



Annual Report 2008

Partnering for better diagnosis for all

Message from the CEO and Chairman of the Board

The year 2008 was especially significant for FIND, as it marked the Foundation's fifth year anniversary since its launch at the World Health Assembly in May 2003. To commemorate this occasion, we published a special report - *Delivering on the promise 2003-2008* - which described the milestones and achievements in the first five years of FIND's existence. We also improved our branding and produced a modified logo. In a short period of time, and together with our many partners from both the public and private sectors, several significant achievements are delivering encouraging results. This is an inspiration for all of us to continue our commitment and dedication to developing better diagnostic solutions for infectious diseases.

Tuberculosis programme

In February of this year, FIND committed, in a partnership with Hain Lifescience, to undertake large-scale demonstration projects for the rapid screening of multidrug-resistant TB in several regions worldwide. The largest of these is underway in South Africa where the Hain GenoType® MTBDRplus test is being used to screen 20,000 at-risk patients over the course of one year.

In collaboration with our partner Eiken Chemical, Ltd., developers of clinical molecular diagnostics, we announced in March of this year a major technical advance to further develop and refine the LAMP assay.

In May, we signed a Memorandum of Understanding with bioMérieux, a leader in the field of *in vitro* diagnostics, to jointly undertake development projects in the field of infectious disease diagnostics.

With technical support from FIND, Carl Zeiss developed the Primo Star iLED fluorescence microscope which should allow faster and more sensitive detection of TB and other parasitic infections than traditional microscopes. This improved technology is particularly exciting as a multi-platform technology for HAT and malaria.

On 30 June, FIND, the Global Drug Facility, UNITAID, and WHO's Stop TB Department announced a new initiative to make available rapid tests for the detection of MDR-TB in several developing countries during a press conference held at Palais des Nations in Geneva. This initiative consists of two projects supported by a grant of US\$ 60 million from UNITAID. One of the aims is to introduce the line probe assay, a rapid test for the diagnosis of MDR-TB, and another is to provide a supply of affordable drugs needed to treat MDR-TB in 54 endemic countries.

On 1 July 2008, FIND together with scientists from the South African Medical Research Council and the National Health Laboratory Service combined efforts with National and Provincial Departments of Health to demonstrate the utility of the line probe assay. The study from South Africa showed that the test is highly effective in diagnosing MDR-TB and can be used in laboratory settings in developing countries. The test will be rolled out to all provinces in South Africa following the acceptance of a new diagnostic algorithm by the National TB Control Programme.

FIND also signed an MOU with the American Society for Microbiology (ASM) on 31 July 2008 confirming an agreement to work in partnership for projects aimed at strengthening infectious disease diagnosis and service integration in resource-poor and transitional countries. This collaboration gave rise to a pilot project that FIND and ASM have been conducting in Côte d'Ivoire since April 2008, for which FIND is providing the diagnostic tests while ASM will provide the experts in clinical microbiology for training and technical assistance in the implementation of the tests.

On 24 November 2008, the first ever TB molecular platform for MDR-TB diagnosis was introduced in record time in Maseru, Lesotho, becoming further evidence of what can be achieved in laboratory capacity building as a result of the concerted efforts of private public partnerships. This key milestone is encouraging evidence for turning policy into practice. The Central TB Laboratory, Queen Elizabeth II Hospital in Maseru, Lesotho, was inaugurated by Dr Mphu Ramatlapeng, the Honourable Minister of Health and Social Welfare. The new TB

Molecular Biology Facility was established by FIND, in collaboration with the WHO, Partners in Health and the Lesotho Ministry of Health. These new, state-of-the-art TB facilities will also serve as training centers in the region.

Another rewarding achievement was the inauguration of a new TB laboratory in Kampala, Uganda on 4 December 2008 by FIND and partners in response to the need to accelerate the uptake of new TB technologies in the region. Housed within the National Tuberculosis Reference Laboratory, the facility was renovated and equipped within five months in close cooperation with the Uganda National Tuberculosis and Leprosy Programme. It is equipped with state of the art technologies, including liquid culture and line probe assays which were approved by WHO in 2007 and 2008 for uptake in disease endemic regions.

HAT programme

In the short period since we launched programme on diagnostics for human African trypanosomiasis (HAT), or sleeping sickness, we have made tremendous progress in our efforts to develop new and improved diagnostics for this neglected disease, and would like to acknowledge the collaborative support of the WHO and a variety of partners in research, industry and government towards making this possible.

Several achievements were made in 2008, among them:

- the development of LAMP technology, which has the potential to serve as a molecular platform not only for TB but also for HAT and malaria;
- improvements in parasite detection through a collaboration with the Institute of Tropical Medicine in Antwerp, Belgium, to improve the mini anion exchange centrifugation technique (mAECT) and more importantly to transfer the production of the mAECT kits to a facility in the Democratic Republic of Congo;
- progress in efforts to develop an alternative serological assay that is simpler, more sensitive and specific than current tests through use of recombinant or synthetic antigens;
- collaboration with scientists at the University of Geneva, to identify unique proteins in the cerebrospinal fluid of sleeping sickness patients which can discriminate between early and late (central nervous system) stages of the disease;
- partnering with the WHO in the establishment of a HAT specimen bank that has guaranteed more efficient use of limited resources, reduced the need for repeated collections, promoted product comparisons and facilitated quality control;
- promoting HAT advocacy activities through PATTEC to encourage governments of endemic countries to prioritize African trypanosomiasis surveillance and control by ensuring adequate budgetary allocation, making sustainable introduction of new diagnostic tests in the public sectors of endemic countries possible, and increasing community awareness of the disease.

Malaria programme

As for malaria, accurate diagnosis of this often fatal disease is vital to ensuring good management of febrile patients in malaria-endemic regions, particularly in sub-Saharan Africa, and for monitoring the incidence of this potentially fatal disease. In 2008, Round 1 of the WHO-FIND Malaria Rapid Diagnostic Tests (RDT) Evaluation Programme was completed. Forty-one RDT products currently on the market were evaluated between May and November at CDC in Atlanta. The results of this evaluation will be published early next year in order to serve as a tool for countries to make informed choices, from among the dozens of tests commercially available, on the purchase and use of rapid diagnostics that are best suited to local requirements.

Another exciting development has been the lot-testing programme, which is part of a controlled product testing scheme to provide mechanisms needed for local or regional testing of purchased RDT lots before they are distributed for use. Health Ministries need rapid access to information on the quality of the tests they are buying. Together with WHO, we have established three regional lot-testing sites that have the capacity to carry out rapid and high-quality performance evaluations of RDTs sent from anywhere in the world. These centers also provide a secondary service of storing and retesting the RDTs over time to ensure that they still function up to the time of their expiry date.

Financial results

Financial results for 2008 again showed strong growth, with analytical and project expenditure up by 64% for the year to \$25.5 million compared with \$15.5 million in 2007 and \$9 million in 2006. Total expenditure increased by almost the same percentage from \$17.7 million to \$28.8 million, but continuing tight management controls on support and infrastructure costs resulted in a higher percentage of spending on projects - over 88% of the total in 2008 compared with 85% in 2007 and 84% in 2006.

The almost threefold expansion in project activities over the past two years could not have been managed successfully without having effective financial controls and management systems in place to provide accurate and prompt information to project managers. Software and systems are being continually upgraded and refined to adapt easily to future expansion, thus safeguarding the efficient project management standards that are a hallmark of FIND's work with project partners.

Accounting standards for revenue recognition provide for contributions from donors to be recognized over the full term of each grant agreement. In 2008 revenue thus determined plus sundry income amounted to \$27,786,000 (2007 - \$19,267,000), which resulted in an excess of expenditure over income of almost \$1.1 million. This was deducted from previous accumulated surpluses of \$3.35 million to leave a total of just on \$2.28 million at the end of 2008. Further information on FIND's financial results in 2008 can be found in the Auditors' Report, Financial Statements and Notes elsewhere in this Report.

The year 2009 promises to be another rewarding year, for we anticipate the fruition of several projects currently underway in our pipeline. Our private-public partnership model is supported by the capabilities of all who are working to improve diagnostic services in developing countries and draws us into collaborative and productive arrangements to achieve attainable goals for better health for all. Our motivated team has proved the success of an ISO-certified product management policy as we try to overcome the complex challenges that often keep promising new technologies from reaching the people who need them most. We look forward to working with you and our partners to make this happen!

Product development activities – an overview

Tuberculosis programme

TB is one of the greatest threats to health worldwide, with nearly nine million new cases and 1.6 million deaths each year. There is an urgent need for improved, simple and more affordable diagnostics to replace the century-old microscopy which remains a standard in many regions. With its partners, FIND is taking upon these crucial health challenges to better fight this disease especially in high burden countries where new tests and better health systems are most needed today. Some of the tools being developed by FIND are expected to be introduced into TB national control programs and will be either major improvements on existing technologies or new.

Major accomplishments in 2008 include the advancement of three tools for use in developing countries into final clinical evaluations. These technologies, including a high quality but low cost battery powered microscope with dual fluorescence capability (Zeiss), a simple molecular case detection test based on LAMP, and a fully automated, 90 minute test for TB and drug resistance (Cepheid), are all targeted for use in laboratories currently performing only routine microscopy. STAG endorsement's of the line probe assay for MDR TB screening in high-burden countries results in WHO recommendations of this test was another crucial successful achievement.

FIND's project management system follows best industry practices with each project being structured into phases and milestones which require detailed and documented evidence of the attainment of pre-defined targets. The progress made in 2008 for each project is further described below.

Antigen discovery

Diagnosing active disease by detecting TB antigens

The goal of this project is 1) to develop an improved assay against the lipopolysaccharide target lipoarabinomannan (LAM) and 2) to identify additional targets by appropriate biomarker discovery efforts.

Several prototype immunoassays for the sensitive detection of LAM were developed during a research collaboration between FIND and the Swedish institute of Infectious diseases. FIND has also conducted evaluations with a number of researchers in developing countries to describe the performance characteristics of a commercial 1st generation LAM assay. While assay development work has been completed resulting in five prototype assays in different test formats and detection technologies, the clinical evaluations are ongoing.

Another collaboration with the Forsyth Institute in Boston and the Tablin proteomics laboratory at Harvard University resulted in the identification of four novel peptides from the TB bacterium that were discovered in patient urine by state of the art mass spectrometry. FIND is currently developing immunoassay detection methods to validate those findings.

It is assumed that either LAM or one or more of the additional markers identified will be finally converted into a rapid test format for point of care TB case detection.

Antibody detection

Diagnosing active TB by detection of antibodies

The goal of this project is to determine a set of serodiagnostic TB antigens for diagnosis of active disease.

In a joint project with three partners based in the US, FIND has developed the first ever whole proteome array chip of *M. tuberculosis*, containing more than 4,000 individual proteins. This breakthrough achievement enabled the serological profiling of several hundred fully documented serum samples (patients and endemic controls) from the FIND sample repository in combination with materials received from WHO and two other clinical sites. This unique sample set represented a cross-section of various geographic areas and disease states.

The final result was a set of 61 TB antigens that, when applied in combination, identified patients with active TB with very high discriminating power. A respective manuscript has been prepared and will be submitted for publication in October 2009.

In a next step technical and clinical validation studies will be conducted in order to verify the screening data to arrive at a final minimal set of antigens to be used in a rapid test format for field use in developing countries.

Increasing sensitivity lateral flow tests for TB antigen detection

The goal of this project is to evaluate detection technologies that can enable diagnostic marker detection with the highest possible sensitivity.

Research conducted by FIND and other groups have been known that some of the putative diagnostic TB biomarkers are present in body fluids in very low concentrations only and would thereby not be readily detectable by most conventional assay methods.

Based on in-house technology scouting analyses and the literature FIND has chosen five assay technologies and determined maximum analytical sensitivities employing LAM and malaria antigens as model cases. The results of this project will now enable the selection of assay technologies best suited for detection of specific diagnostic markers in body fluids that have come out of FIND's biomarker research activities as described above. This project is therefore complementary to the antigen and antibody detection projects, respectively.

Speciation: Capilia TB

The goal of this project is to provide a simple instrument-free, lateral flow immunochromatographic (LFI) assay for species identification of *M. tuberculosis* complex strains. The technology platform approach was already submitted and endorsed by the WHO in 2007. During 2008 FIND continued to support pilot projects and handled the logistics process to distribute the tests to all study sites.

Latent tuberculosis infection diagnosis

Interferon-gamma release assays (IGRAs) are now being used widely in developed countries for the diagnosis of latent tuberculosis infection (LTBI). Two IGRAs are commercially available and offer considerably improved operational performance characteristics compared to the tuberculin skin test (TST), the traditional test for LTBI diagnosis.

However, there are few published data on the use of these tests for LTBI screening of high-risk groups (e.g., HIV infected persons and childhood household contacts of infectious TB patients) in low-income countries. There are virtually no data on the predictive value of IGRAs for future TB in these groups in high TB incidence settings. FIND has partnered with Cellestis, Ltd., on evaluation studies of their IGRA, the QuantiFERON Gold In-Tube (QFT) assay, to address these questions.

FIND's evaluation studies, including a large study of 8000 TB patients and household contacts followed over a 3-year period in Zambia and South Africa and will not be completed until the second half of 2010. Preliminary results from two small studies nested in Aeras neonatal cohort studies in Africa and India suggest that the QFT is not useful in the diagnosis of active TB in very young children.

Automated TB DNA (Cepheid)

The goal of this project is to develop a sophisticated, highly engineered system that maximizes ease of use and delivers additional data on drug sensitivity.

In 2008 the development of the product was finished and the development milestone completed. The sites for evaluation studies were selected, the sites trained and the evaluation studies commenced in mid-2008. The expected date for finishing the studies is December 2008 and the trial report should be available in April/May 2009 to allow release of the CE-marked product for demonstration trials mid-2009.

Manual TB DNA (Eiken)

The goal of this project is to establish and validate a manual LAMP-based assay format that can replace microscopy at peripheral clinics in the developing world.

In 2008 FIND and Eiken carried out rapid prototyping process in the field to simplify the assay components with a focus on (a) precision transfer volume to reaction tube; (b) direct sputum sampling device; (c) DNA contamination minimization. A third feasibility study was also carried out in Vietnam with the modified components. The main goals for 2009 are to finalize the product design, start Japanese registration studies and to start FIND evaluation studies by the end of the year.

Line probe assay for MDR TB

FIND has partnered with Hain Lifescience, GmbH, on the evaluation and demonstration of the MTBDRplus test, a rapid molecular line-probe assay (LPA) for the diagnosis of MDR TB directly from AFB smear-positive sputum specimens. Following a large evaluation study in a public health laboratory in Cape Town that found that the assay performed better than standard culture and DST, FIND initiated a series of large-scale demonstration projects. The first of these projects began in South Africa in late 2007. This project based in public health laboratories in 4 provinces screened over 20,000 MDR TB suspects with the LPA over the course of one year. Although data on patient impact are still being collected, the initial results found high test accuracy, rapid turn-around time, and total laboratory costs for testing that were significantly less than those for conventional phenotypic culture and drug susceptibility testing.

Based on preliminary data from the project in South Africa, as well as published evaluation studies, WHO approved LPAs for MDR TB screening in low-income countries in June 2008. Additional demonstration projects supported by FIND are underway in Thailand, Vietnam, India, the Philippines, and China.

LAM detection in urine

Diagnosing active disease by detecting TB antigens

The three goals of this project are to: 1) develop an improved assay against the proven lipopolysaccharide target lipoarabinomannan (LAM); 2) identify additional targets; and 3) improve the sensitivity of rapid tests so that low-abundance targets can be detected.

1) The selection and characterization of the two most promising anti-LAM antibodies has been completed. Based on BiaCore analysis, affinity of these antibodies was determined to be very high (low nmol/l range). The assessment of a preliminary research prototype assay produced by *Genovac* using the identified antibody set showed a sensitivity of 60% in a set of smear positive urine samples from Peru and Zimbabwe. *Future Diagnostics (FD)*, a Dutch biotechnology company located in Nijmegen, has been contracted to generate a quality-assured prototype ELISA based on two reference antibodies. During an intense technological handover phase, know-how was transferred from Svenson's academic group in Sweden to the Dutch R&D company in Nijmegen. Thereby, access to cell lines, antibodies, antigen and reagents – manufactured according to good manufacturing practices – was secured. Pilot lots have been shipped to South Africa and Zimbabwe, where FIND's development study will start in July 09.

2) Given the lack of knowledge of LAM biokinetics in humans, *Colorado State University* and *University of Singapore* have respectively been contracted to identify and purify LAM molecular forms or related lipopolysaccharides from urine, using NMR and MALDI-ToF MS/MS following a urine concentration step.

All partners have received well-characterized samples from FIND and are expected to complete their analyses in approximately 6 months from now.

3) In parallel, contracted partner institutions are working on the identification of additional antigens in urine and sputum that may be appropriate for TB detection. These could be used either in combination with LAM or as "plan B" markers in case LAM does not meet required specifications.

Sensitive prototype LAM assays based on various detection systems have been developed with four independent partner companies. Provided clinical evaluation of the Future Diagnostics LAM assay is successful, FIND is in an excellent starting position for immediate transfer of this marker into POC assay development.

Light-emitting diodes (LED) study

A demonstration project was initiated in coordination with National and Regional TB Control Programs in India, Vietnam, Thailand, Cambodia, South Africa, Lesotho, Ethiopia, Russia and Peru. FIND criteria for country selection for the study were: an agreement at National/Regional Levels (MOU) with NTP and/or MOH; a high-burden of TB; a low or middle income ranking; local presence of FIND or an implementing partner; and settings representative of the global TB and HIV situation. There were 28 microscopy centers and 12 supervisory sites chosen for this large study, with site selection based on the rate of smear-positivity, training of microscopists, volume of work, reliability of AC power (sites with intermittent power supply were intentionally selected), interest in the project, and accessibility of study sites for supervisory visits. None of the microscopy centers had prior experience with fluorescence microscopy (FM).

The objectives of the project were to:

1. Assess the feasibility of implementing Primo Star iLED for TB diagnosis at microscopy centers without prior experience with FM in low- to moderate-income settings and to identify barriers to implementation;
2. Determine the false positivity and negativity rate of LED fluorescence reading compared to a Ziehl-Neelsen (ZN) baseline and results from the supervisory site ;
3. Determine the trend of false positivity and negativity rates of LED fluorescence reading over time (with increasing experience);
4. Assess the impact of this implementation on daily workload and case detection rates for low, middle and high-volume settings;
5. Determine lab technicians' appraisal of Primo Star iLED;
6. Evaluate detailed costs associated with LED-based FM in comparison with conventional methods;
7. Identify minimal training needs and develop training modules accordingly.

Substudies were conducted to:

1. Establish comparative performance data for alternative LED-based approaches;
2. Compare fluorescence staining methods;
3. Assess effects of fading speed on external quality assurance by rechecking;

The size and complexity of the demonstration study reflects the importance of having true performance data from sites without prior experience in FM. LED-based FM is likely to see markedly expanded use in the coming few years, and it will be critical to understand the training and supervisory needs for peripheral microscopy sites using this technology as compared with conventional brightfield examination of ZN-stained slides. Data from these demonstration projects as well as other published and unpublished documentation will be submitted to WHO expert committees for review in the 3rd quarter of 2009.

Liquid culture and DST

Mycobacteria Growth Indicator Tube (MGIT) liquid culture and DST demonstration projects that were begun in 2005 were completed in 2008. WHO review of preliminary data from these

projects, as well as a large body of published literature on liquid culture and DST systems led to WHO endorsement of this technology in November 2007.

The first MGIT culture demonstration studies were nested in three CREATE (Consortium to Respond Effectively to the AIDS/TB Epidemic) projects in Zambia, South Africa and Brazil: 1) ZAMSTAR, a household TB/HIV intervention study conducted jointly by the Zambart group in Lusaka and investigators from Stellenbosch in Cape Town, 2) Thibela, a evaluation of community-wide isoniazid preventive therapy (IPT) in South Africa gold miners conducted by Aurum Institute for Health Research, and 3) THRio, an assessment of the impact of IPT among adults in HIV/AIDS care programs in Rio de Janeiro conducted by Johns Hopkins University. All three demonstration projects had somewhat different albeit related objects and each included a cost-effectiveness analysis.

The ZAMSTAR study in Zambia and South Africa analyzed laboratory costs for different culture methods and concluded that manual MGIT culture was more cost-effective per case detected compared with automated MGIT and two LJ culture systems. The Thibela study found that the higher yield and faster time to positive culture with MGIT vs. LJ culture must be balanced against the relatively high costs. The high proportion of NTM underscores the need for rapid speciation tests. The THRio study concluded that culture (solid or liquid) is potentially effective and cost-effective for HIV-positive patients in resource-constrained settings. However, reliable transmission of culture results to patients and integration with existing systems are essential.

MGIT culture and DST was introduced in 4 laboratories in Nepal, the Philippines, Uzbekistan and the Russian Federation. Laboratory turn-around-times (TAT) and time to initiation of appropriate treatment were measured and compared before and after MGIT culture and DST were fully operational. Laboratory TATs after implementation of liquid culture and DST varied by site with decreases in median culture TAT of up to 30 days and decreases in median TAT for culture plus DST of up to 117 days. The impact of MGIT on time to treatment initiation was related to whether empiric regimens were used in the TB program. For example, in the Russian Federation where empiric treatment was utilized, the median time from diagnostic specimen collection to initiation of appropriate therapy from was 10 days with solid media and 6 days with MGIT. Conversely, in the Philippines, where treatment was initiated only after culture and DST results were complete, MGIT implementation decreased time to treatment initiation by 111 days relative to solid culture and DST. Detailed costing analyses in Samara and Manila found MGIT culture/DST to be marginally more costly than LJ. However, laboratory optimization and strengthening activities have the potential to significantly affect the impacts achieved by implementation of accurate and rapid TB laboratory diagnostics.

Clinical Infrastructure (Reference Materials)

The availability of reference clinical materials and study populations in TB-endemic countries is critical for the efficient completion of the development and clinical trial cycle of new diagnostics.

FIND has a central repository in Bangkok that stores, manages and distributes collected specimens and related data. The repository currently holds TB reference materials from patients in five countries (33,587 aliquots).

Most FIND projects have already benefitted from collected specimens, notably the POC projects. As a result, the number of study-specific demands for specimens has increased: for example, several biomarker discovery projects have required either small quantities of fresh (non-frozen) specimens or large volume specimens. It has therefore become necessary to tailor-make specimen collection to meet the needs of individual projects. This has made the collection process more demanding, which has, in turn, had an effect on routine specimen collection. The selection of one additional collection site is planned in order to meet these additional demands.

FIND's trial site infrastructure has undergone a streamlining and prioritization process with the selection of 10 trial sites for development and evaluation studies. The overall number of trial sites has, however, not decreased as routine microscopy centers are needed for ongoing LED FM and Xpert demonstration studies.

The clinical trial team will be expanding early in 2009 with the appointment of a Junior Study Coordinator and the position of Clinical Trials Data Manager is expected to be filled before the end of the year.

Transrenal TB DNA

The major goal of FIND's transrenal TB detection project has been to develop a simple method to extract and preserve DNA from urine, to eventually couple with a rapid assay detecting *M. tuberculosis* DNA. This diagnostic test was envisioned for use at the level of a microscopy center to detect adult and pediatric patients with pulmonary or extrapulmonary TB, with a major advantage over sputum-based techniques the ease and safety of sample collection.

The Transrenal TB DNA Consortium, of which FIND is a founding member, has conducted and published research into DNA stability in urine, methods of DNA extraction from urine, and completed research toward detection of transrenal DNA using a small amplicon target. For independent validation of research outcomes from the Consortium, a contract has also been established for a parallel effort by the David Alland laboratory at UMDNJ.

Proof of principle for the sensitivity and specificity of transrenal TB DNA detection has not been demonstrated. Inadequate sensitivity and specificity have been observed through the feasibility trials of the Consortium and well-conducted experiments using the sensitive Cepheid platform have been to-date unsuccessful for detection of spiked DNA into urine.

Transrenal TB DNA may be absent or present at the limit of PCR detection. Current (and perhaps final) feasibility investigations are underway and will determine the future of this project.

Volatile Organic Compounds

Identification of TB VOCs in breath or in the headspace of sputum specimens from TB suspects is a highly attractive target for TB diagnosis. FIND has established collaboration with field leaders, and is validating initial feasibility data in well-defined samples and patients.

Disappointing performance of the E-nose for VOC pattern detection with KIT and two Dutch academic institutions redirected activities to specific VOC discovery rather than dependence on VOC pattern recognition. Intriguing proof of principle for the utility of VOCs for TB detection is currently coming from the APOPO group, which uses sniffer rats for detection of TB in the headspace of sputum samples. FIND is considering the practical implications of the rat-based system, including development of diagnostic algorithms and additional investigations into the specific VOCs which the rats are detecting. Establishment of an important new collaboration for VOC detection from sputum (and possibly eventually breath) is underway with the Draper Laboratories, which is also negotiating support from Becton Dickinson.

Immediate demonstrations of feasibility of VOC detection is challenged by high limits of detection, poor reproducibility, and the current lack of micromachines for field use.

FIND Quality Management

FIND successfully passed the first surveillance audit for ISO 13485:2003 and ISO 9001:2000 for Project Management for Design, Development and Manufacturing of IVD, Evaluation and Demonstration of IVDs. The surveillance audit was conducted in June 2008 by the Swiss TS certification group.

The FIND offices in Uganda and India, and the FIND Research Laboratory in Uganda have developed and implemented Quality Management Systems to apply for ISO certification and Laboratory Accreditation in 2009. FIND achieved all Quality Objectives (FIND key performance indicators) in 2008.

Operations

In 2008, FIND's staff grew in number and totaled 39 at the end of 2008, thereof 27 in Geneva, 7 in Kampala and 5 in New Delhi. Most of staff members in India and Uganda are project leaders or provide project support. All projects are managed in compliance with FIND standard operating procedures.

FIND COUNTRY PROGRAMMES

FIND India

Facilitating access to better diagnosis

FIND is focusing on India as a priority region for demonstration of access to new diagnostic technologies. There is a demand for uptake of rapid diagnostics in the country, and a large amount of expertise, which can be honed with capacity building, is readily available. Also, a large market like India can contribute significantly to bringing down costs rapidly.

The FIND India project is structured in three milestones and 19 checkpoints over four years.

Activities in 2008

FIND India office was inaugurated in August 2007, and the year 2008 marked a rapid transition of FIND into one of the frontrunners amongst the Government of India's Revised National TB Control Programme's (RNTCP) partners.

The following highlights FIND India activities in 2008:

1. Registration of Liaison office under the Ministry of Finance, Government of India
2. Human Resources – The following additional staff were selected and recruited in 2008: Medical Officer, Associate Medical Officer, Malaria Logistics Manager, Data Manager, Part-time logistics officer and Data entry operators.
3. Office support – The office operations were scaled up to provide support by the following consultancies – Regulatory affairs consultant, Customs clearance agent. Travel and meetings by staff were also supported.
4. Activities in collaboration with the Ministry of Health and Family Welfare (MoHFW) : FIND India office worked closely with the Central TB Division of the MoHFW for the following:
 - a. Initiation of demonstration studies implemented at various trial sites and involved trainings, meetings and capacity building activities at laboratories. Activities included trial site assessment & certification and proficiency testing of the laboratory.
 - i. iLED Fluorescence microscopy demonstration study at three sites and 9 microscopy centres. The study completed the following phases in 2008: Baseline, Training and Validation and implementation (partially)
 - ii. Line Probe assay demonstration study was initiated at 3 sites out of 6 planned. The validation phase was underway by the end of 2008
 - iii. Liquid culture implementation project at 2 sites out of 4 planned. Delays in laboratory upgrading to BSL 3 level also delayed uptake of liquid culture at other sites.
 - b. Participation in National Laboratory Committee of the National TB Programme to provide inputs on programme issues and policy development. FIND participated in the 14th and 15th Lab Committee meetings of RNTCP.
 - c. Participation in GFATM round-8 proposal: FIND participated in the proposal development process along with other civil society partners for the GF round-8 with the support of the Central TB Division of the Ministry of Health for a project on Reference lab strengthening. The proposal was not cleared by the GF and there were no comments on FIND activities by GF.
 - d. Preparation of the National TB programme's Laboratory Scale-up plan and MDR-TB management plan (DOTS Plus Plan) derived significantly from FIND inputs especially

related to lab strengthening and MDR-TB diagnosis, under the proposed GF round-8 proposal and under a proposed UNITAID supported diagnostics expansion plan.

- e. Provided laboratory design expertise by consultants to two state level reference laboratories.
5. Implementation of ISO compliant documentation and achievement of ISO certification. FIND India office underwent the ISO audit successfully in 2008.
6. Regulatory Affairs management and logistics and supply chain management: FIND (India) was able to obtain a one year no-objection certificate for all non-registered IVD imports required for FIND projects from the office of FDA of India, namely Drug Controller General (India), DCGI. Such a clearance was obtained under reference of the Ministry of Health & Family Welfare. A dialogue was initiated for customs duty exemption of IVDs under FIND projects. A logistics support agency provided needed support for transportation of IVDs to various parts of the country.
7. Advocacy activities: FIND (India) office participated in a number of advocacy activities in the area of TB control such as participation in the Global Fund Private Sector meeting (India) from 7 to 8 March 2008 at the Sheraton Hotel, New Delhi, Participation at the Partners Forum of Global Alliance for TB Drug development, Intercontinental Hotel, New Delhi, 05 and 06 May 2008, activities leading to formation of the India Coalition Against TB (ICAT) formation and signing of MOU in April 2008, participation in activities leading to FIND (India) being one of the founding member of National Partnership for TB Care and Control Meeting on 04th November 2008 at LRS Institute, New Delhi
8. Activities with PDPs: In India the following PDPs of FIND have a presence – BD (India) and Hain Lifesciences GmbH through their distributor bioMérieux India Ltd. The PDPs provided customer support trainings for their respective products in 2008. These trainings were funded and managed by FIND (India)
9. Data management support for all iLED Fluorescence Microscopy demonstration sites globally was provided (10 countries) by a data management team.

Partners

In India FIND works in close collaboration with the Central TB Division of the Ministry of Health and Family Welfare, under the guidance of WHO India. There are a number of collaborating centres and trial sites which are usually higher level reference laboratories of the National TB Programme and related Health programmes or are academic institutions, and they are – LRS Institute of TB and allied diseases, Delhi, JALMA National Institute of Leprosy and mycobacterial diseases, Agra, State TB Demonstration Centre in BJ Medical College, Ahmedabad, SMS Medical College, Jaipur, Christian Medical College, Vellore, P. D. Hinduja National Hospital and Research Centre amongst others.

Linkages with Indian industry:

FIND (India) became a member of the Association of Diagnostic Manufacturers (ADMI) of India and FIND participated in their meetings. FIND also had interactions with the Confederation of Indian Industry (CII). In 2008, FIND staff visited offices and manufacturing premises of Reamatrix, Bangalore, Tulip Diagnostics, Goa, Span Diagnostics, Surat and Himedia Laboratories, Mumbai, so as to discuss issues of mutual interest and explore avenues of collaboration.

Challenges

The laboratory strengthening activities of the National TB Programme is expected to lead to considerable enhancement of capacity of Indian reference laboratories to undertake culture and DST and use new diagnostic tools for TB. It is expected that FIND will be able to provide technical inputs on uptake of new diagnostics in programme settings from demonstration study observations.

FIND Uganda

Establishment of FIND Uganda office

Following a request from the Ministry of Health (MOH), FIND signed a Memorandum of Understanding with the MOH in April 2008 and established a country office, starting operations with 2 in-country employees, an Office Manager and a Senior Scientist/Head of Laboratory Research. Intensive support was provided by FIND Geneva staff in establishing financial, procurement and project management systems in Uganda, as well as providing technical support to projects.

Between June and August 2008, an additional 5 local staff members were hired: two TB laboratory scientists, a resident advisor for the laboratory strengthening project, and a medical officer and coordinator of malaria diagnostics programme. Consultants were also engaged to work on specific activities, mostly in development of the national laboratory policy.

FIND Uganda moved to new office premises in July 2008 (close to MOH) to accommodate the increased number of staff and planned activities. With support from FIND's Office of Project Management, standard operating procedures were developed and implemented for the FIND Uganda office as well as the TB research laboratory, and were fully harmonized with Geneva SOPs, thus becoming compliant with ISO 13425:2003 and 9001:2008.

In November 2008, the Board for Non-Government Organizations registered FIND as a foreign NGO and issued a Certificate of Registration (1 year).

FIND Uganda hosted the FIND Board Meeting in December 2008 and the official opening of the FIND Research Lab and FIND Office was conducted.

FIND Uganda is involved in a wide range of programmes and activities, from technology development all the way through to gathering evidence for scale-up of diagnostics. Our activities in Uganda include TB, malaria and HAT, not to mention laboratory capacity strengthening as a pre-requisite for introduction of new diagnostic technologies. Details of programmes are given below under the specific projects.

Tuberculosis Research Programme

The FIND TB Research Laboratory was established as a near-to-patient R&D facility in a high-burden setting to increase the availability of specimens and accelerate diagnostics development. The laboratory is based within the National TB Reference Laboratory in Kampala and is a biosafety level 3 facility which meets the requirements recommended by the World Health Organization and is ISO 13425:2003 and 9001:2008 compliant.

The laboratory has several roles: (1) a specimen processing research facility to improve and simplify diagnostic tests for TB; (2) an on-site diagnostics development laboratory; (3) an incubator of new technologies for transfer to the National Tuberculosis and Leprosy Control Programme; (4) a regional training facility for new technologies.

The main focus in 2008 was on renovating and equipping the facility, recruitment and training of laboratory staff and establishing gold standard diagnostic methods including solid and liquid culture, line probe assays for MDR-TB screening and speciation, and LED-based fluorescence microscopy. These activities were successfully completed by the end of 2008.

Initial research studies commenced in 2008 included:

- Genotype MTBDRplus local validation for rapid screening of MDR-TB suspects (partners: National Tuberculosis and Leprosy Programme, Makerere University)
- Comparison of 3 LED-based FM systems (iLED, Lumin and Fraen systems) (partners: National TB and Leprosy Programme, Infectious Disease Institute, Mulago Hospital).

- Preparation for other studies planned for 2009 was also undertaken, including feasibility of magnetic bead concentration method, and development of local partnerships for specimen access for specimen processing development projects. Other activities have included support to NTLP in planning for laboratory capacity strengthening for culture and line probe assays for MDR-TB screening at the regional level.

Malaria Programme

FIND Uganda's malaria programme is focused on providing evidence for scale-up of quality-assured use of rapid diagnostic tests (RDTs), which can be used as a model for implementation in other settings. Two main areas of activity are undertaken: (1) coordination of malaria RDT implementation, (2) malaria diagnostics field research studies.

Coordination of malaria RDT implementation

FIND has worked closely with the National Malaria Control Program and WHO Uganda to bring relevant partners together to deliver evidence-based, quality assured and systematic RDT deployment. FIND's key roles include coordination of quality assurance, procurement and distribution, training and communication, and monitoring and evaluation activities.

A project plan for RDT implementation was prepared. Initial roll-out districts were identified based on epidemiological evidence (hypo-endemic, hyper-endemic and epidemic prone regions) and existing preventive interventions (LLINs, IRS) and partners roles and responsibilities were agreed upon. FIND has initiated and coordinated regular stakeholder meetings for RDT implementation. Through this forum the National Malaria Control Policy and guidelines for malaria parasite-based diagnosis were formulated, reviewed and endorsed by the MoH, and tools for training of national trainers and end-point health workers have been developed. Major stakeholders include: Malaria Consortium (MC), WHO, MSH, Uganda Malaria Research Centre (UMRC), CDC, Uganda Malaria Surveillance Project (UMSP), Infectious Disease Institute (IDI), Joint Uganda Malaria Project (JUMP), National Drug Authority (NDA), National Medical Stores (NMS), Uganda Virus Research Institute (UVRI), Central Public Health Laboratories (CPHL), Population Services International (PSI- now PACE), AMREF, Uganda Health Marketing Group (UHMG) and National Malaria Control Program (NMCP).

FIND has been active in engaging RDT funding, including advocating for RDT funding among in-country partners, and supporting NMCP in Global Fund applications. In procurement and distribution, FIND has advocated for implementation and monitoring of storage and transportation conditions for RDTs, and coordinated distribution plans and harmonization of RDT logistics training and lot testing. FIND has coordinated the dissemination of the National Malaria Control Policy guidelines on malaria case management, lot testing results of the RDTs to health workers and training institutions, and production of training tools, treatment guidelines, and RDT job aids, and district based sensitization of the community about malaria diagnosis. FIND has worked with the National Drug Authority to produce the National Malaria RDT Regulatory Guidelines.

Malaria Diagnostics Field Research Studies

Planning for a number of field research studies was initiated in 2008.

1. Evaluation of blood collection and transfer devices for use with malaria RDTs

This study aims to evaluate a range of devices for ease of use, blood safety, and accuracy and consistency of blood volume transfer. The purpose of this evaluation is to identify the most appropriate blood transfer device/s for use with malaria RDTs in routine health care, and to provide this information to RDT manufacturers and purchasers to encourage marketplace availability of such devices.

2. Pilot field evaluation of job aid and training messages for positive control wells (PCWs)

PCWs have been developed for use as a point-of-care quality control tool, as part of a proposed tiered national quality assurance program for malaria RDTs. PCWs are designed to be used by health workers to test stocks of RDTs stored and used at their health facilities, to ensure their validity and accuracy.

3. RDTs in pregnancy

Malaria prevention measures for pregnant women are necessary and available, but the efficacy/effectiveness of current approaches appears to be dropping with parasite resistance. Preliminary evidence suggests that detection of parasite antigen may provide the best indicator of clinically significant infections and predict pregnancy outcomes. Therefore, screening with RDTs may offer an accurate and practical way to identify pregnant women who will benefit from targeted therapy for placental malaria infection. FIND is working with WHO/TDR, advised by key researchers in the area, to develop a protocol to test this hypothesis, with potential for significant policy and public health impact. Participating clinical sites have been identified in Uganda, Nigeria and Burkina Faso.

Laboratory strengthening

Current gaps in laboratory services in Uganda include the lack of a guiding framework for laboratory services, shortages in skilled human resources, infrastructure, equipment, supplies, and funding. Strengthening of the laboratory services is a pre-requisite for successful introduction of new diagnostics. FIND has supported the MOH in development of a National Health Laboratory Services Policy (NHLSP) and a National Health Laboratory Strategic Plan. From June 2008, FIND has been actively engaged in leading the process of developing the NHLSP through mobilization of stakeholders and partners. Draft 1 of the Policy, which was produced at the end of August 2008, went through several reviews during the latter part of the year, with a final draft to be completed in April 2009. It is intended for the new Laboratory Policy to be launched September of 2009.

Continuous engagement of the many stakeholders in the laboratory sector at all stages of the process has been critical during the process of developing the NHLSP and Strategic Plan. Key stakeholders include: World Health Organization –Country office, Central Public Health Laboratories, National Tuberculosis Reference Laboratory, Center for Disease Control and Prevention – Uganda, African Medical Research Foundation, Joint Clinical Research Center, AIDS Control Program, Uganda Virus Research Institute, Infectious Diseases Institute, Medical Training Institutions, and Health Professionals' Associations.

Towards the end of 2008, development of the National Laboratory Strategic Plan was initiated, with FIND playing a leading role in engagement and coordination of stakeholders. The process is ongoing, with development of a first draft in February 2009.

FIND is an active member of the National Laboratory Technical and Advisory Committee, charged with advising the Ministry of Health on laboratory systems improvements.

Laboratory strengthening in Ethiopia

Based on the consensus reached between the Ministry of Health and government of Ethiopia and FIND (EXPAND-TB), a Memorandum of Understanding was signed between the Ethiopian Health and Nutrition Research Institute (EHNRI) in Addis Ababa and FIND on 29th January 2008. The objective of this partnership was to establish a state-of-the-art, National Tuberculosis Reference Laboratory (NTRL), one laboratory in a specialized TB hospital (St Peter's) and four regional tuberculosis reference laboratories. The various activities for the central and regional labs were rapid TB culture using MGIT, species identification of *M. tuberculosis* complex strains using Capilia TB test and identification of *M. tuberculosis* and detection of MDR TB using line probe assay. In addition, following the installation of negative pressure facility, the NTRL is to perform drug susceptibility testing using MGIT 960 system and act as a referral centre for other laboratories. The objectives of the activities to be performed at the diagnostic centre level also included the establishment of EQA for smear microscopy and to evaluate LED based fluorescent microscopy at three sites.

The assessment of the six laboratories was performed by FIND in consultation with EHNRI and recommendations were made for renovation and establishment of negative pressure facility. For negative pressure installation a company from South Africa, Clean Room Maintenance (CRM) was selected by the government of Ethiopia and the process was started based on agreement made between EHNRI and CRM.

For newer diagnostics and safety issues, four people from different laboratories were trained in ACLIT, Johannesburg. Training was also undertaken in EHNRI on LED based microscopy and fourteen individuals selected from EHNRI, two health centres, one hospital and one regional laboratory were trained.

A study was undertaken in selected sites of Amhara Region to compare Lot Quality Assurance System sampling method (LQAS) with the one practiced by Ethiopian TB control programme.

FIND participated in the revision and writing of documents pertaining to TB laboratory activities in Ethiopia. These included AFB microscopy manual, TB EQA guidelines, smear microscopy job aid and ABF microscopy training package.

Johns Hopkins University assisted St. Peter's Hospital in establishing negative pressure and improving the laboratory infrastructure facilities and provided some basic equipment. FIND procured equipment for liquid culture and line probe assay for St Peter's and for the line probe assay for EHNRI. FIND also provided some basic laboratory equipment for EHNRI and gave further support to the laboratory program by providing a full time, on site consultant.

Communications and Advocacy

The year 2008 marked FIND's 5th anniversary since it was launched at the World Health Assembly in May 2003. For this occasion, FIND published a special anniversary brochure - *Delivering on the promise 2003-2008*, which reviewed the many milestones and achievements in the first 5 years of the organization's existence. A modified logo and a new graphic line were introduced. These aim to convey in a clearer and more effective way the organization's values and objectives. Work was also begun on a new FIND website, which was launched in early 2009. The new website distinctly reflects the recent rebranding and includes improvements with regards to navigation, search options, content and structure.

Along with these efforts, FIND's Scientific Officers were very active in participating and presenting at international conferences and published extensively; they also reported on the first regional success stories providing evidence for scaling up laboratory and diagnostics capacity.

Key advocacy and media events

FIND hosts media briefing

A media briefing on new methods for diagnosing diseases of the poor was held on 10 June 2008 at the FIND offices in Geneva.

Speakers at the press briefing were Drs. Giorgio Roscigno, CEO, FIND, Bernard Mach, FIND Board Member, Founder and Chairman of Novimmune, Mark Perkins, Chief Scientific Officer, FIND, and Jean-Charles Sanchez, Head of the Biomedical Proteomics Research Group, University of Geneva. The main objective of the press briefing was to present FIND's groundbreaking work through its collaborative project with the research group at the University of Geneva.

39th Union World Conference

FIND participated actively in the 39th Union World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union) which was held at the Palais des Congrès in Paris, France, from 16 to 20 October 2008. This year's theme "Global threats to lung health: the importance of health system responses". FIND notably organized a special FIND Scientific Forum on Recent Advances in TB Diagnostics to also mark the foundation's 5th anniversary. Several presentations were given by FIND staff members and partners who provided an overview of progress made on TB diagnostics and also sponsored a meeting on MTBDR_{plus} assay. FIND also had a booth during the conference.

Other key advocacy and media events during the conference included:

- A "Meet the experts" session hosted by Dr. Mark Perkins on the "Development of Diagnostics".
- A training workshop for journalists organized by the STOP TB Partnership on the role of the media in fighting TB. Jewel Thomas, FIND Communications Officer (TB), and other communications and advocacy representatives from Aeras and The TB Alliance also participated in the workshop.
- A FIND-Zeiss media briefing on the jointly developed fluorescence microscope based on LED technology.
- An open session on new tools at the "Advocate's Corner".

FIND rings the closing bell with partners to mark World TB Day

The New York Stock Exchange marked World TB Day on 24 March by inviting Dr. Jorge Sampaio, the UN Secretary General's Special Envoy to Stop TB, Dr. Edward J. Ludwig, Chairman, President and CEO of BD (Becton, Dickinson and Company), and Dr. Giorgio Roscigno, CEO of FIND to ring the closing bell.

Capitol Hill TB Diagnostics Briefing

FIND was invited to a congressional briefing on "The Urgent Need to Stop TB: Increasing Diagnostic Testing and Developing New Diagnostic Tools" on 22 January 2008 in Washington, DC. Dr Giorgio Roscigno delivered a presentation on the status and challenges of TB diagnosis and presented FIND's TB diagnostic pipeline.

FIND participates in TB Seminar in Barcelona

FIND participated in a TB seminar on 19 November 2008 with other PDPs and health organizations and civil society representatives in Barcelona, Spain. Organized by Planeta Salud, the aim of the event was to increase awareness of tuberculosis and the need for improved tools and concerted efforts to control the disease. Several representatives of the Spanish Public Health and Foreign Affairs departments also participated in the seminar. FIND was represented by Dr Gerd Michel, FIND Senior Technology Officer and Jewel Thomas, FIND Communications Officer (TB).

HAT programme

Diagnosis of human African trypanosomiasis, or sleeping sickness, remains a major and neglected problem. At present, diagnosis and subsequent treatment cannot be properly applied because existing tools are difficult to implement in remote, impoverished settings where the impact of the disease is greatest. Control of HAT depends primarily on a combination of active and passive case detection and curative treatment to reduce or remove human reservoirs of infection from the population. In addition, most of the drugs used to treat sleeping sickness are not only toxic but also difficult to administer. To address this challenge, not only better drugs, including possible oral regimens, are urgently needed but also better diagnostic tools.

Major breakthrough in staging sleeping sickness

Dr. Jean-Charles Sanchez, head of the Biochemical and Proteomics Research Group (BPRG) at the University of Geneva, and his team were carrying out analysis on cerebrospinal fluid (CSF) from 100 sleeping sickness patients when they discovered that a number of molecules were consistently elevated in patients who were in late stage disease. Among 16 molecules studied, IP-10 can distinguish between early and late stage patients with a sensitivity of 91% and a specificity of 100%. While this discovery is significant on its own, more exciting information was generated when the scientists used statistical methods to determine what would happen if they combined the results of two or more molecules. The outcome was a panel of three molecules, IP-10, GSTP1 and IL-8, which together can distinguish late stage patients with a sensitivity of 97% and a specificity of 100%. This collaborative effort is being made together with Makerere University in Uganda and the Institute of Tropical Medicine (ITM) in Belgium, and is being funded by FIND.

Manufacture of diagnostic kit for sleeping sickness in the DRC

Since 2006, when we initiated collaboration with the Institute of Tropical Medicine (ITM) in Antwerp and the Institut National de Recherche Biomédicale (INRB) in Kinshasa, DRC, we have made tremendous progress at improving the capacity of INRB to manufacture the mAECT kit. Our support has included refurbishment of the laboratory for a new manufacturing line of minicolumns (one of the components of the mAECT kit), providing training for technicians, setting up a manufacturing quality control process, and review of costs to guarantee sustainability of production. The INRB has over the past year been marketing and distributing mAECT in the DRC, the country most severely affected by sleeping sickness, and to other endemic regions on the continent.

Taking molecular diagnostics to the treatment center

FIND and partners are intensifying efforts to develop a simplified DNA amplification test that allows rapid detection of parasites with high accuracy. One of the reasons loop-mediated isothermal amplification (LAMP) of trypanosome DNA is becoming the most exciting new addition to the diagnostic portfolio for HAT is the fact that blood can be used as the starting material for the amplification reaction, and the test can be used easily in any endemic country laboratory and by technicians with minimal experience.

Working with the African Union to drum up support for HAT

In the area of neglected diseases, there is general agreement that speeding up the process of sleeping sickness elimination can only be done through the combined efforts of stakeholders, including researchers, governments of endemic countries, healthcare providers, and communities that are at risk of infection in endemic areas. In January of this year, FIND signed a Memorandum of Understanding with the African Union Commission (AUC) to step up efforts being made to eradicate the disease from sub-Saharan Africa. The initiative to increase awareness of the problem and find solutions that will guarantee elimination of HAT is led by the Pan African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC) coordination office of the AUC. PATTEC works with African governments that are members of the AU and encourages them to unite and mount sustained action to tackle this disease, and all its ramifications, on a continent-wide basis. While the PATTEC initiative has generated the political goodwill that has contributed immensely to the achievements in trypanosomiasis control that are

visible today, many endemic countries still fail to give adequate priority to control of the disease in their health sector programmes. PATTEC, with FIND support, has developed a strategic plan on advocacy for HAT, which will be implemented over the next three years.

A strategic Plan on Advocacy (SPA) for African trypanosomiasis was developed and launched at a stakeholders' workshop in May 2008. Twelve endemic countries have nominated contact persons, who are responsible for implementation of the SPA in their countries, with support from both FIND and PATTEC. An induction meeting of the contact persons was held in September 2008. Each of the participating countries is developing a work plan for implementation of the SPA over the next year.

British Society for Parasitology meets in Newcastle, UK

Scientists met in Newcastle at the spring meeting of the British Society for Parasitology from 30 March- 02 April 2008 to confer about new developments in research on trypanosomiasis, leishmaniasis and malaria. FIND sponsored the meeting and gave poster presentations on strides being made together with other partners in the search for new tests for the diagnosis and staging of HAT. The approaches being explored include detecting whole parasites or antigens that are common to *T.b. gambiense* and *T.b. rhodesiense*, the parasites that cause HAT.

Malaria programme

A major advance in malaria diagnosis has been the development of rapid diagnostic tests (RDTs) which can detect malaria antigens in a finger prick blood sample. However, the proliferation of test manufacturers has presented difficulties for national malaria control programs in determining which tests are reliable. In addition, many of the RDTs are susceptible to degradation at temperatures commonly found in countries where malaria is a problem.

FIND's malaria programme, undertaken in partnership with the WHO, has been directed at creating a global solution to ensure the quality of malaria rapid diagnostic tests (RDTs) used in national disease control programs. The programme aims to evaluate the performance of existing RDTs and to identify improvements that can be incorporated into new tests. Large scale product testing has begun in collaboration with the U.S. Centers for Disease Control and Prevention and the Hospital of Tropical Diseases in London. The program has already yielded the following results:

- Establishment of a globally-representative reference collection of blood from infected individuals, as well as extensive characterization and gene sequencing to form a stable reference panel that can be used to reproducibly evaluate RDTs.
- To ensure the quality of test kits already purchased and held by national disease control programmes, three regional lot-testing sites – in the Philippines, Cambodia, and Ethiopia – are supported to carry out rapid quality checks of RDTs after purchase for national programs.
- A development and supply agreement has been signed to provide positive control wells; a simple tool that will empower community health workers to assess the quality of RDTs at the point of use of the test kits. Large scale field trials of a prototype are that can be used to diagnose complex cases, support clinical trials and detect infections with low parasite numbers.

FIND and partners begin quality testing of rapid malaria tests

A collaboration between WHO and FIND to develop quality assurance systems for malaria diagnostics has led FIND to begin implementing an accelerated three-step solution to introduce well performing malaria RDTs in national disease control programs. These urgently needed mechanisms are intended to a) indicate which RDTs are manufactured with the quality and performance needed by public health programs (Evaluation of RDTs); b) determine whether individual production lots of RDTs are performing up to expectations after being shipped to countries but before they are used in remote field sites (Lot-testing of RDTs); and c) provide technicians and health workers with the means not only to verify that the RDTs they are using are still satisfactory but also to prepare and interpret them accurately (use of Positive Control

Wells). Once their accuracy is assured, other matters concerning RDT usage can be addressed, thus clearing the way for the revolutionary potential these tests can have in the management of febrile disease in malaria-endemic regions.

FIND and WHO establish lot testing infrastructure

Lot testing centers have been established through collaboration between FIND and WHO in order to ensure that only quality RDTs are used in the field. Lot testing means:

- Good quality RDTs can better guide malaria treatment in fever case management.
- Accuracy of RDTs saves lives by guiding correct treatment.
- Lot-to-lot variation has been noted in RDTs and transport to countries can affect test performance. It is therefore advised to check RDT quality *before* tests go to the field.
- Guaranteeing the quality of RDTs gives clinicians, health workers and patients the assurance necessary to base treatment on RDT results.
- To achieve and maintain confidence in RDT-based diagnosis, a system for quality control and performance monitoring of RDTs should be in place.
- National malaria control programmes can now access quality control and performance monitoring of RDTs in the form of lot testing.

Using positive control wells to confirm quality of rapid tests

FIND and WHO are working with research partners to develop stable, positive control wells (PCWs) containing the major target antigens of commercially-available RDTs. These wells can provide a simple, low-cost method to verify RDT performance and guarantee quality-monitoring from manufacture to the end-user. On April 9 of this year, FIND organized a meeting between product development partners at the Hospital for Tropical Diseases (HTD) in London. During the meeting, a license and technology agreement was signed with the non-profit National Bioproducts Institute (NBI), and the partners agreed the terms and conditions for a development and supply agreement with ReaMetrix. Development of PCWs will be followed by large-scale field trials, the results of which are anticipated in 2010.

Molecular tools for malaria diagnosis

The Loop-Mediated Isothermal Amplification (LAMP) is a simple molecular diagnostic test developed by Eiken Chemical Co. from Japan. This technology is highly sensitive and specific, faster than PCR, isothermal, requires minimal processing and minimal instrumentation, and allows result detection with naked eye. LAMP for malaria is intended to be a field reference standard against which RDTs and other malaria diagnostics could be evaluated, to confirm the presence or absence of malaria parasites in complex cases, and to support clinical trials.

The first step of this project during the last year was the identification of suitable gene targets in *Plasmodium* species to be amplified by LAMP. This work has been done by the London Hospital of Tropical Diseases (LHTD) in England with the support of Eiken. Primers to amplify 16 different genes were designed taking into account the known sequence data for *P. malariae* and *P. ovale* genomes. Seven primer sets amplified >10 parasites/ μ l in less than 60 minutes: two pan-specific, two specific for *P. falciparum*, two specific for *P. vivax*, and one specific for *P. malariae*. These results allowed the selection of a single gene to produce optimized primers able to detect >2 parasites/ μ l in 30 minutes.

Primer sets amplifying *Plasmodium* genus and *P. falciparum* have been used to test different methods for DNA extraction. A very simple method requiring just boiling of anti-coagulated blood or blood dried in a filter paper was established. The evaluation of optimized conditions of sample processing and LAMP amplification in a real time environment where clinical samples are tested as they arrive is planned to start at the beginning of 2009.

For the completion of assay development and commercial manufacture, Eiken has agreed to carry out activities to get to a manufacturable malaria LAMP product by 1 year. They have presented a timeline that showed they would be ready for external feasibility studies in June 2009, plus 6 months to finalize manufacturing transfer for production; ie ready to supply the market end 2009.

Streamlining FIND's brand identity

This is a short project which was implemented by the communications team with the support of a part-time consultant and an intern. The project arose out of the necessity to streamline our communications tools. The project aimed at 1) creating a clear identity that projects the image and attributes of FIND; and 2) establishing standards and providing guidelines to ensure consistent application of its new identity system across all communications tools. The project drew to a close at the end of May.

FIND increases staff to meet growing project demands

In order to manage existing projects and future engagements, including laboratory preparedness, we have been compelled to increase the number of our staff.



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**Foundation for Innovative New
Diagnostics (FIND), Geneva**

*Financial Statements for the
Year ended 31 December 2008
and Auditor's Report*

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 income, cash flow statement and notes for the year ended 31 December 2008.

Foundation Board'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 statutes 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.

Opinion

In our opinion, the financial statements for the year ended 31 December 2008 comply with Swiss law and the statutes of the Foundation.

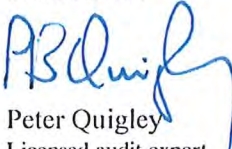
Report on Other Legal Requirements


We confirm that we meet the legal requirements on licensing according to the Auditor Oversight Act (AOA) and independence (article 728 of the Swiss Code of Obligations) and that there are no circumstances incompatible with our independence.

In accordance with article 728a paragraph 1 item 3 of the Swiss Code of Obligations 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 Foundation.

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

Deloitte SA


Peter Quigley
Licensed audit expert
Auditor in charge


Michael Salama
Licensed audit expert

August 10, 2009

Attached : Financial Statements (balance sheet, statement of income, cash flow statement and notes)

FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)

Geneva, Switzerland

BALANCE SHEET AS AT 31 DECEMBER 2008

(all amounts in US dollars)

	<u>2008</u>	<u>2007</u>
<u>ASSETS</u>		
Current assets		
Cash on hand	2 945	2 730
Bank Current accounts	1 298 072	399 281
Short-term Deposits	20 890 000	19 411 800
Rental Guarantee Deposit	77 965	72 722
Accounts receivable	695 476	429 780
Prepayments	2 880 087	30 267
	<hr/>	<hr/>
	25 844 545	20 346 580
Fixed assets		
Office furniture & fittings	45 470	40 706
Computers & printers	45 973	67 210
Electrical installations	7 504	16 605
Fax machine & telephones	1 683	3 661
	<hr/>	<hr/>
	100 630	128 182
Patents	30 828	38 535
	<hr/>	<hr/>
Total assets	<hr/> <hr/>	<hr/> <hr/>
	25 976 003	20 513 297
 <u>LIABILITIES AND CAPITAL</u>		
Current liabilities		
Accounts payable	2 435 894	1 022 199
Accrued expenses	297 670	169 862
Contributions received in advance	20 924 076	15 931 019
	<hr/>	<hr/>
	23 657 640	17 123 080
Capital and reserves		
Capital	40 430	40 430
Accumulated surplus	2 277 933	3 349 787
	<hr/>	<hr/>
Total liabilities and capital	<hr/> <hr/>	<hr/> <hr/>
	25 976 003	20 513 297

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

FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)

Geneva, Switzerland

STATEMENT OF INCOME AND EXPENDITURE FOR THE YEAR ENDED 31 DECEMBER 2008

(all amounts in US dollars)

	<u>2008</u>	<u>2007</u>
<u>INCOME</u>		
Contributions income	27 370 155	18 392 263
Sundry income	416 121	572 608
Exchange gains	-	302 379
Total income	<u>27 786 276</u>	<u>19 267 250</u>
<u>EXPENDITURE</u>		
Analytical & Project Work		
Tuberculosis	18 403 300	11 915 954
Human African Trypanosomiasis	3 591 018	2 042 103
Malaria	3 541 023	1 621 032
HIV	24 868	6 410
	<u>25 560 209</u>	<u>15 585 499</u>
Information & Communication		
Publications production	147 236	84 197
Website	26 970	15 185
Communications consultants	24 303	46 431
	<u>198 509</u>	<u>145 813</u>
Governing & Advisory Bodies		
Foundation Board	43 081	37 744
	<u>43 081</u>	<u>37 744</u>
General Administration		
Staff costs and travel	1 263 442	791 564
IT expenses	304 195	205 903
Photocopies, stationery, printing & sundries	117 605	153 938
Rent of premises	391 115	334 198
Repairs & maintenance	77 886	116 226
Telecommunications	118 563	107 964
	<u>2 272 806</u>	<u>1 709 793</u>
Finance & Service Expenses		
Auditing & accounting	61 720	45 024
Bank charges	19 670	12 534
Exchange losses	308 603	-
Legal fees	140 152	71 186
Insurance	164 300	110 645
	<u>694 445</u>	<u>239 389</u>
Depreciation	89 080	66 743
Total expenses	<u>28 858 130</u>	<u>17 784 981</u>
(Excess) surplus of income over expenditure for year	(1 071 854)	1 482 269
Accumulated surplus brought forward	3 349 787	1 867 518
<u>Accumulated surplus carried forward</u>	<u>2 277 933</u>	<u>3 349 787</u>

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

FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)

Geneva, Switzerland

CASH FLOW STATEMENT FOR THE YEAR ENDED 31 DECEMBER 2008

(all amounts in US dollars)

	<u>2008</u>	<u>2007</u>
Excess of income over expenditure for the year	(1 071 854)	1 482 269
Add back non-cash charge - depreciation	89 080	66 743
	<u>(982 774)</u>	<u>1 549 012</u>
Cash flows - operating activities		
Increase/(decrease) in contributions in advance	4 993 057	4 768 559
Increase/(decrease) in accounts payable	1 413 695	(182 158)
Increase/(decrease) in accrued expenses	127 808	25 048
(Increase)/decrease in accounts receivable	(265 696)	(273 604)
(Increase)/decrease in prepayments	(2 849 820)	52 622
	<u>3 419 044</u>	<u>4 390 467</u>
Cash flows - investing activities		
Additional office furniture & fittings	(23 251)	(6 808)
Additional computers & printers	(30 570)	(58 989)
New electrical installations	-	-
(Increase)/decrease in rental guarantee account	(5 243)	(5 601)
	<u>(59 064)</u>	<u>(71 398)</u>
<u>Net increase in cash and cash equivalents for year</u>	<u>\$ 2 377 206</u>	<u>5 868 081</u>
Cash and cash equivalents at start of year		
Cash on hand	2 730	3 797
Current accounts & short-term deposits	19 811 081	13 941 933
	<u>19 813 811</u>	<u>13 945 730</u>
Cash and cash equivalents at end of year		
Cash on hand	2 945	2 730
Current accounts & short-term deposits	22 188 072	19 811 081
	<u>22 191 017</u>	<u>19 813 811</u>
<u>Net increase in cash and cash equivalents for year</u>	<u>\$ 2 377 206</u>	<u>5 868 081</u>

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

FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)

Geneva, Switzerland

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2008

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 22 July 2003.

FIND's mission is to support and promote the health of people in developing countries through the development and introduction of new but affordable diagnostics for infectious diseases.

FIND is exempt from federal and cantonal income and capital taxes.

2. Significant accounting policies

2.1 Basis of presentation The financial statements are prepared under the historical cost convention.

2.2 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.

2.3 Patents The 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 over their remaining useful life (five years).

2.4 Foreign currency Accounting records are maintained in US dollars. Income 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 2008 the rate of exchange used for the Swiss franc, the main foreign currency for 2008, was USD/CHF = 1.06 (2007 – 1.13). Exchange gains and losses are included in the determination of net income.

2.5 Recognition of revenue Contributions received are recorded according to the grant period agreed with donors, with amounts received relating to periods extending beyond balance sheet date recorded as contributions received in advance. Donor agreements in effect at 31 December 2008 provide for a total of USD 35.9 million to be paid to FIND between January 2009 and August 2012.

FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)

Geneva, Switzerland

NOTES TO THE FINANCIAL STATEMENTS

(continued)

2.6 Accounts payable and accrued expenses With the exception of emoluments payable to staff, which are accounted for when paid, accounts payable and accrued expenses represent expenditures chargeable in the 2008 financial year, for which invoices were not received for payment before year-end. Settlements are charged to the accruals in the following financial period.

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

2.8 Projects Payments to project partners during 2008 under contracts signed up to 31 December 2008 totalled USD 14,370,210 (2007 – USD 8,580,367). Commitments at 31 December 2008 for future payments under those contracts total USD 10,766,905 (2007 – USD 8,377,847).

3. Fixed assets and intellectual property

3.1 Fixed assets as at 31 December 2008 were as follows:

	<u>2008</u>	<u>2007</u>
Cost price		
Office furniture & fittings	106,582	83,331
Computers & printers	185,702	155,132
Electrical installations	45,509	45,509
Fax machine & telephones	9,891	9,891
	-----	-----
	347,684	293,863
<u>Less:</u> Accumulated depreciation	247,054	165,681
	-----	-----
Net book value	USD 100,630	128,182
	=====	=====

Fire insurance cover as at 31 December 2008 was USD 124,528 (2007 – USD 116,814).

3.2 Intellectual property as at 31 December 2008 was as follows:

	<u>2008</u>	<u>2007</u>
Patents – cost price	53,949	53,949
	-----	-----
	53,949	53,949
<u>Less:</u> Accumulated depreciation	23,121	15,414
	-----	-----
Net book value	USD 30,828	38,535
	=====	=====

FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS (FIND)

Geneva, Switzerland

NOTES TO THE FINANCIAL STATEMENTS

(continued)

4. Pension Fund liabilities

No amounts were due to the pension fund at 31 December 2008 (2007 – nil).

5. Rent commitments

At 31 December 2008 FIND had future rent commitments totalling USD 198,728 up to 30 June 2009 (2007 – USD 518,510).

6. 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.

7. Events subsequent to 31 December 2008

There were no events occurring subsequent to 31 December 2008 which could have a material impact on the understanding of these financial statements.

FIND Board of Directors, Management and Staff

As at 31 December 2008

Board of Directors

Dr. Gerald Moeller (Chairman of the Board)

Dr. Jan Gheuens (Member)

Dr. Bernard Mach (Member)

Dr. Callisto Modavo (Member)

FIND Team Geneva

Giorgio Roscigno: Chief Executive Officer

Eric Adam: Project Manager and Regulatory Affairs

Audrey Albertini: Scientific Assistant for Malaria Diagnostics

Sylvain Biéler: Project Manager

Catharina Boehme: Senior Medical Officer

Nora Champouillon: Logistics Officer

Louisa Chaubert: Accounting Manager

Diana Choa: Personal Assistant to the CEO

Herbert Clemens: Chief Financial Officer

Rossana Gambin: Human Resources Officer

Iveth Gonzalez: Scientific Officer, Malaria Programme

Beatrice Gordis: Communications Officer – HAT & Malaria

Julian Gordon*: Medical Diagnostic Technologies & IP

Linda Hinni: Accounting Assistant

Peter Koller*: Quality Manager

Heather Alexander Konopka*: Health Scientist

Evan Lee: Senior Medical Officer

Gerd Michel: Senior Technology Officer

Pamela Nabeta: Associate Medical Officer

Rahul Narang*: TB Laboratory Support

Joseph Ndung'u: Head of HAT Diagnostics Programme

Richard O'Brien: Head of Product Evaluation and Demonstration

Madhukar Pai*: Consultant for latent TB infection

C.N. Paramasivan: Head of TB Laboratory Support

Mark Perkins: Chief Scientific Officer

Antoine Pierson: Senior Scientist, Project Leader, Lab Support - TB

Bärbel Porstmann: Senior Operating Officer

Sharon Saaks: Document Controller

Hoon Sohn*: Health Economist

Akos Somoskövi: Senior Scientist, Project Leader, Lab Support - TB

Ranald Sutherland*: Technology and Business Development

Jewel Thomas: Communications Officer - TB

Alessandra Varga*: Events and Image Development

Julie Vercruysse: TB Scientific Team Administrator

Balasangameshwara Vollepore*: Expert, TB Laboratory Support

Hanna Yirga: HAT Scientific Team Administrator

Diego Zallocco*: TB Projects Specialist

FIND Team Uganda

Julius Patrick Ademun: Scientific Officer

Heidi Albert: Senior Scientist, Head of Laboratory Research

Caroline Asimwe: Coordinator-Malaria Diagnostics Implementation Project

Heidi Hopkins: Medical Officer

George Lukyamuzi: Scientific Officer

Zoe Nakuya: Lead Advisor

Vinand Nantulya*: FIND Global Access

Jean Nsekera: Office Manager

FIND Team India

Jacques Debayle: Liaison Office Manager

Prabhat Deva: Logistics Data Manager for Malaria

Ralf Linke*: Quality Manager

Yamuna Mundade: Medical Officer

R. Narayanaswamy*: Deputy Drugs Controller

Shailaja Paramathma: Administrative Assistant

Neeraj Raizada: Associate Medical Officer

* Consultants

FIND Donors

- Bill & Melinda Gates Foundation, USA
- European Union
- Google, USA
- Government of the Netherlands
- Irish Aid, Ireland
- UNITAID

