

# Biomarkers for acute febrile illness at the point-of-care in low-resource settings

Technical working session  
Meeting pre-reads

Hosted by Unitaid and FIND  
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# Introduction

Fever is the single most common infection symptom, whether bacterial, viral, fungal, or parasitic. It is also one of the most common presenting symptoms at clinics in low- and middle-income countries (LMICs). Biomarker-based assays that can accurately and reliably support the diagnosis of febrile illness at lower levels of care could therefore play an integral role in reducing mortality, improving health outcomes, and delaying the emergence of antimicrobial resistance (AMR).

Unitaid and FIND hosted a technical working session aiming to:

- Refresh the understanding of the public health needs, challenges, and use cases driving the development and introduction of new diagnostics for acute febrile illness (AFI)
- Gather thoughts and build consensus on priority use cases for biomarker-based diagnostics and near- and longer-term opportunities for product development, evaluation, and introduction. Near-term opportunities could include advancing late-stage diagnostic tests, such as through targeted research or market-based interventions to accelerate emerging products. Longer-term opportunities may focus on addressing unmet needs and gaps with new product development, including revisiting target product profile (TPP) criteria to align on priority characteristics and adjust expectations based on new knowledge

The following set of pre-reads were developed to support the meeting, covering the product pipeline and biomarker research progress, market challenges, and the results of focus group (FG) discussions with key stakeholders. A meeting report was also developed and is available on [FIND](#) and [Unitaid](#)'s websites.

# PRE-READ 1:

Centering the needs  
of health care  
providers diagnosing  
and managing acute  
febrile illness – Focus  
Group report

## BACKGROUND

# Focus group

### Focus group discussion objectives

At a high level, the many challenges diagnosing and managing acute febrile illness (AFI) are known and understood. However, in order to advance the agenda, in particular around diagnostics, a deeper understanding of contextual differences (e.g. by patient, provider, setting) and the relative prioritization of issues and solutions is beneficial. Additionally, we sought to appreciate how COVID-19 is impacting AFI in low-resource settings.

Through the focus group (FG) discussions, we aimed to understand and prioritize the challenges facing health care workers seeing patients with AFI in greater detail, in order to appreciate the need for new diagnostic technologies and other interventions in resource-limited settings. Despite five years of progress towards new diagnostics for fever, significant gaps in the pipeline remain. However, there are existing tools that could be deployed and have the potential to make a difference in carefully defined use cases and populations.

The FG results serve to enhance and refine our understanding of the potential uses cases that new innovations (e.g. diagnostic tests, devices, and clinical decision support apps) and programmatic interventions might address.

### Our process

#### Pre-reads

- **FGD:** use case understanding; current intervention priorities
- Tech landscape
- Market backdrop

#### Technical working session

##### Near term agenda:

- Are there innovations that could be implemented now?

##### Long term:

- What are the R&D priorities?

# METHODOLOGY

## METHODOLOGY

# Recruitment

### **Targeted three participants groups**

- Targeted three participants groups (providers, policymakers, and researchers) across four geographies: (1) Asia, (2) Latin America, (3) East Africa and (4) West Africa

### **Multi-pronged recruitment process:**

- Targeted emails to individuals at ministries of health and national malaria control programs, mainly drawing on FIND and Unitaid stakeholder networks
- Referral requests from researchers and implementers in FIND's and Unitaid's network
- Targeted social media campaigns via Twitter, LinkedIn and Facebook. Interested participants completed a survey and were subsequently selected based on their focus areas, country of expertise and availability

### **Focus groups were split by geographical regions and grouped into:**

- Providers (e.g. clinical officers, medical doctors, nurses)
- Policymakers (e.g. Ministry of Health, NMCP)
- Local researchers (e.g. locally based researchers).

**Recruitment was carried out in English, French, and Spanish**

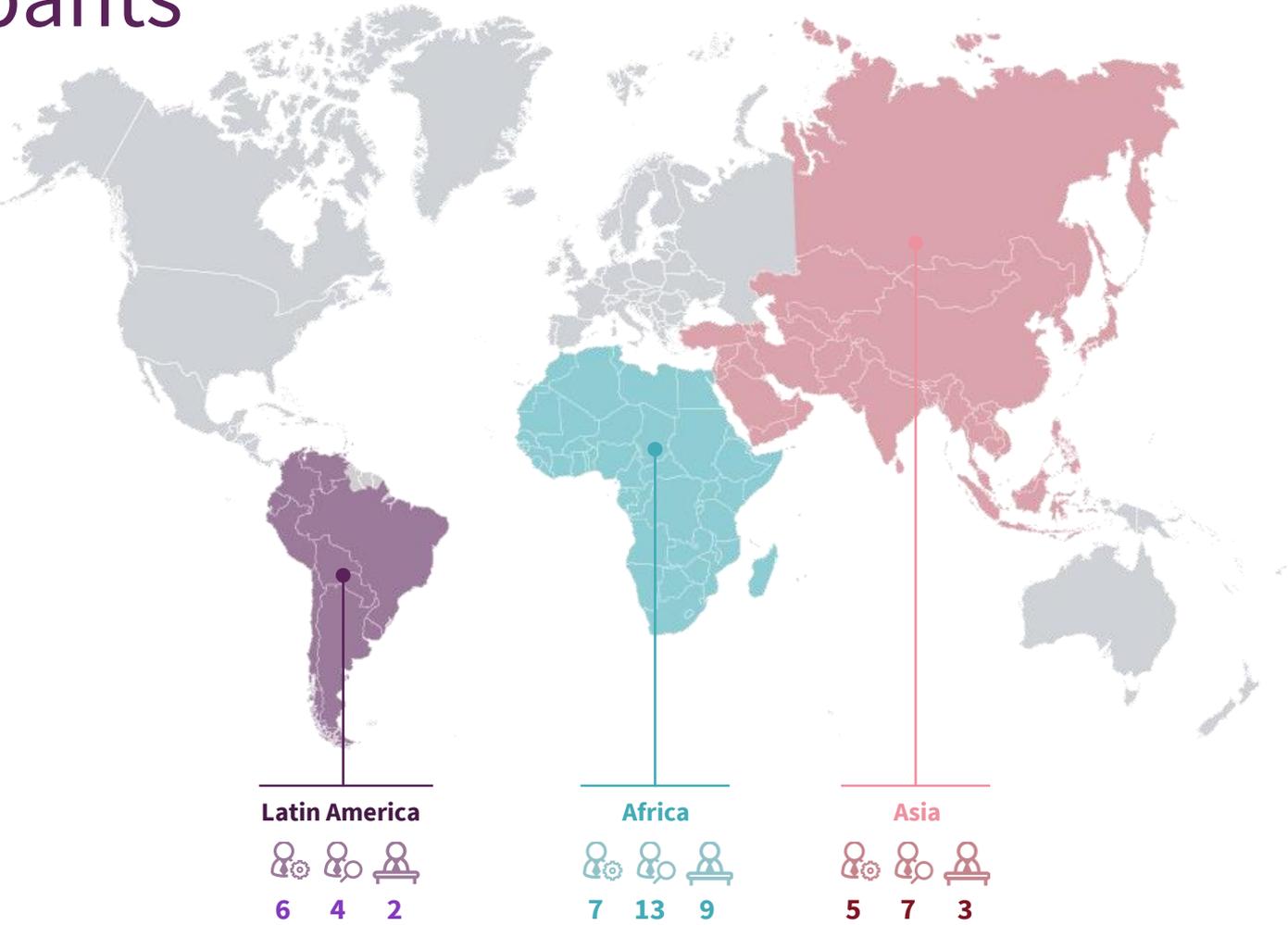
**No compensation was provided for participation in the focus groups**

## METHODOLOGY

# Participants

### Infographic map:

-  Providers
-  Researchers
-  Policymakers



## METHODOLOGY

# Focus group discussion content and scope

### Focus group questions focused on:

- Identifying and prioritizing the challenges affecting frontline health workers triaging and diagnosing acute febrile illness (AFI)
- Prioritizing interventions to improve AFI
- Use of host response biomarkers for differentiating bacterial and non-bacterial infections
- Use of host-response biomarkers for identifying impending severity or risk

### Data collection – Scope

As fever is a broad area, we considered only patients presenting with acute febrile illness (i.e. not chronic fever or conditions).

- The acute fever may be measured when the patient presents, or it can be a recent history of fever
- The fever can be with or without other symptoms, but, generally not a localized infection
- We focused on both adults and children, but not newborns or very young children (e.g. <2 months)
- We focused on front-line providers managing AFI at the community level, at primary care facilities, as well as in the outpatient or emergency department (OPD/ ED) of hospitals, primarily in the public sector
- We did not focus on inpatients

## METHODOLOGY

# Data collection – Process and analysis

- Focus group discussions were conducted on Zoom in three languages and each lasted ~1.5 hours
  - English for Asia and East Africa (all groups) as well as researchers from Latin America
  - French for policymakers, researchers and providers from West Africa
  - Spanish for providers and policymakers from Latin America
- Structured interview guides were used by all facilitators and the same guides and slides were used in all focus groups
- Focus group discussions were audio recorded for note taking purposes, after collecting verbal consent from all participants. Notes were taken by the same facilitator for all groups conducted in English and French
- Collation of results and semi-quantitative assessments were performed by one person for consistency and all facilitators reviewed and revised key findings

# **FGD FINDINGS**

Health care worker challenges  
managing acute febrile illness

## CHALLENGES

# Challenges

We asked about challenges that healthcare workers (HCW) face when seeing patients with AFI.

We asked them to be specific about whether the challenges were universal or applied only in specific situations (e.g. certain provider types, levels of care, population groups).

We also asked the FGs to prioritize these challenges.

## HEALTH WORKER CHALLENGES

# Lack of training and skills – High Priority

Insufficient skill and training among HCW, particularly at the lower levels of the health system, results in limited capacity to diagnose fever beyond malaria. **This challenge was consistently mentioned across all regions.**

### Low awareness of local epidemiology contributes to misdiagnosis

- Particularly mentioned for health care workers at lower levels, but also a challenge for any providers in areas where data on local epidemiology is lacking

### Lack of training includes not only pre-service / in-service training but also other learning opportunities such as:

- Mentorship
- Consultation with senior doctors or specialists
- Training on management of health facilities
- Feedback on patient outcomes following referral, allowing opportunity to learn the cause and treatment

*“It is very important that the health workers know the different diagnostics and what could be the primary underlying conditions of febrile illness; to know symptoms of malaria, pneumonia, measles, ear pain, any kind of diseases with different symptoms.” (Provider, Africa)*

*“Competency of health professionals is a big challenge for diagnosing fever and making decisions to keep or refer a patient and to start antibiotics or not. We can address this in two ways: standardize clinical guides and they can refer; guidelines can be uploaded to tablets and training of health professional... You give them a guideline and you train them on that.” (Policymaker, Africa)*

## HEALTH WORKER CHALLENGES

# Guidelines: many are inadequate, and poorly adhered to in some settings – High Priority

### Inadequacy

#### Weaknesses with the current guidelines and algorithms:

- IMCI and IMNCI guidelines are outdated (e.g. prior to rollout of many vaccines) and have a bias towards malaria. The lacking utility contributes to poor adherence
- Most guidelines do not focus on adults

#### Incorporating regional epidemiological differences

- Adds a level of difficulty to draft algorithms and flow charts
- Prioritizes diseases that come and go

#### There is an ambiguity when applying algorithms beyond detecting and treating malaria. What defines “fever”: “reported history of fever”? current fever? actual temperature recordings?

- Fever means different things in different languages
- What is an actionable temperature?
- How has fever been measured? How was it described by the patient? Availability of tools?

*“We are seeing patient repeatedly coming with fever, treated over and over for malaria month after month, being repeatedly treated the same way, without considering other diseases. Did this algorithm fail, or is it the response to treatment? This is not working; the algorithm needs to go further. (Policymaker, Africa)*

*“Patients are never treated according to the guidelines: HCWs do not have time to refer, they are busy. In rural areas, they refer up to 50 patients in the day. The guidelines are not built to be practically used. Many HCWs do clinical examination and then do ATBs.” (Provider, Asia)*

## HEALTH WORKER CHALLENGES

# Guidelines: many are inadequate, and poorly adhered to in some settings – High Priority

*“People usually don't follow guidelines; so it doesn't go to the end user. People are using their experience and what they learned in school-days; in-service and pre-service training in the schools training HCW. This is where people learn; not from the guidelines.” (Provider, Africa)*

### **Lack of knowledge of and adherence to guidelines**

- Lack of training on guidelines and mentorship leads to under-use of guidelines
- Over reliance on clinical judgement leads to under-use of guidelines
- Health leadership at facility sets the tone for providers, affecting whether guidelines are used or implemented and if continuous trainings on guidelines takes place

### **Need for an integrated approach**

- The integrated nature and provider-centered focus of some guidelines are appreciated
- Where disease-specific algorithms are used (e.g. those that guide outpatient and admission of dengue), one assumes that the provider first identifies the disease correctly

## HEALTH WORKER CHALLENGES

# Lack of diagnostic tests, medicines, and equipment – High Priority

### Stock outs and supply chain challenges cause deviation from guidelines

- Lack of necessary products, including:
  - Diagnostic tests or reagents
  - Essential medicines
  - Devices for measuring vitals
- Raised particularly in Africa, and also in Asia

*“At lower level, public health facilities need to have tools like thermometers, respiratory rate timers, essential drugs, stop watches, pulse oximeters to see oxygen concentration.”(Provider, Africa)*

### Laboratory systems and policy challenge differential diagnosis and management of AFI

- Where testing is possible, limited testing infrastructure and staff capacity leads to delayed test results, and loss to follow up
- POC tests for relevant diseases are not available below hospital level (Asia, LATAM)
- In some district hospitals, only RDTs are available, basic tests beyond RDTs are unavailable (Africa, Asia)

*“We don't have the equipment to do many tests, very few places at primary level have the capacity to do throat swab/strep, urine or blood culture. Sometimes even secondary level care, hospitals don't have the possibility to do full blood count, so you get referred to a hospital that doesn't have the diagnostic tools.” (Researcher, Africa)*

## REFERRAL

# Over-referral and under-referral are challenging

## Low health worker competency at community and primary level to identify severe illness and refer appropriately

### OVER-REFERRAL

- “Better safe than sorry” attitude; sometimes the provider lacks confidence in their ability to treat a patient should they progress and require a service or intervention that is not available locally
- Pressure from patients who insist on seeing a medical doctor, would like to go to a higher level of care, or lack trust in the health care worker

**Under-referral was considered a greater issue than over-referral.**

### UNDER-REFERRAL

- Health workers at lower levels, in particular, lack sufficient skill and training to detect signs of severe disease
- Lack of diagnostic tools to inform referral
- Difficulty with transportation, logistics of arranging the referral, especially in rural / remote areas
- Provider is cognizant of the financial burden of referral on the patient or assumes patient will not comply
- Patients or caregiver refuses referral, due to:
  - Financial burden
  - Other priorities like care for other children

## REFERRAL

# Referral issues vary

### Africa

*"I rarely see a patient at the tertiary hospital where the patient should have been referred."* (Policymaker, Africa)

*"If there are no malaria danger signs (coma, low level of consciousness), patients, especially adults, are usually treated as an outpatient. Coma is the main sign for referral."* (Policymaker, Africa)

*"We are seeing mid-level nurses, health officers [...] the problem is they lack full confidence to make a decision to keep the kids for 1 day or adults for 1-2 days to see what is going on, rather [they] prefer to push to the next level..."* (Policymaker, Africa)

*"At lower levels, it is important to have efficient referral systems. Even when you recognize symptoms at community level it is difficult to get people to another level due to issues such as transportation."* (Policymaker, Africa)

### Asia

*"Referral is a massive problem, sometimes the community health workers refer a patient to a health center. Then, the patient needs to travel 4-5 hours, which in the rainy season proves to be very difficult."* (Provider, Asia)

*"Referral systems are easy in India; there is a huge network of ambulances that can pick up from villages, on door-step."* (Provider, Asia)

*"In rural areas, even if doctors are present, it's easier for them to refer a patient if their [the patient's] socio-economic status allows them to."* (Provider, Asia)

### Latin America

*"In rural areas referring a patient means having an ambulance which solves many other logistical constraints... What impacts most of the decision [to refer] is the clinical assessment done by the healthcare provider including the clinical history of the patient, the signs/symptoms, and measurement of vital signs. In a hospital, there is access to clinical testing, such as CRP or hemogram and it is easier to know if it is necessary or not to admit a patient."* (Policymaker, LATAM)

*"In a rural area it is very difficult to be referred to a hospital (far from cities). In the urban area, it is easy to get referred because there are economic incentives for the doctors who refer patients and for the doctors that admit them."* (Policymaker, LATAM)

## THINKING BEYOND MALARIA

# Malaria and outbreaks dominate thinking and limit recognition of other potential causes

In highly malaria endemic areas, the focus on malaria at all levels (all cadres, even doctors), derails health care workers and inhibits them from considering other causes of fever.

- Similarly, a local epidemic or seasonal upticks in malaria will affect diagnosis patterns. Health care workers tend to consider only the epidemic happening at the time, focusing only on those specific diseases, overlooking other potential causes, either due to workloads or to lack of awareness and skill
- Conversely, some healthcare providers are not aware of epidemiological differences across a single country and may misdiagnose a patient

Lack of Dx tools for many specific diseases at POC was raised in Latin America and Asia in particular.

*“In the primary level there are a lot of limitations in terms of diagnostic tests, for instance there are no diagnostic tests for dengue, and there are areas with other infectious diseases, such as salmonellosis, for which the diagnosis is clinical.” (Provider, LATAM)*

*“Malaria is endemic in Brazil but not in Rio, therefore diagnostic is not done in a timely manner because doctors are not aware. They do not ask for the right test.” (Provider, LATAM)*

*“Clinicians rely on what they know and observe. A fever is synonymous with malaria, first thing they need to rule out is malaria. Not malaria, not falling into any other clear case group.” (Researcher, Africa)*

*“We have policies in terms of malaria. Everybody who comes with a history of fever, will take malaria RDTs. It depends on season, but also on the area. In some areas with a lot of malaria, HCWs can test more than 150 people/day for malaria and more than 130 will have be positive.” (Provider, Africa)*

## ANTIBIOTIC USE

# Antibiotic misuse – High Priority

### Over-use

- Antibiotic overuse is a huge concern, and the use of antibiotics is a challenge across all levels of the system. Providers, policymakers, and researchers expressed concern about overuse
- “In my [SE Asian] country, 80% of patients are given antibiotics” (Provider, Asia)

### This issue was particularly highlighted in Africa, SEA, and LATAM.

- Availability of antibiotics through shops, pharmacies (OTC) is a major concern
- In Latin America, particularly in public settings, there are stricter rules for antibiotic prescription

### Lack of diagnostics in rural environment leads to over prescription

- Prescription made on clinical assessment rather than diagnostic tests

*“If you work in settings with malaria, we have RDTs and microscopy, but then if they test negative for malaria, then the biggest question is should I give antibiotics or not. That's across the system, right from lower level to advanced.”*  
(Researcher, Africa)

*“We are probably in an [AMR] pandemic we just haven't measured it.”* (Policymaker, Africa)

*“The more we can minimize use of antibiotics, or use them properly, we are on the winning side because we are getting worried.”*  
(Policymaker, Africa)

*“The only test that we do for febrile illness is malaria, then you are stuck, if it is not malaria then you don't know what it is, we need rapid test that can give you the information if is a bacteria or a virus if it is not malaria.”* (Provider, Africa)

## ANTIBIOTIC USE

# Antibiotic misuse – High Priority

*“Patients start using the antibiotics on their own and stop when they think that it is relevant. When they don't have enough money, patients buy antibiotics only for two days and that is a recipe for resistance.” (Policymaker, Africa)*

### Under-use / Lack of access

- Under-use usually results from lack of availability of the right type of antibiotics
- Patients can be underdosed due to economic factors when purchasing antibiotics on their own

FGs expressed concerns around these shorter treatment courses and inappropriate choice of antibiotics leading to increased resistance.

**Underuse of antibiotics was not mentioned as much by FG participants.**

We did not hear concerns about undertreatment with antibiotics resulting from misclassification of pneumonia using IMCI

## PATIENT-CENTERED CHALLENGES

# Patient-centered challenges – Mid Priority

### Socio-economic challenges

- Late presentation from home remains an issue due to family burden, financial pressure
- The patient's socio-economic situation influences the provider's decision making, a patient's ability to pay (e.g. for a test and treatment) or their ability to return to the clinic
- These factors may cause a HCW to knowingly deviate from the guidelines. Healthcare providers need to balance diagnostic tests and prescription due to patient's financial means, leading to empiric treatment decisions. This was particularly described in West Africa
- Higher socio-economic status of patients plays a role in their capacity to be referred, particularly in Asia

*“60-70% deaths happen at home in some parts of Malawi, so late presentation.”*  
(Researcher, Africa)

### Patient's expectations and credibility towards healthcare providers

- There is a culture of antibiotic use, patients expect to receive antibiotics
- Leads to prescribing malaria treatment even when mRDT is negative
- Health workers find it difficult to manage patient / caregiver expectations, especially pressures to provide antibiotics
- Patients can sometimes exacerbate symptoms to ensure prescription of antibiotics

**Sometimes due to ignorance and lack of education of patients, care takers have difficulty agreeing to the recommended treatment for a child.**

## HEALTH SYSTEM CHALLENGES

# Health system specific challenges – High Priority

**HCWs acknowledge that when workloads are high, especially at the lower levels, they rush and may miss something important or misdiagnose**

- This issue is specifically observed during epidemics and/or wet season

**Supply chain and availability of medicines, tests, equipment continues to hinder management**

- Healthcare workers are frustrated and angry because they know what to do, but the equipment to carry it out is not available
- This is an issue across all settings as well as levels of care

**There is a lack of qualified technicians to perform tests**

**Sustainability of interventions (beyond pilots) is difficult to ensure**

- No sustainable funding for laboratory equipment outside of vertical silos (Asia/Africa++)

*“Seeing 200 patients per day is quite hectic; 400 in wet season is another thing altogether. We work against time all the time. When you see a lot of patients, it is possible to miss something taking the history, exploring them, its possible to miss something due to workload.” (Provider, Africa)*

## COVID-19

# COVID-19 specific challenges

### Patients under-used health care facilities

- Patients preferred to stay at home at the beginning of the pandemic
- Growing stigma around the disease caused fear of being diagnosed with COVID-19, reducing care-seeking

*“Everything has been put off. Patients are not welcoming healthcare workers into their home. They are scared.”*  
(Policymakers, Asia)

### Rise in malaria in some regions due to interruption or slow-down of interventions such as net distributions

### Providers started to associate every fever with COVID-19, but overuse of antibiotics remains

- When available, all patients were given a COVID-19 test, upon negative results, patient were given antibiotics

# **FGD FINDINGS**

Interventions for improving the management of fever

## INTERVENTION PRIORITIES

# Approaches to improving AFI diagnosis and management

Patient education	Digital clinical algorithms (IMCI) on tablets	Point of care tests for to guide antibiotic prescribing
<i>POC hematology tests (WBC, hb)</i>	Point of care tests to support triage, identify severity / risk	Devices for monitoring vital signs: respiratory rate, pulse oximeter, thermometer, heart rate, other
Training health workers	Updated clinical guidelines	Epidemiological data on cause of fever locally

We presented the FGs with a list of potential approaches to improving AFI and asked that they first add to the list and then to prioritize their top 2-3.

Key

Added by FGD

Our suggestions

## INTERVENTION PRIORITIES

# Top three priorities

### 1. Training, especially at the lowest levels (primary and community)

- Leverage digital tools to support training
- Importance of mentorship, supportive supervision
- Increasing health worker awareness of the local epidemiology (and regional if patients travel frequently) is important especially in Latin America and Asia, and in Africa, knowing for example the percentage of fevers caused by malaria

### 2. Devices measuring vital signs

- Ensure vital signs measurements are actionable with clear guidelines
- Vitals are important for severity triage in adults
- Need to synergize any new devices with existing devices and resources

### 3. POC Host response biomarker tests

- Respondents were enthusiastic about host response biomarker tests. There was more interest in the bacterial vs. non-bacterial test compared to a test assessing severity
- Many felt that a simple POC bacterial/non-bacterial would be the most impactful and useful at all levels of the health system

*“I don't know if this is on the market, can we have one that says bacterial or not bacterial? That's where we are going wrong. For us to know if its viral or bacterial.” (Provider, Africa)*

*“We do [Pulse oximetry] on those with respiratory distress. Here is how we decide what to do:*

- *If oxygen saturation is ok, then we know [the patient] doesn't have chest infection; we do not bother to give them antibiotics*
- *If oxygen saturation is low, we prescribe antibiotics*
- *If oxygen is too low, we refer them to the hospital. We have had some kids and we sent them and they got oxygen and survived. So the pulse oximeter is very important.” (Provider, Africa)*

## INTERVENTION PRIORITIES

# Additional high-priority interventions

### Updating guidelines was a top priority.

- Adapt guidelines to local clinical settings, reflecting the **current epidemiological data**
- Integrated approaches are important, especially for primary care. In countries where disease specific algorithms are common, providers can struggle to decide which algorithm to apply
- Algorithms must be validated to be trusted by providers

*“Relevant guidelines is a priority. Investing in guidelines that are relevant in the context (epidemiology and etiology of febrile illness in the area) makes them useful and relevant to the clinicians. Then training the clinician on how to use it.” (Researcher, Africa)*

*“Improve IMCI, not replace it.”  
(Provider/researcher,  
Asia)*

### Yet, opinions on digital clinical guidelines are mixed.

- Some countries are already piloting and others are enthusiastic, considering digital clinical supports as “all encompassing” for providing guidelines, capturing data, and advising on patient communications / education
- Others raise implementation and feasibility concerns, with some noting they are more feasible at higher level facilities than at the primary and community level

*“I am not putting money on algorithms / tablets, not yet. Do the guidelines first; putting guidelines on tablet won't make them more accessible to the clinicians.” (Researcher, Africa)*

*“If we can update our clinical guidelines and put them on a digital platform, this will be very beautiful. Avoid printing; you can also update certain sections only. I'm thinking, emergency and critical care systems, from health surveillance assistants to the highest level. Digital clinical guidelines that integrate with other guidelines would be quite interesting.” (Policymaker, Africa)*

## INTERVENTION PRIORITIES

# Additional priorities

- Point of care tests to support triage, identify severity / risk are seen as important for the lowest level
- In Asia and Latin America, additional POC (rapid, simple) diagnostic capacity, including disease specific tests, are priorities. This was not mentioned frequently by African FGs
- Several FGs raised the importance of patient focused interventions: education and sensitization on health issues, ranging from “normal hospital and community talks” to reminders to bring children for care when they have fever. Education on the use of antibiotics is another priority
- Related to training / learning as well as the levels of care, several groups raised the importance of feedback loops between providers at primary and referral facilities to learn from how the patient was managed. Additionally, FGs suggested that lower levels have remote access to senior physicians or specialists

*“We need a combined approach of POC tests, triage tests, and training of HCWs.” (Provider, Asia)*

*“First we **need to understand our epidemiology** that is the starting point how many malaria cases are there, how many dengue, RSV... Once that data is solidified, **then we need better packaging of what we have, including algorithms** that speak to our epidemiology, look at positive predictive values.... **For that I think the tools that are there are good enough, they give us a reasonable approach. The CRPs, the PCTs, which would speak to the epidemiology because [we] need a picture to speak to. Then after that, more and more training and mentorship to the lower levels.**” (Policymaker, Africa)*

## INTERVENTION PRIORITIES

# Prioritization considerations

Given the difficulty of prioritizing among many potentially beneficial and complementary interventions, several FGs discussed the topic of how to prioritize, outlining several considerations:

- The importance of considering the context closely was stressed, different levels of the health system need different solutions; as do different cadres of health workers
- The additional data or information provided to the HCW must be actionable taking into consideration their scope of practice and the context (e.g. the availability of medicines, services, and referrals)
- Several FGs highlighted the need for integrated and holistic approaches, especially at primary care level. Bundles of interventions were proposed, for example a system supporting emergency and care could include a digital algorithm, devices for measuring vitals, and POC tests

*“While searching for improved diagnostics and specific tests we should think around available tests [that could] be used in different case scenarios...multiple tests are available while some may take some time to come; how best to use what we already have.”*  
(Provider/Researcher, Asia)

*“Primary care clinicians are likely to accept tools that are not just acute fever, but everything that they might see.”*  
(Provider/researcher, Africa)

*“What is the decision that is going to be done? Will it make a difference, especially in remote conditions? What are the available options: medicines, services, facility, capacity of the care provider.”* (Policymaker, Africa)

*“I am trying to run away from focusing on one thing (e.g. fever alone) we need to put a bundle of interventions together. Once we have it, then push it. Way we have been doing it in past, we have been leaving the system weak.”*  
(Research/Policymaker Africa)

*“Understanding our situation, our epi is important. Tailor interventions to the various levels. We have health workers in the community, not so sophisticated the interventions that they can do. As we move to primary/secondary level, the sophistication gets better. So if we understand the epi, the levels and the various investigations available to us, then we can tailor to that.”* (Policymaker, Africa)

## INTERVENTION PRIORITIES

# Optimizing implementation and considering systems

### **Because AFI is a cross cutting disease, some FGs suggested potential entry points for fever interventions:**

- Jointly managed between malaria and child health programs
- Based in emergency/critical care, linked with ETAT and triage
- A priority focus within Primary Health Care

### **FGs also emphasized several means of sustaining improvements through:**

- Supply chain strengthening
- Instilling at the facilities a culture of continuous improvement, including monitoring, reporting, measuring progress against the “gaps,” at the facility level
- Critical while designing the interventions to keep human management in mind. In particular FGs noted that weak leadership can affect care throughout the facility, including poor use of guidelines; poor triage; and excessive workloads

# **FGD FINDINGS**

Host response biomarker test

## POC HOST RESPONSE BIOMARKER TESTS

# Enthusiasm for bacterial vs. non-bacterial test

### **There was a great deal of enthusiasm for POC tests to support antibiotic treatment decisions, across all countries.**

Use scenarios for these tests included all levels, however, FGs pointed out the differing contexts for use, and the associated needs.

**At the district hospital level, outpatient/emergency departments, there is more capacity among staff for clinical reasoning and differential diagnosis.**

- District hospitals do not always have access to lab tests beyond RDTs
- Where lab capacity is good, and providers are skilled, a scenario may include using results from a HRB test to inform what additional investigations to make
- At highest levels, the HRB test for bacterial/non-bacterial may also give an indication of severity (e.g. PCT, CRP)
- Quantitative tests may be acceptable at this level
- Consider the training and “packaging” that goes with the test to sensitize HCWs to the limitations and how to use it, and interpret it

**At the primary level and/or with lower skilled health workers, performance akin to a mRDT is needed, with a simple yes / no answer.**

*“What is frustrating for people on the ground is that we are training them without the tools. For example, I should be rational in my antibiotics, but I don't have a CRP POC test. When we training people it should be hand and hand with giving them the tools. At the core of every health worker is keeping the patient alive. They choose between abusing an antibiotic and waiting for these things to come from the lab which takes ages.”*  
(Policymaker, Africa)

*“Top on the list is having something to guide antibiotic prescribing. Even in regions with high prevalence of malaria, people need to know when to mix antimalarials and antibiotics. We know AMR may be the next pandemic. We think about how much patients spend, how much institutions spend on antibiotics, increased duration of admission, and deaths, complications due to misuse of antibiotics. Every patient [with fever] going to a drug shop at a community, a lot of time they will leave with an antibiotic.”* (Researcher, Africa)

## POC HOST RESPONSE BIOMARKER TESTS

# To start, perfect performance is not required for a bacterial vs non bacterial test

For a bacterial vs non-bacterial test, FGs suggested that higher skilled cadres could begin using tests that do not perform as well as TPP requirements.

Many FG participants referred to 'imperfect' tests, CRP, PCT, WBC and suggested these could be used today, with the correct training and packaging. For lower skilled providers, performance and simplicity, akin to a malaria RDT, are needed.

***“[My hospital has added PCT] and it has helped. If the test classifies correctly 80% of the patients it would be useful, even tests with lower performance would still be useful.”***  
(Provider, LATAM)

***“Something is better than nothing, it is improving. Need to look at the gaps of what is left with sensitivity and specificity; and address these [through other means - algorithms, training, etc.]”***  
(Provider, Africa)

***“CRP seems to be a good answer for viral and bacterial infection currently.”***  
(Policymaker, Asia)

*I don't know how well CRP and PCT [perform], the evidence isn't that great, **but...do we need to wait for better studies, better evidence?** Or can we just do what we have?*

***I think there is a way that what is there can still be used if we can simplify it enough, and obviously accept that the recommendation might not be that strong.*** It should be accepted that the evidence is not that good. But we can't say that the misuse of antibiotics can go on. *“CRP not high don't give [antibiotics]” something like that. ....that is how public health works, some lose and some win. I wouldn't place the bar very high, because I don't think in the foreseeable tools we will have anything that great. **Its packaging the tools we have and accepting their limitations.***

*.... Concerning what's the sensitivity, I don't think it needs to be very very high. [For] example, Covid tests, even PCR is 60-70% sensitive and its well accepted, and anything with that is ok. Specificity can even be lower. But, it doesn't have to be a “super test” it's how the test is presented, it should not be complicated. It needs to be Yes or no answer and it can be improved upon over time as we get better tests. For me I think sensitivity of 60-70% is good enough.”*  
(Policymaker, Africa)

## POC HOST RESPONSE BIOMARKER TESTS

# Yet, bacterial vs. non-bacterial test must be simple and quick

- Malaria RDTs are often referred to as an example of ease-of-use, speed, and simplicity in a POCT test

*“Something with a performance similar to the malaria rapid test would be very helpful.” (Policymaker, Africa)*

*“Need rapid test that can give you—is it a bacteria or a virus?... After triaging, then you do a rapid test; you treat the right thing... How can we help the health workers to make relatively fast and accurate [diagnosis] –it cannot be 100%; less than 10% wrong is okay.” (Provider, Africa)*

*“The challenge is to have rapid tests that can say if something is viral or bacterial. This is where we are going wrong, and a rapid test would be very useful.” (Provider, Africa)*

- Simple presentation which can be widely used at primary health care or community health care level

*“We really need to come up with a POC test that should help clinicians at all levels. The majority of people in the countries such as Kenya are low skilled to know whether to give an antibiotic or not. That test should be quite resilient to a lot of changes [staff turnover changes]. It would be very easy to train and learn. If you have things that require interpretation, in time nobody knows how to interpret. Having something very simple would be good.” (Research, Africa)*

- A quick result is a priority
- Ideally, Simple to use, no electricity or complicated reader

## POC HOST RESPONSE BIOMARKER TESTS

# Severity test is a lower priority, yet quite relevant

- Many, but not all, FGs thought a HRB test for severity would be useful, primary at the lowest levels (community and primary)
- Although optimally one would have both, the FGs did not prioritize a HRB test for predicting severe disease as highly as they did a bacterial/nonbacterial test. Some implied that training of health care workers and using vital signs could address shortcomings in severity triage at lowest levels

*“It would be helpful for primary care or remote settings. In this case it would be interesting to have a more sensitive and less specific test. A test that allows early identification of serious patients, that would allow less hospitalization time for the patient. Easy test to implement. This test should have an impact at the hospital.” (Policymaker, LATAM)*

*“Both are equally important. For example, there are children with cough and flu. If breathing not fast, IMCI advises to take plenty fluids and send home. If you use biomarkers that are predictors of severity, if elevated, the child qualifies for admission, as much as the IMCI says outpatient. But in the true clinics setting the child should be admitted for observation in case the patient goes in the other direction.”  
(Policymaker, Africa)*

*“But if someone is not giving an antibiotic and sending the child home, often they are saying did I make the right decision so having something that says this child also scored low on severity scores this would be quite helpful.” (Researcher, Africa)*

## POC HOST RESPONSE BIOMARKER TESTS

# Use cases for a severity test

**Highest priority use case** is at the lowest levels of care, where skills are lacking and where referral is hardest.

The goal of the test would be to reduce delays in referral of severe patients. It would serve as a signal for healthcare workers to seek additional support and refer.

### Other use cases:

- Useful in specific diseases (e.g. Japanese encephalitis) in knowing whether to refer or not
- Where providers are more trained, and at higher level facilities, the test was less relevant, with some exceptions
- A low severity score may give providers more confidence in their decision to withhold an antibiotic, or to treat as an outpatient
- Teaching and larger hospitals often have many trainees, recent graduates, performing triage and initial patient consultations in OPD/ED. A severity test may be useful here

**There is also scope for using a severity test alongside a POC for bacterial vs. non-bacterial tests**

### Requirements

- Qualitative yes/no required. A quantitative format limits use to where staff are sufficiently skilled to interpret results
- Most felt sensitivity needed to be high
- Ease of use and simplicity was key
- Would need to be included in algorithms and as part of the diagnosis pathway

*“8 out of 10 [for diagnostic accuracy] would be used in almost all health posts or district hospitals where they have limited resources. More than 70% would be very good – because they don’t have any other tools – for severe disease.” (Provider/researcher, Asia)*

# Reflections & discussion

Refining and prioritizing use cases for HRB tests

## REFLECTIONS & DISCUSSION

# Understanding challenges in order to refine use cases

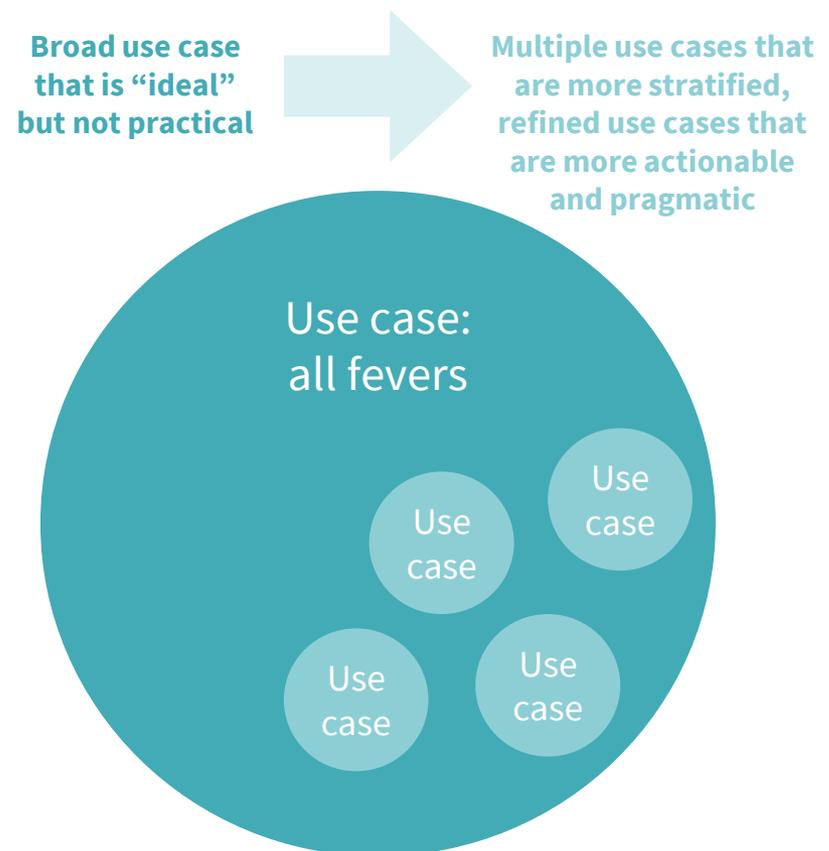
The FGs provided a useful opportunity to reconfirm our high level understanding of the challenges HCWs face in diagnosing and managing AFI, and their relative prioritization by stakeholders in LMICs.

Our intention was not to exhaustively inventory the challenges, as many are already known, but to gain further insights that would help develop more nuanced understanding of problems faced, in order to then stratify the current broad use case, “all febrile illness,” in ways that might be more actionable in the near term.

In general, the challenges are common across all settings geographies, **but generalizations about priorities are difficult** to make, given varied contexts and perspectives.

The discussions around prioritization of interventions, while hard, provided perspective on the most acute issues as well as insight into the pragmatic factors around feasibility of implementing some of the proposed Interventions.

While we asked about many challenges and interventions, the focus of use cases (for now) is on HRB tests.



## REFLECTIONS & DISCUSSION

# Key messages for HRB tests from the prioritization discussions

- **Antibiotic overuse is a huge concern.** FG participants are aware of overuse by providers as well as misuse by patients outside of the health care settings
- **The struggle around antibiotics in patients with negative malaria RDTs is acute and top of mind.** The lack of guidance and tools forces HCWs to rely on clinical judgement
- There is enthusiasm for a POC HRB based test for bacterial/non bacterial infections, even if it is not perfect
- Irrational use of antibiotics is a bigger problem than poor access. In low income countries we often think that access is a bigger problem than excess, though both obviously coexist. FGs saw the excess issue as a higher priority problem
- We heard a lot about the “confidence” of the health care worker, when they aren’t confident, they over prescribe, and over refer. For some HCWs, this suggests there may be scope for providing more ‘data’ points from diagnostics and devices that can improve confidence, rather than being definitive test results
- Improved recognition of severity is a challenge at lower levels of the health system, the need is less acute at higher levels
- FGs saw the value in a HRB test to support severity triage, but did not prioritize it as highly as a test for bacterial /non-bacterial discrimination. Reasons may include the ability of other approaches to support triage decisions (e.g. training and vital sign measurement). Only a few articulated the potential impact on hospitals, (i.e. decreasing length of hospital stays for patients) perhaps this issue is not as visible

## REFLECTIONS & DISCUSSION

# FGs identified many potential problems that HRB POCTs could address



Key Bacterial / nonbacterial test Both Severity

## REFLECTIONS & DISCUSSION

# Building on FGD themes: an approach for refining and stratifying use cases

FGD stressed the importance of thinking about the context. For example, different levels of the health system need different solutions; importance of appreciating the health worker's training and qualification, the settings and situations where these technologies or interventions may find themselves.

- While they talked about levels of care, frequently FGs delineated and described challenges and interventions based **on the health care worker's competency, skills, and qualifications:**
- For example, the community and primary levels in Africa and rural areas of Latin America struggle with low skilled health care workers
- This is opposed to the physician with capacity to consider a test result or other data as one piece of the clinical picture and with more ability to apply clinical reasoning



**FGD suggest segmenting and stratifying the use case by the health care worker's level of training and scope of practice is useful.**

**Patient related factors, were not frequently mentioned, e.g.**

- Risk stratification, co-morbidities were infrequently raised
- There was little discussion of use of HRB based tests or other interventions in specific populations (other than pediatricians, since FGs included several pediatricians)
- While symptoms beyond fever were mentioned (e.g. respiratory) FGs did not use symptoms as a way of grouping patients



Are patient factors less useful ways of defining and refining use cases? Or are they another layer down, i.e. would only be incorporated at a later stage in use case development process?

## REFLECTIONS & DISCUSSION

# Suggested refinement of use cases for bacterial / non bacterial tests

**Overall, there appears to be “openness” to trying new approaches, even if they are not perfect, so long as they are packaged appropriately, and supported with training.**

- For HRB tests, FGs tended to segment health care workers into those that have some clinical reasoning skills, who can take a less than perfect test or data point and use a piece of the puzzle vs. lower skilled health care workers who require a definitive yes / no decision
- The staffing of health facilities differs by country, in some countries the majority of PHCs have a medical doctor, in others doctors are placed at busy primary health centers only; and in others doctors are only available from district hospital and higher
- For these higher skilled providers, (i.e. working in hospital OPD, EDs, and in busy PHCs), a perfect test is not needed to curb antibiotic overuse and to improve practices



**high priority**

**Use case:**  
Bacterial / non bacterial HRB test  
for high-skilled HCWs

**high priority**

**Use case:**  
Bacterial / non bacterial HRB for all  
providers, including minimally  
skilled HCWs

## REFLECTIONS & DISCUSSION

# Other, niche, nuanced use cases for bacterial / non-bacterial test

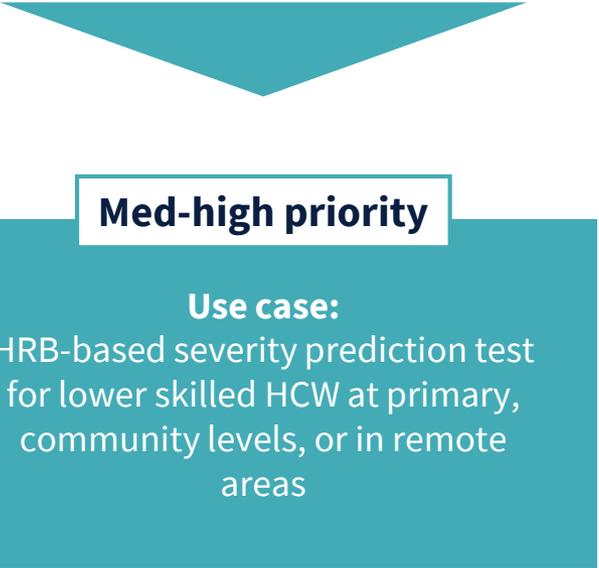
### **FGs raised other more “niche” use cases for a bacterial / non bacterial test:**

1. Use of CRP at facilities that have additional laboratory capacity to then guide additional assessments and investigations
2. During epidemics (e.g. wet/malaria season in Malawi, influenza in Ethiopia, dengue in Brazil), workloads climb and health workers tend to focus exclusively on the epidemic-causing disease, severity triage and management of other infections suffers, and antibiotic overuse is more common. There is scope for using a HRB bacterial / non-bacterial test in these situations to support rational use of antibiotics

## REFLECTIONS & DISCUSSION

# Suggested refinement of use cases for bacterial / non bacterial tests

**The highest priority application of severity tests was where skills are insufficient leading to errors in triage and delays in referral. A HRB-based POC severity test for lower skilled HCW would allow them to quickly action the care seeking and referral process.**



### Med-high priority

#### Use case:

HRB-based severity prediction test for lower skilled HCW at primary, community levels, or in remote areas

**Other more nuanced use cases were suggested in the FGDs, and are worth exploring further. For example:**

- A use case that is defined by how difficult it is to implement a referral in light of logistical constraints, setting (e.g. rural) or possibly taking into consideration patient factors (financial cost, or hardship of supporting a hospital admission). A HRB-based test for severity would inform and give confidence to the provider and patient in this situation.
- A use case could be defined by the workload, and importance of triage when workloads are high, as triage often suffers in these situations. For example, HRB-based severity tests could be deployed during a specific disease outbreak; at high volume clinics only; and during seasonal surges in malaria.
- Severity tests could guide decision making in certain diseases, (for example Japanese encephalitis, dengue) to help inform the decision around referral or admission. Since a diagnosis would have been made, the HCW applying the test would likely be more skilled.

# Reflections & discussion

Other interventions

## REFLECTIONS & DISCUSSION

# Key points for other interventions (1 of 2)

- Generally speaking, technology is not a panacea, it has a role, but FGs clearly prioritized training as the number one priority
- Training in traditional sense is needed, but other learning opportunities should also be explored: mentorship, use of technology to deliver / reinforce training, to provide access to senior clinicians and specialists
- Devices for measuring vitals are important priority, as important as HRB-based POC tests, and on-going work in this area should continue
- Guidelines need to be integrated, and reflect latest evidence base, including additional information on local epidemiology
- Awareness of the different causes of fever varied, and potentially drives the need for and prioritization of additional disease specific point of care tests. For example:
  - FGs in Latin America and Asia frequently mentioned specific diseases (dengue, scrub typhus etc) that were present locally, and also frequently mentioned the lack of POC testing for specific diseases, (with the exception of malaria) outside of larger facilities
- African FGs did not speak as much to the need for POC disease specific tests, but also spoke to a need for greater information on epidemiology of fever
- Finding ways to package data coming from major fever studies in ways that are actionable and accessible to HCWs of varying levels (doctors to less skilled) would seem a near-term priority

## REFLECTIONS & DISCUSSION

# Key points for other interventions (2 of 2)

- COVID-19 did not feature prominently in the FGs
  - Early on COVID-19 disrupted care and was “very distressing” as patients did not seek care. Systems responded by educating the community (e.g. on washing hands and using masks). Currently, care is resuming, with additional PPE and “pre screening” measures. For example, prior to entering a health facility, a fever/cough/exposure screening happens. FGs did point out that COVID-19 screening is likely contributing to delayed presentation in some patients, as triage is not often implemented well by the screeners
  - There was a notable emphasis on the lack of infrared thermometers
- Community and patient education are important, and technology (mHealth) may play a role here. Key messages are mix of old (importance of seeking care for fever quickly, recognizing danger signs) and new (education on antibiotic overuse/harm)
- In Africa, malaria continues to dominate provider thinking. While in some settings malaria is the dominant health concern, more awareness of and consideration of other causes of fever is needed. Outbreaks and epidemics have a similar effect (influenza, dengue). Communications to HCW and training should give additional attention to other relevant diseases
- Additionally, strengthening basic surveillance and ensuring that relevant information is disseminated in an accessible way to health workers of varying levels, whether through training, reports, electronic updates or incorporation in guideline updates

# Abbreviations

- **AFI** Acute febrile illness
- **AMR** Antimicrobial resistance
- **ATB** Antibiotic
- **CRP** C-reactive protein
- **Dx** Diagnostic
- **ED** Emergency department
- **ETAT** Emergency triage assessment and treatment
- **FG** Focus group
- **FGD** Focus groups discussions
- **FIND** Foundation for Innovative New Diagnostics
- **HCW** Health care worker
- **HW** Health worker
- **IMCI** Integrated Management of Childhood Illness
- **LATAM** Latin America
- **LMIC** Low- and middle-income country
- **mRDT** malaria Rapid diagnostic test
- **NMCP** National malaria control programme
- **OPD** Outpatient department
- **OTC** Over the counter
- **PCR** Polymerase chain reaction
- **PCT** Procalcitonin
- **PHC** Primary health care
- **POC** Point-of-care
- **PPE** Personal protective equipment
- **R&D** Research and development
- **RDT** Rapid diagnostic test
- **SEA** South East Asia
- **TPP** Target product profile
- **URTI** Upper respiratory tract infection

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# PRE-READ 2:

Host response biomarkers  
for fever - Recent progress  
and future challenges

# Disclaimer

This slide deck builds on other reviews and work in this area.

The methodology included review of publicly available information, published and unpublished reports, and discussions with stakeholders and technology developers.

The aim was not to be exhaustive, but rather to provide some background on ongoing work in the area of host biomarker-based diagnostic tests for acute febrile illness management.

This slide deck highlights FIND's work in this area in particular. The technologies in the pipeline have been identified primarily through discussion with experts and review of reports, supplemented by literature searches.

# INTRODUCTION

## INTRODUCTION

# Acute febrile illness diagnosis – brief background

## The challenges

Fever, also referred to as acute febrile illness (AFI), is the most common symptom amongst patients, including children, presenting to healthcare services in low- and middle-income countries (LMICs).

There are many causes of fever (e.g. infectious diseases, septicaemia etc). An accurate, rapid diagnosis and triage of acute fever can reduce mortality by identifying those patients that need a specific treatment (e.g. antibiotics or anti-malarial drug) and those that need additional care.

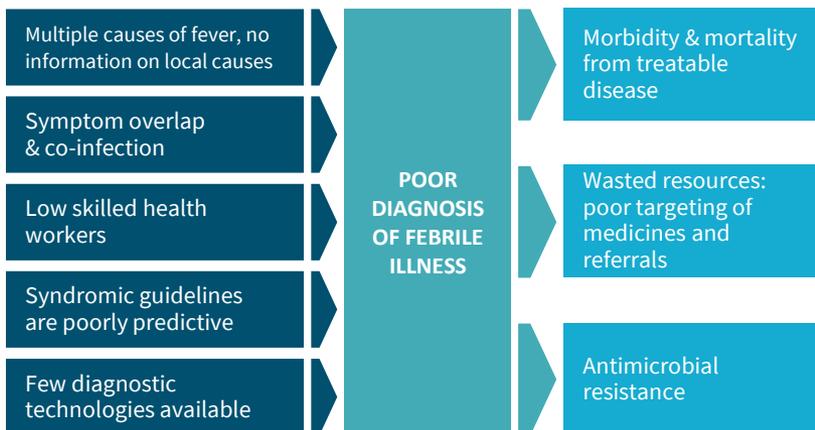
## The potential for host response biomarkers

A variety of programmatic and technology interventions are promising for improving AFI management.

There is potential for host response biomarkers based tests to play an essential role in management of fever:

A point-of-care (POC) fever triage tests that can distinguish between bacterial and non-bacterial AFIs.

Tools that can determine the severity of an infection



## INTRODUCTION

# Fever diagnosis – recent progress

## Progress made in the past 5 years

Several activities have been completed to address the challenges associated with the diagnosis and prognosis of AFIs. These studies have included:

- The development of target product profiles (TPPs) to identify promising biomarker-based assays for use in the target populations identified
- The establishment of a biobank, comprising of 400,000 well-characterized specimens, which are available to diagnostics development partners
- The creation of next generation CDSAs to assist in the diagnosis of AFIs and support decision-making by healthcare workers
- The undertaking of various impact studies to evaluate these initiatives in the field
- The continuing exploration of new pipeline technologies and other innovative approaches to tackling the challenges presented by the diagnosis of fevers globally



Adapted from: Ryan Ruiz

## INTRODUCTION

# Fever diagnosis – status check

## Despite progress, the optimal host response biomarker test is elusive

Numerous challenges remain, even though there are both existing technologies and newer ones in the pipeline that are under evaluation to improve the diagnosis of AFIs.

Many of these new technologies are at early stages of development or have been evaluated in studies with small sample sizes and/or small numbers of participants; none are widely used across a range of settings. Performance in LMIC has yet to be demonstrated, and where it has been evaluated the results are not compelling.

While the need for improving AFI diagnosis and management is acute, it is clear that additional technology and programmatic investment is needed. Given the ambitious and broad use case initially targeted (i.e. “all fevers”), focusing on specific use cases, and determining the minimum requirements for these, may be a pragmatic approach. In this scenario, certain HRB tests might be deployed in the near term in specific use cases, and development of HRB tests for “all fevers” would be the ultimate, longer term goal.



Adapted from: FIND/J. Rae

# **BACTERIAL VS. NON- BACTERIAL TEST**

## BACTERIAL VS. NON-BACTERIAL TEST: BACKGROUND

# Distinguishing bacterial and non-bacterial causes of AFI

Bacterial infections account for a relatively small proportion of AFIs; however, in the absence of a simple diagnostic test to guide clinical decisions, healthcare professionals often presume that a non-malarial febrile illness is bacterial in origin, potentially resulting in inappropriate antibiotic use.

An accurate differential diagnostic tool for AFIs is thus essential, to both limit antibiotic use to bacterial infections and address the antimicrobial resistance crisis that is emerging globally, without resorting to multiple or complex pathogen-specific assays.

Host biomarkers have been suggested as an appropriate means of meeting the challenge of differentiating bacterial from non-bacterial infections

**A simple tool for distinguishing bacterial versus non-bacterial infections would radically improve patient management and reduce indiscriminate antibiotic use.**

## BACTERIAL VS. NON-BACTERIAL TEST: BACKGROUND

# Host-biomarker test TPP

### 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 based on a meeting of experts .

#### 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;**
- price should not exceed US\$ 5.00, and optimally should be <US\$ 1.00.

- To define the needs of LMICs, a consortium of experts in global health and diagnostics developed a target product profile (TPP), which identified the need for an assay based on host biomarkers to distinguish bacterial from non-bacterial infections in low-resource settings (e.g. corresponding to community-based healthcare settings as well as primary care centres) to support evidence-based treatment guidance.
- From this consensus effort, the ideal characteristics for such a test were defined and the target population was identified as the general febrile population and included all age groups.

## BACTERIAL VS. NON-BACTERIAL TEST: BACKGROUND

# Several biomarkers, yet little evidence of performance in LMIC populations

### Existing markers

C-reactive protein (CRP) and procalcitonin (PCT) are long-established biomarkers used to guide clinical decisions in hospitals in high-income countries (HICs). Hematology parameters are also used (e.g. WBC) to guide antibiotics in HICs.

However, studies in LMICs generally found that CRP and PCT had lower performance and limited ability to discriminate between bacterial and non-bacterial infections in these settings probably due to the impact of co-infections (HIV, *P. falciparum*, soil-transmitted helminths) and co-morbidities (malnutrition, untreated diabetes) that interfere with the expression of the biomarker.

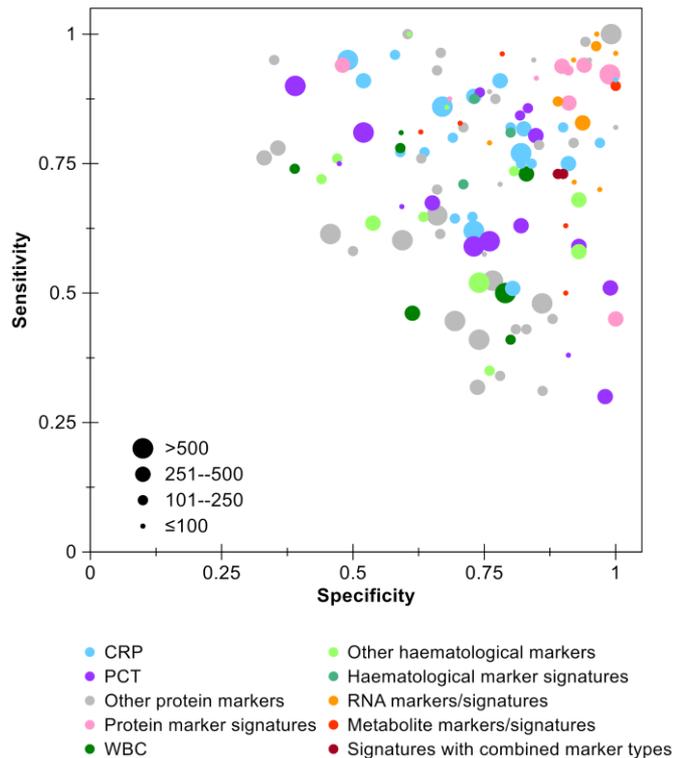
### Novel markers

More recently, several other host biomarkers have been evaluated for distinguish bacterial from non-bacterial infections e.g HNL, HBP, CHI3L1. Commercial POC tests for these don't yet exist.

However, there are some recently launched tests and others in the pipeline using unique combinations of host response biomarkers. These biomarkers and biomarker signatures reported promising performances, in general higher performances than CRP and PCT. However, most of them were only evaluated in HICs and thus the effect of co-infections and co-morbidities, common in LMICs, is unknown.

## BACTERIAL VS. NON-BACTERIAL TEST: SYSTEMATIC REVIEW

# Systematic review: Host-biomarkers for distinguishing bacterial versus non-bacterial causes of AFI



### Scope

- Systematic review included studies comparing diagnostic performances of host biomarkers in patients with bacterial versus non-bacterial infections were included, published between 2015-2019 from any countries and both in- and out-patients.
- 55 publications included, with 265 biomarkers/signatures.

### Findings

Performance for most biomarkers is lower than the minimum TPP performance criteria. The performance requirements of this ambitious TPP appear to be unachievable, at least in the short-term. Therefore, the TPP might need to be revisited and re-assessed.

### Challenges

- most studies have focused on severe and/or hospitalized patients, which is a different use-case than identified in the TPP.
- Many studies conducted in HICs meaning that the co-infections and diseases might not be comparable with other countries
- Many studies are retrospective, with convenience sampling, and case-control study design and low sample sizes
- Lack of a homogeneous reference standard for bacterial infections (definition of how bacterial and non-bacterial infections are classified)

## BACTERIAL VS. NON-BACTERIAL TEST: EVALUATION

# Biomarker for Fever-Diagnostic (BFF-Dx) study – cross-sectional study



## Background

BFF-Dx is, to the best of our knowledge, the largest fever biomarker study ever undertaken: 18 biomarkers were evaluated in the intended target population and setting (according with the TPP)

Prospective sample collection from consecutive ~2000 non-severe patients 1-60 years old from Malawi, Brazil, and Gabon, Extensive testing was performed to aid in the classification of patients into the bacterial and non-bacterial groups.

*Additional details including methodology, protocol, bacterial versus non-bacterial AFIs differentiation and use of analytic tools have been described in Escadafal C et al, 2020. Submitted for publication.*

## Main Goals

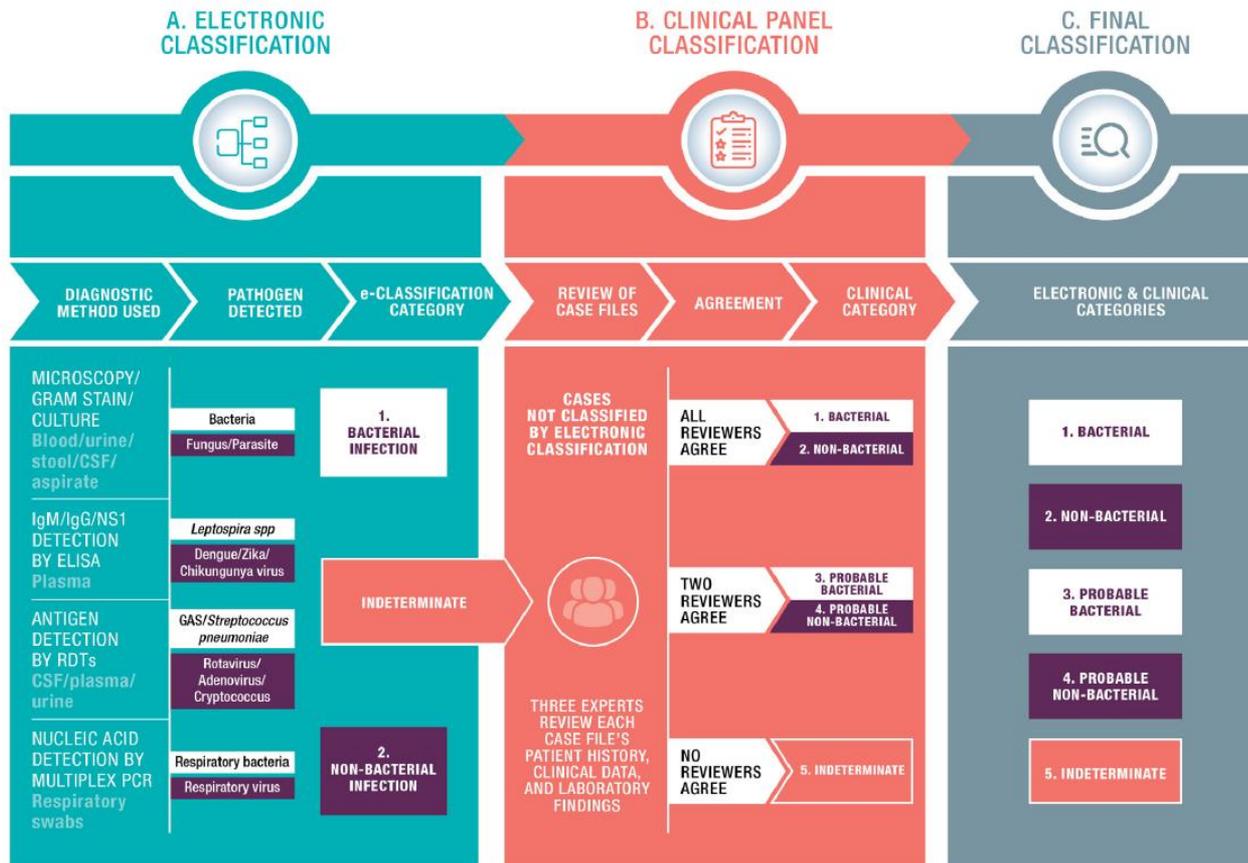
- Evaluate the performance of several biomarkers in the general febrile population in LMICs, thus overcoming the current knowledge gap
- Identify top-performing individual biomarkers and/or biomarker combinations that could subsequently be used develop an assay to distinguish bacterial from non-bacterial infections

## Biomarkers evaluated (selected based on Kapasi et al. systematic review and key publications in the field)

CRP, PCT, HNL, Galectin-9, IP-10, Haptoglobin, IL-4, IL-6, sPLA2, TRAIL, HBP, IFN-gamma, LBP, sTREM-1, CHI3L1, A-1-acid glycoprotein, complement 2, complement C4b, NGAL, FebriDx (Mxa+CRP)

## BACTERIAL VS. NON-BACTERIAL TEST: EVALUATION

# How was “bacterial” and “non-bacterial” defined?



Several clinical and microbiological markers were collected/measured. Firstly, we used an electronic algorithm including a subset of these characteristics for patient classification. All cases without classification by the algorithm were reviewed and classified by a panel of three clinical experts based on patient history, clinical and microbiological data.

## BACTERIAL VS. NON-BACTERIAL TEST: EVALUATION

# BFF-Dx population overview – Preliminary results



	Lambarene (Gabon)	Chilumba (Malawi)	Rio de Janeiro (Brazil)
<b>0-5 years (Median, IQR, n)</b>	3, [72, 5], 182	3, [2, 4], 367	3, [2, 4], 45
<b>6- 14 years (Median, IQR, n)</b>	9, [7, 11], 203	9, [7, 11.8], 266	10, [8, 13], 71
<b>Above 15 years (Median, IQR, n)</b>	16, [15, 16], 30	27, [20, 36], 367	32.5, [23, 45], 384
<b>Male (% , n)</b>	45.1%, 187	42.7%, 427	49.6%, 248
<b>Temperature (°C) (TEMPERATURE)</b>	36.8, [36.4, 37.4], 415	38.1, [37.7, 38.8], 999	37.7, [36.7, 38.4], 500
<b>WBC count (Median, IQR, n)</b>	7.75, [5.7, 10], 412	6.8, [5.1, 9.3], 988	7.28, [5.47, 10.45], 495
<b>Neutrophil count (Median, IQR, n)</b>	2.78, [1.96, 3.93], 412	4.3, [3, 6.2], 909	4.9691, [3.63, 7.46], 495
<b>Haematocrit count(Median, IQR, n)</b>	33.2, [29.4, 35.8], 412	36.25, [33.2, 39.6], 988	40.1, [36.5, 43.2], 495
<b>Lymphocyte count(Median, IQR, n)</b>	2.74, [1.83, 4.19], 412	1.5, [1.1, 2.7], 986	1.1556, [0.70, 1.99], 495
<b>Respiratory rate (RESP_RATE) (Median, IQR, n)</b>	20, [18.5, 32], 407	28, [19, 36], 846	21, [19, 24], 500
<b>Malaria RDT positive (% all, n)</b>	56.39, 234	45.89, 458	0.2, 1
<b>HIV RDT positive (% all, n)</b>	1.20, 5	4.21, 42	1.4, 7

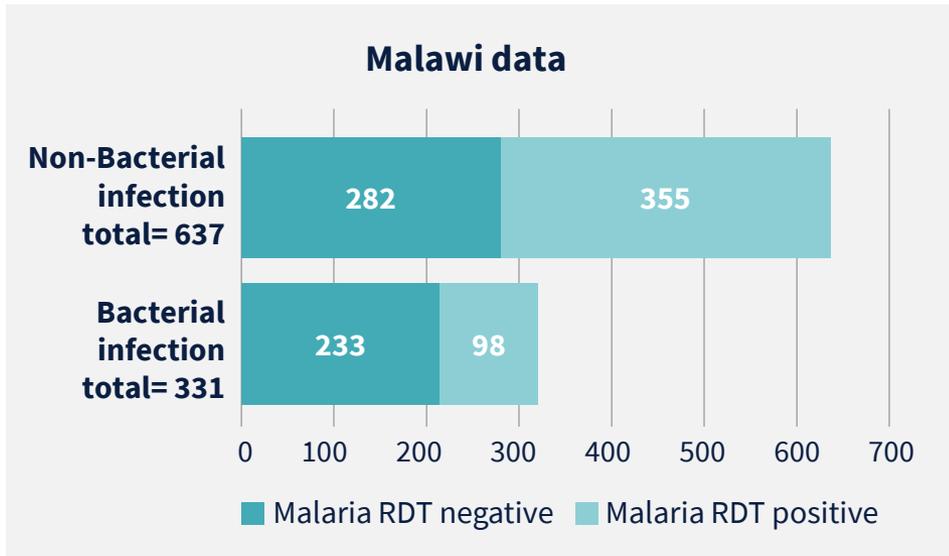
BACTERIAL VS. NON-BACTERIAL TEST: EVALUATION

# BFF-Dx population – by outcome and syndromes

## – Preliminary results



	n	n bacterial infection	n non-bacterial infection	Undetermined
Malawi	1000	331	631	38
Brazil	500	122	327	51



Gabon data not yet available

Diagram showing the distribution of bacterial and non-bacterial infections

## BACTERIAL VS. NON-BACTERIAL TEST: EVALUATION

# AUROC – Preliminary results



	Malawi						Brazil					
	Electronic classification			Electronic classification + clinical panel			Electronic classification			Electronic classification + clinical panel		
	ROC (%)	CI (%)	N	ROC (%)	CI (%)	n	ROC (%)	CI (%)	n	ROC	CI	n
WBC	69.3	62.4 - 76.3	253	69.7	66.1 - 73.4	954	80	73.6 - 86.5	191	83.6	79.0 - 88.2	423
Haematocrit	55.2	47.2 - 63.1	253	54.2	50.4 - 58.0	954	57.3	48.6 - 66.0	191	56.4	50.1 - 62.7	423
Lymphocyte count	62.8	54.9 - 70.6	253	55.3	51.4 - 59.1	952	67.7	59.8 - 75.7	191	67.1	61.4 - 72.8	423
Neutrophil count	67.5	60.0 - 75.0	237	69.7	65.9 - 73.5	879	75	67.5 - 82.4	191	80.1	74.9 - 85.3	423
CRP	50.9	42.5 - 59.2	252	52.6	48.8 - 56.4	950	58.6	49.6 - 67.5	191	60.8	54.5 - 67.2	425
PCT	63.7	51.9 - 75.5	106	53	46.6 - 59.4	331	54.4	44.0 - 64.9	133	52.4	44.3 - 60.5	294

Gabon data not yet available

BACTERIAL VS. NON-BACTERIAL TEST: EVALUATION

# BFF-Dx FebriDx

## – Preliminary results



	SENS % (95%CI)	SPEC % (95%CI)	n
Electronic classification			
All patients <sup>#</sup>	44.8 (37.5-52.3)	59.7 (47.5-70.9)	255
Malaria positive	54.8 (41.8-67.3)	35.5 (19.8-54.6)	93
Malaria negative	40.0 (31.3-49.4)	80.0 (63.9-90.4)	160
Electronic classification + clinical panel			
All patients <sup>#</sup>	47.6 (42.1-53.1)	53.4 (49.4-57.3)	964
Malaria positive	54.4 (44.3-64.1)	44.8 (39.6-50.2)	447
Malaria negative	39.8 (33.7-46.3)	63.8 (57.8-69.4)	510
Seld WH <i>et. al.</i> 2017* (n=203)			
All patients	64 (56-72)	76 (66-86)	
Malaria positive	N.A.	N.A.	
Malaria negative	N.A.	N.A.	

### Diagnostic accuracy values for FebriDx compared to different outcome classifications

The preliminary data suggests that host biomarker tests alone might not be sufficiently accurate but could potentially be integrated into adapted clinical care algorithms to improve specificity and sensitivity of both tests and algorithm

\* Seld WH *et. al.* (2017) uses an algorithm endorsed by the test developer (Lumos Diagnostics) and it is shown for competition. # Not all patients had malaria RDT data. **N.A.** Not analysed.

## BACTERIAL VS. NON-BACTERIAL TEST: PRODUCTS

# Fiebre study



Fiebre is a large, multi-partner multi-center study that is recruiting a total of 9600 children and adults and 2400 community controls in order to generate a detailed description of the infections cause of fever in Zimbabwe, Mozambique, Laos, Malawi.

Fiebre will include evaluation of several biomarkers that show promise for bacterial vs non bacterial infection differentiation as well as biomarkers for severe disease.

**The Biomarkers of host immune and endothelial activation included in Fiebre include (add table below):**

### The main research objectives are to:



Identify the most common infectious causes of fever that are treatable and/or preventable



Provide data on antimicrobial susceptibility of bacterial infections



Learn how local perceptions of fever affect treatment practices, including the use of diagnostics and antimicrobial drugs



Inform clinical guidelines and algorithms on how to manage patients with fever

Ang-1	IL-8
Ang-2	IP-10
Azu/HRP	MxA
Chitinase	PCT
CRP	sTNFR-1
FLT-1	sTREM-1
IL-10	TRAIL
IL-6	

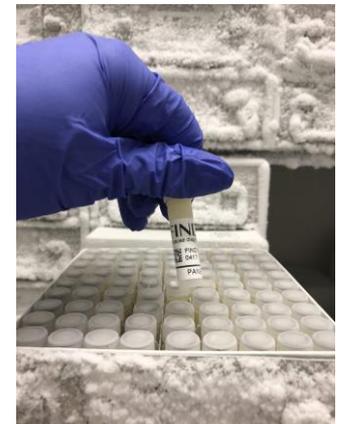
## BACTERIAL VS. NON-BACTERIAL TEST

# Key publications

- Wellcome Trust. Review of approaches to triage of acute fever. 2019
- Escadafal C et al. The good and the bad: using C reactive protein to distinguish bacterial from non-bacterial infection among febrile patients in low-resource settings. *BMJ Global Health*. 2020
- Escadafal C et al. Bacterial versus non-bacterial infections: a methodology to support use-case-driven product development of diagnostics. *BMJ Global Health*. 2020
- Fernandez-Carballo BL et al. Distinguishing bacterial versus non-bacterial causes of febrile illness – a systematic review of host biomarkers. Submitted for publication to *Journal of Infection*. 2020
- Kapasi A et al. Host Biomarkers for Distinguishing Bacterial from Non-Bacterial Causes of Acute Febrile Illness: A Comprehensive Review. *PLOS ONE*. 2016
- Unitaid. *Fever Diagnostic Technology Landscape 1st Edition*, February 2018.
- Dittrich S et al. Target Product Profile for a Diagnostic Assay to Differentiate between Bacterial and Non-Bacterial Infections and Reduce Antimicrobial Overuse in Resource-Limited Settings: An Expert Consensus. *PLOS ONE*. 2016
- Dittrich S et al. Commercial host biomarker-based diagnostics to differentiate between bacterial and non-bacterial infections in a highly malaria-endemic setting in Malawi. *ASTMH* 2019. LB-5141

## Resources

- BFF-Dx Sample collection - available to researchers and companies. The FIND biobank comprises 400,000 well-characterized specimens - helps accelerate product development of new diagnostic tools.
- For more information visit: <https://www.finddx.org/specimen-bank/specimens-fev/>



Adapted from: Jennifer Ogden,  
Manager, Materials Management,  
Septometrix

# **HOST BIOMARKERS FOR SEVERITY TRIAGE**

## HOST BIOMARKERS FOR SEVERITY TRIAGE

# Need for severity triage

- A significant proportion of avoidable mortality and long-term morbidity in both LMICs and HICs arises through delayed recognition and appropriate management of impending severe illness.
- Host biomarkers that are used to assist in making a prognosis (e.g. white blood cell counts, haemoglobin measurement, PCT and lactate) are generally insufficient as the sole basis for treatment decisions, due to their lack of specificity, and must be incorporated into broader clinical algorithms.
- Currently, there are no tests based on host biomarkers that are routinely used to triage febrile illness by severity; tests based on host biomarkers of severity of infection would be a useful development to enable this.

**Incorporating severity prediction assays could result in a large reduction in mortality and long-term morbidity.**

## HOST BIOMARKERS USED FOR SEVERITY TRIAGE

# Developments in severity triage

The intention of severity prediction biomarker assays is that they will either provide more accurate prediction of deterioration, much earlier prediction of deterioration, or both. Candidate assays fall into a few broad categories:

- Early markers of developing inflammatory or host immune/endothelial response (HIER)
- Proteins or other agents involved in signaling or within various pathways leading to disseminated responses
- mRNA coding for the same.
- Changes in concentrations of metabolites resulting from impaired organ function, or changed concentrations of substances essential for organ or cell function.



Adapted from:  
<https://premaslifesciences.com>

## HOST BIOMARKERS FOR SEVERITY TRIAGE

# Systematic review findings

### Background

Host biomarkers may identify patients with AFI who require a higher level of care; choosing appropriate biomarkers for this role among an expanding pool of candidates is challenging.

### Method

PubMed was searched for studies reporting the association of host biomarker levels and a measure of disease severity among patients with a suspected or diagnosed cause of AFI published from 2013-2018.

### Results and findings

- 281 manuscripts were included and data was extracted for 278 biomarkers.
- Proadrenomedullin, copeptin, proANP, sTREM-1, CHI3L1, and the pediatric sepsis biomarker risk model showed a weighted mean AUC >0.75 (range 0.75-0.84) in >500 patients over >2 studies.
- Although several biomarkers show promise in predicting AFI severity across multiple studies, their test characteristics do not suggest that they may be used alone to determine AFI prognosis.

## HOST BIOMARKERS FOR SEVERITY TRIAGE

# Spot Sepsis



Prediction of disease severity in young children presenting with AFI in resource limited settings, or “Spot Sepsis” is a multi-country study led by MSF and MORU aiming to develop risk prediction algorithms, combining measurements of host biomarkers and clinical features for children presenting with AFI in resource limited settings.

Many host biomarkers, selected for their feasibility to measure using POC technologies, will be evaluated to determine if they are predictive of disease severity. Similarly an optimal combination of clinical features that are feasible for limited-skill health workers to assess, will be evaluated (demographics, anthropometric data, history, vital signs, clinical signs, clinical symptoms) for prediction of disease severity. The performance of a new algorithm will also be explored using the Cambodia site.

Over 15 months, Spot Sepsis is enrolling 4,900 children between the age of one month and five years with acute febrile illness presenting to outpatient and emergency departments of hospitals across Asia (Indonesia, the Philippines, Cambodia, Laos, Vietnam and Bangladesh). Key historical variables will be collected, clinical features will be recorded, host biomarker profiles measured, and fever etiology for key target pathogens will be determined. To ascertain clinical outcome, children will be followed up at 48 hours and 28 days. This data will be used to predict progression to severe disease.

### Preliminary list of biomarkers that Spot Sepsis will evaluate

Ang-1	IP-10
Ang-2	Lactate
CHI3L1	PCT
CRP	sFlt-1
CXCL-10)	s-Flt-2
Glucose	sICAM-1
Haemoglobin	sTM
IL-10	sTNFR-1
IL-6	sTREM-1
IL-8	sVCAM-1

## HOST BIOMARKERS FOR SEVERITY TRIAGE

# Key publications

- Robinson ML et al. Host biomarkers to predict the severity of acute febrile illness: A scoping review (preprint). Medrxiv. 2019
- Wellcome Trust. Review of approaches to triage of acute fever. 2019
- Fung JST et al. Determining predictors of sepsis at triage among children under 5 years of age in resource-limited settings: A modified Delphi process. PLOS ONE. 2019
- Ackerman H et al. A biomarker approach to syndrome-based treatment of severe childhood illness in malaria-endemic areas. 2018
- Valim C et al. Responses to Bacteria, Virus, and Malaria Distinguish the Etiology of Pediatric Clinical Pneumonia. American Journal of Respiratory and Critical Care Medicine. 2016
- Huang H et al. Discovery and validation of biomarkers to guide clinical management of pneumonia in African children. Clinical Infectious Diseases. 2014
- Craig JC et al. The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15,781 febrile illnesses. BMJ. 2010
- Carrol ED et al. The Diagnostic and Prognostic Accuracy of Five Markers of Serious Bacterial Infection in Malawian Children with Signs of Severe Infection. PLOS ONE. 2009

# **COMPLEMENTARY TECHNOLOGIES**

## COMPLEMENTARY TECHNOLOGIES: eCDAs, VITAL SIGNS

# Complementary technologies: electronic clinical decision supports and vital signs

It is important to consider the potential use of host response biomarker tests in the context of other interventions, both programmatic, and technology innovations.

### **Recent work to improve fever management has focused on two technologies:**

1. Electronic clinical decision support algorithms
2. Devices for measuring key vital signs

Given their importance to AFI management, we provide a high-level overview, with illustrative examples, for context. Ultimately it will be important to consider how host response, electronic decision support, and vital sign technologies, along with programmatic interventions, work together for optimal impact. Advances in one area may reduce the benefit of another.

## COMPLEMENTARY TECHNOLOGY eCDAs

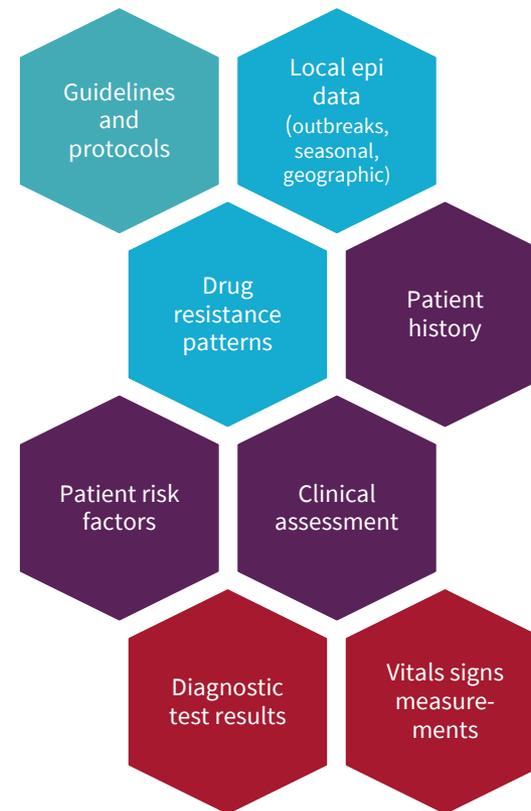
# Electronic clinical decision support algorithms

Clinical Decision Support Algorithms (eCDAs) running on smartphones or tablets can support frontline health workers, for example by assisting with:

- Following to recommended protocols
- Taking patient histories
- Performing clinical examinations
- Providing diagnostic recommendations and supporting interpretation of test results and vitals measurements
- Providing patient management recommendations

Electronic decision supports can address the need for simplicity and accommodate a more nuanced diagnosis, taking into consideration patient factors (e.g. examination findings, symptoms, clinical history) as well as external factors (e.g. local disease prevalence) and provide the flexibility needed to update guidelines rapidly as new evidence emerges.

## Potential components of eCDAs



## COMPLEMENTARY TECHNOLOGY eCDAs

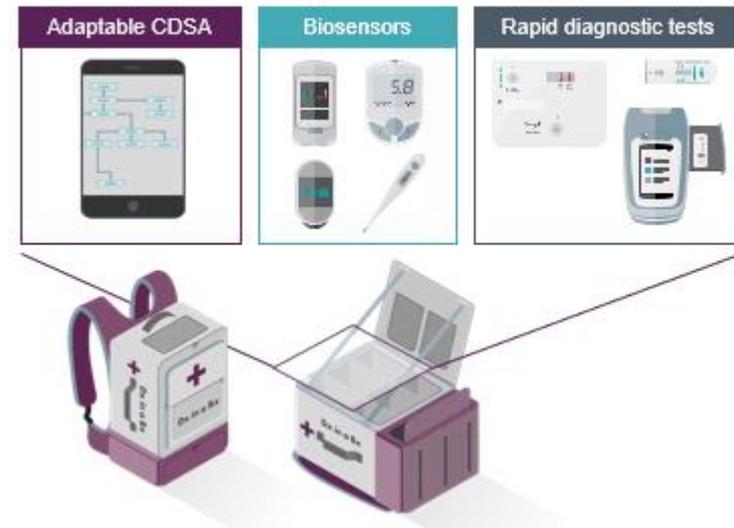
# Types of eCDAs available

An eCDA is not a diagnostic test in and of itself. It is designed to operate off-line and to communicate with a central server when an internet connection is available. While today eCDAs may require operators to input data from devices or tests, Ultimately, biosensors and diagnostics that are connected or built into the handheld device are envisioned.

Different types of CDSAs that have been developed for low-resource settings addressing acute fevers include:

1. Guideline-based: digital adaptations of WHO's Integrated Community Case Management (iCCM) or Integrated Management of Childhood Illness (IMCI) guidelines.
2. Next generation: algorithms that enhance iCCM/IMCI in some way, for example by incorporating additional clinical signs or data from diagnostic tests not included in the IMCI guideline.
3. Beyond this are eCDAs that incorporate real-time surveillance and machine learning to improve the algorithms.

Although there is no TPP for electronic clinical decision support algorithms per se, a TPP has been developed for the overall toolkit combining diagnostic biomarkers and/or devices with the appropriate algorithms.



Adapted from: Pellé K et al. BMJ Global Health. February 2020

## COMPLEMENTARY TECHNOLOGY eCDAs

# eCDA technology landscape is advancing, (yet implementation is slow)

The field of electronic decision supports is evolving rapidly, and a multitude of electronic decision-support systems are in development or have recently been launched.

While promising, many challenges stand in the way of widespread use and impact, primarily:

1. The digital infrastructure in each country varies, success depends on working within this system and infrastructure
2. Implementation and design considerations to ensure sustainability; there have been many pilots that fail to scale
3. The speed of innovation has resulted in a poor understanding of the product offering and a paucity of evidence on electronic clinical decision effectiveness. More often than not, the release of clinical decision support apps outpaces the evidence.

### eIMCI

- iDea, Terre des Hommes & Burkina Faso MoH.
- Mangologic (and others) by D-Tree International.
- Various platforms running on CommCare/MOTECH platform developed by Dimagi.
- Various iCCM tools by Medic mobile.

### Enhanced eIMCI and eICCM

- MEDSINC by THINKMD.
- ALMANACH, ePOCT+ by Swiss Tropical Health.
- Trigger Sepsis by University of British Columbia .
- e-CARE by MSF.
- Upscale by Malaria Consortium & Mozambique MoH

## COMPLEMENTARY TECHNOLOGY: VITAL SIGNS

# Devices to measure vital signs

Key vital signs parameters can also be useful in assessing the condition of patients with AFI.

These parameters include respiratory rate, heart rate, and blood oxygen and haemoglobin levels, as well as temperature and blood pressure. Although a variety of automated, multimodal patient monitoring devices are in use in HICs, they have not yet been adapted for use in the type of settings where AFI children present for care in LMICs.

However some promising new devices are on the horizon and the product landscape is evolving quickly. In addition, Covid-19 has increased use of pulse oximeters and thermometers and the market for multi-modal technology is growing. Most product development remains focused on HIC and increased development of wearables and integrated digital tools.

At right, the RAD-G™ from Massimo is an example of a multi-modal device that measures oxygen saturation, pulse rate and respiratory rate and there are others in the pipeline with potential for use in LMICs.

### Various parameters are possible



Adapted from: Bell et al. Am J Trop Med Hyg. 2018

## COMPLEMENTARY TECHNOLOGY: VITAL SIGNS

# Device implementation and challenges

There is substantial work going on in the area of devices to measure vital signs, largely focused on pneumonia diagnostics and improved respiratory rate counters.

UNICEF and the Malaria Consortium have led several studies operational feasibility and usability of automated respiratory rate counters and pulse oximeters under the ARIDA (Acute Respiratory Infection Diagnostic Aid) project.

Other key outcomes included:

- A TPP for automated RR timers
- Partnerships with industry to develop new products



Adapted from: <https://www.unicef.org/innovation/arida>

## COMPLEMENTARY TECHNOLOGY: VITAL SIGNS

# Device implementation research

### Unitaid awards are driving evidence generation and market entry of new devices

The TIMCI and AIRE studies, led by PATH and Alima respectively, focus on: Improving PHC workers' ability to diagnose severe disease by equipping them with pulse oximetry devices and decision support tools.

Through generating evidence on impact, operational feasibility, and cost-effectiveness of pulse oximetry, the projects aim to:

- Support country level decisions on scale-up of pulse oximetry and clinical decision support tools in primary care settings
- Inform global-level decisions to update policy and guidelines

**TIMCI**  
Tools for Integrated  
Management of  
Childhood Illness



In addition, PATH is working to accelerate the development and market entry of multi-modal devices, measuring oxygen saturation in addition to other vital signs, including:

- Developing a TPP for multi-modal devices
- Leading a field validation study assessing comparative accuracy and operational feasibility of several emerging tools

# **IMPACT CASE STUDIES**

## IMPACT CASE STUDIES

# CRP study, Vietnam

### Background

Assessed whether C-reactive protein point-of-care testing can safely reduce antibiotic use in patients with non-severe acute respiratory tract infections in Vietnam.

### Method

A multicentre open-label randomized controlled trial in ten primary health-care centres in northern Vietnam was conducted. Patients aged 1–65 years with at least one focal and one systemic symptom of acute respiratory tract infection were assigned 1:1 to receive either C-reactive protein point-of-care testing or routine care, following which antibiotic prescribing decisions were made. The primary outcome was antibiotic use within 14 days of follow-up.

### Results and Findings

- Between March 17, 2014, and July 3, 2015, 2037 patients (1028 children and 1009 adults) were enrolled and randomized.
- C-reactive protein point-of-care testing reduced antibiotic use for non-severe acute respiratory tract infection without compromising patients' recovery in primary health care in Vietnam. Health-care providers might have become familiar with the clinical picture of low C-reactive protein, leading to reduction in antibiotic prescribing in both groups, but this would have led to a reduction in observed effect, rather than overestimation.

## IMPACT CASE STUDIES

# CRP study, Thailand and Myanmar - multicentre, open-label, randomized, controlled trial

## Background

The objective of this trial was to explore whether C-reactive protein (CRP) testing at point of care could rationalize antibiotic prescription in primary care, comparing two proposed thresholds to classify CRP concentrations as low or high to guide antibiotic treatment.

## Method

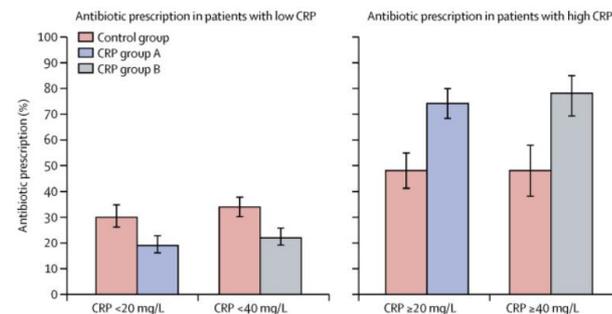
- Participants aged at least 1 year with a documented fever or a chief complaint of recruited from 6 public primary care units in Thailand and 3 primary care clinics and 1 outpatient department in Myanmar.
- Individuals were randomly assigned at a ratio of 1:1:1 to either the control group or one of two CRP testing groups, which used thresholds of 20 mg/L (group A) or 40 mg/L CRP (group B) to guide antibiotic prescription.

## The primary outcome:

The prescription of any antibiotic from day 0 to day 5 and the proportion of patients who were prescribed an antibiotic when CRP concentrations were above and below the 20 mg/L or 40 mg/L thresholds

## Results and Findings

- Between June, 2016, and Aug, 2017, 2410 patients were recruited.
- In febrile patients attending primary care, testing for CRP at point of care with a threshold of 40 mg/L resulted in a modest but significant reduction in antibiotic prescribing, with patients with high CRP being more likely to be prescribed an antibiotic, and no evidence of a difference in clinical outcomes.



## IMPACT CASE STUDIES

# Other ongoing studies in South-East Asia

### ICAT

- Recruitment ongoing until May 2021
- Large implementation study of CRP-based antibiotic prescription decisions in respiratory tract infections
- This cluster randomized trial will include 24 health centres supplied with CRP tests for acute respiratory illnesses (ARIs) and 24 health centres as controls, for a total enrolment of approximately 24,000 adults and children.

### South-East Asia Community Trials Network

- MORU is leading the South-East Asia Community Trials Network. Its aims are to: 1) to capture the key causes of morbidity and mortality in rural, underserved populations in South and Southeast Asia, and 2) to run implementation trials of scalable, high impact interventions (e.g. severity triage algorithms and new POCTs from SpotSepsis, eCDAs).
- Initially, the research program is focused on the epidemiology of febrile illness in rural areas of Asia, where malaria is declining and access to health care is limited. The trial will focus on incidence, causes and outcomes of febrile illness in patients presenting to village health workers/primary care (n=100,000) and some higher level facilities (PHC, district hospital n=7,500). Studies are taking place in Bangladesh, Cambodia, Lao PDR, and Myanmar. Qualitative research will explore care-seeking at village health workers, and potential expanded roles for VHWs.

## IMPACT CASE STUDIES

# FIND Diagnostic Use Accelerator

FIND's Diagnostics Use Accelerator project aims to improve the targeting of antibiotics used to treat AFIs in children and adolescents; it will include CRP testing.

This is a pragmatic, year-long study that to be conducted in 3 African and 4 Asian sites. Recruitment is ongoing in the 3 sites in Africa in 2020 (others delayed due to COVID-19).

The protocols are uniform (as much as possible) across sites and will include commercially available POC diagnostic tools as well as behaviour change initiatives (e.g. guidelines, training, algorithms, etc).



Adapted from: FIND\_Dx-Use-Accelerator\_Nov-2019.pdf

Diagnostic tests used in the intervention package are selected based on local needs:

### Pathogen-specific tests:

- Dengue virus,
- *Streptococcus pyogenes*,
- *Salmonella enterica serovar Typhi*,
- *Orientia tsutsugamushi* (scrub typhus), Influenza virus
- Chikungunya virus
- *Streptococcus pneumoniae*
- Respiratory syncytial virus,
- *Leptospira interrogans* (leptospirosis),  
*Plasmodium Sp.* (malaria)

### Non pathogen-specific POCTs:

- White blood cell total and differential counts (WBC/diff)
- Urine dipstick
- C-reactive protein (CRP)

## IMPACT CASE STUDIES

# Key publications

- Keitel K et al. A novel electronic algorithm using host biomarker point-of-care tests for the management of febrile illnesses in Tanzanian children (e-POCT): A randomized, controlled non-inferiority trial. PLOS MEDICINE. 2017
- Wellcome Trust Review of Approaches to Triage of Acute Fever. 2019
- Do NG et al. Point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in Vietnamese primary health care: a randomised controlled trial. The lancet Global Health. 2018
- Althaus T et al. Effect of point-of-care C-reactive protein testing on antibiotic prescription in febrile patients attending primary care in Thailand and Myanmar: an open-label, randomised, controlled trial. The lancet Global health. 2019
- Salami T et al. Impact of a Package of Diagnostic Tools, Clinical Algorithm, and Training and Communication on Outpatient Acute Fever Case Management in Low- and Middle-Income Countries: Protocol for a Randomized Controlled Trial. Trials. 2019
- Bell D et al. Dynamic Clinical Algorithms: Digital Technology Can Transform Health Care Decision-Making. Am J Trop Med Hyg. 2018
- Finette BA et al. Development and Initial Validation of a Frontline Health Worker mHealth Assessment Platform (MEDSINC<sup>®</sup>) for Children 2-60 Months of Age. J Trop Med Hyg. 2019
- World Health Organization. WHO Guideline: recommendations on digital interventions for health system strengthening. 2019

**PIPELINE**

## BACTERIAL VS. NON-BACTERIAL TEST: PRODUCTS

# Host-biomarkers available and pipeline products

### Qualitative lateral flow assays

- CRP (multiple tests with 10mg/L cut-offs)
- PCT (several tests)\*
- FebriDx (CRP+MxA)

### Semi-quantitative lateral flow assays

- CRP (several with cut-offs including 10/40/80, 3/10, 10/30, 10/60 mg/L)
- PCT (several tests)\*
- Transfer of the sTREM biomarker to a semi-quantitative RDT is ongoing

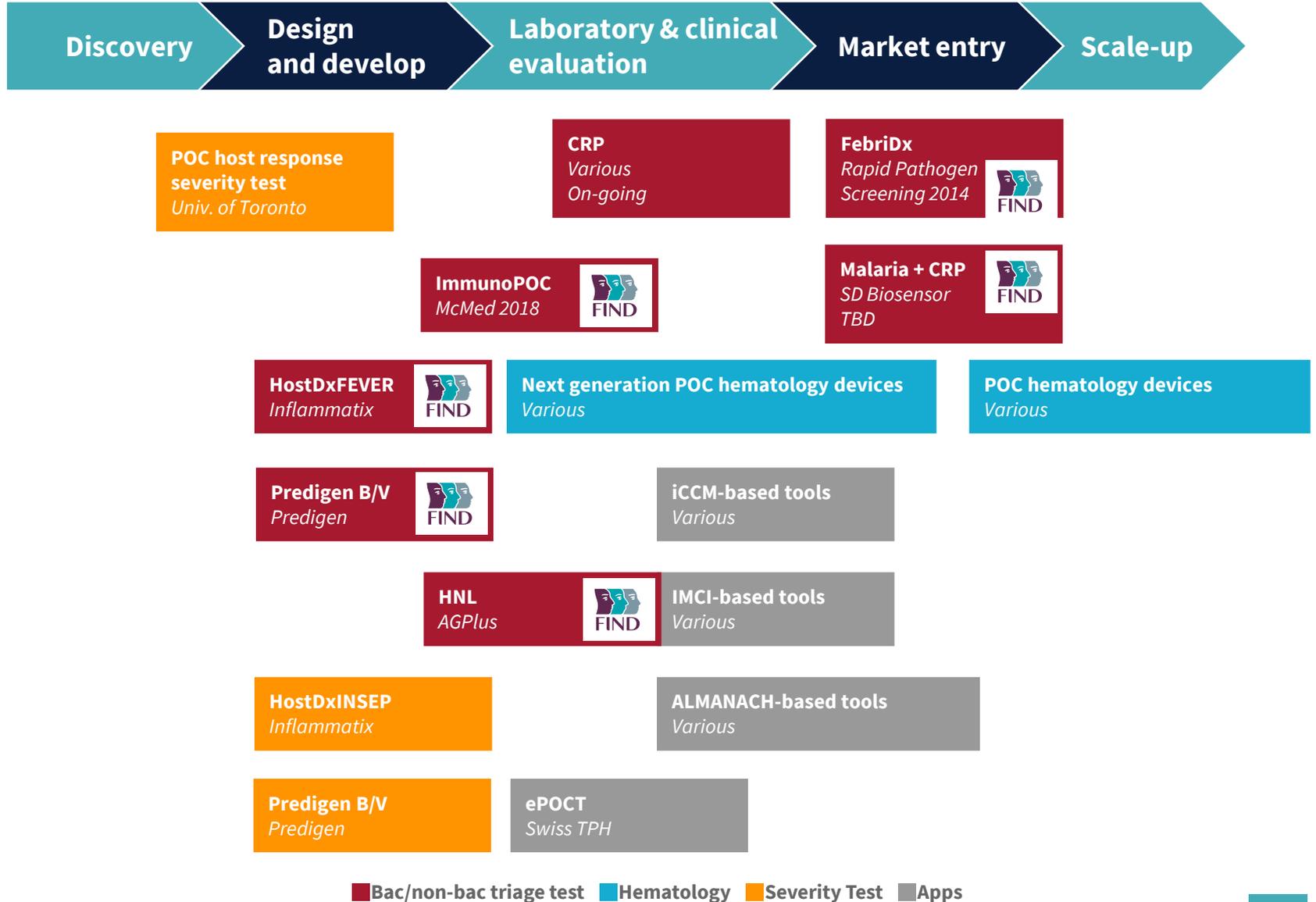
### Malaria-CRP combinations for low malaria-endemic settings

### POC hematology devices

- Several devices

\*many use serum/plasma, requiring blood draw and centrifuge

## PIPELINE



# Abbreviations

- **AFI** Acute febrile illness
- **A-1** acid glycoprotein
- **AMR** Antimicrobial resistance
- **Ang-1** Angiotensin-1
- **Ang-2** Angiotensin-2
- **ARI** Acute respiratory illness
- **Azu/HRP** azurocidin 1/heparin binding protein
- **CHI3L1** Chitinase-3-like protein-1
- **CHW** Community health worker
- **CRP** C-reactive protein
- **CXCL-10** C-X-C motif chemokine-10
- **eCDA** Electronic clinical decision algorithm
- **FIND** Foundation for Innovative New Diagnostics
- **FLT-1** fms-like tyrosine kinase-1
- **HBP** Heparin-binding protein HBP
- **HIC** High-income country
- **HNL** Human neutrophil lipocalin
- **iCCM** Integrated Community Case Management
- **IFN-gamma** Interferon gamma IFN-gamma
- **IL-10** Interleukin-10
- **IL-4** Interleukin-4
- **IL-6** Interleukin-6
- **IL-8** Interleukin-8
- **IMCI** Integrated Management of Childhood Illness
- **IP-10** Interferon-γ induced protein-10
- **LBP** Lipopolysaccharide binding protein
- **LMIC** Low- and middle-income country
- **MoH** Ministry of Health
- **Neutrophil** gelatinase-associated lipocalin
- **PCT** Procalcitonin
- **POC** Point-of-care
- **R&D** Research and development
- **RDT** Rapid diagnostic test
- **sFlt-1** Soluble fms-like tyrosine kinase- 1
- **sFlt-2** Soluble fms-like tyrosine kinase- 1
- **sICAM-1** Soluble intercellular adhesion molecule-1
- **sPLA2** Secretory phospholipase 2
- **sTM** Soluble thrombomodulin
- **sTNFR-1** Soluble tumour necrosis factor receptor-1
- **sTREM-1** Soluble triggering receptor expressed on myeloid cells-1
- **sVCAM-1** Soluble vascular adhesion molecule-1
- **TPP** Target product profile
- **TRAIL** TNF-related apoptosis-inducing ligand
- **WHO** World Health Organization

# What would have the greatest impact to improve healthcare in LMICs?

- [bacterial vs. non-bacterial triage test](#)
- [host biomarkers used for severity triage](#)
- [electronic decision-support systems](#)

# What is the most important to you?

These questions drove discussion at the Technical Working Session on 14 December 2020.

# PRE-READ 3:

Market challenges  
facing host response  
biomarker tests for  
fever

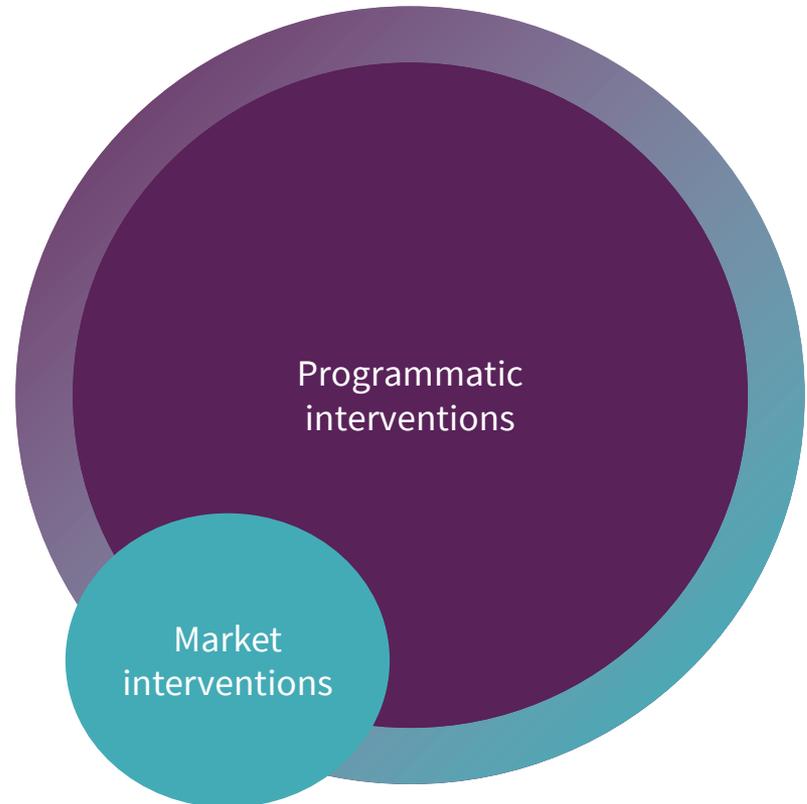
## INTRODUCTION

# Why markets matter

*Global health is inextricably linked to the health of the marketplace that delivers life-saving products to low-income populations. A well-functioning healthcare market with public and private sector participation requires manufacturers to produce high-quality products, distributors to deliver the necessary quantities, providers to administer them correctly, and patients to be educated and active participants in their own health. However, markets sometimes fall short. Developers may not see enough demand to develop a new product, manufacturers may not know how much to produce, and distributors may not see enough profit to justify delivery. The unfortunate reality is that a single breakdown in this complex system can keep life-saving products from those most in need.*

**USAID,  
Healthy markets for global health**

Market interventions are only one piece of the puzzle; they are dependent on substantial, ongoing programmatic interventions.



## INTRODUCTION

# There are many dimensions of market health

### Innovation & availability



- There is a robust pipeline of new products, regimens or formulations intended to improve clinical efficacy, reduce cost, or better meet the needs of end users, providers or supply chain managers.
- New and/or superior, evidence-supported, adapted products are commercially available and ready for rapid introduction in LMICs.

### Quality



- The medicine or technology is available at stringent standard of quality and there is reliable information on the quality of the product.
- This includes also the quality of starting and intermediary materials.

### Affordability



- The medicine or technology is offered at the lowest possible price that is sustainable for suppliers and does not impose an unreasonable financial burden on governments, donors, individuals, or other payers.

### Demand & adoption



- Countries, programs, providers (e.g., healthcare providers, retailers), and end users rapidly introduce and adopt the most cost-effective products (within their local context).

### Supply & delivery

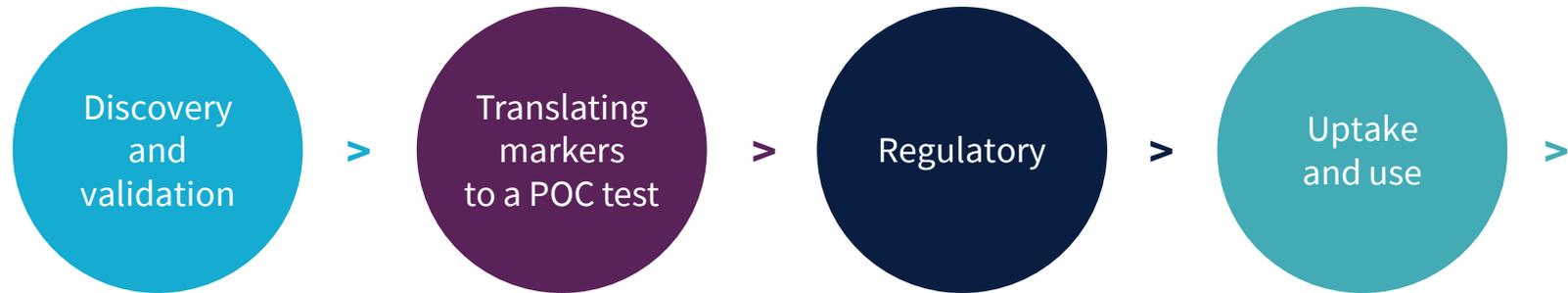


- Supply chain systems (including quantification, procurement, storage, and distribution) function effectively to ensure that products reach end users in a reliable and timely way.
- Adequate and sustainable supply exists to meet global needs.

# MARKET CHALLENGES

## INNOVATION AND AVAILABILITY CHALLENGES FOR HRB TESTS

# Risks are high at every step



- Risk of failure is higher than other tests. Because a variety of factors affect how the body responds to infection, there is high risk that biomarker discovery efforts may not yield markers that are generalizable to a broad population.
- Once validated, the marker, or combination of markers, needs to be translated to a simple POC platform that is both affordable and suitable for use in LMICs. Depending on the markers, the technical feasibility risk is high.
- Regulatory requirements for this class of diagnostics are only emerging. For product developers, the lack of certainty around performance requirements, study design, and comparator methods makes it difficult to plan clinical trials and increases risk that study design will not meet regulatory requirements.
- There is considerable uncertainty for any new class of diagnostics about the timelines for policy adoption and uptake by health care providers. Similarly, the level of evidence required to support decision making at the policy level is unclear, as is the investment required to influence change among providers and patients.

## INNOVATION AND AVAILABILITY CHALLENGES FOR HRB TESTS

# A series of long, complex, and costly trials are required

### Comparator methods are complex

- For bacterial infections, there is no gold standard diagnostic, rather a panel of expert clinicians and augmented laboratory testing are required to validate markers. Augmented laboratory testing is often absent in the locations where trials take place, requiring extensive sample transportation. Comparators for severity prediction tests are also problematic: while many clinical scoring systems exist, most are used on patients already admitted and none are widely used in LMICs.

### Large, diverse study populations required

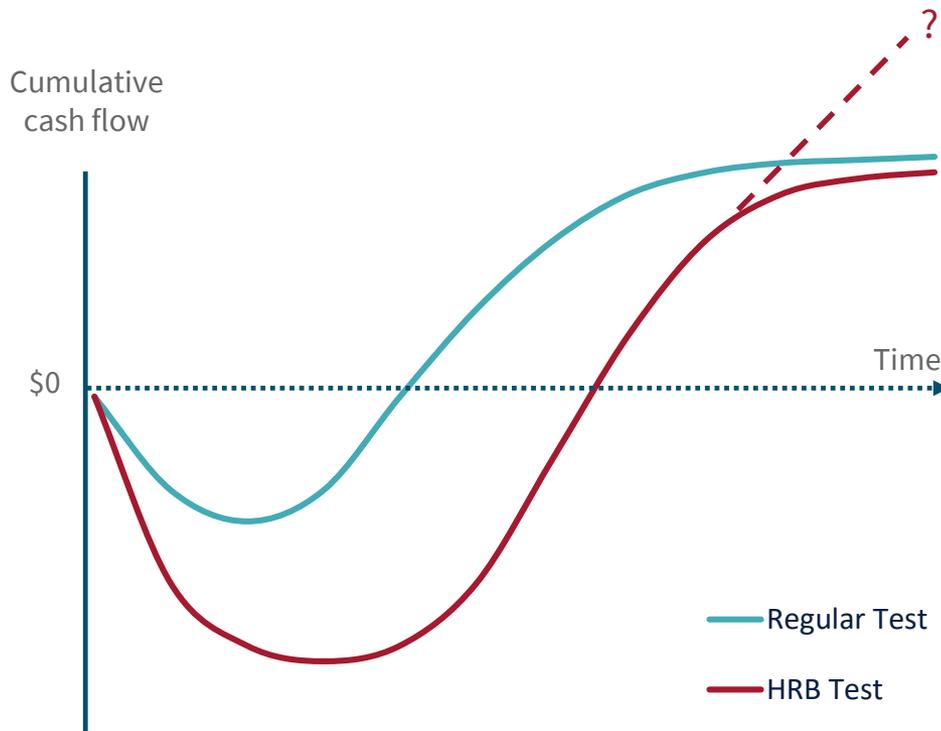
- HRB based tests need to demonstrate performance across a wide variety of patient populations, reflecting multitude of fever etiologies, as well as common comorbidities / coinfections. This range of potential cofounders (age, etiology, underlying disease states) demands large sample sizes across diverse settings. Results will need to be stratified to determine the impact of pre-existing conditions.

### Demonstrated impact and cost effectiveness

- As with the introduction of any new approach, evidence requirements to support policy change and adoption are likely to be high, and will initially include evidence of safety, usability and effectiveness, and followed by broader impact and cost-effectiveness studies. In the case of HB-based tests, looking at these tests in comparison to other markers (e.g. oxygen saturation, measures of malnutrition), will be important as will understanding benefit in cases where focal infections or disease is identified early by clinical algorithms.

## INNOVATION AND AVAILABILITY CHALLENGES FOR HRB TESTS

# High cost and delayed payback make R&D investment unattractive



Companies evaluate R&D opportunities based not only on the size of the payback, but also on how soon payback will come after initial investment.

- Complex large trials are not only costly, but they have long timelines, delaying the payback.
- Additionally, the lack of clarity around the market size (e.g. populations, use indications, and rate of uptake) introduces uncertainty about the size and timing of the payback.

As a result, investments in host response biomarker based tests may be less attractive than other product development opportunities, for example, another new technology may have less costly and time consuming trials and a clear market that is more assured in timing of revenues.

## DEMAND AND ADOPTION

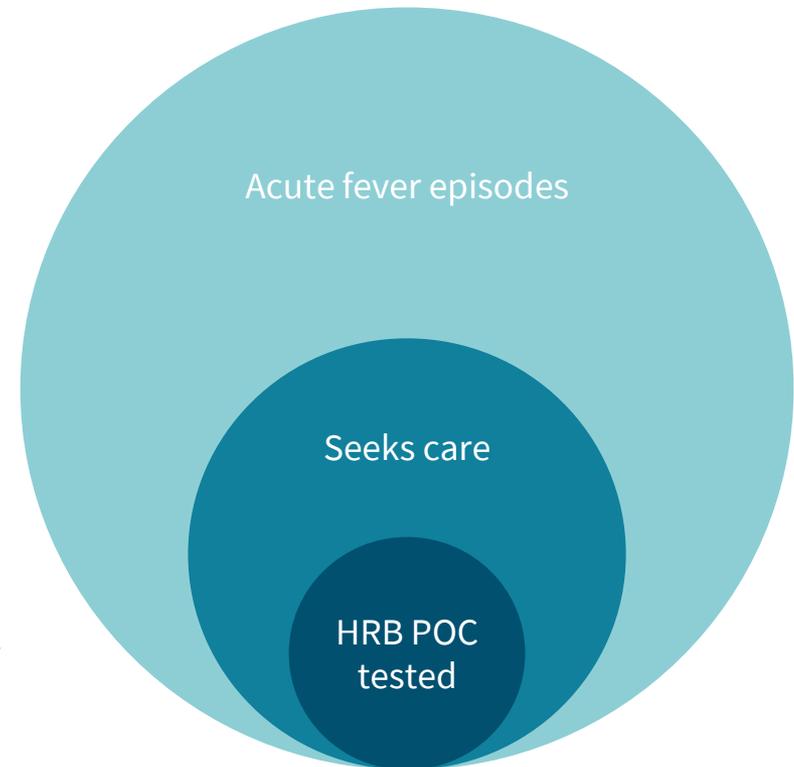
# LMIC demand is uncertain

### Premise: large, robust demand exists in LMICs

- Enormous number of acute febrile illness, episodes, millions seek care and might benefit from severity or bacterial/non-bacterial HRB tests.
- Tests address major challenges that health care workers face in seeing febrile patients, e.g. need to refer/admit? Antibiotic or not?

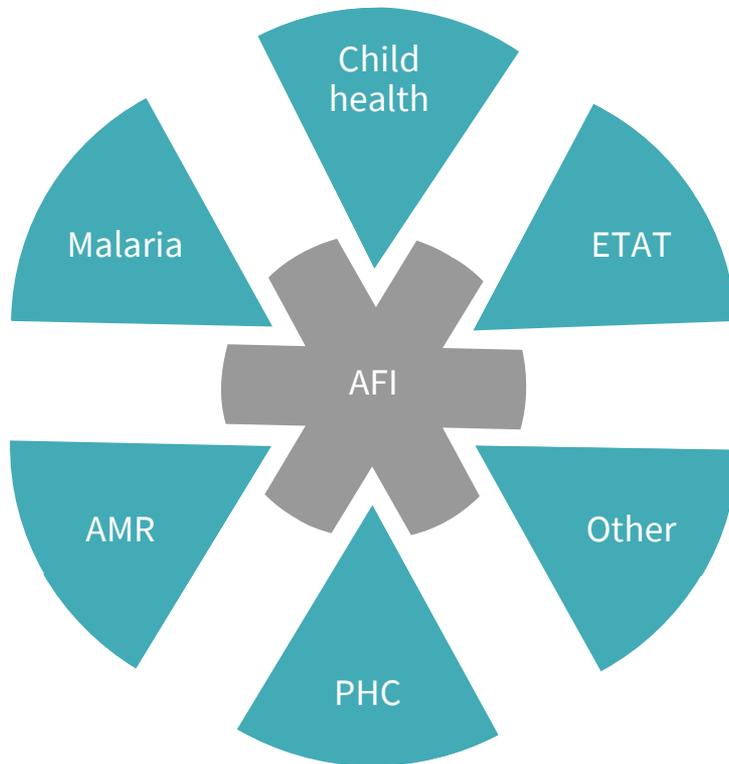
### Yet, many questions

- How many tests are needed, where, for whom? Additionally, in the near term, the pipeline is unlikely to produce a product meeting the "optimal" profile, i.e. a high performing test that could be applied to "all acute febrile illness" at primary and community levels. Acceptance and utility of a "lesser" test is unclear.
- In many ways, malaria RDTs "anchor" program expectations around the price of POC tests, these prices are unlikely realistic for new technologies.
- Who will fund procurement of these tests, especially if their use is widespread? Could an initial scale up funding be sustained?
- Substantial programmatic support is needed for introduction and ongoing monitoring of tests. Can support be mobilized and sustained?



## DEMAND AND ADOPTION

# Acute febrile illness cuts across many areas



Healthy systems are not organized optimally to develop markets for host response biomarker tests for acute febrile illness. Often, donors, Ministries of Health, and budgets are organized around specific diseases. At the same time resources for integrated programs such as child health are few and spread across multiple priorities. Crosscutting focus areas are emerging, for example AMR, yet these lack significant budget.

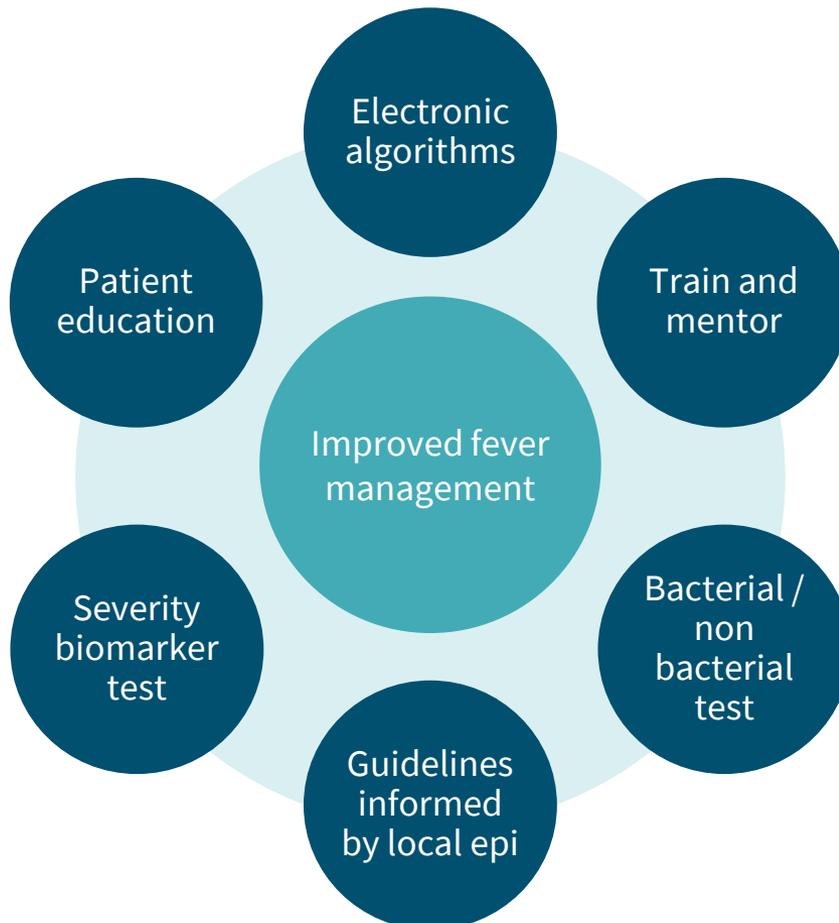
For AFI, there is seldom one focal point because acute fever touches multiple different diseases and health programs.

**While integrated approaches are needed, the lack of clear “owner” raises many questions, for example:**

- Who will develop guidelines and policy for host response biomarker tests?
- Who will mobilize funding to support introduction, scale up, and on-going procurement?
- Who will monitor program implementation?

## DEMAND AND ADOPTION

# Use case: how do host response biomarker based tests fit?



Host response biomarker based tests need to be considered in context of other interventions, including other devices or tests, and systems strengthening activities such as training for health workers and patient education.

## AFFORDABILITY

# Affordability potentially results in cycle of high prices, low demand

### Demand

At the systems level, programs adopting HRB tests are adding a new budget line item where today there is no direct cost (although the indirect costs are potentially high).

Because fever is a common presentation, the number of patients targeted for testing is also quite high, resulting in large testing budgets.

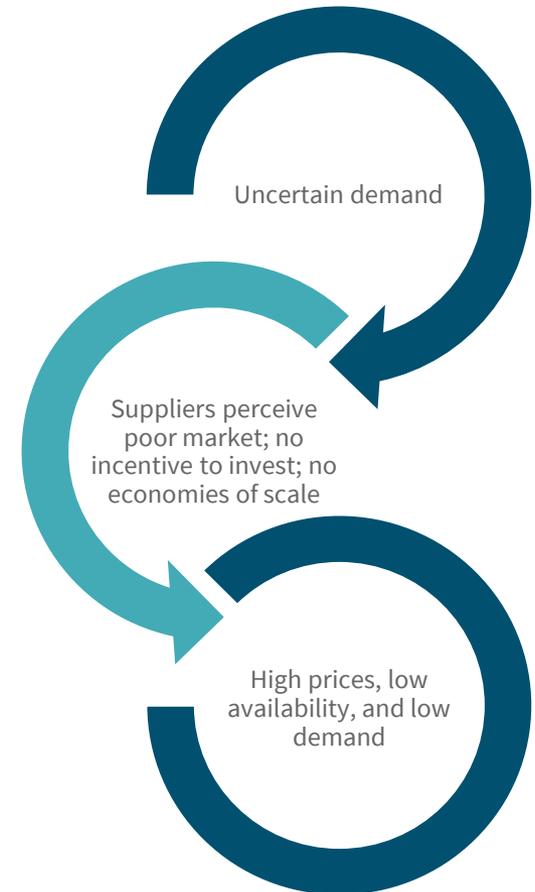
There is no dedicated programmatic donor supporting fever, AMR, or primary care, and as a result, HRB-based tests are likely to compete with other “high-priority” interventions for general health funds.

### Supply

Uncertainty around the market size and sustainability limits manufacturers' incentive to invest in long-term supply of HRB based tests.

While price reductions, resulting from economies of scale, may be possible achieving these high volumes requires sustained demand.

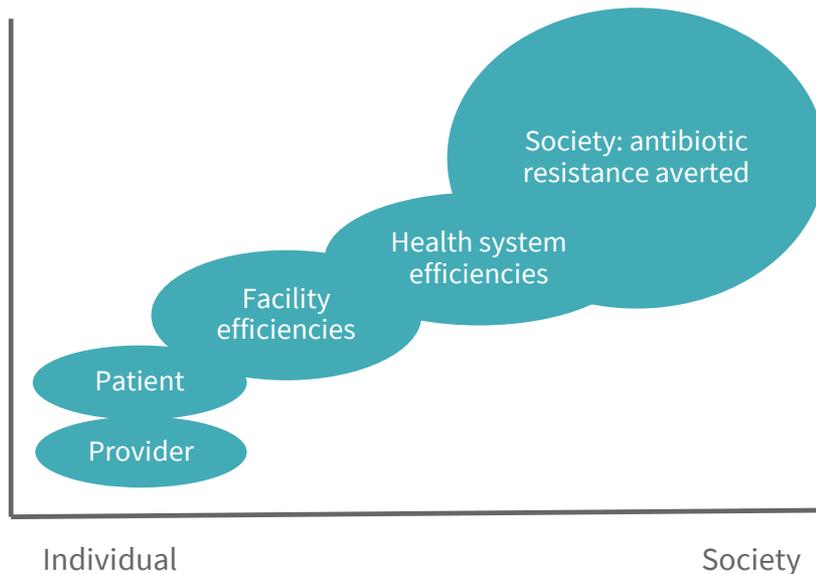
For some host response biomarkers, it may not be possible to achieve necessary performance or multiplexing using the least expensive testing platform (lateral flow assay). Some novel biomarkers are only detected using recent technological advances and methods that are still expensive.



## AFFORDABILITY

# Building the investment case requires new economic models

Benefit of  
HRB test

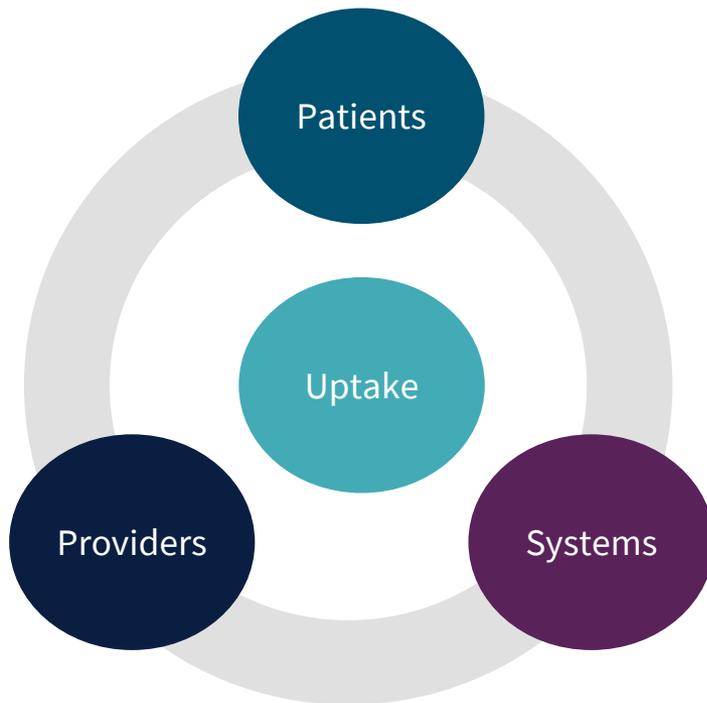


- At the individual level, the incentive to test is often not apparent or compelling. For patients or providers considering an antibiotic, there is no financial incentive to test because the antibiotic costs less than the test itself, and it is faster to prescribe an antibiotic than to run a test. Severity tests are so often going to return a negative result, for provider and patient it may be hard to justify the expense or time.
- Given the affordability challenges and limited incentive to test at the individual patient/provider level, the public health investment case for host response biomarker based tests will rely on strong impact and cost-effectiveness data.
- In the case of bacterial/non-bacterial tests and severity tests, new approaches and economic models for analyzing impact beyond the individual level are needed, as many of the benefits accrue at the health facility and systems level (e.g. efficient use of resources, shorter hospital stays, savings on unnecessary medicines or referrals), or at the society level (e.g. antibiotic averted). These are not always easily visible nor do we have well-developed ways of measuring or quantifying these benefits. While some work on CRP has begun, additional studies are needed.\*

\*See: [Economic considerations support C-reactive protein testing alongside malaria rapid diagnostic tests to guide antimicrobial therapy for patients with febrile illness in settings with low malaria endemicity](#)

## DEMAND AND ADOPTION

# Uptake may be slow: behavior change takes time



- Many patient related factors influence current care, including beliefs and expectations around antibiotics, as well as referral. Patient acceptance of a change in practice resulting from use of HRB tests will require education and sensitization, and even then socioeconomic factors (ability to return to the clinic, or where not covered, ability pay for a test) may influence compliance with guidelines.
- Many aspects of the health system require change to support uptake. Initially, guidelines and policy must be adopted to incorporate HRB tests; the program must training health workers on use of the new technology and guidelines, and ensure continued monitoring and support. Supplies must be available, and referral systems likely need strengthening in many settings.
- Use of host response biomarker based tests may represent a significant change in practice, i.e. introducing a new step in the clinical assessment, withholding antibiotics, and changing referral practices. Health workers will require evidence, training, practice, and mentoring to increase confidence in new practice.

## DEMAND, SUPPLY AND DELIVERY

# Procurement, supply chain and quality mechanisms are needed

### Procurement and supply chain

- Procurement of laboratory tests and “fever” or primary care commodities, outside of major donor channels, is fragmented, with each country doing its own procurement.
- For host response biomarker tests, driving demand to robust, good quality, affordable products will be difficult without a trusted mechanisms for understanding the product offering.
- LMIC supply chains also need strengthening, as essential commodities often fail to reach the lowest levels of the system, where many host response biomarker tests would be most beneficial.

### Quality

- Currently, host response biomarker POC tests are not included in the WHO PQ program. While PQ’s scope is expanding, host biomarker tests are not in the scope, and the expansion is likely to be delayed due to current focus on Emergency Use Listings for Covid-19 tests.
- Additionally, there is limited regulatory precedent for host biomarker tests for the proposed use cases, i.e. guiding antibiotic use and referral decisions. For example, although procalcitonin tests have been on the market for several years, only in 2017 did FDA clear it for antibiotic management decisions in patients with lower respiratory tract infections. Because there is no gold standard test for “bacterial infections,” the studies supporting this approval were pragmatic trials, with varying endpoints related to treatment, they were not diagnostic accuracy trials.

## DEMAND, SUPPLY AND DELIVERY

# Covid-19 impact



### Country context

- Since fever is a common Covid-19 symptom, there is increased measurement of temperature and therefore screening for febrile illness at health facilities
- Some increased use of host response biomarkers for in patients with COVID
- Disruption in malaria services, with setbacks likely
- Funding directed to COVID 19 efforts



### Research & Development

- Studies have been interrupted and delayed
- Diagnostic test developers have shifted resources and focus to Covid-19 diagnostics



### POC test supply landscape

- Immediate shifts of production to Covid-19 diagnostics
- Expanded RDT manufacturing capacity
- Acceleration in development of POC diagnostic platforms that are potentially well suited platforms for novel host response biomarkers

# **ADDRESSING MARKET CHALLENGES**

## NEXT STEPS

# Summary of key market failures

- Product development & commercialization risks are high
- A series of long, complex, and costly trials are required.
- High costs and delayed payback make R&D investment unattractive
- LMIC demand is uncertain
- Acute fever cuts across many areas, no single focal point
- Use cases aren't clear
- Building the investment case requires new economic models
- Uptake may be slow: behaviour change takes time
- Procurement, supply chain and quality

NEXT STEPS

# Addressing market failures: example interventions (1/2)

Intervention	What is it?	Relevance
<b>Cost effectiveness and impact evidence base</b>	Studies looking at cost-effectiveness and impact for specific use cases.	The investment case challenges for host response biomarker tests highlight the need for strong cost-effectiveness data and clinical impact in different settings.
<b>Advanced market commitment</b>	Agreement by buyers to guarantee a market for new products that match TPP at a specified price.	New economic models are needed for AMR diagnostics; an AMC would offset supply risk for HRB tests given uncertain demand and would provide an incentive to introduce products in LMIC as opposed to focus on HICs
<b>Master diagnostics trials</b>	“Master diagnostics trial” are trials that allow evaluation of multiple diagnostics from different companies simultaneously.	<p>“Master Diagnostic Trials” alleviate the burden of expensive, complex, and costly trials by:</p> <ul style="list-style-type: none"> <li>▪ Reducing the cost to each company of enrolling patients because these costs are shared.</li> <li>▪ Standardizing ‘reference standards’ and protocols, easing comparison of tests. Data generated from these evaluations can be submitted to regulatory / registration.</li> <li>▪ For host response biomarker tests, these trials might build on existing platforms (FINDs BFF-Dx, FIEBRE, Spot Sepsis, MORU). Additionally, many developers are small companies and start ups that can not afford extensive trials.</li> </ul>
<b>Quality assessments</b>	Objective, publicly available information on product quality	Buyers need objective information to select high quality products. Suppliers also need incentives to increase quality, despite pressures for ‘low cost.’ Protects high quality suppliers from low quality cheap products.

NEXT STEPS

# Addressing market failures: example interventions (2/2)

Intervention	What is it?	Relevance
<b>Procurement mechanism</b>	Coordinated or pooled procurement	Without large donor/procurers, procurement is likely to be fragmented. Centralized information on product offering, quality and value are needed; scope for pooled procurement to improve affordability and lower transaction costs for suppliers.
<b>Essential diagnostics list and guidelines</b>	Adding HRB tests to WHO and country EDLs and guidelines; monitoring implementation.	<ul style="list-style-type: none"> <li>▪ Guideline inclusion is critical for reinforcing product use and creating demand for new products.</li> <li>▪ Adoption in multiple countries simultaneously supports development of market / incentives for suppliers</li> </ul>
<b>Demand generation activities</b>	Time limited efforts to generate demand for a new class of products.	Activities focused on providers and patients will be needed, especially where the incentive to test is limited (easier to prescribe an antibiotic than to test) to induce uptake at point of service.
<b>Procurement mechanism</b>	Coordinated or pooled procurement	Without large donor/procurers, procurement is likely to be fragmented. Centralized information on product offering, quality and value are needed; scope for pooled procurement to improve affordability and lower transaction costs for suppliers.

# SELECTED RESOURCES

## SELECTED RESOURCES

### **Unitaid fever diagnostic technology landscape, 2019**

[https://unitaid.org/assets/Fever\\_diagnostic\\_technology\\_and\\_market\\_landscape.pdf](https://unitaid.org/assets/Fever_diagnostic_technology_and_market_landscape.pdf)

### **Wellcome Trust, Review of approaches to triage of acute fever, 2019**

<https://app.box.com/s/5wtbrz80x5ehr8ub4rx1gwr5lnbn3h25>

### **FIND's malaria and fever programme website**

<https://www.finddx.org/mal-fev/>

### **New Biomarkers and Diagnostic Tools for the Management of Fever in Low- and Middle-Income Countries: An Overview of the Challenges**

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5617944/>

### **Host biomarkers for fever: recent progress and future challenges** (Technical pre-read for workshop)

<https://drive.google.com/file/d/1W6klkbSVU4Apv-mIQ28UlwGxalHbRNN2/view?usp=sharing>

### **USAID's Center for Innovation and Impact's (CII's) Healthy markets for global health: market shaping primer**

<https://www.usaid.gov/cii/market-shaping-primer>

# Abbreviations

- **AMR** Antimicrobial resistance
- **AMC** Advanced market commitment
- **CHW** Community health worker
- **EDL** Essential diagnostics list
- **ETAT** Emergency triage assessment and treatment
- **FDA** U.S. Food and Drug Administration
- **HIC** High-income country
- **HRB** Host response biomarker
- **IMCI** Integrated Management of Childhood Illness
- **LMIC** Low- and middle-income country
- **MoH** Ministry of Health
- **PHC** Primary health care
- **POC** Point-of-care
- **QA** Quality assurance
- **R&D** Research and development
- **RDT** Rapid diagnostic test
- **TPP** Target product profile
- **USAID** United States Agency for International Development
- **WHO** World Health Organization
- **WHO PQ** WHO prequalification of diagnostics programme

# Thank you!

