FIND
Because diagnosis matters

**STRATEGY
FOR NEGLECTED
TROPICAL DISEASES**

2015-2020

ABOUT FIND

FIND was established in 2003 to bridge existing development gaps for essential diagnostics by initiating and coordinating research and development (R&D) projects in collaboration with the international research community, the public sector and the *in vitro* diagnostics industry. Today, FIND is a leading partner across the value chain of diagnostics development and delivery. We have programmes in tuberculosis and lower respiratory tract infections, malaria and acute febrile syndrome, Hepatitis C, neglected tropical diseases and Ebola. We also have mini-portfolios in areas affecting reproductive and child health: HIV; sexually transmitted infections; and infections and nutritional deficiencies in children under five years. At FIND, we envision a world where diagnostics guide the way to health for all people. We turn complex diagnostic challenges into simple solutions and transform lives by overcoming diseases of poverty. To do this we focus on four strategic goals throughout all the disease areas in which we work:

■ Catalyse development

Identify needed diagnostic solutions and remove barriers to their development.

■ Guide use & policy

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

■ Accelerate access

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

■ Shape the agenda

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

FIND's Vision

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

FIND's Mission

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

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ABBREVIATIONS

CL	cutaneous leishmaniasis
CSF	cerebrospinal fluid
ELISA	enzyme-linked immunosorbent assay
HAT	human African trypanosomiasis
ICT	immunochromatographic tests
LAMP	loop-mediated isothermal amplification
LED FM	light emitting diode fluorescence microscopy
MDA	mass drug administration
NTDs	neglected tropical diseases
PCR	polymerase chain reaction
PKDL	post-kala azar dermal leishmaniasis
RDT	rapid diagnostic test
TLC	thin layer chromatography
ToC	Test of cure
VL	visceral leishmaniasis
WHO	World Health Organization
WHO/TDR	World Health Organization's Special Programme on Research and Training in Tropical Diseases

ABOUT NEGLECTED TROPICAL DISEASES

Neglected tropical diseases (NTDs) are a group of infections that are endemic among low-income populations in developing regions of the world, especially Africa, Asia and the Americas. These diseases are classified as neglected because they have not been adequately addressed by public health interventions or drug and diagnostics developers. Of the 149 countries and territories where NTDs are reported, at least 100 countries are endemic for two or more diseases, with 30 countries endemic for six or more. Today, NTDs cause unacceptable human suffering and death in all affected regions. In sub-Saharan Africa, for example, the impact of NTDs as a whole is comparable to the global burden of both malaria and tuberculosis. Through co-infection, many NTDs also make diseases such as HIV/AIDS and tuberculosis more deadly. While a number of preventive measures or medical treatments for these diseases are available in high-income countries, these are not universally accessible in low- and middle-income countries.

Despite their medical diversity, the 17 NTDs that are prioritized by the World Health Organization (WHO) have been grouped together based on their tendency to co-exist geographically and to share certain criteria. Grouping several diseases together facilitates estimation of collective burden and relevance to public health, and raises their profile to enhance resource mobilization. Despite the burden of NTDs, other diseases such as HIV/AIDS, tuberculosis and malaria have generally received more funding for treatment and research.

The global health community has recently recognized the high burden of NTDs and increased efforts to combat them. In 2012, governments, non-profit organizations, pharmaceutical companies and the WHO signed the London Declaration to support WHO's roadmap to eradicate, eliminate, or bring under control 10 NTDs. WHO's 2012 roadmap on NTDs aims to eradicate Guinea worm and eliminate visceral leishmaniasis (in the Indian subcontinent), lymphatic filariasis, leprosy, sleeping sickness and blinding trachoma by 2020. Schistosomiasis, soil transmitted helminthiases (STHs), Chagas disease and river blindness are targeted for control by 2020. Following the London Declaration, there has been a significant increase in funding for drugs for NTDs that are controlled through mass drug administration (MDA), but funding for diagnostics for early detection remains inadequate.

A major challenge to fulfilling the goals of the London Declaration lies in the lack of readily available, easy-to-use, reliable and low-cost diagnostic tools to identify infected patients, detect disease re-emergence, monitor the impact of MDA and guide delivery of appropriate control measures. Diagnostics are essential in assessing the intensity of transmission, supporting decision-making on when MDA programmes should be stopped, verifying the cessation of transmission, and monitoring to ensure sustained elimination. Diagnostics provide objective and quantitative data for discerning the presence or absence of a disease and guiding treatment decisions. For NTDs such as leprosy, sleeping sickness, leishmaniasis and Chagas disease, which are not controlled through MDA, diagnostics are required for identification of individual patients in order for treatment to be given. In addition, among the seven top research priorities identified by the WHO's Special Programme for Research and Training in Tropical Diseases (WHO/TDR) for Chagas disease, human African trypanosomiasis (HAT) and leishmaniasis, the first is *Diagnostics for case detection and characterization, including tests for drug resistance and tests of cure.* Thus, for the London Declaration's goals to be realized, addressing the diagnostic needs for these NTDs has become a major priority.

PAST AND CURRENT ACTIVITIES

FIND began working on diagnostics for NTDs in 2006 when HAT became the first NTD to be included in its portfolio. Leishmaniasis was added as a core disease in 2010, Chagas disease in 2012 and Buruli ulcer in 2013.

Since the launch of its HAT programme, FIND has supported:

- Development and introduction of a first-generation rapid diagnostic test (RDT) to screen suspected individuals and at-risk populations for *T.b. gambiense*, the chronic form of HAT;

- Development and introduction of light-emitting diode fluorescence microscopy (LED FM) and associated sample preparation methods;

- Development and introduction of a molecular test to detect parasite DNA in blood samples based on the loop-mediated isothermal amplification (LAMP) platform;

- Identification of cerebrospinal fluid (CSF) biomarkers for staging and follow-up and development of a prototype rapid test;

- Establishment of a sample bank with WHO and sample collections with two academic partners;

- Initiation of implementation research projects in the Democratic Republic of the Congo (DRC), Uganda, Malawi, Guinea, Chad, Nigeria and South Sudan.

FIND's current work on HAT diagnostics focuses on:

- Implementation research in endemic countries using a number of new technologies in combination, including the first generation RDT, LED FM and LAMP as part of innovative strategies to improve coverage of the population screened and to accelerate disease elimination;

- Development of a second-generation RDT for screening HAT based on new antigens;

- Development of an RDT for combined testing for HAT and malaria;

- Development of a rapid test for staging using CSF;

- Evaluation of improved LAMP methods and demonstration of LED fluorescence microscopy.

Since 2010, FIND has been working with partners to develop molecular tests for confirmatory diagnosis of visceral leishmaniasis (VL), cutaneous leishmaniasis (CL) and congenital Chagas disease based on the LAMP platform. Research is ongoing to improve methods of preparing samples before performing LAMP. An enzyme-linked immunosorbent assay (ELISA) for VL parasite antigens in urine is under evaluation, while the feasibility of using the ELISA reagents to develop a rapid test is also being explored.

GOALS AND OBJECTIVES OF THE FIND NTD PROGRAMME

Neglected tropical diseases are a group of infections that are endemic in low-resource settings in developing regions, especially those in Africa, Asia and the Americas, where they cause unacceptable human suffering and death. These diseases have been largely neglected by public health interventions as well as drug and diagnostics developers. FIND's NTD programme is supporting the World Health Organization's 2020 Roadmap and the London Declaration of 2012 to eliminate or bring under control 10 NTDs by developing diagnostic solutions for the following priority diseases: HAT, leishmaniasis, Chagas disease, Buruli ulcer, dengue and soil-transmitted helminthiases.

The focus is on the following diagnostic solutions:

- Tools and strategies for screening and confirmation to accelerate elimination of both HAT and Buruli ulcer;

- Point-of-care tests for congenital Chagas disease, visceral (VL) and cutaneous leishmaniasis (CL);

- Test of cure for VL and Chagas disease;

- Tools to monitor efficacy of VL elimination in the Indian subcontinent;

- Improved tools for diagnosis of dengue and soil-transmitted helminthiases.

The main objectives are to:

- catalyze development and evaluation of new diagnostic tools;

- liaise with other organizations, governments and funding agencies to accelerate roll-out of diagnostic solutions;

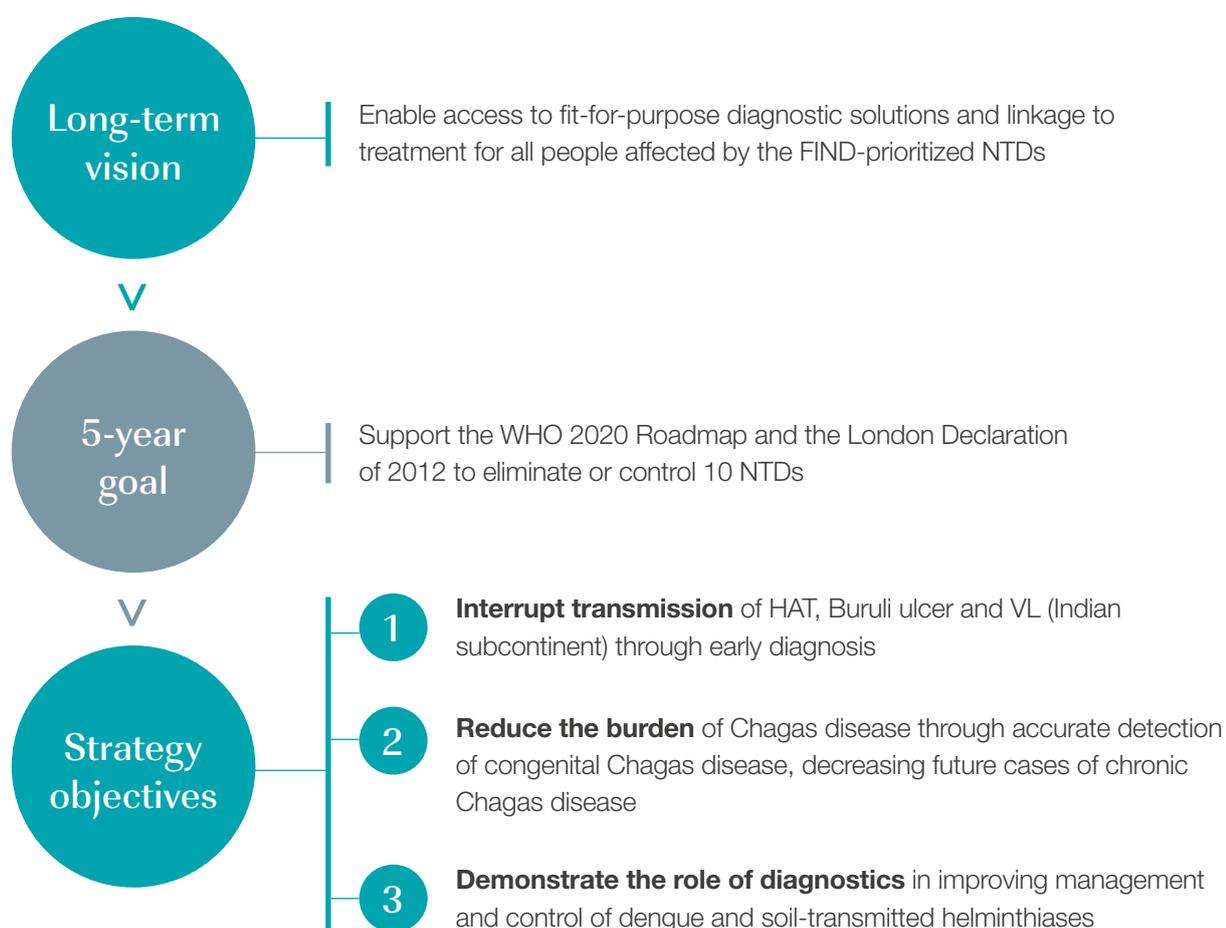- promote early and accurate diagnosis.

GLOBAL DIAGNOSTIC NEEDS IN NTDs

Despite the progress that has been made in the area of NTD diagnostics over the past decade by FIND and other stakeholders, a range of gaps remain across diseases. Of the 17 NTDs on the WHO list that were analysed during the process of developing FIND's strategy, 12 have a significant need for new diagnostic tests (see Figure 1). Beyond development of new tests, there is also a need to better understand how and where to use existing tools and to ensure that they are used appropriately in a quality-assured manner as part of country programmes. The strategy development process also revealed the following crosscutting themes in the field of NTDs:

- **Suitable and easily accessible specimen collections** are not available for most NTDs, making development of new diagnostics particularly difficult;

- A **syndromic approach** is of crucial importance in diseases with similar presentation and geographic overlap;

- There are increasing calls for **attention to diagnostics** for MDA diseases to ensure appropriate monitoring and evaluation, and to enhance drug impact;

- To support the effort and contribute to the success of ongoing elimination programmes, a good understanding of the role of **asymptomatic carriers** in transmission is important;

- **Sustainability of funding for diagnostics** is a major challenge for many NTDs, while access to drugs is dependent on drug donations.

Addressing challenges to meet the NTD programme goals

Long-term vision

Enable access to fit-for-purpose diagnostic solutions and linkage to treatment for all people affected by the FIND-prioritized NTDs

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5-year goal

Support the WHO 2020 Roadmap and the London Declaration of 2012 to eliminate or control 10 NTDs

∨

Strategy objectives

1 **Interrupt transmission** of HAT, Buruli ulcer and VL (Indian subcontinent) through early diagnosis

2 **Reduce the burden** of Chagas disease through accurate detection of congenital Chagas disease, decreasing future cases of chronic Chagas disease

3 **Demonstrate the role of diagnostics** in improving management and control of dengue and soil-transmitted helminthiases

FIND'S NTD MANDATE FOR 2015-2020

Recognizing that there are widespread diagnostic needs for nearly all NTDs, we are focusing on a number of core diseases with the greatest unmet needs and for which there is limited attention by other stakeholders, while at the same time providing broad support for other NTDs (see Figure 1). The process of selecting the NTDs to be prioritized by FIND included extensive consultations with stakeholders, interviews with experts, review of relevant documents, and review and approval by FIND's Scientific Advisory Committee. In identifying its strategic priorities for the next five years, we considered several factors, including the diagnostic needs in a given area and the fit with FIND's strategy and capabilities. Based on detailed analysis, **human African trypanosomiasis, Chagas disease, Buruli ulcer, leishmaniasis, soil-transmitted** **helminthiases and dengue** were identified as the core strategic priority diseases for 2015-2020.

Support to non-core diseases includes contributing to the development of target product profiles – specifications of the necessary and optimal features of new diagnostic tests – and facilitating access to biological materials. Across all NTDs, relationships with manufacturing companies are leveraged to expand diagnostic platforms and to deal with groups of related diseases simultaneously. Periodic re-evaluation of strategic priorities and emerging opportunities will allow FIND to expand or shift focus in response to changes in the landscape. Given the broad scope and limited funding for NTD diagnostics, working in close partnership with other stakeholders is critical, while ensuring that our activities are complementary and closely linked to treatment programmes and priorities.

	Diagnostic need						
Disease	**Method of detection**	**Confirmation**	**Stating**	**Prognostic evolution**	**Less invasive biomarkers**	**Test of cure**	**Distinguishing vaccinated from sick**
Buruli ulcer	Clinical	Microscopy, Culture, PRC					
Chagas disease	Serology, Parasitology	Serology, Parasitology, PCR					
Leshmaniasis	Clinical, RDT	Microscopy, DAT Culture, PCR					
HAT	Serology	Parasitology	CSF		CSF currently needed		
Soil-transmitted Helminthiases	Kato-Katz	FLOTAC, PRC					
Dengue	No quality assured tests	PCR, Virus isolation		Severe Dengue			
Lymohatic filariasis	RDT (ICT), PCR					RDT (ICT)	
Leprosy	Clinical	Clinical, PCR	Bacillo-scopy, Clinical	Neuro evolution			
Schistosomiasis	Kato-Katz, Filtration	Antibody tests, PCR				Ag detection 2 weeks	
Echinococcosis	Serology, Ultrasound	Granulo-multiloc Ab test					
Neurocysticercosis	Test under development	Imaging					
Foodborne trematodiases	Microscopy	Serology for diff species					
Onchocerciasis	Clinical, Microscopy	Microscopy, PCR				OV16, DEC patches, PCR	
Guinea Worm	Clinical	Clinical					
Blinding trachoma	Clinical	Clinical		Clinical			
Rabies	Dog bite	Animal saliva					

Row groups (left margin): FIND core diseases (Buruli ulcer – Dengue); FIND has a supportive role (Lymohatic filariasis – Foodborne trematodiases); Most diagnostic needs addressed (Onchocerciasis – Rabies).

Diagnostic needs for the 17 neglected tropical diseases in the WHO roadmap of 2012. FIND selected Buruli ulcer, Chagas disease, leishmaniasis, HAT, soil-transmitted helminthiases and dengue as those with the highest unmet diagnostic needs, not adequately served by other partners.

Current method
- Adequate
- To be improved
- To be developed
- Not applicable

Human African Trypanosomiasis

Overview and objectives

Human African trypanosomiasis (HAT), or sleeping sickness, is caused by protozoan parasites of the genus *Trypanosoma* and is transmitted by tsetse flies. The disease is endemic in 36 sub-Saharan African countries. During the early or first stage of the disease, parasites are found in the haemolymphatic system. With time, the disease progresses to a second or late stage, in which the central nervous system is invaded. In recent years, the number of new cases reported to WHO has decreased dramatically, from 25,945 in 2000 to 6,228 cases in 2013. However, the actual number of cases is estimated to be much higher, as many patients remain undiagnosed or unreported. WHO targets include elimination of HAT by 2020.

Diagnosis of HAT includes screening to identify suspects, confirmation of disease and staging to determine the treatment to be used. Screening has until now been performed using the card agglutination test for trypanosomiasis, which requires heavy logistics and has sub-optimal sensitivity. Infection is confirmed by demonstration of parasites using various parasitological methods that are labour intensive and have unsatisfactory sensitivity, such as capillary tube centrifugation or miniature anion-exchange chromatography techniques. Finally, staging is an invasive and uncomfortable procedure requiring a lumbar puncture and has limited accuracy.

FIND and its partners have transformed the HAT diagnostics landscape through the delivery of the first rapid diagnostic test (RDT) to screen for HAT, and LED fluorescence microscopy and molecular diagnostic tools for confirming the disease. However, diagnostic needs still remain, including development of implementation strategies to accelerate control of HAT and ensure that elimination is achieved and sustained. FIND's goal is to contribute to elimination of HAT by supporting the development of simple and highly accurate tests for early detection in order to interrupt disease transmission and to enable wide introduction of a new oral treatment, as well as to improve surveillance to sustain elimination. Our specific objectives are:

- To **increase early detection of cases** through improved screening tools and strategies;

- To **facilitate and improve confirmation** of cases.

Diagnostic needs

Screening: Current screening strategies have an unsatisfactory sensitivity and require heavy logistics. This means that a significant number of HAT cases remain undetected and only a small fraction of the at-risk population is tested. Although a first-generation RDT for *T. brucei gambiense* HAT has recently been introduced and is helping to address these challenges, a second-generation RDT based on recombinant antigens, which are easier to produce than the native antigens used in the current test, is needed. This will enable sustainable and affordable large-scale production. While the WHO has already recommended using RDTs in passive and active screening under specific circumstances, additional data and advocacy are needed to obtain global guidance on their broad use in all screening settings, so that a higher proportion of HAT cases can be detected at an early stage and disease transmission can be interrupted. It will also be necessary to secure long-term commitments from donors to provide subsidies for the tests, in order to guarantee widespread access. Finally, as prevalence of the disease declines, the proportion of the population screened for HAT is likely to decrease. To ensure continued surveillance and detection of cases and prevent re-emergence, and since all settings where HAT is found are also endemic

AS HAT PREVALENCE DECLINES
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CARE SYSTEM.

for malaria, development and introduction of an RDT to simultaneously detect HAT and malaria will be an attractive approach. This test will also be important in surveillance to sustain elimination.

Confirmation of disease in suspected HAT cases is a necessity because the treatment options that are currently available can cause serious side effects. Determination of the stage of disease is also important, as treatments for stage 1 and stage 2 are different. However, new oral drugs that have the potential to revolutionize diagnostic requirements are expected to be launched in the near future. In particular, if a significantly better safety profile can be achieved, a shift to a "test and treat" approach, in which serological suspects identified with an RDT would be treated without the need for parasitological confirmation, could be considered. The availability of a new drug that is suitable to treat patients regardless of the stage of the disease would also represent a paradigm shift, as staging would no longer be required before initiating treatment.

Case confirmation: Current methods are either insensitive, labour intensive or not widely available because of production and logistical constraints. Extra efforts are needed to develop and introduce new tools that are more sensitive and easier to implement so that cases can be detected more widely and efficiently. This will include both

microscopy (e.g. by combining capillary tube centrifugation with fluorescence microscopy) and molecular methods such as LAMP. The LAMP technology achieves adequate performance and appears to be suitable for use in resource-limited settings. It is therefore a very good candidate to eventually replace microscopy and to be used as a surveillance tool to sustain elimination. To achieve this, it will be necessary to generate more data on performance from multiple countries and advocate for a shift in case confirmation from microscopy to molecular methods.

Staging: Staging and confirmation of cure involve performing an invasive and uncomfortable lumbar puncture followed by examination of the spinal fluid by microscopy, which has limited accuracy. While a safe and effective drug for both stages of the disease may become available in the next few years, it is necessary to develop new staging tools for use until this drug is widely available. In the event that the new drug does not meet expectations for multi-stage use, staging tools are needed in order to avoid exposing stage 1 patients to toxic stage 2 drugs. A diagnostic tool for staging could also be used to confirm cure after treatment, with the advantage of requiring fewer lumbar punctures. An improved staging test using blood rather than spinal fluid would result in a less invasive procedure and improved ease of use.

Delivery and implementation

Appropriate implementation strategies for the screening and confirmatory tests supported by FIND and partners depend on a number of factors, including prevalence of disease, geographic settings and whether the tests are used in active or passive screening. Implementation research is needed to define cost-effective and impactful strategies for using the tests in different geographic and epidemiological settings.

Current landscape

As the prevalence of *T.b. gambiense* HAT declines, active screening becomes uneconomical. As a result, national control programmes are integrating control and surveillance activities in the general health care system. However, some of the available diagnostic tests are not compatible with the limited infrastructure that is found in primary health care facilities,

especially in rural areas, hindering the participation of such facilities in effective control and surveillance of the disease.

Until the recent availability of the HAT RDT, screening for HAT was exclusively done using the card agglutination test for trypanosomiasis, which has

suboptimal sensitivity and requires electricity and a cold chain, thereby preventing early detection of many cases. These challenges are being addressed by a number of research organizations and diagnostics companies, which have invested in development of RDTs for HAT screening. Two RDTs have been developed using native parasite antigens: the SD BIOLINE HAT by Alere/Standard Diagnostics (Korea), with support from FIND and partners, and the HAT Sero-K-SeT by Coris BioConcept (Belgium) and the Institute of Tropical Medicine (Belgium).

Demonstration of *T.b. gambiense* parasites in blood by direct microscopy is insensitive because parasitaemia is usually very low. Microscopy is therefore combined with methods for concentrating parasites, such as capillary tube centrifugation and miniature anion-exchange chromatography techniques (mAECT). While mAECT is the most sensitive test that is in routine use, its production is limited and prone to frequent quality and availability problems. The high cost of this test and the need for a cold chain have also been hindrances to its widespread use. Even with concentration methods,

up to 30% of cases are still missed, leaving an undetected reservoir for disease transmission. Thus, confirmatory diagnostic tests that are more sensitive, reliable, affordable and easy to perform in basic health settings are desperately needed, as are tests for staging and confirmation of cure that are less invasive and more accurate.

Some of the organizations carrying out research on HAT diagnostics include: Institute of Tropical Medicine (Belgium); Institut de Recherche pour le Développement (France); Makerere University (Uganda); Institut National de Recherche Biomédicale (DRC); University of Kinshasa (DRC); University of Limoges (France); University of Aberdeen (UK); University of Dundee (UK); University of Edinburgh (UK); University of Glasgow (UK); Institute of Primate Research (Kenya); University of Geneva (Switzerland); and Swiss Tropical and Public Health Institute. Efforts to eliminate HAT are led by the national sleeping sickness control programmes of endemic countries, with support from, among others, WHO and the Pan African Tsetse and Trypanosomiasis Eradication Campaign office of the African Union Commission.

Prioritized activities for HAT

FIND's activities in HAT diagnostics have been prioritized based on identifying the most critical gaps in the current diagnostics landscape, the technical feasibility of developing new tools, availability of funding, the likelihood of successful implementation in settings with limited infrastructure, and the magnitude of the expected impact on HAT control and elimination. Four interventions have been selected for test development:

A. **Screening:** (i) development and introduction of a second generation RDT; (ii) development and introduction of an RDT for simultaneous detection of HAT and malaria;

B. **Case confirmation:** (iii) development and introduction of improved microscopy tools (e.g. by combining capillary tube centrifugation with fluorescence microscopy); (iv) evaluation and introduction of a highly sensitive molecular method based on LAMP.
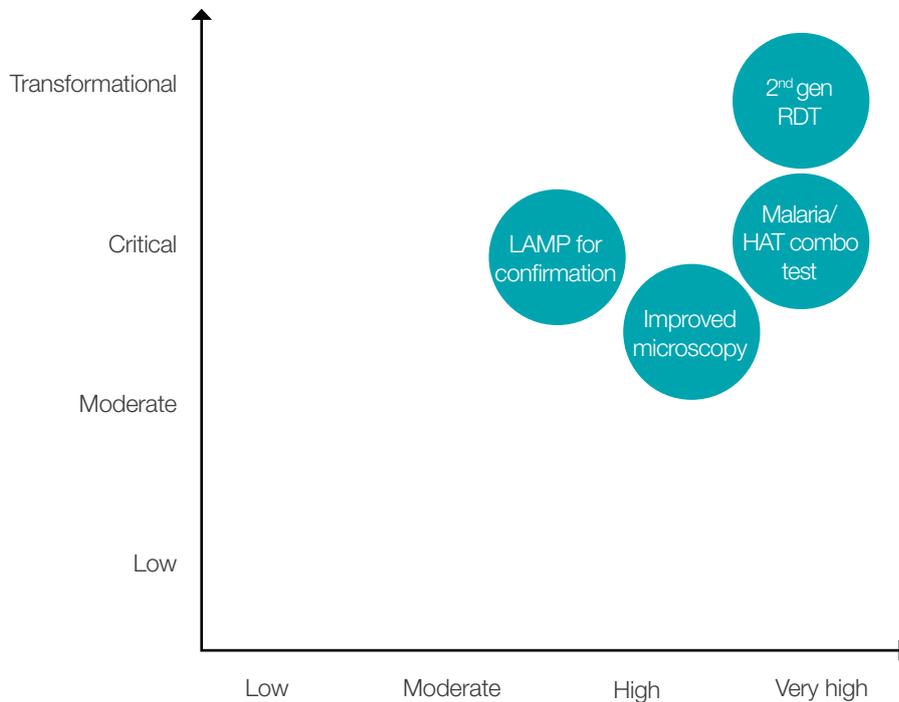
Enabling interventions

FIND creates an enabling environment to achieve its objectives for HAT diagnostics by supporting related policy, access and advocacy activities. To improve coverage of the population at risk and accelerate elimination of the disease, advocacy must be intensified in endemic countries, including

raising awareness about new diagnostic strategies, targeting national authorities, healthcare workers and communities. Data generated will be used to inform global policy and guide endemic countries in formulating national HAT control and surveillance guidelines and elimination strategies.

Transformational

2ⁿᵈ gen RDT

Critical

LAMP for confirmation

Malaria/ HAT combo test

Improved microscopy

Moderate

Low

Low   Moderate   High   Very high

Likelihood of success
- Technical feasibility
- Availability of funding
- Fit with FIND's capabilities/strategy

Key

● Core FIND focus

Expected impact

Introduction of new diagnostic tools for HAT will enable earlier and easier identification of suspects and their referral, confirmatory diagnosis and appropriate treatment. Coverage of the population at risk will be improved, reducing the distance that sick people have to travel to access diagnosis. As a result, it is expected that by 2017, population coverage will have gone up to 40%, rising to 70% by 2020. Since infected people act as reservoirs, their treatment will reduce disease transmission and accelerate elimination. Increased passive screening at health facilities and less reliance on active screening using large mobile teams will reduce costs of control programmes. Implementation of novel surveillance strategies will contribute to the targeted reduction of new cases per year down to 3,500 by 2017 and less than 2,000 by 2020. Once elimination is achieved, use of a malaria test that simultaneously screens for HAT will ensure continued surveillance and sustained elimination of the disease.

Potential partners

To achieve the goals for new HAT diagnostics, we shall continue establishing and strengthening partnerships with the following critical stakeholders:

- Academic institutions

- Ministries of health in HAT-endemic countries

- Diagnostics development companies, such as Alere/Standard Diagnostics and Concile GmbH

- World Health Organization

- NGOs such as Médecins Sans Frontières and Malteser International

THE PREVALENCE OF
CHAGAS DISEASE IS WIDELY
UNDERESTIMATED, PARTLY
DUE TO LIMITED ACCESS
TO DIAGNOSTICS AND ALSO
TO FREQUENT ABSENCE OF
SYMPTOMS.

Chagas disease

Overview and objectives

Chagas disease is a potentially life-threatening disease found mostly in Latin America but also, due to global migration of infected people, in many non-endemic regions as well. The disease, caused by the protozoan parasite *Trypanosoma cruzi*, is transmitted cyclically by triatomine bugs through consumption of contaminated food, blood transfusion or organ transplantation. More than 6 million people are infected with *Trypanosoma cruzi*. However, the prevalence of Chagas disease is largely underestimated due to limited access to diagnostics, heterogeneity of the disease and frequent absence of symptoms. Indeed, early diagnosis of the disease and accurate prognosis are crucially important but often hampered by the absence of specific symptoms. Patients, therefore, often present for diagnosis when the disease is at an advanced stage, with irreversible cardiac and gastrointestinal manifestations.

FIND's goal is to support intensified global control efforts through the following specific objectives:

- To **reduce the burden** of congenital Chagas disease through improved diagnostic solutions;

- To **improve monitoring of treatment efficacy** for chronically infected patients.

Diagnostic needs

For **congenital Chagas disease**, the best time for parasitological or molecular diagnosis is during the first few weeks after birth when parasitaemia is often high. This is difficult, however, due to limitations in infrastructure and resources. As a result, children born from infected mothers have to wait for up to ten months after birth before they can be tested by serology (serological tests are only useful after maternal antibodies have waned). Many children are thus lost to follow-up during this waiting period. A point-of-care test for congenital Chagas disease to enable testing of neonates at the place of birth would ensure early detection and safer treatment.

A test of cure, preferably an RDT, is urgently needed. Such a test could also be used for diagnosis of chronic Chagas disease (including cardiac and immunocompromised patients), since treatment of chronic cases is not always successful. Treatment should also be based on accurate diagnosis as it is lengthy, and drugs often have toxic side effects. Tests that detect parasite antigens or DNA/RNA would be the most appropriate for monitoring therapy, since antibody detection tests require long durations to confirm cure (patients are followed up for years until they are serologically negative). Novel biomarkers, if validated, and new technologies to concentrate parasite antigens in urine have shown promise for development of a new test. While direct observation of parasites by microscopy has been improved by techniques such as the capillary tube centrifugation test, its sensitivity could be further enhanced by techniques such as fluorescence staining. An alternative test to detect the presence, absence or reduction of parasites that is faster than seroconversion is needed.

Development and introduction of diagnostics for Chagas disease needs to be coupled with awareness campaigns among at-risk communities and health workers. There is currently limited active surveillance of Chagas disease in most endemic countries, and access to diagnostics, treatment and information is a major challenge in remote regions. There is need for reinforcement of national control initiatives and improved screening of neonates with better diagnostic tools. Programmes for blood and organ

screening, as well as integration of Chagas disease testing into pregnancy management guidelines, are important. Surveillance programmes that consider the attribution of a "risk factor" (such as geographic location, family history of Chagas dise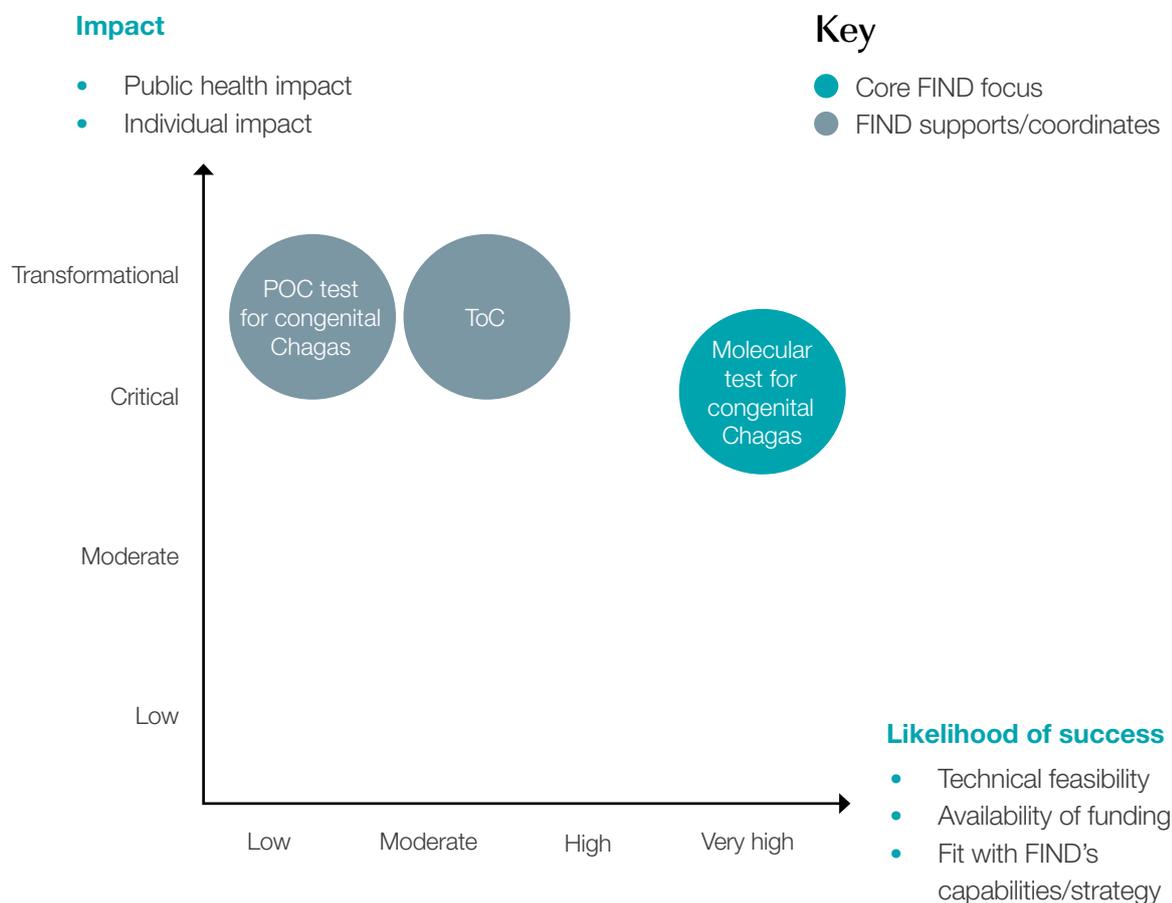ase) would permit individuals at higher risk to be actively tested, allowing detection of early infection and asymptomatic cases. Detection of Chagas disease in endemic areas and at-risk groups in non-endemic areas should be part of the antenatal and postnatal care package, including follow-up of children born to infected mothers.

Current landscape

The acute phase of Chagas disease can last between a few weeks and a few months. During this phase, trypanosomes are circulating in the blood and direct detection by microscopy, xenodiagnosis or polymerase chain reaction (PCR) is considered to be efficient. During the chronic phase, the number of parasites in the blood is low and they are typically found in tissues. Although most patients with chronic disease remain asymptomatic, 20-30% of infected people develop cardiac disease or gastrointestinal complications. At this stage, direct detection of parasites is difficult and diagnosis depends on detection of antibodies by at least two different serological methods. Six of the available rapid tests are highly effective in diagnosing Chagas disease, and there are no significant variations in their performance in different geographic settings. However, gaps in diagnosis exist and are addressed below.

The drugs used for treatment of Chagas disease (benznidazole and nifurtimox) are effective in the often subclinical acute phase but may lack efficacy in the chronic phase, especially if a patient has been infected for many years.

Impact

- Public health impact
- Individual impact

Key

- Core FIND focus
- FIND supports/coordinates

Likelihood of success

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

Public health research institutions and biotechnology companies are carrying out research to identify biomarkers, preferentially in serum or plasma, for use in development of tests for staging, assessment of prognosis and monitoring therapy. Research and exchange of knowledge and experience in this field is being fostered by consortia such as the Ibero-American network, New Tools for the Diagnosis and Evaluation of Chagas Disease (NHEPACHA), the South Cone Initiative coordinated by PAHO and the Global Chagas Disease Coalition (led by the Drugs for Neglected Diseases *initiative* (DNDi), in collaboration with the Barcelona Institute for Global Health (ISGlobal), Instituto Carlos Slim de la Salud, the Sabin Vaccine Institute, and Fundación Mundo Sano). In addition, a number of stakeholders, including Médecins Sans Frontières, International Federation of People Affected by Chagas Disease and local groups are carrying out various advocacy activities in South America. Movie clips and cartoons are accessible online, and games are being designed to raise awareness. Other preventive measures range from etiologic treatment of women before pregnancy to building of houses that are resistant to invasion by triatomine bugs.

Prioritized activities for Chagas disease

Following identification of the most critical gaps in the current diagnostics landscape for Chagas disease, three activities have been prioritized:

- Development of a test of cure: FIND will support the validation of promising biomarkers and their use in development of a test-of-cure RDT. These biomarkers could be either of parasite origin (parasite protein, RNA, DNA) or a host marker that is altered or whose concentration is changed by the presence of parasites.

- Development of a molecular test for congenital Chagas disease: Currently, apart from serologic tests that are inadequate for neonates, the most sensitive methods for diagnosis of Chagas disease require a molecular biology laboratory. LAMP is a good alternative that provides the sensitivity of molecular tests, relative ease of use by personnel who are not molecular biologists, and does not require expensive equipment. FIND is supporting development of a LAMP test for congenital Chagas disease. The test will be evaluated in a number of endemic countries in Latin America and Europe, in comparison with the PCR tests that are in current use.

- In the event that appropriate reagents become available, FIND will support the development of a point-of-care test for congenital Chagas disease.

Enabling interventions

In order to improve access to diagnostic solutions for Chagas disease, FIND will support advocacy activities that create an enabling environment for introduction of new tools. This will include engaging governments to put in place appropriate policies, and training of health workers in endemic and non-endemic settings. The lack of access to information on Chagas disease will be addressed, especially for asymptomatic pregnant women who can transmit the disease to their babies. Improved awareness of the risk of transmission will decrease the number of infants lost to follow-up. Relevant authorities will be engaged to establish or review policies on Chagas disease relating to blood and organ donations, and antenatal care packages.

Expected impact

A highly accurate test for congenital Chagas disease (mother-to-child transmission), such as LAMP, and increased screening of pregnant women will ensure early and successful treatment of infected babies and considerably reduce the incidence of congenital Chagas disease (estimated at 8,668 cases per year in Latin America). It will also allow the detection of chronic cases among infected mothers (an estimated 300,000 pregnant women per year in Latin America and 1.1 million infected women of childbearing age). If 50% of this at-risk population is reached, the impact will be: a reduction in the incidence of congenital Chagas disease to less than 4,334 cases per year (a significant contribution considering that vector and congenital transmission together account for 38,593 new cases each year); and a reduction of more than 10% prevalence in women of child-bearing age (or 2.5% of the total prevalence of 6 million). In this sense, if 100% of the mother-to-child cases has access to accurate diagnosis, 308,668 individuals would receive treatment, contributing to a marked decrease in chronic Chagas disease in the future.

Vector control activities have been useful in reducing the incidence of Chagas disease; however, such activities have little effect on chronic disease. If only 20% of these patients received proper diagnosis and treatment as a result of improved communication, access and awareness, the decrease in prevalence would have a substantial economic impact: a reduction by US$ 1.6 billion out of the total US$ 7.19 billion estimated global costs due to Chagas disease per year.

Potential partners

Development of LAMP for congenital Chagas disease is being done in partnership with Eiken Chemical Co. (Japan), Pontificia Universidad Javeriana (Colombia) and Instituto de Investigaciones en Ingeniería Genética y Biología Molecular (Argentina). The test will be evaluated in a number of endemic countries in Latin America and Europe. Its introduction, and support for information and access, will be carried out in partnership with regional organizations and health authorities of endemic and non-endemic countries where the disease is reported.

Validation of new biomarkers and technologies for use in development of a test of cure will be done in partnership with networks and organizations that have access to such biomarkers, tools and test development companies. FIND will engage regional and local authorities, health ministries and WHO in advocacy and development of policies and guidelines on Chagas disease.

Buruli ulcer

Overview and objectives

Buruli ulcer is a debilitating and stigmatizing disease caused by *Mycobacterium ulcerans*. More than 6,000 cases of the disease are reported annually from 15 of the 33 endemic countries. It is among the most neglected of all the 17 NTDs on WHO's list. Although its overall burden is comparatively low, the disease has been prioritized by FIND because of the potentially transformational impact that improved diagnostics can have on patients. Diagnostic tools for detection of *M. ulcerans* with high sensitivity and specificity (culture and PCR) are limited to sophisticated tertiary level laboratories. Culture is currently the only method used to detect viable bacteria, and therefore to monitor treatment. Microscopy of Ziehl-Neelsen stained smears, the only method that can be used outside of the specialist laboratory setting, has a low sensitivity (40-60%). Early diagnosis of Buruli ulcer in the pre-ulcerative stage is mostly clinical, and in the early stages,

nodules are difficult to differentiate from other potential causes. Confirmation of the disease can therefore be greatly delayed due to the necessity of referring specimens to tertiary level laboratories, which can result in incorrect treatment and progression of the disease to a more advanced and debilitating stage.

FIND's strategy on diagnostics for Buruli ulcer is to contribute to accelerated control of the disease through early and near-patient detection of cases, focusing on two objectives:

- To support the use of **improved case finding strategies**;

- To establish diagnostic solutions for **early detection of Buruli ulcer** close to where people live and faster, less-burdensome **confirmation of disease** through improved tools.

Diagnostic needs

There is need for a **confirmatory test** closer to the patient that would have significant positive predictive value so that appropriate treatment can start immediately. In the short term, this is most feasible at the level of the district hospital where some laboratory infrastructure exists. This will allow interventions to take place using simple molecular platforms as well as antigen and antibody-based testing.

A **test for screening symptomatic individuals** at the primary or community level would be important for efficient referral to the district level. The test should be simple to use, without the need for regular power supply or specialist training. A test based on a rapid immunochromatographic platform may be the most suitable. The current focus is on tests for the detection of the bacterial toxins mycolactones, which

are important in the pathogenesis of Buruli ulcer. Other tests focus on detection of antigens and DNA of *M. ulcerans* and on *mycolic* acids.

Development of diagnostics for Buruli ulcer should be coupled with awareness campaigns among communities and healthcare workers to ensure that individuals present to health services and get tested in the early stages of the disease. Additionally, frontline clinical staff should be trained to recognise, test and manage Buruli ulcer. This will require robust referral networks to ensure efficient transportation of specimens to facilities where confirmatory testing is done. A test that can detect asymptomatic infection or latent disease would allow the development of improved strategies for active case finding and surveillance of Buruli ulcer.

FIND AIMS TO ESTABLISH
SOLUTIONS FOR EARLIER
DETECTION OF BURULI ULCER
CLOSER TO WHERE PEOPLE
LIVE, AND FASTER DISEASE
CONFIRMATION.

Current landscape

WHO is heavily involved in supporting Buruli ulcer partnerships. Ghana has two institutes carrying out Buruli ulcer research, including the Kwame Nkrumah University of Science and Technology (KNUST) in Kumasi and the Noguchi Memorial Institute for Medical Research (NMIMR) in Accra. NMIMR is involved in the development of a LAMP assay for Buruli ulcer.

Other academic institutions involved in research on tests for Buruli ulcer include Johns Hopkins University (USA), which is working on mycolactone detection using fluorescent thin-layer chromatography. The Swiss Tropical and Public Health Institute (Swiss TPH) is identifying biomarkers for antigen capture assays

and antibodies against mycolactones. Institut Pasteur (France) is working on a mycolactone detection assay based on its binding to the Wiskott–Aldrich Syndrome Proteins. Bangor University (UK) is developing an assay for detection of *M. tuberculosis* based on its mycolic acids, and some of the esters they have identified could be adapted for Buruli ulcer.

WHO, KNUST, NMIMR, Swiss TPH and the Institute of Tropical Medicine (Belgium) are members of the Stop Buruli consortium, which also has members in Cameroon, Benin, DR Congo and Australia, offering potential for additional field sites and research collaborations.

Impact

- Public health impact
- Individual impact
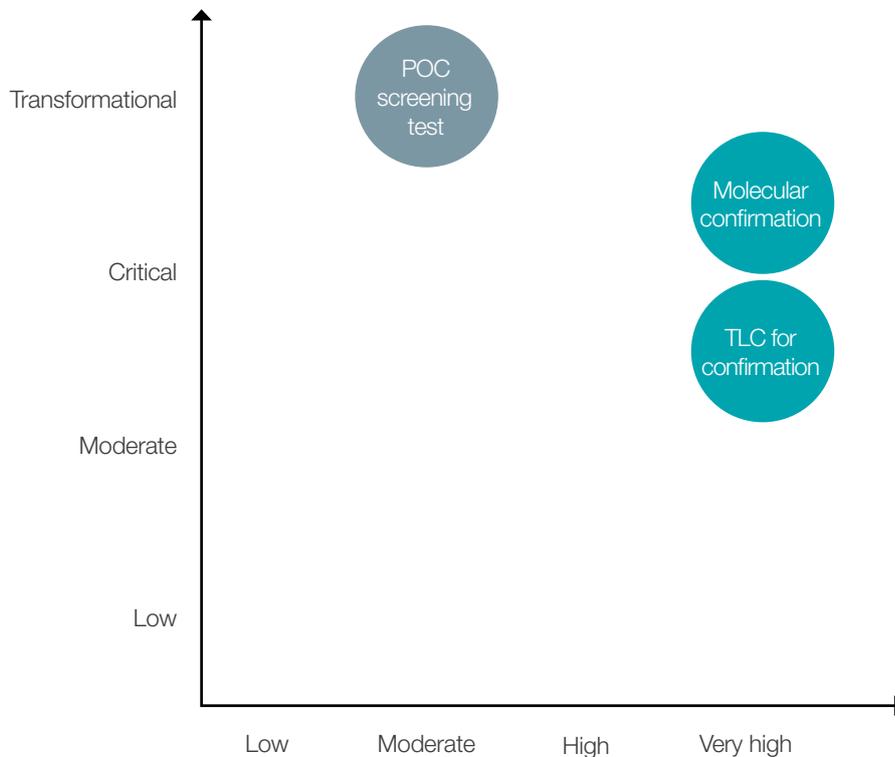
Likelihood of success

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

Key

- ● Core FIND focus
- ● FIND supports/coordinates

Prioritized activities for Buruli ulcer

Prioritization of FIND activities in Buruli ulcer diagnostics considers the need for an efficient system of surveillance and early detection of cases. While fluorescent thin-layer chromatography as a tool for case confirmation appears quite advanced in development, its implementation in endemic areas could face infrastructural challenges that may be overcome by a molecular test based on LAMP. FIND is therefore supporting efforts in development of both technologies. A point-of-care test for screening and possibly confirming disease at the community level would transform surveillance and control of Buruli ulcer. FIND will support and coordinate research on biomarkers and advance promising biomarkers to test development.

Enabling Interventions

In addition to focusing on the above development priorities, FIND will support advocacy activities that create an environment for improved access to Buruli ulcer diagnostics. Further, we will work closely with WHO to support the Buruli ulcer research and control community by improving access to specimens, advocacy, regular convening, and joint goal and priority setting.

Expected impact

Diagnostic test for the early detection of Buruli ulcer

The test should have a minimum 90% sensitivity and 80% specificity against the gold standard PCR targeting IS2404 on fine needle aspirate and swabs, demonstrated in a district hospital setting in endemic countries. Specificity of clinical diagnosis is variable in different settings, possibly depending on level of training. The test is likely to have greatest impact in the identification of new geographic areas where clinical experience with the disease will be lower. As the sensitivity of clinical diagnosis is not well characterized, a broader clinical definition for referral may lead to a rise in the number of cases presenting.

A diagnostic test for the early detection of Buruli ulcer would increase the number of confirmed cases and provide information on prevalence of the disease at a sub-national level. An initial target should be 90% of diagnosed cases confirmed in districts offering this service. It will also improve the detection of shifting infections according to changes in the ecology of different regions. Furthermore, it has the potential to increase early case detection and decrease Category III lesions and limitations of movement by 50%.

The test would reduce time for a confirmatory diagnosis to one day for patients presenting at the district testing facility. For referred specimens, results could feasibly be delivered the day after collection when coupled with innovative reporting.

Screening test at primary or community level for symptomatic patients with ulcer

Reporting of Buruli ulcer is a major problem, and the majority of cases are not detected by the health system. A simple test to screen symptomatic individuals, coupled with a laboratory-based confirmatory test, would have a huge impact on the number of cases detected, especially in sub-Saharan Africa where the majority of those affected by Buruli ulcer live. The test has the potential to increase the number of cases detected by 70% per year when combined with community and health worker education, and active case finding. As with the

test for early detection, it could also decrease the development of Category III lesions and limitation of movement by 50%.

Like the test for early detection, the screening test should have a minimum 90% sensitivity and 80% specificity against IS2404 PCR on swabs, demonstrated in primary health care and/or community settings in endemic countries. In order to reduce loss of patients to follow-up, the test should take no longer than two hours to produce a result.

Potential partners

FIND will support WHO's efforts to complete evaluation and introduction of a fluorescent thin-layer chromatography test for mycolactones, and NMIMR to select appropriate targets for a LAMP assay. The selected LAMP targets will be used by Eiken to develop a kit, which will be evaluated at multiple sites in endemic countries. We are collaborating with Swiss TPH to identify biomarkers for antigen capture assays and antibodies against mycolactones, and with Alere/Standard Diagnostics (Korea) to develop a point-of-care rapid test. Other partners will include Institut Pasteur (France) and Bangor University (UK). Endemic countries such as Cameroon, Benin, DR Congo and Australia will be critical in ensuring access to clinical samples and trial sites.
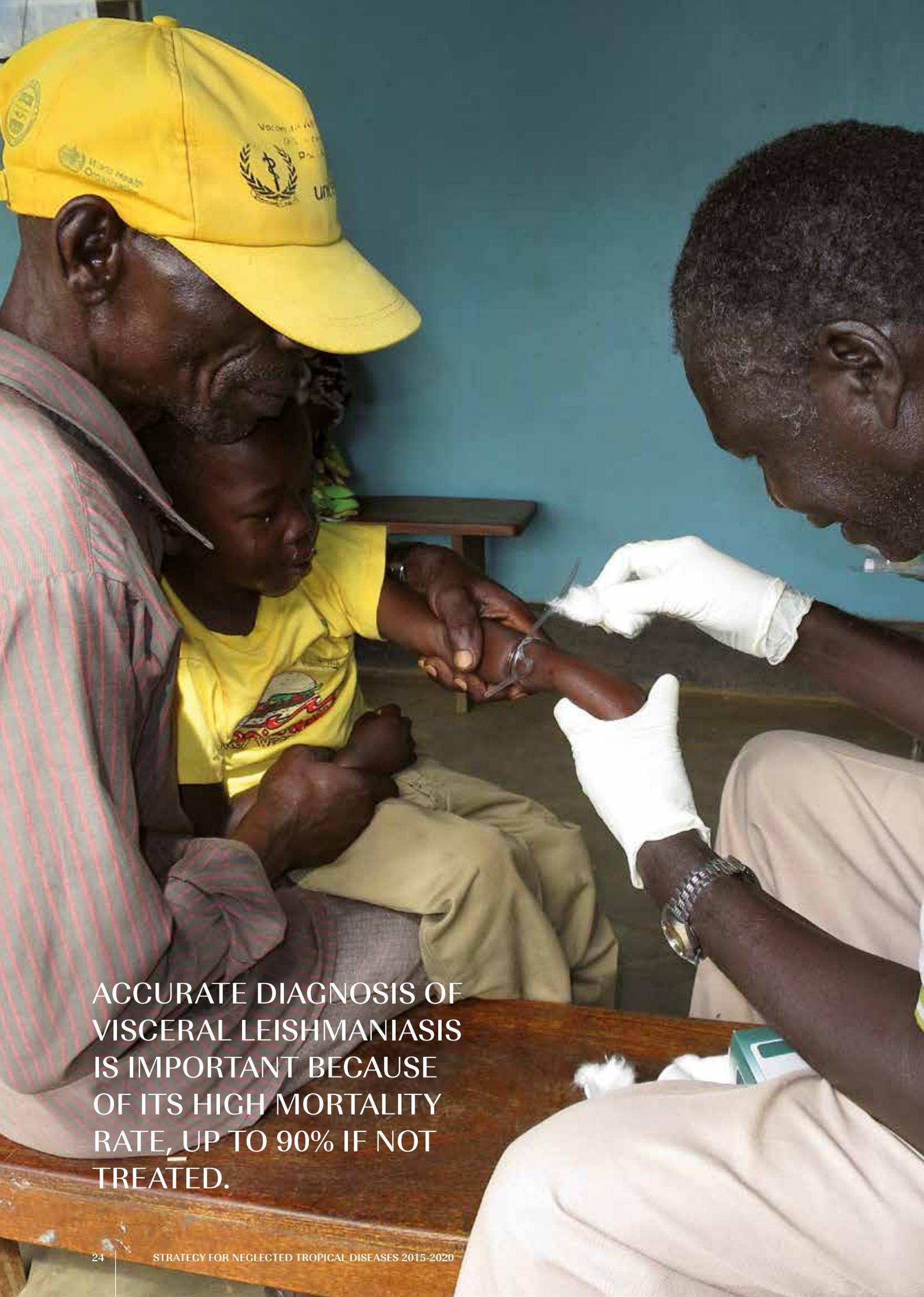
ACCURATE DIAGNOSIS OF
VISCERAL LEISHMANIASIS
IS IMPORTANT BECAUSE
OF ITS HIGH MORTALITY
RATE, UP TO 90% IF NOT
TREATED.

Leishmaniasis

Overview and objectives

Leishmaniasis is a complex group of infections caused by protozoan parasites of the genus *Leishmania*. The disease is endemic in 98 countries across Africa, Asia, Europe and the Americas. There are approximately 200,000 to 400,000 visceral leishmaniasis (VL) cases and 700,000 to 1.2 million cutaneous leishmaniasis (CL) cases each year. There is a wide range of clinical manifestations between the poles of localized CL and VL; each poses a challenge for diagnosis and management.

Accurate VL diagnosis is important because of its high mortality rate, up to 90% if not treated. Treatment can be lengthy, toxic and difficult to implement in resource-limited settings; it is also costly, thus confirmatory diagnosis is desirable. In areas of anthroponotic transmission, early diagnosis and treatment is important for both the patient and the community, as untreated patients would contribute to transmission. In eastern Africa and the Indian subcontinent, a proportion of VL patients later develop post-kala azar dermal leishmaniasis (PKDL) with lesions that can harbour parasites, and such patients can contribute to ongoing transmission. There is no way of predicting which patients will develop PKDL. This is particularly true in the Indian subcontinent, where PKDL generally appears one to two years after the VL episode. Parasitological confirmation of PKDL can be done by microscopy, although parasites are difficult to demonstrate in macular lesions. While PCR is more sensitive, this technology needs equipped laboratories. PKDL patients may require therapy over lengthy periods.

HIV co-infection poses another challenge to VL diagnosis; HIV impairs the immune system and therefore antibody production, decreasing the sensitivity of serological tests. A test for monitoring treatment efficacy is also needed, as VL relapses are frequent in co-infected patients. Such a test would also be of great value in clinical trials.

There is a lack of appropriate diagnostic tests for CL, despite the high proportion of cases relative to VL, and the associated stigma and morbidity. Antibody detection is useless here; CL diagnosis is usually based on microscopy, which is not always available in remote endemic areas where most of the cases occur. Depending on the infecting species, a proportion of patients develop complicated forms of the disease such as: i) diffuse CL, associated with *Leishmania aethiopica* in eastern Africa and *L. amazonenesis* in Latin America, that do not respond to treatment unless the cell-mediated immune response recovers; ii) mucocutaneous leishmaniasis, which affects the oral and nasal mucosa and may lead to serious disfigurement, associated with *L. braziliensis* in Latin America; or iii) CL recidivans, caused by *L. tropica*, which can occur years after a CL lesion has healed, and which tends to be resistant to treatment. Different treatment approaches are needed for these conditions, and thus diagnosis should aim for point-of-care testing, prognosis and species identification. Given the sound advantage of molecular diagnosis, Eiken is working with FIND and other partners to develop LAMP for diagnosis of CL.

The proportion of asymptomatic infections in VL-endemic regions is relatively high, and their role in the epidemiology of the disease is unknown. Detection of asymptomatic infections and the assessment of their contribution to transmission is of great interest for VL elimination programmes.

FIND's strategy on leishmaniasis is to contribute to VL elimination by developing diagnostic solutions with the following objectives:

- To validate a **sensitive POC for primary diagnosis**;

- To specifically address a **test-of-cure**;

- To **improve detection** and understanding of **asymptomatic infections and cases of PKDL** in regions targeted for elimination.

FIND also aims to identify solutions for better management of the different clinical evolutions of localized CL.

Reducing leishmaniasis transmission through early diagnosis requires innovative, user-friendly tools that can be used at the lower levels of the health system, as well as improving accessibility. Gaps have been identified in three areas: primary diagnosis, treatment monitoring and asymptomatic infection.

Diagnostic needs

Sensitive point-of-care test for VL
Until the late 1980s, VL diagnosis was mainly based on microscopy or culture of tissue aspirates (lymph node, bone marrow or spleen) obtained by invasive procedures that are not possible to carry out in many health centres. The use of direct agglutination tests was the first serological method viable for field use, and current versions are robust, with good sensitivity and specificity. More recently, user-friendly and easy-to-perform immunochromatographic tests (ICT), based on recombinant antigens, were introduced. Although these tests have almost replaced parasitological diagnosis at the primary health care level, they are still imperfect. They cannot distinguish between active disease, subclinical infection or past infection. The direct agglutination test is not a rapid diagnostic test, as it requires substantial manipulation and results are obtained in eight to 24 hours. As well, ICTs are less sensitive in eastern Africa than on the Indian subcontinent and Brazil (85.3%, 97.0% and 93% respectively). A point-of-care test with better sensitivity (preferably detecting antigens) is therefore needed.

Antigen-detection tests
Detection of antigens would provide a better option for VL diagnosis, since antigen levels are broadly correlated with the parasite load. It would also be an ideal alternative to antibody detection in patients co-infected with HIV. Detection of antigens in urine has an advantage over serum/plasma, especially in chronic VL infections. As a result, a Latex Agglutination test (KAtex) for the detection of *Leishmania* antigens in urine was developed, and although it appeared to be a good candidate as a

test of cure, its variable sensitivity in different studies and the need to boil urine precluded its use. More recently, the test was re-developed into an ELISA, which is being evaluated in a number of clinical studies by FIND in collaboration with DNDi and other partners. A point-of-care RDT based on the same principle is also being developed by Alere/Standard Diagnostics in partnership with FIND.

Molecular diagnostic tools
Molecular tests are highly sensitive and specific, but since they are complex to implement in most VL-endemic countries, they are restricted to a few hospitals and reference laboratories. The main barriers for implementation are cost, ease of use and standardization. However, molecular diagnosis has shown some advantages: it allows highly sensitive VL diagnosis using less invasive sampling (peripheral blood instead of bone marrow or splenic aspirate); its high sensitivity is particularly evident when CL lesions have more than six months of evolution, and when the sensitivity of culture and microscopy decrease dramatically. Simplification of molecular diagnosis (e.g. isothermal platforms such as LAMP) could contribute to a wider use of such tests. Ease of sample preparation and robustness of reagents under sub-optimal laboratory conditions would ease the implementation of molecular diagnosis. FIND is working with Eiken Chemical Co. (Japan) and other partners to develop a LAMP assay for leishmaniasis.

Test of cure
There is no test to assess whether treatment of VL, which has potentially harmful side effects, is working. Such a test would allow abbreviation of treatment in

some patients, introduction or stopping of prophylaxis in others, and help to manage relapses. There is a need for new markers to assess cure and predict relapses. With new drugs being developed and tested by DNDi and partners, there is an important need for accurate tools to evaluate their efficacy. A test of this kind would provide useful information about the evolution towards PKDL.

Accurate diagnosis, key to control of VL

Interrupting transmission of VL will only be successful if coupled with adequate assessment and management of asymptomatic infections and of PKDL patients. WHO has targeted elimination of leishmaniasis in the Indian subcontinent by 2020. It is likely that antigen detection tests, combined with molecular methods, will play a crucial role in surveillance of the disease. The DNDi network of clinical trials and the Leishmaniasis East Africa Platform are initiatives that have also created opportunities for multi-country clinical research, including the evaluation of diagnostic tests. A current research priority of the PKDL consortium, an international group of health care organizations that includes FIND, is to provide sound evidence of the infectiousness of the different forms of PKDL.

Current landscape

An antibody detection RDT for VL based on the recombinant antigen rK28 is being developed by Infectious Disease Research Institute (USA) and InBios, and is expected to overcome the problem of low sensitivity reported for rK39 in eastern Africa. FIND and partners are evaluating a new approach to detect *Leishmania* antigens in urine (ELISA and lateral flow assay) and a LAMP test for both VL and CL. There is currently no test of cure or a test for monitoring treatment; a test to detect antigens in urine and LAMP would fit this purpose. It is likely that research on additional biomarkers will be needed. *Xenodiagnosis* is currently the only reliable method of determining the role played by PKDL patients and *Leishmania*-infected asymptomatic individuals in transmission. A surrogate marker of infectiousness is needed, as none has yet been identified.

Prioritized activities for leishmaniasis

We will focus on the most critical gaps in the current diagnostic landscape, technical feasibility of developing new tools, availability of funding and the likelihood of successful implementation in settings with limited infrastructure. The following priorities have been identified:

Test to improve detection of VL in eastern Africa, and to detect VL in immunocompromised patients: (i) point-of-care test for detecting *Leishmania* antigens in urine.

Test of cure for VL and PKDL: (ii) development and introduction of a test to detect treatment failure, (iii) evaluation and introduction of a highly sensitive molecular test based on LAMP, and (iv) detection of *Leishmania* antigens in urine.

FIND will support research on biomarkers to address these objectives.

Impact
- Public health impact
- Individual impact
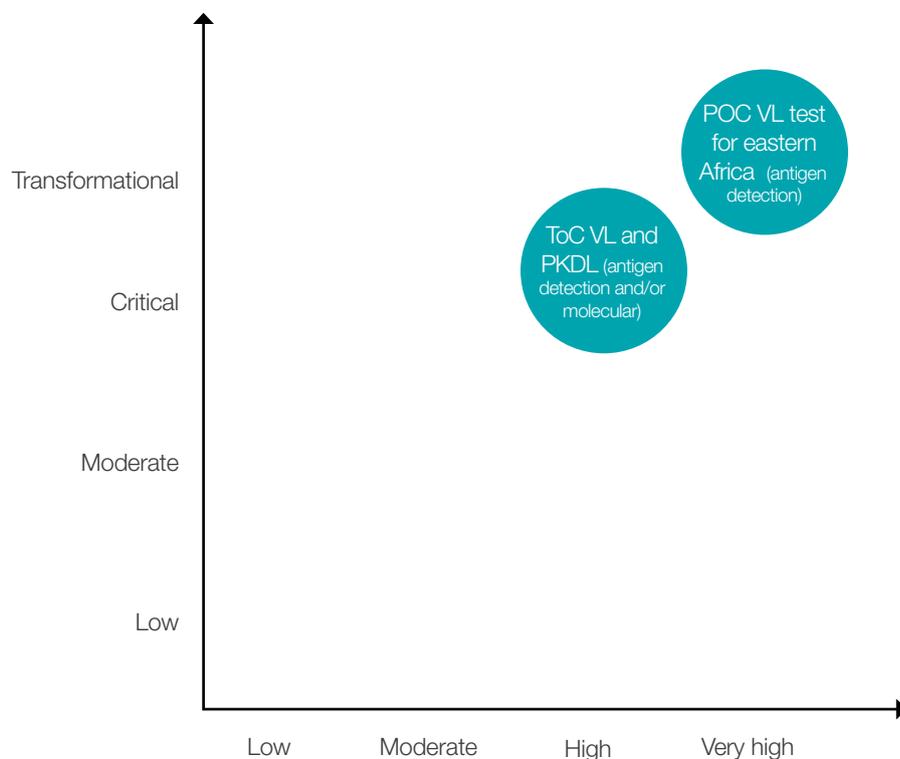
Likelihood of success
- Technical feasibility
- Availability of funding
- Fit with FIND's capabilities/strategy

Key

● Core FIND focus

Enabling interventions

We will continue supporting activities that create an enabling environment for faster development and improved access to technologies for accelerated control and elimination of leishmaniasis. This includes advocacy to ensure updated policies and guidelines on surveillance and control of the disease are available. For this, FIND will continue promoting collaborations with key partners, such as DNDi, the PKDL consortium and WHO.

Expected impact

A more sensitive test for VL will increase the proportion of patients with an accurate diagnosis, especially in eastern Africa where rk39 is not sensitive enough. This new tool will contribute to the WHO roadmap and London Declaration of 2012 on NTDs to control VL by 2020. The impact of the proposed diagnostic solutions will be a reduction in mortality by 20% among VL patients in high burden countries by 2020.

A test of cure will improve monitoring of treatment and will enable a reduction in the follow-up period in good responders, and prediction of relapses and treatment failure in non-responders. In Southeast Asia, the average cost of treating a VL patient is estimated to be 17.5% of the average household income; the average economic cost to the household (i.e. cost of treatment plus the opportunity cost of work days lost) represents 44.4% of the average household income. If a patient does not respond well to treatment and requires second-line therapy, early detection of such cases will limit the additional costs for retreatment and reduce the burden on the family.

Potential partners

The test for *Leishmania* antigens in urine and the LAMP assay are being developed in collaboration with Eiken Chemical Co. (Japan), Kalon Biologicals (UK), DNDi (Switzerland), Royal Tropical Institute (Netherlands), Institute of Endemic Diseases (Sudan) and the Infectious Disease Research Institute (USA), among others. The diagnostic tests will be evaluated in a number of endemic countries in eastern Africa, Southeast Asia and South America, and will include collaboration with health ministries. For validation of new biomarkers and development of a sensitive point-of-care test, FIND will partner with existing networks and organizations.
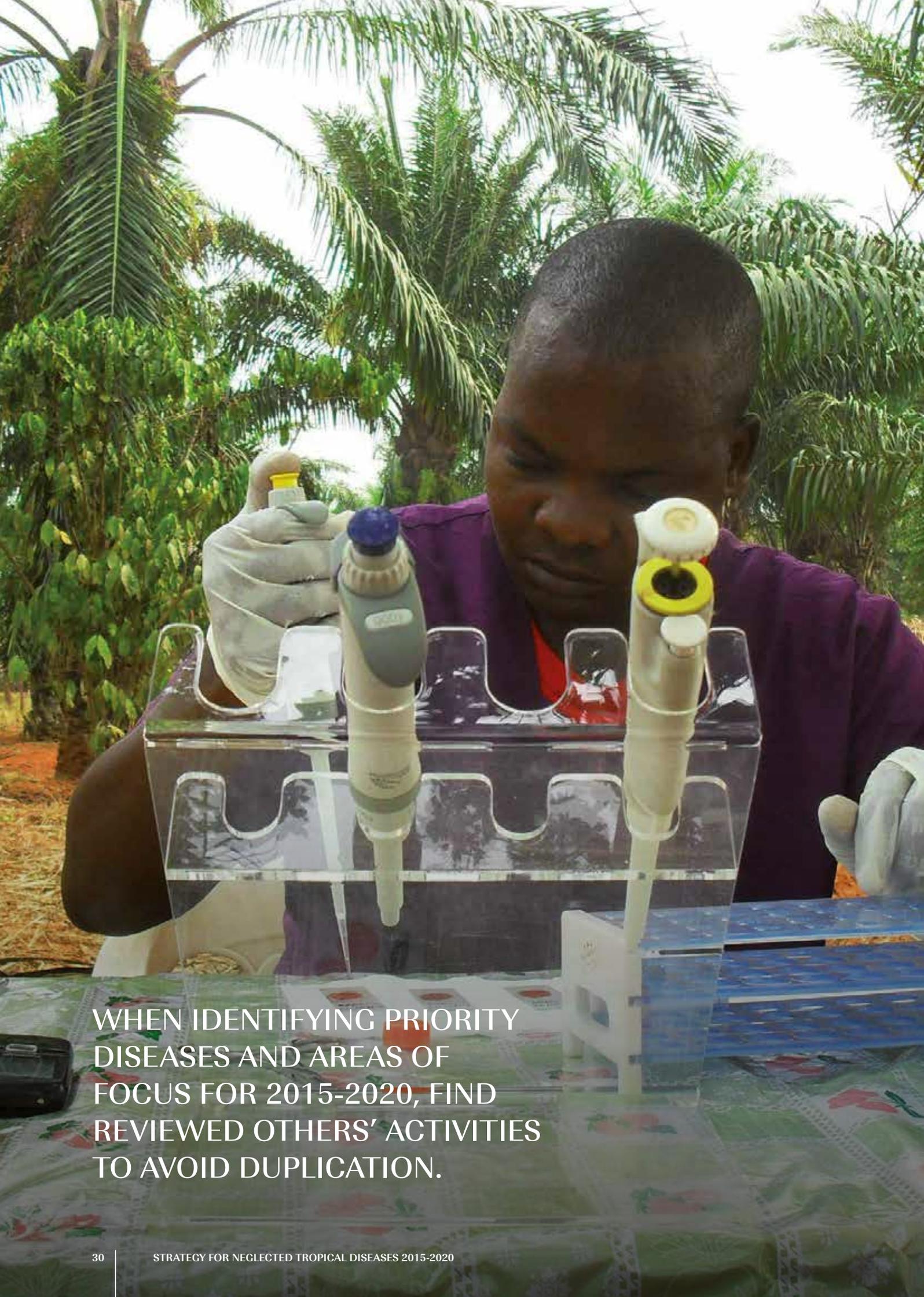
WHEN IDENTIFYING PRIORITY
DISEASES AND AREAS OF
FOCUS FOR 2015-2020, FIND
REVIEWED OTHERS' ACTIVITIES
TO AVOID DUPLICATION.

Soil-transmitted helminthiases and dengue

As part of the NTD strategy, we have included soil-transmitted helminthiases and dengue as priority diseases. Because these are new disease areas for FIND, we will undertake extensive landscape analysis and hold expert meetings to develop appropriate strategies in each area. The resulting strategies will be included in a future update to the NTD strategy. Below we summarize the preliminary rationale on each of these diseases and reasons for selection.

Soil-transmitted helminthiases – This group of worms – including roundworms (ascariasis), whipworms (trichuriasis), hookworms and species of the genus *Strongyloides* – has been prioritized because of the need for improved diagnostics and the limited number of other stakeholders involved in the field. Current strategies for controlling a number of NTDs, including soil-transmitted helminthiases, rely on stool microscopy and mass drug administration (MDA). Since diagnostics are significantly more expensive than treatment and current tests are not sensitive enough, a "test and treat" approach has been considered unfavourable. Preliminary expert consultations indicate that many MDA projects are conducted without proper surveillance planning or monitoring and evaluation, and disease burdens can quickly relapse to pre-treatment levels.

As we develop our strategy for soil-transmitted helminthiases, we will also support the development of diagnostics that aid implementation of MDA and inform population-level decision-making (not individual case management). Diagnostics are essential in identification of target communities for application of MDA programmes, assessing the intensity of transmission, monitoring efficacy of MDA as well as drugs, determining when elimination has been achieved to justify interruption of the programme and for continued monitoring to ensure sustained elimination. We will also examine opportunities for programmatic synergies (e.g., through combination tests or working closely with the animal health community). However, given differences in biology, we will likely explore separate tests for strongyloidiasis and the other soil-transmitted helminthiases.

As with soil-transmitted helminthiases, **dengue** has been carefully chosen because it has unique needs around quality, prioritization and access to diagnostics. The current situation of dengue virus infection (as well as **Chikungunya virus**) is that of frequent epidemics, with spread of the virus to new regions. In the last decade, research on a dengue vaccine has attracted much attention and funding; indeed, different vaccine candidates have been tested in clinical trials with promising results. There remain gaps, however, concerning the lack of a uniform approach to surveillance, outbreak detection and response and the incomplete implementation of vector control. A new diagnostic challenge will arise once the vaccines are made available in endemic areas: the current dengue vaccines are based on a cocktail of viral antigens (including whole inactivated virus or recombinant proteins) from the four dengue virus types. Vaccinated individuals would elicit pan-dengue antibodies, which will impede diagnosis based on antibody detection. While diagnostic approaches to detect viral antigens or nucleic acids would be appropriate in this scenario, they lack sensitivity after five to six days of infection. Available detection methods are expensive and require some degree of technical expertise to be performed. Thus, a robust, quality-assured, antigen-based RDT is urgently needed, and different approaches to detect NS1, a non-structural protein, are currently under evaluation.

Because global dengue initiatives are not focused on diagnostics, there is a clear gap to be filled, according to WHO. The identification of markers of severity is also crucial from a clinical standpoint; this is particularly important in the current situation of spread and overlap of both dengue and Chikungunya virus where the latter may mimic the febrile phase of dengue infection. There are also unique opportunities for interacting with other FIND initiatives through our programmes in malaria and acute febrile syndrome. The dengue strategy process will therefore include identification of FIND's specific role in this area.

FIND'S IMPACT IN THE FIGHT AGAINST NTDs

Intervention	Direct indicators by 2020	Patient-important outcomes and population-level indicators
Increase early detection of HAT cases through improved tools and screening strategies	• HAT RDT being used in 70% of all at risk populations (≥1 HAT case/10^6 inhabitants/year) • Feasibility and impact of using 2nd generation test in a "test and treat" approach • HAT/malaria combo test being used in 30% of all at-risk populations (≥1 HAT case/10^6 inhabitants/year)	Patient-important outcomes: • Earlier and easier identification of suspects and referral Population-level indicators: • Contribute to reduction in global number of new cases to 3,500 per year by 2017, and to less than 2,000 by 2020 • Increase in the population under surveillance for HAT • Reduced proportion of patients detected with advanced disease • Reduced disease transmission • Reduced disease prevalence • Elimination of HAT is accelerated and sustained
Improve confirmation of HAT cases	• LED fluorescence microscopy and highly sensitive molecular detection method being used in 70% of all at-risk populations (≥1 HAT case/106 inhabitants/year)	Patient-important outcomes: • Earlier and easier access to diagnosis and appropriate treatment Population-level indicators: • Contribute to reduction in global number of new cases to 3,500 per year by 2017 and to less than 2,000 by 2020
Improve detection and early treatment of congenital Chagas disease	• Sensitive point-of-care test for congenital Chagas disease to test newborns at place of birth developed and evaluation initiated in 3 countries • Field-implementable molecular test for congenital Chagas disease to test newborns introduced in 5 countries	Patient-important outcomes: • Increased proportion of cases of congenital Chagas disease detected at birth • Reduced proportion of cases of congenital Chagas disease that advance into chronic disease • Improved treatment outcomes in congenital Chagas disease Population-level indicators: • Population coverage in screening for congenital Chagas disease increased • Decrease in the prevalence of Chagas disease

Intervention	Direct indicators by 2020	Patient-important outcomes and population-level indicators
Develop a test of cure for Chagas disease, which could also be used to diagnose chronic and immunocompromised patients	• Biomarkers validated and evaluated in 3 countries	Patient-important outcomes: • Increased proportion of Chagas disease cases with an early diagnosis • Reduction in time to confirm cure • Early identification of treatment failure and initiation of re-treatment Population-level indicators: • Reduction in Chagas disease prevalence • Reduced mortality from Chagas disease
Prevent disease progression by early detection of Buruli ulcer in symptomatic patients	• A highly sensitive test for detection of Buruli ulcer in symptomatic patients is rolled out in 60% of endemic countries	Patient-important outcomes: • Increased proportion of Buruli ulcer cases that are detected early and put on appropriate therapy • Reduced proportion of patients with ulcer that are misdiagnosed as Buruli ulcer Population-level indicators: • Prevalence of Buruli ulcer reduced • The stigma associated with Buruli ulcer is reduced through early treatment
Identify Buruli ulcer cases among symptomatic patients using a test for screening at the primary or community level	• A point-of-care screening test for Buruli ulcer is rolled out in 50% of endemic countries	Patient-important outcomes: • Earlier and easier identification of suspects and referral for confirmation Population-level indicators: • Population under surveillance for Buruli ulcer increased • Prevalence of Buruli ulcer reduced • The stigma associated with Buruli ulcer is reduced through early treatment

Intervention	Direct indicators by 2020	Patient-important outcomes and population-level indicators
Contribute to leishmaniasis elimination by developing highly accurate tests for case detection, monitoring therapy and surveillance	• Sensitive point-of-care test for VL available and in use in 6 high-burden countries • Test for Leishmania antigen detection in urine and LAMP in use in 6 high-burden countries to follow up therapy and to assess cure	Patient-important outcomes: • Percentage of patients with an accurate diagnosis increased • Proportion of patients put on appropriate therapy with positive prognosis • Early detection of relapses, and initiation of alternative therapy/prophylaxis • Reduction in the period of follow-up to confirm cure, number of lost to follow-up decreased and the quality outcome of clinical trials increased Population-level indicators: • 20% reduction of visceral leishmaniasis incidence • 10% reduction of visceral leishmaniasis-associated mortality
Improve detection and understanding of the epidemiological role of asymptomatic infections and PKDL patients in regions targeted for Leishmaniasis elimination	• Appropriate diagnostic methods selected and role of asymptomatic infection and PKDL patients clarified • Sensitive test for VL developed and introduced in regions targeted for elimination	Patient important outcomes: • Improved management of PKDL patients and asymptomatic carriers Population level indicators: • Elimination of leishmaniasis is accelerated and sustained

THE NEXT STEPS

This strategy clarifies our role in supporting the development of diagnostic solutions in the field of NTDs, paying special attention to diseases included in the WHO Roadmap on NTDs and the London Declaration of 2012. When identifying priority diseases and specific areas on which to focus in the period of 2015-2020, we took into consideration the activities of other actors fighting NTDs in order to minimize duplication of efforts. Activities that were ongoing before operationalization of the strategy will continue to a logical conclusion, while future efforts will be guided by the strategy.

Going forward, FIND will intensify its work with WHO and expert groups to build consensus on the unmet needs and priorities for soil-transmitted helminthiases and dengue. Priority will be given to projects that can exploit available diagnostic platforms and test development partnerships. A major role for FIND will be working closely with WHO to ensure regular convening and goal setting around these and other NTDs. For these goals to be met, lobbying for global financial commitments to support NTD diagnostics will be a critical activity.

STRATEGY FOR NEGLECTED TROPICAL DISEASES

2015-2020