Unitaid
Innovation in Global Health

TECHNOLOGY LANDSCAPE

FEVER DIAGNOSTIC TECHNOLOGY LANDSCAPE, 1ST EDITION

FEBRUARY 2018

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Abbreviations

ACT	artemisinin-based combination therapy
AMR	antimicrobial resistance
ARI	acute respiratory illness
ARIDA	Acute Respiratory Illness Diagnostic Aid
ARLG	Antibacterial resistance leadership group (US)
BARDA	Biomedical Advanced Research and Development Authority (US)
BMGF	Bill & Melinda Gates Foundation
CDDEP	Center for Disease Dynamics Economics and Policy
CHAI	Clinton Health Access Initiative
CRP	C-reactive protein
CHW	Community health worker
DPP®	Dual Path Platform
FIND	Foundation for Innovative New Diagnostics
GAPPD	Global Action Plan for Pneumonia and Diarrhea
GARP	Global Antibiotic Resistance Partnership
GFF	Global Financing Facility
GLASS	Global Antimicrobial Resistance Surveillance System
Global Fund	The Global Fund to Fight AIDS, Tuberculosis and Malaria
HIC	High income country
HNL	human neutrophil lipocalin
iCCM	integrated community case management
IMCI	integrated management of childhood illness
IP-10	Interferon-gamma-inducible protein 10
LMIC	low- and middle-income countries
mRDT	malaria rapid diagnostic test
MDG	Millennium Development Goals
MFD	Multiplex fever diagnostic
MoH	Ministry of Health
MORU	Mahidol Oxford Tropical Medicine Research Unit
MSF	Médecins Sans Frontières
MxA	Myxovirus resistance protein A
ORS	oral rehydration salts
PCR	polymerase chain reaction
PCT	procalcitonin
POC	point-of-care
RDT	rapid diagnostic test
RMNCAH-N	Reproductive, maternal, newborn, child and adolescent health and nutrition
RR	respiratory rate
RSV	Respiratory Syncytial Virus
SDG	Sustainable Development Goals

SpO2	Blood oxygen saturation level
SRA	Stringent regulatory authority
TPP	Target product profile
TRAIL	TNH-related apoptosis-inducing ligand
UN	United Nations
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization
WHO PQ	World Health Organization Prequalification

Executive summary

Introduction

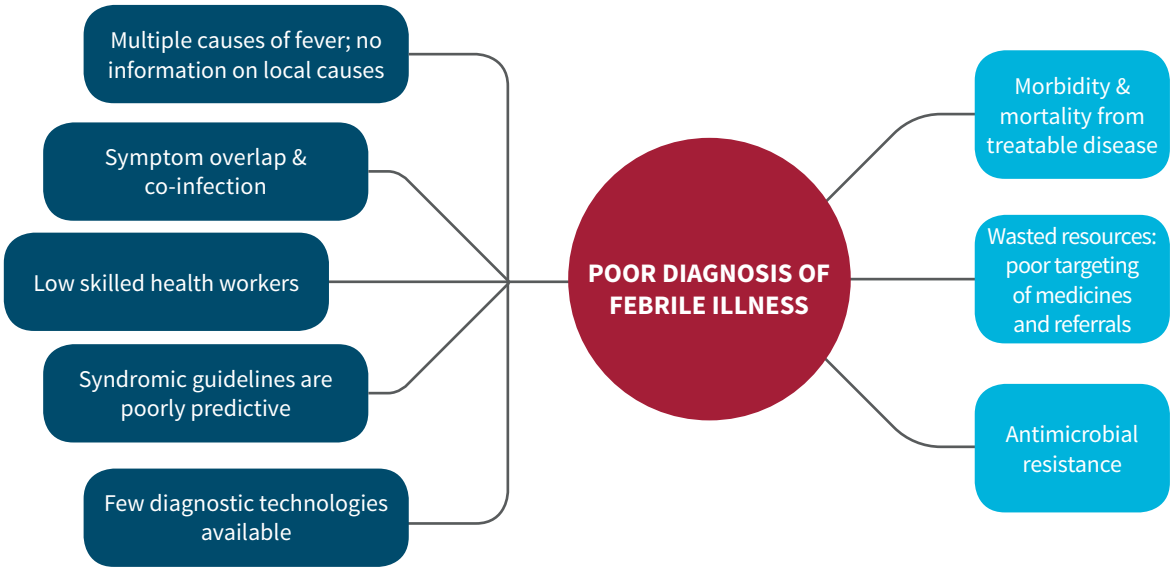
Since their introduction and scale-up, malaria rapid diagnostic tests mRDTs have improved malaria case management by reducing overtreatment with antimalarials. While mRDTs should be further scaled to achieve universal access, this should be accompanied by simultaneous efforts to strengthen diagnosis of febrile illness that is not caused by malaria and an integrated approach to diagnosing and managing febrile illness in children. This report explores the potential for new diagnostic technologies to improve diagnosis of febrile illness in children. A dynamic understanding of existing and pipeline technologies, as well as the work of other stakeholders, is key for Unitaid in facilitating access to appropriate tools through market-based interventions.

Public health challenge: diagnosing febrile illness in children

Fever, the main symptom of malaria, is the most common presenting symptom to health workers in low-income countries. While fever has many different causes, at the community and primary levels, most febrile illness is caused by self-limiting viral infections. However, of the millions of febrile illness episodes that occur each year in children in malaria-endemic areas, a fraction require a specific treatment (e.g. antimalarial, antibiotic) and an even smaller fraction is severely ill. In 2016 an estimated 5.6 million children still died before their fifth birthday. Pneumonia (24%), diarrhoea (15%), and malaria (9%) remain the leading causes of death in children ages 1 – 59 months, and, malnutrition as an underlying factor is associated with nearly half of under-five deaths. At the same time, the effectiveness of treatments used to cure these illnesses are at risk: resistance to artemisinin-based combination therapies (ACTs) is spreading in South-East Asia and antibiotic resistance is a growing concern in lower-middle-income and high-income countries (LMICs and HICs) alike.

Accurate diagnosis of febrile illness in children can decrease mortality by identifying children in need of a specific treatment earlier and by referring those needing additional care in a timely manner. It can also assist with targeting of treatments to those who need it, reducing waste and safeguarding antimicrobials. However, the differential diagnosis of a febrile child can be challenging, even in well-resourced settings. In low-resource settings, several additional complexities contribute to higher morbidity and mortality, wasted resources, and acceleration of antimicrobial resistance (AMR).

Factors contributing to poor febrile illness diagnosis in children in low-resource settings and their effects

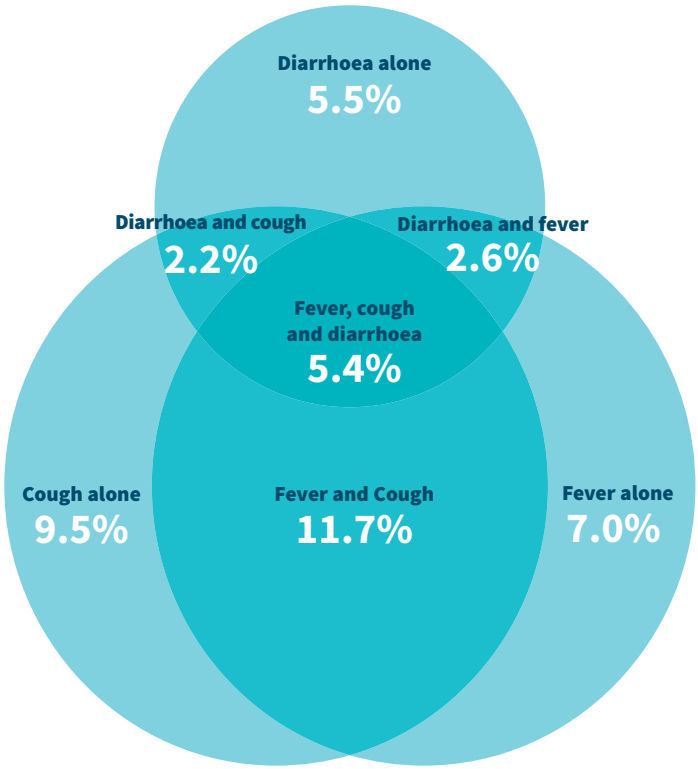


- First, there are multiple potential causes of febrile illness in children; however, there is very seldom any local disease-prevalence or drug-susceptibility data for health workers to consider in assessing the likelihood of a child having a particular disease and in selecting the best treatment.

- Second, many children present with fever in combination with other non-specific signs, such as cough and diarrhoea, necessitating an integrated approach to diagnosing and managing febrile illness.

- Third, clinical expertise is limited at the frontline in low-resource settings. To address this, the World Health Organization (WHO) has developed programmes, Integrated Management of Childhood Illness (IMCI) and Integrated Community Case Management (iCCM), to support prevention, treatment and care for sick children in order to reduce childhood mortality. These programmes take a syndromic approach to childhood illness and focus on the main causes of childhood mortality. They are based on history, signs and symptoms that can be easily assessed by low-skilled health workers. While IMCI has many strengths, it also has some shortfalls e.g. while the empiric guidelines are highly sensitive, they can be insufficiently specific leading to overtreatment. In light of new evidence and changes in underlying epidemiology, the recently initiated IMCI redesign is timely.

Community-level prevalence of fever, diarrhoea and cough in children under-five*

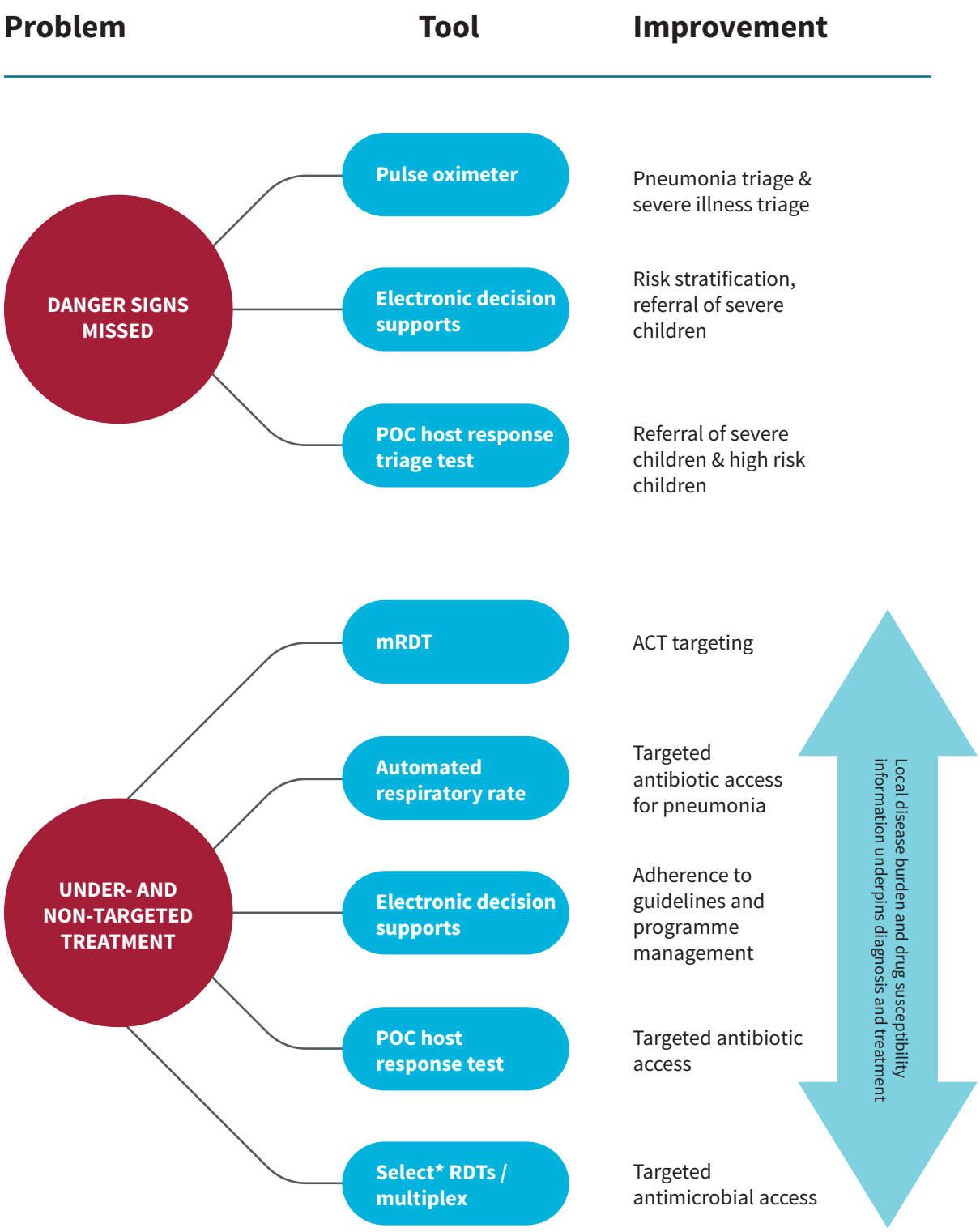


* Surveyed in standard demographic and health surveys (DHS), 1986 - 2012, N = 1 200 986
Source: Prasad N, et al. Community Prevalence of Fever and Relationship with Malaria among Infants and Children in Low-Resource Areas, The American Journal of Tropical Medicine and Hygiene 93, 178 (2015); https://doi org/10.4269/ajtmh.14-0646

- Finally, there are very few diagnostic technologies for febrile illness available to frontline health workers: mRDTs and HIV RDTs are available, and respiratory rate counting may be supported by assistive devices (e.g. beads and timers). Other diagnostic technologies are not available, either because the technology has not been developed, or where it has, it is not available for a variety of reasons (e.g. unaffordable; lack of point-of-care (POC) formats suitable for low-resource use; and/or insufficient evidence to support adoption).

These challenges of diagnosing febrile illness at the frontline result in failure to identify severe disease in children and poor targeting of treatments to those who need it.

Mapping diagnostic tools to weaknesses in febrile illness diagnosis at the front line *



* Select tests for priority diseases, based on local data, for which results are actionable (e.g. diseases that require specific supportive care or medicines that are available)

Commodity access

Scarce data make it difficult to assess progress in coverage of key interventions for fever case management and in access to the few diagnostic technologies that exist. Limited data suggests that there is scope for improving care-seeking behavior as well as the uptake of IMCI/iCCM. While tremendous progress has been made in scaling malaria diagnosis, there is room for improvement, in particular an urgent need to address overtreatment with antibiotics that can be linked to the scale-up of mRDTs. Additionally, although WHO recommends use of pulse oximeters where available, evidence from a few countries suggests that access at the frontline is limited. Meanwhile, high rates of mortality from pneumonia, diarrhoea, and malaria persist, especially in those countries with the greatest burdens of disease.

Technology landscape

There are a number of existing and pipeline technologies that could improve diagnosis of febrile illness in children at the frontline in low-resource settings.

First, tools to improve recognition of danger signs and severe disease in children include:

- **Handheld pulse oximeters.** WHO recommends use of pulse oximeters to detect hypoxemia, a potentially fatal complication of severe pneumonia (as well as other conditions including severe malaria). Pulse oximeters are devices that non-invasively measure oxygen saturation of hemoglobin in the blood. Many handheld pulse oximeters are available; few have been vetted for quality and suitability for use at the frontline in LMICs. Lifebox, a UK charity, markets one affordable, robust pulse oximeter to low-resource settings.

- **POC host response-based diagnostics to support triage.** Only a small proportion of children have severe disease, presenting a challenge to frontline health workers who have limited clinical expertise and are tasked with identifying children who need additional interventions (e.g. referral and hospitalization). Additionally, some clinical signs only appear late in disease progression, and therefore a diagnostic that can identify disease severity in children earlier on would have great impact. Although tests are being developed for sepsis detection in high-income countries, there is one POC, host response-based test being developed for children in malaria-endemic settings. This test uses biomarkers of immune and endothelial activation to identify children at risk of becoming critically ill. Currently, the biomarkers are undergoing additional validation in Africa and prototype lateral flow tests are being developed.

Second, tools to improve targeting of treatments in febrile children include:

- **Automated respiratory rate counters.** Under IMCI and iCCM protocols, to classify a child as having pneumonia meriting antibiotic treatment, health workers count the number of breaths the child takes in a minute and compare the result to age-based cutoffs. In routine practice, counting a child's respiratory rate is difficult and often neglected. While technology that automates respiratory rate counting is not new, existing devices are high cost and not adapted for use on children in outpatient settings in LMICs. UNICEF's Acute Respiratory Illness Diagnostic Aid (ARIDA) project aims to encourage development and adoption of new automated respiratory rate counters for low-resource settings, and one device has recently entered field trials.

- **POC host response-based tests for identifying children needing antibiotics.** Host response-based diagnostic tests that have potential to differentiate between bacterial and non-bacterial infections in non-severe febrile children in LMICs include POC tests based on existing host response biomarkers (such as C-reactive protein (CRP) and procalcitonin (PCT) tests) and POC tests based on novel host-response biomarkers. PCT and CRP are increasingly used in developed countries; however, evidence on their potential use and impact in LMIC settings is lacking. CRP has been available for many years and is available in RDT format; however, PCT is a newer biomarker with fewer POC options available. Beyond CRP and PCT, there are four novel biomarker based tests being developed with potential to differentiate between bacterial and non-bacterial infections in low-resource settings. One has obtained regulatory approvals in Europe and a few other markets and is undergoing additional outcomes and cost-effectiveness studies to support adoption. Others are at various stages of development and are targeting 2018 – 2021 availability. These tests, as well as other potential biomarkers, have largely been studied in the context of developed countries. To extend their use to febrile children in LMICs validations are needed in populations whose host response may be altered by other common conditions (e.g. high rates of malnutrition, HIV prevalence, other co-infections). FIND is conducting an initial validation of selected biomarkers in low-resource settings.

- Selected **single pathogen RDTs**. While it would be overly complex to incorporate a large number of additional RDTs into the initial assessment at the point-of-care, it could be useful to identify and scale-up a few key RDTs. RDTs for several diseases exist, however, there are no RDTs for pneumonia or diarrhoea, due in part to the multiple causative agents. Malaria RDTs are already a critical diagnostic tool used at the frontline and are covered separately in Unitaid's malaria diagnostic technology and market landscape (*Malaria Diagnostic Technology and Market Landscape, 3rd edition, April 2019*).

- **Multiplex diagnostics** are those that can detect multiple pathogens or other biomarkers simultaneously, obviating the need to run multiple individual tests. These systems typically detect DNA/RNA, antigens, or antibodies. Two efforts to develop multiplex tests are underway: one company is developing disposable lateral flow immunoassay platforms while other efforts aim to develop "sample in answer out" multiplex fever diagnostic systems. It remains to be seen how these tests could be used at primary level for individual patient care, given the limited clinical expertise and treatments options available. However, there is a compelling epidemiologic use case that would support fever management at the frontline: data from multiplex testing conducted at higher levels should be aggregated and offered regularly to frontline health workers to improve their understanding of the local causes of disease.

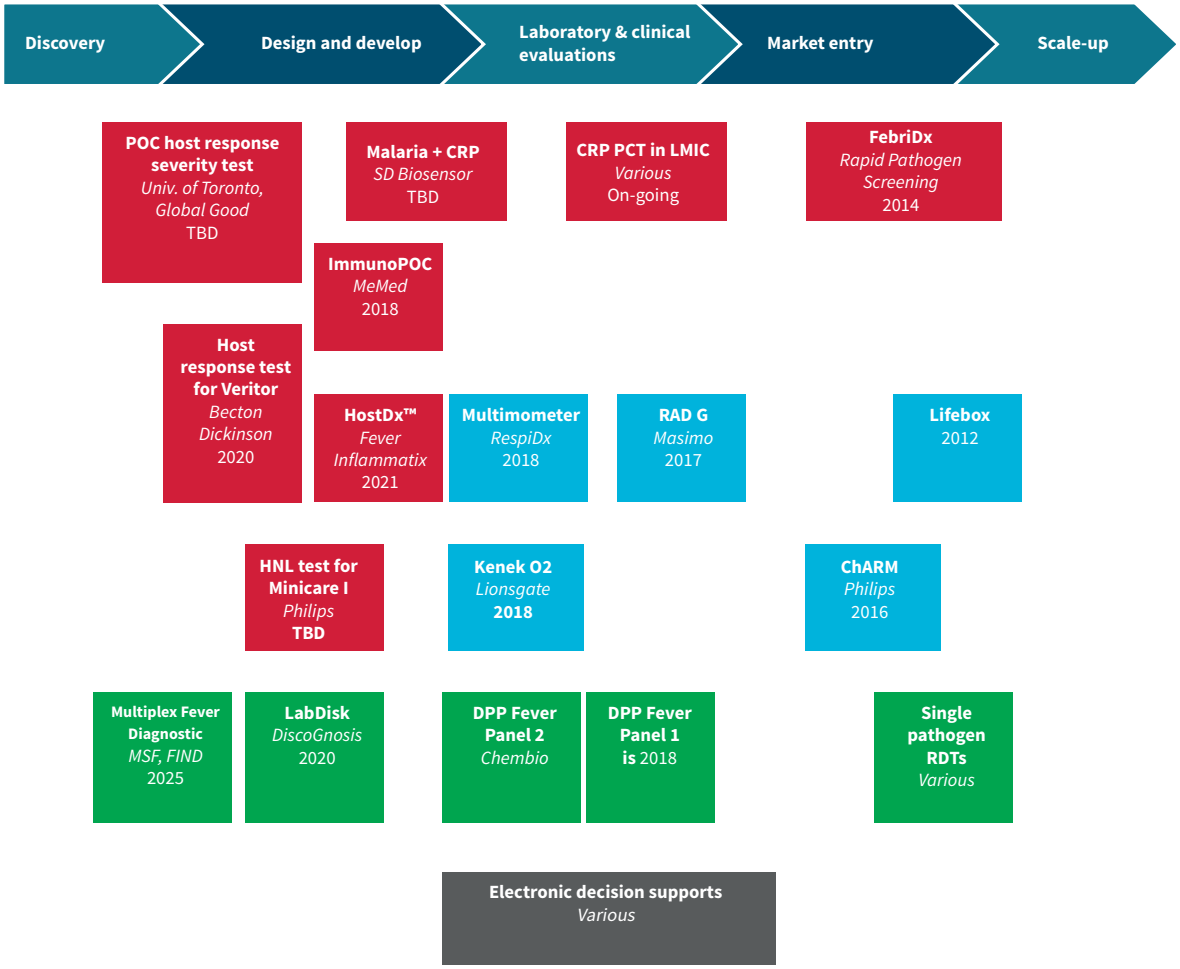
- As with the epidemiological application of multiplex pathogen detection tests, **aggregating microbiology test results** from secondary and tertiary facilities, including pathogen identification and drug-sensitivity testing, could play an important role in informing diagnosis at the frontline and ensuring that empiric treatments are effective. Although these tests are critical for inpatient care, they are not consistently available in LMIC hospitals and their quality is not assured. There is a limited pipeline of technologies that could greatly simplify and improve microbiology testing in LMIC. Recently, industry investments have not aligned well with LMIC needs, (e.g. focus on non-culture, genotypic methods; expensive platforms and assays that require stable electricity etc.).

Third, tools with cross functionality include:

Multimodal handheld devices combine automatic respiratory rate counters, pulse oximeters, and possibly other measurements. There are at least four in the pipeline; one incorporates a thermometer, and another developer is considering non-invasive hemoglobin measurement. The wide applicability of these devices for febrile illness diagnosis and triage, as well as potential applicability to other disease areas and conditions, makes them attractive.

Electronic decision support software systems, running on smartphones or tablets, can guide frontline health workers through the assessment and management of febrile children. While some programmes are electronic versions of IMCI, others incorporate additional data or new evidence and have potential to collect realtime data on fever. These systems can improve adherence to algorithms, reminding health workers to check for danger signs and guiding them through all steps of the assessment, (often incorporating job aids or brief training videos). Electronic systems can facilitate a more nuanced and integrated assessment of the child, which would be difficult to do in paper based algorithms. They can suggest additional diagnostics for certain patients and incorporate these diagnostic data points (e.g. additional clinical assessments, results from RDTs or pulse oximeters) into the evaluation of the child. In doing so, they help health workers translate what would otherwise be complex guidelines into practice, thereby improving targeting of medicines and timely referrals. These systems may also translate local epidemiological data (e.g. gathered from multiplex and microbiology testing at national/provincial levels) into actionable insights for frontline providers. By capturing and transmitting data to the central level, program managers have more visibility into work at the frontline. While there are several applications in development, and preliminary evidence is positive, none have been implemented at national scale and additional implementation studies are needed.

Pipeline of diagnostic technologies for febrile illness



Note: Pipeline is non-exhaustive

Market challenges

While there is a range of products in the development pipeline, there are technical challenges, as well as a number of market challenges impeding progress.

Common market challenges for febrile illness diagnostics technologies include:

Lack of investment in Research and Development (R&D): the pipeline for febrile illness diagnostics has not been advancing as rapidly as the pipelines for HIV, Tuberculosis (TB) and malaria diagnostics. From a commercial technology developer's perspective, the case for R&D investment is limited by three factors: i) uncertainty about demand for new products in LMIC, ii) downward pressure on pricing for LMIC diagnostics generally; and iii) increasingly time-consuming and costly evidence requirements to support adoption. Often developers lack insight into the user needs, in terms of use case scenarios, product specifications, and the value and willingness to pay for new diagnostic technologies.

The fragmented donor and procurement landscape for child health commodities is likely to present future market challenges, including: assuring the quality of products; balancing supply and demand for products; and rapidly translating new evidence into policy recommendations. Once products are introduced into markets, change in clinical practice is likely to be a challenge, in particular for those technologies that result in recommendations to withhold treatment.

There are specific market challenges for each of the technologies as well, for example:

Additional evidence is needed to inform use of new automated respiratory rate counters, including cost-effectiveness studies that demonstrate the value-add. For handheld pulse oximeters, supply chain markups, decentralized procurement, and lack of information on product quality and suitability for frontline use in low-resource settings are gaps. Multimodal devices are an attractive option; however, developers need input on which of the parameters are most useful. Because any of these devices would cost more than the existing tools, their value-add must be demonstrated, as there are many competing priorities for child health funding.

Development costs of host response-based biomarker tests are generally quite high, because of technical challenges, evidence requirements, and regulatory uncertainty. There is significant market opportunity in high-income countries for tests that reduce unnecessary antibiotic use, and there are a few prize funds designed to stimulate development of these

tests. However, even with these incentives, the trials needed to support adoption are extensive and complex. These trials must be conducted in a variety of target populations and geographies in order to validate their use in LMIC settings. From an economic perspective, developers are likely to prioritize more lucrative high-income markets first, delaying trials and introduction of potentially game-changing diagnostics LMIC. Market challenges for host response-based tests that detect markers of severity are similar; however, even less work has been done to develop an investment case for commercial investment in these tests for LMIC.

While there are several existing RDTs on the market that might be relevant in LMICs, a lack of data on fever etiology limits their uptake. Additionally, the quality of many of these RDTs has not been verified as it has for HIV and mRDTs. A highly fragmented market could emerge for pathogen detecting tests, with seasonal and geographic variation even within one country. Operationalizing a programme that included multiple RDTs could be a challenge, e.g. orienting health workers on when to perform certain tests, how to manage based on the result, and ensuring adequate supply of multiple RDTs in a highly decentralized system.

For multiplex pathogen detection tests, currently there is great uncertainty about the need for and potential impact of any specific fever panels due to the lack of local fever etiology data. Additionally, due to the potential heterogeneity in fever causes, the market for any one panel could be extremely fragmented. The pathogens on multiplex fever panels that are available in HIC are not very relevant to low-resources settings, and these tests are highly priced, suggesting that affordability will be a challenge if multiplex fever tests for low-resource settings come to market. Microbiology testing, using traditional culture methods, while essential for individual hospitalized patients as well as for epidemiological purposes, is under-utilized and caught in a cycle of low supply and low demand. Quality programmes and training, as well as affordability and supply chain weaknesses contribute to the issues.

Electronic decision support tools for childhood fever diagnosis and management are nascent and there is limited data on their efficacy and effectiveness. There are many products being developed, and no standards for assessing them or reviews of their impact. Models for going to scale are needed as sustainability requires multiple elements of the mHealth ecosystem be in place.

Selected opportunities for market intervention

There are a range of potential opportunities for market intervention to support febrile illness diagnosis in children in low-resource settings. Across the product categories, opportunities include market stimulus for innovation; work at the global level to prioritize needs, develop use scenarios and target product profiles (TPPs). Additionally, analysis of the market opportunity for each technology category, based on evidence from fever etiology studies is needed. Evidence from low-resource settings is needed to inform and support adoption, and it is important to develop standardized methods for conducting outcomes and cost-effectiveness research for new technologies that often have impact not only to the individual patient, but also to the system as a whole (e.g. cost savings, resistance averted). At the global level, there is a need to coordinate leadership, to outline the regulatory pathway (in particular evidence requirements), and to strengthen global institutions so that new evidence is quickly reviewed and incorporated into policy recommendations and guidelines. As products come to market, work to accelerate uptake and improve affordability through demand generation and procurement commitments may be needed, including support for clinical practice change to ensure appropriate management based on results.

Opportunities related to specific product categories also exist, for example market shaping work for existing technologies (e.g. handheld pulse oximeters) and financial support for product development and market entry for more novel approaches. For host response-based tests in particular, funding for validations or development of innovative mechanisms to reduce development costs (shared clinical trial platforms, biobanks) could offset high R&D costs. For those products that are close to market, such as automated respiratory rate counters and decision support platforms, support for implementation trials is needed.

Conclusion

Given the pipeline that is emerging, it is timely for the global community to work together to develop a vision for how the future could look for febrile illness diagnosis and management at the frontline in LMICs, and to develop an agenda for achieving this vision.

There is an urgent need to strengthen funding for integrated child health programmes as well as to develop the enabling environment. Specifically, global leadership needs strengthening in order to improve coordination across vertical disease areas. Additionally, global mechanisms for evidence review and policy development need strengthening, as do delivery platforms, such as IMCI and iCCM. Global dialogue with technology developers on priorities, specific needs, and market opportunities in LMICs will help focus resources and investments and ultimately accelerate access to diagnostic technologies that will have an impact on fever management in children and on child health overall in low-resource settings.

Introduction

While there has been significant progress in reducing many leading causes of childhood mortality, in 2016, an estimated 5.6 million children still died before their fifth birthday, mostly from conditions that are readily preventable or treatable with proven, cost-effective interventions. Pneumonia (24%), diarrhoea (15%) and malaria (9%) remain the top killers of postnatal children; malnutrition as an underlying factor is associated with nearly half of under-five deaths *(1)*.

In children, these three diseases responsible for most deaths, as well as many other serious conditions, frequently present with non-specific symptoms. Fever is especially common: it is estimated that children under-five in malaria-endemic areas experience from two to nine fevers per year, and more than three fourths of children presenting to frontline health workers have fever. Few children, however, have isolated fever. Febrile children often present with multiple symptoms (e.g. cough, difficulty breathing, diarrhoea, dehydration), and an integrated approach is critical to improving case management of fever and meeting global targets for child survival. While platforms for integrated case management exist (e.g. IMCI), they have not been implemented consistently and their funding is waning.

Ideally, frontline health workers (e.g. primary care nurses, community health workers/CHWs, pharmacists) in low-resource settings would be equipped to diagnose the multiple causes of febrile disease in children and to treat or refer them appropriately. However, at the frontline, both clinical expertise and diagnostic tools are in short supply, and as a result many children are misdiagnosed and do not receive the appropriate care. Today, on the heels of the 2010 WHO recommendation to test before treatment, only malaria rapid diagnostic tests (mRDTs) are widely used to guide the diagnosis of causes of fever. While the scale-up of mRDTs has had a tremendous impact on the quality of malaria case management, it has also highlighted a major shortcoming in frontline health worker's ability to diagnose non-malaria fever.

At the present time, diagnostic tests for other common causes of fever and for the other leading causes of childhood mortality are not available at the frontline. Moreover, often the cause of disease cannot be pinpointed, even when advanced clinical skills and sophisticated diagnostics are available. Health workers also lack tools to identify danger signs in children (requiring immediate intervention or up-referral), and subsequently dispense antimicrobials and antimalarials indiscriminately. Both undertreatment due to poor access and overtreatment due to inadequate diagnosis are concerns in low-resource settings. On the one hand, far too few children who need an antibiotic or an antimalarial receive them. At the same time, overtreatment is common and increasingly concerning as antimicrobial resistance (AMR) spreads globally.

In view of these challenges around integrated fever management, this report explores the potential for new diagnostic technologies to improve diagnosis and management of fever in children. A dynamic understanding of existing and pipeline technologies, as well as the work of other stakeholders, is key for Unitaid in facilitating access to appropriate tools through market-based interventions. This 2018 landscape report is the first edition, and is intended to stimulate discussion and inform potential opportunities for market intervention to improve access to effective febrile illness diagnostics.

Fever is an incredibly broad category, encompassing multiple clinical conditions and affecting billions of people, with hundreds of causative agents, and several possible diagnostic approaches (e.g. measuring host response versus pathogen identification). In view of this, the focus has been on integrated fever management in populations most affected by malaria, i.e. postnatal children under-five presenting to community and frontline providers in low-resource settings. The emphasis is also on those diseases that present similarly to malaria and are major causes of death among postnatal children. Certainly, there are additional opportunities to improve fever management in other populations (e.g. newborns, adults, hospitalized in-patients) and some of the tools described in this landscape report would be relevant to these groups; however, these populations are not the primary focus of this report.

The material in this report was gathered from review of publicly available information, published and unpublished reports, and discussions with an extensive number of stakeholders and technology developers. The technologies in the pipeline have been identified primarily through discussion with experts and review of reports, supplemented by unstructured, targeted, literature searches. The operational characteristics of the devices and diagnostic tests were generally provided by the developers or through publicly available information.

As such, the product specifications (including performance), product development timelines and prices reported here are indicative, and subject to change over time.

An important limitation with respect to the scope of this report stems from the exceptionally broad nature of the topic (febrile illness and its multitude of causative agents) and the dynamic nature of the technology pipeline. This report is not exhaustive, and several areas have been emphasized intentionally. For example, technologies that are most relevant to frontline providers in resource-limited settings have been prioritized (e.g. point-of-care/POC tests, with application at the primary care level). Additionally, focus on diagnostic tools for HIV, HICV, TB and other Coinfections is limited in scope in this landscape as it is covered in-depth in other landscapes such as the Unitaid landscape, *Multi-disease Diagnostic Landscape For Integrated Management of HIV, HCV, TB and Other Coinfections*. Given the large number of potential technologies in some categories, technologies that are on the market or that appear close to launch are covered in more depth than technologies further back in the development pipeline. Additionally, the distinction between technologies that are most applicable at the community versus primary versus hospital levels may depend on the local context. Thus, a few technologies that have greater relevance to individual patient care at the hospital level are included (e.g. microbiology and multiplex testing), given their potential for indirect impact on improving care at the lower levels of the system (e.g. by providing more information on diseases circulating in the community).

A dynamic understanding of existing and forthcoming technologies is key for Unitaid in facilitating access to appropriate fever diagnostic tools through market-based interventions. As such, this landscape report is intended to be a living document, which can be updated as the fever diagnostics market evolves.

This landscape builds on and complements previous diagnostic landscapes published by Unitaid, including HIV Diagnostic Technology Landscape, TB Diagnostic Technology Landscape, Malaria Diagnostics Technology Landscape, HCV Diagnostic Technology Landscape, and HIV Dual elimination of mother-to-child transmission of HIV and congenital syphilis Diagnostic technology landscape (https://unitaid.eu/publications/#en).

Background: febrile illness in children

Incidence of fever in children

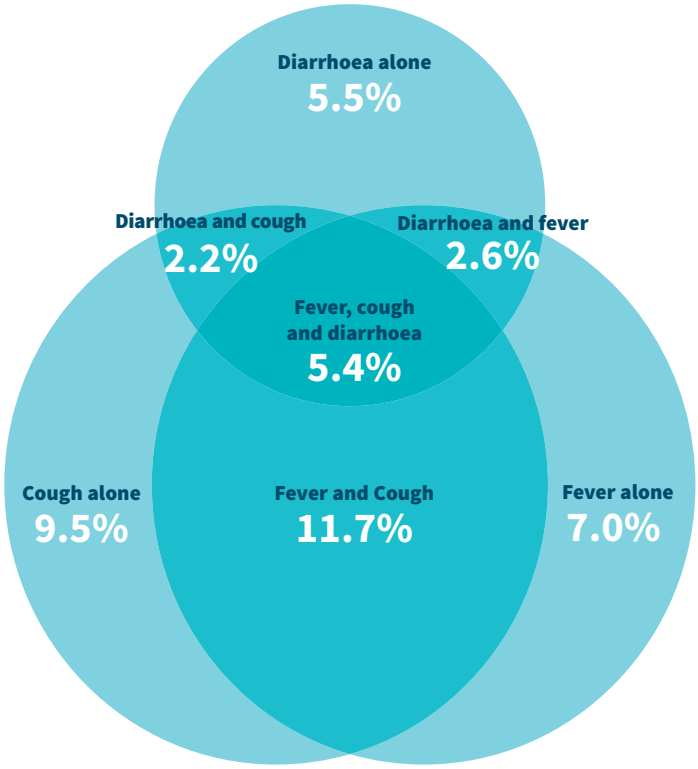
Febrile illness is the most common presenting symptom in sick children worldwide, regardless of where children live or their economic situation. Fever represents the body's natural response to an infection. Although estimates are highly variable, children under-five in malaria-endemic areas may experience from two to nine fevers per year *(2)*; and there are over 656 million fevers among children under-five each year in malaria-endemic Africa *(3)*.

Data from studies on presenting symptoms and classifications of illness in malaria-endemic areas find that on average three quarters of children presenting to CHWs or primary care facilities have fever; by comparison, 40% have cough or difficult breathing, and 20–30% have diarrhoea *(4)*. Children often present with multiple symptoms, and few children (<10%) present with isolated fever, suggesting that an integrated approach is needed (Figures 1 and 2) *(5) (6)*.

While fevers can result from infectious and non-infectious causes, self-limiting viral infections are the most common causes of fever in all age groups *(2) (4)*. Many fevers will resolve on their own and do not require specific treatment other than supportive care to increase comfort (e.g. antipyretics) to alleviate symptoms and avoid dehydration. While the cause of fever is often undiagnosed, evidence suggests that at the primary level, acute respiratory illnesses (ARIs)[1] are most common, and non-malaria fever is often viral *(2)*.

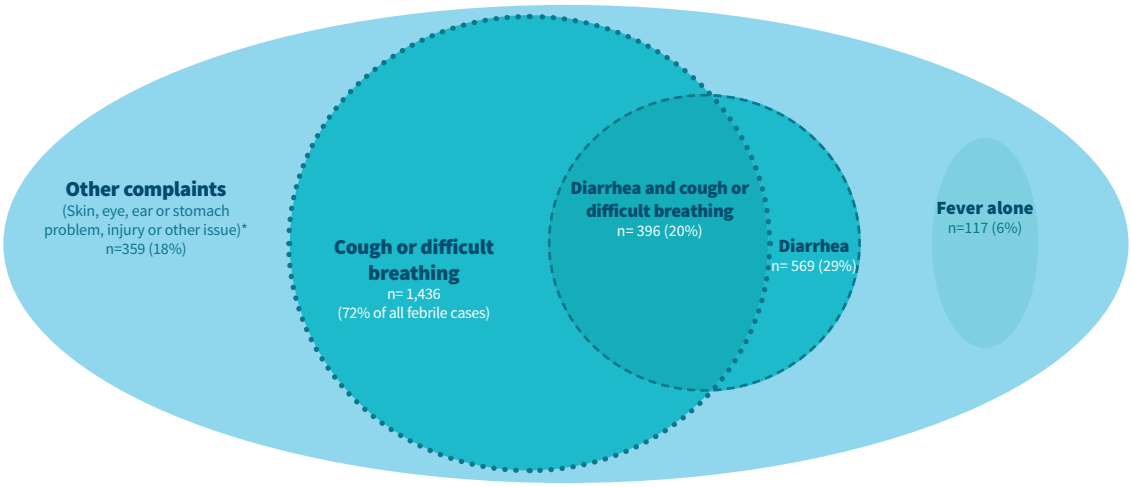
[1] ARIs include upper respiratory tract infections (e.g. common cold, otitis media, sinusitis, pharyngitis) and lower respiratory tract infections (e.g. laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia). In postnatal children, acute lower respiratory tract infections are the most common reason for hospital admission and pneumonia is the largest contributor to death.

FIGURE 1.
Community-level prevalence of fever, diarrhoea and cough in children under-five



Notes: Data from 1.2 million children collected through household surveys asking whether the child had any of these symptoms in the past two weeks, irrespective of whether they sought care. Data reflect 1 200 986 children surveyed in Demographic and Health Surveys (DHS), 1986–2012, from 73 countries.
Source: Prasad et al. 2015 *(6)*.

FIGURE 2.
Facility-level presenting symptoms of febrile children (ages 2–59 months) seen by frontline health workers in Malawi



Notes: Data reflect encounters with 1981 children across 977 facilities audited during 2013–2014 with the Malawi Service Provision Assessment.
Source: Johansson et al. 2016 *(5)*.

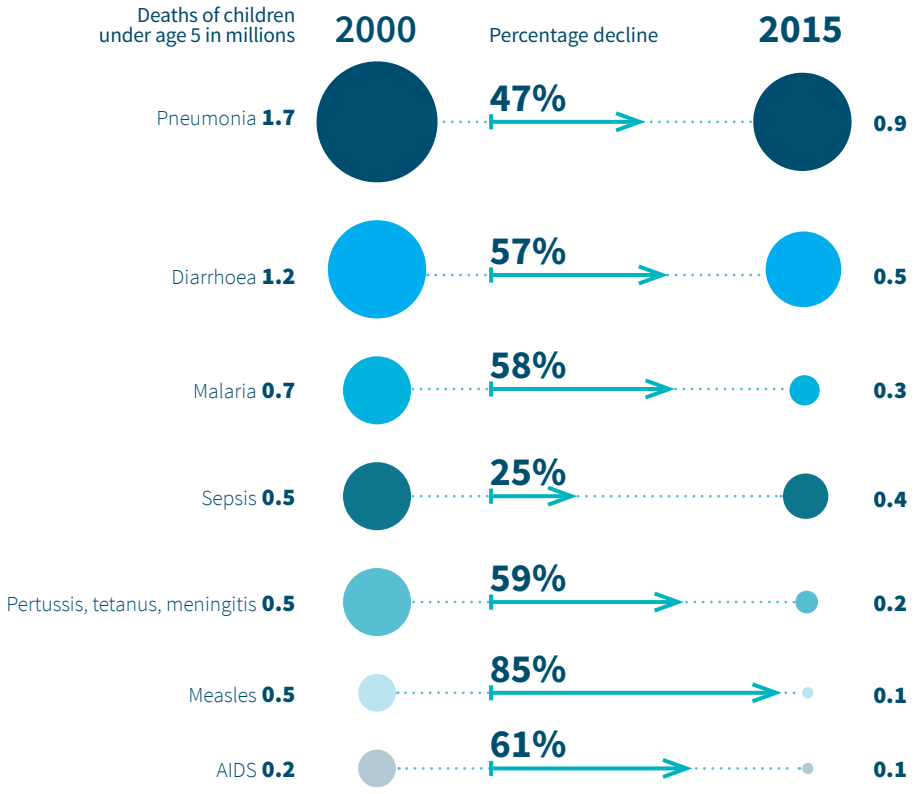
Childhood mortality

Although fever is quite common in children, even in malaria-endemic countries the majority are self-limiting requiring no intervention beyond measures to improve comfort and prevent dehydration. However, a small fraction of febrile illnesses results in severe disease and death.

While there has been significant progress in reducing many leading causes of childhood mortality, in 2016, an estimated 5.6 million children still died before their fifth birthday, mostly from conditions that are readily preventable or treatable with proven cost-effective interventions (Figures 3 and 4).

FIGURE 3.

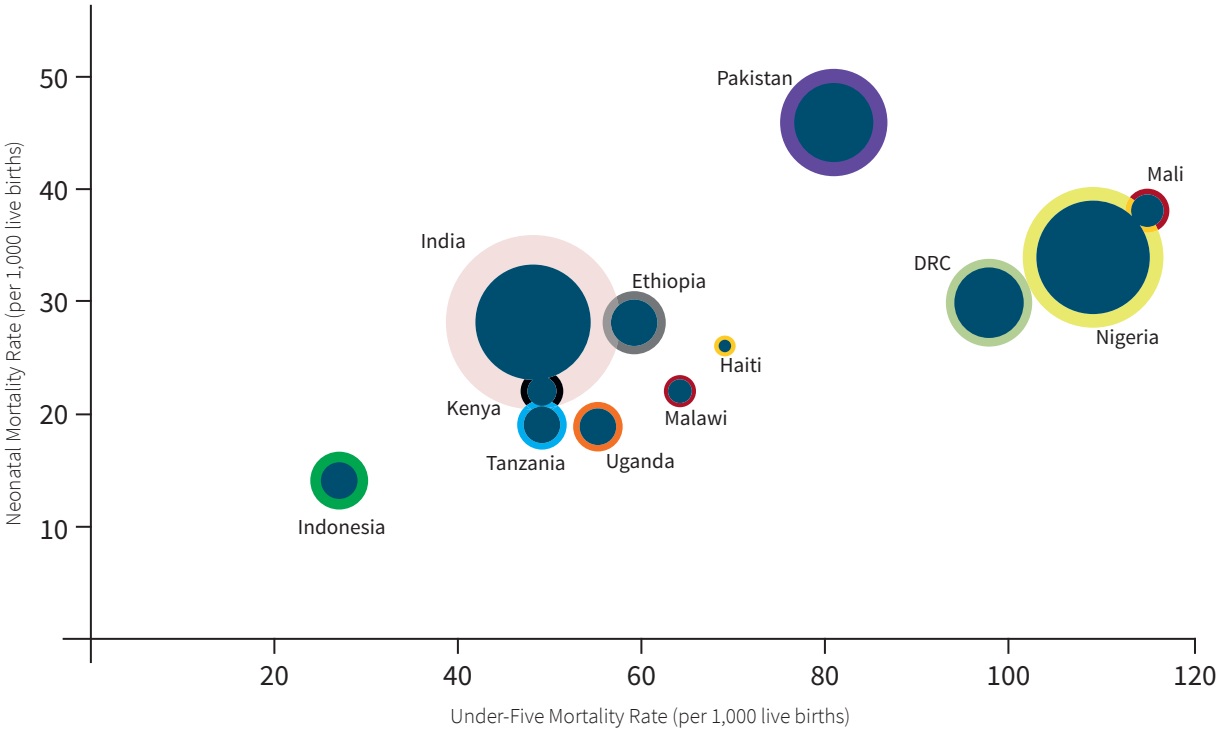
Reductions in child mortality for common childhood illnesses, 2000-2015



Source: UNICEF, based on WHO and Maternal and Child Epidemiology Estimation Group (MCEE) estimates 2015 in *(7)*.

FIGURE 4.

Under-five and neonatal mortality rate (per 1000 live births) and non-newborn deaths versus under-five deaths in selected low-resource countries



Note: The size of the bubble is proportional to the number of deaths
Source: Taylor et al. 2016 *(8)*

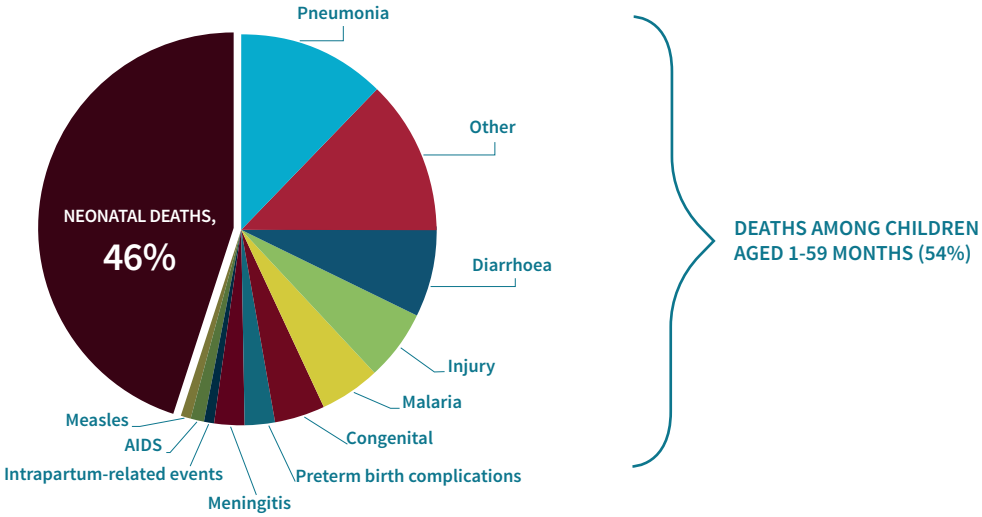
Of the 5.6 million deaths in 2016, 54% occurred in the postnatal period, i.e. in children ages 1-59 months.[2] Looking specifically at the postnatal cause of death in children, half are associated with febrile illness (Figure 5). After the first month of life, the main causes of death in children under-five are pneumonia, diarrhoea and malaria. In addition, malnutrition is an underlying factor associated with nearly half of under-five deaths *(1)*.

[2] Successful implementation of many initiatives targeted to achieving the Millennium Development Goals has led to an average annual decrease of approximately 5% in under-five mortality over the last 2 decades. However, the rate of decrease in neonatal mortality is lagging at approximately 3% annually, and neonatal mortality now accounts for about 45% of all under-five mortality.

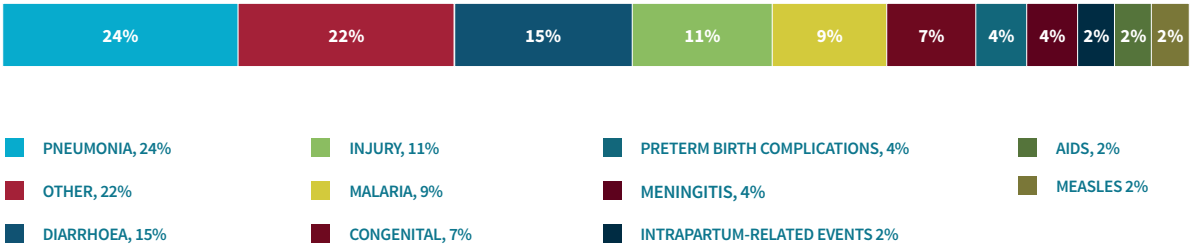
FIGURE 5.

Global distribution of deaths among children under age five and global distribution of deaths among children ages (ages 1-59 months), 2016

Global distribution of deaths among children under age five, 2016



Global distribution of deaths among children ages 1-59 months, by cause, 2016



Note: Estimates are rounded and therefore may not sum up to 100%.
Source: Author analysis of UN Inter-agency Group for Child Mortality Estimation data *(1)* as per original document.

AMR

Low- and middle-income countries (LMICs) suffer from a high burden of infectious diseases and, therefore, the rapid increase in AMR in these settings is a major threat. When the underlying cause of fever is uncertain or unknown, overtreatment with both antibiotics and/or antimalarial medicines is common *(9) (10) (11)*. The overuse of antimicrobials increases selection pressure and accelerates the development of drug resistance. Therefore, the issue of AMR is tightly linked to the need to improve fever case management in children.

Although the global burden of antimicrobial-resistant infections has been difficult to estimate, WHO, the United Nations and other leading global actors recognize AMR as one of the biggest threats to global public health *(12) (13) (14) 15)*. Globally, in most countries, about 80% of antibiotics are for outpatient use, either prescribed by health workers or obtained over the counter, and up to half of community use of antibiotics is inappropriate, adding to the burden of resistance *(16)*. At hospitals in LMICs, evidence suggests that in-patient prescription appropriateness is also challenging *(16) (17)*.

Similarly, the AMR burden on children in LMICs has not been well documented; however, emerging evidence suggests that resistant infections are common in LMICs *(18) (19) (20)* and that the issues associated with AMR could be magnified in low-resource settings. Beyond higher case fatality rates from drug-resistant infections, there are also increased costs of care as resistant infections require more expensive treatments which often have more adverse effects, illness is prolonged as is hospitalization, all of which unnecessarily burden health-care systems. Additionally, the resistant genes can be incorporated into the body's microbiome and can remerge as a new bacterial infection in the future.

Global targets

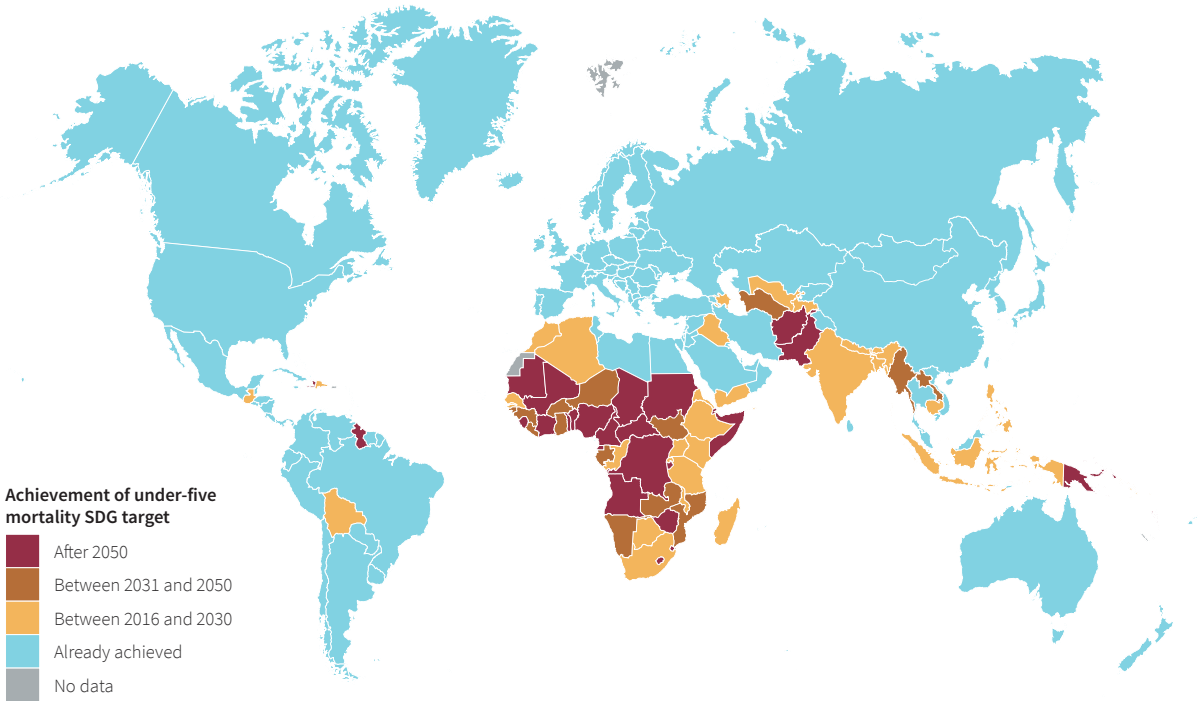
Despite significant gains in overall child health achieved across the globe since 1990, the world fell short of reaching the Millennium Development Goals (MDG) of reducing 1990 under-5 mortality by two-thirds by 2015. Since then, Sustainable Development Goals (SDGs) have been established. SDG 3, ensure healthy lives and promote well-being for all at all ages, has several sub-targets related to child health. Target 3.2 focuses on ending preventable deaths of newborns and under-five children by 2030, and Target 3.8 focuses on access to essential medicines and vaccines for all. Countries have committed to achieving the SDG targets under the Global Strategy for Women's, Children's and Adolescents' Health (2016-2030). This strategy sets out a roadmap to end preventable deaths of women, children, and adolescents (SURVIVE), to ensure their health and well-being (THRIVE), and their habitation in safe and health enabling environments (TRANSFORM). The main delivery strategies for targets related to childhood illness are the WHO's integrated management of childhood illness (IMCI) program (developed more than 20 years ago) and the WHO/UNICEF integrated community case management program (iCCM), which extends key components of IMCI to the community level.

To date, progress has not been rapid enough to meet the new child health targets of reducing mortality to 25 or fewer deaths per 1000 live births in children under the age of 5 years by 2030. Accelerated action is urgently needed in high mortality countries in Africa and in Southern Asia (Figure 6) *(21)*.[3]

[3] In sub-Saharan Africa, 1 in 12 children dies before their fifth birthday; and in Southern Asia, 1 in 19 children dies before their fifth birthday, compared to 1 in 147 in HICs.

FIGURE 6.

Achievement of SDG target on child mortality by year, and by country, if current trends continue in each country



Source: United Nations: Levels and trends in child mortality, report 2015 *(21)*.

Several other global action plans and targets are relevant to improving febrile illness diagnosis in children. In 2013, WHO and UNICEF launched the Global Action Plan for Pneumonia and Diarrhoea (GAPPD), which proposes integrated approaches to reducing severe disease, stunting and deaths from pneumonia and diarrhoea. The 2016 *Pneumonia and diarrhoea progress report: reaching goals through action and innovation* shows that, even when countries have officially introduced nearly every GAPPD intervention, they repeatedly miss the GAPPD target coverage rates (i.e. 90% of suspected pneumonia cases seen by an appropriate provider and given appropriate antibiotics, and 90% of diarrhoea cases treated with oral rehydration salts and zinc). The report found the time taken to scale up and reach all those who need these interventions is repeatedly taking years, if not decades *(22)*.

In May 2015, the World Health Assembly adopted the Global Technical Strategy for Malaria 2016–2030. The milestones for 2020 include: reducing malaria case incidence and mortality by at least 40%; and eliminating malaria in at least 10 countries. In 2016, WHO reported that

progress towards the elimination milestone is on track, but only 40 of the 91 malaria-endemic countries are on track to meet the milestone of a 40% reduction in malaria case incidence by 2020 *(23)*.

Global targets related to combatting AMR include the 2015 WHO Global Action Plan on Antimicrobial Resistance. Under this Plan, countries are developing multisectoral national action plans and WHO is monitoring progress on their development and implementation.

Not surprisingly, these progress reports, addressing the leading causes of childhood death, illustrate a persisting pattern across all three of the greatest killers of children: countries with the greatest burdens of pneumonia, diarrhoea and malaria report the least progress.

Public health challenge: diagnosing febrile illness in children

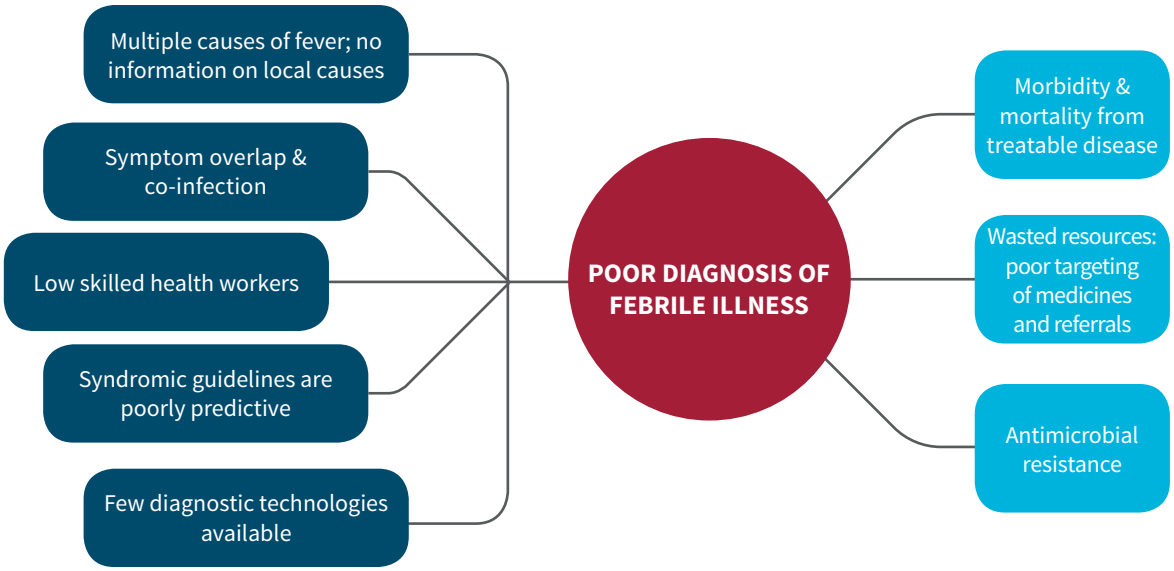
Febrile illness in children often presents a diagnostic dilemma. Before the availability of mRDTs, most health-care providers in malaria-endemic countries presumed that malaria was the cause of most fevers. Since 2010, WHO has recommended diagnosis before treatment, and as a result of the mRDT scale-up, febrile children are increasingly tested for malaria. The diagnostic scale-up has led to reductions in indiscriminate use of antimalarial medicines, and simultaneously unmasked the problem of overdiagnosis of malaria in many settings. It has also shined a spotlight on the difficulty of diagnosing the specific cause of fever at the frontline. Today, health workers are increasingly faced with negative mRDTs and non-malarial fevers and struggle to identify the appropriate diagnosis and treatment.

Moreover, in many parts of the world, malaria prevention efforts are reducing the incidence of malaria, and only a small proportion of febrile children actually have malaria. While many of these febrile children are likely to have self-limiting diseases, a few (perhaps as few as 5% at the community level; 5–10% at the primary level *(24)*) are infected with pathogens that require additional specific treatment, including antibiotics. Therefore, even when malaria can be ruled out, health workers are faced with ongoing diagnostic needs: they must identify those children who could benefit from additional available treatments; and those who require referral to higher levels of care for advanced diagnosis, treatments and supportive care. Given public health concerns about both overuse and underuse of antimalarials and antibiotics and AMR, improved diagnostic tools for frontline health-care workers in low-resource settings are urgently needed.

Although the differential diagnosis of fever in a febrile child can present a challenge to health workers worldwide, additional complexities in resource-poor settings result in higher morbidity and mortality, wasted resources and accelerated AMR (Figure 7).

FIGURE 7.

Factors contributing to poor febrile illness diagnosis in children in low-resource settings and their effects



Limited understanding of what causes fever in children

Symptom overlap, co-morbidity, colonization[4] and lack of information on the local fever etiologies (to better inform syndromic algorithms) all complicate diagnosis of fever in low-resource settings.

Many febrile illnesses, especially in children, present with highly non-specific and overlapping signs and symptoms that are difficult to distinguish clinically. Multiple studies have documented the overlap in clinical symptoms of malaria and pneumonia *(25) (26) (27)*. Without advanced clinical skills or diagnostics, it can be difficult to distinguish between the two: as children infected with malaria will often present with cough and shortness of breath.

[4] Colonization refers to the multiplication of foreign organisms, such as bacteria, in a host body. This process is not necessarily harmful; a microorganism is present (and detectable using a diagnostic test), but it is not causing a pathogenic immune response – i.e. the person is not sick from the microorganism. Carriage is the condition of harbouring a pathogen within the body, usually without any symptoms of the disease, but with the ability to transmit the pathogen.

Malaria RDTs can be used to rule out malaria with high accuracy; however, inexpensive POC tests for ARIs are not yet available. Diagnosis of bacterial pneumonia is based on a single clinical sign: the presence of fast breathing. While fast breathing is highly sensitive for pneumonia, it is not very specific: fever and malaria-related anaemia may also cause fast breathing in a child. Co-morbidity also presents a challenge.[5] A febrile child, chronically infected with malaria may be parasitaemia-detected by an mRDT, but malaria may not be the primary cause of illness and a health worker may fail to identify other diseases and delay care for concurrent illness, potentially leading to death *(28)*.

Although the mechanisms are not clear, studies also suggest that malaria infection increases the risk of bacteraemia in children *(29)*, and bacterial pneumonia can be a secondary complication in children with severe malaria as well as other infections.

Recent evidence has also raised awareness of a diagnostic challenge associated with TB and pneumonia in children. *Mycobacterium tuberculosis* is thought to be an underdiagnosed cause of childhood pneumonia, and may increase children's susceptibility to bacterial pneumonia. A recent review found that between 1% and 23% of pneumonia cases had concomitant TB *(30)*.

Optimally, clinicians are aware of pathogens circulating in their community, and this knowledge informs their assessment of a febrile child. However, in low-resource settings, the local disease burden and local epidemiology are essentially unknown. Furthermore, local epidemiology changes over time, particularly as vaccines, preventative efforts, environmental changes and economic development arrive in a community. Even within a country, the presence of particular pathogens can vary significantly, for example, between urban versus rural locations and by season. This means frontline health workers must classify illnesses with little access to diagnostics or epidemiologic data at hand. Currently, several etiology studies have been published and are under way to better understand the causes of death and febrile illnesses among

[5] There are limited data on coinfection. One study in the United Republic of Tanzania diagnosed pneumonia in 8% of malaria-infected children attending outpatient clinics. Other studies, looking at children admitted to hospital for pneumonia found 1–20% were also infected with malaria, depending on the location and local malaria prevalence.

[6] For example, see (accessed 30 September 2017):

- NIDIAG (better diagnosis of neglected infectious diseases) http://nidiag.org/;
- GEMS (Global Enteric Multicenter Study) http://www.medschool.umaryland.edu/GEMS/;
- PERCH (Pneumonia Etiology Research for Child Health) http://www.jhsph.edu/research/centers-and-institutes/ivac/projects/perch/;
- BARNARDS (Burden of Antibiotic Resistance in Neonates from Developing Societies) http://www.cardiff.ac.uk/research/explore/research-units/burden-of-antibiotic-resistance-in-neonates-from-developing-societies-barnards;
- FIEBRE (Febrile Illness Evaluation in a Broad Range of Endemicities) http://amr.lshtm.ac.uk/2017/04/19/febrile-illness-etiologies-broad-range-endemicities-fiebre/;
- ANDEMIA (African Network for improved Diagnostics, Epidemiology and Management of Common Infectious Agents) https://www.researchgate.net/project/ANDEMIA-African-Network-for-improved-Diagnostics-Epidemiology-and-Management-of-Common-Infectious-Agents;
- CHAMPs (Child Health and Mortality Prevention Surveillance) https://champshealth.org;
- CHAIN (Childhood Acute Illness and Nutrition Network) http://www.chainnetwork.org; NFMI by WARN (Non-malarial febrile illness map by Worldwide Antimalarial Resistance Network) http://www.wwarn.org/non-malarial-febrile-illness-nmfi-map

children with different presenting symptoms, in different geographies and settings, and with different presenting symptoms.[6]

Even when sophisticated diagnostic tests are available (i.e. in a research setting), often the microbiological cause of illness cannot be identified. Moreover, when specific pathogens are identified, the true cause of a child's febrile illness may still remain uncertain. For example, in fever etiology studies using highly sensitive diagnostics, sick children have been found positive for multiple pathogens, and it can be difficult to identify which pathogen(s) are the cause of active disease. True infection can be difficult to differentiate from colonization, and illness can be caused by more than one pathogen. Additionally, these fever etiology studies have detected several pathogens in children who are enrolled as "healthy" controls, suggesting that they are asymptomatic carriers who lack a clinically significant infection.[7]

Limited clinical expertise

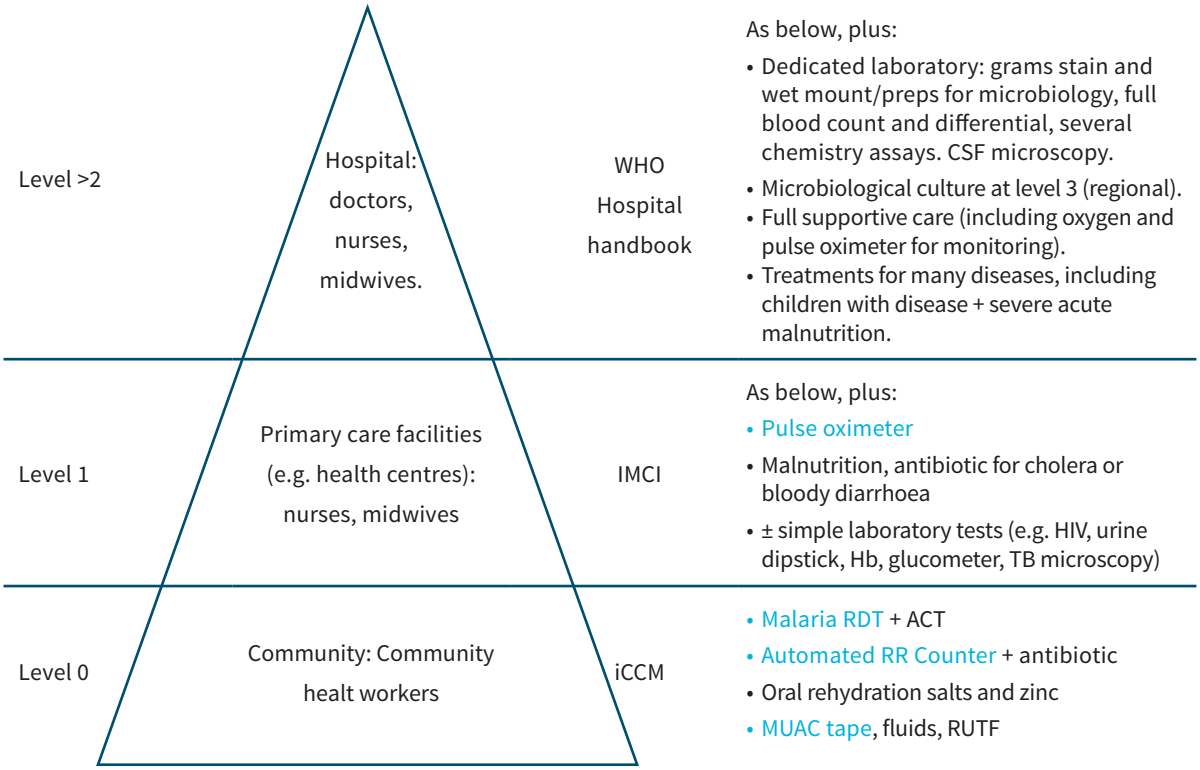
Health systems in low-resource settings are underfunded, have weak supply chains and suffer from chronic human resource shortages. Fever case management is impaired by the lack of clinical expertise for identifying serious illness and for diagnosing disease at the primary and community levels.

Typically, CHWs (lay persons with varying depth of training and supportive supervision) are the initial point of contact in the community, and nurses and clinical officers staff primary level facilities (e.g. health centres and health posts). Doctors are usually only found at the district hospital level and higher (Figure 8).

[7] In HICs, highly sensitive molecular diagnostics are increasingly available and allow for identification of many pathogens that have potential to cause illness. However, advanced clinical skills, additional tests (e.g. markers of inflammation, blood counts) and knowledge of local etiologies help clinicians decide if the identified pathogens are actually clinically significant.

FIGURE 8.

Levels of care and points of contact for children with febrile illness in LMICs, with a focus on: malaria, diarrhoea, pneumonia and malnutrition/dehydration



* Laboratory tests included are those recommended by IMCI or iCCM (blue) and those recommended by the Maputo Declaration that are relevant to diagnosing febrile illness in children.
CFS: cerebrospinal fluid; Hb: haemoglobin; MUAC: mid-upper arm circumference; ORS: oral rehydration salts; RR: respiratory rate; RUTF: ready to use therapeutic food.

IMCI and iCCM guidelines

In light of these health systems challenges, WHO and UNICEF have developed and are helping countries implement the integrated strategies, IMCI and iCCM to support prevention, treatment and care for sick children at various levels to reduce under-five mortality rates. The package has three components: improving health worker skills; strengthening health systems – including procurement and supply systems and monitoring and evaluation; and improving family and community behaviours. The success of these platforms has varied (see the commodity access section below) and requires strong coordinated health systems, trained workforces, political support, sufficient funding and availability of quality tools at the frontline, including medicines and diagnostics.

IMCI guidelines target first-level health facilities and focus on the main causes of child mortality, e.g. pneumonia, diarrhoea, malaria and malnutrition. IMCI guidelines provide an integrated, syndromic approach to childhood illness, relying on history, signs and symptoms that can be easily assessed by health workers who do not have extensive professional training. The WHO IMCI guidelines are evidence based, generic and, in principle, are adapted locally – for example, to incorporate other diseases, health-system characteristics and local culture. In 2003, care for sick newborns was added, and many countries have adopted the acronym "IMNCI".

Recognizing that, in many countries, facility-based services are not adequate, especially not within the crucial window of 24 hours after onset of symptoms, WHO and UNICEF released operational guidelines on iCCM in 2011. iCCM extends key services outlined in IMCI to the community level, through CHWs. iCCM involves training, supplying and supervising CHWs to diagnose and treat diarrhoea, malaria and pneumonia and to detect severe malnutrition in children.

Among the objectives of the IMCI and iCCM programmes is extending care for major childhood illnesses into the community so that children who might benefit from specific treatment (e.g. antimalarials or antibiotics) can be treated early and appropriately, and avoid progression to severe disease. Another goal is to identify children who are already very sick for rapid referral. This approach of putting services as close to the community as possible and empowering health workers to confidently treat the majority of illnesses in the community or at the primary level, also reduces the burden on upper level health facilities, thereby reducing costs and saving time.

Additional background on IMCI and iCCM is provided in Annex 1.

Recent IMCI/iCCM guideline updates

Since the release of the iCCM operational guidelines, changes to IMCI and iCCM have largely related to pneumonia. In 2014, WHO simplified pneumonia guidelines, allowing for more cases to be managed at home with oral amoxicillin without referral to a hospital.[8] This change has diagnostics implications, but allows for earlier treatment initiation and reduces the burden of referrals for hospitals.

[8] Studies in LMICs have shown that most pneumonia deaths in children were due to severe cases, which require early identification, early referral and access to high-quality higher-level care. Less severe cases of pneumonia could be safely managed at home with oral antibiotics, allowing for early treatment initiation and lower costs to the system and patients. See: http://apps.who.int/iris/bitstream/10665/137319/1/9789241507813_eng.pdf, accessed 10 October 2017.

In 2016, WHO issued guidance on management of hypoxaemia,[9] published through a series on oxygen use for children in low-resource settings *(31)*. Hypoxaemia is a potentially fatal complication of severe pneumonia and correlates with disease severity. It is treated with oxygen therapy, which is typically available only at the hospital level. WHO recommends use of pulse oximeters – non-invasive medical devices that measure oxygen saturation in the blood (SpO2) – to identify hypoxaemia in pneumonia patients at primary ("where available"), secondary and tertiary facilities.[10] Hypoxic patients should be referred for oxygen therapy. Studies show that pulse oximetry can identify 20–30% more cases of hypoxaemia than clinical signs alone *(32)*. A recent modelling exercise, covering 15 high-burden countries, predicted that pulse oximeters could avert up to 148 000 deaths from pneumonia, assuming 90% availability of pulse oximeters and oxygen therapy [11] *(33)*. Moreover, pulse oximeters have many use cases beyond childhood febrile illness.[12] WHO expects to publish technical specifications for pulse oximeters for low-resource settings in 2017.

Future IMCI/iCCM guideline improvements

A 2016 Cochrane review found that effective implementation of IMCI reduced all cause child mortality by 15% *(34)*. Providers particularly appreciate its simplicity and comprehensiveness as it relates to the major killers of children *(35)*. Despite IMCI's strengths, new evidence is emerging, and in late 2017 the WHO began an IMCI redesign process. Discussions with experts and recent publications suggest that there are several priority areas for consideration, where epidemiology has changed and new evidence is emerging. Two important areas related to febrile illness diagnosis are described here.

Further stratification of high-risk children. There are data indicating that certain children are more vulnerable to progressing to severe disease and mortality, and these children could be triaged for additional diagnostic work-up, care or follow-up *(36)*.When these children do make it to higher levels of care, they are often already severely ill and fatality rates are high. Early identification of children who are severely ill or who are at high risk of progressing to severe disease could reduce mortality. For example, pulse oximeters have been recommended for scale-up at the primary level to identify children needing referral for lifesaving oxygen therapy and closer monitoring. Similarly, malnourished children

[9] Hypoxaemia is an abnormally low level of oxygen in the blood.

[10] Experts debate whether pulse oximetry should be used routinely at the community level. On the one hand, CHWs may see so few cases of hypoxaemia that it is not a worthwhile investment compared to the number of cases identified and referrals made. However, there is value in providing lower-level health workers with a tool that allows them to rule out hypoxaemia and confidently manage a child in the community. WHO is leading a multicountry cluster-randomized trial in Bangladesh, Ethiopia, India and Malawi to evaluate, among other things, the use of pulse oximeters by CHWs. (See: http://apps.who.int/iris/bitstream/10665/205631/1/9789241510356_eng.pdf?ua=1, accessed 17 September 2017).

[11] This modelling exercise found that pulse oximetry and oxygen therapy would reduce pneumonia deaths by one sixth. In comparison, complete elimination of low birth weight or elimination of malnutrition would prevent 25% of pneumonia deaths in developing countries and deployment of PCV10 vaccines has been predicted to avert 262 000 deaths in children under-five.

[12] These include: neonatal care, pre-eclampsia screening, monitoring patients under anesthesia in surgery, and hypoxaemia identification in children with other severe diseases (e.g. sepsis, severe malaria, meningitis, malnutrition, TB and asthma).

are at higher risk of progressing to severe disease and death, and nearly half of global under-five deaths are associated with nutrition-related factors *(37)*. Anaemia, which can be caused by nutritional deficits as well as other factors, can be a direct cause of death when severe, or an indirect contributor to death in children *(38)*. There is also considerable work being done on socio-economic determinants of health as it is poor, rural children who are least likely to receive services and who are more likely malnourished, leaving them at a greater risk of progressing quickly to severe disease and death.

Improved targeting of treatments. The two main antimicrobial treatments supported by IMCI and iCCM protocols are artemisinin-based combination therapies (ACTs) and antibiotics (especially oral and dispersible amoxicillin). IMCI and iCCM rely on mRDTs to accurately identify patients needing or not an ACT. Due to increased malaria preventive efforts, malaria has declined recently in many settings. While malaria testing has increased and further improved targeting of ACTs, uptake and adherence to test results is variable *(9) (39)*. Studies confirm that limited provider knowledge of integrated case management and/or access to alternative diagnoses and treatments contribute to poor adherence to mRDTs results, irrational use of ACTs, and increases in unnecessary antibiotic prescriptions *(11)*.

With respect to antibiotics, IMCI is designed to be highly sensitive for identifying children who may have a severe bacterial infection requiring antibiotic treatment. However, the signs and symptoms used by IMCI for bacterial infection are not specific and, in light of global AMR, there is a desire to further focus antibiotic therapy to children with severe disease and those who have bacterial infections. For example, within the pneumonia classification, IMCI is prescriptive about children who should receive antibiotics; however, in other areas it is more ambiguous. IMCI is not clear in identifying those who do not need antibiotics and, to be on the safe side, health workers frequently provide antibiotics.

Pneumonia also presents a dilemma: the current IMCI criteria for antibiotics are cough plus fast breathing; however, up to 65% of cases meeting these criteria are viral and would not benefit from antibiotics, and a proportion of the remainder are likely to have a self-limiting infection *(40)*. Although this approach overtreats many, it maximizes the number of children reached, including those with mild bacterial pneumonia and those with viral pneumonia who may later develop a secondary bacterial infection.

In addition to improved diagnostic tests to enable identification of children needing antibiotics, several options for improving targeting of treatments have been proposed, for example: additional or refresher training, further incentives for supportive supervision to increase

quality of care, *(35)*; incorporation of new clinical assessment criteria (e.g. higher respiratory rate cutoffs for pneumonia, tender abdomen for typhoid); clearer indications for when an anti-pyretic should be administered, and addition of a new classification category that does not require antibiotic or antimalarial treatment (e.g. "common cold/ cough" or "suspected viral illness") *(41)*.

AMR guidance: increasing access without excess

Given the increasing global importance of AMR and its link to managing childhood febrile illness, issues around appropriate use of antimicrobials and the consequences of misuse are key drivers of initiatives aiming to improve febrile illness diagnosis and management in children.

In general, health workers evaluating a febrile child are faced with the immediate need to determine if the individual will benefit from antibiotics. Identifying whether the disease is caused by a bacterium is a key first step; knowing which antibiotics would be most effective and the drug susceptibility of the bacteria in question is a key second step. Knowing the specific pathogen causing the infection supports targeted antibiotic use; as a rule, narrow-spectrum antibiotics are preferred if they are likely to be effective, while broad-spectrum antibiotics are reserved for more serious infections. Having information on drug resistance or, preferably, the complete drug susceptibility profile of the bacteria in question, allows the health worker to select the most effective antibiotic for that infection. Dose, duration and side-effect profiles are also important considerations.

To support health workers with this decision, a set of clinical diagnostic tools are needed, including: tests that differentiate bacterial versus non-bacterial infections; tests to identify specific pathogens, or subgroups that require special antibiotics (e.g. doxycycline or tetracycline responding bacterium); and tests to establish drug susceptibility. While it is not feasible for all of these to be deployed at the frontline, tests that help the health worker to decide if the patient would benefit from an antibiotic, or has an infection requiring another specific treatment, would be helpful.

Today, given the lack of diagnostics tests, empiric treatment is the norm both in high-income countries (HICs) and LMICs, leading to significant overtreatment and poor targeting of antibiotics. Even without new rapid POC diagnostics to guide antibiotic treatment in LMICs, there is scope for improvement. At the national level, the choice of antimicrobials and algorithms used at the primary level needs continuous review to ensure continued effectiveness, taking into account local pathogens and their resistance profiles *(42)*. Ideally, epidemiologic surveillance data collected routinely on a local basis, and made available to clinicians, would guide empiric antibiotic choices in the absence of more specific diagnostic tests at the frontline. However, these data are not available from many LMICs, and where they are available, quality is a major concern due to the lack

of standardization in methods and interpretation, as well as limited quality assurance *(43)(44).*

In HICs, AMR stewardship programmes are increasingly being implemented to minimize unnecessary use of antibiotics and to promote use of the most appropriate, targeted antibiotics. In LMICs and, in particular, for children, increasing access to antimicrobials is a greater priority than restricting access *(19)*, however, in light of the AMR crisis, efforts to increase access must remain mindful of appropriate antimicrobial use. Evidence also suggests that there are significant levels of resistance to commonly used antibiotics, including those typically recommended as first- and second-line use under IMCI and similar guidelines for adults *(43)*. Although awareness of AMR is increasing in LMICs, guidelines for ARM management – including use of clinical diagnostics and epidemiological tools – do not yet exist.

Limited availability of diagnostic tools to support integrated fever case management

Ideally, POC diagnostic tests would be available to diagnose all diseases that are the primary causes of childhood mortality. Operational guidelines for IMCI and iCCM have been updated since the 2010 WHO recommendation to test all suspected cases of malaria with an RDT. Additionally, HIV RDTs are used in IMCI, and pulse oximeters, if available, are recommended. Aids may also be used to assist with respiratory rate count. However, other diagnostics do not feature in IMCI and iCCM guidelines, either because tests do not exist, or where they do (e.g. multiplex molecular diagnostic panels for respiratory illness), they are not available to frontline health workers in resource-poor settings for a variety of reasons (such as high cost, lack of POC formats amenable for use in settings with limited laboratory capacity and infrastructure, lack of evidence regarding performance and quality, and/or lack of suitable panels).

Policy and regulatory approval pathways for febrile illness diagnostic tools in LMICs

In addition to the availability of appropriate diagnostic technologies, policy and regulatory systems are needed to move these advances into widespread use. While they vary by country, generally, in low-resource settings the processes and standards for registration of many medical devices and in vitro diagnostics are limited and/or poorly enforced. WHO plays an important role in assessing products for priority disease areas and in making recommendations about their use. Additionally, depending on the country, many public health programmes look to WHO for normative guidance and on diagnostic and treatment protocols, as do many global health donors.

Regulatory pathways: quality, safety and efficacy review

The WHO Prequalification (WHO PQ) process of in vitro diagnostics aims to ensure that diagnostics for high-burden diseases meet global standards of quality, safety and efficacy, in order to optimize use of health resources and improve health outcomes. The WHO PQ programme includes a dossier review, laboratory evaluation of the product to assess operational and performance characteristics, and an inspection to assess compliance with international quality management standards. While the stated priority of the WHO PQ process is to review and recommend diagnostics of sufficient quality for United Nations procurement, in practice, WHO diagnostics prequalification status is used more broadly, with many national programmes and donors relying on the WHO lists of prequalified products, due to the absence of robust regulatory processes for diagnostic tests at the country level.

Currently, the WHO PQ diagnostics programme reviews diagnostics for HIV, hepatitis B and C, HPV and malaria. Provisions for assessing tests for glucose-6-phosphate-dehydrogenase deficiency as well as cholera, Ebola and Zika are also in place. The scope of the WHO PQ programme is now limited to these areas, and expansion to other diagnostics depends on priority needs identified by WHO as well as on the availability of funding.

There is no WHO PQ process for medical devices (such as a pulse oximeter), nor are assessments of devices undertaken routinely. However, the WHO medical devices group is supporting development of robust regulatory systems at the country level, and increasingly plays a role in developing minimum specifications for devices to support improved access to high-quality, safe and effective devices, as well as to support adequate planning for the upkeep of such devices.

WHO publishes an annual *Compendium of innovative health technologies for low-resource settings,* which aims to identify innovative products that address global health challenges and are amenable to use in low-resource settings. The publication aims to be an objective resource that serves to raise awareness of new technologies and to foster dialogue between stakeholders. Developers apply to have their devices included in the Compendium series.

Policy development

While the WHO PQ process aims to identify products that are efficacious; it does not consider more broadly whether they are effective (e.g. how a product works in routine practice, which patients should be tested, outcomes) or whether it is a worthwhile investment (e.g. what is the value for patients and for society). The technical

[13] See: http://www.who.int/medicines/news/2017/WHO_develop_essential_diagnostics_list/en/, accessed 19 June 2017.

departments within WHO typically lead these reviews of evidence on outcomes and cost-effectiveness, and publish related guidance. Many ministries of health (MoHs) as well as global health donors look to WHO for this guidance. There is currently no essential diagnostics list, although there is a nascent effort at WHO to develop one.[13]

The systems for developing policies and normative guidance and for recommending new products differ by WHO department.[14] In child health, a recent review found: "Although WHO has a process for considering new recommendations for integration into IMCI, there is no global multi-stakeholder scientific advisory body to advise in a systematic way on translating useful innovations into guidelines and delivery strategies, taking into account how they fit into integrated programming" *(35).*

With respect to devices, in 2016, WHO and partners published an *Interagency list of priority medical devices for essential interventions for reproductive, maternal, newborn and child health.* This list comprises the medical devices required to provide the essential reproductive, maternal, newborn and child health interventions defined by existing WHO guidelines and publications. The aim of developing the list was to improve access to these devices, support quality of care and strengthen health-care systems. The medical devices are each assigned to the appropriate level of the health system (e.g. health post, health centre, district hospital).

[13] See: http://www.who.int/medicines/news/2017/WHO_develop_essential_diagnostics_list/en/, accessed 19 June 2017.

[14] For example, the Malaria Policy Advisory Committee was established in 2011 and convenes twice a year to provide independent strategic advice to WHO on developing policy recommendations on malaria control and elimination. The Strategic and Technical Advisory Group for Tuberculosis convenes annually to review proposed changes in policy based on new evidence. The Vector Control Advisory Group was established in 2012 to assess the public health value of new product classes in vector control.

Diagnostics-related commodity access problem

Data on access to quality fever case management are scarce. While there are ongoing efforts to extend data platforms to the community level (e.g. the District Health Information Software 2), progress is slow. For pneumonia, treatment coverage is primarily monitored through care-seeking indicators obtained through periodic household surveys; however, data are often outdated or of questionable quality *(22)*. Additionally, little representative data exist regarding whether children have been properly assessed and managed according to guidelines, and concerning whether treatments are appropriate.

Care seeking

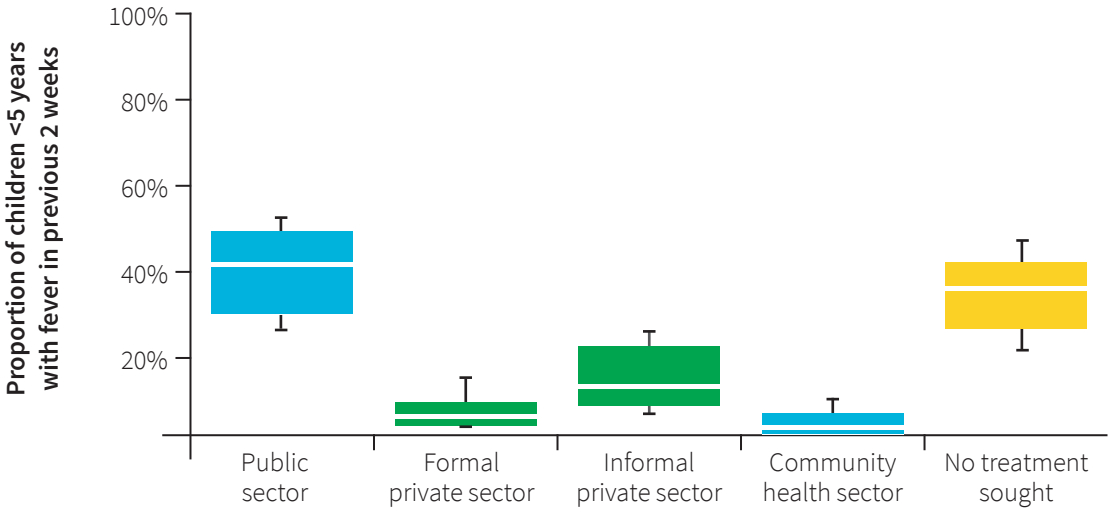
In general, caregivers of children with fever have multiple options for seeking care, they may go to a public or private facility, consult a CHW, a retail outlet (pharmacy, drug shop, informal), traditional healers, or seek no care. Care-seeking behaviour varies by location, and depends on the strength of the public and private health system, urban/rural locations, socio-economic factors (e.g. the wealth quintile of the family), age of the child, perceived severity, availability of tests and medicines.

Overall, care seeking for major causes of childhood mortality is suboptimal: in sub-Saharan Africa in 2013–2015, a median of 54% of febrile children were taken to a trained provider (i.e. to public sector health facilities, formal private sector facilities or CHWs); 36% were not brought for care; and 10% sought care from untrained providers (Figure 9) *(23)*.

For pneumonia specifically, rates of seeking treatment from an appropriate health-care provider for children with suspected pneumonia did not exceed 77% for any of the 15 highest-burden countries, and were as low as 13%. The leading countries for appropriate care seeking for pneumonia are India, Indonesia and the United Republic of Tanzania. In contrast, in Chad, Ethiopia and Somalia less than 30% of children with suspected pneumonia were taken to an appropriate health-care provider *(22)*.

FIGURE 9.

Proportion of febrile children seeking care, by health sector, in sub-Saharan Africa, 2013–2015



Note: Based on demographic and health surveys and malaria indicator surveys in 23 countries.
Source: WHO World Malaria Report 2016 *(23)*.

Coverage of key case management interventions

Given limited data on diagnostics access, it is useful to consider coverage of key interventions such as IMCI and iCCM. More than 100 countries have adopted IMCI, including almost all African countries; however, implementation has been variable, limiting the impact. iCCM is a newer programme, and implementation varies greatly. As of 2016, 26 malaria-affected countries in Africa had policies in place, of which 24 had started national or subnational implementation. In each of the WHO regions of South-East Asia, Eastern Mediterranean and the Americas, seven countries had iCCM policies in place. However, two of these countries have not embarked on any implementation. Few countries have nationwide implementation of iCCM, but data on the level of implementation and quality of services are unavailable for most countries at this time (Figure 10) *(35)*.

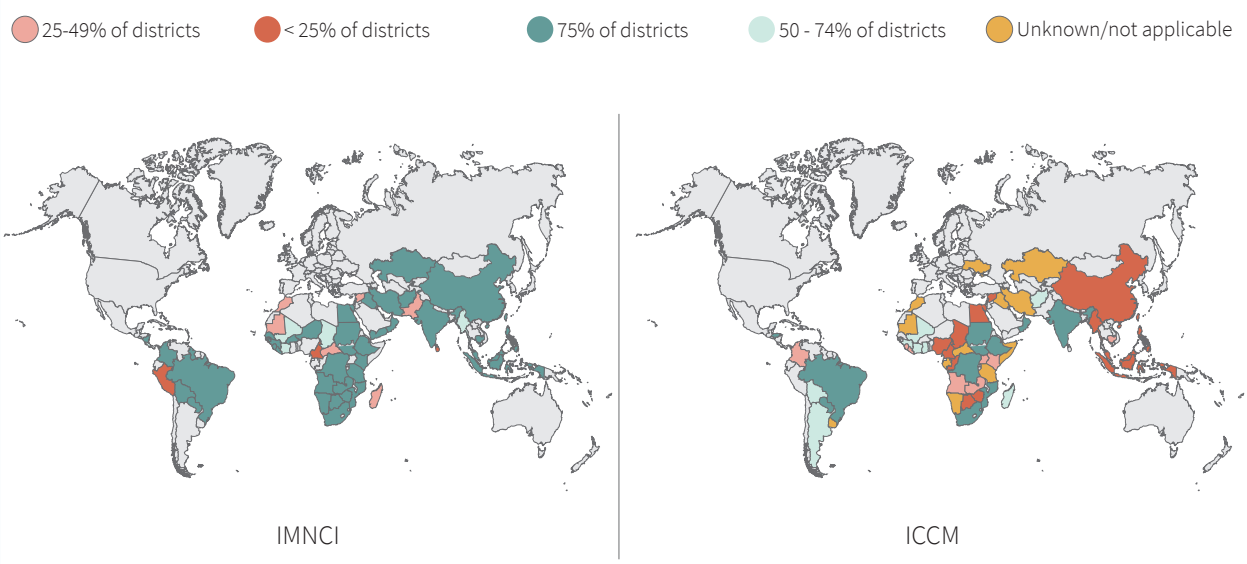
In light of the need to extend services beyond health facilities *(45)*, there are many efforts to expand coverage of febrile case management in low-resource settings, among them the WHO-led Rapid Access Expansion Programme iCCM scale-up,[15] the Unitaid-funded access to malaria diagnosis in the private sector initiative,[16] and the UNICEF-Global Fund memorandum of understanding (MoU) focused on community health.[17] Additionally, an interagency taskforce has been established to support and promote iCCM.[18]

[15] See: http://www.who.int/malaria/areas/rapid_access_expansion_2015/en/, accessed 15 June 2017.
[16] See: https://www.unitaid.eu/project/creating-private-sector-market-quality-assured-rdts/, accessed 15 June 2017.
[17] The MOU leveraged $125 million within Global Fund grants for iCCM implementation across 36 countries. The Global Fund Board approved that malaria commodities, training, monitoring and evaluation and procurement and supply management strengthening for iCCM are all eligible for funding, only non-malaria commodities (e.g. ORS/Zinc, antibiotics, respiratory timers) can not be financed with Global Fund monies and must be sourced from other funds.
[18] See: http://ccmcentral.com, accessed 1 August 2017.

Although IMCI and iCCM have been adopted by many countries, implementation complexities and challenges around scale up have limited their efficacy *(8)*. A 2016 strategic review of IMCI concluded that IMCI was a powerful tool with significant potential, but its implementation has been uneven and needs to be strengthened. A number of challenges also hinder the full scale-up of iCCM. Effective iCCM relies heavily on CHWs being properly trained, equipped and supervised, which in turn requires government stewardship and investment, but resources are often inadequate. However, there is increasing recognition of the need to institutionalize CHWs into the formal health system to ensure continued provision of their services.

To address these challenges, health systems will need to be strengthened to ensure adequate training, supervision, supplies and referrals. As evidenced from the care-seeking data, there has not been sufficient community engagement to raise awareness of the need to seek prompt care from qualified providers. Fragmentation of actors at the global and national level have aggravated issues around integrated funding for child health. Given such fragmentation, only countries with strong government leadership and political commitment were "able to engage in the unified, country-led planning necessary to support scaling up" *(35)*. Finally, a lack of integrated targets and indicators has impeded monitoring and evaluation.

FIGURE 10.
Map of global implementation of IMCI and iCCM



Source: World Health Organization 2016 *(35)*.

QUALITY OF FEBRILE ILLNESS DIAGNOSIS AND MANAGEMENT

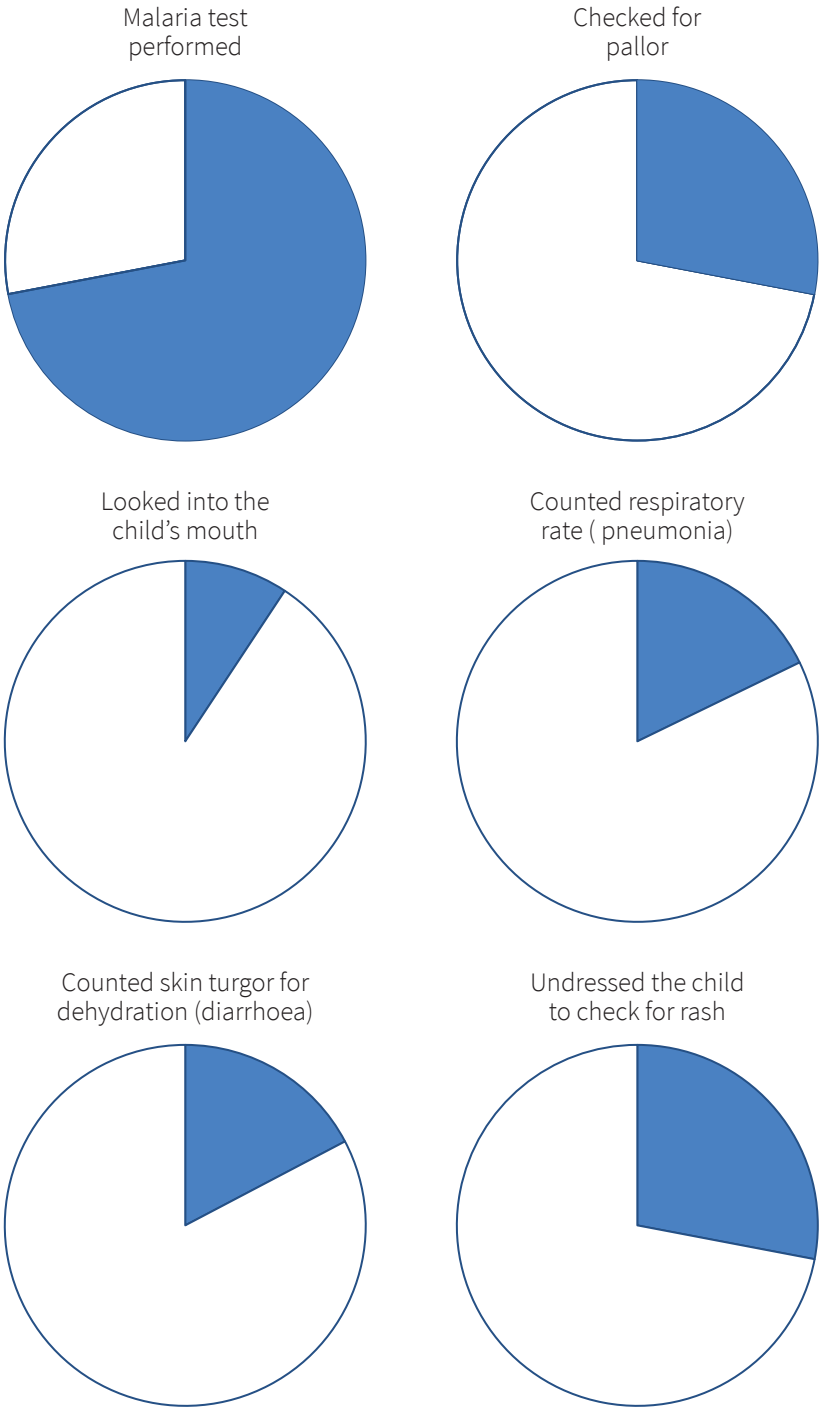
Minimal data on the quality of febrile illness diagnosis and management in children are collected routinely. For example, for malaria, the proportion of suspected cases who are tested is reported by national malaria programmes and collected through routine household surveys; however, data on adherence to test results are not captured at the individual level, and are only measured indirectly in aggregate by comparing the volume of ACTs distributed to the volume of malaria tests performed across a national programme.

For other aspects of febrile illness diagnosis, there are no routinely reported indicators, and the only data derive from special surveys or studies, or extrapolations from malaria data.

One weakness in the quality of fever case management is assessing children for danger signs. No national or large-scale reviews were found on this issue. Smaller studies clearly suggest variations and shortcomings. For example: in one study, danger signs were only checked in 3% of children *(41)*; in another, only 12% of health workers trained in IMCI evaluated danger signs in every child, and only 53% of children classified with severe illness were correctly identified *(46)*. Another study looking at severe malaria indicated diagnosis was correct <30% of the time *(47)*. Finally, a study looking at pneumonia care under IMCI protocols found that 40% of children requiring hospitalization were missed *(48)*.

Recently, data from a service provision assessment in Malawi were analysed to assess the quality of fever management in children *(5)*. This study used data from a survey of >90% of health facilities in Malawi in which 1981 paediatric fever encounters were observed. The study concluded that integrated fever management in children was suboptimal, and called for a shift away from a "malaria test and treat" strategy towards "IMCI with testing". Despite compliance with the malaria treatment guidelines, many of the other aspects of IMCI were not completed (Figure 11). The study also found that 28% of children who should have received a pneumonia classification were not treated with an antibiotic and that 59% of children who had no indication for antibiotic under IMCI protocols received an antibiotic (overtreatment). Although these data are from one country, the scale of the study is significant, and experts and other published studies echo its findings.

FIGURE 11.
Facility-based health worker compliance with various aspects of IMCI assessment for febrile children



Notes: i) Performing a malaria test, checking for pallor, looking into the child's mouth and undressing the child to check for rash are key steps in IMCI assessment of a febrile child. n = 1981 children with fever, ages 2–59 months. ii) Counted respiratory rate is indicated by IMCI for children with cough or difficulty breathing. n = 1436 children with fever and cough, ages 2–59 months. iii) Checked skin turgor for dehydration is indicated by IMCI for children with diarrhoea. n = 569 children with fever and diarrhoea, ages 2–59 months.
Source: Data extracted from Johansson et al. 2016 *(5).*

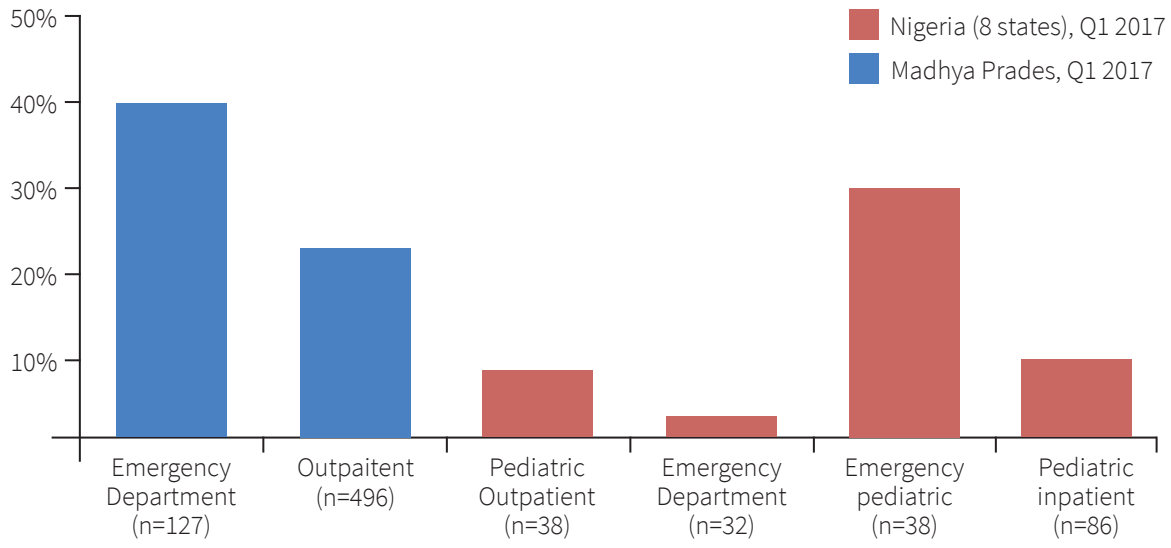
Diagnostic technologies access estimate

Currently, only a few diagnostic technologies are available to guide the management of childhood febrile illness: respiratory rate counting aids; pulse oximeters; and mRDTs. Moreover, data on the availability, uptake and impact of these technologies in low-resource settings are scarce.

Respiratory rate counting aids (for use at all levels, to assist with respiratory rate counting as per iCCM and IMCI protocols). Respiratory rate is extremely challenging to count, even among highly trained providers there are discrepancies. Several tools are available to assist health workers with respiratory rate assessment, however, there are minimal data on access to these tools. For example, in the last five years, UNICEF has supplied nearly half a million ARI timers to over 70 countries. Unfortunately, these aids lack automation and multiple studies show that health workers routinely struggle to count respiratory rate, even with assistive devices, thus fully automated counters are needed (see the *Technology landscape and pipeline* section for details on available respiratory rate counters and pipeline).

FIGURE 12.

Percentage of facilities with a functional pulse oximeter, selected states in India and Nigeria, 2017



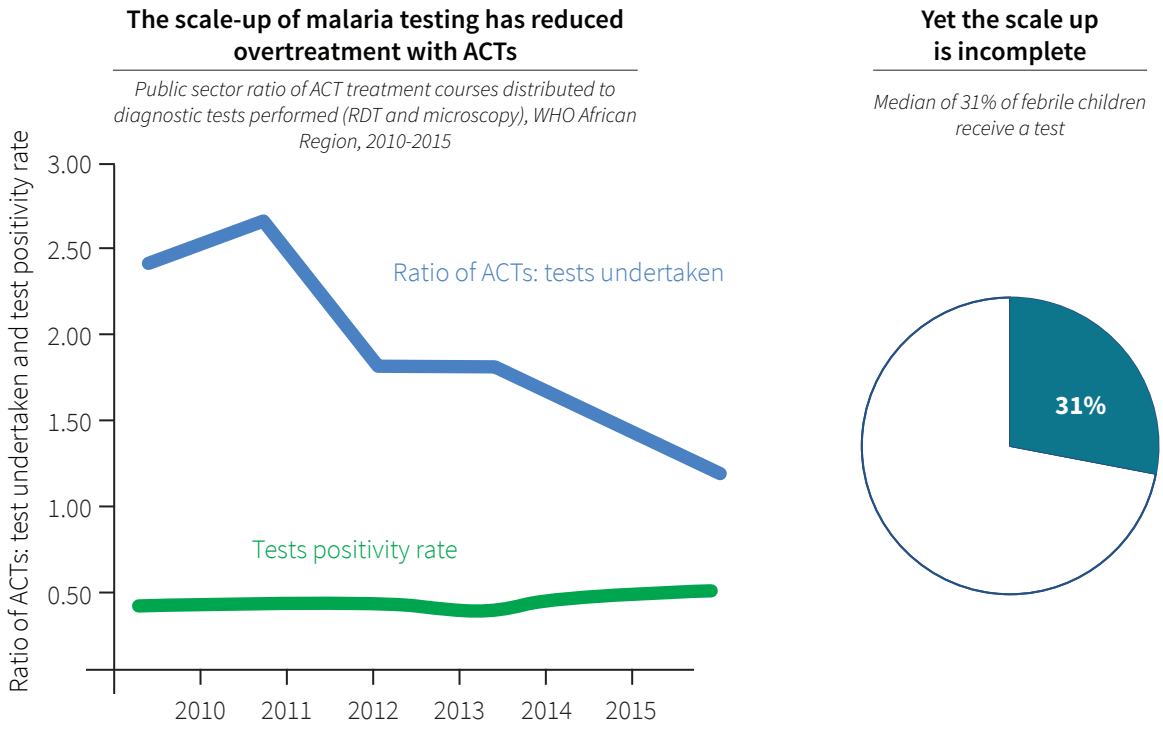
Notes: Nigeria data are based on a survey of all secondary and tertiary health facilities in Bauchi, Cross River, Kaduna, Kano, Katsina, Lagos, Niger, and Rivers. The survey includes other departments/wards within the hospital, but only those relevant to paediatric fever management are shown here. Percentages represent the proportion of outpatient and emergency departments (as well as the paediatric in-patient ward) with a functional pulse oximeter. India data are from a survey of all 51 districts in Madhya Pradesh. Only public facilities were surveyed, including district hospitals, medical colleges, civil hospitals, community health centres and primary health centres. Percentages represent the number of facilities with any functional pulse oximeter in their emergency or outpatient department observed by the surveyor.
Source: Clinton Health Access Initiative, unpublished data, May 2017.

Pulse oximeters (recommended at the primary level and higher, IMCI).[19] Pulse oximeters are largely unavailable in frontline settings for pneumonia triage. Where available, they are very rarely found in outpatient settings, they are most common in surgery and in-patient wards, and occasionally in emergency or labour departments.

A review in 22 LMICs found that of 394 hospitals that reported on pulse oximeter availability, only 51% had functional pulse oximeters *(49)*. Surveys from selected states in India and Nigeria indicate low availability of pulse oximeters in settings where febrile children with suspected pneumonia would typically be screened (Figure 12), although these data are from a limited set of countries. In addition to functioning pulse oximeters, children with hypoxaemia need to be referred to hospitals for oxygen therapy; however, access to oxygen is inconsistent across most referral facilities in LMICs.

Malaria microscopy or RDTs (recommended at all levels, iCCM and IMCI). Access to malaria diagnosis varies. In the public sector, testing uptake is relatively high, and targeting of ACTs has improved since RDTs were introduced in 2010. For example, in 2015, 148 million ACTs were distributed versus 170 million tests performed in the public sector in Africa. This ratio, 87 : 100 tests, is an improvement over the past, however, the target ratio, in line with test positivity rate, is 52: 100 (Figure 13) *(23)*.

FIGURE 13.
Malaria testing rates in Africa



Source: WHO World malaria report 2016 *(23)*.

[19] WHO is leading a multicountry cluster-randomized trial in Bangladesh, Ethiopia, India and Malawi to evaluate, among other things, the use of pulse oximeters by CHWs (http://apps.who.int/iris/bitstream/10665/205631/1/9789241510356_eng.pdf?ua=1).

Despite progress in the public sector, high care seeking but low testing in the private sector result in an overall median of 31% of febrile children receiving a malaria test in Africa (based on household surveys in 22 countries, 2013–2015, interquartile range: 16–37%) *(23).*

Impact of poor diagnosis of febrile illness in children

Taken together, the complexity of diagnosing the causes of fever in children, the lack of clinical expertise in low-resource settings and the limited diagnostic tools available to support health workers all contribute to increased childhood morbidity and mortality, acceleration of AMR and wasted resources (e.g. inappropriate treatment that is, at best, unhelpful, and, at worst, quite harmful).

As previously shown, access to integrated case management is a major problem. One third of children are not taken to any provider, either due to poor access or to low caregiver awareness. One analysis estimated that 38% of severe pneumonia cases do not reach hospitals, and that most (81%) pneumonia deaths occur in this group *(45)*. Community behavior change and sensitization programmes to encourage prompt care seeking are needed, as well as improved capacity to assess children across the spectrum of disease.

Even when children are taken to a qualified provider, health workers miss danger signs and undertreat critical disease. In the Malawi study, 28% of children who should have been diagnosed with pneumonia and given an antibiotic were missed *(5)*. For frontline health workers, especially at the community level, it is a challenge to identify and refer those very few critically ill children in time for them to access higher levels of care. Among the many millions of febrile children each year, the majority will not require referral. IMCI reviews indicate that health workers fail to recognize danger signs, both because they see them infrequently and because they neglect to check for them.

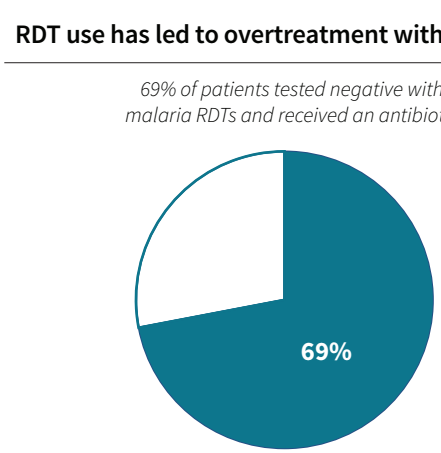
Today, the lack of access to antibiotics and antimalarials is likely contributing to more childhood deaths in LMICs than AMR. For example, researchers estimate that universal provision of antibiotics could reduce pneumonia deaths by 75% in children under-five (averting 445 000 deaths out of 590 000 community acquired pneumonia deaths in children under-five) *(19).*

Conversely, given the need to reach as many children as possible, the IMCI guidelines are based on a limited set of signs and symptoms designed to be highly sensitive. However, this can lead to high rates of overtreatment. Until mRDTs were introduced, overtreatment for malaria was the norm. Currently, there has been a shift to overtreatment with antibiotics. For example, a recent review of half a million patients found that that 69% of patients with a negative mRDT received antibiotics (Figure 14) *(11)*. While the

primary issue in low-resource settings is access to treatment, at the same time, the current rates of overtreatment are also harmful. When children are treated for diseases they do not have, it potentially causes them harm (e.g. side-effects, lack of treatment for disease they do have, inappropriate antibiotic treatment adversely affecting their microbiome), contributing to unnecessary expenditure for individuals and systems, and accelerating the development of AMR.

FIGURE 14.

Percentage of patients testing negative for malaria receiving an antibiotic



Source: : Hopkins et al. 2017 *(11)*.

In addition, there are immediate and longer-term financial consequences of poor diagnostic practices for febrile illness. In the near term, poor targeting of antimalarials and antibiotics increases direct and indirect costs to patients and the health system (e.g. loss of productivity, opportunity cost to provide better care to the same or other patients). Furthermore, when providers over-refer and patients bypass their immediate health service point *(50)*, it unnecessarily overburdens the higher-level facilities, and increases costs. In the longer term, overtreatment accelerates the development of AMR. Resistant infections are more expensive to treat, require specialized medications, and often require longer hospitalization.

Overall, the scale up of mRDTs has had a tremendous impact on improving care for febrile children through specific diagnosis. However, the use of mRDTs requires a high-quality integrated approach to disease management in children, especially in light of the significant overlap in clinical manifestations of many diseases that affect children in low-resource settings, and the possibility of coinfections. Point-of-care, easy to use diagnostic technologies that can aid in the differential diagnosis of fever, in particular, in light of human resource constraints, need to play a critical role in integrated case management of febrile children in low-resource settings.

Technology landscape and pipeline

This section describes a selection of promising innovations for improving diagnosis of febrile illness in children in malaria-endemic LMICs. Several of the technologies are on the market and others are in the later stages of product development. Ideally, these technologies would address key weaknesses in current practice: (i) frontline health workers triage children poorly, sometimes missing danger signs and risk factors; and (ii) frontline health workers have limited clinical expertise and diagnostic capacity, leading to both undertreatment as well as non-targeted treatment of diseases (Figure 15).

Representative examples of the different approaches to improving febrile illness diagnosis are described below (Figure 16) and further detail on a selection of individual products can be found in Annex 2.

Malaria diagnostics, although critical to diagnosis of febrile illness, are not specifically discussed in this report as they are covered in detail elsewhere (see the Unitaid *Malaria diagnostics market and technology landscapes*).[20]

Similarly, multi-disease diagnostics for HIV, tuberculosis (TB), HCV and other coinfections are comprehensively detailed in the Unitaid *Multi-disease Diagnostic Landscape For Integrated Management of HIV, HCV, TB and Other Coinfections.*

In general, there are a variety of technical challenges related to developing diagnostic tests for febrile disease in children. For diagnostics that aim to identify specific pathogens (or host responses directly linked to that pathogen), the main challenges include:

- **Multiplicity of causative organisms.** Unlike malaria, HIV and TB infections, fever, pneumonia and diarrhoea have multiple causative organisms. For example, pneumonia can be caused by bacteria (of which Streptococcus pneumonia is the most common), viruses (e.g. RSV, influenza virus) or fungi, or a combination of these.[21] Additionally, in some cases, the underlying etiology in the community is changing rapidly: for example, the scale-up of pneumococcal and *Haemophilus influenzae* type b vaccinations will affect the major causative agents of pneumonia in children.

[20] See: https://unitaid.eu/assets/Malaria_Diagnostics_Technology_and_Market_Landscape_3rd_Edition_April_2016-1.pdf, accessed 1 August 2017.
[21] Additional important pathogens common in certain high-risk groups, such as malnourished children, neonates and children with HIV infection, include Staphylococcus aureus, enteric Gram-negative bacilli such as Escherichia coli and Klebsiella species, Pneumocystis jiroveci (often called PCP) and Mycobacterium tuberculosis.

- **Pathogen inaccessibility.** For many infections, specimens are not accessible (e.g. for ear, sinus and lung infections) without invasive procedures that are not commonly performed. Sampling other more accessible sites, such as the nasopharynx, is not generally informative due to non-pathogenic colonization that can lead to false-positive test results.

- **Colonization and carriage.** Many children harbour potentially pathogenic microorganisms, yet are healthy (or asymptomatic). Additionally, people will be affected differently by the same microbial challenge – especially depending on their nutritional status. Thus, detecting an organism is not necessarily clinically meaningful, and some tests are, therefore, non-specific, identifying the presence of pathogens that are not necessarily causing disease.

- **Disease kinetics and pathogenesis.** Due to disease kinetics and pathogenesis, a number of common, infectious pathogens are intrinsically hard to detect in available samples with available methods. For example, invasive Salmonella typhi (typhoid fever), has very low pathogen load in the blood, making it difficult to detect. An additional complication is that for many diseases, such as dengue, different methods (serology versus molecular) are used to detect the acute versus chronic phase of infection. Since patients can present to health-care providers at different stages of illness, more than one test per disease might be needed.

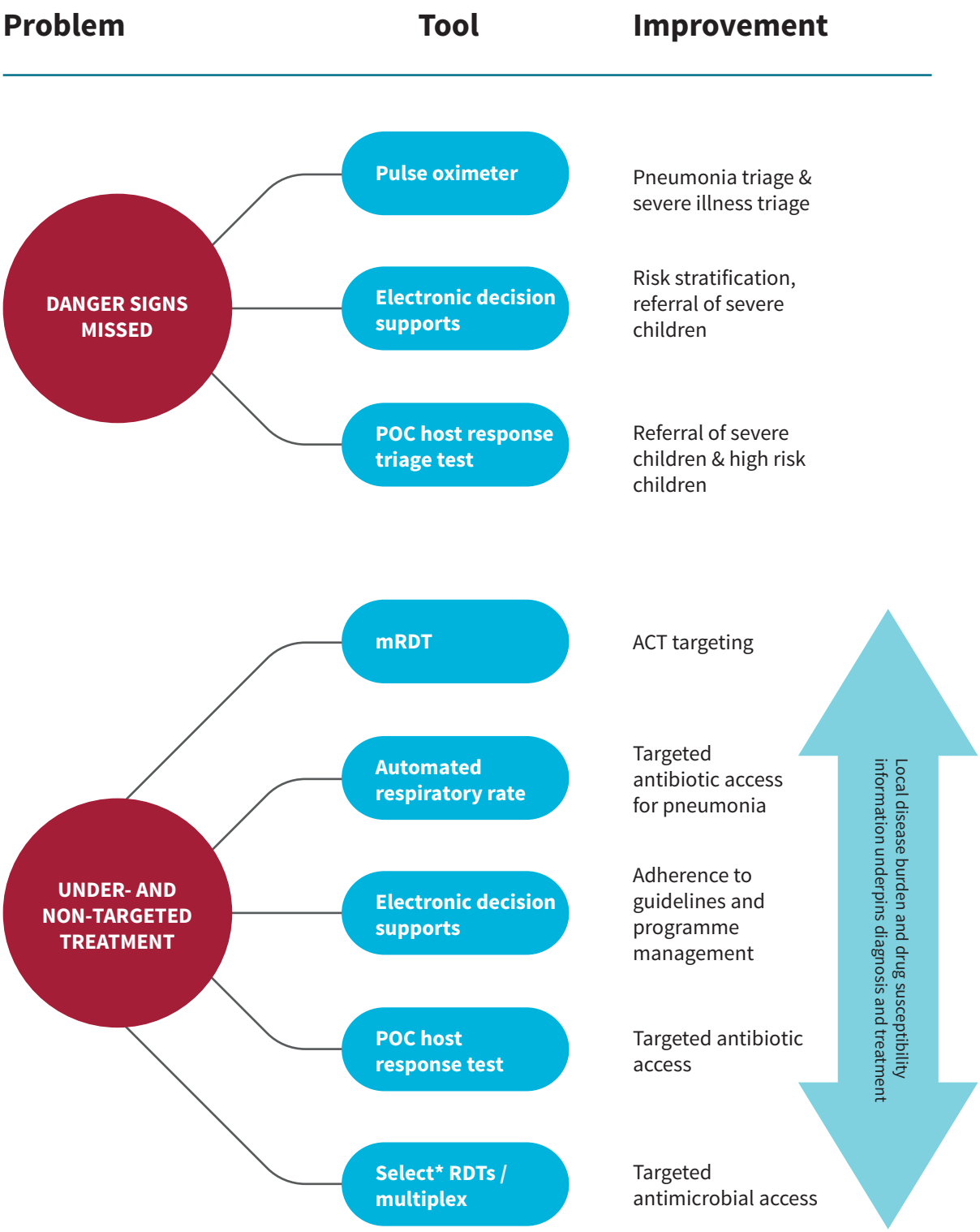
Given these challenges, an emerging diagnostic approach is to identify host response[22] biomarkers that can guide treatment and management, either independently or in conjunction with pathogen identification. There are two main approaches here: (i) diagnostics that indicate the particular class of infection (on the principle that, for instance, viral infections will elicit a different host response than bacterial infections); and (ii) diagnostics that provide information on severity or prognosis (i.e. the likelihood of progressing to severe disease, and need for hospital admission).

Developing a new diagnostic test based on host response requires both biomarker discovery (i.e. identifying biomarkers or combinations) and then biomarker validation to ensure the host signature is reproducible and generalizable in the context of intended use. This is because the level of biomarkers may be affected by underlying factors unrelated to the illness in question (e.g. some biomarkers may be elevated in malnourished patients, patients with parasitic worm infections, HIV, TB or other coinfected patients, or children versus adults, etc.).

[22] Host response refers to molecules produced in response to infection or inflammation, which may vary qualitatively or quantitatively depending on the pathogen, but are not diagnostic of a specific pathogen.

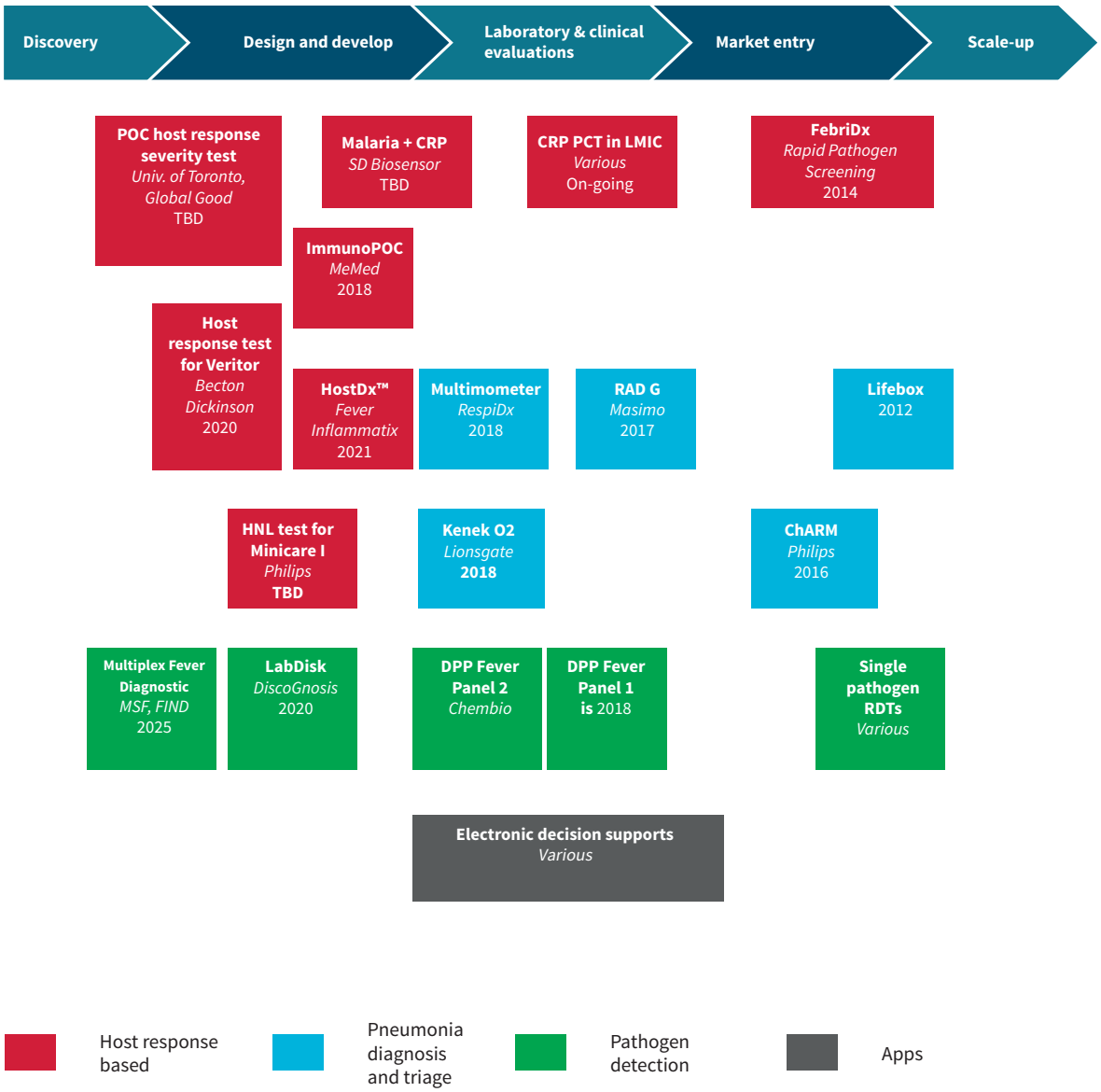
FIGURE 15.

Mapping diagnostic tools to weaknesses in febrile illness diagnosis at the frontline



* Select tests for priority diseases, based on local data, for which results are actionable (e.g. diseases that require specific supportive care or medicines that are available)

FIGURE 16.
Pipeline of diagnostic technologies for febrile illness



Note: Pipeline is non-exhaustive

Pneumonia diagnosis and triage

According to a recent review of innovations with potential to impact maternal, newborn and child mortality, better methods of pneumonia diagnosis, using automated respiratory rate monitors and portable pulse oximeters, could save more than one million lives between 2016 and 2030 *(51)*.

Both respiratory rate and oxygen saturation monitoring technologies are widely used in HIC settings. For the most part, they are incorporated into multimodal tabletop, or bedside patient monitoring devices. By contrast, robust devices suitable for "spot check" scenarios in low-resource settings (e.g. febrile illness diagnosis by frontline health workers) are not available or widely used.

For pneumonia diagnosis and triage use cases, fully automated[23] technologies can be divided into three groups described below: (i) automated respiratory rate counters; (ii) portable handheld pulse oximeters; and (iii) portable, handheld multimodal devices that combine respiratory rate and pulse oximetery in addition to other parameters (e.g. temperature, heart rate, blood pressure, haemoglobin) (Figure 17).

FIGURE 17.
Pneumonia diagnosis and triage devices

	Automated RR counter	Handheld POX	Multimodal RR & POX
Use case	• RR count required by iCCM and IMCI. • Community & primary level.	• If POX available, IMIC recommends measuring oxygen saturation as part of pneumonia assessment. • Primary level. Community level TBD.	• Guidelines recommend counting RR and POX if available, other parameters are TBD. • Primary level. Community level TBD.
Existing tools	Assistive devices (timers, counting beads, phone apps) automate some aspects of RR count. Automated technology in HIC.	Over 100 (handheld and tabletop) devices with SRA approval.*	Handheld and tabletop devices available in HIC.
Limitations of existing tools	Innovation and availability: assistive devices are not automated enough. Existing automated devices are tabletop and not robust/suitable for LMICs spot checking use.	• Innovation and availability: little evidence on suitability of existing products. • Demand and adoption: many products on the market + highly decentralized / fragmented procurement. Buyers lack information on product offering and quality; evidence on acceptance and cost-effectiveness. • Affordability: high price variance, markups.	• Existing devices are poorly adapted for LMICs spot checking use and high cost. Lack of evidence for use case at community level and impact of other parameters generally.
New tools	• ChARM by Philips (2016).	• Lifebox, manufactured by Acare Technology, by Lifebox (2012). • i SpO2 Rx by Masimo, mobile phone-based POX (2014).	• Rad-G by Masimo, RR & POX (late 2017). • Kenek O2 by LisonsGate Techologies, RR & POX, (2018). • Multimometer by RespiDx, RR & POX (2018). • 2nd generation ChARM by Philips, RR & POX, (TBD).

HW= health worker; POX= pulse oximeter; RR= respiratory rate SRA = Stringent regulatory authority
* PATH 2017 landscaping, unpublished

[23] Note that several devices that assist with some aspect of respiratory rate counting are in use in low-resource settings, including timers, beads to assist counting and phone apps where the device is tapped each time a breath is visualized. These devices assist with or automate some aspect of the count, but do not fully automate counting.

Automated respiratory rate counters

Approach and use case

Cough combined with elevated respiratory rate are the IMCI and iCCM criteria for pneumonia meriting antibiotic treatment.

Under IMCI/iCCM protocols, health workers visually monitor and count a child's breath for one minute and compare the number of breaths per minute to age-specific cutoffs. Unfortunately, counting a child's respiratory rate accurately is difficult. Health workers may struggle to simultaneously monitor time, while visually detecting and counting breaths in children, who are often upset and moving.

As a result, many devices for supporting this task have been developed. "Assisted count technologies" range from timers, to beads, to phone apps in which the health worker taps the device each time they see a breath. They still require the health worker to perform some steps. In contrast, automated respiratory rate counters automate the entire process. Recent research by the Malaria Consortium has shown that, even with the existing assisted count technologies, health workers perform poorly at measuring respiratory rate, and that fully automated respiratory rate counters are preferred.[24] UNICEF user research also supports these findings *(52)*.

Availability

Although numerous automated respiratory rate monitoring technologies are available, most have not been adapted for use where children present for care, but instead have been developed for HIC settings and are high cost, not portable, not suitable for use in children and newborns, and based on equipment that is neither simple nor robust.

PATH (October 2013) *(53)* and the Malaria Consortium (February 2014) *(52)* have landscaped automated respiratory rate technologies. The Malaria Consortium focused on devices suitable for frontline health workers diagnosing pneumonia in children. Of the many technologies, only one, the ChARM device from Philips, is currently available and has been developed with low-resource settings in mind.

[24] The Malaria Consortium conducted an evaluation of existing respiratory rate aids (n = 9, including two phone apps) and found that they were not useful in helping community and frontline health workers identify children who have pneumonia. While the devices may have supported health workers to keep track of time, or count, the evaluation found that counting respiratory rate is very difficult, especially in young children. The Malaria Consortium evaluation did not recommend taking any of these devices forward, but instead emphasized the need for fully automated devices. See: Baker K. Malaria Consortium. Presentation at the American Society of Tropical Medicine and Hygiene Annual Meeting, Atlanta, 13–17 November 2016.

UNICEF INNOVATION PROJECT: ACUTE RESPIRATORY INFECTION DIAGNOSTIC AID (ARIDA)

The UNICEF ARIDA project aims to stimulate development of devices that automatically detect and display respiratory rate. The intended use is pneumonia diagnosis; both community- and facility-based frontline health workers in low-resource settings are the target users. The UNICEF Innovation group focuses on market shaping to stimulate development and improve the availability of new health technologies, in particular, on the "pull" side of the market. The ARIDA project has been supported by La Caixa Banking Foundation (5 million Euros).

Broadly, the ARIDA project aims to demonstrate the value of new respiratory rate counters for the wider market. It will evaluate several devices to make recommendations on their suitability for use by frontline health workers in LMICs. As such, in November 2014, UNICEF launched a target product profile (TPP) summarizing the desired characteristics of an automated respiratory rate device, based on extensive end-user research. Following this, in July 2016, UNICEF launched a request for proposals for developers who would like to have regulatory approved devices meeting the TPP included in field trials that are currently being conducted by the Malaria Consortium.

Evaluation comprises the following components: an accuracy study in controlled conditions to evaluate agreement with the reference standard; and field trials in various settings to assess effectiveness and acceptability to frontline health workers and caregivers, and cost-effectiveness.

The Philips ChARM is the first device to undergo evaluations, which began in mid-2017. Masimo's Rad-G device (below) is expected to begin evaluations in late 2017.

Handheld pulse oximeters

Approach and use case

WHO recommends use of pulse oximeters to detect hypoxaemia, a potentially fatal complication of severe pneumonia (as well as other conditions including severe malaria). Pulse oximeters are devices that measure oxygen saturation of haemoglobin in the blood by comparing the absorbance of light of different wavelengths across a translucent part of the body. They work non-invasively and are simple to use.

Many types of portable pulse oximeters are available, falling into the following categories:

1. Fingertip: least expensive <US$ 50, often "consumer grade" or "recreational use" and sold in drug stores. Designed for home use, sports or chronic disease management. Few are designed for young children and infants.

2. Handheld: usually for professional use, may have separate fingertip probes for adults, children and newborns.

3. Mobile phone applications plus external fingertip probes: often these have not been designed for clinical purposes, nor tested on children and newborns; app is usually free to download, but requires phone and probe purchase.

4. Wrist oximeter: usually not designed for children and newborns.

The Malaria Consortium has conducted a landscape, extensive field evaluation and acceptability studies for several pulse oximeters for use by CHWs and frontline health workers. The study has not yet been published, but preliminary results support the handheld versions and versions with multiple probes.[25] The Malaria Consortium evaluation found that low-cost, fingertip pulse oximeters (e.g. those available in retail outlets for home use) were not well suited for use in frontline health settings, and that only a few handheld pulse oximeters were accurate and easy for frontline workers to operate.

Availability

Although many handheld pulse oximeters are available, they can be expensive, their quality has not been routinely assessed and many are neither robust nor suitable for the conditions of use in low-resource settings. Handheld versions designed and marketed specifically to low-resource settings include Lifebox's handheld Pulse Oximeter and Masimo's phone-based iSpO2 Rx. Additional pulse oximeters are potentially relevant for use in LMICs; but given the number on the market, it was not possible to review all of them. Also, a few efforts to combine both respiratory rate counting and pulse oximeters are described below (multimodal handheld devices).

Consumables include adult and paediatric sized probes, which generally last 6–12 months and rechargeable batteries.

[25] Often probes are restricted in terms of age or weight range and do not fit small children or infants.

LIFEBOX

Lifebox is a United Kingdom charity founded to improve the safety of surgery in low-resource settings. As part of its mission, it aims to make pulse oximeters available in all operating theaters. The device that it supplies is also suitable for outpatient uses such as screening for pneumonia in children, and Lifebox reports growing interest in this application.

Lifebox does not itself manufacture oximeters: rather, it plays a market-shaping role. Five years ago, Lifebox issued a request for proposals for affordable, accurate and robust pulse oximeters. Several companies responded and Acare Technology (Taiwan, China) was selected. In this business model, Lifebox assumes many local distributor functions because it identified these as an important barrier to access (e.g. selecting high-quality, well-adapted products; affordability; registration procedures; training on devices). The Acare Technology device is available through the Lifebox website, shipping included, for $250, and Lifebox supports in-country training. Thus far, more than 15 500 pulse oximeters have been placed in low-resource settings. Lifebox works frequently with other donors who purchase on behalf of countries, and with local professional associations (e.g. surgery, anesthesia, paediatrics) that directly procure pulse oximeters. Uptake has been greatest in private and nongovernmental/faith-based organization facilities. Lifebox expects to conduct another request for proposals process in late 2017 to take advantage of technological advances and to improve pricing. In 2017 Lifebox, with support from the Bill & Melinda Gates Foundation (BMGF), completed development of a more sensitive, easy to use probe for infants and young children. The intellectual property and design will be freely available.

KEY HIGHLIGHTS: PULSE OXIMETER MARKET[26]

Market size and growth. The global pulse oximeter market is sizeable (~US$ 1.5 billion), mature and growing, driven by trends around increasing patient monitoring and the potential to save lives through earlier detection of respiratory problems. North America and Europe are the largest markets, and the Asia Pacific is the fastest growing region. By product type, tabletop/bedside pulse oximeters dominate; sales are highest to hospital and clinic settings *(54)*. Product lifecycles tend to be shorter for devices than pharmaceuticals: for handheld pulse oximeters, replacement of devices (as opposed to repair) with more advanced models drives sales.

Product range, suppliers and availability. Globally, market leaders produce premium products, and many other suppliers produce more affordable offerings. Research in four low-resource countries found a range of pulse oximeter suppliers registered locally (>15 with stringent regulatory authority/SRA approval per country), with products ranging from tabletop to handheld devices. Many products were manufactured by companies in China or the United States.

[26] This section draws largely on PATH's market analysis, which included four focus countries (Ethiopia, India, Indonesia, and Kenya) supplemented by discussion with other stakeholders (e.g. suppliers, Lifebox, CHAI, Malaria Consortium).

The relative number of suppliers registered in some lower-income countries suggests that local registration is not a barrier for SRA-approved products; however, research has focused on only a few countries (e.g. Ethiopia, India, Indonesia, Kenya), and experiences have been mixed.

In low-resource settings, however, availability of pulse oximeters in the outpatient and primary care departments is very limited and most of the products sold are found in operating theaters, recovery wards, and occasionally in the emergency department.

Price. There is a considerable range in pulse oximeter pricing. While manufacturers may sell handheld versions at US$ 50–500, prices paid by countries suggest there can be significant markups associated with distributor margins, and to a lesser extent shipping and customs. In fact, the Lifebox model is predicated on avoiding the distributor markups by selling direct from manufacturer to customer at a price that includes shipping.

Demand assessment. Initial efforts to increase access to pulse oximeters in low-resource settings focused on anesthesia and safe surgery, led by Lifebox's work to scale up affordable pulse oximeters. More recent efforts focus on pneumonia, and increasing access to oxygen therapy for treatment of severe pneumonia. While there are limited data on the availability of pulse oximeters in low-resource settings, all indications suggest a large need (e.g. all surgeries, recovery wards, intensive care units, emergency departments, maternity wards, neonatal wards and outpatient/primary care departments should be equipped) with very limited uptake. Anecdotal evidence suggests that while the need for pulse oximeters in the outpatient setting is acknowledged, it is considered to be just one among many competing priorities.

Procurement tends to be highly fragmented, and decentralized to the district level or even the facility level. As a result, there can be considerable variability in terms of brand, model and price obtained. Within the public system, procurement processes are slow and typically occur in 5-year cycles, whereas private and faith-based facilities may have more rapid procurement cycles and processes. The multiplicity of variants within a country would present a challenge for replacing probes and batteries, as well as volume-based pricing.

Supply assessment. Globally, the market is heavily saturated, with many suppliers of SRA approved devices, as well as suppliers without regulatory oversight. From a supply perspective, barriers to entry are low, with the technology being relatively easy to replicate. Distribution models vary: some manufacturers have their own distributors, while the majority contract with local medical device distributors who may carry multiple brands. Differentiation among the market leaders is based on performance, technical advances and high quality.[27] A recent review of inexpensive pulse oximeters found that many were inaccurate; however, a small proportion performed similarly to more expensive United States Federal Drug Administration (FDA)-cleared units, leading the authors to conclude that development of accurate, low-cost oximeters is feasible *(55)*. Following on this trend, two donor-supported efforts to develop low-cost accurate oximeters exist: Lifebox and BMGF's investment in Masimo.

[27] For example, poor perfusion and patient movement significantly affect pulse oximeter accuracy, and higher-performing products address these factors.

Multimodal handheld devices combining respiratory rate counters and pulse oximeters

Approach and use case

Rugged, handheld, multimodal devices that combine respiratory rate, pulse oximetry, temperature, and other key triage/vital signs are in development. Handheld portable versions combining the desired characteristics of automated respiratory rate counters and pulse oximeters described above are envisioned. The addition of other parameters such as temperature, heart rate, blood pressure and haemoglobin, is possible, and might increase the value of the device in assessing febrile children, as well as other applications (e.g. antenatal visits).

Availability

Although numerous automated multimodal patient monitoring devices are available in tabletop or benchtop devices for HICs, they are not adapted for use in low-resource settings where children present for care. There are several development efforts; among the most advanced is the Masimo Rad-G, a handheld pulse oximetry and respiratory rate device launched in late 2017. Additionally, LionsGate Technologies is developing a phone-based system, the Kenek O2, that combines pulse oximetry and automated respiratory rate counting; Philips is developing a second-generation ChARM device that includes respiratory rate, and RespiDx is developing the Multimometer, a device that resembles a digital oral thermometer and measures temperature, respiratory rate and oxygen concentration.

Host response-based diagnostics to identify children needing antibiotics

Approach

Host response-based diagnostic tests that have potential to differentiate between bacterial and non-bacterial infections in febrile children in LMICs include POC tests based on existing host response biomarkers (such as CRP and PCT tests) and POC tests based on novel host response biomarkers (Figure 18).

This approach involves detecting one or more host response biomarkers[28] that can differentiate between bacterial and non-bacterial infections and obviates the need to identify a specific pathogen. In these assays the response can be measured using one or more biomarkers. Certain markers have been associated with bacterial infection, while others are more closely linked to viral infection. Often, tests are based on measuring the quantities of a particular host response biomarker(s), and then thresholds or algorithmic scores are applied to classify the illness as likely to be caused by bacteria versus virus. Most results are easily classified, but some cases will be indeterminate. In the near term, since it would be technologically challenging to have a test that works for all febrile patients, it is likely that test differentiating between bacterial and non-bacterial infections would be performed in subgroups of febrile children, optimally those subgroups that present most frequently (e.g. cough and fever, fever without focus, fever and diarrhoea).

[28] Host response biomarkers are molecules of the human immune system that are part of the body's response to an infection or other invasion.

FIGURE 18.
Host response-based biomarker tests with potential to differentiate between bacterial and non-bacterial illness in LMICs

	CRP and PCT	Novel biomarkers
Use case	• TBD. Would need to be incorporated into guidelines/ algorithms, most likely to be applied to patients meeting specific criteria (e.g. non-severe, low risk, mRDT negative) to reduce overtreatment. • Level of use is TBD.	• TBD. Would need to be incorporated in to guidelines, likely population specific, depending on performance. • Level of use is TBD. Optimally, community and primary level.
Existing tools	• CRP: many SRA approved CRP tests on market in HIC, however very few in RDT format, relevant thresholds TBD. • PCT: compared to CRP, fewer PCT tests on the market in HIC, however largely lab-based systems used in HIC.	Not applicable.
Limitations of existing tools	• Demand & adoption: more evidence needed to support impact; very little evidence especially from low-resource settings. • Innovation & availability: few test formats suitable for use in low-resource settings.	Not applicable.
New tools	• Efforts to generate evidence for CRP ± PCT use in low-resource settings (MORU, STH, FIND). • Combined malaria + CRP RDT by SD Biosensor, (design lock 2017, availability TBD).	• FebriDx by Rapid Pathogen Screening, MxA & CRP (2014). • ImmunoPOC by MeMed, CRP, IP-10, TRAIL (2018). • HostDx™Fever by Inflammatix, mRNA markers (2021). • Test name TBD, for Veritor platform by Becton Dickinson, markers TBD, (2020).

mRNA = messenger ribonucleic acid, STH = Swiss Tropical Health. See the Abbreviations and Acronyms list at the beginning of this report for other definitions

The global momentum around AMR, and the emphasis it places on diagnostics, presents an opportunity to leverage technological advances in host response-based POC testing for use in febrile disease in LMICs. One important difference between HIC and LMIC settings is the higher prevalence of coinfections (e.g. malaria, TB) and co-morbidities (HIV, malnutrition) in LMIC. Many of the host response-based tests in development are validated in HIC settings, and it remains to be seen how these tests perform in LMICs, especially in coinfected or co-morbid populations.

Additionally, the objectives in HICs and LMICs differ somewhat: in HICs the prevailing need is to reduce unnecessary antibiotic prescribing; in LMICs both overuse of antibiotics and underuse are problems. In LMICs, the extent of overtreatment is not well known and likely varies by setting[29] *(11) (57) (58)*. Overall, in LMICs, lack of access to antibiotics likely leads to more childhood mortality than over prescription *(19) (42)*, and a highly sensitive test for bacterial infection would help ensure that no child is undertreated due to misdiagnosis and that all infections meriting antibiotic treatment are detected earlier than they are today. On the other hand, the more specific the test for bacterial infection, the better it would be at reducing overtreatment, which is essential to protect antibiotics.

TPP OF A TEST THAT DIFFERENTIATES BACTERIAL FROM NON-BACTERIAL INFECTIONS IN NON-SEVERE PATIENTS

In 2016, a working group convened by WHO, MSF, ReAct and the Foundation for Innovative New Diagnostics (FIND) published a TPP for a test that can distinguish between bacterial and non-bacterial infections, suitable for use on *non-severe patients*, in low-resource settings was published in 2016 based on a meeting of experts *(59)*. Key features include:

- suitable for use at the community level, with limited infrastructure, i.e. simple to use, requires minimal training, battery powered or disposable;
- rapid turnaround time; aim is to not add significantly to existing consultation time;
- >90–95% sensitivity and >80–90% specificity; and
- price should not exceed US$ 5.00, and optimally should be <US$ 1.00.

Use case

In a febrile child, after assessing danger signs and ruling out malaria with an RDT, frontline health workers must then look for other causes of fever. Pragmatically, given the available treatments, the next question that a provider would want to ascertain is whether the child would benefit from an antibiotic treatment. Given limited clinical expertise among frontline health workers, a POC test that could safely identify only those patients that need antibiotics would have an impact at several levels: the patient receives an informed treatment decision and timely, appropriate treatment, which prevents progression to severe disease, reduces any adverse effects from unnecessary drugs and improves satisfaction with services because they respond to the treatment.

[29] The reasons for lack of access to antibiotics are not well documented, but are likely multifactorial, including failure to seek care, misdiagnosis, lack of availability or lack of affordability.

For providers as well as patients, as with mRDTs, a reliable test can increase confidence in decisions to use or withhold particular treatments. At the health systems level, a test that differentiates between bacterial and non-bacterial infection ensures that antibiotic treatments are not wasted. Societal-level benefits include preservation of existing medicines. Reduced AMR in turn lowers costs of care and reduces mortality, because resistant infections are both more expensive to manage (e.g. second-line treatments are more expensive, need for more advanced care for drug-resistant infections) and have higher mortality rates. A 2006 modelling analysis by RAND showed that a diagnostic test like this, if deployed at the community and primary care settings and targeting only acute lower respiratory infections, could save approximately 405 000 lives from bacterial pneumonia in children under-five each year. In Africa, most of the benefit of the new diagnostic would result from decreasing the burden of disease, whereas, in Asia and Latin America most of the lives saved would be attributed to reductions in overtreatment *(56).*

This approach avoids the challenge of colonization, because a positive result suggests that the body's immune system is fighting an infection. However, not specifically identifying the pathogen means that antibiotic selection remains empiric, and the most effective antibiotic for a particular pathogen cannot be selected. While some infections respond best to particular antibiotics, pragmatically, current health systems constraints (e.g. weak supply chains and limited clinical expertise and training) limit the selection of treatments available at the frontline.

Diagnostic strategy

Although host response-based testing has been used in some parts of Europe since the 1970s, the host-based approach for classifying bacterial versus non-bacterial etiologies is relatively novel in many settings. As a result, there is limited precedent for this approach, and few established diagnostic strategies, in particular, guidance on which patients to test and how to manage based on the results.

In LMICs, a diagnostic strategy using host response tests for bacterial versus non-bacterial infection would first triage out children who are severely ill or at high risk of progression to severe complication, and then use a validated host response-based test (plus an mRDT) on only non-severe, low risk children. Initially, it is likely that a limited set of children would undergo this testing strategy, but this group might expand over time as more validations and outcomes studies are conducted. Because this is a novel approach, implementation will likely be piecemeal (e.g. limited geographically, and limited to particular groups of children). Validation in specific populations (e.g. HIV-infected, TB-infected, malnourished children, etc.) will be needed to increase the evidence base before testing algorithms could become more widely adopted. At the frontline, algorithms will be necessary to guide clinicians on which test to perform in which subgroup of febrile patients.

Availability

A few POC host response-based tests are used in HICs today, and there are ongoing initiatives to expand indications for use and to improve uptake of these tests. Additionally, ongoing biomarker discovery work and diagnostic development projects aim to improve upon the discriminatory power of host response biomarker based tests (Figure 19).

Existing host response biomarker POC tests

Tests based on CRP and PCT[30] are currently used in some HIC settings to discriminate between bacterial and non-bacterial infections. CRP is available in the RDT format, as a POC device and in centralized lab systems;[31] PCT is generally a laboratory-based test, although increasingly POC PCT assays have become available (e.g. Samsung IB BRAHMS PCT is a portable device based PCT test). Most frequently, CRP and PCT test results are quantitative, requiring physician interpretation; however, lateral flow format semi-quantitative and qualitative tests exist, based on threshold levels (e.g. thresholds for CRP range from <20 mg/L to <80 mg/L in different settings) where patients below these thresholds would not receive antibiotics.[32]

In HICs, CRP and PCT tests are used by well-trained clinicians as one piece of the clinical picture, along with clinical assessment and other diagnostic tests. In Scandinavian countries, CRP is used routinely to guide antibiotic use in lower respiratory tract infections. In the United Kingdom, the uptake of CRP for guiding antibiotic use has been slow, despite efforts to increase its use (e.g. by incorporation into guidelines) *(63)*. PCT is a newer biomarker (discovered in 1993) initially used to guide management of sepsis. More recently, European studies have snown that PCT is useful in discriminating bacterial and viral respiratory infections in hospital, emergency department and outpatient settings *(60)* and in 2017 the United States FDA cleared the expanded use of a PCT assay to help guide antibiotic treatment in lower respiratory tract infections and sepsis *(61)(62).*

Overall, experts have differed on whether CRP and PCT perform well enough to guide antibiotic use in children in LMICs. For frontline use, these tests would be incorporated into a clinical algorithm that takes into account other factors; it is less likely that they would be used as a standalone test.

[30] CRP and PCT are both markers of inflammation in the body. Inflammation is a host response to tissue damage by pathogens, trauma, toxins, etc. Both CRP and PCT increase in bacterial infections.
[31] Many large laboratory analyzers include CRP in testing menus; POC device formats include QuikRead CRP (Orion Diagnostics), Nycocard II Reader (Alere), Affinion (Alere), Eurolyser smart (Eurolyser Diagnostics).
[32] Among the PCT tests is the BRAHMS PCT-Q by Thermo Fisher Scientific Inc. is a semi-quantitative PCT disposable lateral flow test, but not optimal for frontline health worker use in low-income countries. It requires 200 ul of serum/plasma (requires centrifuge, venipuncture) and a 30 minute incubation period. Colour intensity is proportional to PCT concentration and the test is read with a reference card and patients are classified into four categories.

There is relatively little evidence on their performance in LMIC settings, and concern about how these markers might be affected by coinfection and co-morbid conditions common in low-resource settings (e.g. chronic parasitic infections, HIV infection, malnutrition, etc.) *(57)(64)(65)*. Additionally, the relevant thresholds are a subject of debate. For example, in lower respiratory tract infections normally CRP <20 mg/L would indicate a self-limiting respiratory infection not meriting antibiotics, while CRP >100 mg/L would be considered high risk for bacterial pneumonia warranting antibiotic therapy. Between these two extremes, CRP levels of 20–100 mg/L typically requires clinical judgment.

Recently, there have been some promising results using CRP in low-resource settings to identify patients who would benefit from antibiotics, including several studies supported by the Mahidol Oxford Tropical Medicine Research Unit (MORU) in South-East Asia on the use of CRP to identify patients with non-severe respiratory tract infections who need antibiotics *(66)* as well as smaller studies on African children *(67) (68)*. The Thai MoH, MORU and FIND are expected to begin a large implementation study of CRP-based antibiotic prescription in lower respiratory tract infections in early 2018.[33] The WHO Special Programme for Research and Training in Tropical Diseases is currently testing African samples retrospectively to see if results achieved in South-East Asia can be duplicated in Africa.

POC CRP tests are available, both in a device format as well as in lateral flow formats. For the lateral flow tests, relevant thresholds and suitability for use in outpatient settings need review and consensus guidelines. Additionally, at least one company is developing a test that combines CRP and malaria testing in one RDT.

Data on PCT in low-resource settings are not yet available, in part because most testing is done on laboratory analyzers and not in a rapid test format. A few initiatives to develop POC device-based CRP+PCT have been identified (e.g. Nanomix eLab system).

Novel host response biomarker POC tests

Many additional biomarkers have been identified or are under investigation for their potential to discriminate between bacterial and viral infection. However, from a product development standpoint, this is a relatively nascent area, and little of the research to discover new biomarkers has advanced to late-stage product development. As of 2013, >90% of reported biomarkers (>100 unique host biomarkers) have been assessed in laboratory research only and have not been translated into clinical use *(69).* Many have only been evaluated in small sample sizes and in narrow age groups, and the majority of evaluations do not include patients from LMICs *(70).*

[33] The study will include >40 000 patients and approximately 30 primary health centres.

Of these less-studied biomarkers, a handful have been incorporated into diagnostics or are being considered, including: HNL, MxA, HbP, CH3L1, TRAIL, and IP-10. However, few groups are evaluating these biomarkers (or sets of them) in LMICs. Notably, FIND is conducting a validation of several promising biomarkers (CRP, PCT, CRP+MxA, HNL, CH13LI, and HBP) in Malawi and other LMIC sites. The study started in 2017 and is assessing the ability of these biomarkers to identify bacterial infections compared to clinical and microbiology results. Developers with products on the market include Rapid Pathogen Screening's FebriDx, and MeMed's ImmunoXpert and ImmunoPOC (the latter still in development). Inflammatix Inc., and Becton Dickinson are also developing POC diagnostics that differentiate bacterial and viral infections.

In addition, there are several efforts to identify novel host biomarkers using new "omics" molecular technologies (e.g. genomics, transcriptomics, proteomics, metabolomics) that take thousands to millions of measurements from a set of samples and then use bioinformatics to process these large datasets and identify unique host response signatures for different classes of infection. As noted above, after the biomarker discovery phase, these signatures must be validated, both retrospectively (in some cases it is possible to take advantage of published gene expression datasets for validations) and then prospectively. Proponents believe that these technologies have the potential to be more discriminating than markers such as CRP and PCT *(71).* However, one challenge is that many of these efforts rely on multiple biomarkers and require advanced molecular detection techniques that may not be easily translated to POC platforms. Selected "omics"-based efforts include:

- Ocatvio Ramilo and colleagues at Ohio State University reported in 2007 on the use of host gene expression techniques for identifying biomarkers classifying viral and bacterial infections in children *(72)* and have subsequently been developing these transcriptional profiling methods.

- BMGF-funded work for pneumonia and malaria by the Broad Institute has identified a set of analytes that differentiate malaria, bacterial pneumonia and viral pneumonia *(73) (74)*.

- Ephraim Tsalik and Chris Wood's group at Duke University has developed a host gene response assay for classifying viral and bacterial respiratory infections, and initial work to translate these signatures to a commercial, laboratory-based molecular platform is under way *(75).*

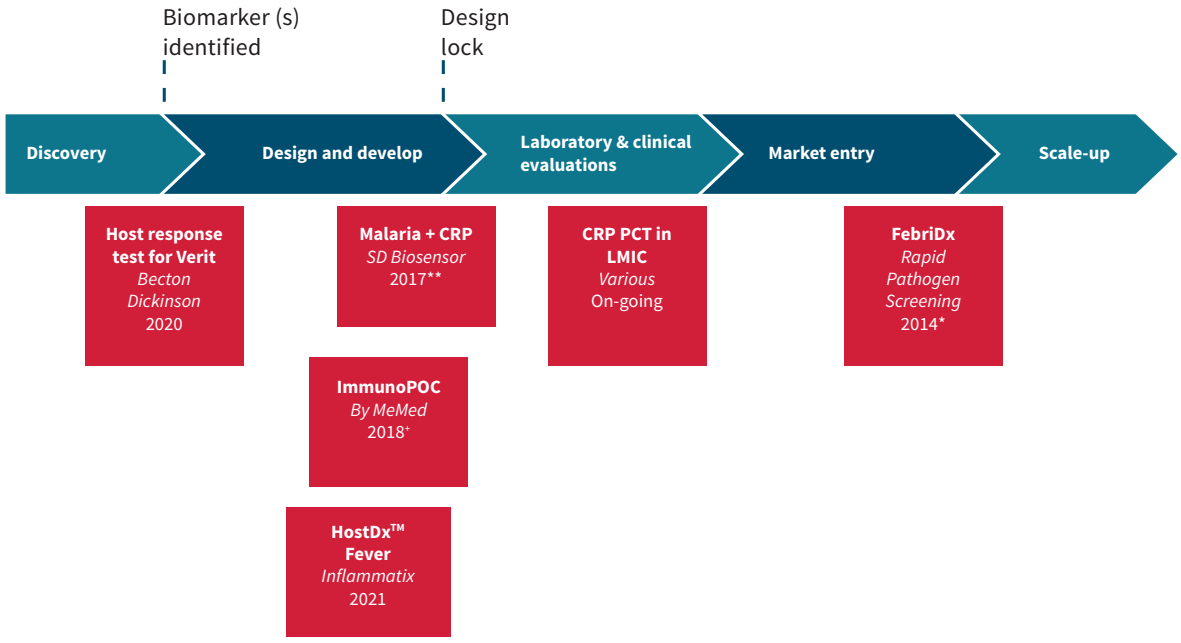
- Researchers in Europe have recently published on the discovery and preliminary validation of a 2-transcript RNA signature for discriminating bacterial versus viral infection in children; additional validation in a wider set of children is needed *(76).*

- Tim Sweeney and Purvesh Khatri have founded Inflammatix Inc. to commercialize research from Stanford University that identified signatures for distinguishing between viral and bacterial infections as well as a classifier for sepsis.

At the present time, most of this work is early stage and based in academic institutions. Research for this report found that only researchers at Stanford are focused on near-patient platforms that might be suitable for use in low-resource settings and have advanced to commercial product development (Inflammatix).

FIGURE 19.

Host response-based biomarker tests with potential to differentiate between bacterial and non-bacterial illness in LMICs, by development phase



POC diagnostic tests to identify children with severe disease or at risk of developing serious complications

Approach and use case

Most fevers in children are self-limiting and can be managed on an outpatient basis. Only a small proportion of children are at risk of progression to severe disease and serious complications, presenting a challenge to frontline health workers who have limited clinical expertise and are tasked with identifying children who need additional interventions (e.g. referral and hospitalization). The IMCI and iCCM diagnostic and treatment algorithms identify several danger signs that health workers should assess, but these are frequently missed or neglected. Clinical signs for conditions including hypoxaemia and anaemia can be difficult to recognize, especially for health workers with limited training. For example, IMCI recommends the use of conjunctival, palmar and nailbed pallor to diagnose anaemia; however, in practice, sensitivity and specificity can be modest and vary depending on the setting and population *(77)*. Additionally, some clinical signs only appear late in disease progression and, therefore, a diagnostic that can identify disease severity in children earlier on would have great impact on mortality and disability.

Availability

Currently, there are no tests routinely used to triage febrile children by severity in low- or high-resource settings.

In HICs, and to a much lesser extent in LMICs, white blood cell counts, haemoglobin measurement, PCT and lactate are ordered by clinicians to assist with prognosis, however, these are primarily available in hospital settings and are generally insufficient as the sole basis for treatment decisions due to lack of specificity. A few rapid POC blood count systems (e.g. Ativa MicroLAB by Ativa Technologies, OLO by Sight Diagnostics) are being developed, which could also play a role in stratifying children by severity in low-resource settings, although additional evidence is required to show how they add value, given their specificity and cost.[34]

[34] For example, red blood cell width is commonly part of the standard blood count and is associated with severity in many diseases and might be useful in low-resource settings; however, there is a lack of evidence on clinical performance.

Haemoglobin measurement devices are currently available and may also contribute to improved triage of children with febrile illness; however, additional research is needed to assess the impact on morbidity and mortality as well as the cost-effectiveness of routinely screening children for anaemia. Anaemia is very common in low-resource settings and has multiple causes that must be identified to ensure proper treatment. From a triage perspective, anaemia increases a child's susceptibility to infections: severe anaemia can directly cause death, while mild and moderate anaemia put children at higher risk of complications and death from other diseases *(38) (78)*. Routinely measuring haemoglobin may be a useful means of identifying children at high risk for severe disease and who need referral, closer monitoring or other interventions.

A variety of methods for POC haemoglobin measurement exist; the most well known is the HemoCue system, a portable haemoglobin meter that provides rapid, quality-assured, quantitative haemoglobin measurements using a small amount of blood and a micro cuvette. Increasingly, portable non-invasive haemoglobin measurement devices are becoming available, including the Pronto systems by Masimo, TouchB by Biosense, Haemospect by MBF Optical Systems, and NBM-200 by OrSense *(79).*

Novel approaches focused on triaging febrile children in malaria-endemic areas include collaboration between the University of Toronto and the Global Good Fund at Intellectual Ventures to develop tests using host response markers of endothelial activation and vascular permeability (Figure 20). These tests aim to identify those children who are at risk of progressing to severe disease earlier (e.g. upon first presentation to community or primary care) so that these children can be referred immediately and receive additional interventions before it is too late, thereby reducing mortality and the neurological and cognitive deficits associated with severe illness. University of Toronto researchers have identified promising biomarkers of immune and endothelial activation that identify children at risk of becoming critically ill and that can be measured in fingerstick blood. Global Good is developing prototype lateral flow tests based on these biomarkers that will be used for prospective field studies in low-resource settings. At the same time, the markers have been put on Proteinsimple's POC ELISA device, Ella, which takes one hour to run and provides quantitative results. The markers, running on the Ella platform, are currently being validated in Africa and studied for sepsis triage in HICs.

While there has been significant focus on triage diagnostics for sepsis in HICs (due to strong economic incentives and a large market opportunity) and advances in this area exist, few of these efforts are currently targeting ill children presenting to outpatient settings in LMICs. However, monitoring developments in this area for potential applicability of tests to children in low-resource settings is worthwhile.

FIGURE 20.

Host response-based diagnostic tests for identifying children with severe disease or at risk of developing serious complications

	Triage biomarkers
Use case	• TBD. Would need to be incorporated into guidelines/algorithms, and be used to identify children who need additional supportive care (oxygen, fluids, IV treatments etc.) versus those who can be safely treated on an outpatient basis. • TBD. Optimally, community & primary level.
Existing tools	• PCT, white blood cell counts are sometimes used in HIC to assist in identification of patients needing admission. • Hb for screening anemia.
Limitations of existing tools	• Innovation and availability: poorly adapted formats for frontline, low-resource setting use. • Demand and adoption: no evidence for their use in low-resource settings.
New tools	• Development of lateral flow tests based on novel biomarkers (Intellectual Ventures Global Good/University of Toronto).

Single-pathogen RDTs

Approach and use case

RDTs for singular diseases, similar to mRDTs, could be easily implemented by health workers at primary care facilities and possibly in the community, and might aid in diagnosing causes of fever. While it would be overly complex to incorporate a large number of additional RDTs into the initial assessment at the frontline, it could be useful to identify and scale-up a few key RDTs.

Although this approach could take advantage of rapid diagnostics that now exist, this strategy has not been widely deployed because there are no data to inform decisions about which tests would impact clinical outcomes. Furthermore, the set of relevant RDTs is likely to vary geographically, and even seasonally; and it is not clear whether a particular algorithm and set of RDTs could be generalized across a region (e.g. West Africa) or even within a country (e.g. urban versus rural settings). There is also a risk that using a particular RDT in low-prevalence areas could result in more false-positives than true-positives (due to cross-reactivity and background antibody levels, for example). A strategy, based on local evidence, to identify priority diseases for which test results would be actionable (e.g. diseases that are potentially severe, require specific supportive care and are treatable with available medications, or those requiring particular antibiotics) could have many benefits (Figure 21). Several etiology studies that have been recently completed or are under way that may provide more insight into relevant single pathogen tests.

Availability

- There is an established RDT market for many diseases in both HICs and LMICs, for example, urine dipsticks, streptococcal RDTs, typhoid RDTs, HIV RDTs, influenza RDTs, RSV RDTs, dengue RDTs and tests for neglected tropical diseases. For some RDTs, performance and quality are well established (and are WHO prequalified or SRA approved), for others, especially infectious diseases that are rare in HICs, such evidence is lacking.

- There are no RDTs for diseases that result in the highest childhood mortality, e.g. pneumonia and diarrhoea, in part because there is no single pathogen that causes these diseases and in part because of challenges with the sample matrices (sputum and stool).

- Some of the most widely available RDTs in HICs are less relevant in low-resource settings, e.g. RSV or influenza RDTs, since the result is unlikely to change management in low-resource settings.[35]

- An additional complication is that for many diseases a rapid test may exist to detect the acute or the chronic phase of infection, but not both. Since patients can present to health-care providers at different stages of illness, more than one test per disease might be needed.

See other Unitaid landscapes for specific information on mRDTs, HIV, TB and HCV (hepatitis C virus) POC tests.

[35] In HICs, these influenza tests may be used to cohort admitted children, a practice that is rarely implemented in low-resource settings.

FIGURE 21.
Single-pathogen RDTs and multiplex tests

	Singular pathogen RDTs	Multiplex tests
Use case	• Would need to be incorporated into guidelines, possibly at a subnational level depending on local burden of disease. • Primarily primary facilities, possibly community.	• TBD. Would need to be incorporated into guidelines, possibly at a subnational level depending on local burden of disease. • Primary facilities.
Existing tools	• Multiple tests exist: urine dipsticks, streptococcal RDTs, typhoid RDTs, HIV RDTs, influenza RDTs, RSV RDTs, dengue RDTs, neglected tropical disease tests.	Not applicable, POC tests with appropriate panels do not exist.
Limitations of existing tools	• Demand and adoption: no local data to inform decision about most clinically relevant RDTs. Evidence on impact versus cost is required to support adoption. • Supply and delivery: limitation on the number of individual tests a health worker can reasonably perform during one visit. • Quality: insufficient evidence for many RDTs. • Demand and adoption: buyers lack comprehensive information on product offerings and quality. • Innovation and availability: lack of high-performing RDTs for some diseases.	Not applicable.
New tools	Depends on disease area, novel RDTs may be in development.	• DPP Fever Panel 1, Chembio,(2018). • DPP Fever Panel 2, Chembio (TBD). • Multiplex Fever Diagnostic Project, MSF/ FIND, (2025). • LabDisk, DiscoGonosis Consortium (2020).

Multiplex diagnostics

Approach and use case

Multiplex tests are those that can detect multiple pathogens or other biomarkers simultaneously, obviating the need to run multiple individual tests. These systems typically detect DNA/RNA, antigens and/or antibodies. While combining detection of different analytes in one panel is optimal, it can be technically very challenging.

There are two main applications of multiplex tests. First, multiplex tests can be used to inform patient care. Given the limited clinical expertise and treatment options available at the community and primary care levels, multiplex tests are likely to be more relevant at the hospital level to identify pathogens in admitted patients.[36] The cost and ease of use of multiplex tests will also factor into whether a multiplex test could play a role at primary facilities.

[36] For example, one of the challenges relating to molecular multiplex tests is colonization: highly sensitive diagnostics can detect organisms (colonization) that are not actually causing a clinically significant infection, and without additional laboratory information and clinical expertise to aid in interpretation of multiplex test results, use of these tests may lead to overprescribing and mismanagement of the patient.

More relevant to frontline health workers is a second, epidemiologic use case: data from multiplex testing conducted at the hospital level are aggregated in order to improve frontline health worker's understanding of the local causes of severe disease. Regularly offering this information to frontline providers (via locally tailored case management guidelines, electronic decision support technologies and/or training) would help focus differential diagnosis on common illnesses and raise awareness of potentially serious diseases that are circulating in the community.

One of the challenges to multiplex testing is the lack of data on common causes of fever in children in LMICs that would inform decisions about which pathogens should be included in a multiplex panel. As with single-pathogen RDTs, the set of relevant tests is likely to vary geographically, and even seasonally; and a particular panel is unlikely to be generalizable across multiple regions. There is also a risk that using a particular test in a low-prevalence area could result in more false-positives than true-positives. In determining the most relevant pathogens for inclusion in a multiplex panel, priority must be given to pathogens most commonly causing disease, and to diseases that are potentially severe, require supportive care, those that are treatable, or those requiring particular antibiotics.

Availability

Today, a few walk-away molecular technologies are available, and they primarily target hospital laboratories in HIC markets.[37] Given their high cost, as well as the challenges acting on the information that they provide (e.g. not all relevant pathogens are included on the panel; often clinicians are not familiar with all the pathogens that are tested for in the panel; organism colonization/carriage), even clinicians in HICs debate and limit the use of these tests *(61).*

While no options for multiplex fever diagnostics for hospitals in low-resource settings exist today, the POC molecular diagnostics pipeline includes several systems/platforms that could potentially accommodate multiplex febrile illness panels in LMIC, especially at the hospital level.[38] However, at this point it is challenging to identify those platforms in development that have the most potential. Additionally, while fever panels could be developed for multiplex platforms that are already being deployed in low-resource settings for HIV and TB diagnosis (e.g. Cepheid Omni, Alere q), companies do not appear to be prioritizing this area, given technology and market challenges.

[37] For example, bioMerieux's BioFire FilmArray system includes molecular panels for particular syndromes, such as diarrhoea, respiratory disease, and meningitis/encephalitis and blood culture identification. The system simultaneously tests for multiple pathogens that could be causing the syndrome, along with a few key resistance mutations, and results are available in one hour. The system is expensive: US$ 40 000 for the instrument and >US$ 100 per test.

[38] For example (not exhaustive): Alere q; Biomeme; Cephid's Omni; DxNA's GenePOC; GeneSTATm; DiagCORE; Epistem's Genedrive; GenePOC; Insilixa; QuantuMDx; STAT Diagnostica; TwistDx.

There are a few efforts to develop febrile illness multiplex tests that are affordable and suitable to resource-poor settings; (Figure 21) however, their main use is likely to be in hospitals, with use at primary health care highly dependent on cost, ease of use, and whether the results are actionable at that level.

There are limited, but some efforts to develop disposable, lateral flow based multiplex fever tests. In particular, Chembio Diagnostic Systems Inc. is developing several multiplex tests using its Dual Path Platform technology to combine both antibiody and antigen detection. These tests combine detection of several pathogens in one multiplex lateral flow test, which could be used at hospital level, and possibly primary level assuming that the tests are affordable, that the pathogens detected by the panels are prevelant in the area, and that the results of the test are actionable at the level of care where testing occurs. In particular, the diagnostic strategy (which level of care to test) and the cost-effectiveness of this approach (the value of each test in the panel) need to be developed.

Other multiplex efforts focus on developing device-based platforms that are more expensive and slightly more complex to implement. However, device based tests often combine both antigen/antibody detection with molecular testing modalities. These devices are likely to be used primarly at hospital level, given high costs and limitations on how actionable the results are (e.g. treatments available). Device-based efforts include the early-stage Multiplex Fever Diagnostic Project, a collaboration between Médecins sans Frontières (MSF) and FIND, as well as academic efforts such as DiscoGnosis Consortium's effort to develop a febrile tropical disease panel for its LabDisk platform.

For further information on other multiplex diagnostics in the pipeline, see Unitaid's complimentary landscape, *Multi-disease Diagnostic Landscape For Integrated Management of HIV, HCV, TB and Other Coinfections.*

MULTIPLEX FEVER DIAGNOSTIC PROJECT

MSF and FIND are collaborating to explore and potentially develop an open- or semi-open source multiplex fever diagnostic system. The first assay for the system would target the pathogenic diagnosis of severe fever without a source. The Project is currently in a due diligence period: in 2019, potential funding opportunities may be announced for interested partners to develop a suitable diagnostic, with a 6–8 year timeline.

The Project incorporates many innovative approaches explored during the recently ended WHO Consultative Expert Working Group on research and development (R&D). This WHO working group spent a decade exploring new approaches to support R&D for global health, focusing on innovative financing mechanisms, patent pools and approaches that delink the cost of R&D from the price of the product. The Project is likely to be structured as a two-stage process with innovative push/pull funding to delink the cost of R&D from the end price to better serve public health needs and to facilitate affordable pricing. Grant funding will support early stage work, followed by a prize for the final stage.

The envisioned multiplex fever diagnostic system would simultaneously detect 6–12 priority pathogens and may incorporate host response-based biomarkers of bacterial/viral infection. The device would be multimodal, incorporating nucleic acid detection and immunoassays. The system is intended for use in in-patient facilities in low-resource settings, and would be used for adults and children who present with difficult-to-diagnose, non-specific febrile illness. The target cost is US$ 10 000–20 000 for the instrument and US$ 5–15 for cartridges. Consensus TPPs for the instrument, cartridge, and fever panel assays are being developed in 2017-2018.

Microbiological culture to optimize antimicrobial use

Approach and use case

Microbiology testing, especially culture, plays a role in identifying the cause of many febrile illnesses and provides information on the most effective treatment. For many bacterial and fungal infections, culture is the primary diagnostic test. Additionally, culture methods are the only way to obtain drug susceptibility information. Often in severe disease, detecting and identifying specific pathogens is critical to providing appropriate treatment (e.g. antibiotics or antifungals). Resistance and susceptibility testing,[39] if available, further guides treatment choice.

As with multiplex testing, there are two use scenarios.

[39] Resistance testing is defined as genotypic, molecular testing. Susceptibility testing is defined as phenotypic, culture-based testing.

First, culture is an important diagnostic tool for managing hospitalized patients. However, more important to the frontline is the second use case: aggregating data on local patterns of pathogen prevalence (as above with multiplex testing) and drug susceptibility. The absence of drug resistance and susceptibility data in low-resource settings[40] leads to delayed or suboptimal revisions of treatment guidelines, contributes to inappropriate use of antibiotics (e.g. narrow-spectrum antibiotics preferred over broad-spectrum antibiotics) and could lead to use and scale-up of ineffective treatments *(80)(43)*. Many experts prioritize the potential impact that compiling local data on circulating pathogens and their drug susceptibility could have on fever management in low-resource settings. At the national level, this information could help ensure that the antibiotics recommended for use at the frontline are effective and available. At the local level, it would also inform the initial course of empiric therapy for admitted patients, as even when microbiology testing is available at a facility, it often takes several days to receive complete results (Figure 22).

Despite this need, many LMICs lack capacity to perform quality microbiology testing, even at national level *(43)*.

FIGURE 22.
Microbiology testing to support febrile illness diagnosis

	Microbiological testing and culture
Use case	• In-patient setting: where available, tests for pathogen identification, resistance and susceptibility testing are already included in guidelines. • Surveillance: a few guidelines for national-level surveillance for key diseases exist, however, they are being expanded in connection to global AMR and outbreak response programmes. Local/facility-level guidance is limited (e.g. antibiograms are seldom available).
Existing tools	• Traditional microbiology culture methods. • Molecular testing for a limited set of pathogens and resistance genes.
Limitations of existing tools	• Affordability: traditional culture can be unaffordable due to low volumes, short reagent shelf life, and supply chain markups. New molecular tests are not affordable. • Supply and delivery: underutilization of testing services in low-resource settings; aggregate results are not analysed and used to inform care (e.g. to inform empiric treatment decisions). • Innovation and availability: traditional culture is poorly adapted due to long turnaround times, need for sophisticated laboratory and trained staff, short shelf life of reagents, extensive quality requirements. New molecular tests do not provide comprehensive information (e.g. not phenotypic), limited resistance genes; pathogen identification panels not suited to LMIC needs.
New tools	• Work to improve phenotypic microbiology tests are largely early stage.

[40] Surveillance is often better for vaccine-preventable diseases, as this is tracked to monitor the impact of vaccination.

Availability

Today, in low- and high-resource settings, most microbiology testing is based on traditional culture methods that have not changed in decades. The process comprises: (i) culturing the specimen; (ii) identifying pathogens present; and (ii) performing drug susceptibility testing. Currently, this process takes several days and requires highly trained laboratory technicians, careful sample collection and complex procedures that require a large number of different consumables and, therefore, a robust laboratory supply chain. Moreover, significant expertise is needed to interpret the results and advise on appropriate treatment. In HIC laboratories, systems are available to automate many of these steps, however these systems are expensive. Compared to automated culture systems, the capital requirements for manual culture are relatively minimal, however, the high number of consumables, the short shelf life of reagents and the highly skilled labour required drive up costs. Culture also requires a dedicated laboratory space and stable electricity for incubators. Quality-assured culture bottle systems are commercially available, with Becton Dickinson and bioMerieux being the leading providers. In developed countries, where volumes are high, testing is <US$ 10 per test; however, in low-resource settings, costs can be twice as high. Given affordability challenges, it is not uncommon in those low-resource settings where trained technicians are available (e.g. India and other Asian countries) for laboratories to prepare culture reagents in-house.

Often, in low-resource settings microbiology labs are caught in a vicious supply and demand trap. First, testing may be interrupted due to the absence of trained laboratory staff (of which there are very few, especially in Africa) or stockouts of necessary supplies. Second, given low technical skills of health workers collecting samples and laboratory technicians, as well as limited quality-control measures, clinicians often question the quality of testing services. As a result, clinicians stop asking for these tests, and lower demand leads to general neglect for supplies and staffing.

Outside of TB, the impact of recent advances in microbiology testing has been limited to HICs due to high cost and limited applications.[41] While there are a handful of promising technologies that can improve upon traditional culture methods, many are still early stage. FIND is working on a TPP for simplified blood cultures and expects to publish it in 2018.

[41] For example, for selected pathogens, new molecular tests can provide rapid pathogen identification and in some cases resistance information. These technologies may identify organisms in positive blood culture bottles (e.g. FilmArray Blood Culture Panel) or work as standalone tests for direct detection of pathogens from samples (e.g. FilmArray panels, GeneXpert). Disadvantages include the limited number of organisms tested for (relative to culture), potential for lower sensitivity compared to blood culture, high cost and the tradeoffs between having genotypic resistance information available quickly, as opposed to phenotypic susceptibility, which is more broadly useful. Another technology increasingly used in HIC microbiology labs is matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS), which can identify organisms grown in culture in as little as three minutes. Although these new technologies are available, they are relatively expensive and, even in HICs, cost-effectiveness and effect on clinical outcomes are carefully scrutinized and debated, and often they are most effective when implemented with antimicrobial stewardship programmes.

Electronic decision support systems for diagnosing febrile illness

An electronic decision support system is a supportive tool for frontline health workers that integrates with diagnostic tests and devices such as those described above, but is not a diagnostic test in and of itself.

Approach and use case

In low-resource settings, electronic decision support software running on smartphones or tablets can help support frontline health workers with history taking and clinical exam, and improve guideline adherence. These systems also capture data, and are designed to run off-line and to transmit data to a central server when an internet connection is available.

When IMCI was first developed, mobile technology was not as ubiquitous as it is today. Health workers usually received a paper booklet of protocols, which are akin to flow charts in a tabular format, to be followed in a stepwise fashion. While simplicity is one of the advantages of IMCI, both updating and implementing the IMCI guidelines can be a challenge. Electronic platforms can address the need for simplicity, accommodate a more nuanced differential diagnosis (with the possibility of including additional diagnostic data such as respiratory rate, pulse oximetry, RDT results, etc.) and provide the flexibility needed to update guidelines based on new evidence.

For patient care, decision support technology can improve adherence to guidelines and/or a more comprehensive assessment and management of fever in children. These devices also serve as a platform that can reduce management costs and streamline supervision of frontline health workers. When data captured in the apps (e.g. on the number of patients seen, presenting symptoms, diagnosis and treatments administered) are transmitted to a central server, managers can view utilization and assess health worker performance in order to target workers for additional training or supervision. Additionally, these data can be analysed to better understand local epidemiology. Apps also serve as two-way communictions platforms for example, managers can communicate about disease outbreaks or guideline updates to healthworkers via the app. They may also reduce training needs by incorporating brief instructional videos or electronic job aids.

Availability

Several electronic decision support systems are in development or have recently launched (see Annex 2 for a selection). In general, there are two categories: (i) systems based on IMCI guidelines (eIMCI); and (ii) systems that enhance IMCI in some way, by incorporating additional clinical signs or data from diagnostic tests not included in the IMCI algorithm. These enhanced electronic systems can also address shortcomings in IMCI; for example, they can incorporate new evidence, provide a more integrated assessment (e.g. by identifying and treating both malaria and dehydration) or include additional classifications (e.g. "suspected viral infection, self-limiting") (Figure 23).

While there are a multitude of mHealth (mobile health) products and suppliers working in low-resource settings, there are a limited number of electronic decisions support systems for frontline health workers that aid in the assessment of febrile children, and none have reached national scale. While decision support systems often work well in pilots, implementation at a large scale has yet to be evaluated in terms of efficacy and cost-effectiveness. Additionally, a complex ecosystem must be in place to support these systems at scale, and in many countries this ecosystem is absent.[42] Scale and institutionalization requires a systematic approach addressing each element of this ecosystem, and must align with MoH digital strategy.

FIGURE 23.
New electronic decision support software

	eIMCI	Enhanced eIMCI & eiCCM
Use case	• eIMCI or eiCCM follow existing guidelines, therefore no evidence review needed. • Primary and to a lesser extent community levels.	• TBD. Changes to IMCI or iCCM must undergo evidence review. • Primary and community levels.
Existing tools	• Paper-based IMCI / iCCM charts and patient registers.	• Paper-based IMCI / iCCM charts and patient registers.
Limitations of existing tools	• Supply and delivery: inconsistent health worker use and acceptance of tests, limited support and oversight: e.g. supervision, refresher training, monitoring and evaluation. • Supply and delivery: supply chain weaknesses lead to inconsistent commodity availability. • Innovation and availability: existing system is not well adapted, e.g. need for processes/systems for customization at national level, difficult to update as new evidence and tools become available, paper-based systems lead to limited aggregation and use of data.	• Same as the first column.
New tools	• iDea, Terre des Hommes & Burkina Faso MoH (2014). • Mangologic (and others) by D-Tree International. • Various platforms running on CommCare/MOTECH platform developed by Dimagi. • Various iCCM tools by Medic mobile.	• MEDSINC by THINKMD (2017). • ALMANACH (2015) and ePOCT (2017) by Swiss Tropical Health. • PICNIC by University of British Columbia (TBD). • e-CARE by MSF (2017).

[42] For example, beyond initial app software development and deployment of hardware (e.g. phones, tablets), the following must also be addressed and funded: data and communications plans; hardware maintenance and replacement plans; server or cloud for hosting, management and maintenance of software and data; system administration; technical and customer support; training for end users, managers and technical support staff; and provisions for data security.

Partner landscape

Many partners and donors are organized around disease areas that may touch on fever in children; however, there are few large global health partners focused specifically on febrile illness diagnosis or exclusively on child health. Because fever in children is a sign of many illnesses, there are a variety of relevant stakeholders. This section highlights some of the key donors and partners in child health and diagnostics development for febrile disease as well as for AMR.

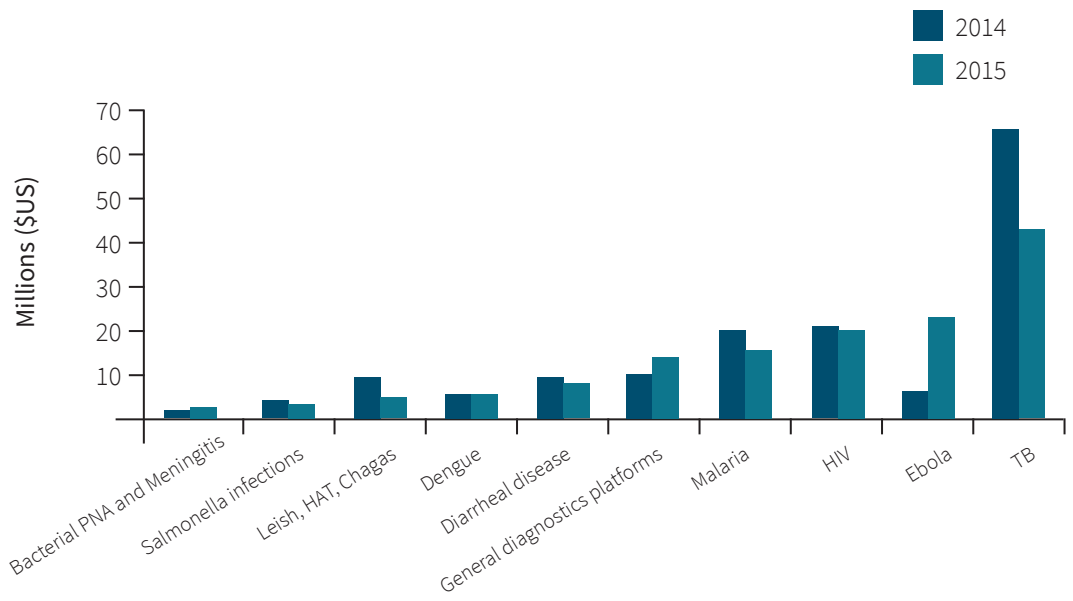
R&D landscape

Overall, R&D funding for diagnostics that are relevant to childhood fever has been limited. Those with perhaps the greatest relevance (e.g. malaria, diarrhoeal disease, bacterial pneumonia) have received considerably less funding than diagnostics for HIV, TB and Ebola (Figure 24).

In addition, there has been significant public and private investment recently in development of diagnostics related to AMR, in particular, in tests that can differentiate between bacterial and non-bacterial illness, as well as tests for sepsis. The level of investment in diagnostics for AMR was not specifically researched for this report; however, as an example, diagnostics represented 10% of the European Union's publicly funded AMR projects between 2007 and 2013, for a total of 38 million euros across 13 projects *(81).*

FIGURE 24.

R&D funding for diagnostics in 2014 and 2015



Source: Data from G-Finder public search tool, by Policy Cures.

Key donors supporting R&D of fever diagnostics for global health include:

Global Good, a fund supported by Bill Gates and drawing on the invention expertise of Intellectual Ventures, is collaborating with University of Toronto to support development of diagnostics based on predictive markers of severity for earlier identification of children needing additional interventions. Global Good is also exploring the potential use of its molecular and lateral flow platforms for pathogen-specific testing (early stage) as well as pulse oximeters in connection with its efforts around oxygen scale-up.

The Bill & Melinda Gates Foundation (BMGF) has various technical groups working on febrile illness diagnosis (e.g. malaria, pneumonia, delivery, diagnostics and integrated technology solutions) with investments relating to diagnostic technologies for fever in children. Recent and current BMGF investments include: several child survival and febrile illness etiology studies; oxygen scale-up demonstration projects; diarrhoea and pneumonia care scale-up projects; product development investments for pulse oximeters (e.g. Masimo, Lifebox, LionsGate Technologies); decision support programmes (iDEA) and early-stage host response-based diagnostics development projects based on "omics" technologies (e.g. Broad Institute, Octavio Ramilo's group).

Prize funds and public funding. Governments of several countries have launched prize funds and special grant funding initiatives to incentivize development of diagnostics in connection with AMR. These include the Horizon Prizes (European Commission, 1 million euros), the Longitude Prize (£10 million) and the Antimicrobial Resistance Diagnostic Challenge (National Institutes of Health, US$ 20 million). In addition to prizes, there are many smaller programmes supporting diagnostics for AMR. For example, the United States is supporting the Antibiotic Resistance Leadership Group (ARLG) that identifies, prioritizes and supports implementation of clinical research to combat AMR, with a focus on late-stage product development and implementation science. ARLG-funded diagnostics projects include a study to expand the use of PCT as a marker for bacterial versus viral infection in the United States and support for development of gene expression-based diagnostics that differentiate between bacterial and viral diseases.

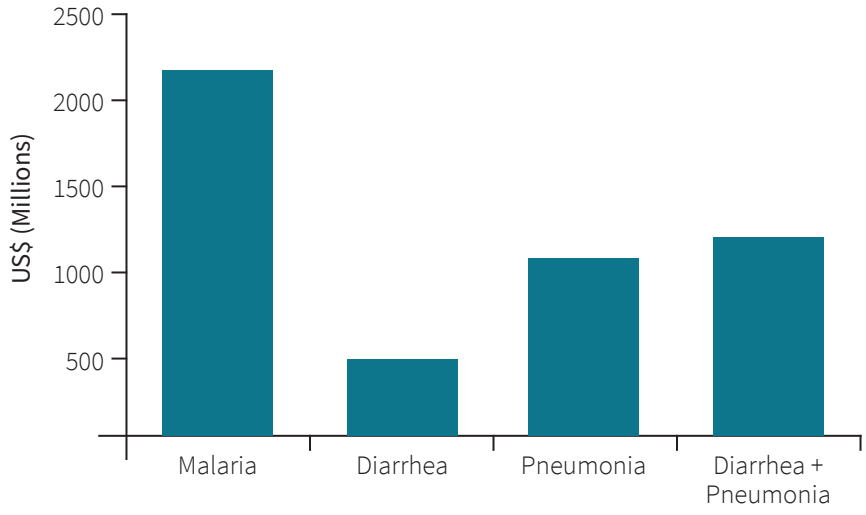
Funding for child health programmes

Unlike HIV, TB, malaria and vaccines, which have large dedicated donors, many child health programmes rely on a patchwork combination of domestic resources and bilateral aid/donor support that is often earmarked for specific projects.

Development assistance for pneumonia and diarrhoea totalled US$ 2.8 billion in 2013, with the vast majority of this funding supporting vaccinations and nutrition (Figure 25).

FIGURE 25.

Development assistance in 2013 for malaria, diarrhoea and pneumonia

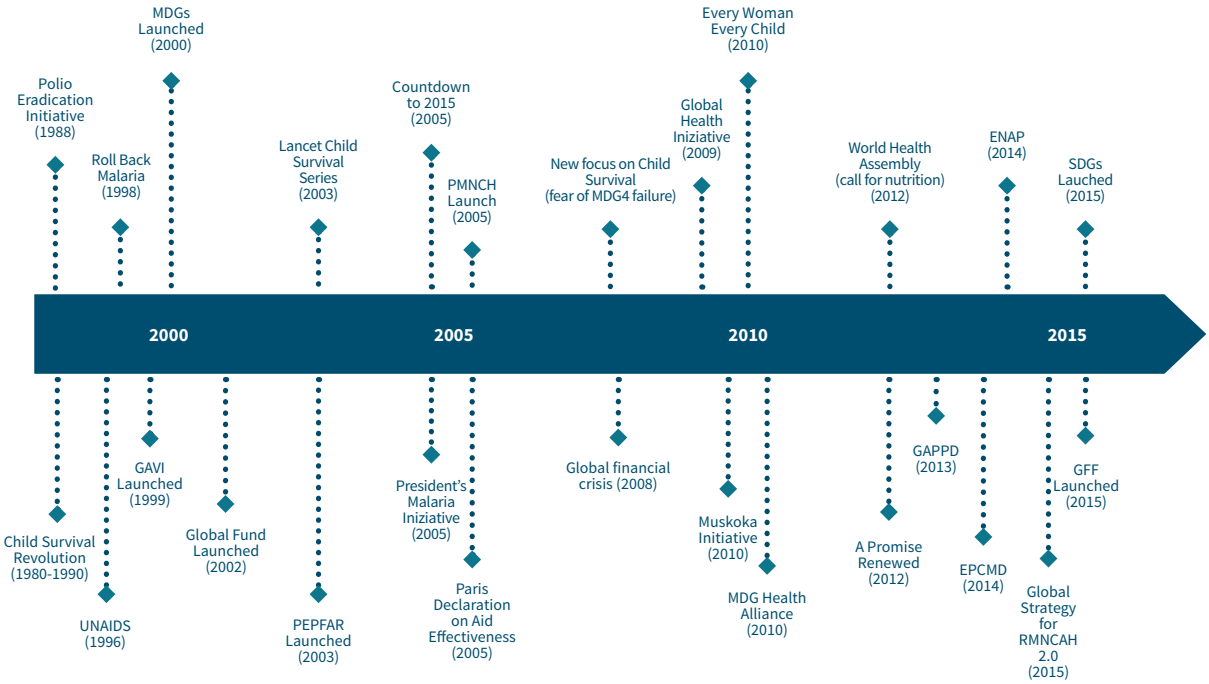


Sources: 2014 World Malaria Report *(82)*; UNICEF 2016 *(7)*.

Child health partners

Partners have introduced a number of initiatives and strategies for child health in the last 20 years (Figure 26). Recently, an independent group of experts conducted a global strategic review of IMCI to provide the strategic direction on how to achieve goals around child survival and how to promote child health and development in the context of the SDGs *(35)*. While the momentum around the MDG's contributed to gains in child health, the fragmentation of partners and lack of strong leadership, among other things, has hindered progress *(8)*. The independent review group made several recommendations for strengthening IMCI programmes moving forward, and WHO and UNICEF, along with key partners, are expected to take these into consideration as they chart a new way forward for child health, just as a new architecture for the SDGs and Reproductive, Maternal, Newborn, Child and Adolescent Health and Nutrition (RMNCAH-N) are emerging.

FIGURE 26.
Key events and initiatives in child health



ENAP: Every Newborn Action Plan; EPCMD: Ending Preventable Child and Maternal Deaths; GAPPD: Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea; GAVI: Gavi, the Vaccine Alliance; GFF: Global Financing Facility; MDGs: Millennium Development Goals; PEPFAR: President's Emergency Plan for AIDS Relief; PMNCH: Partnership for Maternal, Newborn, and Child Health; RMNCAH: Reproductive, Maternal, Newborn, Child and Adolescent Health; SDGs: Sustainable Development Goals; UNAIDS: Joint United Nations Programme on HIV/AIDS
Source: Taylor et al. 2016 *(8)*.

WHO is the lead technical agency in child health and its maternal, child and adolescent health group works to support the Global Strategy for Women's, Children's and Adolescent's Health (2016–2030) by developing guidelines, supporting countries to implement programmes and monitoring global progress. The WHO also has a research programme that includes work on child survival. In the coming years, the WHO is expected to redesign IMCI guidelines and guidance materials to reflect changing epidemiology, health systems capacity and recent technological advances. In addition, the WHO child health programme is expected to establish an independent Strategic and Technical Expert Panel *(83).*

The **UNICEF** 2016–2030 Strategy for Health reflects an increasing focus on maternal and newborn health as well as a shift towards health systems strengthening approaches, as opposed to vertical disease and intervention-specific programmes. UNICEF's supply division conducts market-shaping work, in particular, the ARIDA project (funded by La Caixa Banking Foundation) and, together with WHO, the Oxygen Scale Up project (funded by BMGF). Both of these projects aim to support automated respiratory rate and pulse oximeter devices for improved pneumonia diagnosis and management in children.

The **Global Financing Facility (GFF**) is a new financing facility, hosted by the World Bank, that supports the WHO Global Strategy for Women's, Children's and Adolescent's Health (2016–2030) and the Every Woman Every Child movement. GFF's objective is to close the financing gap for RMNCAH-N by making existing funding more efficient, mobilizing domestic resources and further mobilizing external assistance, while coordinating this financing. GFF was launched in 2015 with four frontrunner countries, expanded to 12 countries in 2016 and 2017, and aims to cover a total of 62 high-burden countries in the future.[43]

GFF includes new sources of grant funding as well as World Bank funding and domestic resources, both public and private. Funding priorities are established at the country level through prioritization and development of an investment case. GFF aims to improve efficiency and scale up resources by better aligning partners around one country-driven investment case for Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCAH). While half of the initial countries had completed this process and are implementing, the other half are still developing their investment cases and programmes. Although under-five mortality is among the core GFF indicators, it is not yet clear what level of support GFF will bring to child health delivery platforms (e.g. IMCI and iCCM) and commodities such as diagnostics for fever management.

[43] As of September 2017, 16 countries are implementing the GFF approach and several more working towards implementation.

The work of the **United States' Agency for International Development (USAID)** related to fever case management in children includes the President's Malaria Initiative (PMI) support of integrated case management as well as the child health groups' support of iCCM programmes. USAID provides direct and indirect support for iCCM implementation, coordination at the national level, global advocacy, technical assistance and learning synthesis.

While the **Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund)** is focused on its three core diseases, it is increasingly supportive of integrated approaches, in particular, iCCM. Countries may access support for iCCM through both malaria and health systems strengthening Global Fund grants. While The Global Fund supports many aspects of iCCM (e.g. training and salary for CHWs, malaria commodities, supervision, procurement and supply chain, data systems, referral systems and demand generation), it does not fund pneumonia- and diarrhoea-related health commodities. The Global Fund and UNICEF have an agreement (MOU) to work together to identify co-financing for unfunded components of iCCM. Broader health systems strengthening activities such as development of policy, guidelines and referral systems, investment supervision and management systems, and strengthening of laboratory systems are also relevant to fever management and are Global Fund eligible.

Diagnostic technology focused partners

FIND has been active in febrile illness diagnostics since 2012, initially with work to better understand fever etiology, and more recently through several efforts to validate promising biomarkers in low-resource settings to support product development of host response-based tests as well as multiplex pathogen detection projects. In 2017, FIND updated its strategy for febrile illness, AMR and outbreak diagnostics.

Médecins sans Frontières (MSF), in collaboration with FIND, is leading the Multiplex Fever Diagnostic Project.

Partners specifically working on devices for pneumonia diagnosis and triage include **Lifebox Foundation**'s work on pulse oximeters, the **UNICEF ARIDA** project to support the introduction of automated respiratory rate counters, and the **Malaria Consortium's** evaluations of respiratory rate counters and pulse oximeters. Additionally, **PATH** has a market dynamics programme focused on pulse oximeters in connection with its Oxygen Initiative. **Save the Children** is supporting several trials related to the potential of lung ultrasound for pneumonia diagnosis, improvements to iCCM pneumonia guidelines, proof-of-concept studies for respiratory rate counters and pulse oximeters. The **Clinton Health Access Initiative (CHAI)** is also working to address market challenges that limit access to key diarrhoea and pneumonia commodities in multiple high-burden countries.

The **Pneumonia Innovations Team**, an open access global network of innovators working on pneumonia, was created in 2013 to mobilize resources, advocate and provide guidance to industry in development of new technologies.

Several academic groups and institutes are driving much of the discovery and validation work of new technologies, including diagnostics, devices and decision support systems. Other academics are working on fever etiology studies and developing platforms for studying new interventions and diagnostic technologies. *These partners are supporting several of the products that are described in more detail in the technology section of this landscape report.*

Global AMR partners with a diagnostic focus

Numerous governments have launched AMR initiatives recently, such as the United Kingdom's Review on Antimicrobial Resistance *(15)*, the Organization for Economic Cooperation and Development/G7 Antimicrobial Resistance report *(84)*, the G20 declaration on AMR R&D and establishment of an international R&D Collaboration Hub for AMR *(85)*, the Generating Antibiotics Incentives (GAIN) Act, and the United States President's Council of Advisors on Science and Technology's report on combating antibiotic resistance *(86)*.

For LMICs, as a first step, there is a need to better understand the extent and nature of AMR problems in order to drive action and prioritize responses. Relevant AMR stakeholders for low-resource settings include:

- The WHO Global Antimicrobial Resistance Surveillance System (GLASS) is a result of the WHO 2015 Global Action Plan on Antimicrobial Resistance. Among the Action Plan's objectives is strengthening the evidence base through enhanced global AMR surveillance and research into particular areas. AMR surveillance is required to understand the burden and to inform action at the local, national and global level. GLASS is a platform for global data sharing on AMR, which will inform national, regional and global decision-making. It aims to foster national AMR surveillance and to standardize methods, so that analysis can be done at the global/regional level. Countries participate in GLASS by establishing national AMR surveillance systems, comprising surveillance sites, laboratories and a national coordinator. The programme, which can be implemented in a stepwise manner, includes capacity-building (e.g. manuals, software), a web-based platform, support from WHO collaborating centres and reporting on the global AMR situation and trends. It will initially focus on eight high-risk bacterial pathogens.

- The Fleming Fund is a £265 million One Health[44] programme to support LMICs in tackling AMR, in particular, support for implementing GLASS. It aims to improve laboratory capacity and diagnosis as well as data and surveillance of AMR in LMICs through a One Health approach: building capacity to collect drug resistance data; enabling the sharing of drug resistance data locally, regionally and internationally; collating data on AMR; and encouraging the application of these data to promote the rational use of antimicrobials.

- The Center for Disease Dynamics, Economics & Policy (CDDEP) is a public health research organization leading the Global Antibiotic Resistance Partnership (GARP). It focuses on local policy analysis and capacity-building related to AMR in LMICs. It has facilitated multisector national-level working groups in eight countries (India, Kenya, Mozambique, Nepal, South Africa, Uganda, United Republic of Tanzania and Viet Nam) to conduct a situation analysis on local antibiotic use and resistance to serve as an evidence base for developing policy and taking action. Working with government, national strategies and implementation plans are then developed to preserve antibiotic effectiveness, slow resistance and improve access. In addition to supporting these eight countries, the Partnership is developing models that can be replicated in other countries. It began in 2008–2009 and is in its third phase (2016–2018) whereby the initial eight countries are mentoring new countries as they go through a similar process.

[44] One Health is an approach in which many sectors communicate and work together to achieve better public health outcomes. Often, these approaches address human health, animal health and the health of the environment collectively.

Outbreak diagnostics

Recent Zika, Ebola and Middle East Respiratory Syndrome (MERS) epidemics have drawn attention to the need for improving the global response to diseases with epidemic potential. In particular, many of the diseases with outbreak potential present with fever and symptoms similar to malaria, and in the 2014 Ebola outbreak the inability to rapidly differentiate between malaria and Ebola led to unnecessary mortality and morbidity and wasted resources.

WHO launched an R&D Blueprint for action to prevent epidemics after the May 2015 World Health Assembly meeting. The R&D Blueprint is a global strategy and preparedness plan that includes an R&D agenda for priority pathogens[45] as well as mechanisms to enable rollout of an emergency R&D response during epidemics. The R&D Blueprint covers diagnostics as well as medicines and vaccines. WHO is developing technology maps and TPPs for each of the priority pathogens. The TPPs for diagnostics may also include syndromic diagnostics depending on the strategies identified in the roadmap development for each pathogen. Most of the priority pathogens present as non-specific febrile illness or haemorrhagic febrile illness.

[45] As of January 2017, the priority diseases include: arenaviral haemorrhagic fevers (including Lassa fever); Crimean-Congo haemorrhagic fever; filoviral diseases (including Ebola and Marburg); Middle East Respiratory Syndrome Coronavirus (MERS-CoV); other highly pathogenic coronaviral diseases (such as Severe Acute Respiratory Syndrome/SARS); Nipah and related henipaviral diseases; Rift Valley fever; Severe Fever with Thrombocytopenia Syndrome; and Zika.

Market challenges

In addition to the technical challenges of developing diagnostics for integrated fever management in children in LMICs, there are market challenges related to product development and introduction of new innovative diagnostic products and to increasing access to existing diagnostic products.

Common market-related challenges are described below, followed by specific challenges for each diagnostic technology category.

Common challenges

Innovation and availability

With the exception of mRDTs, there has been relatively little R&D investment in diagnostics to improve fever management in children (outside of short-term funding for outbreak diagnostics, e.g. Zika and Ebola). As a result, the pipeline for fever management diagnostics has not been advancing as rapidly as the pipelines for HIV, TB and malaria diagnostics *(15)*. From the technology developer's perspective, the case for R&D investment is limited by three factors: (i) uncertainty about demand for new products in LMICs; (ii) downward pressure on pricing for LMIC diagnostics generally; and (iii) increasingly time consuming and costly evidence requirements to support adoption.

First, from a supplier perspective, there is uncertainty about the market opportunity for any potential product related to febrile illness diagnosis, especially in low-resource settings. While the need might be quite substantial, actual funded demand is more limited, and developers have limited visibility into this area. In many global heath areas, domestic budgets are supplemented extensively by programmatic funding from donors such as the Global Fund, the President's Emergency Plan for AIDS Relief (PEPFAR) and PMI. However, the funding architectures for fever and child health are more fragmented and the donor support for IMCI or iCCM programmes is much smaller. While resources to support maternal, newborn and child health are growing (e.g. GFF), there are many competing interests.

Second, expectations about the prices that can be obtained for diagnostics for fever are low, while the level of risk and potential costs of development are quite high. On the pricing side, global health procurers and LMIC buyers generally emphasize low prices for diagnostics. In many cases, lacking cost-effectiveness analyses, new diagnostics are seen only as adding costs to existing case management budgets. Moreover, the treatments for febrile illness are often inexpensive – less than the cost of the new test – creating a financial incentive to treat without testing. The case for diagnostic tests is easier to make when the treatments are expensive or complex; for example, diagnostic test prices for HIV and TB can be relatively high and still save overall programme costs. At the same time, the cost and risks associated with developing new diagnostics for febrile illness may be sizeable, especially in the case of host response-based tests and multiplex fever tests. For novel host response-based tests, the discovery and validation costs can be quite high, and often developers are bringing together multiple disciplines and making use of relatively new technological advances and methods that may be expensive. For multiplex testing, the technological challenges of optimizing multiple assays on one device cannot be underestimated, especially when multiple modalities of testing are required. Since these novel technologies can often be applied to more financially rewarding applications – in-patient sepsis in HICs, for example – the investment case for LMICs is weak.

Third, the evidence needed to support adoption of febrile illness diagnostic technologies is increasing, adding significant time and cost to product development and thereby decreasing the potential return on investment. The use case for many of the technologies in this report represents a major departure from current practice (e.g. adding a test where there is none, withholding antibiotics or antimalarials) and the evidence requirements to support adoption and acceptance of new testing paradigms are typically high. Initially, evidence is needed to support the performance and quality of the product. Then, evidence is needed to demonstrate impact on patient outcomes in routine practice, as well as the cost-effectiveness and overall value of interventions employing the new diagnostic technology.

Diagnostic test developers typically generate this first set of evidence (i.e. product safety, quality and performance) for regulatory approvals; however, they have less experience with outcomes studies in LMICs, and assessing the impact to the system more generally (e.g. cost savings, delayed development of resistance). These studies require significant funding and expertise, and technology developers must often partner with other institutions to undertake this work. For companies that are developing products for both HIC and LMIC markets, undertaking these studies in HIC markets is generally a priority, delaying introduction in LMICs. Adding to this is the need for developers to navigate and coordinate the multiplicity of potential donors, country programmes and institutions as each may have differing evidence requirements.

Given these familiar market challenges, often the global health field would rely on public and private donors to invest heavily in supporting R&D. With a few exceptions, donors are only now recognizing and prioritizing the challenge of diagnosing non-malaria febrile illness in children, as the impact and limitations of the mRDT scale-up are seen, at the same time as integrated approaches are increasingly valued, and the potential threat of AMR is increasingly appreciated. Another challenge for donors is organizational structure: most donors are organized around disease areas; while a donor may be able to support a disease-specific intervention, integrated approaches can be difficult.

Demand and adoption, quality

The absence of major programmatic donors and a fragmented procurement landscape for child health commodities also present several potential downstream market challenges, including: ensuring that high-quality products are procured, and that suppliers of quality-assured products can differentiate themselves from lesser quality products; affordability of products may be reduced by lack of buying power; and supply challenges due to lack of accurate demand forecasts.

As products come to market, there is a need for an established process for global and national evidence reviews and incorporation into guidelines to accelerate introduction. In particular, given the need to increase access to treatments, as well as to limit overtreatment, careful consideration of the performance of tests (sensitivity to detect as many cases as possible, specificity to limit overtreatment) and of whom to test (depending on disease prevalence and test performance, specific population groups might be tested as opposed to widespread testing) is needed.

Acceptance and behaviour change are likely to be challenges as many of the products are introducing a new step in the clinical assessment or require providers to be comfortable withholding antibiotics or not referring children. Patient expectations are also important, patients may not appreciate the value of a test, especially when it costs additional money, adds time to their visit, or they live in countries where antibiotics are available without a prescription. Lessons from the mRDT scale-up will no doubt be informative for the introduction of new fever case management diagnostic technologies.

Market challenges by product category

This section provides product category-specific details on the general challenges and highlights the challenges that are unique to a particular product category.

Limited availability of well-adapted automated respiratory rate counters

Innovation and availability

Existing respiratory rate aids are poorly adapted for fever management in low-resource settings and there are few advanced products in the pipeline. Reasons for the challenge include the relatively recent prioritization of fully automated respiratory rate counters (e.g. 2014 TPPs by UNICEF) and the limited market incentives for suppliers of respiratory rate counting devices in HICs to adapt their products for low-income countries.

Affordability

Automated respiratory rate counting devices will cost 10-times that of existing respiratory rate timers and counting beads.

Demand and adoption

Additional evidence is needed to inform use of new automated counters. For example, guidance on product offerings will be needed (price, product expected life, quality, specifications) as well as evidence of effectiveness and acceptance.

Limited use of high-quality well-adapted handheld pulse oximeters for pneumonia

Innovation and availability

Oxygen therapy was only recently prioritized by WHO (2016), and there is not enough evidence on whether existing handheld pulse oximeters are suitable for use in low-resource settings.

Affordability

Pulse oximeters are additional to existing child health budgets, and are often unaffordable. High-quality handheld devices can be expensive (~US$ 250) from manufacturers, plus prices to end users are highly variable, with significant distribution markups. Fragmented demand and highly decentralized procurement limits a buyer's ability to take advantage of volume discounts.

Quality

There is insufficient information on quality. While there are many SRA approved products, many of the more affordable products do not have SRA approval and their performance and quality are unknown. For quality-assured suppliers, the inability of consumers to distinguish high-quality products from poor-quality ones increases the risk of "me too" devices and may limit incentives to invest in this area.

Demand and adoption

Comprehensive product information and additional evidence are needed to better inform procurement and use of pulse oximeters, for example, procurers are highly decentralized and lack complete information on available products, including assessment of a device's performance and suitability for the intended use. Product specifications are needed, as well as analysis of how devices compare on key specifications (e.g. price, product expected life, performance, quality, total cost of ownership over the life of the product).

These could be summarized in reviews and recommended product lists. Note that WHO will issue product specifications in 2017. Evidence is lacking on acceptance and impact of pulse oximeters at the community level and the public health value of higher-performing oximeters compared to cheaper alternatives needs analysis.

Supply and delivery

Fragmentation of demand leads to many product variants and makes procurement of replacement probes and batteries difficult, resulting in non-functioning devices.

Limited availability of multimodal devices

Multimodal devices face some of the same challenges as automated respiratory rate counters and pulse oximeters, although if affordably priced they may have wider application than single-function devices. However, developers lack insight into user needs in terms of what functionality should be included in the devices, and the value and willingness to pay for those additional functions. Currently, there are a handful of promising products in the pipeline, with some in very late-stage development. However actual demand is quite uncertain.

Lack of host response-based diagnostics that identify children who need antibiotics

Innovation and availability

There is a lack of novel diagnostics to identify children needing antibiotics at the frontline in low-resource settings. There are multiple reasons for this challenge, including the recent prioritization, high development costs and a high level of risk associated with regulatory approval. More specifically, the diagnostic challenge of non-malaria fever and work to define user needs is recent in low-resource settings (TPP published in 2016) *(59)*. Additionally, a technological driven focus on pathogen-specific technologies has distracted industry from appreciating more pragmatic user needs (i.e. whether a patient has a bacterial infection and needs an antibiotic versus testing for specific pathogens) *(87).*

The development costs of a host response-based test are significant, and the prize funds for AMR are not necessarily structured in a way that incentivizes their development, especially among global companies that are well positioned to market new tests in both HICs and LMICs. Smaller diagnostics developers will struggle to conduct the necessary trials to support effectiveness and adoption.

As noted previously, discovery can be costly and validations extensive and complex. Particular challenges include the lack of reference standards,[46] resulting in the use of complex methods such as panels of "expert clinicians" and augmented laboratory testing, both of which are expensive and not readily available at trial sites (e.g. rural sites) *(88)*. The multitude of potential fever causes and co-morbidities requires extensive laboratory testing, usually conducted offsite at international laboratories. Additionally, it is likely that extensive studies will be needed to validate biomarkers across different geographies, ages, health-care settings (e.g. community, facility, in-patient) and populations with common co-morbidities *(88)*. Patient recruitment can also be complicated, depending on presenting symptoms.

Regulatory requirements have not been clear for this new class of diagnostics, further increasing risk to developers as relevant performance standards, study design and comparator methods are not well defined *(88) (89)*. Moreover, many of the tests in the pipeline are being developed with HIC markets in mind, and their intended use and target population may differ slightly from the needs of LMIC settings. Additional trials in relevant low-resource settings and populations will be required to validate the tests in LMICs. From an economic perspective, developers are likely to prioritize the HIC markets, and may not see the case for validating and marketing these products in LMICs.

Demand and adoption

In order to support adoption of a new class of tests, evidence of impact and value is needed. Demonstrating the financial value of diagnostic technologies for fever is a challenge. In general, diagnostics are often undervalued relative to their role in providing quality care. For host response-based tests, the value of the test is in targeting treatment to those who need it and in limiting overtreatment and, therefore, the test has many effects that need to be taken into consideration when assessing its value. To date, there has been a failure to develop economic models assessing value at multiple levels: to society (e.g. valuing the public good of preventing resistance by reducing antibiotic overuse), to health systems (e.g. testing at the primary care level and appropriate treatment, averts costs of treating resistant infection) and to the individual patient (e.g. harm from overtreatment).

[46] For many febrile diseases, there is no good reference standard/comparator method. For example, for many diseases, blood culture is the gold standard, however, it is insensitive. While highly sensitive molecular diagnostics may detect a particular pathogen, it may not be clinically significant and colonization must be considered. Many studies use chest X-ray as a gold standard for pneumonia, however, X-ray lags behind clinical presentation and is subject to interpretation. A recent pneumonia etiology study found that 30–50% of children admitted to the hospital with WHO-identified severe or very severe pneumonia had no X-ray findings. See: Hammitt L. PERCH descriptive results. Pneumonia Etiology Research for Child Health. Presentation at the American Society of Tropical Medicine and Hygiene Annual Meeting, Atlanta, 13–17 November 2016.

Demand and adoption

While there are a few existing products on the market today (e.g. CRP, PCT tests) that might be of value, there has been insufficient evidence to support their efficacy in relevant populations in low-resource settings; not to mention their effectiveness in routine use and their cost-effectiveness. Note that MORU and FIND are leading work in this area for CRP tests.

Affordability

High pricing for novel tests may limit uptake, and affordability is likely to be an issue in low-resource settings unless significant discounts for LMICs and high volumes are possible. In the case of an individual paying out of pocket, there is often little financial incentive for diagnosis prior to treatment with an antibiotic or ACT.

Lack of host response-based POC diagnostics for children with severe disease to support triage

The lack of triage diagnostics results from many of the same challenges associated with host response-based diagnostics for differentiating between bacterial and non-bacterial infections. Despite evidence of health workers missing severe disease in children, there has been little prioritization of diagnostics to support triage and less work undertaken to define the user needs (e.g. no TPP exists). As with other host response diagnostics, the focus on pathogen specific technologies has distracted industry from understanding more pragmatic clinical needs. R&D costs are also likely to be high because extensive evidence will be needed to support use of the biomarkers in different patient cohorts in different geographies. The diagnostic strategy and cost-efficetiveness of using the tests in different scenarios also need to be determined through field studies and modeling. Affordability at scale may be a challenge; while one of the devleopers is targeting $US1 per test, the number of children who require testing could be quite high, and funded demand is uncertain.

Low uptake and variable availability of single-pathogen RDTs

Demand and adoption

While there are several existing RDTs currently on the market that might improve outcomes, a lack of data on fever etiology and impact limits their uptake. Specifically, there is a need for local data to inform decisions about the most clinically relevant RDTs by location. Because the test needed in one area might differ from that in another, local processes are needed for incorporation of new tests into treatment guidelines (e.g. define which children that should receive the test; the level of the health system; how to manage based on outcomes). Additionally, programmes lack comprehensive information on the available product selection.

Affordability

Although individual RDTs tend to be relatively inexpensive diagnostic tests, using multiple RDTs would be unaffordable.

Quality

For many existing RDTs, product performance and quality have not been adequately demonstrated, and there are no reliable, comprehensive product performance reviews that potential buyers can use to identify high-quality products like there are with mRDTs and HIV RDTs. The most relevant diseases are not known and therefore have not been prioritized for inclusion in by the WHO PQ programme and there is often weak diagnostics regulation (on the supply and demand side) for products that are primarily relevant in low-resource settings. For quality-assured suppliers, the inability of consumers to distinguish high-quality products from poor-quality ones increases the risk of "me too" diagnostics and limits incentives to invest in this area.

Innovation and availability

There is a lack of high-performing RDTs for some diseases due to limited business incentives to invest in their development. In particular, the need for these tests is poorly documented and the available budget for many disease-specific tests is uncertain.

No multiplex diagnostics suitable for use in low-resource settings

Innovation

The pipeline for POC, multiplex tests with fever panels that are relevant for use in low-resource settings is thin for a variety of reasons. Foremost, the diagnostic challenge of non-malaria fever has not been prioritized until recently and there is limited understanding of need and use case for this type of test; no TPPs exist. From a commercial perspective, there is uncertainty about the need and potential impact of specific panels due to lack of local fever etiology data to inform decisions about most clinically relevant pathogens by location. Due to the potential heterogeneity in fever causes, the market for any panel could be extremely fragmented. As is the case for multiplex tests in HICs, diagnostic strategies are needed (e.g. defining which children should receive the test; at what level of the health system; how to manage based on outcomes) as are assessments of overall value of testing to patients and the health system. Development costs associated with multiplexing are high, and regulatory approvals can drive up development costs: if one of the assays on the panel fails the regulatory review, then the entire device does. An alternate, but more expensive approach is to seek individual approvals for each test rather than for the entire panel.

Affordability

Multiplex tests are likely to be unaffordable, as the cost of goods may be high due to technological complexity.

Limited use of microbiological culture

Innovation

There is a limited pipeline of technologies suitable for improving microbiology testing in LMICs. Recently, industry investments have not aligned well with LMIC needs; for example, there has been a technological focus on non-culture genotypic methods, which can be expensive as multiple tests are often needed. Additionally, industry has focused on tests that are reimbursed at high rates in HICs (e.g. hospital acquired infections). The platforms for these tests tend to be poorly adapted to low-income settings (e.g. high cost, need for stable electricity, etc.).

Affordability

Traditional blood culture bottles as well as reagents and consumables required to culture, identify and perform susceptibility testing can be expensive in LMICs because of supply chain markups and low volumes.

Quality

Due to affordability, some laboratories in LMICs prepare culture materials in-house and their quality cannot be assured. Limited capacity to interpret results and lack of standardization also affect the quality of testing.

Supply and delivery

Existing microbiology services are essential to caring for in-patients with severe disease; however, traditional culture testing is underutilized, appearing to be caught in a cycle of low supply and low demand. Testing services are interrupted for a number of reasons: supply chain challenges (e.g. multiple consumables and reagents must all be available to perform testing) lead to stockouts and often there is a shortage of trained technicians to undertake testing. When testing is not available, clinicians may stop asking for tests. There are also challenges around the quality of testing that contribute to low demand from clinicians for culture testing.

Overall, the low utilization of existing testing limits potential public health impact: data generated through microbiology testing, where they exist, are not routinely fed back to providers in order to develop a picture of local disease prevalence, to inform empiric treatment strategies and to inform local AMR strategies.

Limited availability and uptake of electronic decision support systems

Demand and adoption

Electronic decision support tools for childhood febrile illness diagnosis and management are nascent and there are limited data on their efficacy and effectiveness. Implementation, often on a small scale, frequently outpaces evidence. One of the greatest challenges is the lack of a standardized approach to assessing impact of electronic decision support systems. For example, the technology may have multiple levels of impact and savings, and there is no standardized way of documenting benefits and costs. Outcome studies could be expensive and pragmatic approaches are required, as developers and programmes lack funding and experience to conduct these evaluations.

Because it is a fast-moving field, potential buyers also lack information on the various products and their effectiveness. There is low awareness among MoHs of product offerings for febrile illness or child health; no reviews exist. Additionally, these tools exist alongside a confusing array of mHelath products, focusing on different areas (e.g. reproductive health, maternal health, etc.) and supporting different functions (e.g. supply chain management, data reporting, decision support). There is no global process for reviewing these products and recommending them.

Supply and delivery

Models for going to scale do not exist. Sustainability requires that multiple elements of the mHealth ecosystem be in place.

Affordability

The total cost of ownership may present affordability challenges, however, it is not well documented.

Selected opportunities for market intervention

This section provides an initial view of potential market opportunities for increasing availability and access to diagnostic technologies to improve integrated fever case management in children. It is not specific to the Unitaid mandate and business model; rather, it represents a range of market-based interventions that could be undertaken by different global health actors and stakeholders. While some of these interventions could be acted on immediately, others are medium or longer term. Similarly, while some potential interventions described below are well developed, others deserve further exploration; this list is intended to be illustrative and is not exhaustive.

Opportunities that are generalizable to several of the product categories are described first, followed by additional opportunities that are specific to each product category.

General opportunities

Market stimulus for innovation

Compared to major infectious diseases such as HIV, TB and malaria, the R&D pipeline for fever diagnostic technologies is less advanced. Global work to identify priority areas for R&D investment should be considered, and any funding should take into consideration the public health impact as well as the potential for a sustainable market to develop. The most effective approach (push or pull) and structure would depend on the particular market. Alternatively, programmatic funding such as an AMR fund, or a fund focused on improving child health, could also serve to stimulate innovation.

Fever etiology data and business case development

There is a substantial gap in knowledge on the causes of fever in children in low-resource outpatient settings; better epidemiological data on causes of fever from different geographic areas are needed. This information could be used to better define the “needs” for new diagnostic tests and should be translated into business cases (e.g. the potential market size) to engage technology developers. This data can also be used to improve syndromic treatment algorithms and to inform adoption of new tests.

Standardized methods for conducting outcomes and cost-effectiveness research

Beyond assessing the performance of new diagnostic technologies, to ensure adoption and uptake it is important to demonstrate the impact on clinical outcomes and value. In view of limited funding for fever diagnostics and competing priorities, it is especially important to develop a strong evidence base showing impact and cost-effectiveness. However, as outlined in the market challenges section, developers of pipeline technologies struggle with this work, due to lack of expertise, the cost of conducting these studies and difficulties navigating differing requirements of various donors, countries and institutions. In addition to funding outcomes and cost-effectiveness studies required to support adoption and resource mobilization, work to harmonize requirements could reduce costs of these studies, as could development of shared platforms for conducting these outcomes studies.

Favourable global policy environment and strategy

Globally, infrastructure and systems for introduction of new technologies for child health do not appear as robust as they are in areas such as HIV diagnostics. For example, there have been few efforts to steer investment towards the most needed innovations. There is no precedent for WHO PQ review of technologies to support non-malaria febrile illness diagnosis, and the PQ scope would need to be expanded to include this. A recent IMCI review pointed out the lack of an institutionalized process reviewing new evidence, and recommended establishing a standing evidence review group at the global level to accelerate uptake of key health technologies for child health. Additionally, because many of these technologies touch on areas beyond child health (e.g. malaria, nutrition, AMR), a mechanism for coordination is needed.

Accelerating initial uptake through demand generation and procurement commitments

Since affordability is likely to be a challenge for many fever diagnostic technologies, programmes to aggregate demand and fund initial procurement of novel fever diagnostic products could be considered. Such programmes could accelerate widespread use and reduce prices by lowering transactions costs and accelerating achievement of optimal manufacturing scale. However, by definition, market-shaping interventions are time limited, and the sustainability of the market, given reliance on domestic budgets and piecemeal donor funding, is a concern. Working exclusively in countries with strong local child health leadership may mitigate this risk; or working in countries where related projects are already under way (e.g. strong MoH-supported iCCM/CHW programmes, countries directing significant GFF funding to relevant child health interventions and IMCI, countries committed to scaling oxygen therapy). While some of the countries fitting these criteria have high disease burdens, this approach may initially exclude countries where the impact could be greater. Selecting implementing partners that are well established in target countries will also be critical.

Changing patient and provider expectations

As products are introduced, lessons from the mRDT introduction and scale-up suggest that information, education and communication programmes focused on provider and patient behaviour change will be needed to support test uptake and appropriate management based on results. In some countries, work to improve the financial incentives for testing will be critical, in light of the availability and low cost of antibiotic treatments and the role of the private sector in fever management.

Devices to support pneumonia diagnosis and triage

Short-term work focuses on establishing global priorities and developing evidenced-based guidance to support adoption and procurement. Specifically, given limited budgets there is a need to prioritize among different technologies (e.g. respiratory rate alone, pulse oximeters alone, multimodal devices or devices that include additional parameters), and to understand where they would be most effectively deployed. If multimodal devices are a priority, TPPs are needed to guide potential developers on the necessary parameters and use cases. Additionally, because there are relatively few products in advanced stages of development, the business cases are worth assessing, taking into consideration device prices, market size and market sustainability.

For existing products and those in the advanced development stage (e.g. automated respiratory rate counters, pulse oximeters), minimum product specifications are needed as well as reviews of how available products align with specifications. Evidence of health worker acceptance and cost-effectiveness are also needed, and the ARIDA project is beginning to generate this information for automated respiratory rate counters. The results of these reviews should be disseminated widely to ensure that they are accessible to local decision-makers.

In the medium term, as new products come to market, supporting their introduction will accelerate impact (e.g. awareness raising, registration, piloting, incorporation into local guidelines, initial procurement, provider training on benefits and use). Where procurement is decentralized (e.g. pulse oximeters), work to encourage harmonization of product variants could be valuable. Additionally, it would be worthwhile to explore opportunities for coordinated ordering (e.g. pre-negotiated prices that multiple buyers can access) and price sharing forums (e.g. sharing price information, both by procurers and manufacturers) to reduce pricing variation, increase transparency around distributor markups and make volume discounts more visible. Lastly, work to strengthen supply chain systems (e.g. quantification, procurement, distribution) to ensure availability of replacement probes, batteries and devices would ensure that devices remain functional.

In order to have an impact, any work to accelerate access to pneumonia diagnosis and triage tools must be closely coordinated with efforts to increase access to dispersible amoxicillin where it is not yet available, as well as efforts to improve referral systems and access to oxygen therapy.

Diagnostics that identify children who require antibiotics

New potentially game-changing diagnostics are being developed for differentiation of bacterial and non-bacterial infection. Few of these diagnostics are being developed with low-resource settings in mind, instead more lucrative markets in HICs are often first priority. Efforts to ensure affordability and to accelerate evidence generation in children from LMICs could have an important role in achieving global targets for child survival and in slowing the development and impact of drug resistance. Specific interventions are described below.

Expand the evidence base in low-resource settings for existing host response biomarker based tests

In the near term, additional work is needed to improve the evidence base for existing host response-based diagnostics and to appreciate whether and where these tests could add value. For example, near-term studies of CRP's efficacy in Africa are needed, as well as a study of test acceptance, impact in routine use and cost-effectiveness. These studies should be designed with input from relevant policy-makers, such as WHO and the local MoH, to ensure that the study design meets evidence requirements and answers key questions.

Engage product developers around diagnostic test needs and markets in low-resource settings

Further engagement of product developers on the needs and markets in low-resource settings is needed to ensure that new technologies are well adapted for LMICs and that studies are conducted in relevant populations. For example, although a TPP for a test that differentiates between bacterial and non-bacterial illness exists, are developers aware of the requirements, and how are they prioritizing them? What can be done to reduce prices and what is the potential for funding commitments to address affordability via rapidly achieving economies of scale? Developers also need guidance on evidence requirements to support global health adoption.

Support validations and clinical trials of novel biomarkers and new diagnostics in low-resource settings

Given the high costs of developing host response-based diagnostics, support for R&D should be considered. Specifically, validations in low-resource settings are a priority because developers are likely to initially focus their validations in HICs given the greater financial opportunities in these markets. Depending on the stage of development this could mean providing access to well-characterized specimens, supporting early-stage biomarker validation in relevant LMIC populations, or validation of new diagnostic tests that are based on these biomarkers.

Given the complexities of conducting these studies, it would make sense to further explore the value of shared trial sites, biobanks and other efficiencies. For example, is it possible to include multiple biomarkers or products within one larger study, using standardized protocols and comparators? Would centralized reference laboratory testing be of value? Could frameworks and protocols for measuring outcomes, cost-effectiveness and health worker acceptance be established? Is there scope for including these diagnostics in larger ongoing studies of childhood illness and mortality?

Longer term, there are several potential market-shaping interventions for which planning could begin now

For example, outcomes and cost–benefit analysis will be needed to support adoption, and frameworks for this do not exist. In the case of host response-based tests, in particular, holistic approaches are needed, taking into consideration the impact of the diagnostic on multiple levels: (i) on the patient (e.g. timely and appropriate treatment, aversion of adverse events); (ii) on the health system (e.g. cost savings due to proper drug targeting); and (iii) to society (e.g. delayed development of resistance is a public good that needs to be captured). Considering the limited budgets for child health programmes and the many competing priorities, this type of evidence would likely be required in order to mobilize resources for new diagnostic tests. Additionally, the evidence requirements for regulatory and policy endorsements should be mapped out and shared with test developers.

Diagnostics to identify children with severe disease or at risk for complications to support triage

Efforts to develop host response-based diagnostics that identify children who are at risk of progressing to severe disease are less advanced than diagnostics for bacterial versus non-bacterial infection. A TPP and initial business case showing the market and public health impact of these types of tests would raise awareness of the need among potential product developers. As the evidence base required to support adoption of these tesets will be substantial, support for biomarker validation in multiple LMIC populations, followed by large scale field testing would accelerate introduction of new products. In addition to assessing outcomes, evidence will be needed to informing the optimal diagnostic strategy and to analyze cost effectiveness of testing. For these diagnostics to have an impact, referral networks and advanced care at receiving facilities must also be in place.

Single-pathogen RDTs

There are several market opportunities related to mRDTs, which are outlined in the Unitaid malaria diagnostic test landscapes. For other single-pathogen RDTs, near-term opportunities begin with a better understanding of the potential demand and market, including improving the knowledge of locally relevant pathogens contributing to non-

malaria fever in children (i.e. high-priority pathogens) and appreciating where diagnostic uncertainty is high. In addition, in order for the test to have an impact, the diagnosis must be actionable by the health worker – a specific treatment or intervention should be available (or withheld).

In the medium term, once clinically relevant RDTs have been identified, several global activities are needed to support uptake, including: assessments of cost-effectiveness to support adoption and resource mobilization; conducting evaluations of product performance and quality; and developing diagnostic strategies and guidelines for use. At the local level, work will be needed to raise awareness of product offerings among decision-makers and procurers, to facilitate product registrations and procurement, and to adopt guidelines and to train providers. If affordability is a challenge, coordinated or pooled procurement might be explored.

Multiplex diagnostics

For high priority pathogens where existing products are inadequate (e.g. suboptimal performance or unsuitable test formats) a business case can be developed and shared with potential suppliers to incentivize product development and to assess the need for additional R&D incentives.

The pipeline for multiplex diagnostics is thin. For the few products in development, performance evaluations and development of diagnostics strategies (e.g. whom to test, which settings, how to manage based on results) as well as cost-effectiveness and impact studies are a priority.

Additional market intervention opportunities to consider would focus on stimulating innovation in order to offset the high risks and costs of developing a multiplex diagnostic that is suitable for use in LMICs. In the near term, opportunities focus on building the investment case, defining the use case for multiplex testing and development of TPP(s). Critical to this work will be identifying the most clinically relevant pathogens and prioritization of test panels based on public health impact as well as market impact (i.e. whether a sustainable market be developed). Based on this, the market opportunity (e.g. market size, market value) can be analysed along with other data to assess market stimulation requirements (e.g. size of funding, structure of investments).

Microbiological culture

Interventions to break the cycle of low demand and supply of traditional culture deserve more exploration. For example, determining if there is value in working with companies supplying culture products to expand the number of trained technicians and to address supply chain challenges through bundling. This could be pursued in connection with national level surveillance work that is being implemented in support of the WHO

GLASS initiative, and gradually expanded to lower level hospitals. To have the greatest impact, this work should be combined with the development of systems for aggregating microbiology testing data and feeding it back to providers and MoH officials in order to inform diagnosis at the frontline and to improve the choice of empiric treatments.

Electronic decision support systems

In the near term, there are opportunities to support validations of electronic decision support systems, including trials of any improvements to the IMCI guidelines, and assessments of these tools' efficacy, acceptance and impact in practice. A few of these technologies have undergone preliminary field assessments, however, others require evaluation. There is also a need to explore the impact of these platforms in different settings, in particular, the retail private sector. Additionally, a framework for cost-effectiveness analysis is needed; the total cost of ownership is often poorly documented, and systematic approaches are needed to analyse costs and benefits that can accrue at multiple levels (e.g. patient outcomes, savings to the health system, etc.).

Longer term, once products have been assessed, there will be a need to increase awareness of the product offerings and available evidence among countries in order for decision-makers to navigate the array of mHealth offerings available today. There is a need to develop models for going to scale; strategic and operational plans are needed, taking into consideration all elements necessary to support large-scale introduction and sustained implementation of electronic decision support technologies.

Conclusion

Since their introduction and scale-up, mRDTs have improved malaria case management, in particular, by reducing overtreatment with antimalarials. While mRDTs need to be further scaled to achieve universal access, this should be accompanied by simultaneous efforts to strengthen differential diagnosis of fevers that are not caused by malaria and an integrated approach to diagnosing and managing fever in children.

Fever, the main symptom of malaria, is the most common presenting symptom to health workers in low-income countries and has many different causes. Given the tremendous progress in reducing malaria prevalence, malaria is no longer the leading cause of fever in many populations. However, beyond mRDTs, frontline health workers in low-resource settings have little to go on; there are few suitable diagnostics available for non-malaria fever and as a result, for years, many potentially fatal diseases in children have relied on unspecific diagnostic techniques, educated guessing and empiric treatment.

However, in the recent decades, technological advances in diagnostic testing have been rapid, including improvements in performance, discovery of novel biomarkers and development of POC tests that are easily deployable outside of central laboratories. Indeed, this first edition of the Unitaid landscape report for febrile illness diagnostics has revealed a number of promising technologies to improve differential diagnosis of fever in children, ranging from devices that diagnose and triage pneumonia to novel in vitro diagnostic tests that identify children needing referral or a specific treatment.

While there is a range of products in the development pipeline, there are also a number of market challenges threatening progress. In particular, there is a need to focus now on scale-up by strengthening implementation of integrated delivery platforms for child health and identifying long-term programmatic funding for child health. While funding for RMNCH is increasing, the prioritization of integrated case management among other areas is not clear. Additionally, there is a need to institutionalize evidence review processes globally and locally, so as to keep up with medical and technological advances. Here, work is needed both to develop systems for evaluating test safety and efficacy, as well as to review evidence for policy recommendations.

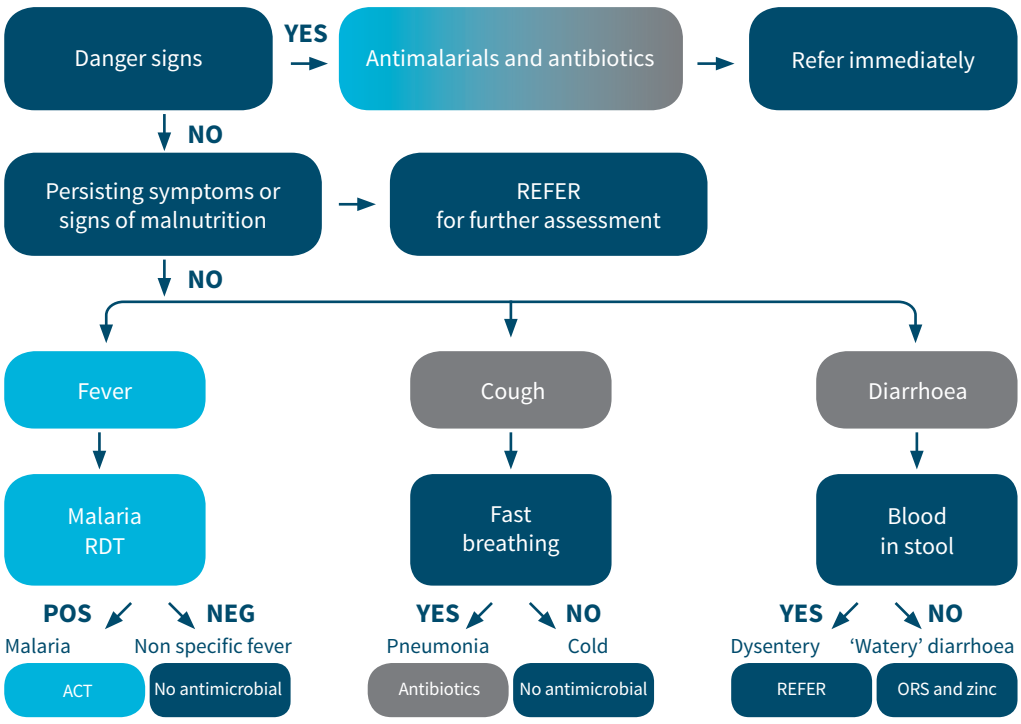
Additionally, there has been little engagement with technology developers, both in communicating priorities and specific needs for global child health, as well as in developing the business case required to support commercial investment. Ultimately, if these challenges are not addressed, technologies will fail to advance through the development pipeline or to achieve meaningful scale and impact.

The stakes are high, achievement of the SDGs is not possible without improving child survival, and this depends on integrated approaches to childhood illness. Improving diagnosis of febrile illness is an important step in improving child health and in preserving antimicrobials. Failure to act not only jeopardizes achievement of SDGs and related targets, but also will dampen interest of technology developers in this vital area.

Annex 1: Background on IMCI and iCCM

The primary guidelines for febrile children are IMCI and iCCM. In general, these guidelines first direct the health worker to check for signs of danger and severe illness and to initiate referral if appropriate. Then, the child is assessed for several main symptoms (e.g. fever, cough, diarrhoea) and tested with an mRDT if appropriate. Nutritional status, HIV and measles immunization are also assessed. These assessments are based on a very limited set of clinical signs. Following the assessment, patients are classified into one or more symptom groups: pink indicates immediate referral; yellow indicates a specific treatment; and green indicates supportive home care.

FIGURE A1.1
Core elements of IMCI



Source: World Health Organization 2013 (4).

FIGURE A1.2
Core elements of IMCI

Does the child have fever?
(by history or feels hot or temperature 37.5º or above)

If yes:

Decide Malaria Risk: high or low

Then ask: Look and feel:
- For how long?
- If more than 7 days, has fever been present every day?
- Has the child had measles within the last 3 months?

Look and feel:
- Look or feel for stiff neck.
- Look for runny nose.
- Look for any bacterial cause of fever**.
- Look for signs of MEASLES.
  - Generalized rash and
  - One of these: cough, runny nose, or red eyes.

- **Do a malaria test***: If NO severe classification**
- In all fever cases if High malaria risk.
- In Low malaria risk if no obvious cause of fever present

High or Low Malaria Risk

Classify FEVER

• Any general danger sign or • Stiff neck.	***Pink:*** **VERY SEVERE FEBRILE DISEASE**	• **Give first dose of artesunate or quinine for severe malaria** • **Give first dose of an appropriate antibiotic** • **Treat the child to prevent low blood sugar** • **Give one dose of paracetmol in clinical for high fever (38.5º C or above)** • **Refer URGENTLY to hospital**
• Malaria test POSITIVE.	***Yellow:*** **MALARIA**	• **Give recommended first line oral antimalarial** • **Give one dose of paracetmol in clinical for high fever (38.5º C or above)** • Give appropriate antibiotic treatment foran identified bacterial cause of fever • Advise mother when to return immediately • Follow-up in 3 days if fever persists • If fever is present every day for more than 7 days, refer for assessment
• Malaria test NEGATIVE • Other cause of fever PRESENT.	***Green:*** **FEVER: NO MALARIA**	• **Give one dose of paracetmol in clinical for high fever (38.5º C or above)** **Give appropriate antibiotic treatment** for an identified bacterial cause of fever • Advise mother when to return immediately • Follow-up in 3 days if fever persists • If fever is present every day for more than 7 days, refer for assessment

No Malaria Risk and No Travel to Malaria Risk Area

• Any general danger sign • Stiff neck.	***Pink:*** **VERY SEVERE FEBRILE DISEASE**	• **Give first dose of an appropriate antibiotic.** • **Treat the child to prevent low blood sugar.** • **Give one dose of paracetmol in clinical for high fever (38.5º C or above).** • **Refer URGENTLY to hospital.**
• No general danger signs • No stiff neck.	***Green:*** **FEVER**	• **Give one dose of paracetmol in clinical for high fever (38.5º C or above)** • **Give appropriate antibiotic treatment** for any identified bacterial cause of fever • Advise mother when to return immediately • Follow-up in 3 days if fever persists • If fever is present every day for more than 7 days, refer for assessment

f the child has measles now or within the last 3 months:
- Look for mouth ulcers.
  Are they deep and extensive?
- Look for pus draining from the eye.
- Look for clouding of the cornea.

If MEASLES now or within last 3 months, Classify

• Any general danger sign or • Clouding of cornea or • Deep or extensive mouth ulcers.	***Pink:*** **SEVERE COMPLICATED MEASLES****	• **Give Vitamin A treatment** • **Give first dose of an appropriate antibiotic** • **If clouding of the cornea or pus draining from the eye, apply tetracycline eye ointment** • **Refer URGENTLY to hospital**
• Pus draining from the eye or • Mouth ulcers.	***Yellow:*** **MEASLES WITH EYE OR MOUTH** COMPLICATIONS****	• **Give Vitamin A treatment** • **If pus draining from the eye, treat eye infection with tetracycline eye ointment** • If mouth ulcers, treat with gentian violet • Follow-up in 3 days
• Measles now or within the last 3 months.	***Green:*** **MEASLES**	• **Give Vitamin A treatment**

* These temperatures are based on axillary temperature. Rectal temperature readings are approximately 0.5º C higher·
** Look for local tenderness; oral sores; refusal to use a limb; hot tender swelling; red tender skin or boils; lower abdominal pain or pain on passing urine in older children.
*** If no malaria test available: High malaria risk - classify as MALARIA; Low malaria risk AND NO obvious cause of fever - classify as MALARIA.
**** Other important complications of measles - pneumonia, stridor, diarrhoea, ear infection, and acute malnutrition- are classified in other tables

Source: World health Organization 2014 *(90)*

Annex 2: Febrile illness diagnostics technology pipeline

Respiratory rate counters and pulse oximeters

Philips

The Philips ChARM (Children's Automated Respiratory Monitor) is an automated respiratory rate counting device that was developed in response to frontline health worker needs in low-resource settings. Philips is a Dutch global technology company and a leading medical device supplier. ChARM uses a 3D accelerometer with advanced signal processing to measure the specific abdominal motions related to breathing in young children. Health workers place the device around the child's belly, it measures respiratory rate and classifies fast breathing according to WHO guidelines, flashing green or red depending on the child's rate and age. The device has been CE marked (Class 2A), initial sales have occurred and it is undergoing field trials (see the ARIDA project). The price is 40–60 euros for non-rechargeable devices and approximately 20 euros more for rechargeable devices.

Philips is in the research phase of a second-generation ChARM device that combines respiratory rate and pulse oximetry. An early prototype will be tested in Malawi with Save the Children (Saving Lives at Birth) in late 2018, assuming a favourable market for ChARM. Target pricing is $US 150–250.

FIGURE A2.1

Philips ChARM (Children's Automated Respiratory Monitor)

Source: Philips

Product name Developer	ChARM (Children's Automated Respiratory Monitor) Philips
Parameters measured	Respiratory rate counter.
Description	Automated respiratory rate counting device based on a 3D accelerometer with advanced signal processing to measure the specific abdominal motions related to breathing in young children.
Availability	Launched in 2016.
Development phase	Available, undergoing field trials through the UNICEF ARIDA project.
Approximate price per device	40-60 euros non-rechargeable device; additional 20 euros for a rechargeable device.
Operational life	2000 measurements guaranteed for the non-rechargeable device, approximately 2–3 years.
Operation and readout	Fully automated respiratory rate counting and classification. Health workers place the device around the child's belly, it measures respiratory rate, provides a beep sound and LED indication upon completion of measurement and classifies fast breathing according to WHO guidelines, flashing green or red depending on the child's rate and age.
Performance and accuracy	±2 breaths per minute, when measured under recommended conditions; measurement range of 10–150 breaths per minute.
Consumables	None
Power	Non-rechargeable device has an internally sealed battery. For sites with grid access, rechargeable device has a mini-USB port and medical grade adaptor, 200 measurements per charge.
Regulatory	CE marked (July 2016).

Lifebox

Lifebox is a United Kingdom charity founded to improve the safety of surgery in low-resource settings. The device that it supplies is also suitable for outpatient spot checking use, such as screening for pneumonia in children. Lifebox does not itself manufacture oximeters, rather it contracts with suppliers to provide them. Currently, Acare Technology (Taiwan, China) manufacturers pulse oximeters for Lifebox, which are available through the Lifebox website for US $250 (including shipping).

In 2018, Lifebox expects to conduct another request for proposals process to take advantage of technological advances in pulse oximetry and to improve pricing.

Although it already has a paediatric probe, in 2015 Lifebox received funding from BMGF (US$ 1 million) to develop a more sensitive and user friendly probe for use in infants and young children. The probe has been deisgned and the design will be freely available to manufacturers. Lifebox expects these new probes to cost US $15-25.

FIGURE A2.2

Lifebox pulse oximeter and accessories

Source: Lifebox

Product name Developer	Lifebox, manufactured by Acare Technology Lifebox
Parameters measured	SpO2, pulse rate.
Description	Highly accurate and portable handheld pulse oximeter, initially targeting surgical settings in LMICs. Universal probe is appropriate for children >3 months and adults; includes a paediatric probe, pillow clip and multicountry charger. Includes CD-ROM educational materials. Displays audible and visual alarms, runs on battery or mains power.
Availability	Commercially available since 2012. (A new tender will be conducted in 2018). Lifebox has refined the design of paediatric and neonatal probes to improve performance and ease of use. It is finalizing the clinical assessment of the probe and will make the detailed technical design files available to manufacturers freely so that the manufacturers can implement the improvements.
Development phase	Commercially available, has been distributed to >100 countries, primarily for surgical settings, some paediatric use for pneumonia.
Approximate price per device	US$ 250 (covers shipping globally, not customs clearance); US$ 25 for replacement probes; US$10 for batteries
Operational life	Warranty: two years for the box and one year for the probes; in practice, up to five years.
Operation and readout	Fully automated. Digital SpO2, pulse rate, pleth bar and SpO2 waveform; audible alarm.
Performance and accuracy	70–100%: ±2%
Consumables	Probes and batteries.
Power	Rechargeable lithium ion battery: runs for 14 hours. Requires 100/220V power supply for recharging. Can use 3 AA alkaline batteries.
Regulatory	This model is CE marked, meets United States FDA standards and conforms to IEC 60601-1 and ISO 9919, the international standard for pulse oximetry. Manufacturer must produce the units under conditions that meet the international standard ISO 13485:2003.

Masimo

Masimo is a global supplier of non-invasive patient monitors, leading the supply of pulse oximeters to hospitals. In response to discussions with global health stakeholders about the role of pulse oximeters in pneumonia, Masimo is developing several products. Its first system, the Masimo phone pulse oximeter (iSpO2 Rx), uses a phone and probes to measure SpO2. The system includes an app and probes, it requires a cell phone (Android and iOS apps available). There is both a consumer and medical professional version, it is CE marked and sells for US$ 250–500.

In order to better meet the needs of pneumonia case management, in late 2017 Masimo soft launched[47] the Rad-G, a combined respiratory rate and pulse oximeter that has been designed specifically for frontline health workers in low-resource settings. In March 2016, Masimo received BMGF funding (US$ 5 million) to both develop an affordable, rugged device, with long battery life, and to evaluate its impact on diagnosis and identification of severe pneumonia cases for referral in Ethiopia. Masimo is also developing an extensive training package to support product introduction. The CE mark is planned for early 2018, and details on the product are embargoed until release. Pricing is not established, however, US$ 250 is the benchmark.

Masimo is developing another multimodal device that will measure haemoglobin, SpO2, respiratory rate, pulse rate and perfusion index. Haemoglobin measurement is based on Masimo's existing Pronto device, which is a commercially available pulse oximeter that also measures haemoglobin transdermally.

FIGURE A2.3
Masimo Rad-G

Source: Masimo

[47] The Rad G launched in limited markets, broader release will occur after CE approval, expected in early 2018.

Product name Developer	Rad-G Masimo
Parameters measured	Respiratory rate counter, SpO2, pulse rate and perfusion index.
Description	Rad-G is a combined respiratory rate counter and pulse oximeter designed for frontline use in low-resource settings. Small, portable handheld standalone device, designed to be low cost, rugged and have an ultra-long rechargeable battery life. Uses Masimo Measure-through Motion and Low Perfusion™ SET® pulse oximetry technology to measure SpO2, respiratory rate from the pleth (RRp™), pulse rate, and perfusion index (Pi). Measurements are taken through a fingerclip.
Availability	Limited launch in late 2017, broader release in early 2018 upon CE marking.
Development phase	Masimo has conducted clinical-based evaluations in Ethiopia, India and Nigeria. Field trials through the UNICEF ARIDA project planned for late 2017–2018.
Approximate price per device	US$ 250 benchmark, contingent on volume.
Operational life	Ultra-long. Specifics to be available upon release/regulatory clearance.
Operation and readout	Fully automated. Specifics to be available upon release/ regulatory clearance.
Performance and accuracy	RadG will use signal extraction technology, expected to be 97% accuracy; 95% sensitivity.
Consumables	None
Power	Rechargeable, ultra-long battery life. Specifics to be available upon release/regulatory clearance.
Regulatory	Expect CE mark in early 2018

LionsGate Technologies

LionsGate Technologies (LGTmedical) is a Canadian social enterprise that was launched to produce mobile medical devices for vital sign measurement. The company's research partners at the University of British Columbia and the Center for International Child Health at BC Children's Hospital have developed the Kenek family of vital sign monitors and sensors to support an electronic decision support and data collection systems for pregnant women and children through a Grand Challenges Canada grant. A clinical-grade pulse oximeter was the team's first focus because it can diagnose late-stage pre-eclampsia as well as sepsis and pneumonia. An adult version of the Kenek SpO2 system is available commercially; paediatric and neonatal versions are expected. Respiratory rate is in an advanced stage of development and will be incorporated soon; in the future, blood pressure and temperature are expected.

FIGURE A2.4

Kenek O2 Sensor by LionsGate Technologies

Source: LionsGate Technologies

Product name Developer	Kenek O2 sensor LionsGate Technologies
Parameters measured	Respiratory rate counter and SpO2 (along with clinical mobile data collection).
Description	Mobile platform allows for multifunctionality sensing (i.e. phone can host many different sensors for detecting vital signs) that is combined with smart data driven decision algorithms. A finger probe is used to provide a photoplethymograph that is analysed for respiratory rate, pulse rate and SpO2; the phone application interprets data. Blood pressure and temperature sensors are planned, depending on funding, 2019/2020.
Availability	2018 for paediatric SpO2 and respiratory rate functions. Adult SpO2 only product launched commercially in 2013.
Development phase	Adult: SpO2 only product validated and launched commercially in 2013. Respiratory rate to be incorporated and validated in 2018. Paediatric and neonatal: probes have been developed, SpO2 has been internally validated, formal validations planned for 2018. Respiratory technology has been developed to be incorporated into system and validated in 2018.
Approximate price per device	Pulse oximetry module and sensors (US$ 150 for three sensors – adult, paediatric, neonatal). Mobile devices (US$ 150–200).
Operational life	Two to three years per sensor.
Operation and readout	Minimal training required, the user is directed through the application on the phone. Automated recommendations (e.g. risk prediction and treatment) are provided through customizable software on mobile phone.
Performance and accuracy	In formal independent breathdown testing based on 12 adult subjects against gold-standard blood gas co-oximeters the Kenek mobile pulse oximeter performed well within validation requirements (root mean square deviation RMSD under 3% over the range of 70–100% SpO2). For adult sensors on iOS (Apple), RMSD was 1.81%; for adult sensors on Android, RMSD was 1.55%; for paediatric sensors on iOS, RMSD was 1.64%. Respiratory rate validation planned for 2018.
Consumables	Probes: adult, paediatric, neonatal.
Power	Rechargeable, 24 hours on a charge.
Regulatory	Adult version of the pulse oximeter running on iOS (Apple) has Health Canada approval. Android, paediatric and neonatal approvals are expected in 2018. CE mark is planned for all sensors.

RespiDx

RespiDx, is a start-up formed by Israeli entrepreneurs with extensive experience bringing new medical devices to market. The group has two technologies in development, the RespiDx for respiratory rate and temperature, and the Multimometer, which measures respiratory rate, temperature and oxygen concentration. They have been designed in response to the need for simple means of diagnosing and triaging pneumonia in low-resource settings. Both devices resemble a digital oral thermometer; however, they incorporate additional sensors and provide a binary output based on the child's age. The devices are in prototype stage, and prospective trials are expected to begin in late 2017 in the Democratic Republic of the Congo to evaluate the final device's performance and its acceptability to CHWs. Manufacturing will be contracted, and initial work to transfer engineering to mass production has begun. The group has received over US$ 500 000 from USAID and Grand Challenges Canada.

FIGURE A2.5

RespiDx Multimometer

Source: RespiDx

Product name Developer	Multimometer RespiDx
Parameters measured	Respiratory rate counter, temperature, heart rate and SpO2.
Description	Styled like a digital thermometer and inserted into the child's mouth like a pacifier. Provides the data after a 30-second reading. Respiratory rate detection is based on sensing the temperate fluctuations of the breathing, as sensed at the nostrils using a low-thermal-mass thermistor, while measuring and averaging the inter-peak distance. Heart rate and SpO2 measured using a reflective pulse-oximeter sensor held against the upper lip. All sensors are located on the protrusion from the thermometer body that points towards the nostrils.
Availability	Targeting 2018
Development phase	In bench testing (Q2 2017). Clinical testing and usability testing by CHWs in the Democratic Republic of the Congo (2018).
Approximate price per device	Targeting US$ 25 per unit for quantities of >100 000 in low-resource settings.
Operational life	Estimated two years.
Operation and readout	One button activation, with progress bar (30 seconds) and display of the vital-signs at the end. The four vital signs are shown on the screen after the 30-second measurement. If the respiratory rate threshold is passed (indicating pneumonia according to WHO guidelines), then the LED under the icon showing the age-category of the child is changed from green to red.
Performance and accuracy	TBD – clinical testing under way.
Consumables	Alcohol pads/liquid is the only consumable required; serves to disinfect the device from patient to patient.
Power	Batteries are sealed internally, not replaceable and support the full 2-year use.
Regulatory	United States FDA/CE regulatory submissions will be performed during transition to mass-manufacture.

POC tests to identify children needing antibiotics: existing biomarkers

SD Biosensor

In early 2017, FIND and SD Biosensor announced a collaboration to develop a malaria+CRP combination RDT. SD Biosensor, founded in 2010 out of a spinoff from SD Bioline/Alere, is a Korean company developing POC lateral flow and handheld device-based tests. The RDT will be based on SD Biosensor's existing malaria and CRP technologies. Collaboration with FIND involves reagent development, prototype development and performance evaluation. SD Biosensor aims to begin evaluation of a designed locked product in India by the end of 2017. Additional evaluations will follow, as well as pricing. The regulatory strategy has yet to be determined because CRP is not within the WHO PQ scope.

POC tests to identify children needing antibiotics: novel host response biomarkers

Rapid Pathogen Screening (RPS Diagnostics)

Rapid Pathogen Screening (RPS Diagnostics) is a privately held diagnostics company based in the United States. It launched the FebriDx rapid test in 2014 that is based on detection of MxA and CRP for differentiating between clinically significant bacterial infections in patients with a febrile acute respiratory tract infection. The format is a disposable lateral flow based test, using a fingerstick blood sample. Results are interpreted visually after 15 minutes. The test price is ~US$ 15. This test is included in the FIND biomarker validation studies described above.

FIGURE A2.6

Rapid Pathogen Screening (RPS Diagnostics) -FebriDX

Source: Rapid Pathogen Screening (RPS Diagnostics)

Product name Developer	FebriDx Rapid Pathogen Screening (RPS Diagnostics)
Biomarkers	MxA and CRP.
Description	Single-use, disposable, lateral flow based test, using a fingerstick blood sample to produce a qualitative result that is interpreted visually after 10 minutes. MxA provides specificity to CRP. If MxA is elevated with or without an elevated CRP, it is a viral infection; if CRP is elevated without elevated MxA, it is deemed a bacterial infection; if neither MxA or CRP is elevated, it is deemed clinically insignificant.
Intended use and target population	Identifies clinically significant infections in patients presenting with a febrile acute respiratory tract infection.
Availability	Launched in 2014, available in many markets.
Development phase	Introduction and adoption phase. Soft launched in 2014 with CE mark. Currently undergoing health outcomes assessments and pursuing additional regulatory clearances in key markets. In 2017, FIND began an evaluation in three LMICs of promising biomarkers, including the FebriDx test.
Approximate price of test/cartridge	US$ 15.
Approximate price of instrument	No instrument.
Performance	97% NPV bacterial infections; 80% sensitivity and 94% specificity for bacterial infections. 87% sensitive and 83% specificity for viral infection (91).
Sample	5 µ l fingerstick blood sample.
Turnaround time and processing	10–15 minutes per test.
Operating steps	Similar to a rapid test: collect fingerstick sample, transfer to strip, close snap, add buffer and wait for result.
Readout	Visual readout; qualitative result.
Regulatory	CE mark 2014, Canada clearance 2015, both Singapore and Gulf Cooperation Council clearance 2016. Beginning trials in 2017 for United States FDA clearance.

MeMed

MeMed is an Israeli company founded in 2009 that is dedicated to improving patient lives through research, development and commercialization of pioneering tests that monitor the body's immune state. MeMed is currently focused on developing diagnostics based on the measurement of three host-protein biomarkers (CRP, IP-10 and TRAIL) and a computer algorithm that interprets the measurements and provides a score that indicates the likelihood of bacterial versus non-bacterial infection. Their first product, ImmunoXpert, was launched in 2014 (CE marked for Europe, cleared in Israel) and is a lab-based kit. Their second product, ImmunoPOC, is based on the same technology and will be a POC instrument using disposable cartridges that should be available in 2018. The company is targeting rapid results (15 minutes) from fingerprick blood. Pricing is to be determined, however, the company is cognizant of the need in LMICs and of the benchmarks suggested in the TPP developed by FIND and partners for tests to discriminate between bacterial and non-bacterial infection in low-resource settings *(59).*

FIGURE A2.7

MeMed ImmunoPOC

Source: MeMed

Product name Developer	ImmunoPOC MeMed
Biomarkers	CRP+IP-10+TRAIL.
Description	Small benchtop device, using disposable cartridges. Sample in-answer out. Test measures three immune system biomarkers in serum; computer algorithm used to compute score indicating the likelihood of bacterial versus non-bacterial immune response. The diagnostic value of the algorithm is attributable to the distinctive and complementary expression dynamics of the three proteins in bacterial versus viral infections. In particular, TRAIL expression is induced in response to viral infections and significantly reduced in bacterial-infected patients.
Intended use and target population	Patients with suspicion of acute bacterial or viral infection, a fever within the last seven days and symptom duration of less than seven days. Outpatient, emergency and hospital professional and trained non-professional use.
Availability	Targeting 2018.
Development phase	Biomarker and algorithm validation complete, builds on ImmunoXpert, a commercially available ELISA kit that received the CE mark and is used in Europe. MeMed is currently focused on design and validation of the POC device and cartridge.
Approximate price of test/cartridge	TBD, targeting competitive pricing for LMICs as per the TPP.
Approximate price of instrument	TBD
Performance	TBD for POC system. Studies of the commercially available ELISA-based kit using the same biomarkers. Curiosity study: 94% sensitivity; 93% specificity (n = 765). Opportunity study: 88% sensitivity; 93% Specificity (n = 577 children) (92) (93) (94).
Sample	TBD. Initially, serum/plasma sample, aim for fingerstick.
Turnaround time and processing	~15 minutes.
Operating steps	Targeting sample to answer with no operator interventions.
Readout	TBD. Likely to provide a score and interpretation. (ELISA version provides score, interpretation and values for each of the biomarkers).
Regulatory	United States FDA and CE mark are planned.

Inflammatix Inc.

Inflammatix was founded based on research done at Stanford University that identified sets of immune biomarkers for the diagnosis of infectious disease. The technology is based on a set of mRNA markers that is rapidly quantitated and their values turned into a diagnostic score (probability of bacterial infection) via an algorithm. The biomarkers have been validated in various patient cohorts, with AUROC 0.92 in discriminating bacterial and viral infections across several populations. Inflammatix is now developing HostDx™ Fever a small handheld or POC molecular analyzer that will read disposable cartridges, targeting <30-minute TAT and use of whole blood, possibly fingerstick samples. Inflammatix is prototyping a rapid device, and expects a product that is ready for prospective trials by the end of 2018 and to launch in the United States in 2020, and beyond the United States in 2021. In addition to classifying viral and bacterial infections, the team is developing a sepsis assay, and has identified gene expression signatures for malaria and TB *(95).*

Product name Developer	HostDx™ Fever Inflammatix Inc.
Biomarkers	Set of mRNA markers.
Description	Product form TBD, a handheld or small benchtop real time molecular device with disposable cartridges, sample in-answer out. Technology is based on host response gene expression from whole blood, whereby a set of mRNA is rapidly quantitated and their values turned into a diagnostic score (probability of bacterial infection) via an algorithm.
Intended use and target population	Bacterial/viral discrimination intended for use in patients with signs of acute infection, in the hospital and ambulatory setting.
Availability	2020 in the United States, 2021 elsewhere.
Development phase	Prototyping a rapid device, expect to begin prospective trials by the end of 2018. Significant validation of the set of markers has been achieved.
Approximate price of test/cartridge	TBD, targeting competitive pricing for LMICs.
Approximate price of instrument	TBD
Performance	Biomarker validation (largely in published gene expression datasets) shows AUROC 0.92 in discriminating bacterial and viral infections across several populations (96). Additional prospective studies of the signature and system are planned.
Sample	Whole blood, possibly fingerstick
Turnaround time and processing	Targeting <30 minutes per sample, one sample processed at a time per device.
Operating steps	Targeting sample to answer with no operator interventions.
Readout	Risk bands for bacterial infection and risk bands for viral infection.
Regulatory	United States FDA and CE mark are planned.

Becton, Dickinson and company

BD (Becton, Dickinson and company) is a global medical technology company with a corporate-wide AMR initiative. Among a suite of AMR-related products, BD's Diagnostics Systems unit is developing a test to differentiate between bacterial and viral infections for its Veritor™ platform. The BD Veritor™ system is a POC platform for rapid (<10 minutes) immunoassay testing using disposable cartridges.

The platform is already on the market (e.g. it is used extensively for diagnosing flu, Group A Strep, and RSV in settings that include physician offices, hospitals, retail clinics and pharmacies); however, the test for bacterial versus viral infection is in the feasibility stage and BD is targeting completion by 2020. The bacterial versus viral test is being designed with both developed and developing country applications in mind, from both initial validation and affordability perspectives. BD has a partnership with FIND to support development of a prototype assay for the BD Veritor™ platform.

FIGURE A2.8
Becton Dickinson Veritor™ platform

Source: Becton Dickinson

POC tests for triaging children

University of Toronto

Researchers at the University of Toronto are collaborating with the Global Good Fund to develop lateral flow tests based on host response markers of endothelial activation and vascular permeability. These markers signify activation of pathways associated with critical illness, allowing for earlier and objective identification of at risk children. The test, which would measure these markers in fingerstick blood, would aid in triaging children at the periphery by identifying those children at risk of becoming critically ill who need admission/referral or close monitoring. Global Good is developing prototype disposable lateral flow tests based on these biomarkers for prospective studies in LMICs that are expected to begin in 2018. Additionally, given the potential to apply these markers for sepsis diagnosis in HICs, the markers have been put on Protiensimple's POC ELISA device, Ella, which takes one hour to run and provides quantitative results. The markers, running on the Ella platform, are currently being validated in Africa and studied for sepsis triage in HICs.

Product name Developer	Product name TBD University of Toronto, partnering with Global Good Fund at Intellectual Ventures
Biomarkers	Not yet released, likely one or more (maximum is three) markers of vascular integrity/endothelial activation and inflammation.
Description	Single-use, disposable, rapid, lateral flow based test, using a fingerstick blood sample to produce a qualitative result that is interpreted visually. Biomarkers signal that a pathway of critical illness has been activated in the patient and provides the health worker with actionable results (low risk: treat on an outpatient basis, medium risk: treat with close monitoring versus, high risk: refer urgently for admission).
Intended use and target population	All cause fever in low-resource settings.
Availability	TBD, initial field studies using prototype tests (RDT format) expected to begin in 2018.
Development phase	Biomarkers have been validated in 2100 children in Uganda and replicated in Tanzanian adults (unpublished). An ELISA-based POC benchtop device (Ella by Protiensimple) is in place to further validate biomarkers in Mozambique. Prototype lateral flow tests expected before the end of 2018 at which time prospective trials will begin.
Approximate price of test/cartridge	Targeting US$ 1.
Approximate price of instrument	No instrument required but a reader that incorporates clinical assessment is being considered.
Performance	Preliminary validations: ROC curves >.95.
Sample	Targeting whole blood from fingerstick; to date have used EDTA.
Turnaround time and processing	~10 minutes.
Operating steps	Similar to an mRDT.
Readout	Two versions of the test are envisioned: 1.For CHWs/minimally skilled health workers the readout would be either: use oral treatments and manage at home; or refer patient for additional care. 2.Where clinical assessment skills are higher (e.g. at a health facility) the readout will generate three clinical response groups, for example: (i) no evidence of critical illness, very low-risk patient who can be managed as an outpatient; (ii) moderate-risk, monitor/follow-up patient; and (iii) high-risk patient, requires urgent admission and management.
Regulatory	TBD

Multiplex diagnostics

Chembio Diagnostic Systems Inc.

Chembio Diagnostic Systems Inc. is a United States company that is developing several multiplex diagnostic technologies for fever management. The tests are based on Chembio's patented Dual Path Platform (DPP®), which offers improved performance over traditional lateral flow technology, as well as simultaneous detection capabilities of both antigen and antibody in a disposable rapid test format. A small handheld, battery operated reader, the DPP® Micro Reader, can be used with the assay to eliminate user error during test interpretation and to provide quantitative information. Additional features include data capture and transmission to a smartphone, tablet or personal computer.

Chembio's DPP Zika, Chikungunya, Dengue IgM/IgG Assay System is in development through a partnership with the Paul G Allen Family Foundation, the United States Centers for Disease Control and the United States Biomedical Advanced Research and Development Authority (BARDA). It is a disposable multiplex POC test for three febrile diseases with current expansion in multiple countries. The test will incorporate simultaneous detection of IgM and IgG antibodies against dengue, Zika and chikungunya in a single fingerstick blood sample. The DPP® Micro Reader is used to interpret the test results and provide information on antibody titer. Chembio has developed a prototype (late 2016); field testing has been ongoing since Q2 2017.

Product name Developer	DPP® Zika, chikungunya, dengue IgM/IgG Assay System Chembio in partnership with Paul Allen, CDC, BARDA
Biomarkers	Dengue, Zika, chikungunya IgM and IgG detection.
Description	Disposable rapid test based on Chembio's Dual Path Platform and the DPP® Micro Reader, a small handheld, battery operated reader.
Intended use and target population	Febrile patients in outpatient settings worldwide where Zika, chikungunya and dengue detection required.
Availability	TBD
Development phase	In development, ongoing field testing in 2017.
Approximate price of test/cartridge	TBD
Approximate price of instrument	US$ 300–400.
Performance	TBD
Sample	Fingerstick whole blood sample.
Turnaround time and processing	20 minutes.
Operating steps	Typical of a lateral flow test.
Readout	DPP® Micro Reader interprets the test results for the operator.
Regulatory	CE mark, United States FDA, ANVISA planned.

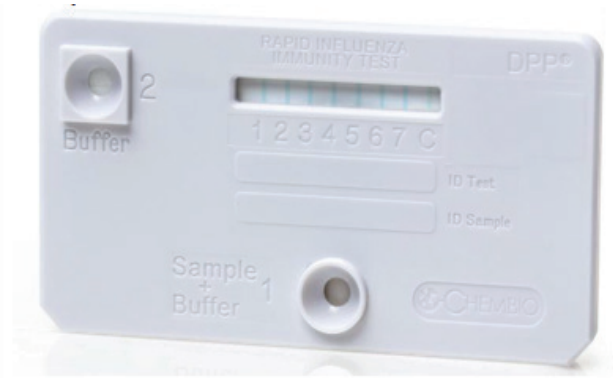
Chembio's DPP® Fever Panel 2 is in development through a partnership with FIND. It is a disposable multiplex POC test for several febrile diseases that are particularly relevant in South-East Asia. The test will incorporate both antigen and antibody testing, and will simultaneously detect malaria, dengue, Zika, chikungunya, leptospirosis, scrub typhus, murine typhus and Burkholderia pseudomallei. The DPP® Micro Reader is used to interpret the test results. Chembio expects to have a prototype by early 2018 and to begin field testing later in the year.

Product name Developer	DPP® Fever Panel 2 Chembio in partnership with FIND
Biomarkers	Malaria (pLDH and HRP2), dengue, Zika, chikungunya, leptospirosis, Rickettsia typhi (causative agent of murine typhus), Burkholderia pseudomallei, Orientia tsutsugamushi (causative agent of scrub typhus). Detection of antibody and antigen.
Description	Disposable rapid test based on Chembio's Dual Path Platform and the DPP® Micro Reader, a small handheld, battery operated reader.
Intended use and target population	Febrile patients in outpatient settings, South-East Asia.
Availability	TBD
Development phase	In development, expect to begin field testing in 2018.
Approximate price of test/cartridge	TBD
Approximate price of instrument	US$ 300–400.
Performance	TBD
Sample	Fingerstick whole blood sample.
Turnaround time and processing	20 minutes.
Operating steps	Typical of a lateral flow test.
Readout	The DPP® Micro Reader interprets the test results for the operator.
Regulatory	CE mark.

Chembio's DPP® Fever Panel 1, developed with funding from the Paul G Allen Family Foundation, is a response to the Ebola outbreaks and is intended to support fever case management in adults and children in situations where outbreak risk is high. The test detects malaria, Ebola, Lassa, Marburg, dengue, chikungunya and Zika. Product design has been finalized; clinical studies are ongoing in 2017 for several of the markers. Individual submission to the United States FDA for the malaria and Ebola components is planned by end of 2017; submissions for other disease markers will follow. The test is expected to be commercially available in 2018.

Product name Developer	DPP® Fever Panel 1 Chembio in collaboration with the Paul G Allen Family Foundation, for Africa
Biomarkers	Malaria (pLDH and HRP-2), Ebola (VP40), Lassa (NP), Marburg (VP40), dengue (NS1), chikungunya (E), Zika (NS1).
Description	Disposable rapid test based on Chembio's Dual Path Platform and the DPP® Micro Reader, a small handheld, battery operated reader.
Intended use and target population	Febrile patients in outpatient settings. High-risk outbreak settings; Africa.
Availability	2018
Development phase	Design lock achieved; clinical trials under way in Nigeria and Peru.
Approximate price of test/cartridge	TBD
Approximate price of instrument	US$ 300–400.
Performance	TBD
Sample	Fingerstick whole blood sample.
Turnaround time and processing	20 minutes.
Operating steps	Typical of a lateral flow test.
Readout	DPP® Micro Reader interprets the test results for the operator.
Regulatory	United States FDA clearance (individual submissions) is being sought for the malaria and Ebola assays. Other tests will follow after malaria and Ebola are FDA-cleared.

FIGURE A2.9
Chembio Diagnostic Systems Inc. Dual Path Platform (DPP®): Multiplex Example



Source: Chembio Diagnostic Systems

FIGURE A2.10
Chembio Diagnostic Systems Inc. Dual Path Platform (DPP®): Multiplex Example

Source: Chembio Diagnostic Systems

FIGURE A2.11
Chembio Diagnostic Systems Inc. DPP® Micro Reader

Source: Chembio Diagnostic Systems

DiscoGnosis Consortium

The LabDisk system being developed by the DiscoGnosis Consortium,[48] is a POC lab-on-a-disc *(99)* that tests for several febrile tropical diseases (malaria, dengue, chikungunya, Zika, typhoid, pneumonia) simultaneously. The LabDisk platform has multiple applications; a European Union Framework 7 grant-supported (www.discognosis.eu)[49] proof-of-principle and initial validations of the febrile tropical disease panel at the Institut Pasteur de Dakar, Senegal, and the Central Laboratory Khartoum, Sudan. During the validation the detection of coinfections demonstrated an added feature of the system. In this system, 200 µL of blood is collected and transferred to a disposable disc containing all the reagents to perform the assays. The disc is inserted into the LabDisk Player and results are available within 70–120 minutes (time includes the on-disc sample preparation step) with no further operator input. Prototypes of the LabDisk and LabDisk Player have been developed, as have instruments for disc fabrication and packaging. While a tropical disease panel is being developed initially, the system is designed to be modular, and it will be possible to customize the assays on the disc to meet the needs of a particular geographic region, health facility-level or sample matrix.

[48] Led by the Department of Microsystems Engineering (IMTEK), University of Freiburg, and its strategic partner Hahn-Schickard in Germany. Other consortium members include: Rohrer AG (Switzerland); University Hospital Basel (Switzerland); European Foundation for Clinical Nanomedicine (Switzerland); University Medical Center Göttingen (Germany); University of Stirling (United Kingdom); Magnamedics Diagnostics BV (Netherlands); and MAST Group Ltd (United Kingdom). Associated members hosting validation tests: Institut Pasteur de Dakar (Senegal); and Central Laboratory Khartoum (Sudan)

[49] https://www.youtube.com/watch?v=UvcZwOXTRuk&feature=youtu.be

Product name Developer	LabDisk DiscoGnosis Consortium
Biomarkers	Malaria (DNA: P. falciparum, P. vivax, P. malariae, P. ovale and P. knowlesi), dengue (RNA: all four serotypes), chikungunya (RNA), zika (RNA), Salmonella typhi/paratyphi (DNA), Streptococcus pneumoniae (DNA).
Description	Disc-shaped disposable chips contain all reagents and buffers to perform the assays simultaneously (including lyophilized amplification reagents and extraction kit). Disc uses microfluidic unit operations to fully automate nucleic acid assays for both DNA and RNA detection. The LabDisk Player device is a small benchtop device (26 x 17 x 9 centimetres; 2 kilograms) that can perform isothermal amplification (LAMP) and thermocycling (polymerase chain reaction) (PCR) and protein detection, when needed. It detects the outcome via real-time fluorescence/(chemi) luminescence signal and displays results on a screen.
Intended use and target population	Patients with febrile syndrome of unknown origin, tropical disease settings; suitable for sentinel sites for epidemics surveillance.
Availability	2020 for the entire system; components (such as individual assays or extraction kit) may be available earlier in the market.
Development phase	Late-stage development (Technology Readiness Level 5–6).
Approximate price of test/cartridge	Targeting <US$ 10 when produced at scale.
Approximate price of instrument	Targeting less than a few thousand US$ per device.
Performance	First proof-of-principle LabDisk tests in Senegal and Sudan (biobanked and fresh samples) were confirmed with the reference methods available at each site. Further performance data will be derived once funding is made available for large-scale clinical studies.
Sample	200 µL whole blood, serum.
Turnaround time and processing	70–120 minutes per sample, depending on the assay (total time, including on-disc sample preparation).
Operating steps	Sample in-answer out. Operator hands-on time <5 minutes. Steps: transfer blood to the disc, insert disc into the device and read results.
Readout	Results displayed on graphical user interface. Data storage capacity. Potential to incorporate algorithm-based decision support software.
Regulatory	TBD

FIGURE A2.12

DiscoGnosis Consortium LabDisk and Player platform

Source: Hahn-Schickard, Bernard Müller Fotografie.

Microbiological culture to optimize diagnosis and treatment of patients as well as antimicrobial use

While there are a handful of promising technologies that can improve upon traditional culture methods, many are still early stage, laboratory based or require several hours or days to complete. Examples include:

- Work by the Broad Institute to develop a phenotypic drug sensitivity testing by measuring changes in genes required for cell function. (Proof-of-concept stage.)
- Specific Technologies is developing a colorimetric array detecting the change in volatile substances in the gas phase. FIND has been working with the group in 2017 on a feasibility study to expand classifiers to pathogens relevant for LMICs such as Salmonella spp. (Seeking partners for clinical trials.)
- Accelerate is a United States company developing real-time microscopy that automates susceptibility testing by watching growth and processing images on positive cultures. (Prototype developed and going to trials.)
- LifeScale AST is a United States company developing a rapid phenotype-based antibiotic susceptibility test based on resonant mass method technology. The system automates much of the process, the kits and consumables are stored at room temperature. (Expected availability in 2017.)

Selected electronic decision support systems for diagnosis of febrile illness[50]

Terre des Hommes, a Swiss non-profit, has developed iDea, an eIMCI programme that has been piloted and is being scaled up in Burkina Faso. The software, developed using Dimagi's CommCare, aims to drastically improve compliance with national guidelines at the primary level and to support health systems in becoming more data driven and performance oriented. It appears to be the most widely implemented electronic decision support systems for the primary level, with 1795 nurses in 272 heath centres covered, representing 10–15% of Burkina Faso's health system and approximately 1 million consultations. To date, acceptance is high, and even remote facilities have been able to find solutions to tablet care and charging. The London School of Hygiene and Tropical Medicine is currently conducting an evaluation expected to show high utilization rates but mixed results in terms of outcomes. Originally funded by BMGF (through 2017), the government is seeking additional resources for further scale-up and institutionalization of the system. The Global Fund is also supporting some aspects of the scale-up, although additional resources are required.

THINKMD is a United States benefit corporation, founded in 2014 by two paediatricians from the University of Vermont. It has developed MEDSINC, a mobile application that walks minimally skilled health workers through a 35-point assessment, patient history and physical exam. Using Bayesian analysis to better combine the data points and mimic an expert clinician, the app supports assessment of illness severity and provides evidence-based triage and treatment recommendations that are in line with WHO IMCI and iCCM. The app has a programme whereby health workers tap the screen to record heart rate and respiratory rate, and it can be customized to accommodate additional data points (e.g. from pulse oximeters, RDTs). Data from each patient encounter are captured and can be pushed to a data aggregation and analysis system that enables clinical outcome analysis, surveillance, population health and predictive disease modelling as well as monitoring and evaluation of health workers. It has been evaluated in the field by partners showing >85–90% agreement between CHWs and expert physicians (unpublished data).

Academics at Swiss Tropical and Public Health Institute have been developing medical content and advising other groups on the medical aspects of decision support software. They have created two electronic decisions support systems. ALMANACH was developed first using a set of open-source software from Open Data Kit and Open MRS to run on Android mobile devices (smartphones and tablets). It is very similar to IMCI with a few modifications and additional RDTs *(100)*. It has been evaluated, with a few publications *(101) (41)* showing increased rates of checking danger signs, decreased antibiotic prescribing, but low agreement between health workers and experts on pneumonia classification.

[50] Note: the information on electronic decision support systems draws primarily from publically available sources and was not consistently verified with the developers.

One limitation of IMCI and ALMANACH is the continued reliance on a subjective, challenging clinical assessment skill (i.e. counting respiratory rate as the primary criteria for pneumonia). A second system, ePOCT, relies on additional, more objective measurements that are generated through devices and diagnostics, including: mRDT; haemoglobin; oximeter; glucometer for all patients; and CRP, PCT and glucometer for selected subgroups. By incorporating POC tests, ePOCT aims to improve both the identification of children with severe infections and children in need of antibiotic treatment. ePOCT performed well in an initial non-inferiority study in the United Republic of Tanzania, effectively identifying children with severe disease and reducing antibiotic treatment for lower respiratory tract infections (publication forthcoming). In the study, there was a shift in antibiotic prescribing towards children with severe disease and away from children with non-severe respiratory infections that are likely viral in origin due to the use of PCT and CRP tests in suspected bacterial pneumonia cases. ePOCT has not been validated as extensively as ALMANACH, and further implementation studies are needed. For both ALMANACH and ePOCT, Swiss Tropical Health develops the initial programme, evaluates it and then licenses it for free, playing a limited role (e.g. technical advisor) in its deployment.

The Center for International Child Health at the BC Children's Hospital and the University of British Columbia are also developing electronic decision support systems. They have already developed an app to improve post-discharge outcomes for children and one for screening for preeclampsia, incorporating pulse oximetry. For fever, they are developing PICNIC (Platform for Identification of Critically Ill Neonates, Infants, and Children), an app that guides health workers seeing children through the assessment and integrates pulse oximetry sensors as well as heart rate and respiratory rate. This is combined with a prediction algorithm to make triage, diagnosis, referral and management recommendations. Using predictive analytics, PICNIC aims to provide recommendations that are driven by validated clinical data and are more sophisticated than what can be done using paper-based classification charts such as IMCI. The group has funding from Google.org to complete technology development and is seeking funding for a feasibility trial in African health facilities.

D-Tree international is a nongovernmental organization that supports use of eIMCI and eiCCM apps that are tailored to countries. It has implemented such an app, an mHealth app called Mangologic, in several districts in Malawi (375 CHW as of February 2016). It charges a base fee for pre-built mobile apps and dashboards, training of staff to manage and maintain the system, and server infrastructure and support based on the number of users. After the first year, the cost is on a per-user basis, declining with larger numbers of users (e.g. >500).

Dimagi is a United States public benefit corporation developing open-source software solutions for low-resource settings. In the area of mHealth, it developed CommCare, (now part of the MOTECH suite) a mobile platform for collecting data that can be customized to provide electronic decision support. The system comprises apps that health workers use to collect data and assess and manage patients. Additionally, a web application allows programmes to create and deploy the app and analyse returned data. While CommCare supports the front end, the MOTECH suite is focused on the backend (e.g. data storage, analytics) and is a platform that countries can adopt to support multiple, integrated m-health programmes at scale. Dimagi provides implementation services and mhealth programmes as well as software as a service.

The Malaria Consortium has used CommCare to develop mobile apps, called inScale, to support motivation, reporting and supervision of CHWs in Mozambique and Uganda. The phone application serves as a job aid for CHWs by walking them through each step of a patient consultation. It also includes a respiratory rate timer and aid to assist with counting breaths. The collected data are sent to a server over the 3Gnetwork, with weekly summary reports to the supervisors. The programme also supports a closed phone network whereby the CHWs can freely call supervisors.

Medic Mobile is a United States non-profit organization that designs, delivers and supports open-source software for health workers and health systems. Among the decision support systems that it has developed is software for ICCM that guides the health worker through the assessment, diagnosis and management of the sick child. The programme is meant to be integrated and can be combined with a suite of other tools, such as software for antenatal and postnatal care, immunizations, nutrition, outbreak surveillance and health worker performance management. It includes follow-up visit reminders for the health worker. The system runs on Android phones, and web-based analytics are available to managers.

MSF has developed MSFeCARE, an app to improve management of fever and acute illness in children under-five at the primary level in order to address rational use of antimicrobials and high childhood mortality. Drawing on a review of available evidence and guidelines, MSF developed best practices to safely assess, classify and treat acutely ill children in MSF primary care contexts. These were translated into an integrated set of unambiguous clinical pathways, available as an app, running on an Android tablet. In December 2016, MSFeCARE was deployed in three health centres supported by MSF in the Central African Republic. From February 2017 onwards, more than 80% of the under-five consultations were done with MSFeCARE in the three Health centres. MSFeCARE was well received by nurses and their supervisors, who felt that it had improved nurses' clinical assessment skills and helped them to apply knowledge they had received in former training, but that had not yet been translated in their consultation practice. Reported antibiotic prescription rates decreased (50% before to less than 20% after MSFeCARE introduction). Additional deployments are planned to take place in several African MSF sites.

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Unitaid Secretariat

Chemin de Blandonnet 10
BIBC III – 8th Floor
1214 Vernier
Switzerland

T +41 22 791 12 00
F +41 22 791 48 90
unitaid@who.int

www.unitaid.org

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In case of queries, write to Unitaid-communications@who.int

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