FIND
foundation
for innovative new diagnostics

MALARIA
STRATEGY

September 2012

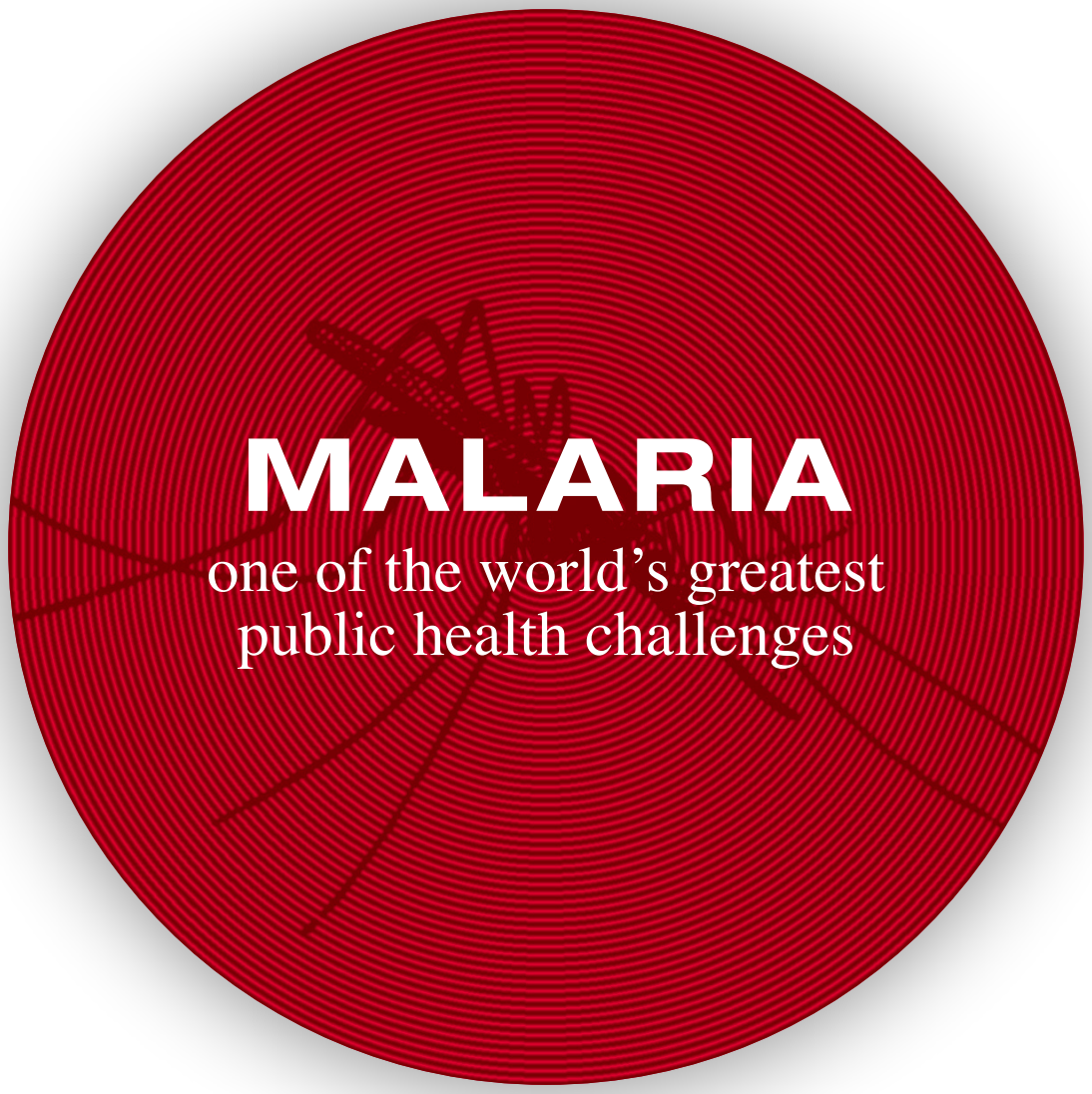
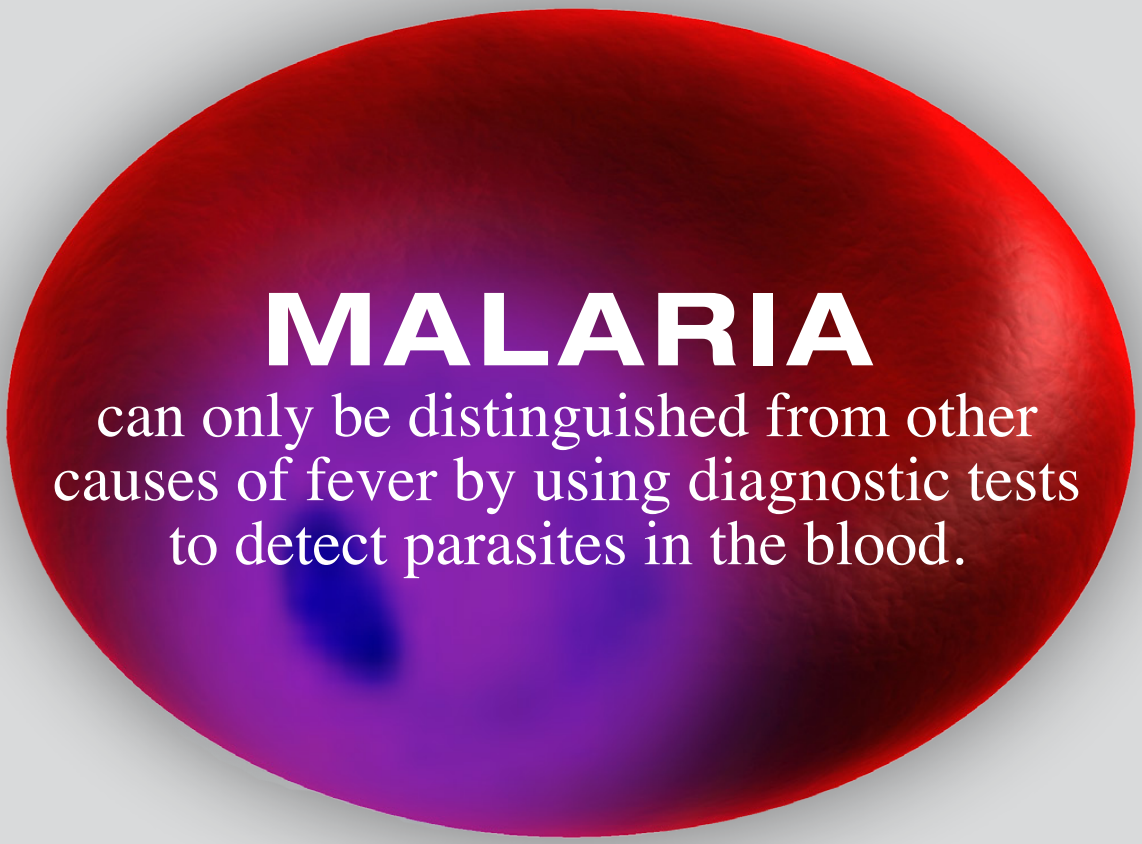

MALARIA
one of the world's greatest
public health challenges

Table of contents

FIND

is dedicated to deliver the malaria diagnostic tools necessary for the world to reduce malaria as a public health burden and ultimately fulfil its goal of elimination.


MALARIA
can only be distinguished from other causes of fever by using diagnostic tests to detect parasites in the blood.

Preface

FIND malaria strategy

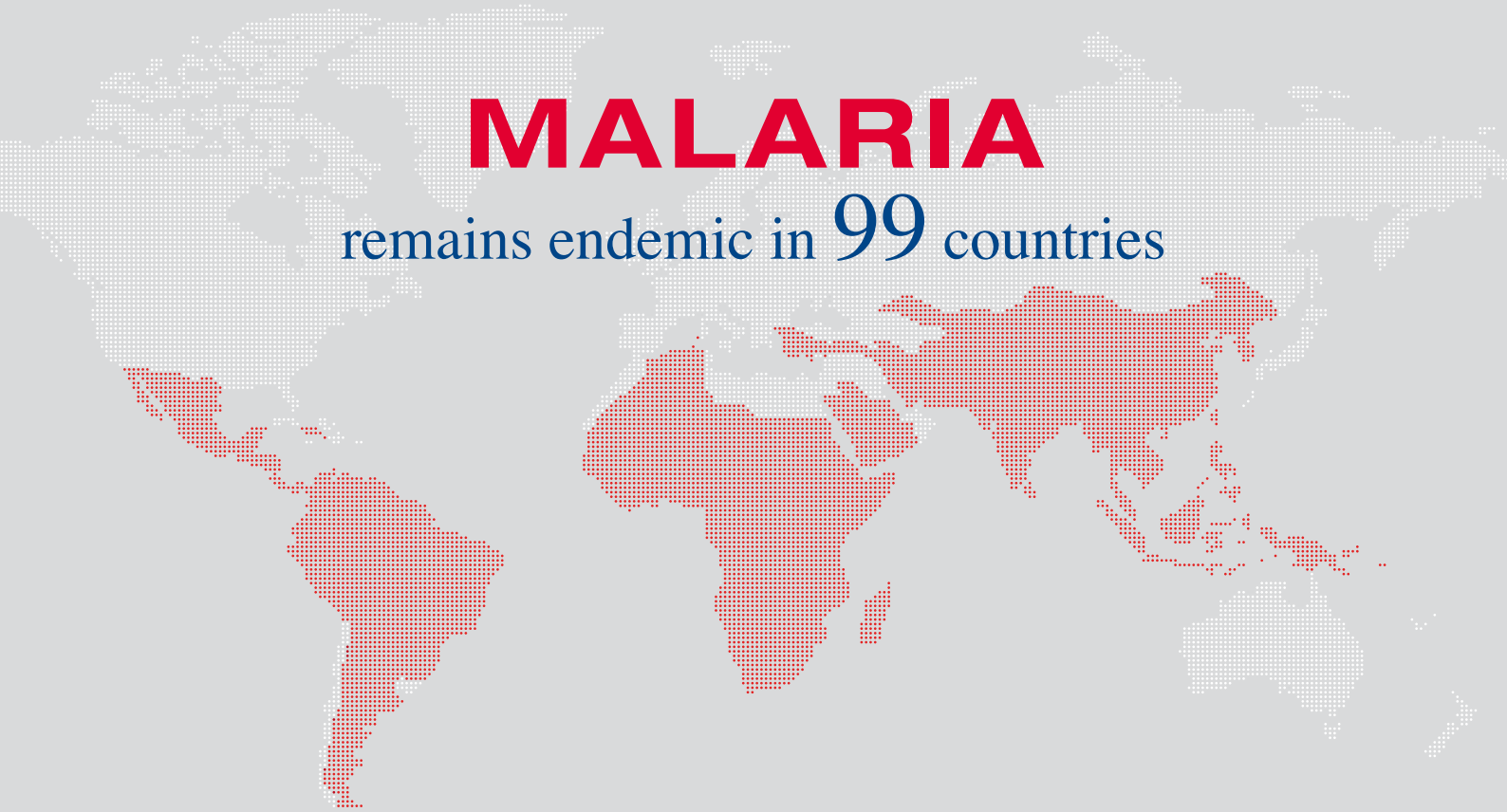
Diseases can only be treated, and eliminated, if they can be accurately identified. Malaria is no exception. Although it is both curable and preventable, malaria remains one of the main causes of mortality due to infectious disease. People, especially children, continue to get sick and die, while anti-malarial drugs are given to people who have other diseases, and could be saved if given correct, effective medicines. This makes no sense in the modern world.

We believe it is possible for the burden of malaria to be dramatically reduced and in many cases eliminated, improving peoples' health and strengthening the ability of communities and countries to lift themselves out of poverty. To achieve this, people at risk must have access to basic diagnosis, distinguishing malaria from other treatable diseases. Countries must have the information necessary to target the arsenal of effective malaria resources to communities that would most benefit. Donors must be able to see the impact and benefits of their funding. This requires access to accurate malaria diagnosis whenever someone at risk of malaria has symptoms. Accurate malaria diagnosis is now a global policy, but remains inaccessible to most people who would benefit from it.

By development of new tests and more effective use of existing tests, we can more intelligently manage the current anti-malarial arsenal, including drugs, bed-nets and, in the future, vaccines, to control and eliminate this disease. This requires a relatively low investment in terms of overall malaria research and development, but without this, recent gains and future progress in malaria control are at risk. FIND is dedicated to addressing this gap, identifying and addressing the needs of malaria diagnosis to deliver the tools necessary for the world to reduce malaria as a public health burden and ultimately fulfil its goal of elimination.

MALARIA

kills over 750,000 people annually, 90% of them children in low-income African countries.


MALARIA
remains endemic in 99 countries

Introduction to malaria diagnostics and FIND

The need for high quality malaria diagnosis

The greatest obstacle to the care and control of many diseases in the developing world is a lack of accurate and appropriate diagnostic tests – reliable and inexpensive tools that can rapidly and accurately identify who is sick, and why.

Successful health care relies on the information that good diagnosis delivers: Information for correct treatment, and information on where diseases are occurring, and whether the interventions aimed at them are working.

Without these tools, patients are often misdiagnosed and the causes of their illness may remain unrecognized until too late. Delayed diagnosis can result in more expensive and less effective effectual treatment, spread of infection to other people, and severe illness and death. The inability to diagnose diseases properly frustrates care provider and reduces patients' faith in the healthcare system. Poor monitoring of disease and interventions wastes resources that could be used more appropriately elsewhere.

Importance of diagnostics: inaccurate vs. accurate diagnosis

	Individual health	Public health	Overall impact
Syndrome-based diagnosis leads to	Potential mis-treatment leading to continued illness	Continued transmission	Growing prevalence & burden of disease
	Potential death	Waste of resources	Misallocation of resources
		Loss of confidence in the health system	Loss of output & increased poverty
			Lack of data to guide planning
Disease mangement based on accurate diagnosis means	Correct treatment & management	Reduced disease transmission	Improved management
	Good health	Confidence in the health system	Accurate disease statistics
			Well-targeted resources

Malaria is one of the main scourges in many low-resource countries. The disease remains endemic in over 99 countries and 95% of the population in sub-Saharan Africa is at risk of infection. It has one of the highest mortality rates of any infectious

disease globally, killing over 750,000 people annually, 90% of them children in low-income African countries.[1] Non-malarial fever also exerts high mortality, emphasizing the need to distinguish one from the other. In nearly all cases, mortality is avoidable if the correct treatment is given early for both malaria and non-malarial fever.

Effective drugs are available for treating malaria, usually artemisinin-based combination therapy for *P. falciparum* infection, and chloroquine for other species. Lack of good quality, reliable malaria diagnosis results in waste of anti-malarial drugs, and prevents the targeting of bednets, indoor residual spraying and other expensive control measures to the areas where they are most needed.

Malaria cannot be reliably distinguished from other causes of fever without the use of diagnostic tests that detect the presence of malaria parasites in the patient's blood. In fact, even in areas that are generally considered to have high malaria prevalence, only a minority of individuals with malaria-like symptoms may actually have malaria. WHO now recommends parasite-based diagnosis in all cases of fever, to decide whether anti-malarial drugs should be given to the patient. Increasing efforts to eliminate malaria in many countries make diagnosis even more vital. FIND is addressing this need for high quality diagnosis by finding innovative ways to improve the use of existing tools and through the development of new technologies.

This focus on malaria diagnosis is pursued at FIND within the context of the wider field of acute management of fever, and the need to effectively integrate implementation of tools developed under FIND's initiatives into the wider health system. Ultimately, good diagnosis will reduce childhood and adult mortality, enable other interventions to achieve their potential, and provide the information necessary to eliminate malaria.

FIND's rationale

FIND exists to address the market failures that have resulted in the paucity of appropriate diagnostics in disease-endemic, low-resource countries. The Organization focuses on two main areas of malaria diagnostics: Case management and Elimination. In both these areas, FIND's expertise is in the development of new tools to fill gaps or open new possibilities for intervention, and in innovative solutions to deficiencies in the use and implementation of existing ones. This requires the ability to match needs on the ground with technological know-how, and is based on a sound understanding of the business of diagnostics development.

The development of diagnostics specifically aimed at low-resource settings has been relatively ignored in the past, and the problem has been particularly acute in the case of malaria. FIND is uniquely placed – through its partnerships with industry, national disease programmes, research institutions and NGOs. It concentrates on diagnostic platforms with

1 *WHO: World Malaria Report 2010:* World Health Organization; Geneva.

2 *Staying the Course? Malaria Research and Development in a Time of Economic Uncertainty* Seattle: PATH; 2011.

potential to identify multiple diseases –identifying technologies likely to have high impact and accelerating their entry into the field. Additionally, FIND's know-how and partnerships with implementing agencies permits it to clearly demonstrate how and where these innovations can fit into, and improve, existing health system structures.

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

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

FIND's place in the development of diagnostic tests for infectious diseases

Research partners / industry	FIND	Implementation agencies
• Technical lab-based expertise • Primary research in the field • Research institutes in endemic and non-endemic countries • Industry – Manufacturers and suppliers	• Over 250 partners in research, implementation and industry • Technical expertise in product development and roll-out policy • Experience in other diseases • A focus on applicability to the field, quality assurance and evaluation	• Large scale implementation agencies /PDPs/NGOs • National ministries of health and in-country partnerships • Endorsement by the WHO

FIND works closely with both technical and advocacy working groups within the WHO and the Roll Back Malaria partnership. It maintains strong collaborations with research institutions in both endemic and non-endemic countries. FIND also works closely with other product development partnerships (PDPs), which together play a central role in malaria R&D, and have been responsible for the introduction of virtually all new malaria products delivered in the past five years.[2]

The current state of malaria diagnostics

Diagnostics for case management

Most patients in malaria-endemic countries are still diagnosed on the basis of non-specific symptoms. The resultant over-treatment of malaria from this syndrome-based management wastes valuable anti-malarial drugs, and results in the neglect and mistreatment of other common causes of fever. The alternative to this situation was generally the use of microscopy to detect parasites in the blood of patients. The quality of microscopy can vary significantly based on the lab technician, and requires considerable training. Given the widespread lack and unreliability of microscopy services in most endemic countries, simple rapid diagnostic tests (RDTs) that can detect circulating *Plasmodium* antigens in a drop of finger prick blood have been widely adopted in recent years to fill the gap in diagnostic capacity. While good quality RDTs can be cheap, easy to use and very effective when used well, their widespread acceptance has required a change in mindset on the part of governments, caregivers and patients due to the commonly held but mistaken belief that "fever equals malaria" and therefore a specific test is not necessary. Introduction in the private sector, a major conduit of health care delivery in many countries, will require many further changes in practice and understanding of complex health seeking and provider interactions, but is no less essential to achieve universal diagnostic access.

The success of diagnostic strategies using these tools has depended on the reliability and accuracy of the tests at the point of use, a reliable supply chain and effective use of results. These are challenges. Test improvement is also needed in some aspects, particularly for detection of non-falciparum malaria, to fulfil their potential in malaria management. However, with systematic and well planned implementation, diagnostics can be used productively on a broad scale, bringing effective case management within reach of virtually all people and transforming malaria programme management (Box below).[3]

3 Thiam S, Thior M, Faye B, Ndiop M, Diouf ML, et al. (2011) *Major Reduction in Anti-Malarial Drug Consumption in Senegal after Nationwide Introduction of Malaria Rapid Diagnostic Tests*. PLoS ONE 6(4): e18419. doi:10.1371/journal.pone.0018419

4 *Staying the Course? Malaria Research and Development in a Time of Economic Uncertainty* Seattle: PATH; 2011.

Senegal case study

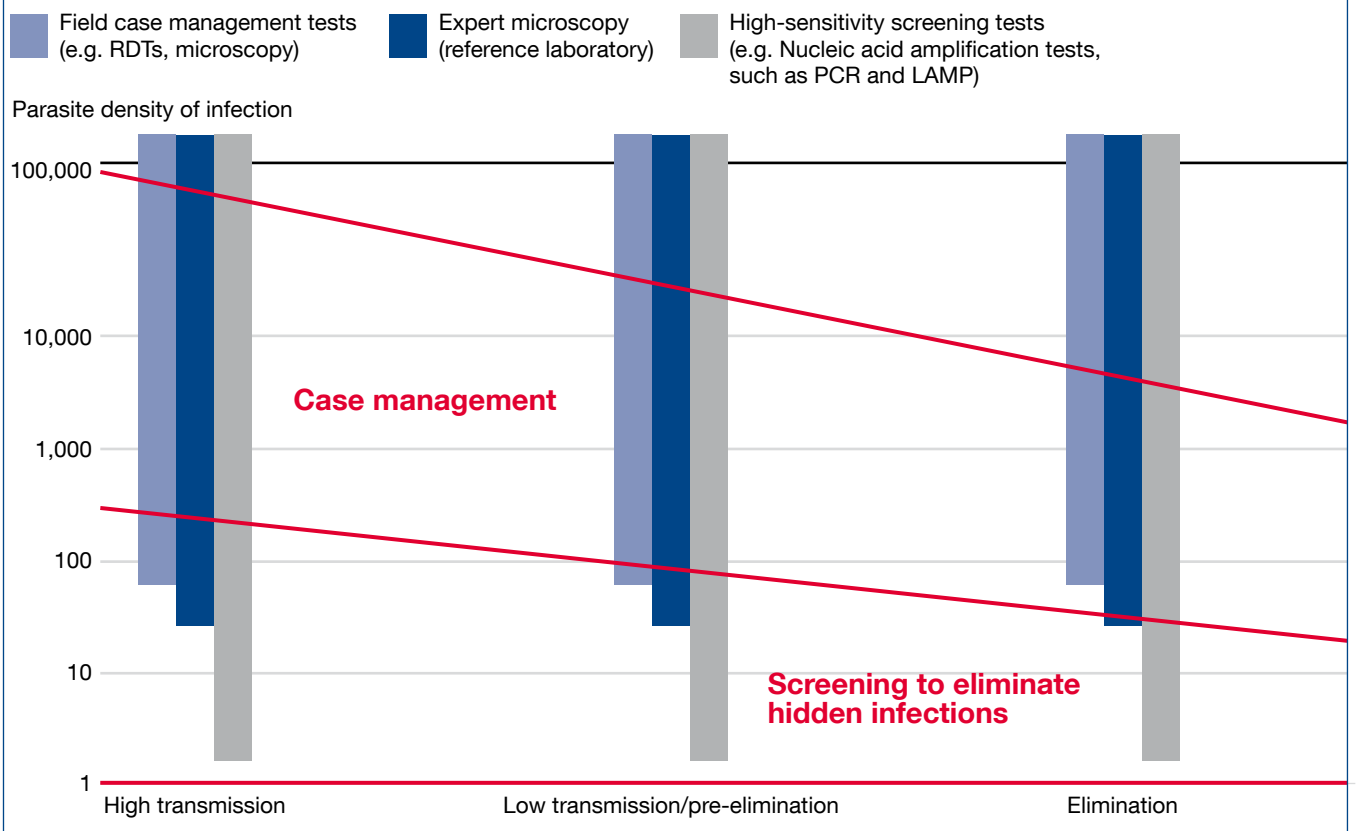
Country-wide introduction of quality-assured RDTs can have a significant impact – only with strong partnership of the national government.

In 2007, the Senegal national malaria control programme started to introduce universal parasite-based diagnosis using malaria RDTs in all public health facilities. Parasite-based diagnosis increased nationally from 3.9% of reported malaria-like febrile illness to 86% over a three year period[4]. The prescription of ACT dropped throughout this period from **72.9%** of malaria-like febrile illness to **31.5%**, reaching close equivalence to confirmed malaria (29.9% of 584,837 suspected fever cases). An estimated **516,576** courses of inappropriate ACT prescription were averted. In 2009, the Global Fund could retain an estimated **$1.57** million in unused funds allocated to ACT procurement in the previously agreed grant for the Senegal programme.
The move from symptom-based to parasite-based diagnosis demonstrates that effective roll-out and use of malaria RDTs is achievable on a national scale through well-planned and structured implementation. Today, accurately predicting anti-malarial drug requirements allows Senegal to procure the appropriate quantities of drugs and allows concentration of resources on areas of actual higher malarial burden and need.

Diagnostics in elimination programmes

As new tools and funding have reduced malaria prevalence in recent years, the elimination of malaria has resurfaced as an achievable goal. The global community has been increasingly devoting attention and resources to interrupt the transmission of this disease in high-prevalence areas. However, the tools likely needed to achieve this goal - including low-cost broad-scale high-specificity survey assays and technologies for the detection of continuing reservoirs of infection and cases of low parasite density in the field – remain unavailable or too expensive to enable sustainability in national malaria programmes. Currently, tests that are sufficiently sensitive require specialised laboratory equipment and highly trained personnel. Based on nucleic acid detection, such as PCR, they are often restricted to national reference laboratories of developing countries, or capacity does not exist at all. Without these tools, however, it will be impossible to find areas of continuing transmission and target them effectively (Figure below).

The place of various diagnostic tests in malaria detection



Where transmission is high (left), people with symptoms will nearly always have detectable levels of parasites. Microscopy and RDTs are usually adequate. When malaria becomes rare, however, (right of chart) and elimination is considered, it becomes increasingly important to have highly sensitive detection tests to identify cases who have no symptoms, but who may be significantly contributing to transmission.

Addressing non-malarial fever

Similarly, a gap remains in the availability and use of tools to detect common, treatable causes of non-malarial febrile illness (NMFI). These tests are essential to ensuring that fever is managed effectively and, in turn, that malaria programmes remain credible in regions where malaria is the cause of a small and shrinking fraction of febrile illness. This is a major area of need that must be addressed in a manner closely integrated with malaria, and is a major future focus for FIND. To this end FIND has developed a Non-malarial Febrile Illness Strategy (see AFS-NMFI strategy for more detail)[5].

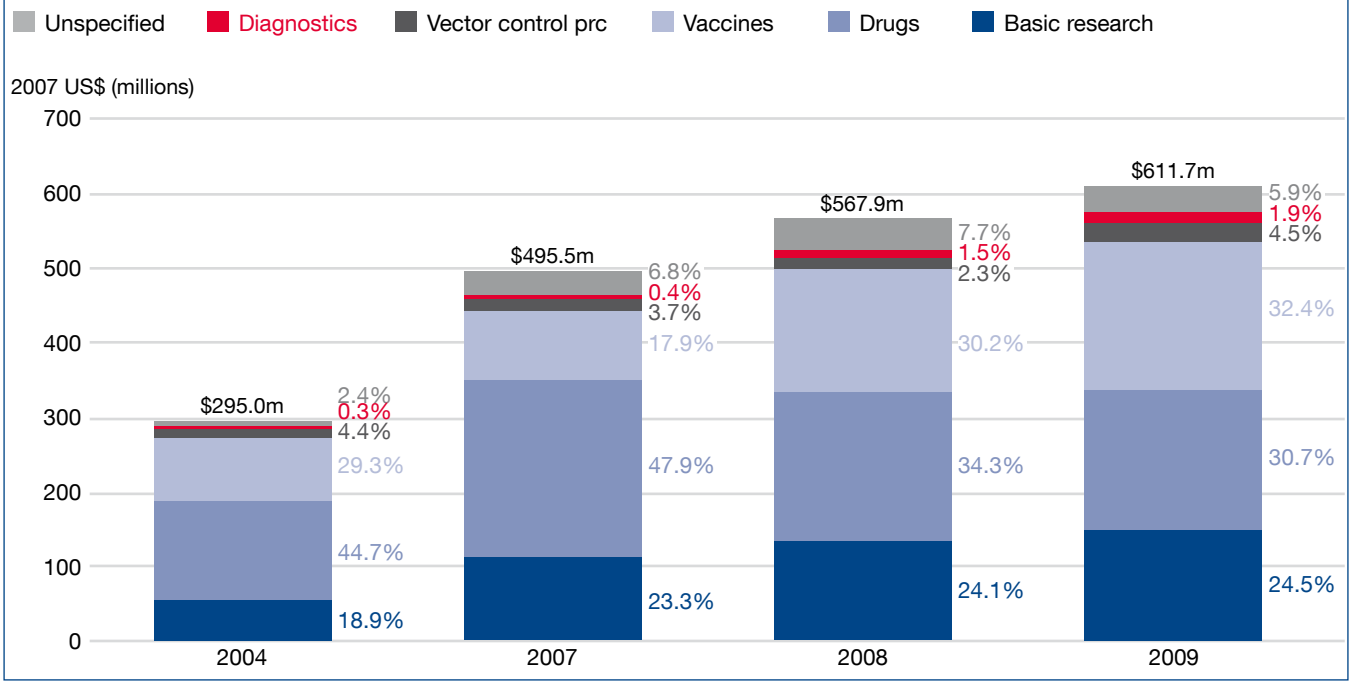
The need for greater investments in R&D for malaria diagnostics

Malaria diagnostics received just 0.3% of the total malaria R&D funding in 2007, and this proportion increased to 1.9% in 2009 (Figure below). However, funding remains well below the levels needed for successful advancement in the field, especially as countries move towards elimination. Diagnostics have the potential to 'deliver a high health impact for a relatively modest investment of resources', and to greatly improve the impact of other interventions[6].

5 http://www.finddiagnostics.org/programs/malaria-afs/

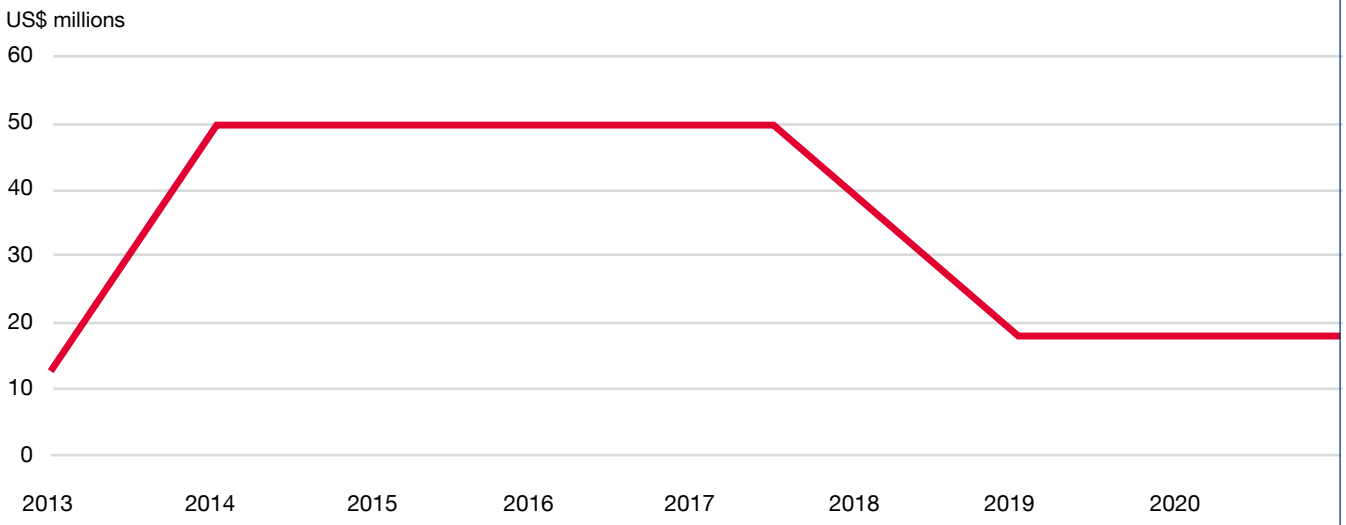
6 *Staying the Course? Malaria Research and Development in a Time of Economic Uncertainty* Seattle: PATH; 2011.

Malaria R&D funding, 2004-2009[6]



In its 2011 report on malaria R&D funding, PolicyCures recommended an immediate quadrupling of malaria support to around $50 million per year if targets and goals are going to be met. As effective diagnostics are needed to support the development of all other malaria control tools as well, a lag in diagnostics development will further impede the impact of investments elsewhere. If this increase can be realized, funding needs would then drop rapidly after 5 years when the first new diagnostics have been completed and made available (Figure below). It is clear in R&D that 'maximum savings in lives and dollars will be achieved by adequate up-front funding, rather than provision of inadequate funds over many years[7].

Funding needs for malaria diagnostics R&D



Projected malaria diagnostic R&D funding needs. An increase in investment from the 2012 level, quadrupling current funding, though still low in terms of total malaria R&D funding, would enable delivery of high-need products, This will reduce future R&D requirements and increasing the impact of other interventions, current and under development. (Modified from PolicyCures)[8]

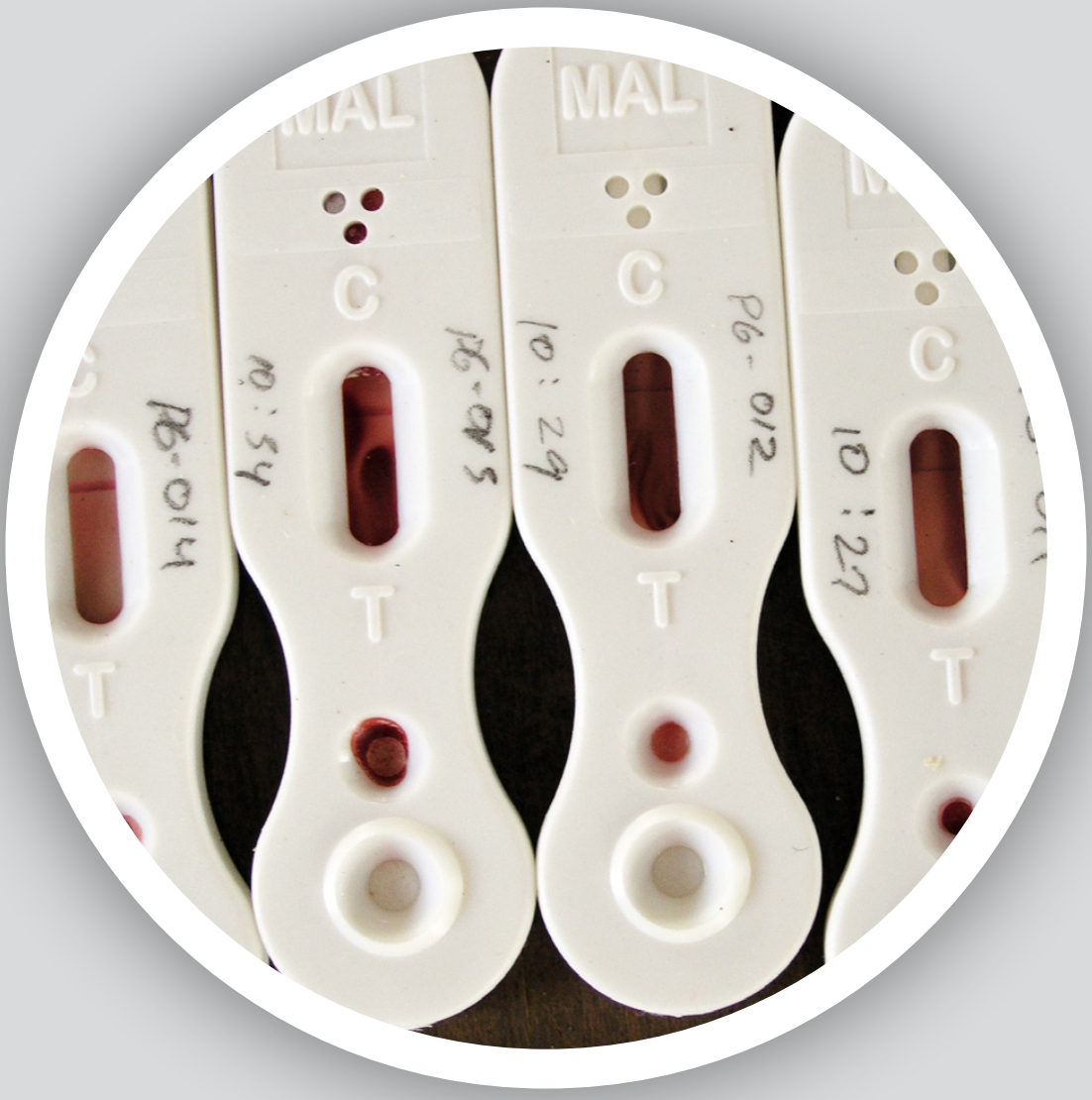
PolicyCures goes on to highlight the need for investment in strengthening regulatory capacity in Africa.[9] A major focus of FIND's work so far has been on the development of standardized quality control materials for national and clinic-based lot testing of RDTs. This will enable a greater degree of national ownership over the current international system, thereby reducing the need for ongoing donor support.

7 http://www.georgeinstitute.org.au/sites/default/files/pdfs/G-FINDER_2008_Report.pdf

8 *Staying the Course? Malaria Research and Development in a Time of Economic Uncertainty* Seattle: PATH; 2011.

9 Moran M, Strub-Wourgaft N, Guzman J, Boulet P, Wu L, et al. (2011) *Registering New Drugs for Low-Income Countries: The African Challenge.* PLoS Med 8(2): e1000411. doi:10.1371/journal.pmed.1000411

FIND's work in malaria started in 2007 with a focus on developing quality control systems for RDTs and has since expanded to include other ways to maximise impact of RDTs and the development of new tools.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FIND's impact on the malaria landscape to date

Achievements and impact in the development of new products

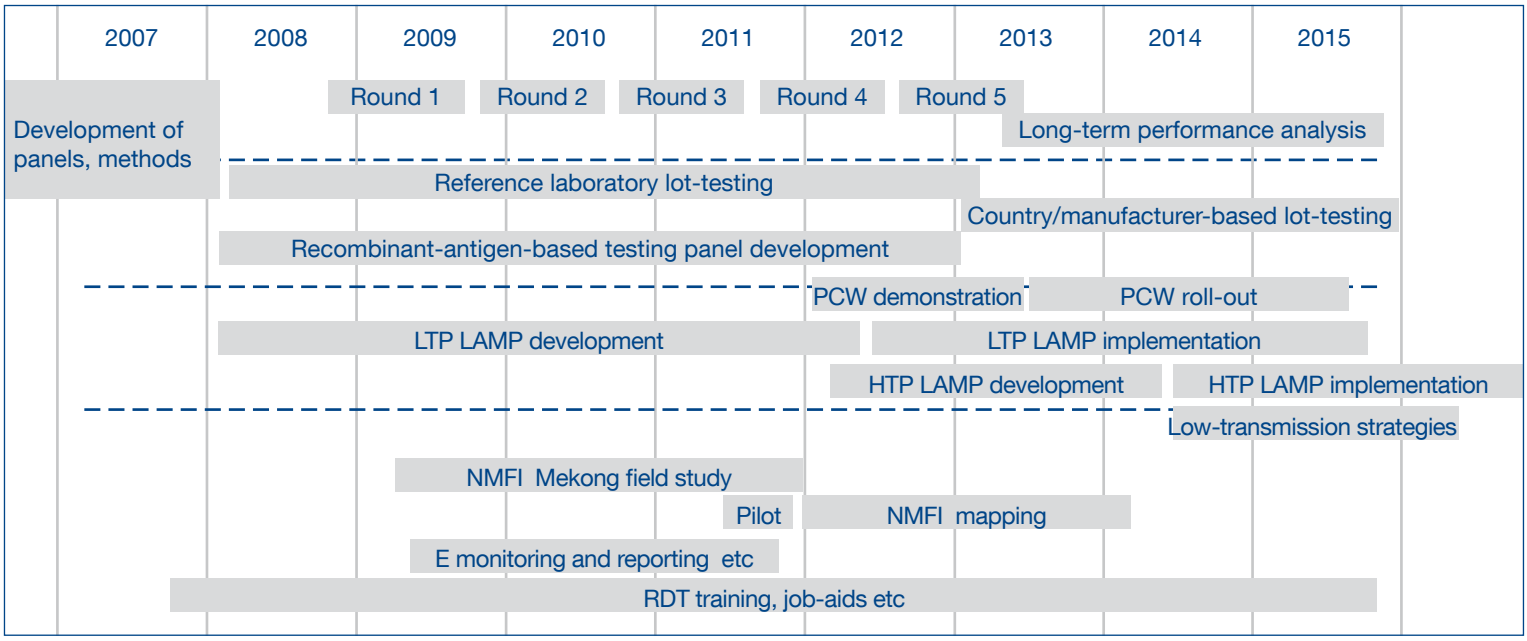
FIND has focused its activities on addressing the gaps in the malaria diagnostic landscape. To this end, FIND's work has relied on both maximizing the impact of diagnostic tools that already exist, and on developing new tools where these are needed. FIND's work in malaria started in 2007 with a focus on developing quality control systems for RDTs - which was and remains essential to building confidence in the quality of these tests – and has since expanded to include other ways to maximise impact of RDTs and the development of new tools. The main achievements so far include:

Focus	Achievements
New products	
Malaria LAMP	A first generation, highly sensitive nucleic acid detection test that allows PCR-level sensitivity for malaria diagnosis to be achieved in a near-field situation from an off-the-shelf test. This assay promises to open new doors in detection of infection in elimination situations, and a range of specific applications previously difficult to support in many endemic countries.
New solutions to current problems in implementation of malaria RDTs	
Blood transfer device	FIND coordinated design, evaluation and manufacturing of new blood transfer device, shown to be simpler and safer than existing designs. These are now being used with malaria rapid tests, to the order of millions, in low-income countries.
SMS-messaging for stock management	With Uganda Ministry of Health and Columbia University's Earth Institute, FIND implemented a pilot programme using SMS-messaging to manage malaria drug stocks and to report malaria diagnostic results and other disease incidence in Uganda. This programme is now being scaled up nationwide by the Uganda MoH.
RDT job-aids and training	FIND and partners have developed and tested a range of instructions and training materials shown to improve the quality of RDT use by health workers in remote field situations. These are now available in multiple languages, for a wide range of RDT products.
Systematic quality control of malaria RDTs	In partnership with WHO and several institutions in endemic and non-endemic countries, FIND has developed and coordinated a global evaluation programme that guides most public sector procurement of malaria RDTs, and ensures they are safe to use before deployment to the field. Since the programme commenced, procurement has shifted markedly to higher-quality products and products improvement has been driven.

Other activities include monitoring of temperatures, work on low-technology cool storage and published guidance on RDT transport and storage. Together with a range of partners, FIND is finalizing an implementation manual to guide country programmes in the introduction and use of malaria RDTs.

Current malaria product pipeline

The evolution of FIND's activities over the years can be seen in the image below:



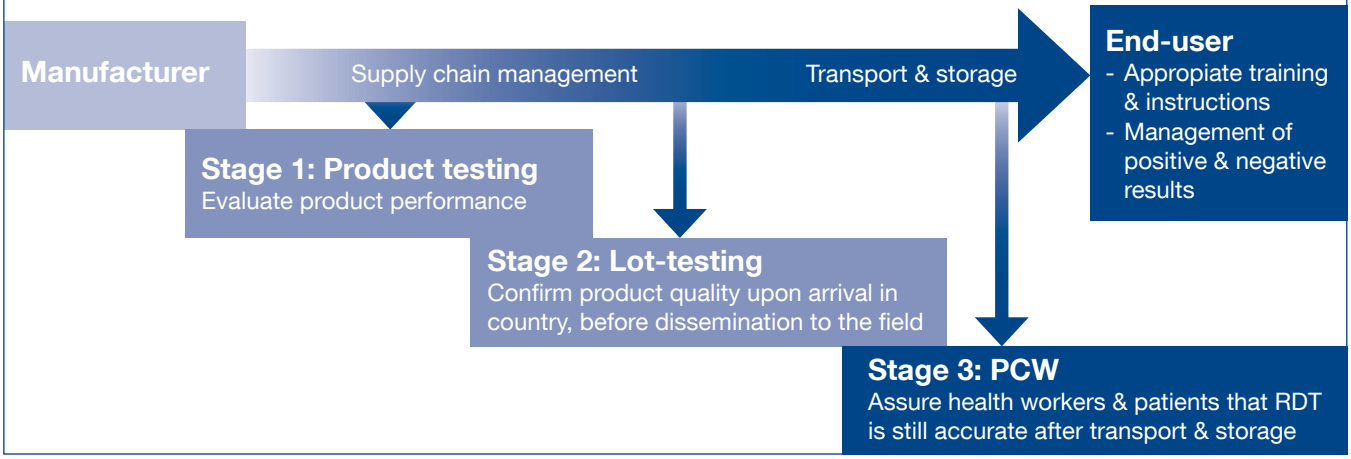
The programme on quality control of RDTs illustrates how a seemingly niche activity can actually significantly address a market failure, and have a substantial impact on the overall market for RDTs (see box oposite page). There are more than 40 manufacturers of malaria RDTs, most of which are relatively small companies with limited capacity to conduct R&D. Until now, a lack of international standards for RDT performance had made it difficult for manufacturers to control quality of products and maintain high standards. The performance of RDTs has been shown to be highly variable, and degradation can occur at temperatures common in the working environment in tropical settings. This created a high degree of uncertainty in endemic countries about the appropriate selection and use of these tests.

FIND's quality control programme for malaria RDTs

FIND and partners have developed a 3-tiered model to ensure the quality of malaria RDTs all the way down to the point of use. This could serve as a model for the quality assurance of other point-of-care tests in low-resource settings.

Product and lot testing evaluations (stages 1 and 2 above) conducted by FIND, WHO and partners have provided a standard against which malaria rapid tests can be compared.

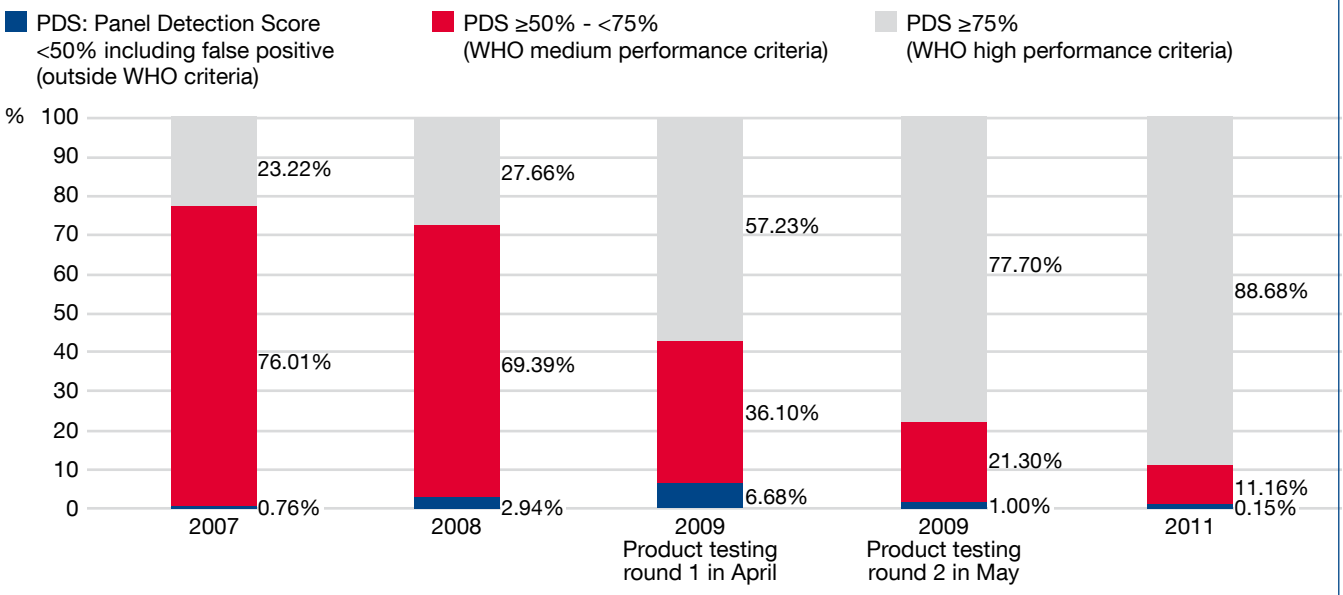
FIND model for point of care diagnostics quality control



Over 120 products have now been evaluated through the global product testing activity, with reports published in 2010 and 2011, and further results to be published in 2012. The results of the evaluations are now directly informing procurement by UN and other agencies, shifting the emphasis from price to quality. This has established a basis for the quality policy on malaria diagnostics of the Global Fund to Fight AIDS, TB and Malaria.

A preliminary analysis has shown that the relative market share of high quality RDTs has increased substantially over the past few years (see graph below). The lot testing programme found at two reference laboratories in Asia tests up to 50% of current public sector procurement, ensuring that each batch of tests is safe to use before deployment to the field.

Manufacturing output based on WHO procurement criteria



Preliminary analysis of RDTs manufactured 2007-2011 show an overall increase in the proportion of high performing RDTs produced and a decrease in proportion of low performance RDTs.

CASE MANAGEMENT

ELIMINATION

FIND's strategy can be broadly divided into two major priority areas: case management & elimination.

Improved management of *P. vivax* will be vital for elimination in many regions.

FIND's main areas of focus moving forward

FIND's strategy on malaria diagnostics to pursue both the development of new tools and the optimization of the use of existing ones, is closely aligned with the priorities identified in the malERA Consultative Group's conclusions on research needs for malaria diagnostics[10], and can be broadly divided into the 2 major priority areas:

- Management of very low transmission and elimination
- Improvement of case management.

In addition, FIND will also work on the development of new tools to support other interventions (utilizing FIND's product development expertise to support other areas of malaria R&D), and on tools to better manage non-malarial febrile illness (detailed in FIND's Acute Febrile Syndrome strategy).

Management of very low-transmission and elimination

The focus here is to screen populations, prioritize interventions and target anti-malaria resources more effectively.

FIND will work on:

- Development of tests suitable for surveys of wide geographical range to identify areas where transmission is continuing and how much, or where transmission has ceased and elimination been achieved (e.g. robust field serological tests).
- Development and demonstration of high-throughput, highly-sensitive tests to detect individually infected people within small *foci* of continued transmission, to speed up elimination in these remaining 'hot-spots'.
- Improved understanding of the role of these techniques, case management and active case finding in areas with different transmission intensities, to better understand the most efficient ways to continue to reduce malaria transmission in an affordable way.
- New and improved tests to prevent relapse of *P. vivax* by detecting G6PD deficiency.

Serology advancement

Serology tests enable the screening of large populations at relatively low cost to determine transmission intensity and to target resources. Current ELISA and lateral flow tests are

10 malERA: A research agenda for malaria eradication: diagnoses and diagnostics. PLoS Med 2011, 8:e1000396.

insufficiently simple, or have insufficiently-defined specificity to determine recency of infection. Further development of serological tools will be important to improve specificity and make the technology supportable in low-resource settings. FIND plans to work with a range of experienced partners, providing the product development expertise to drive the development and demonstration of new methods.

Rapid molecular surveillance tools

Highly sensitive tests are needed to detect lower levels of parasitaemia than those detectable by microscopy or RDTs. Although very low level parasitaemia is of less clinical importance, these parasite 'reservoirs' have significant implications for elimination strategies, especially in areas with potentially high transmission (high vectorial capacity). Identification of low-density infections will enable accurate determination of infection prevalence. Moving current PCR testing closer to study sites is hampered by the complexity and lack of robustness of the method, and high levels of external funding would be required to build and maintain capacity to conduct PCR in the affected countries.

FIND and partners have developed a malaria LAMP assay, a molecular diagnostic platform which can detect target DNA from patient samples with very high specificity and sensitivity. This test uses stable, dried-down reagents and is sufficiently robust to be used at a clinic level for screening purposes. FIND is engaged in optimizing the LAMP test to process higher numbers of samples at lower cost, and also identifying other assays that may in future address this need.

New strategies for low-transmission malaria management: incorporating tools and methods for improved screening and case management

FIND will focus on strategies to enable the continued use of malaria diagnostics in areas of very low transmission, where malaria itself ceases to be a major, immediate health priority. Emerging diagnostic technologies for stratification and screening need to be incorporated into broader health strategies, whilst identifying more effective ways to integrate malaria management into management of acute febrile disease in general. As malaria prevalence decreases, a shift in priorities is a real danger; under-resourced health services may no longer consider it financially or politically justifiable to continue implementing the current, relatively expensive models for malaria control. Resources will be channeled to other regions and to other, more pressing, health issues. However, the underlying conditions that allow for the spread of the disease remain. If these new realities are not addressed, any gains from the aggressive anti-malarial strategies in place now are likely to be lost in resurgence of the disease. Carefully controlled trials of new tools and methods, with strong health service involvement and field management expertise, are essential now to achieve this, setting new strategies for an intelligent, information-based approach to disease management.

P. vivax detection and management

Improved management of *P. vivax* will be vital for elimination in many regions. Determination of the safety of 8-aminoquniline drug use to eliminate the parasite from the body and prevent relapse will be vital to vivax malaria elimination. Detection of liver-stage vivax (potentially through identification of surrogates such as serology) may also be possible, and would allow more effective screening. FIND will work on prioritizing *P. vivax* detection in the development of the LAMP platform, and seeks to identify low-cost pathways to the identification of G6PD deficiency.

Improved case management

FIND will focus on increasing access to good quality tests to detect malaria disease.

In particular, FIND will:

- Target specific areas of need in the management of *P. vivax:*
  - G6PD testing, to allow safe use of effective current and emerging drugs
  - More sensitive detection of *P. vivax* infection

- Quality control of RDTs
  - Maintain global capacity to quality control existing and new RDTs
  - Complete development of recombinant antigen panels and positive control wells, and transition to these new techniques to ensure long-term sustainability of quality control and high standards for RDTs in the field

- Address key, specific gaps in RDT use, supply management, training and reporting.

- Continue to identify and improve specific improvements in current tools, including RDTs and microscopy.

- Determine the effectiveness of current and emerging tests in specific areas of need, such as ante-natal screening.

Companion diagnostics (e.g. for G6PD-deficiency)

In *P. vivax*-endemic areas, such as much of Asia and South America, treatment of liver-stage parasites will be needed to eliminate malaria. The only drug available to treat the liver stage, the 8-aminoquinolone ‘primaquine’, can be dangerous in people with significant G6PD deficiency, the most common human enzymopathy. Primaquine

also requires multiple doses spread over weeks. A potential long-acting replacement, tafenoquine, could greatly simplify treatment but is unlikely to be released without an effective low-cost field test to screen for G6PD deficiency and ensure drug safety. Such a test is badly needed to allow this new drug to be used and to have an impact on elimination of *P. vivax*.

FIND will work to:

- Improve the use of existing assays for G6PD
  - Gains can be made in standardization of current reference tests and in the development of innovative ways to use these for screening and later data retrieval, obviating the necessity to have them available for point of care testing

- Develop low-cost field tests
  - FIND is investigating the feasibility of new test formats that could be more field-stable and available at much lower cost

- A number of current, commercially available tests promise to move testing closer to patients. Thorough evaluation in a range of settings, these tests need to determine their place in G6PD detection, and to identify ways in which they may be further optimized.

- Develop an economic model to assess the financial feasibility of widespread testing in the settings of mass treatment.

Assure RDT quality and transition to a sustainable Quality Assurance system

The need for up-to-date information on RDT quality will continue to exist as new products enter the market, and the market expands. It is important that such evaluations be managed on a sustainable basis, supported where possible by mainstream programme funds. To this end, FIND, in collaboration with WHO, will continue to work on the development of synthetic panels based on recombinant antigens to replace the current parasite-based testing programme. Work is well advanced in the production of positive control wells (PCWs), which will allow community health workers to monitor the quality of RDTs at their point of use. Completion of these development programmes will provide readily accessible and predictable standards, common throughout the chain from manufacture to national programmes to the end users. FIND plans to roll these new methods out over the next 5 years, leaving the field independent of FIND involvement.

In the coming five years, FIND proposes to:

- Establish sustainable RDT evaluation and quality control based primarily on recombinant proteins.
- Replace the current lot testing process based in regional reference laboratories with standardized panels available to national programmes and manufacturers, referenced against existing data using blood samples. This marks the shift to the next stage of sustainable, country-based RDT lot testing, in a manufacturer- and user-funded programme.
- Roll out of PCWs at point of care level.
- Establish a revised product testing platform that can be performed in a rolling fashion (rather than annually), and that can be supported directly by user fees charged to companies submitting products, under the auspices of WHO or another appropriate body.
- Investigate the application of similar comprehensive and sustainable models of quality assurance to other disease programmes.

Improvements in RDTs

There is some scope for further work on specific improvements to current RDTs, particularly for detection of non-falciparum parasites. It is likely that lateral flow-based detection of malaria parasites, the basis of current field rapid diagnostic tests, is close to the limit of its detection potential. At present, they are adequate for case management in nearly all circumstances, but have limited screening potential for asymptomatic parasite carriage, or for multiplexing to detect other, non-malarial diseases as well as malaria. FIND will continue to investigate options for optimization of the current format, including the use of improved antibodies, and the use of electronic readers. Other gains may be possible in simplification of RDT formats, reducing training and supervision requirements.

Digital microscopy and other new platforms

Microscopy remains important for basic case management as well as for parasite quantitation, drug efficacy monitoring, and as a reference standard for monitoring RDT performance. It is highly dependent on quality of slide preparation and interpretation, requiring considerable technician skill supported by adequate supervision. Automated digital microscopy holds potential to enhance the current role of light microscopy, including identification of non-malarial disease, while greatly reducing the dependence on technician competence, with advantages of improved sensitivity and picture archiving, and potential for rapid adaption to other diseases. FIND will

continue assessing candidate platforms to determine suitability for investment in further development and evaluation.

A number of new technologies are currently under development for detection of malaria parasites. In addition to LAMP, various photonic platforms are under development with the aim of enhancing in-vitro and in-vivo malaria parasite detection. A challenge of these platforms is to match the relatively low cost and reliability of current RDTs. Advantages include the potential for greater sensitivity, elimination of perishable consumables, and disease multiplexing. They also raise the possibility of non-blood sampling. FIND aims to identify prospective platforms for the near to medium term, and work with the developers to add value through product optimization and evaluation.

Addressing other blocks in effective RDT field implementation

Many countries continue to require targeted technical support to address bottlenecks in the effective implementation of comprehensive diagnostics programmes. FIND aims to work with Ministries of Health and implementing agencies in select countries to further develop solutions to the most pressing needs in the roll-out of diagnostics. FIND will also explore ways to address specific market gaps, such as how to encourage diagnostics use in the private sector through innovative public-private cooperation. Other solutions include improvement of electronic reporting platforms to monitor diagnostic test results and stocks at a national scale, encouraging transparency in commodity (RDT and ACT) management, overcoming stock-outs at the local level and providing accurate data on malaria incidence.

Demand continues for training materials and job-aids which have been demonstrated to significantly enhance the quality of RDT-based diagnosis in the field. This is a low-cost but high-impact activity that adds significant value to malaria case management. FIND will continue to seek support for this activity.

Detection tools to support other interventions

Effective use of a number of malaria interventions is hampered for want of specific detection tools, similar to diagnostic tests, to guide and monitor the effectiveness of their use. For instance, tools which can determine whether an insecticide-treated bednet is effective if a wall has been sprayed properly with insecticide, or whether an infected patient is likely to have drug-resistant parasites and so will require a change in treatment can be very useful. These tests share characteristics with other diagnostics, and addressing these needs using existing diagnostic platforms and development programmes may therefore lower costs and shorten timelines.

FIND will work with partners on developing diagnostic technologies or expertise to support the improvement of other malaria interventions, such as simple field tests to

confirm that indoor residual spraying with insecticide has been performed effectively, or tests to enable monitoring of spraying programmes and ensure resources are used efficiently. Simple tests for anti-malarial drug resistance could provide valuable early warning of growing parasite resistance and a need or closer monitoring or change in drug regimens. FIND will work closely with other PDPs with specialization in these areas, supplying specific technical capacity related to diagnostics development where this adds value to the work of PDPs in these fields.

Improved management of non-malarial febrile illness

Malaria cannot be effectively managed without addressing non-malarial febrile illness (NMFI). People who have a negative malaria test result are still sick and therefore still need effective management. Without alternatives to anti-malarial drugs, the negative malaria test result is likely to be ignored and testing is thus of little value. FIND's approach to this problem is to address the sick patient in a holistic manner, as someone with an acute febrile syndrome (AFS). Many of the causes of AFS, including malaria, have potential for severe illness but are responsive to commonly available treatments if these are given early enough. Therefore, diagnostic approaches that enable the health worker to identified and effectively address these treatable infections will have a big impact on mortality, particularly in children. The diagnostic approach to NMFI is therefore a major and important challenge for health systems and for product development. FIND's NMFI strategy is dealt with in more detail in a separate document[11].

11 http://www.finddiagnostics.org/programs/malaria-afs/

FIND

and partners have the capacity to transform the malaria landscape with sustained funding.

We **can** reduce childhood mortality and eliminate malaria.

FIND's added value in malaria diagnostics

With demonstrated expertise in malaria diagnostics, FIND is well placed to achieve the goals set out through specific, targeted and evidence-based projects. While there are multiple options for future development of novel technologies and broadening implementation of those already in use, it will be essential to maintain a rational and evidence-based approach, bringing proven technologies to market and addressing access to quality diagnosis in the near-term. In parallel, it is vital to identify new candidate technologies to address emerging needs, and bring these to market in a form that addresses the requirements of use in low-resource settings. Through FIND's mix of upstream and frontline activities and our partnerships with industry, both national and international implementers, we have been able to show that diagnostics produce results, and that this active field has the potential to provide a huge impact for those most in need.

FIND's strengths

Established relationships/ partnerships	With industrial partners and forging an approach that allows low-cost availability of tools to low-resource, high-burden populations
	With leading research organizations in malaria-endemic and non-endemic countries.
	Potential for cost-savings through synchrony with FIND diagnostics development programmes for other diseases, and access to existing platforms
	Active engagement with WHO, national programmes and implementers, including forums such as RBM Partnership, facilitates feedback into future product and project design.
Expertise	Expertise in medical device development and regulation
	Clear project management guidelines and pathways (including ISO13485 and ISO9001 accreditation for IVD development and implementation, and management, respectively)
	Established record in other focus diseases in getting products rapidly through demonstration and public-sector acceptance, with close collaboration with WHO and implementing partners with defined roles.
Structure and project progression	Use of evidence-based novel technologies in a logical, staged programme of feasibility studies, development, evaluation and demonstration studies followed by scale up.
	Flexible structure within foundation facilitating rapid changes in emphasis/ response to changing needs and product profile requirements.
	Project Evaluation stage includes analysis of the market performance of each product developed, quality control and standardization.
	The data collection involved in the quality control of RDTs is done with transparency and published publicly to attempt to increase competition within the industry for production of good diagnostics.
Focus on sustainability	Moving towards project sustainability through small-scale implementation projects demonstrating specific solutions to enable scale-up by implementation agencies and national programmes.

Impact of investing in malaria diagnostics R&D

With sustained funding, FIND and partners have the capacity to transform the malaria landscape through:

By 2016:

- Self-sustained global quality control programme for malaria RDTs:
  - Product testing becomes a low-cost global evaluation based on recombinant antigen standards
  - Lot-release testing and lot testing of RDTs by manufacturers and countries performed using low-cost standard panels independent of central funding, with recognized global standards of performance
  - Quality control of RDTs at clinic level routinely performed using positive control wells, providing reassurance of accurate diagnosis

- Molecular diagnostic capability in most endemic countries through use of malaria LAMP for screening in malaria surveys and for research and monitoring.

- High-throughput LAMP, serology and RDTs used in coordinated strategy to direct resources in very low-transmission areas:
  - Countries in southern Africa and Asia stratified, with regional elimination programmes
  - Bednets and intensive case management directed to areas of high need

- Accurate incidence data from several countries in each endemic continent through routine diagnostic use and electronic reporting – improved stock management through same.

- Effective methods to ensure availability of information on G6PD deficiency status at low cost, guiding *P. vivax* treatment to prevent relapse.

By 2020:

- Malaria detection and surveillance in most countries resembles that for polio today, with near real-time data on individual cases and ability to map transmission accurately. This information will allow for the distribution of major control commodities to be directed accurately to areas of highest need.

- Large areas, now endemic in southern, far western and north-eastern Africa, and in Asia and South America, will manage malaria as a low-prevalence disease and minor public health problem, with potential for outbreaks. Malaria will be absent from most populations. Real-time surveillance results will guide targeted outbreak management.

- Quality control systems to ensure safe use of point of care diagnostics will have been established for other key diseases whose diagnosis depends on point of care tests, such as HIV and syphilis, and will be based on the malaria model by WHO, FIND, and partners, without need for external funding.

- Point of care tests based on new technologies with multiplex capability will begin to change fever management, enabling identification of most treatable causes, not just malaria.

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Having the right diagnostic tools in place will be essential to achieving current goals in reducing childhood mortality, and reducing and eliminating malaria. The improved targeting of resources enabled by the information that good diagnosis provides can lower the overall costs of other interventions, reducing wastage and mis-treatment. **Diagnostics development is a relatively low-cost, high impact investment.** This investment can deliver measurable outcomes in a relatively short time, whilst greatly increasing the value of investment in other anti-malarial interventions.

We should no longer be working with a blindfold,
but approach malaria as a disease that can be identified,
treated, and eliminated.

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