardized classification scheme. Partners for TB specimen banking include Health Concept International, Thailand (repository), World Courier (shipper), and collection sites. Since 2008, FIND has provided over 12,000 aliquots to several partners. In 2012, more than 2,000 aliquots were distributed to 12 different partners.

Challenges that we are currently facing for this activity include: an increase in restrictions on export permits for clinical materials from an increasing number of countries; aging of specimens; high collection and storage costs; and gaps in certain patient groups (e.g. non-TB/HIV+).

Clinical study platform

Despite the continuous growth in development of TB diagnostics, important gaps remain to be filled. Through regular technology assessments, FIND identifies the most promising matches for predefined Target Product Profiles. We have started to provide support to test developers through our clinical trial platform in order to accelerate development and validation of new technologies.

By offering this platform, FIND intends to facilitate the entry of new commercial groups into the field of TB diagnostics development and offer a rapid clinical pathway towards global policy approval. To avoid that continuous use of the same sites potentially results in overestimation of test performance, flexibility will be maintained to ensure use of more authentic sites for operational studies.



FIND's clinical trial capacity

Map of clinical trial and specimen collection sites

Programs:

TB Malaria HAT

Specimen bank repository:

TB Malaria HAT


Lao PDR
Vietnam
Philippines
India
Cambodia
Thailand
Uganda
Tanzania
South Africa



Malaria & acute febrile syndrome

Malaria & AFS

Feasibility	Development	Evaluation	Demonstration	Early Implementation
• Concept development for G6PD deficiency and fever screening	• Recombinant panels • 20 µl blood transfer device • Malaria high throughput (HTP) LAMP	• Field evaluation of existing RDTs (RDTs in pregnancy study) • Malaria LAMP • Positive control for RDTs	• Obstacles to implementation of RDTs (evaporative cooler box) • RDT testing with reference materials • 5 µl blood transfer device	

Overview

Malaria can be accurately detected and effectively treated. So why is it still having such an impact on the lives of millions, on their communities and on the economic development of their societies? Malaria continues to be a global disease because many of those who live in malarial regions do not have access to good diagnosis, to treatment or to preventive methods. In other words, poor healthcare infrastructure and weak delivery of health services in rural or poor urban communities is a major contributor to the fact that malaria affects some 220 million persons annually, of which up to 1 million will die. Young children under the age of five account for a large part of this shocking statistic.

Diagnostics, and the information they provide, are essential to planning and building more effective health systems. A particular difficulty with the diagnosis of malaria in its early stages is that symptoms are indistinguishable from many other diseases. The challenge for a diagnostic technology is to distinguish malaria from these other diseases rapidly enough, accurately enough, and cheaply enough to guide treatment in a sustainable way. For elimination of malaria, the challenge is even greater to detect very low density infections that may not even be causing illness.

Since their introduction some 20 years ago, malaria rapid diagnostic tests (RDTs) have transformed the diagnosis and management of febrile illness in communities in tropical and sub-tropical countries. However, their introduction and use continue to present great challenges to health systems.

In 2012, FIND and other partners, put the finishing touches to a comprehensive implementation manual to guide country malaria programmes on the introduction of RDTs in the field. In partnership with WHO, evaluations of RDTs continue to guide



global procurement. The WHO-FIND lot-testing programme is meeting a 50% increase in the demand for quality assured RDTs in the field. The product testing of malaria RDTs is now in its fifth round, and continues to guide global procurement.

The development and implementation of new, sensitive and low-cost diagnostic technologies, such as those arising from FIND initiatives and partnerships, are likely to be an increasingly important area for future malaria control and elimination programmes. Innovation is necessary in order to provide field initiatives with the tools they need for success.

Accurate malaria diagnosis is now a global policy, but remains inaccessible to most people who would benefit from it. Integrating the latest and more effective RDTs into the existing anti-malarial arsenal, such as drugs and bed-nets, has the potential to make a definitive impact on the control and elimination of this disease.

In 2012, FIND updated and published its strategy on malaria diagnostics, which focuses on two major priority areas: the management of very low transmission and elimination and improvement of case management.

Malaria projects

Improvement of case management

Programme for quality control of Malaria RDTs

Product Testing
The global malaria RDT product testing programme has been conducted since 2008 at the CDC in Atlanta, USA. Manufacturers submit an increasing number of RDT products each year, highlighting the growing success of the programme. Phase 1 of Round 4 testing was completed in October 2011 and phase 2 testing, stability testing, and the final report were finalized and published in December 2012. Preparations for Round 5 were made in 2012 for specimen bank replenishment, database updating, and publicizing of the call for product submission. A comparison of product testing results of RDTs submitted in previous Rounds and re-evaluated in Round 4 shows a statistically significant improvement in RDT performance, highlighting the apparent impact of the Malaria RDT Evaluation Programme in stimulating RDT manufacturers to improve product quality.

Lot testing
RDT lots are tested for the purpose of detecting those that perform poorly before they are sent to the field. The results are transmitted to Ministries of Health, NGOs, manufacturers, national malaria control programmes and any other institutions that have submitted ordered RDTs for lot-testing, so that they may have rapid access to information about the quality of the product. Laboratories in Cambodia and the Philippines perform this quality control testing; re-testing is done 18 months later to ensure conformity with the expiry date and performance stability. There was a 55% increase in requests for lot-testing in 2012 as compared to 2011. This was chiefly motivated by the publication of the Global Fund's QA policy in March 2011 that recommended lot-testing for all Global Fund recipients. Absorbing this increase in lot-testing requests has put pressure on the labs and demonstrated a need to better ensure stock sample replenishment. There were serious importation issues in the Philippines that required Cambodia to take over responsibility for current testing requests. In case of future problems at one of these testing sites, a back-up site has been selected (London).

FIND/J. Ndung'u

Recombinant panels for malaria antigens
Manufacturers of rapid diagnostic tests (RDT) require low-cost stable reference materials suitable for their internal quality control as well as global product comparison. Recombinant panels of malaria antigens are being developed for this purpose. In 2012, partners at the US CDC tested more than 10 different recombinant proteins against 42 HRP2-based and 29 pLDH-based RDTs from the previous WHO-FIND annual RDT product testing programme. Results of these analyses are the basis for defining antigen concentrations for RDT lot-testing panels. *P. vivax* recombinant LDH (PvLDH) has been consistently detected by most pLDH-based RDTs while some anomalies with *P. falciparum* recombinant LDH (PfLDH) are recorded and are being investigated. Extensive equivalence testing will continue with the intention to complete development of prototypes in 2013.

Positive Control Wells
FIND and partners have developed positive control wells (PCWs) for malaria RDTs as a point of care quality assurance tool for health workers who use RDTs in patient care. To maintain health worker and patient confidence in RDTs, and thereby optimize their utility, the tests must demonstrate consistently reliable results. To this end, a robust but streamlined quality assurance/quality control system, extending to the point of actual RDT use, is a critical component of effective RDT implementation. Throughout 2012, PCWs containing target concentrations of final recombinant malaria or parasite antigens have completed laboratory evaluation with satisfactory results; long-term incubation to define thermostability is on-going.

A field demonstration study of PCWs, designed to assess their utility and acceptability in health care settings where RDTs are in routine use, is planned for early 2013 with partners in Lao PDR and Uganda. Results are expected in December 2013.

Evaluation of existing RDTs in pregnancy

Using RDTs to screen for malaria in pregnancy may offer an accurate and practical way to identify pregnant women who will benefit from targeted therapy for placental malaria infection. The utility of RDTs in this context remains a major gap in diagnostic knowledge. A clinical study has been conducted in Burkina Faso and Uganda to evaluate the accuracy of well-characterised RDTs in detecting placental malaria and to assess the potential efficacy of screening pregnant women with RDTs in order to optimize antimalarial treatment. Results will provide solid and timely data on the suitability of RDT-based screening as a replacement for the wide-spread but failing policy of intermittent presumptive antimalarial treatment in pregnancy (IPTp). Recruitment of participants and data collection has been completed. Since pregnant women are at particular risk of both malaria infection and its consequences for maternal and foetal health, the need for RDTs for both malaria in pregnancy remains one of the major gaps in diagnostic knowledge. FIND is following up on evidence suggesting that detection of circulating parasite antigens by RDTs may give a reliable indicator of placental infections and thereby offer an accurate and practical way to identify pregnant women who will benefit from targeted therapy. Samples collected in 2011 during a clinical study in Burkina Faso and Uganda are undergoing analysis, which is expected to provide solid and timely data on the suitability of RDT-based screening as a replacement for the widespread but failed policy of intermittent presumptive antimalarial treatment in pregnancy.

Documenting and supporting RDT implementation

In response to the need to identify and address specific issues that affect the success of malaria diagnostics, FIND, the WHO and partners have coordinated the development of an implementation manual to guide country malaria programmes on the introduction of RDTs to the field. This manual is a joint project, incorporating input from national programmes and implementation agencies. The manual is completed and will be published online by June 2013. With a view to building evidence and guiding the expansion of RDT usage, FIND and partners in Senegal and Zambia have undertaken an assessment of the impact of wide-scale RDT use on disease reporting and drug consumption. Results from Senegal were published in 2011 and those from Zambia in 2012. Both demonstrated large reductions in ACT consumption, with some reports suggesting sulfadoxine-pyrimethamine was used as a substitute for some RDT-negative cases, highlighting the need to address non-malarial fever management.

Blood transfer devices

An improved blood transfer device (BTD), the "inverted cup" device, for transfer of 5-µl of finger-pick blood to malaria RDTs, was demonstrated in 2011 to be as or more accurate and safer than a number of current devices. Details were published in an open-access peer-reviewed journal, and the device is now in use in commercial RDT kits.

FIND has continued to work on prototypes to transfer higher volumes needed for HIV or HAT RDTs. A 23-µl prototype with easy blood pick up, complete blood deposit, and no risk of spillage, is now available. This device is engineered to avoid the risk of low volume transfer and false negative results. Field evaluation on ease of use and acceptability by health workers is planned.

Management of very low transmission and elimination

Manual NAAT for malaria (LAMP)

A simple and low-infrastructure LAMP malaria assay developed by FIND and partners was released as a CE-marked product in June 2012. This assay, the first malaria molecular test suitable for field use, has demonstrated excellent accuracy, with good equivalence to traditional nested PCR. FIND is now working with industry partners to adapt the assay to a lower-cost high-throughput 96-well format suited to screening populations in endemic settings, as part of surveillance and elimination strategies. Pilot studies to evaluate the feasibility of LAMP for population screening were started in Cambodia and at the Karolinska Institute with samples collected in Cambodia and Zanzibar, respectively. LAMP is also a potentially useful tool in the screening and treatment of malaria in clinical trials and as reference standard against which RDTs and other malaria diagnostics may be evaluated. Discussions are in progress with potential collaborators to develop a multiplexed LAMP platform with the capacity to identify multiple pathogens in clinical samples.

Clinical trial capacity and reference materials

For Malaria & AFS, sample collection and RDT lot-testing activities continue in Cambodia (with Pasteur Institute, and the National Malaria Center), and in the Philippines (Research Institute for Tropical Medicine). A large clinical study to evaluate the performance of malaria RDTs for detection of infection in pregnancy completed sample collection and participant contact in Burkina Faso and Uganda in 2012. Field research in blood transfer device use continues with the University of Lagos in Nigeria and with FIND staff in Uganda. In 2012, field feasibility studies of a high throughput LAMP malaria strategy began with collaborators working in Cambodia and Zanzibar. See FIND's Clinical Trial Capacity map on page 18.

Specimen bank

FIND is contributing to the maintenance of a bank of characterized parasite-positive and -negative specimen for evaluation and quality control of malaria RDTs. The bank is regularly replenished, thus ensuring consistency of the samples preparation procedures and characteristics. In 2012, FIND has continued to support the two collection sites in Cambodia and the Philippines, "re-activated" a third site in Nigeria, and replenished the cultured parasite samples in anticipation of the Round 5 Product Testing in 2013. For characterization of samples, work continues for malaria antigen quantification and for malaria species determination by nested PCR. All samples collected in 2011 have been fully characterized during 2012.


FIND/Sandra Incardona

Acute febrile syndrome (AFS) / Non-malaria febrile illness (NMFI)

Overview

The increasing use of point-of-care diagnostic tests that exclude malaria, coupled with a declining malaria burden in many endemic countries, is highlighting the inability of many health care systems to manage other causes of febrile disease. Non-malarial febrile illness (NMFI) is responsible for much of the burden of preventable childhood mortality in low-income countries today. Progress is hampered by a lack of knowledge on the frequency and distribution of the pathogens involved and a lack of screening and point-of-care diagnostics to identify them, preventing effective management of these generally treatable contributors to disease burden. Addressing this deficiency is a vital first step to improving patient management, and prioritizing further research and diagnostic development.

Knowledge of the geographical distribution of major causes of non-malarial fever and diagnostic facilities in malaria endemic countries remains limited and there is currently no global database to guide future studies. Defining the populations at risk and their geographical distribution is therefore essential to defining the needs for new point of care diagnostics. A map of febrile disease aetiology forms an invaluable resource to identify gaps in knowledge, to advocate for more attention in this area, and to guide further targeted surveys and the development of management strategies.

FIND has moved to fill this knowledge gap with a field study and a mapping project in the Mekong Delta.

If a patient with a fever consults a health worker in a malaria endemic region, it is far more likely that they are not suffering from malaria. However, that patient will most likely be tested for malaria and be given a negative result. This creates a problem, because the patient is still ill and the health worker has little capacity to distinguish what else could be the cause of the fever. Some fevers will subside even if left untreated, while others will worsen and put the patient at risk of death.

The consequences from febrile disease can hold communities back from becoming self-supporting. The cost of severe illness and high transmission of infectious disease in terms of money spent on health care, loss of the family bread-winner due to illness, a reduction in income through time off work, as well as the human cost of a death in the family are difficult to measure. Communities need the capacity to manage these severe but treatable and preventable impacts on the lives of their members.

AFS strategy

Addressing AFS in a holistic manner will require a strategic mix of new knowledge on prevalence and impact of disease, development of new tools, sustainable management algorithms and the infrastructure to support them. These are system-wide issues, providing challenges but also huge opportunities for improvement in healthcare delivery. Emerging technologies in diagnostics raise the potential to address fundamental deficiencies in health services and opportunity in low-resource countries.

Our focus therefore is on management of acute fever, combining the need to improve malaria diagnosis with the need to address the alternative causes of fever, and what to do when the malaria test result is negative. Ultimately, good diagnosis will reduce childhood and adult mortality, enable other interventions to achieve their potential, and provide the information necessary to eliminate a range of diseases.

NMFI projects

Mekong NMFI field study

A study carried out by FIND and partners in the Mekong Delta region has provided evidence to guide management of malaria-test negative fever cases and to assess the need for diagnostic tools applicable in field conditions; a manuscript with Lao PDR results has been submitted for publication and a manuscript from Cambodia is in preparation.

NMFI mapping project

A review of published studies, focusing on the Mekong region of Southeast Asia has also been completed, to record and map the identified major pathogens causing febrile illness in this region; results of this review have been published in an open-access journal (Acestor et al., PLoS ONE 7:9, Sept 2012). FIND and partners are currently moving forward with a global mapping effort, using existing data on causes of fever in tropical and sub-tropical areas, to provide a central resource and guidance for future research and diagnostic development.

HAT & other neglected diseases

HAT & OND

- HAT Antigen detection
- HAT staging markers and test of cure (blood)
- Chagas LAMP
- Leishmaniasis LAMP
- Leishmaniasis ELISA

- HAT staging markers
- HAT test of cure (TOC)
- Generation 2 HAT RDT
- Leishmaniasis TOC

- HAT LAMP
- HAT Rapid Diagnostic Test

- HAT LED fluorescence microscopy

Human African trypanosomiasis (HAT)

Overview

FIND's programme on diagnostics for human African trypanosomiasis (HAT), or sleeping sickness was launched in 2006 in collaboration with the WHO and a number of partners in research, industry and government. It focuses on the development of user-friendly tests that can be easily applied in remote settings, and capable of detecting the disease in its early stages. A major achievement in 2012 was the launch in December of the first ever RDT for sleeping sickness screening, expected to be a major step forward in the elimination of this disease.

Sleeping sickness is one of several neglected infectious diseases today. It is caused by protozoan parasites belonging to the genus *Trypanosoma* which are transmitted to humans through the bites of tsetse flies. More than 70 million people are at risk of being infected in the 36 sub-Saharan African countries where the diseases is endemic. Concerted efforts in surveillance and control of the disease by governments of endemic countries together with the international community has resulted in a progressive fall in the number of cases reported each year, raising hopes that the disease could soon be eliminated. In 2011, only 6,743 new cases were reported to the WHO and the number of persons currently suffering from the disease is estimated at below 30,000.

Diagnosis and subsequent treatment remains difficult because existing analytic tools – which rely in part on the use of microscopy to confirm the presence of parasites in the blood – cannot be used effectively in remote, impoverished settings where the disease is almost always found. Moreover, infection results in few specific symptoms in the early stages and cases are rarely detected until they are in advanced stages



when treatment is difficult and expensive, and the drugs used are highly toxic.

A major accomplishment this year was the lauch of the new rapid test – SD Bioline HAT, developed by FIND and Standard Diagnostics Inc. of the Republic of Korea. It is an immunochromatographic rapid test that detects antibodies against *T. brucei gambiense*, the parasite responsible for more than 90% of sleeping sickness cases. Health workers with minimal training, using fresh blood from a finger prick, can perform this cheap and very simple-to-use test and the results are obtained after only 15 minutes. A unique feature of the test is that storage is at ambient temperature and it does not require specialized equipment or electricity. This makes it ideal for use in very remote settings where most of the infected people are found. It is also the first ever test for sleeping sickness to be CE marked and to be manufactured by an industrial company following ISO 13485:2003 quality requirements.

Development of the rapid test for sleeping sickness has been a joint effort of FIND and numerous partners, among them the Institute of Tropical Medicine (Belgium), MicroCoat Biotechnologie GmbH (Germany), the International Livestock Research Institute (Kenya), the Institute of Tropical Neurology (France), Médecins Sans Frontières (Spain), the National HAT Control Programme of the DRC (PNLTHA, Democratic Republic of the Congo), the Central African Institute of Agronomical Research (Central African Republic), the World Health Organization and Standard Diagnostics, Inc. (Republic of Korea). The Bill & Melinda Gates Foundation and the Department for International Development (DFID) of the United Kingdom have provided much of the financial support required to drive this initiative.

Upstream projects

Markers for staging HAT and confirming cure

Pioneering biomarker discovery work has identified 8 markers of disease progression that discriminate between HAT with and without central nervous system involvement with a high degree of precision. Two of the biomarkers – neopterin and CXCL13 could also confirm cure or predict relapses within 6 months after treatment. FIND and its partners have now initiated the development of a rapid diagnostic test based on these biomarkers for staging patients and confirming cure. The utility of both biomarkers has been confirmed in an experimental primate model of HAT. Meanwhile, the feasibility of optimizing a recently developed rapid test for serum neopterin to work with cerebrospinal fluid is being explored.

HAT LAMP

A loop mediated isothermal amplification (LAMP) kit for confirmatory diagnosis of HAT was developed and launched in 2011. Studies in 2012 confirmed that the test is highly sensitive and specific in detection of *T.b. rhodesiense* patients. LAMP can be performed on blood samples collected and stored for up to 10 weeks when dried on filter papers. This is very important as samples collected from patients by mobile teams or in remote rural health centres can be sent to a central laboratory for testing.

Diagnostic facilities in the DRC and in Uganda have been improved and appropriate training given, with a major impact on their capacity to provide basic health care to the communities they serve. The LAMP kit is now being used in studies to accelerate elimination of HAT, in combination with an RDT for screening, and LED fluorescence microscopy.

Early implementation

Antibody detection rapid diagnostic test

The ultimate goal of this project is to develop an RDT that is effective for both forms of HAT. Development of an RDT for *T. brucei gambiense* HAT has been completed. Demonstration studies, including determination of the cost-effectiveness of using the RDT in various diagnostic algorithms, were initiated in the DRC and Uganda. Since applying the test does not require any instrument, it will be easy to deploy into primary health care systems in remote areas where HAT occurs. The new RDT is made using native parasite antigens that are difficult to produce. As an alternative, significant progress has been made in developing a second generation RDT that is based on recombinant antigens.

LED fluorescence microscopy

Confirmatory diagnosis of HAT relies on demonstration of parasites in blood, lymph fluid or cerebrospinal fluid by microscopy. FIND has optimized and evaluated a parasite detection method based on red blood cell lysis, concentration, staining the sediment with Acridine Orange and examination using a LED fluorescence microscope. During 2012, demonstration studies on the use of this technology in place of bright field microscopy were completed in the DRC and in Uganda. The microscope was also successfully set up to operate on solar energy in several laboratories. The technology has now been formally adopted for clinical use in the DRC and Uganda.

Its widespread introduction in remote areas where the disease occurs is being undertaken as part of studies to accelerate elimination of HAT, in combination with the RDT for screening, and a confirmatory method based on LAMP.

Clinical trial capacity and reference materials

For HAT, trials were carried out at multiple sites in the DRC, Uganda (one site) and the Central African Republic (one site). In the DRC evaluation of a screening test was carried out by one mobile team and two health centres. Evaluation of a LAMP kit for HAT was done at 8 centres, including 4 mobile teams. See FIND's Clinical Trial Capacity map on page 18.

Specimen bank

Some of the critical obstacles in the development of improved assays for HAT include carefully collected and stored reference materials. Sustained field programmes that have the capacity and facilities for long-term follow-up constitute another important challenge. FIND and the Department of Neglected Tropical Diseases (NTD) of the World Health Organization established a HAT specimen bank, which is owned by the WHO. This has guaranteed more efficient use of limited resources, reduced the need for field trials, promoted product comparisons and facilitated quality control.

FIND/J. Ndung'u

Leishmaniasis

Overview

FIND's strategy of expanding technological platforms that can serve more than one disease is proving particularly successful in the case of Leishmaniasis. It is caused by protozoan parasites of the genus *Leishmania*, and is one of the 17 neglected tropical diseases identified by WHO, which despite their medical diversity tend to co-exist geographically and to share certain criteria. Humans are infected when bitten by phlebotomine sand flies, which breed in forest areas, caves, or the burrows of rodents. WHO estimates that 350 million people across the world, mostly in Southeast Asia and Africa, are at risk of contracting leishmaniasis; the diseases kills up to 50'000 people annually.

Leishmaniasis is endemic in 98 countries and 3 territories, and is responsible for approximately 2.35 million DALYs (disability adjusted life years). 90% of the disease burden of visceral leishmaniasis (VL) is in India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia. While 70 to 75% of cases of cutaneous leishmaniasis occur in Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica and Peru.

There are four forms of leishmaniasis, each with its specific symptoms - skin ulcers, lesions on mucous membranes, significant weight loss and anaemia. In the case of VL, also known as Kala Azar, failure to treat can result in a fatality rate as high as 100% within two years. A further complication is that some treated patients can develop a condition known as post-kala azar dermal leishmaniasis (PKDL), and can themselves become reservoirs for further transmission of the disease.

Until recently the diagnostic reference standard for all form of leishmaniasis has been microscopic detection of parasites from lymph nodes, bone marrow, spleen or skin samples, some of which are obtained using highly invasive procedures. To overcome these difficulties, a number of highly sensitive molecular detection methods have recently been developed. However, their clinical application has been hampered by the need for complex sample preparation procedures and expensive equipment, and they are also prone to cross-contamination. Novel parasite targets for use in developing tests to monitor treatment outcome are needed; this is especially important in regions where the number of reported cases of PKDL is high, in order to eliminate the disease reservoir. For such patients, an affordable, easy to use, accurate method for early detection of parasite reactivation would prevent PKDL and improve the response to re-treatment.

FIND is currently working on two assays for leishmaniasis, one based on LAMP – loop-mediated isothermal amplification, and the other an ELISA – Enzyme-linked immunosorbent assay. Both of these address the issue of ease of use in remote and resource poor settings – key criteria in FIND's mission.

Leishmaniasis projects

LAMP for leishmaniasis

Significant progress has been made in development of a very promising prototype LAMP assay for leishmaniasis that can be used in district laboratories in resource-poor settings. The possibility of using this test to monitor treatment is also being explored. Four primer sets targeting 3 *Leishmania* DNA sequences have been produced and performance of the prototype kits evaluated. One of them is very promising for visceral leishmaniasis (VL) while the other could be further improved for the genus. A genus test would have a major impact in the control of both visceral and cutaneous leishmaniasis. The feasibility of developing a format that combines both tests without loss of performance is also being explored. The importance of such a test was highlighted at a meeting of experts hosted by FIND during the year. A strategy to guide future efforts in leishmaniasis diagnostics is also being developed.

ELISA test for Leishmania antigens in urine

A simple assay for detection of leishmania antigens in urine, in a format that can be used at the lowest levels of the health system to screen for leishmaniasis would have obvious advantages. In 2012, FIND focused on selection of the best combination of antibodies for a prototype ELISA. The prototype was tested with samples from South East Asia (Bangladesh) and further testing with samples from Eastern Africa (Kenya) is planned. A protocol for collection of urine samples from VL patients in Kenya was approved by the Kenyan authorities, and collection started in Kimalel in November 2012.

Chagas disease

Overview

Chagas disease or American trypanosomiasis was included in FIND's programme on neglected diseases at the end of 2011. It is a vector-borne anthropozoonosis caused by the protozoan parasite *Trypanosoma cruzi*. The disease is widely spread in Latin America, infecting between 8 and 15 million people, with more than 30 million at risk of infection. Every year there are more than 40,000 new cases and more than 12,000 deaths related to Chagas disease. If left untreated, patients remain infected for life. Pregnant women are frequently susceptible, with prevalence reported to be as high as 51% in some urban centres and up to 81% in rural settings. Perinatal transmission has been reported in 4% to 8% of women of childbearing age with chronic Chagas disease and it is estimated that there are around 15,000 annual congenital *T. cruzi* infections. While the geographic distribution of the disease was reduced from 21 to 18 countries in Latin America between 1990 and 2006, migration from Latin America to the north, to Europe and Asia is now spreading the disease further afield.

Current diagnostic methods using microscopy or serological testing are insufficient to respond to the global challenge of Chagas disease. There is therefore a growing need to develop and make accessible new diagnostic tests that can easily be applied in the remote areas where the disease is endemic, and which perform well enough to determine the appropriate course of clinical care.

FIND is drawing on its experience with loop-mediated isothermal amplification (LAMP) to develop an assay to detect *T. cruzi* DNA. Molecular amplification has shown much better performance than existing methods in the diagnosis of congenital Chagas disease. Although PCR (polymerase chain reaction) studies suggest that molecular methods developed earlier can detect almost all cases within the first weeks of life, the technical complexity of PCR limits its use primarily to research settings, with minimal clinical application. Therefore, a molecular assay such as LAMP, which could be performed in peripheral laboratories, would allow for testing of infants born to mothers living in endemic settings with significant potential to save lives.

Chagas projects

Chagas LAMP

FIND and partners are developing a LAMP assay for the accurate diagnosis of congenital Chagas disease that can be implemented in national screening programmes. The target population is infants who are at risk for neonatal disease, usually tested in hospitals where they are born, or in health centres where early neonatal care is given. During 2012, partnerships were established with organizations with expertise in Chagas disease, and in the development of LAMP assays. Promising DNA targets were identified and primers designed for them. The primers are being evaluated in LAMP assays for sensitivity and specificity, with very promising results. Activities to establish the most appropriate methods for sample preparation for LAMP have also been initiated. Meanwhile a market survey has confirmed that molecular tests such as LAMP, if reasonably priced and made easy to use in settings where the disease occurs, would play an important role in diagnosis of Chagas disease. This will however need to be accompanied by appropriate advocacy and policies in the endemic countries.

FIND India

FIND established its office in New Delhi in 2007 on the basis of a Memorandum of Understanding that was signed with the Ministry of Health & Family Welfare in the recognition by the Government that we could play a key role in helping it to scale up the delivery of strong programmatic management of drug-resistant TB.

The team operates as a fully independent regional office with responsibility not only for India, but also for South-East Asia. We have a robust and efficient multi-disciplinary programme management team consisting of programme managers, medical officers, microbiologists, bio-medical engineers, and logistics, procurement and finance officers.

From an initial focus on participation in evaluation and demonstration studies of FIND co-developed diagnostic tools, activities shifted to laboratory strengthening and capacity building in support of their uptake in country laboratories and health facilities.

The EXPAND-TB project is a pillar of our activities in India. Our aim, under this project, is to establish 40 line probe assay and 30 liquid culture and DST facilities by 2014, at both state and national levels. Among our key accomplishments in 2012, we conducted 15 national and 74 onsite training courses and proficiency testing has been successfully completed for 29 line probe assay sites and 12 liquid culture sites. These are now fully operational. Under EXPAND-TB, UNITAID initially contributed close to US$12 million for expanding access to newer diagnostics for MDR-TB. In 2012, the Global Fund to Fight AIDS, TB and Malaria provided support for five additional laboratories, with human resources, equipment and consumables worth over US$2 million.

A key instrument in support of these activities is the International Centre for Excellence in Laboratory Training (ICELT) that we established in 2011 at the National TB Institute in Bangalore. Activities at ICELT covered training in supervision and monitoring, in addition to the technical skills required to work with the newer rapid diagnostic platforms being employed.

Detection of MDR-TB has increased from nearly 3,000 cases notified in 2009 to above 16,000 cases detected by end of 2012. The National TB Programme has assured satisfactory management of all patients that were diagnosed with TB and MDR-TB and can ensure adequate supplies of second-line drugs for treatment of drug-resistant TB.

Key achievements in 2012

- Under the EXPAND-TB Xpert project: 12 laboratories were established across the country for diagnosis of rifampicin-resistant TB resistant. Upgrading was completed for 8 sites by end 2012.
- A total of 16,028 MDR-TB cases were detected in 2012 with EXPAND-TB support and the annual detection target of 12,926 MDR-TB cases was exceeded.
- A total of 1,068 laboratory staff and health care workers were trained at ICELT.


ICELT

FIND Uganda

FIND established its office and a TB research laboratory in Kampala, Uganda, in 2008. Since then it has been the focal point for FIND's research and field activities in Africa. Most of these have to date been related to TB and malaria, although toward the end of 2012, the Ministry of Health indicated its support for the inclusion of a FIND co-developed molecular test, LAMP for HAT, in the national disease programme's elimination strategy. Activities during 2012 in Uganda have largely been focused on evaluation and early implementation studies for TB and malaria, and projects to look at solutions for case reporting. Large-scale studies for new technologies are accompanied by intensive training and follow-up – a major support in building in-country laboratory capacity. Also, data collected locally during these studies are often used to facilitate and guide the implementation of new tools in the country.

Key achievements in 2012

Introduction of Xpert MTB/RIF in Uganda
A one-year TB REACH-funded project to introduce Xpert MTB/RIF to detect smear negative TB in TB/HIV co-infected patients in Uganda was completed at the end of 2012. Using motorcycle-based samples transport, 56 health facilities in 24 districts were "networked" to the 6 district-level Xpert test sites, greatly enhancing the speed with which samples are tested and patients diagnosed. 1,022 positive TB cases out of 7,551 HIV positive individuals were detected using Xpert, a high TB positivity rate of 17% for this sub-Saharan African setting. The project strengthened the National TB Programme in terms of policy decisions, early roll-out of technology, and documentation of Xpert positive TB cases in Uganda. Peripheral and district level systems were strengthened in terms of technology know-how, test referral and interpretation.

Mobile SMS-based technologies were validated for prompt reporting of the Xpert results and about 50 technicians were trained on how to perform and trouble-shoot the test.

Several vulnerable communities, including the isolated fishermen communities of Lake Victoria islands where living conditions encourage high household contact transmission rates, have benefited from access to this technology.

Potential efficacy of screening pregnant women with malaria RDTs (Burkina Faso and Uganda)
Pregnant women are at particular risk of malaria infection which has negative effects on the mother and on the foetus. Preliminary evidence suggests that screening with RDTs may be an accurate and practical way to identify pregnant women who should be treated for placental malaria infection. Results of this study will be of great interest to the WHO, African ministries of health, and other public health and malaria control stakeholders as they will provide an evidence base for use of malaria RDTs as a routine screening tool to improve maternal and fotal/new-born health. A major achievement of this study was the development of placental histopathology capacity in Uganda: laboratory technicians were trained in techniques to prepare and interpret placental samples for malaria histopathology at a government-sponsored health centre in Tororo, the first time to our knowledge that such work has been done entirely on the continent of Africa.

Point-of-care quality control test for RDTs
(Lao PDR and Uganda)
Malaria RDTs are increasingly recommended for use in areas where good-quality malaria microscopy is not available, but substandard quality and durability issues need to be adequately addressed. FIND and partners have therefore developed positive control wells (PCWs), that can be used by health workers to test stocks of RDTs stored and used at their health facilities. This study will provide critical information on PCW use, utility and acceptability in routine health care settings in malaria-endemic areas, in order to guide rational real-world implementation strategies for PCWs. Results are expected in early 2014.

Implementation guide for the use of RDTs
Between 2008 and 2012, FIND and partners, including the National Malaria Programme of Uganda, worked to produce an international step-by-step guide to implementing RDTs as a diagnostic tool in malaria control programmes with quality assurance. This guide is a significant contribution to supporting the WHO policy for the treatment of malaria based on parasitological diagnosis.

FIND/A. Thirumala

Advocacy, communications and resource mobilization

While there has been significant progress in delivering new products for poverty related and neglected diseases in the past 10 years, the needs of patients in developing countries remain largely unmet.

The London Declaration on Neglected Tropical Diseases boldly stated in January 2012: "Inspired by the World Health Organization's 2020 Roadmap on NTDs, we believe there is a tremendous opportunity to control or eliminate at least 10 of these devastating diseases by the end of the decade. But no one company, organization or government can do it alone. With the right commitment, coordination and collaboration, the public and private sectors will work together to enable the more than a billion people suffering from NTDs to lead healthier and more productive lives – helping the world's poorest build self-sufficiency." This auspicious beginning for the year was a momentous event that shows the importance of attracting attention to these health challenges to build support from government, industry and civil society.

FIND was ideally positioned to play its part in this challenge. The launch of the first rapid test to screen sleeping sickness is an example of how improved diagnostic are a critical component for achievement and sustainability of any elimination programme.

FIND joins other non-profit product developers to advocate in favour of changes in policy to develop and deliver new diagnostics and other tools to improve health in developing countries. Increased and coordinated investments, incentives and innovative financing are necessary if the world is to meet these challenges. The need for adequate and sustainable funding for poverty related and neglected diseases remains crucial. On diagnostics alone, the gap between current funding levels and estimated funding needs are significant. For instance, the Global Plan to Stop TB estimates that investments of $340 million per year are necessary to deliver new improved diagnostics to detect the disease as well as drug resistance. However, in 2011 only $55 million were invested in R&D for new diagnostics for TB.

This shortfall is significant, especially given there are still no point-of-care tests for TB.

Streamlined regulatory processes are also part of speeding up the delivery of effective global health technologies.

FIND was successful in securing $21 million in new Grants in 2012

- WHO India awarded to FIND the amount of $1.44 million for 2012-2013 for the demonstration of TB rapid test in India.
- The Bill & Melinda Gates Foundation awarded to FIND $11.8 million for 2012-2014 for late stage TB diagnostics development.
- The Bill & Melinda Gates Foundation awarded supplemental funding to FIND of $2.6 million for 2012-2014 for malaria diagnostics.
- The Bill & Melinda Gates Foundation made a contribution to FIND of $5 million for operating support.
- The Center for Disease Control (through PEPFAR) awarded $1.4 million to build capacity for diagnostic testing.
- John Hopkins (NIAID) gave a one year grant of $0.08 million for TB diagnostics.
- John Snow Inc gave FIND a 1 year grant for 0.3 million to support malaria RDT quality testing.
- The UBS Optimus Foundation made a contribution of $0.15 million for the elimination model of HAT *T.b. rhodesiense*.

Publications

Mainstream media profile FIND in over 30 articles in 2012. FIND and partners published 30 scientific articles to widely share research results.

Tuberculosis

1. **Genotype MTBDRsl line probe assay shortens time to diagnosis of extensively drug-resistant tuberculosis in a high-throughput diagnostic laboratory** by Barnard M, Warren R, Van Pittius NG, van Helden P, Bosman M, Streicher E, Coetzee G, O'Brien R. *Am J Respir Crit Care Med. 2012 Dec 15.*
2. **"Proof-Of-Concept" Evaluation of an Automated Sputum Smear Microscopy System for Tuberculosis Diagnosis** by Lewis JJ, Chihota VN, van der Meulen M, Fourie PB, Fielding KL, Grand AD, Dorman SE, Churchyard GJ. *PLoS ONE 7(11): e50173.*
3. **Enabling policy planning and innovation management through patent information and co-authorship network analyses: a study of Tuberculosis in Brazil** by Vasconcellos AG, Morel CM. *PLoS ONE 7(10): e45569.*
4. **Proteome-scale antibody responses and outcome of Mycobacterium tuberculosis infection in nonhuman primates and in tuberculosis patients** by Kunnath-Velayudhan S, Davidow AL, Wang HY, Molina DM, Huynh VT, Salamon H, Pine R, Michel G, Perkins MD, Xiaowu L, Felgner PL, Flynn JL, Catanzaro A, Gennaro ML. *J Infect Dis. 2012 Sep;206(5):697-705.*
5. **A diagnostic accuracy study of Xpert MTB/RIF in HIV-positive patients with high clinical suspicion of pulmonary tuberculosis in Lima, Peru** by Carriquiry G, Otero L, González-Lagos E, Zamudio C, Sánchez E, Nabeta P, Campos
6. **Survey of the diagnostic retooling process in national TB reference laboratories, with special focus on rapid speciation tests endorsed** by WHO in 2007 by van Kampen SC, Oskam L, Tuijn CJ, Klatser PR. *PLoS ONE 7(8): e43439.*
7. **Performance characteristics of the Cepheid Xpert MTB/RIF test in a tuberculosis prevalence survey** by Dorman SE, Chihota VN, Lewis JJ, Clark D, Churchyard GJ, Fielding KL. *PLoS ONE 7(8): e43307.*
8. **Transforming TB Diagnosis: Can Patients and Control Programs Afford to Wait?** by Talbot EA, Pape JW, Sundaram L, Boehme CC, Perkins MD. *Am. J. Trop. Med. Hyg., 87(2), 2012, pp. 202–204.*
9. **Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens** by Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W, Nicol MP. *Clinical Infectious Diseases, 10.1093/cid/cis598*
10. **A research agenda for helminth diseases of humans: diagnostics for control and elimination programmes** by McCarthy JS, Lustigman S, Yang G-J, Barakat RM, García HH, Sripa B, Willingham AL, Prichard RK, Basáñez M-G. *PLoS Negl Trop Dis 6(4): e1601.*
11. **Discerning trends in multiplex immunoassay technology with potential for resource-limited settings** by Gordon J, Michel G. *Clinical Chemistry 2012; v. 58, p.690-698*

Malaria

12. **Malaria rapid diagnostic test transport and storage conditions in Burkina Faso, Senegal, Ethiopia and the Philippines** by Albertini A, Lee E, Coulibaly SO, Sleshi M, Faye B, Mationg ML, Ouedraogo K, Tsadik AG, Feleke SM, Diallo I, Gaye O, Luchavez J, Bennet J, Bell D. *Malaria Journal 2012, 11:406*
13. **Feasibility of distributing rapid diagnostic tests for Malaria in the retail sector: Evidence from an implementation study in Uganda** by Cohen J, Fink G, Berg K, Aber F, Jordan M, Maloney K, Dickens W. *PLoS ONE 7(11): e48296*
14. **Finding parasites and finding challenges: improved diagnostic access and trends in reported malaria and anti-malarial drug use in Livingstone district, Zambia** by Masaninga F, Sekeseke-Chinyama M, Malambo T, Moonga H, Babaniyi Olusegun B, Counihan H, Bell D. *Malaria Journal 2012, 11:341*

15. **Mapping the aetiology of non-malarial febrile illness in Southeast Asia through a systematic review – terra incognita impairing treatment policies** by Acestor N, Cooksey R, Newton PN, Ménard D, Guerin PJ, Nakagawa J, Christophel E, González IJ, Bell D. *PLoS ONE 7(9): e44269.*
16. **Parasite-based malaria diagnosis: Are Health Systems in Uganda equipped enough to implement the policy?** by Kyabayinze DJ, Achan J, Nakanjako D, Mpeka B, Mawejje H, Mugizi R, Kalyango JN, D'Alessandro U, Talisuna A, Van geertruyden JP. *BMC Public Health 2012, 12:695*
17. **Reductions in artemisinin-based combination therapy consumption after the nationwide scale up of routine malaria diagnostic testing in Zambia** by Yukich JO, Bennett A, Albertini A, Incardona S, Moonga H, Chisha Z, Hamainza B, Miller JM, Keating J, Eisele TB, Bell D. *Am J Trop Med Hyg. 2012 Jul 30.*
18. **Community health workers use malaria rapid diagnostics tests (RDTs) safely and accurately: results of a longitudinal study in Zambia** by Counihan H, Harvey SA, Sekeseke-Chinyama M, Hamainza B, Banda R, Malambo T, Masaninga F, Bell D. *Am J Trop Med Hyg 2012 vol. 87 no. 1 57-63*
19. **A research agenda for helminth diseases of humans: diagnostics for control and elimination programmes** by McCarthy JS, Lustigman S, Yang G-J, Barakat RM, García HH, Sripa B, Willingham AL, Prichard RK, Basáñez M-G. *PLoS Negl Trop Dis 6(4): e1601.*
20. **Programme level implementation of malaria rapid diagnostic tests (RDTs) use: outcomes and cost of training health workers at lower level health care facilities in Uganda** by Kyabayinze DJ, Asiimwe C, Nakanjako D, Nabakooza J, Bajabaite M, Strachan C, Tibenderana JK, Van Geetruyden JP. *BMC Public Health 2012, 12:291*
21. **Early experiences on the feasibility, acceptability, and use of malaria rapid diagnostic tests at peripheral health centres in Uganda – insights into some barriers and facilitators** by Asiimwe C, Kyabayinze D, Kyalisiima Z, Nabakooza J, Bajabaite M, Counihan H, Tibenderana J. *Implementation Science 2012, 7:5*
22. **Identification of optimal epitopes for Plasmodium falciparum rapid diagnostic tests that target histidine-rich proteins 2 and 3** by Lee N, Gatton ML, Pelecanos A, Bubb M, González IJ, Bell D, Cheng Q, McCarthy JS. *Journal of Clinical Microbiology, doi: 10.1128/JCM.06533-11*
23. **New developments in malaria diagnostics: Monoclonal antibodies against Plasmodium dihydrofolate reductase-thymidylate synthase, heme detoxification protein and glutamate rich protein** by Kattenberg JH, Versteeg I, Mighchelsen SJ, González IJ, Perkins MD, Mens PF, Schallig DFH. *mAbs Volume 4 Issue 1*

Human African Trypanosomiasis (Sleeping Sickness)

24. **Estimating and mapping the population at risk of sleeping sickness** by Simarro P, Cecchi G, Franco JR, Paone M, Diarra A, Ruiz-Postigo JA, Fèvre EM, Mattioli RC, Jannin JG . Editor: Joseph Mathu Ndung'u, FIND, Switzerland. *PLoS Negl Trop Dis 6(10): e1859.*
25. **Cerebrospinal fluid neopterin as marker of the meningo-encephalitic stage of Trypanosoma brucei gambiense sleeping sickness** by Tiberti N, Hainard A, Lejon V, Courtioux B, Matovu E, Enyaru JC, Robin X, Turck N, Kristensson K, Ngoyi DM, Vatunga GML, Krishna S, Büscher P, Bisser S, Ndungu JM, Sanchez J-C. *PLoS ONE 7(7): e40909.*
26. **The human African trypanosomiasis specimen biobank: a necessary tool to support research of new diagnostics** by Franco JR, Simarro PP, Diarra A, Ruiz-Postigo JA, Jannin JG. *PLoS Negl Trop Dis 6(6): e1571.*
27. **Loop-mediated isothermal amplification technology towards point of care diagnostics** by Njiru ZK. *PLoS Negl Trop Dis 6(6): e1572.*
28. **A research agenda for helminth diseases of humans: diagnostics for control and elimination programmes** by McCarthy JS, Lustigman S, Yang G-J, Barakat RM, García HH, Sripa B, Willingham AL, Prichard RK, Basáñez M-G. *PLoS Negl Trop Dis 6(4): e1601.*
29. **Improved detection of Trypanosoma brucei by lysis of red blood cells, concentration and LED fluorescence microscopy** by Biéler S, Matovu E, Mitashi P, Ssewannyana E, Bi Shamamba SK, Bessell PR, Ndung'u JM. *Acta Trop. 2012 Feb; 121(2):135-40*
30. **Towards Point-of-Care Diagnostic and Staging Tools for Human African Trypanosomiasis** by Matovu E, Kazibwe AJ, Mugasa CM, Ndungu JM, Njiru ZK. *Journal of Tropical Medicine, doi:10.1155/2012/340538*

Financial information

Financial Statement
for the Year ended 31 December 2012
and Report of the Statutory Auditor

FINANCIAL SUMMARY

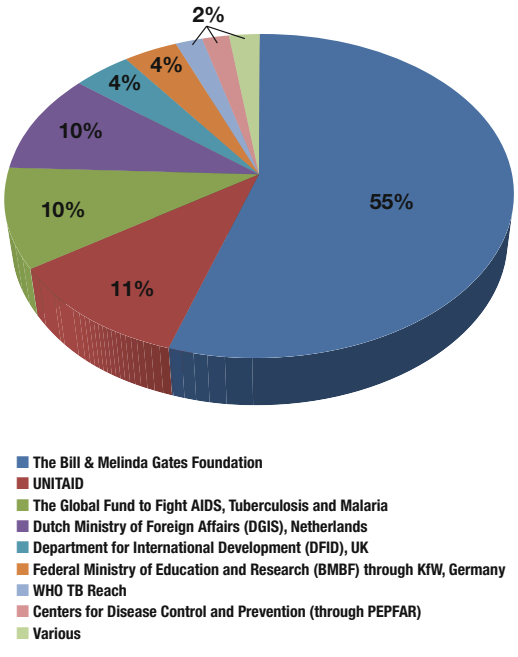
In 2012, FIND reached $24 million in programmatic expenditure, a decrease of 8% from 2011, mainly driven by lower HIV-related activities. In 2012, contributions from donors and other income brought the level of revenue to $33 million, generating an excess of revenue over expenditures of $4.4 million. This excess benefited from an exceptional unrestricted contribution of more than $5 million from major donors.

In 2011, FIND changed its revenue recognition policy to better reflect the funds available to the Foundation at the end of the financial year. This change in accounting policy resulted in a prior year adjustment of $-5.8 million and an accumulated deficit of $6 million.

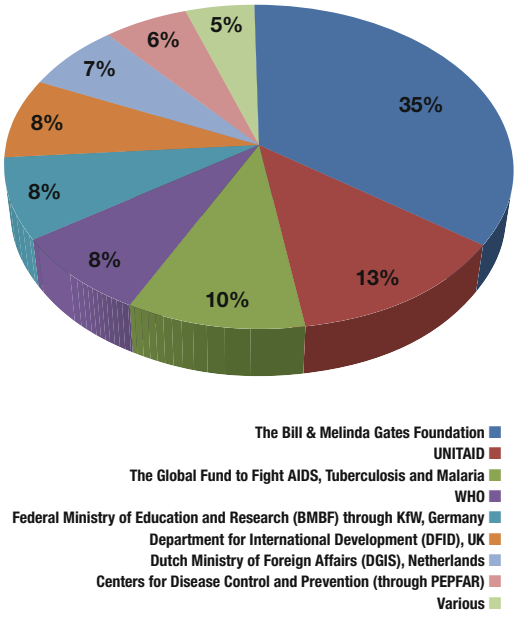
In 2012, the excess of revenue over expenditures of $4.4 million resulted in a reduction of the accumulated deficit to $1.6 million. At the time of writing (September 2013), one of our donors advised FIND that it has initiated a grant process toward the elimination of this deficit by the end of 2013. A series of cost reduction actions were initiated resulting in supporting services expenditure of $4.4 million in 2012 (excluding restructuring costs, $4.8 million in 2011). The management expects to further reduce the level of supporting services expenditure in 2013.

The Board of Directors was expanded to add financial expertise. An audit committee of the Board was constituted in March 2012. The audit committee and the Board of Directors are actively monitoring the progress that management is making of raising additional funds and the other measures that would allow FIND to eliminate the accumulated deficit reflected under the change in revenue recognition policy.

Cumulative donations committed to FIND and/or received in 2012



2012 Revenue by Donor



STATEMENT OF REVENUE AND EXPENDITURE FOR THE YEAR ENDED 31 DECEMBER 2012
(all amounts in US dollars)

	Note	2012	2011
REVENUE			
Grant revenue	7, 8	33,097,887	29,330,675
Sundry income		106,009	211,194
Total revenue		**33,203,896**	**29,541,869**
EXPENDITURE			
Programme services			
Tuberculosis		14,811,112	17,213,991
Human African Trypanosomiasis		1,729,591	2,202,409
Malaria		2,950,748	2,824,730
Human Immunodeficiency Virus		1,344,782	3,471,125
Other/cross disease		3,559,199	846,757
		24,395,432	**26,559,012**
Supporting Services			
Information & communication		58,988	115,823
Governing & advisory bodies		80,078	52,373
General administration		3,096,224	3,250,300
Finance & service expenses		1,062,217	1,248,651
Depreciation & amortization		104,944	119,215
Restructuring costs		-	824,825
		4,402,451	**5,611,187**
Total expenditure		**28,797,883**	**32,170,199**
Excess (deficit) of revenue over expenditure for year		4,406,013	(2,628,330)
Accumulated surplus brought forward		(6,027,494)	2,429,134
Adjustment resulting from change in revenue recognition policy	5	-	(5,828,298)
Accumulated surplus (deficit) carried forward	4	**(1,621,481)**	**(6,027,494)**

The accompanying notes form an integral part of these financial statements.

BALANCE SHEET AS AT 31 DECEMBER 2012
(all amounts in US dollars)

	Note	2012	2011
ASSETS			
Current assets			
Cash and cash equivalents		8,458,675	15,300,705
Accounts receivable		2,721,281	837,566
Prepayments		316,506	432,161
Total current assets		**11,496,462**	**16,570,432**
Non-current assets			
Fixed assets	6.1	90,358	172,296
Patents	6.2	-	7,707
Rental guarantee deposit		210,171	199,768
Total non-current assets		**300,529**	**379,771**
Total assets		**11,796,991**	**16,950,203**
LIABILITIES AND CAPITAL			
Current liabilities			
Accounts payable		1,042,369	3,172,175
Accrued expenses		1,265,401	1,480,528
Deferred revenue		11,070,272	18,163,606
Unrealized exchange gains		-	120,958
Total current liabilities		**13,378,042**	**22,937,267**
Capital and reserves			
Capital	12	40,430	40,430
Accumulated surplus (deficit)		(1,621,481)	(6,027,494)
Total liabilities and capital		**11,796,991**	**16,950,203**

The accompanying notes form an integral part of these financial statements.

CASH FLOW STATEMENT FOR THE YEAR ENDED 31 DECEMBER 2012
(all amounts in US dollars)

	2012	2011
Excess (deficit) of revenue over expenditure for year	4,406,013	(2,628,330)
Add back non-cash charge – depreciation & amortization	104,944	119,215
Adjustment resulting from change in revenue recognition policy	-	(5,828,298)
	4,510,957	**(8,337,413)**
Cash flows – operating activities		
Increase (decrease) in deferred revenue	(7,093,334)	(3,339,309)
Increase (decrease) in accounts payable	(2,129,806)	1,521,426
Increase (decrease) in accrued expenses	(215,127)	424,500
(Increase) decrease in accounts receivable	(1,883,715)	104,293
(Increase) decrease in prepayments	115,655	2,438,283
(Increase) decrease in rental guarantee deposit	(10,403)	-
Increase (decrease) in unrealised exchange gains on foreign currencies	(120,958)	(249,610)
	(11,337,688)	**899,583**
Cash flows – investing activities		
Acquisition of office furniture & fittings	-	(1,968)
Acquisition of computers & printers	(15,299)	(49,087)
Acquisition of faxes & telephones	-	-
	(15,299)	**(51,055)**
Net increase (decrease) in cash and cash equivalents for year	**(6,842,030)**	**(7,488,885)**
Cash and cash equivalents at start of year	15,300,705	22,789,590
Cash and cash equivalents at end of year	8,458,675	15,300,705
Net increase (decrease) in cash and cash equivalents for year	**(6,842,030)**	**(7,488,885)**

The accompanying notes form an integral part of these financial statements.

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2012
(all amounts in US dollars)

1. General

The Foundation for Innovative New Diagnostics (FIND) is an independent non-profit Foundation created under Article 80 of the Swiss Civil Code, and is registered in the Geneva Register of Commerce under statutes dated 28 September 2007.

FIND's mission is to drive the development and implementation of accurate and affordable diagnostic tests that are appropriate to patient care in low-resource settings.

On 9 December 2010, FIND and the Swiss Federal Council signed an agreement granting FIND certain privileges and immunities under the revised Host State Act, which came into force on 1 January 2008. In accordance with this agreement, FIND has been granted exemption from all federal, cantonal and communal taxes, from Value-Added Tax, and from regulations governing the employment of foreign nationals in Switzerland. This agreement came into effect on 1 January 2011.

2. Change in accounting policy

In 2011, the organization changed its revenue recognition policy to better reflect the funds available to the organization at the end of the financial year. From 2011, grant revenue is only recognized to the extent that recoverable expenses are incurred.

In 2010 and previously, revenue was recognized on the basis of planned expenditure per the grant agreements. Note 5 shows the impact of this policy change.

3. Significant accounting policies

3.1 Basis of presentation

The financial statements are prepared under the historical cost convention and in accordance with Swiss law.

3.2 Fixed assets

Fixed assets are recorded at cost and are depreciated under the straight-line method at 20% annually for office furniture and fittings, electrical installations and fax machine and telephones, and 33.3% annually for computers and printers.

3.3 Patents

Certain patents were purchased as part of an agreement completed with a project partner early in 2004, and are subject to amortization under the straight-line method. At 31 December 2012, the patents were fully amortized.

3.4 Foreign currency

Accounting records are maintained in US dollars (USD). Revenue and expenditures in other currencies are recorded at accounting rates approximating actual rates in effect at the time of the transaction. Year-end balances for assets and liabilities in other currencies are translated into US dollars at rates of exchange prevailing at balance sheet date. At 31 December 2012, the rate of exchange used for the Swiss franc, the main foreign currency for 2012, was USD/CHF = 0.915 *(2011 – 0. 935)*. Realized exchange gains as well as realized and unrealized exchange losses are included in the determination of surplus (deficit) for the year. Unrealized exchange gains are deferred

3.5 Recognition of revenue

Revenue on restricted grant is recognized in the period to the extent that the related project expenses and recoverable overheads are incurred. Revenue on unrestricted grant is recognized on a cash basis. Interest income is recognized on an accruals basis and sundry donations are recognized on a cash basis. Grants received relating to activities in future years are recorded in the balance sheet as deferred revenue.

3.6 Accounts payable

Accounts payable represents expenditure chargeable in the 2012 financial year, for which invoices were not received for payment before the year-end.

3.7 Rental guarantee deposit

The guarantee relates to the rental of FIND office premises in Geneva and India and is recoverable in accordance with the rental contract upon vacation of the premises.

4. Going concern

In 2011, FIND changed its revenue recognition policy to better reflect the funds available to the organization at the end of the financial year. This change in accounting policy resulted in a prior year adjustment of (USD 5,828,298) and an accumulated deficit of (USD 6,027,494).

In 2012, FIND raised more than USD 5 million from major donors to reduce the accumulated deficit. The surplus for the period of USD 4,406,013 results in closing reserves of (USD 1,621,481), which reflect an excess of expenses over income.

Management's forecast for 2013 indicates that FIND is likely to incur a deficit but that it has sufficient cash to cover its operations throughout the year. The Board of Directors is fully aware of this situation and, together with management, is exploring strategic initiatives and taking active measures which are described in the next paragraphs to eliminate the accumulated deficit.

Cost reduction actions

FIND has initiated a series of cost reduction actions resulting in lower support services expenditure in 2012. The management expects to further reduce the support service expenditure in 2013.

Further financing

FIND is continuing the process of raising unrestricted funds that would allow the Foundation to eliminate the accumulated deficit reflected under the changed revenue recognition policy. The audit committee and the Board of Directors are actively monitoring the progress to achieve this objective in a timely manner.

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2012 (continued)
(all amounts in US dollars)

5. Effect of change in accounting policy in 2011

The adjustment resulting from the change in revenue recognition policy of USD 5.8 million relates to a prior year adjustment affecting revenue and surplus (deficit) for the year by the same amount. There was no effect on expenditure. See also note 2.

	2010 and earlier
Restated revenue	115,131,279
Previously reported revenue	120,959,577
Total adjustment resulting from change in revenue recognition policy	**(5,828,298)**

6. Fixed assets and intellectual property

6.1 Fixed assets as at 31 December 2012 were as follows:

	2012	2011
At Cost:		
Office furniture & fittings	118,790	118,790
Computers & printers	353,723	449,625
Electrical installations	12,392	12,392
Fax machine & telephones	41,965	41,965
Total cost	**526,870**	**622,772**
Less:		
Accumulated depreciation	436,512	450,476
Net book value	**90,358**	**172,296**

Fire insurance coverage as at 31 December 2012 was USD 109,250 *(2011 – USD 106,950)*.

6.2 Intellectual property as at 31 December 2012 was as follows:

	2012	2011
Patents – at cost	53,949	53,949
Less: Accumulated depreciation	53,949	46,242
Net book value	-	**7,707**

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2012 (continued)
(all amounts in US dollars)

7. Contributions received

During 2012, the following contributions were received from donors *(other currency amounts are converted to USD at exchange rates on date of receipt)*:

	2012	2011
Becton Dickinson and Co	15,584	195,000
Bill & Melinda Gates Foundation	10,884,824	7,708,523
European Union	1,000	403,627
Global BioDiagnostics	50,000	-
Government of Germany	3,133,886	-
Government of the Netherlands	1,785,711	3,514,490
Government of the United Kingdom	2,544,937	2,681,248
Government of the United States	2,210,961	921,991
JSI Research & Training	275,000	125,000
The Global Fund	135,279	2,135,661
TI Pharma	91,918	9,993
UBS	491,188	180,072
UNITAID	-	365,000
WHO	1,545,433	1,265,594
	23,165,721	**19,506,199**

Donor agreements in effect as at 31 December 2012 provide for a total of USD 51.5 million to be paid to FIND between January 2013 and December 2016.

8. Donations in kind

Based upon information provided by various partners, donations in kind totalling USD 798,133 have been included under Grant Revenue (*2011 – USD 292,027*). The same amount has been included as expenditure under Programme Services.

9. Project partners

Payments to project partners during 2012, under contracts signed up to 31 December 2012, totalled USD 6,029,279 *(2011 – USD 11,178,057)*. Commitments at 31 December 2012 for future payments under those contracts total USD 2,841,352 *(2011 – USD 5,437,055)*.

10. Pension fund liabilities

USD 82,262 was due to the pension fund as at 31 December 2012 *(2011 – nil)*.

11. Rent commitments

At 31 December 2012, FIND had future rent commitments totalling USD 1,089,000 up to 30 June 2014 *(2011 – USD 1,868,021 up to 30 June 2014)*.

12. Funds

The Endowment Capital of CHF 50,000 is fully subscribed and equates to USD 40,430 at the rate of exchange on the date of payment.

13. Events subsequent to 31 December 2012

No events occurred subsequent to 31 December 2012 which could have a material impact on the understanding of these financial statements.

REPORT OF THE STATUTORY AUDITORS
On the financial statements

Deloitte.

Deloitte SA
Route de Pré-Bois 20
Case Postale 1808
CH-1215 Genève 15

Tél: +41 (0)58 279 80 00
Fax: +41 (0)58 279 88 00
www.deloitte.ch

Report of the statutory auditor

To the Board of the
Foundation for Innovative New Diagnostics (FIND), Geneva

Report on the financial statements

As statutory auditor, we have audited the accompanying financial statements of the Foundation for Innovative New Diagnostics (FIND), which comprise the balance sheet, statement of revenue and expenditure, cash flow statement and notes for the year ended 31 December 2012.

Board of the Foundation's Responsibility
The Board of the Foundation is responsible for the preparation of the financial statements in accordance with the requirements of Swiss law and the charter of the foundation. This responsibility includes designing, implementing and maintaining an internal control system relevant to the preparation of financial statements that are free from material misstatement, whether due to fraud or error. The Board of the Foundation is further responsible for selecting and applying appropriate accounting policies and making accounting estimates that are reasonable in the circumstances.

Auditor's Responsibility
Our responsibility is to express an opinion on these financial statements based on our audit. We conducted our audit in accordance with Swiss law and Swiss Auditing Standards. Those standards require that we plan and perform the audit to obtain reasonable assurance whether the financial statements are free from material misstatement.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statements. The procedures selected depend on the auditor's judgment, including the assessment of the risks of material misstatement of the financial statements, whether due to fraud or error. In making those risk assessments, the auditor considers the internal control system relevant to the entity's preparation of the financial statements in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control system. An audit also includes evaluating the appropriateness of the accounting policies used and the reasonableness of accounting estimates made, as well as evaluating the overall presentation of the financial statements. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our audit opinion.

REPORT OF THE STATUTORY AUDITORS
On the financial statements

Deloitte.

Foundation for Innovative New Diagnostics (FIND)
Report of the statutory auditor
for the year ended
31 December 2012

Opinion
In our opinion, the financial statements for the year ended 31 December 2012, comply with Swiss law and the charter of the foundation.

Without qualifying our opinion, we draw your attention to note 4 to the financial statements disclosing an uncertainty relating to the company's ability to continue as a going concern. Should the going concern assumption no longer be appropriate, financial statements, based on liquidation values, would have to be prepared.

Should the financial statements prepared using liquidation values disclose a situation of overindebtedness, the Board of the Foundation would need to comply with the requirements of article 84a of the Swiss Civil Code.

Report on other legal requirements
We confirm that we meet the legal requirements on licensing according to the Auditor Oversight Act (AOA) and independence (article 83b CC in connection with article 728 CO) and that there are no circumstances incompatible with our independence.

In accordance with article 728a paragraph 1 item 3 CO and Swiss Auditing Standard 890, we confirm that an internal control system exists, which has been designed for the preparation of financial statements according to the instructions of the Board of the Foundation.

We recommend that the financial statements submitted to you be approved.

Deloitte SA

Peter Quigley
Licensed Audit Expert
Auditor in Charge

Joelle Herbette
Licensed Audit Expert

Geneva, 9 April 2013
PBQ/JOH/jh

Enclosures
Financial statements (balance sheet, statement of income and expenditure, cash flow statement and notes)

Partnering for better diagnosis for all

Production and editing: FIND Communications
Design: www.latitudesign.com
Photo cover page: FIND/Jacques Debayle

FIND
foundation
for innovative new diagnostics

Avenue de Budé 16 • 1202 Geneva • Switzerland • Tel.: +41 (0)22 710 05 90 • Fax: +41 (0)22 710 05 99

wwww.finddiagnostics.org