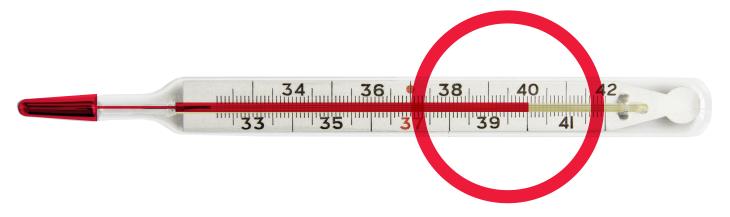


# **ACUTE FEBRILE SYNDROME**



a major challenge to global public health

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The causes of severe acute febrile illness are numerous, and account for most preventable deaths in low-income countries, particularly in children.



# **Preface**

Acute fever (or 'acute febrile syndrome', a rapid onset of fever and symptoms such as headache, chills or muscle and joint pains) is common in the tropics and sub-tropics. Frequently, such fevers resolve without treatment, but fever may also herald the onset of severe, potentially fatal illness. The causes of severe acute febrile illness are numerous, and account for many preventable deaths in lowincome countries, particularly in children.

Improved living conditions in developed countries, together with access to good diagnosis and treatment, have made death from infectious disease rare in these countries. However, much of the world still lives with severe, unpredictable but avoidable illness that extracts a high mortality, particularly among children.

Prevention of severe illness and death relies on early detection (diagnosis), but most patients in developing countries, and most health services that care for them, cannot afford highly sophisticated tests necessary to achieve this. However, new technologies now provide the potential to make practical, affordable and accurate diagnosis accessible to all, improving significantly the effectiveness of public health and infectious disease management.

This document outlines an approach to take us towards that goal – achievable through partnerships of researchers and product developers, manufacturers, health providers and communities that stand to benefit.



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.

# **About FIND**

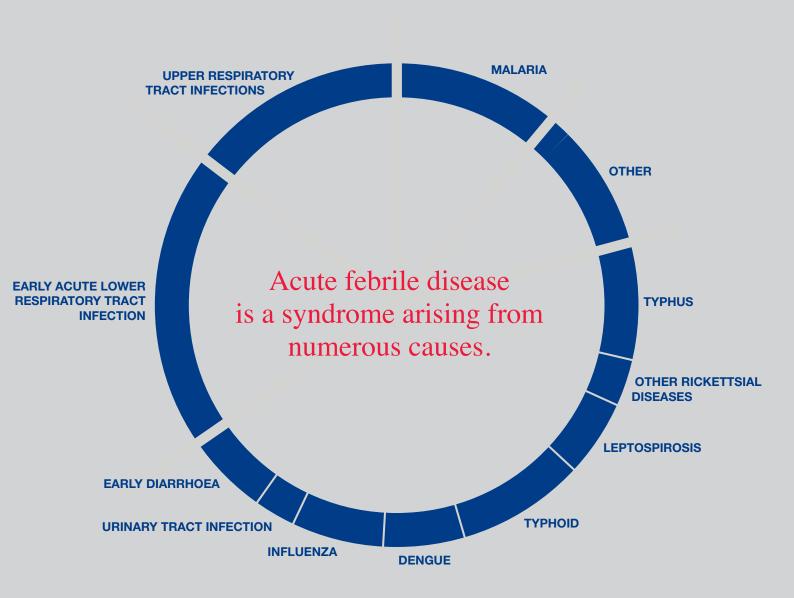
FIND was set up to address some of the market failures that have resulted in the paucity of appropriate diagnostic technologies in disease-endemic countries. FIND's area of expertise is in the development of novel tools to fill gaps or open new possibilities for intervention, and in innovative solutions to deficiencies in the use and implementation of existing ones. This process requires bringing together knowledge of the needs on the ground with technological know-how, and is based on a sound understanding of the industry behind diagnostics development.

The development of diagnostics specifically aimed at low-resource settings has been poorly addressed in the past. Through its partnerships with industry, national disease programmes, research institutions, NGOs and other PDPs, FIND is uniquely placed to address this need and accelerate the entry of promising technologies into fieldready tests. FIND's know-how and partnerships in implementation then permit it to demonstrate how and where they may best fit into existing health systems.

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



**ACUTE FEBRILE SYNDROME** 



Examples of causes of acute febrile illness: The relative frequency of acute febrile syndrome varies widely with geography, living conditions and occupational exposure.

# Acute febrile syndrome, malaria, and non-malarial febrile illness (NMFI)

Acute fever in the tropics and sub-tropics has often been considered to be primarily due to malaria, and has been treated as such. As accurate diagnosis for malaria, based on microscopy and rapid diagnostic tests, is introduced across malaria-endemic regions, it is becoming increasingly apparent that most fevers are due to other causes (i.e. non-malarial febrile illness), particularly in areas where anti-malarial interventions are well implemented. The malaria test is negative, but the patient is still sick.

In this context, 'acute febrile syndrome' means rapid onset of fever, and often other symptoms, that may be due to malaria but are frequently due to infection triggered by a wide variety of pathogens. Many, like malaria, can be severe and deadly, yet are curable if detected early and treated immediately.

In order to address acute febrile syndrome (AFS) in a holistic manner, a strategic mix of new knowledge on prevalence of the various causes of febrile disease, development of new tools, sustainable treatment algorithms and the infrastructure to support them will be required. These are health-system-wide issues, providing challenges but also huge opportunities for improvement in healthcare delivery. The introduction of emerging technologies in diagnostics in coming years will address fundamental deficiencies in health services and provide new opportunities for disease control and elimination in low-resource countries.

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

FIND therefore intends to focus on the development of tools for diagnosis of acute fever, combining the need to improve malaria diagnosis with the need to address the alternative causes of fever; what to do when the malaria test result is negative. While diagnosis of malaria is dealt with in a separate strategy, this document concentrates on an approach to the nonmalarial part of AFS.



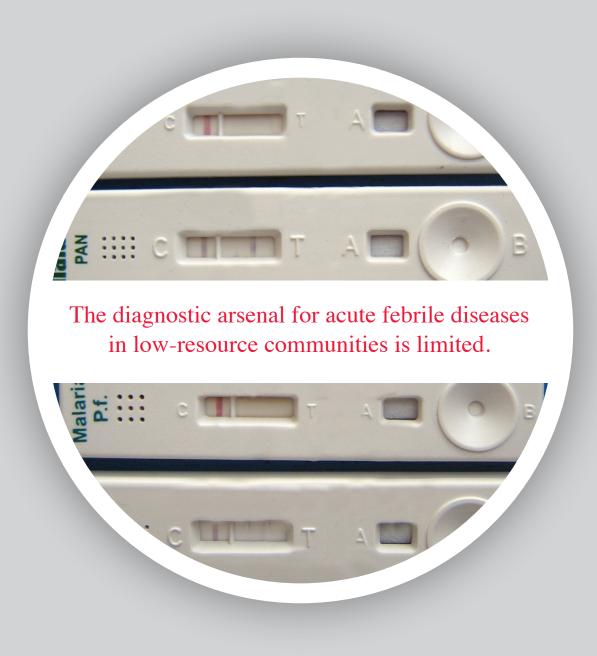
Most fatal cases of NMFI could have been cured if diagnosed and treated early with the right drugs.



# The need for better diagnostics and diagnostic strategies for NMFI

If a febrile patient consults a clinician/health-worker in an area endemic for malaria (and is not just treated presumptively for malaria), he/she is most likely to be tested for malaria by microscopy or an RDT. These tests are frequently negative, as non-malarial causes of fever are generally more common. This creates a problem: the patient is still seeking care, while the health worker has limited capacity to distinguish between the many possible remaining causes of fever in order to decide on the best management. The patient, untreated, will often recover but alternatively the illness may progress to severe sickness and death. Most fatal cases of non-malarial febrile disease could have been cured if diagnosed and treated early with the right drugs.

To improve management of non-malarial fever, it is not always necessary to identify the exact cause of the illness. Some causes of fever, in any country and any population, are mild and self-limiting, and are best managed by just controlling temperature or by simply observing the condition. The illness resolves after a few days. Many mild viral throat infections are examples of this. Careful questioning, observation and examination (clinical diagnosis) may be sufficient to guide management in some cases, and the WHO guidelines for Integrated Management of Childhood Illnesses (IMCI) and Integrated Management of Adolescent and Adult Illnesses (IMAI) are designed to guide health workers, based on this principle. However, good clinical diagnosis is difficult to ensure, and in the best hands is poorly specific; that is, unable to distinguish between many potentially severe infections in their early stages, when treatment is most likely to be effective (e.g. bacterial meningitis, still a burden in developing countries but relatively rare where health systems are strong and specific early diagnosis is possible). The role of a diagnostic test is to provide the information needed to guide timely, effective treatment, whether by identifying evidence requiring specific management in a particular patient, or by providing information on disease prevalence to guide clinical diagnosis.



# The current state of diagnostics for acute febrile syndrome (AFS)

Diagnosis at a community point-of-care level, where early management of disease can have the greatest impact, is currently limited in low-resource countries. Many available technologies are either too expensive to be sustainable in these situations, or require a level of technical skill and laboratory support that is unattainable. Even at hospital level, diagnosis that can distinguish many common causes of severe illness and death is unavailable in tropical and sub-tropical settings.

However, some new or well-established technologies are already in use for specific acute infectious febrile diseases in low-resource, high-burden countries. Examples are microscopy and lateral flow rapid diagnostic tests (RDTs); the former used for detection of a range of organisms in various samples, and RDTs for specific diseases such as malaria, or other infectious diseases such as HIV and syphilis. Other more sophisticated technologies established in developed countries can be adapted to these diseases. Various nucleic acid detection tests (NAAT) are becoming increasingly robust and improved for use in near-field settings; examples being LAMP assays for malaria and trypanosomiasis (the cause of sleeping sickness) and GeneXpert for diagnosis of tuberculosis. While the diagnostic arsenal for the causes of AFS in low-resource communities is relatively limited, the potential to increase it, and thus transform the management of acute fever and reduce avoidable illness and death, is high. Investment in emerging and proven technologies that can meet the needs of high burden diseases in these settings will go a long way to alleviating poverty and the high social costs of widespread illness.

Technologies available and w of acute febrile syndrome (ma	ith potential for case management alaria and non-malarial febrile illness)
	Light microscopy
 Latera	I-flow (immunochromatographic) tests
	(often called Rapid Diagnostic Tests (RDTs))
	Nucleic acid amplification tests (NAAT)

Enzyme-linked Immunosorbent Assay (ELISA)

New and adaptive technologies

Well established for disease management and widely available, allows morphological identification and quantification of a range of organisms. Is relatively low cost, versatile, and technology may be locally supported

Disadvantages include high dependence on user competency, and quality of reagents, resulting in frequent poor reliability of results. Sensitivity depends on having a relatively high concentration of microorganisms in a sample, and the correct sampling and staining. Important in hospital settings, but difficult to support at a village level and with limited applicability in many diseases.

RDTs require relatively low training and support compared to microscopy, and can be low cost. Well-established for some diseases such as malaria, syphilis, and HIV. Only suitable for detection of certain organisms, and it is difficult to include multiple diseases in a single test, so they have limitations when screening for multiple diseases.

Tests detecting nucleic acid (DNA or RNA) can be very sensitive and are commonly used as reference tests. The most widely-used example, polymerase chain reaction (PCR) tests, requires significant laboratory support and is relatively expensive, limiting its accessibility for acute case management. New technologies, using simplified heating steps, sample preparation and reading of results offer potential for near-patient testing at much lower cost in low-resource settings. This could greatly improve the accuracy of point-of-care testing (an example is loop-mediated isothermal amplification (LAMP)). However, few are available for the causes of non-malarial febrile illness.

Well-established in reference laboratory settings, especially for screening purposes. Not well suited to near-patient low-resource settings for case management, due to skill and equipment requirements.

Various new technologies based on photonics, novel methods for detecting chemical markers, or adapting existing tools using new technologies (such as digital microscopy), are under development. Some are already available in high-resource settings. Existing applications for low-resource settings are very limited since target diseases, or support costs, are currently incompatible with low-resource settings. However, such developments will ultimately be necessary to detect the range of pathogens needed to guide effective treatment of fever at a cost and simplicity required to ensure ease of access to those in need. An approach encompassing near and long-term goals is therefore needed.









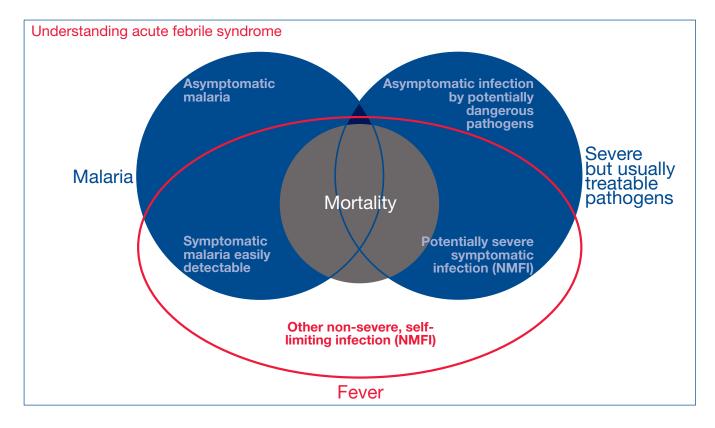
# A rational approach to diagnostics for AFS and NMFI

To manage disease effectively, we need good information:

- **Health workers and patients** need information on the cause of a fever to treat it effectively
- Health services need information on the prevalence and geographical spread of causes of fever to plan and target resources
- **Funding agencies** need this information to determine funding priorities to obtain maximum impact on public health with the funds they make available

The role of diagnosis is to provide such information – to break acute febrile syndrome down into specific diseases for which the correct treatment can be given. In malaria-endemic areas, this means approaching a sick person with acute fever as a person who may have:

- malaria (treatable, must be detected quickly)
- one of a number of other potentially severe infections (severe NMFI – mostly treatable, must be detected quickly)
- Other mild and self-limiting infections, such as viral respiratory tract infection (mild NMFI – supportive treatment, patient can be safely sent home)



FIND's approach is therefore to concentrate on the need to provide key information that will impact on patient management, directly or indirectly, through methods that are sustainable in a low-resource setting. This can be summarized in a 3-tiered approach to development:

- 1. Improve knowledge of aetiology (or cause) to improve current clinical algorithms
- 2. Develop tests for Markers of Severity and Responsiveness to treatment (MSR)
- 3. Develop pathogen–specific tests that are likely to be encountered and are treatable ideally in a multiplex format (e.g. with malaria tests).

Throughout this development process, FIND plans to work with modelers and health economists to determine which modes of diagnostic intervention, and investment in diagnostic development, are most cost-effective. In terms of both direct patient management costs, and costs of developing new products, investment requirements will be expected to rise with increased specificity (and accuracy) of diagnosis. But more importantly, so will direct health benefits, and social and economic advantages to the community through better health. These must be carefully weighed by funders, product developers, and health services.

#### **Syndrome**

a group/cluster of symptoms (e.g. fever, headache, etc.) that occur together and which may be due to a number of causes

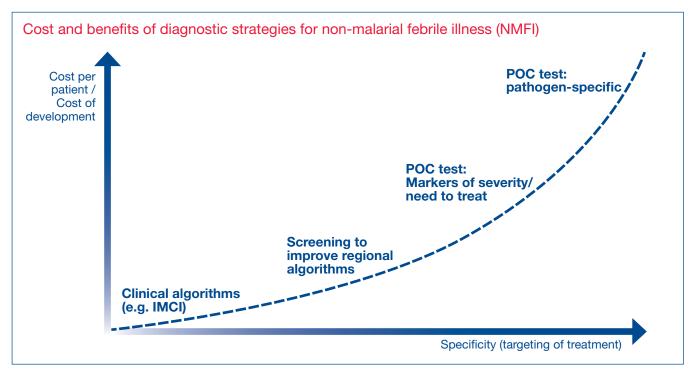
#### **Disease**

a specific pathological abnormality or set of abnormalities, impairing health or function of an organ(s) or system of the body

# Acute febrile syndrome

is caused by a number of diseases, including malaria, and non-malarial diseases such as typhus, typhoid, pneumonia, etc. These need to be distinguished from each other with sufficient accuracy to guide a health worker to provide treatment that will address the cause, and to provide health services with the information needed to plan and prioritize. This may require:

- Case-management tests (tests to guide treatment where patients first seek care)
- Screening tests (tests to identify the most common pathogens in a population to guide presumptive therapy and planning)



The ultimate aim is to have accurate point-of-care (POC) tests for all diseases. In the meantime, much can be gained by investing in less specific tests which are viable with current technology and which will provide immediate impacts.

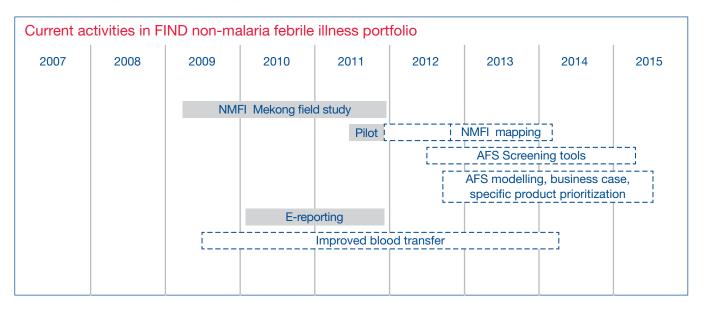
## Requirements in development of point-of-care diagnostics for low-resource settings

- Recognize that resources, both financial and human, are limited in low-income countries, and concentrate on diagnostic interventions that provide the highest return
- Allow more effective use of existing drugs
- Ensure tests/strategies are appropriate for the skills and workplace of clinicians/health workers
- Minimize the need for additional logistical and other resource requirements for health services
- Concentrate on platforms, and tests that are compatible with existing tools (e.g. malaria tests)
- Concentrate on tests/strategies that are sustainable within a national health programme, minimizing need for long-term external support

# FIND's current activities on the NMFI diagnostic landscape

Drawing on its existing diagnostics development programmes for malaria, tuberculosis, trypanosomiasis and other neglected diseases, FIND has developed a number of projects consistent with its diagnostics strategy over the past few years, addressing the first tier of diagnostics need (information on prevalence) and developing tools to improve point-of-care diagnostics implementation:

- Collaboration in a partnership with national health programmes, research institutions and WHO in the Lao PDR and Cambodia to investigate causes of NMFI, as a guide to prioritizing development of diagnostics and screening methods, and improving fever management
- Collaboration in a pilot mapping project on distribution of non-malarial febrile illness with a view to establishing a global database to guide FIND's NMFI diagnostics work
- E-reporting: Development and demonstration of e-reporting of diagnostic results and commodity stocks through SMS messaging
- Production of evidence-based generic job-aids and training materials for lateral flow POC tests (developed for malaria RDTs, and adaptable to other lateral flow tests to enable standardization of instruction materials)
- Improved blood transfer device (safe, simple and accurate blood transfer from finger prick to testing device) – a 5 microlitre device is now in use on the market, and novel higher volume devices are under development
- Early feasibility project for high-throughput screening for causes of acute febrile syndrome (malaria and NMFI)



# A future development pipeline

Going forward, FIND will concentrate on a number of strategic areas that should provide measurable impact. Working with specialized partners who contribute specific skills and experience, the approach is designed to develop tools that will be of use, or provide information of direct use, to implementers and health services working at a community level.

Three tiers of diag	nostic development		
Population screening and mapping of pathogens	<ul> <li>Expansion and refinement of interactive database, mapping pathogen presence</li> <li>Adaption of existing reference laboratory-based multiplex screening technologies for population screening</li> </ul>	Impact modelling and cost- benefit analysis	
Tests for Markers of Severity and Responsiveness (MSR) to treatment	<ul> <li>Identifying non-specific indicators of disease severity and of pathogen groups susceptible to specific treatment alternatives</li> <li>Field trials of existing POC lateral flow formats for MSR</li> </ul>		
Pathogen- specific tests	<ul> <li>Evaluation of existing pathogen-specific assays</li> <li>Feasibility assessment of potential multiplex platforms</li> <li>Product development /adaption for POC platforms targeting pathogens identified as high-burden and treatable</li> </ul>	anaryoro	
Development of en	nabling methods and technologies		
<ul> <li>Reworked copies of generic instructions (job-aids) and training</li> <li>Amendment of blood /specimen transfer devices</li> <li>Adaption of electronic/SMS-based systems for commodity tracking / results management</li> <li>Modification and standardization of methods and devices to improve integration with management of other diseases</li> </ul>			
Tests to support drug therapy	<ul> <li>Tests to detect markers of microbial resistance to certain drugs that are critical to patient management</li> <li>Tests that confirm the safety of certain drugs or guide dosi (companion diagnostics)</li> </ul>	ing	

#### High throughput screening tools and mapping of prevalence

The prevalence of different pathogens varies between regions. Clinical algorithms, such as the WHO protocol on Integrated Management of Childhood Illness (IMCI), are therefore very non-specific. A global clinical procedure must make assumptions regarding the similarity in prevalence of causes of fever between different regions, while these in fact vary widely. A lack of knowledge of the geographical spread and prevalence of various pathogens prevents adapting generic protocols, such as IMCI, to regional specificity, and thus precludes better targeting of drugs and implementation of early, effective management. Studies to screen for pathogen prevalence have been undertaken on a limited scale in certain countries, but diagnosis reliant on conventional reference methods, including PCR and blood culture, is expensive and difficult, and must be repeated after a certain time as prevalence may vary with changing economic or environmental conditions.

Much data on pathogen presence exists, collected incidentally in studies of various diseases, and this can be systematically gleaned from prevailing literature and mapped. A number of recent technological advances have also raised the possibility of performing mass surveys for a range of pathogens at much lower cost than conventional laboratory analysis. Adjustment and implementation of such instruments could greatly increase the quality of existing data, providing reliable maps of distribution and prevalence of non-malarial pathogens. Clinical algorithms could then be adapted, greatly improving targeting of treatment. This information will also provide a basis for modeling of costs and benefits of alternative diagnostic approaches, in addition to empirical evidence to prioritize diagnostics research and development.

#### Tests for Markers of Severity and Responsiveness (MSR)

The ability to detect signs of the severity of an illness, or of a patient's responsiveness to certain therapies, could guide a clinician towards conclusions beyond any information provided by a solely clinical assessment. In a clinic or village setting, such a marker may indicate whether a patient can safely be sent home, or should immediately be referred for further investigation and treatment. In a hospital out-patient setting, this information may guide decisions on whether to admit for higher cost, in-patient management.

Alternatively, markers could indicate whether the infection is caused by a 'one-of-a-group' of pathogens susceptible to a particular anti-microbial, and thus influence specific and effective

treatment without identifying the exact cause. An example is rickettsial species and related pathogens, sensitive to treatment with tetracycline antibiotics.

Some markers are in current use in various contexts, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, differential white blood cell counts, and blood glucose concentration. There is limited information available on the specificity of these markers at community level in tropical and sub-tropical regions. Clarification of marker specificity, an identification of more specific markers, and an adaption into specific or multiplex point-ofcare tests will provide great advances in case management.

#### Identification of specific pathogens

Point-of-care (POC) tests exist for some non-malarial pathogens, including typhus, typhoid, and dengue. However, some of these tests are poorly specific or sensitive (have insufficient accuracy), and some are not in a format, or obtainable at a cost, that is practical for use in low-resource community settings. The value of such POC tests to sick patients depends on their availability and cost, as well as on their impact on the treatment options that exist for health workers helping the patient. Since the geographical range of target pathogens varies, the type of tests appropriate for fever diagnosis will also vary between different geographical regions. Visually-read lateral flow tests, which are the current diagnostic format commonly used in community-level testing, have limited potential for multiplex testing (i.e. detection of a number of different pathogens using a single test). The use of electronic readers may increase adaptability, but also increases the cost and technology requirements. Alternative diagnostic platforms are under development, but are not being produced at a cost and in a format fit for remote clinic or village use. Such tests will be a prominent part of future diagnostics research and development for febrile diseases.

## The importance of modeling and cost-benefit assessment

Research and development (R&D) funding for diagnostic tests for low-resource settings is limited, as are the resources available to support their use. As demonstrated above, these costs are expected to increase as tests become more pathogen-specific. The success of these tests will depend on keeping them within the budgets of both funding agencies and people with little income. Expertise in various aspects of disease management, modeling of expected outcomes, and careful assessment of direct and indirect costs and benefits will help determine R&D priorities. FIND and other product development partnerships rely on engagement with a wide range of agencies to determine which priorities make sense.

## **Enabling effective community implementation**

The successful implementation of diagnostic interventions is driven by the practical utility of the tests themselves, the effectiveness of the health workers/clinicians in using the tests, and the delivery system for good quality tests and necessary therapy. This requires training and supervision, proper supply lines and waste management, and good procurement policy. Delivering this to a village level represents a challenge to any health system, and to product developers in designing tests that will be adaptable to the systems currently available or possible. While FIND is not an agency primarily involved in health system support, we focus on the potential gains of improved technology that can be fully realized in field settings. Without this, new tools can languish for many years before being fully integrated into disease programmes. FIND will continue to engage closely with ministries of health and implementing agencies to address strategic areas of need - the bottlenecks that hinder wide-scale implementation and are directly applicable to our product development portfolio - to ensure that investment in diagnostic research and development achieves its full value.

#### **Diagnostics supporting drug therapy**

Drug resistance is a frequent and evolving problem involving the management of many infectious agents, sometimes necessitating surveillance to detect the emergence of resistance, and tools to determine the susceptibility of pathogens to drug therapy in an individual presenting with infection. Similarly, some drugs may result in side-effects in people with certain abnormalities, acquired or inherited, in the way they respond to therapy. As the management of organisms causing NMFI expands, it is likely that such tests will be needed for controlling certain infections. Recognizing and addressing these needs early will be important to maintaining effective and safe patient supervision, and obtaining the maximum benefit from medicines.





**INVESTING IN A BETTER FUTURE** 



Increased investment in diagnostics for acute febrile disease will go a long way to lower mortality and improve public health in low-resource communities.

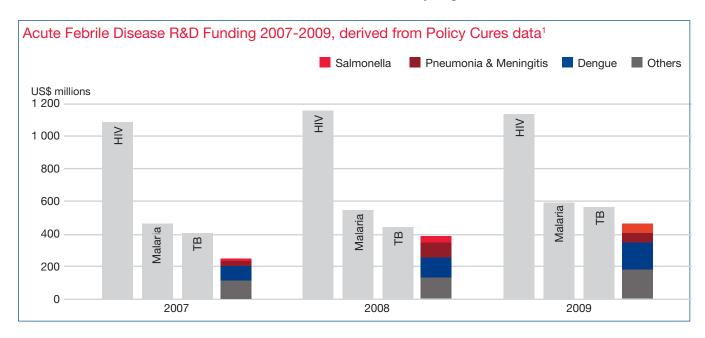


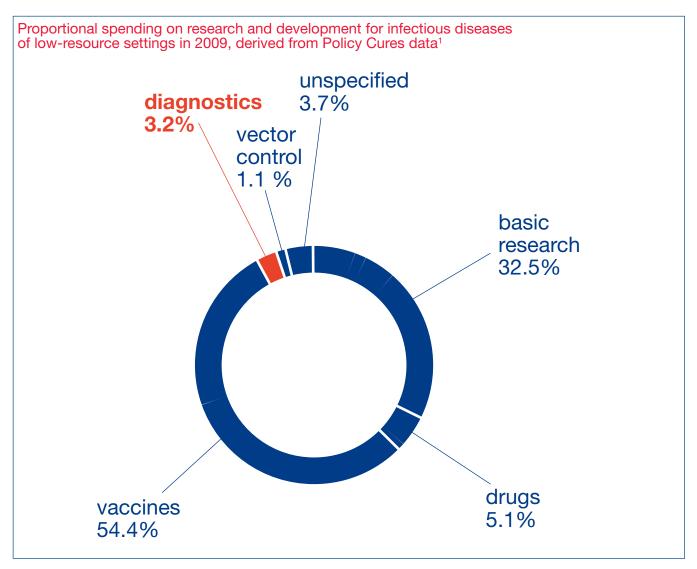
# The case for greater investment in diagnostics for acute febrile disease

Besides vaccination programs, major funding and aid organizations are concentrated on three major disease programmes: HIV, tuberculosis and malaria. The political and structural requirements of funding organizations can restrict the flexibility required to address other causes of fever, even where overlap with these priority diseases is clear. For example, non-TB respiratory disease such as pneumonia or bronchitis could not be readily managed within these three disease programmes. Non-malarial febrile illness lacks a major funding 'champion' to strengthen the cause of diagnostics research and development.

Not only is early accurate diagnosis a direct public health 'good' – shortening the period of illness, reducing transmission and reducing mortality – but the information provided on disease incidence is essential to improve targeting of other interventions. Investment in diagnosis can therefore have impact well beyond direct treatment, adding to the value of investment in other means of health intervention, and reducing the costs of their implementation.

The bulk of R&D funding for infectious diseases in low-resource settings goes to HIV, malaria and tuberculosis, in that order. Combined R&D funding for other causes of acute fever amounts to less than that spent on each of these (Figure below). Funding for diagnostics R&D, in turn, is only 3.2% of the total R&D spent (Figure page 34). Diagnostics R&D is relatively underfunded and the non-malarial causes of acute fever are truly neglected.





While it is important to maintain gains against HIV, tuberculosis and malaria, investment will address these wider causes of mortality and achieve public health goals.

Sustained funding in the area of diagnostics development could realistically transform the acute febrile disease landscape

While increased R&D spending across a range of areas important for health care in low-resource settings will have a considerable impact, increased spending on diagnostics, from its very low base, has potential to deliver very tangible benefits in lower mortality and improved public health within a relatively short period. This can be achieved directly through improving management of ill people, and by enabling more effective use of other interventions. With well targeted investment, much can be achieved within the coming few years:

#### 2015

- Global map of distribution of major causes of non-malarial febrile illness, to identify priorities and 'holes' where further surveys are needed
- · High-throughput screening tool identified and demonstrated, to provide prospective data on pathogen prevalence
- Clarification of effectiveness of existing candidate markers of severity and responsiveness to treatment (MSR) in field, feasibility of incorporation into disease-specific POC tests
- Field feasibility evaluated for alternative multiplex platforms, with at least one large field evaluation underway
- National-scale integrated e-information system demonstrated and fully integrated in one or more countries, including commodity management, disease reporting and guidance for long-term patient follow-up
- Feasibility assessment of one or more new point-of-care (POC) tests for high-burden diseases
- Standardization of instruction formats and blood transfer across common POC tests intended for remote and low-resource settings

#### 2020

- Management of non-malarial febrile illness is integrated with malaria control and elimination in many health programmes, in health-worker training and implementation
- Detailed knowledge of distribution and prevalence of major pathogens, including all population-dense tropical and sub-tropical regions, provided through high throughput screening surveys
- Multiplex POC test(s), detecting malaria and having at least MSR-detection capability, replace lateral flow malaria tests in many areas
- Pathogen-specific tests for at least 3-4 major high-burden pathogens (common lower respiratory-tract infections, typhus, typhoid) in routine use in high-prevalence areas
- Multiple examples of fully-integrated multiplex tests at a hospital / outpatient triage level leading to lower admission rates, earlier discharge and lower in-patient mortality
- A dramatic decline in mortality due to fever, particularly among children, achieved by routine use of early case management - accessible diagnostic testing to guide use of effective medicines

With appropriate investment and a collaborative, rational approach, the way severe febrile disease is managed in low-income communities could be transformed in the coming years in communities where preventable mortality remains common, with dramatic impacts on public health and community life.

# Image copyright: p 12: <sup>®</sup>Medair p 14: <sup>®</sup>FIND p 18: <sup>®</sup>FIND p 20: <sup>®</sup>FIND p 30: <sup>®</sup>MMV

The array of pathogens that cause non-malarial febrile illness is responsible for higher mortality than malaria, and disproportionately affects low-income countries and children. However, with relatively small investment and effort, this major burden of illness can be addressed. Provision of simple, low-cost and reliable tools to warn of high risk of severity, and detect specific pathogens, could have a major impact on this neglected area of public health. Innovative ways for health systems to manage results and support supply lines are now also possible. Together, these developments could transform the information available to effectively manage illness, health system planning and disease monitoring. As malaria burden decreases in many countries, the availability of diagnostic tests and appropriate management for other causes of fever will be increasingly important to maintain the credibility of health programmes tackling malaria.

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