BIOMARKERS FOR ACUTE FEBRILE ILLNESS AT THE POINT-OF-CARE IN LOW-RESOURCE SETTINGS

Meeting Report

December 14, 2020
1:00pm-5:00pm CET– Virtual
Technical Working Session

Unitaid
Innovation in Global Health

FIND
Because diagnosis matters

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ABBREVIATIONS

AFI	Acute febrile illness
AMR	Antimicrobial resistance
AUC	Area under the curve
CHW	Community health worker
CRP	C-reactive protein
ETAT	Emergency triage assessment and treatment
FG	Focus groups
Hb	Hemoglobin
HCW	Health care worker
HRB	Host response biomarker
IMCI	Integrated Management of Childhood Illness
LRS	Low resource setting
LMIC	Low- and middle- income country
PCT	Procalcitonin
POC	Point-of-care
RDT	Rapid diagnostic test
ROC	Receiver-operating curve
sTREM	soluble triggering receptor expressed by myeloid cells 1
TPP	Target product profile

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). 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). Current research shows that biomarkers have the potential to distinguish between bacterial and nonbacterial infections and to support triage/risk stratification of severe disease at the point-of-care (POC). Several are already under evaluation, but progress is slow.

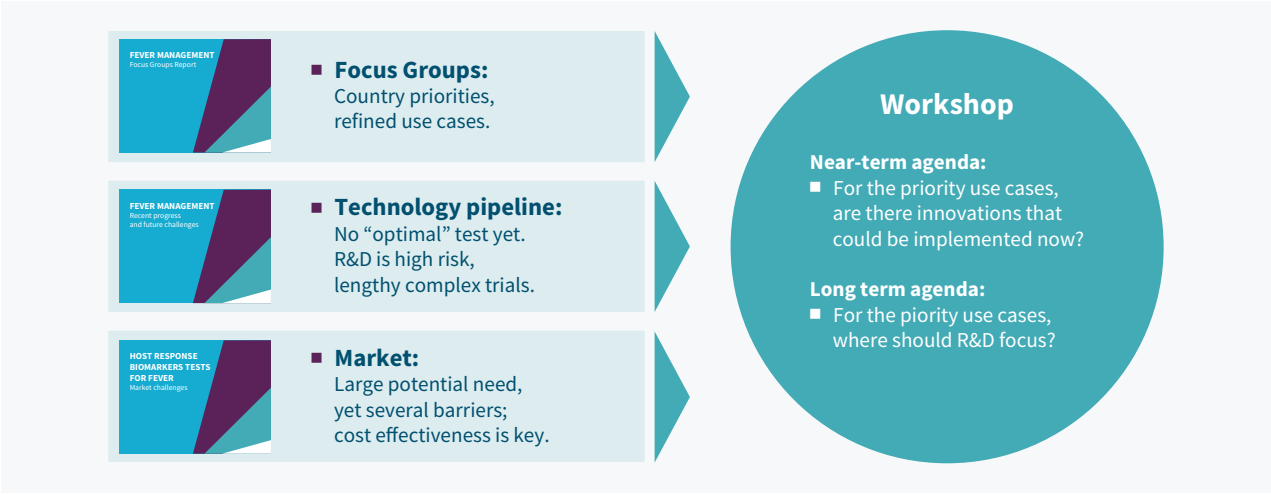
Unitaid is considering how it can best engage to accelerate the development and introduction of new biomarker-based diagnostics for fever management, and FIND is supporting research to demonstrate the potential impact of these tools in LMICs. Together, they hosted a technical working session aiming to:

1. 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)

2. 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

A set of pre-read materials was shared in advance of the session, covering the product pipeline and biomarker research progress, market challenges, and the results of focus group (FG) discussions with key stakeholders (Figure 1). Prior to the technical working session, Unitaid and FIND conducted a series of FGs in October and November 2020 with health care providers, policymakers and researchers working in LMICs. The goal of the FGs was to revisit the challenges facing frontline health workers managing AFI to better understand the use cases for new diagnostic solutions.

Figure 1: Overview of process and workshop objectives



Alexandra Cameron (Unitaid) and Sabine Dittrich (FIND) chaired the virtual meeting and the Executive Director of Unitaid, Philippe Duneton, and CEO of FIND, Catharina Boehme, gave opening remarks. In the first session, Unitaid and FIND's presentations summarized the results of the FGs and the current technology landscape, including a mapping of the priority use cases against the landscape. Both presentations focused on high-level findings, as detailed pre-reads were circulated in advance of the workshop (See Annex II).

Following these presentations, the participants went into five interactive breakout groups to discuss the pre-reads and presentations, and then worked up various use case scenarios proposed during the first session. Lastly, Heidi Hopkins (London School of Hygiene & Tropical Medicine) facilitated a plenary session. The groups shared key points from their discussions, followed by a brief review of major points of consensus and divergence, before wrapping up the workshop.

This report summarizes the meeting discussions, based on a review of the presentations, available recordings of the sessions[1], and notes taken by the organizers.

[1] Available for most but not all of the meeting.

Summary of key points

- The role for host response biomarker (HRB) tests is to add objective measures to clinical algorithms for AFI management in LMICs, complementing existing disease diagnostics.
- The current performance of biomarkers is low, necessitating complex algorithms that are customized to local conditions to support their use and interpretation. Large studies focused on clinical outcomes are needed.
- When considering how HRBs could best add value, most participants at the working session prioritized diagnostics focused on improving detection of severe disease. In contrast, FG participants from LMICs prioritized the need for tests to guide antibiotic use. Yet, given the dual importance for public health (e.g. global mortality measures to meet sustainable development goals, AMR) and individual patient health (e.g. practice of evidence-based medicine at primary care in resource-poor settings), there is a need to integrate these objectives.
- Decisions to implement HRB interventions are shaped by an important tradeoff: acting now with less than perfect tools or delaying action with the prospect of better tools, with more straightforward implementation. Overall, a stepwise approach is warranted, beginning with improving risk assessment and severity detection, followed by the application of existing inflammatory biomarkers to assist with antibiotic decision-making in those patients at low-risk for severe disease. As more evidence becomes available on both novel biomarkers and on withholding antibiotics, an approach that uses HRBs for risk stratification and reduction in antibiotics might be possible.

FRAMING THE NEEDS, USE CASES, AND PRODUCTS

Centering the needs of health care providers identifying and managing acute febrile illness

Kelsey Barrett, Unitaid, presented the FG findings and the suggested use case scenarios for host response biomarkers (HRBs) emerging from the FG discussions. Technology development should be driven by a clear understanding of the challenges and needs in the contexts of use. The FGs intended to ground discussions in these needs.

The FGs reaffirmed that AFI is an important and timely topic, even in the context of the COVID-19 pandemic. The FGs prioritized training, especially at the primary and community levels, increasing the use of vital signs devices, and POC HRB tests. Although optimally, one would have both, the FGs did not prioritize HRB tests for predicting severe disease as highly as they did bacterial/nonbacterial tests.

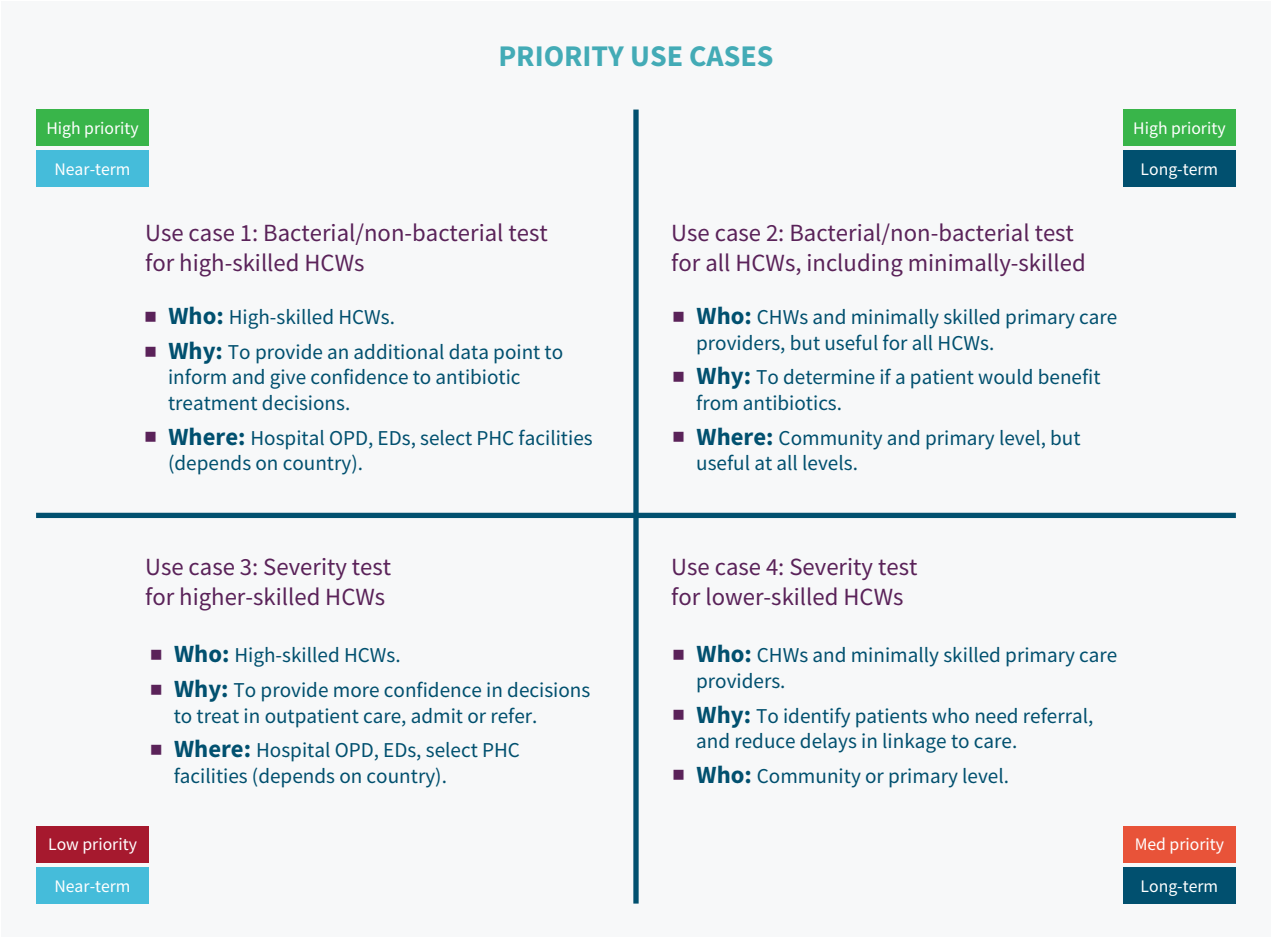
A recurring topic was the "confidence" of the health care worker (HCW). Participants shared the perspective that when they are not confident, they tend to overprescribe and over refer. There was a strong consensus that any additional data or information provided to the HCW must be actionable and tailored to the context. For example, the FGs noted the importance of appreciating the health worker's training and qualifications, their scope of practice, and the treatments, services, and technologies available where they are working.

For HRB tests, FGs tended to segment HCWs into those that have some clinical reasoning skills, who can take a less than perfect test or data point and "use it as one piece of the puzzle" versus lower-skilled HCWs who require definitive "yes/no" guidance. Many FG participants referred to "imperfect" tests (e.g. C-reactive protein (CRP), Procalcitonin (PCT), White blood cell count (WBC)) and suggested these could be used today by skilled HCWs, with the proper training and support. For lower-skilled HCWs, performance and simplicity, akin to a malaria rapid diagnostic test (RDT), would be required.

Stratifying the 'fever' use case

FIND and Unitaid used input from the FGs to revisit the TPP framing and to pragmatically stratify the broad use case of "all AFI" based on the user of the test (i.e. focusing on the differences between HCWs), the problems they face, and where they are working. This analysis resulted in four proposed use cases (Figure 2).

Figure 2. Proposed use cases for HRB tests



Note: Prioritizations are based on the FG discussions and the near- or long-term determinations are based on the pipeline.

Mapping the needs and use cases against the diagnostic development pipeline

Sabine Dittrich, FIND, presented a mapping of these refined use cases to the technology pipeline.

Since the initial landscaping activities for HRB, progress has been slow, with some technologies dropping out of the pipeline. This is likely a reflection of the complexity of developing these tests and of market introduction. The presentation walked through the four use cases (Figure 2), mapping these to existing and pipeline HRB technologies (Table 1). Overall, the presentation showed some tools are available, and others are being developed, yet nothing fits perfectly with the use cases or needs.

Table 1: Key highlights from the HRB test landscape

Near term	Long term
HRB for bacterial/non-bacterial differentiation	
Several tests exist, including CRP/malaria RDTs, qualitative and quantitative CRP, quantitative PCT, FebriDx, and POC hematology analyzers. There are many studies where CRP is used to guide antibiotic treatment decisions, with considerable ranges in sensitivity and AUC (.5-.8), depending on the cutoff used. For semiquantitative or qualitative tests, the cutoffs used in high-income countries (10 mg/mL) are probably too low for LMIC use, so product development would be needed. FIND's BFF-Dx study results from Malawi and Brazil: ■ CRP performed better than other existing markers at differentiating bacterial from nonbacterial infections; for non-malaria patients AUC was 0.6. ■ WBC and Neutrophil have high sensitivity (~70-80%) for differentiating bacterial from nonbacterial infections.	In the BFF-Dx study, human neutrophil lipocalin (HNL) performed better than CRP in malaria-negative patients (0.7AUC, Malawi data only). Additional POC hematology analyzers are in late-stage development for POC use but require product development to improve fit-for-purpose in low-resource settings (LRS).
HRBs for severity triage	
Few options exist, including PCT, lactate POC devices, and a more recent vascular marker, sTREM, available on the Ella platform (not a POC device) for research use only.	sTREM is in development as a semiquantitative device and reader. Others include mRNA signatures run on larger devices. However, the underlying technology would require extensive development to be suitable for use in LRS.

KEY DISCUSSION THEMES

Role of host response biomarker (HRB) tests

For most, **the role of an HRB test is to add objective measures to current algorithms.** For example, an HRB test could address shortcomings in the current Integrated Management of Childhood Illness (IMCI) algorithms by:

- Reducing reliance on subjective signs and symptoms used in the algorithms. In particular, there was considerable discussion around the weakness of current clinically assessed danger signs.
- Addressing the tendency for IMCI to overtreat patients (i.e. wrongly treating some milder cases because they fulfill a "severe" condition).
- Identifying impending severity in patients who lack clinical signs of severity as determined by IMCI (assuming a highly prognostic severity HRB test was available).
- Providing additional guidance in instances of diagnostic uncertainty (i.e. using an HRB test following a negative malaria RDT to guide next steps and treatments).

In addition to providing objective data to the HCW, HRB tests may lend confidence to the HCW's decision, thereby increasing patient and caregiver acceptance of the recommended management. Another potential role is guiding further testing in settings where this is available; HRB tests could help sequence tests, while being mindful of costs.

The value-add of HRB tests

There was extensive discussion around the main objectives of using HRB tests in connection with AFI. Participants grappled with various priorities: improving care, reducing mortality, preventing AMR, or a combination of these goals.

Ultimately, the value of different use cases and HRBs depends on which outcomes are considered most important. For example, a CRP test might be helpful if the aim is reducing AMR and supporting providers with additional data points encouraging evidence-based medicine; however, for mortality, prognostic biomarkers would have a greater impact. **Overall, and in contrast to the FGs, discussions in the working session prioritized outcomes focused on mortality.** Some participants explained that the priority in caring for an acutely febrile patient is assessing severity and that the rationale for treating febrile patients is to prevent mortality. Others suggested that preventing mortality and reducing AMR need not be mutually exclusive; optimally, one would find an approach that would positively impact both.

HRB tests differentiating bacterial vs. nonbacterial infections

Those who prioritized HRB tests for bacterial/nonbacterial differentiation stressed this tool's utility for HCWs and the need to change community expectations around antibiotics. The biomarker test's value is in filling a gap in the guidance for managing febrile patients, especially after ruling out malaria. Proponents pointed out that while the tool may not impact the mortality rate, it would greatly help HCWs, empowering them to make better decisions around antibiotic use.

Attitudes towards antibiotics also need to change; many febrile patients and their caregivers only feel like they have received quality care if prescribed an antibiotic. Participants reflected on the change in expectations that occurred in the decade following malaria RDT introduction and suggested a similar shift might be possible with HRB tests. Prior to malaria RDTs, antimalarials were given for any fever. Now, with the ease of using these tests, and the confidence in their use, communities expect to test before treatment.

Another benefit of HRB tests is protecting the supply of treatments on hand, as their irrational use leads to stockouts. Stockouts occurring in severe disease treatments are especially concerning and not infrequent.

From a global AMR perspective, an HRB POC test for differentiating bacterial from nonbacterial infections is the most pressing need to reduce antibiotic use in LMICs. Its value is in mitigating the longer-term consequences of overtreatment and in preserving tools for future generations. It was acknowledged that the immediate effect on mortality might not be as high as other interventions, but the use of these additional data points paves the way for more evidence-based care at primary levels and mitigates AMR in the long term.

Notably, several participants expressed concern with the "overly simplistic" approach of differentiating between bacterial and nonbacterial infections and suggested **reframing the bacterial/nonbacterial use case as "aiding decisions around the patient's antibiotic needs."** Reasons for this approach include:

i) Co-infection and colonization by bacterial, viral, and other pathogens suggest that it is difficult to attribute illness to a single etiology.

ii) The possibility of safely withholding antibiotics in mild illnesses, irrespective of etiology, since new evidence suggests that mild bacterial infections may be self-limiting and resolve without antibiotics.

iii) A clinician's decision to provide antibiotics is closely linked with severity: the clinical encounter focuses first on assessing how sick the patient is, with severity and risk being the driving factors in deciding who to treat with an antibiotic.

Despite these concerns about the bacterial/nonbacterial framing, participants see a role for HRBs in rational antibiotic use. HCWs often provide antibiotics as a "safety net." Therefore, knowing the patient is not likely to deteriorate increases confidence in a decision to withhold antibiotics. Along these lines, HRB tests may also play a role in addressing patient pressures and expectations for treatment by providing reassurance that the patient is not severely ill and is unlikely to have a bacterial infection that would benefit from antibiotics.

HRB tests that identify severe illness

While not unanimous, **most participants at the working session prioritized HRB POC tests for severity for use by lower-skilled health workers at the lowest tiers of the health system.** Participants argued that this would have the most impact on morbidity and mortality in the near term. Groups working on the severity use cases pointed out that the optimal marker would not only identify patients presenting with severe disease, but importantly would also provide an early indication of severity in patients appearing clinically stable (i.e. a truly prognostic marker that could identify severe disease before overt clinical signs appear). Even if the HRB picked up only some high-risk patients who are not extremely sick when assessed, such a test would be valuable if deployed widely, especially at lower tiers of the health system, because early recognition would allow more time to complete the referral. Additionally, such a test would pick up patients already severely ill, serving as a safety net for lower-skilled health workers who may miss the more overt clinical signs of severity.

There was some discussion about why the FGs did not prioritize severity HRB tests more highly. Meeting participants hypothesized that the FGs might have considered severity triage to be adequately addressed through training, algorithms like IMCI and Emergency Triage and Treatment (ETAT), or increased use of pulse oximetry. Others suggested that FG participants may be less likely to value prognostic tests, particularly those aiming to identify severity before clinical signs appear, because these tests do not yet exist. Differences in prioritization may depend on perspective. For example, many

participants in the FGs were providers with a more immediate focus on individual patient care, while participants in the technical working session tended to be public health-oriented (e.g. focused on mortality outcomes). Alternatively, for participants focusing on the community level, identifying severity is critical to saving lives and engendering trust in HCWs (i.e. if the HCW under refers, the community may not seek care with them in the future).

Overall, despite differing perspectives on priorities, participants felt that **early identification of severe illness and minimizing irrational antibiotic prescribing were both important, signifying the need to integrate these objectives.** For example, HCWs might use HRBs to risk-stratify patients who are more likely to have poor outcomes and target antibiotics to this group. In this scenario, the HRB test improves mortality through early identification of severity and risk and also reduces antibiotic overuse.

Alternatively, two HRB tests may be needed, given the difficulty of finding a single test that can perform all these functions. Along these lines, HCWs would use one test to rule out antibiotics. They would use the second test in patients who do not fit obviously into the spectrum of severely ill versus well, the test would guide decisions about whether the patient needs admission, closer follow-up, or referral. In this instance, it would be ideal to have one technology platform that runs both tests developed by the same company.

Use case refinement and segmentation

There was general agreement around the utility of stratifying the use cases in order to progress these conversations around HRBs for AFI. Participants made suggestions for further refinement, described below.

Refine end-user segmentation by considering scope of practice and setting

In addition to skill level, and perhaps more important, is the HCW's scope of practice (i.e. the actions they are competent and licensed to take) and the available treatments, diagnostics and services at the site where they work. For example, in many countries, community health workers (CHW) do not prescribe antibiotics, and therefore HRB tests supporting antibiotic decision-making would not be relevant for CHWs. Additionally, when considering the HCW's skill level, there is potential for training and supervision to address some competency gaps.

Consider patient factors

A few groups also recommended considering patient factors within the use cases. For severity biomarkers, one suggestion is to call out specific population groups, such as newborns 0-28 days old or 28-90 days old, children under 5, and pregnant women. Considering HRB tests for guiding antibiotics, other participants suggested subsets based on the patient's presenting symptoms, such as fever with or without respiratory illness. The IMCI classifications could provide a useful framework for these divisions.

Define severity

Another group recommended being more explicit about the definition of 'severity.' For example, does severity mean: severe symptoms and clinical signs; need for urgent intervention or referral or special treatment; the level of health care required to intervene; or the presence of elements associated with a fatal outcome? Participants discussed how severity might differ by patient population (e.g. children and immune-compromised patients) and that there may be subgroups within the proposed use case.

Performance of available HRB tests and implications

Participants acknowledged that generally, **the performance of biomarkers in the pipeline is low, necessitating complex algorithms to support their use and interpretation**, especially where HCW skills are low. Others suggested that given their nature and biology, HRB tests will never be "perfect."

Moreover, **one-size-fits-all global guidance will be difficult to develop,** especially for the familiar biomarkers that are affected by various diseases and conditions. For example, malaria, TB, and dengue are all known to impact inflammatory markers like CRP. Therefore, **local epidemiology will influence policy decisions about adopting and using HRB tests in a particular geography. At the same time, other contextual and patient factors may affect who to test and how to interpret the results.** One could envision an algorithm in which various rapid tests eliminate people from the pool tested with an HRB, thereby improving its performance in the tested population. However, such an intervention's complexity underscores the need to support its use with context-specific guidelines, training, and supervision. Implementation may require bespoke regional and possibly country guidelines tailored to different contexts.

One participant summarized: "it is a complicated problem and requires a complex solution which will be an integrated approach between clinical features and biomarkers, integrated in a context-specific way depending on local epidemiology - acknowledge upfront that this is difficult. There is no point simplifying it if it doesn't end up with a solution that we need."

Evidence base and study design improvements

Several participants mentioned **the lack of studies designed to provide data on clinical outcomes** of the biomarkers and the need for studies to establish performance linked to outcomes. This is needed for existing biomarkers as well as those in the pipeline and was flagged as a significant gap.

There was broad agreement on the **need to improve outcome metrics** and study designs. While AUC/ROC provides a snapshot useful for evaluating and comparing biomarker performance, they are less helpful when considering specific contexts and use cases. For the latter, the participants recommend outcomes data presented in ways more familiar to clinicians. For example, along with the sensitivity and specificity, it would be helpful to have associated clinical outcomes such as the number of children missed, morbidity and mortality data, or over and under prescriptions. Predictive values and

likelihood ratios are more intuitive and actionable for clinicians. One group suggested having a few thresholds for assessing sensitivity and specificity of different HRB test algorithms, which would assist in thinking about the clinical decision being made.
For severity biomarkers, while mortality is important, several other outcomes were discussed, including admission to critical care and vital organ support. While these are not as objective as mortality, and might mean different things in different settings, they are pragmatic as mortality is relatively infrequent. Additionally, thus far, many bacterial/nonbacterial studies have not incorporated severity. Building on discussions about linkages between severity and providing antibiotics, severity may be an essential consideration for future bacterial/nonbacterial HRB studies.

Thresholds

Although HRBs lend themselves to gradients, for widespread use, cutoffs are likely needed. Participants discussed whether it would be possible to use specific biomarker thresholds to produce binary test results. While some preferred use of conservative thresholds, others acknowledged that host response biology lends itself to gradients and is an accepted norm. In this instance, interpretation of quantitative biomarker test results would be aided by training and use of sophisticated algorithms, likely digital.

Implementation and the additive, complementary nature of HRB

The group felt strongly that **HRBs would always be integrated into a larger algorithm** (i.e. augmenting IMCI). The HRB must be inserted into a clinical judgment system recognizing different levels of clinical training at lower- and higher- levels and the costs. Participants stressed that it is absolutely not the case of the biomarker replacing the HCW, acknowledging that there might be various degrees of reliance on the test depending on the HCW's background. While HRB tests might replace underperforming aspects of existing clinical algorithms, this also needs to be evaluated carefully for safety and value for money.

Similarly, participants emphasized that use of **HRBs must complement pathogen-specific diagnostics and clinical algorithms.** In some instances, both the pathogen and the biomarker levels may help, for example, where patient trajectories may differ (e.g. dengue). In other cases, having both may not be as relevant. It will be important to consider the sequencing of testing within algorithms to make sure everything is complementary and to train HCWs to use the tests in the right order to maximize the amount of information obtained.

Other discussion points included ensuring integration and consideration of all the expectations for HCWs at the primary level (i.e. the feasibility of completing several lateral flow tests at a small clinic). In addition, participants emphasized the importance of **ensuring the results of any new HRB are actionable.** For example, to determine if a patient needs oxygen, pulse oximeters outperform clinical judgment and with the result, there is a clear next step.

Most groups touched on how HRB tests could complement other tools and interventions (largely pulse oximetry). Participants noted the importance of combining different interventions and the need for well-funded studies with large sample sizes to assess impact. For severity/risk stratification biomarkers, participants suggested evaluating HRBs both independently of and in conjunction with interventions aiming to improve, often singular aspects of, risk assessment (i.e. assessing nutritional status, anemia, and need for oxygen).

Several existing diagnostic technologies are not currently widely available in LRS, but they should be considered with the commonly discussed inflammatory and vascular HRBs. These include:

- **Hemoglobin**, which is helpful in risk stratification and is actionable. The WHO prequalification team plans to establish guidance for portable hemoglobin tests in the coming year.

- **Lactate**, which is a marker of severity that correlates with mortality and is associated with clinical severity scores. In studies of pneumonia in children, it has predicted consolidation on X-ray. POC devices exist and have been studied in LRS. Their use would require additional studies, including defining criteria for use, both to support simplicity of implementation and the predictive value.

- **Blood counts**, which are very familiar to many HCWs in LRS. For example, many clinical officers have been trained to interpret a complete blood count and it can yield useful information. Yet access is lacking, and even in hospitals, routine labs like CBC are not consistently available.

Additionally, despite mixed reactions from the FGs on electronic clinical decision support tools at primary and community levels, participants stressed their relevance in integrating increasing data from various devices and diagnostics.

Participants also discussed a few market and product development topics. One group cautioned that generally, as the use cases become more refined, the market size gets smaller and less attractive to manufacturers. Given the complexities and nuance of implementation, appending the algorithm to the TPP could help developers understand the context and need.

Finally, from a market perspective, considering these tools as a 'class of products' with an existing generation of tests and a second-generation (e.g. novel biomarkers or varying cutoffs) provides helpful framing and positioning to product developers. As studies on operationalizing and using HRB tests are conducted, these should inform what needs to follow (i.e. what the second generation of tests look like).

CONCLUSIONS

Overall, the meeting was a timely touchpoint for stakeholders. Despite the dominance of the COVID-19 pandemic in 2020, HRBs for AFI are still a priority and an important topic. That said, there are differing perspectives on priority applications for HRBs. In some respects, the meeting met objectives; however, with limited consensus on the priority use cases and needs, the overall vision is unclear. Nevertheless, several new insights emerged from the meeting, as well as clear next steps for advancing HRB work in both the near- and long-term.

The meeting highlighted several areas of agreement. First, participants believe there is a role for HRB tests to add objective data to AFI management in LMICs. The meeting affirmed that HRBs would always be part of a more extensive algorithm, and implementation of today's available biomarkers would likely be complex and customized to local conditions. This scenario contrasts with the familiar malaria RDTs, which have good performance, clear indications for use, and binary results that are readily actionable. Meeting participants agreed on the need to strengthen severity assessment and risk stratification in current algorithms like IMCI. They also agreed on the need for more HRB trials, particularly, large studies focused on clinical outcomes. Finally, although the scope of the FGs and this meeting included adults, the vast majority of discussions focused on children under five and IMCI.

There was considerable discussion about how HRBs could best add value, with most participants prioritizing HRB use cases aiming to improve detection of severe disease. Since the FG's prioritized the need for tests to guide antibiotic treatment decisions, it would be worthwhile to further flesh out how to accomplish both reductions in mortality and antimicrobial resistance using HRBs.

For example, participants suggested that the HRB test itself could support severity assessment and indirectly reduce antibiotic overuse, if antibiotics are restricted to those patients deemed severe or at high risk for deterioration. To date, there is emerging, but not equivocal, evidence for withholding antibiotics in children with mild ear or pneumonia infections, even if the etiology may be bacterial. Understanding what level of evidence would be necessary to change clinical practice and existing IMCI guidance is necessary. This long-term paradigm shift merits further exploration, including reviewing key assumptions, the evidence base, and remaining gaps. Alternatively, a scenario using two HRB tests is possible. One HRB test would support antibiotic prescribing in non-severe disease, and a more prognostic test would support admission and referral decisions.

Status of the evidence base

The evidence for HRBs is emerging slowly, although several efforts are underway, delays are common, especially with the COVID-19 pandemic. Considering discussions about the evidence gaps and desired outcomes, it would be useful to map the studies underway, timelines, and outstanding gaps. As a start, several large studies were described in the pre-reads:

- **The BFF-Dx** is providing data on the relative performance of biomarkers in differentiating bacterial from nonbacterial infection, with a specific goal to inform product development as per the 2015 TPP. The study enrolled non-severe patients at first point of contact, aiming to represent the largest population that gets unspecific antibiotics. Disease etiology classification was done for all patients, based on clinical panel assessments, not only microbiological results, to capture the total population that a biomarker test would target. In this evaluation patients were managed per the local standard of care and were not influenced by biomarker levels *(Escadafal et al. 2020)*.

- **FIND AMR Diagnostics Use Accelerator study** is looking at whether an intervention package based on current tools, including CRP, CBC and targeted pathogen-specific RDTs can improve clinical outcomes and reduce unnecessary antibiotic prescription compared to current practice. The study is taking place at 8 sites in 5 countries and will enroll patients with febrile illness (including respiratory symptoms) at outpatient and peripheral health centers. They will be followed up at day 7 and assessed for resolution of symptoms and fever *(Salami et al. 2020)*.

- **Spot Sepsis** should provide comparative data on how well several HRBs predict disease severity in admitted and outpatient children at mid-level facilities (hospitals) serving rural populations in Asia. This prospective observational study is taking place in six Asian countries where children presenting with AFI will be enrolled. A broad panel of clinical and HRBs will be obtained, and outcomes will be assessed at days 2 and 28 (mortality, vital organ support, admission, ongoing symptoms vs resolution of symptoms) *(Chandna, et al. 2021)*.

- **Fiebre, a multi-country fever etiology study**, includes a secondary biomarker evaluation objective. It will assess the performance and potential utility of several HRBs, potentially useful in differentiating bacterial and nonbacterial causes of illness or as prognosticators of severity. Each biomarker and combinations of markers will be compared with mortality and severity scores calculated using clinical data and the subset with microbiological confirmed diagnosis. Patients will be followed up at day 28, and outcomes assessed (complete recovery, improvement, same as day 0, worse, or death) *(Hopkins et al. 2020)*.

- **ICAT, a large implementation study in Vietnam** aims to understand the utilization and impact on antibiotic use of using CRP. CRP is provided as part of normal care packages and outside of controlled study settings in primary health care in Vietnam *(Do et al. 2020)*.

Near- and long-term opportunities

Pragmatically, a stepwise approach is warranted, beginning with the scale-up of existing tools to improve risk assessment and severity detection, followed by the application of existing inflammatory biomarkers to assist with antibiotic decision-making in those patients at low-risk for severe disease.

There is also scope for existing technologies in POC format to play a role (e.g. hematology analyzers) in risk triage and antibiotic prescribing. In the future, as more evidence becomes available on both novel biomarkers and on withholding antibiotics, an approach that uses HRB for risk stratification and reduction in antibiotics might be possible.

Figure 3: Approaches to advancing near- and long-term opportunities

The priorities for longer-term R&D are harder to grapple with unless one has a more singular focus on mortality or AMR, in which case the longer-term path forward is supporting the development of a "next generation" of HRB tests using improved markers in formats suitable for use in LRS.

To guide R&D for prognostic HRBs, it would be useful to put a finer point on the use case and outcomes, including defining severity, emphasizing early identification, and reflecting the different levels of care and available referrals and services. There is no data indicating that existing inflammatory markers are predictive of severe disease in populations relevant to the use cases. Therefore, studies such as Spot Sepsis, evaluating the predictive ability of candidate markers, are needed. Even then, it is known that inflammatory markers (e.g. PCT) are affected by many underlying conditions and would therefore likely require a complex, digital algorithm to support implementation. Ultimately, an HRB that can be applied more universally would be more feasible to implement at the periphery where the impact is highest. In addition to these studies, it will be necessary to evaluate biomarkers in light of what can be accomplished with other risk assessment approaches.

With any of these interventions, there is an important tradeoff to consider: acting now with less than perfect tools versus the prospect of a more straightforward implementation in the future. From a market perspective, this uncertainty and the evidence gaps will hinder engagement with developers and the creation of a market for products. Framing HRB tests as a product class, with the expectation that there will be subsequent generations of improved products over the years as the market becomes more mature, may be useful.

ANNEX I.
ADVANCING RESEARCH AND PRODUCTS BY USE CASE

The use cases and evidence for them were discussed in breakout groups, and the main discussion points are captured below. The annex contains technology-specific notes that were captured by a rapporteur during the breakout groups.

Use case 1: bacterial/nonbacterial test for high-skilled HCWs

Table 2. Summary of revisions to use case — bacterial/nonbacterial test for high-skilled HCWs

Proposed use case		Breakout group revisions
What	Bacterial/ nonbacterial test for high-skilled HCWs	■ Test to guide antibiotic treatment decisions for high-skilled HCWs, noting that bacterial /nonbacterial framework is overly simplistic and that severity and risk should also influence antibiotic provision.
Who	High-skilled HCWs	■ Importance of training and clinical guidelines, even if high-skilled.
Why	To provide an additional data point to inform and give confidence to antibiotic treatment decisions	■ To support decisions around who needs an antibiotic, clinicians need a cost-effective way to say confidently this illness is not a problem, it is not severe, and does not require antibiotics. ■ The value is not in adding care, but in safely withholding antibiotics.
Where	Hospital OPD, EDs, select PHC facilities (depends on country)	■ No revisions.

Target Pop.	Not specified	■ Consider the entry point, is it fever? Or is the target population more specific, fever + respiratory symptoms?
		■ Additional considerations:
		  ■ Endemicity / common causes of fever in a geographical setting may impact the biomarker levels, especially for inflammatory markers.
		  ■ Severity and risk factors for severe disease should influence who gets antibiotics.

Priority	High	■ The group commented that a bacterial vs. nonbacterial framework was overly simplistic, and proposed an alternative framing: does the patient need an antibiotic, irrespective of etiology? ■ They emphasized the need to include disease severity, as often antibiotics are targeted to the sickest patients.
Timing	Near-term	■ Use of existing biomarkers is possible, albeit likely complex implementation and the need for significant training and clear guidelines.

Evidence base and applicability of existing and pipeline HRBs to this use case

One group felt CRP and PCT could be relevant, depending on malaria endemicity and contextual factors, although PCT is more associated with severity and de-escalation of antibiotics. Others, not having had time to closely review the data on biomarker studies in LRS, did not have extensive comments on the markers and tests themselves, but suggested that the biomarkers used would really depend on the data coming out of validations in LRS (i.e. which behaves the best across LRS populations).

While one group considered a CRP+malaria test to be cost effective in malaria settings, the other group felt this test was less valuable for this use case, as higher-skilled HCWs are more likely to be working in settings where malaria testing would be performed at the facility's lab. Additionally, in the case of a referred patient, malaria testing would have been performed already at lower levels of care. One group suggested there was no role for the FebriDx, as it was not performing better than other markers in LMIC populations and was expensive.

Both groups thought POC hematology analyzers could be useful, one suggested they could be used in combination with a CRP or PCT test. Another pointed out the longer-term possibility for simpler tests (e.g. HNL) to serve as surrogates to WBC.

Table 3. Technology summary — bacterial/nonbacterial test for high-skilled HCWs, completed by participants

HRB tests	How well does this HRB test address the problem vs. other tech or interventions?	Would you implement the HRB test largely alone or only with other interventions?	Note any caveats, essential characteristics, implementation considers	If you think other interventions address this problem better than HRB tests, then describe here
Qualitative CRP or PCT POC test algorithm to increase performance	■ CRP: Not perfect but is the most validated test that people are more familiar with and can play a role until we have better tools. ■ PCT: Define severity and de escalation of antibiotics. It is POC/simpler and useful if you have defined threshold (but those would need to be adapted depending on epi conditions, age group, etc). ■ This might provide reassurance not to use antibiotics, but "treat the patient and not the test" (i.e. first priority is the clinical assessment, history, these should always guide and trump a test result, especially in a sick child).	■ Add relevant diagnostics depending on the context (i.e. malaria RDT, HIV, etc). ■ Add WBC depending on price, only look at very high/ low results. ■ Training to interpret the test results. ■ With other interventions, and it is especially important to link to severity. ■ Clinician's role is to determine who is sick (to make a decision about hospitalization, supportive care, broad spectrum antibiotics).	■ Hard to have a global guidance for CRP (depends on underlying epi conditions). ■ Different thresholds needed for different countries and levels of care. It requires a lot of adaptation to be used. ■ Implementation with IMCI, importance of identifying clinical signs. ■ Early use will help to determine if further testing is needed.	■ Semi-quantitative with different thresholds to define severity (rather than bacterial vs non bacterial)? ■ There might be some value to measure lactic acid (POC) for severity.
Quantitative CRP or PCT test	■ PCT: Define severity and de-escalation of antibiotics. You can deploy in different places and then interpret results as needed. ■ CRP - Not perfect but is the most validated test that people are more familiar with and can play a role until we have better tools. ■ Have clear cutoffs but there might be differences of interpretations depending on underlying condition.	■ Add relevant diagnostics depending on the context (i.e. malaria RDT, HIV, etc). ■ Add WBC depending on price, only look at very high/ low results. ■ Training to interpret the test results. ■ Implement with other interventions.	■ Hard to have a global guidance for CRP (depends on underlying epi conditions). ■ It should be part of a larger implementation, using algorithms.	■ Semi-quantitative with different thresholds to define severity (rather than bacterial vs non bacterial)?
CRP + Malaria	■ Current threshold of 20/ mg/ml, although there might be variations threshold. ■ Malaria testing is considered as a given at the sites where highly skilled clinicians are likely practicing, therefore the combination CRP+ malaria is perhaps less useful at these higher levels of care. Malaria testing should always be performed in endemic areas on any patient with fever.	■ Add POC hematology + IMCI + surveillance data that can be incorporated into the algorithms. ■ Training to interpret the test results.	■ Hard to have a global guidance for CRP (depends on underlying epi conditions). ■ Probably more useful at pre-hospital level, when there are patients with fever who are malaria negative, who have no obvious sign / path on IMCI, CRP may also help identify those needing referral.	

■ first group of participants ■ second group of participants

HRB tests	How well does this HRB test address the problem vs. other tech or interventions?	Would you implement the HRB test largely alone or only with other interventions?	Note any caveats, essential characteristics, implementation considers	If you think other interventions address this problem better than HRB tests, then describe here
FebriDx (MxA+CRP)	■ More specificity but less sensitivity than CRP.	■ Designed to be implemented on its own to define viral vs. bacterial. ■ Training to interpret the test results.	■ High cost, look at cost effectiveness? ■ Higher specificity. ■ Mixed infections might decrease confidence of HCWs in the tool.	
POC hematology (WBC etc)	■ Rapid results. ■ Applicability: clinicians will be able to interpret and trust results. ■ Hb has utility, could be important to guide treatment. ■ WBC is useful. Perhaps there are 'surrogates,' such as antigens running on lateral flow that could be even easier to implement at lower levels than POC WBC.	■ Training to interpret the test results.	■ Should we have an adequate lab at this level? Is it worth additional investment vis a vis lab? Cost effectiveness? ■ Problems of stability should be solved in the R&D stage; also need to consider who is tested, how it is used, use cases, etc.	■ Lab infrastructure available at this level?

■ first group of participants ■ second group of participants

Use case 2: bacterial/nonbacterial test for all HCWs, including minimally-skilled

Table 4. Summary of revisions to the use case — bacterial/nonbacterial test for all HCWs, including minimally-skilled

Proposed use case		Breakout group revisions
What	Bacterial/ nonbacterial test for high-skilled HCWs	■ No revisions.
Who	CHWs and minimally skilled primary care providers, but useful for all HCWs	■ Note: Limited to HCWs who prescribe antibiotics, often CHWs do not prescribe.
Why	To determine if a patient would benefit from antibiotics	■ To provide better quality care and reduce unnecessary antibiotic use, protecting supply of medicines that are available. ■ To help the HCW with antibiotic decision-making, as there is currently no guidance or tools. ■ To shift community attitudes towards antibiotics: inserting a test into the algorithm and using it to inform antibiotic prescribing, will bring about change in community's attitude towards antibiotics (i.e. treating all non-malaria fever with antibiotics).
Where	Community and primary level, but useful at all levels.	■ Where antibiotics are available.
Target Pop.	Not specified	■ Non-severe patients, which would require strengthening severity triage in current algorithms (i.e. IMCI). ■ Non-malaria (for inflammatory markers), consider further limiting to only patients with elevated respiratory rates. ■ Focus on settings where overuse of antibiotics is most harmful.
Priority	High	■ Need to consider what the goal of the use case is, is it to impact mortality? To improve the quality of decision making? To play a role in antibiotic stewardship? If goal is to impact mortality, then this is a lower priority; however, if the goal is to improve quality or to play a role in antibiotic stewardship, then prioritization high.
Timing	Long-term	■ Potentially near-term, as the group saw value in conducting studies at primary level using available tests, namely CRP to assess impact and develop models for implementation.

Evidence base and applicability of existing and pipeline HRBs to this use case

The group recommended moving ahead with CRP in the lowest levels of the health system where antibiotics are dispensed, acknowledging that trials are needed, but that these would pave the way for broader use and encourage development of a market for these tests. Among other factors, a key rationale for moving forward in the near term was AMR, and the need to take some steps now, even if not perfect.

The only evidence they were aware of supporting use of HRBs to guide antibiotics was the ePOCT study from Tanzania, and as such, the group recommended additional trials in Africa for lower-skilled health workers using CRP to guide antibiotic decisions. Critically, as a first step, IMCI danger signs and severity risk assessment would need improvement. Following this, a CRP test with a threshold of 60 mg/mL (or lower) could be incorporated into the algorithm, i.e. non-severe, non-malaria fevers would be tested with CRP, (perhaps with elevated respiration or respiratory symptoms) and this would be compared to the standard of care.

Thresholds were discussed extensively, in the context of market size. The group noted there is potentially a variety of "optimal" cutoffs levels, since baseline CRP values differ in populations. For example, children in Africa may have higher levels than adults; regional variation is also expected. This suggests we may need multiple versions of CRP tests, each with different cutoffs. However, from a market perspective, a single test is preferred initially, because the market size would be larger, and manufacturers more inclined to engage. Once the market is established, additional versions of a CRP test with varying thresholds are possible, or, perhaps a "second generation product" based on new more HRB(s) such as HNL or others identified through biomarker studies in LRS. Additionally, from a market perspective, the limitations of existing inflammatory markers preclude their application in patients with malaria and may limit the market size.

Table 5: Technology summary — bacterial/nonbacterial test for all HCWs, including minimally-skilled, completed by participants

HRB test	Would you implement the HRB test largely alone or with key interventions?
Existing: (FebriDx, CRP, CRP malaria)	Near-term: ■ CRP would need to be used with conditions e.g. fever, or respiratory rate, like what is done for malaria. ■ CRP also in conjunction with digital tools, or some form of supportive tool.
In development: (MeMed-POC, HNL-POC, Inflammatix, Predigen)	Longer-term: ■ The tests in development can be thought of as "next generation tests", and further thinking is warranted on the type of studies we need to accelerate their development (acknowledging that they might not be any better than CRP). A CRP test could be thought of as "a class of products", rather than specific biomarker-based products. Several studies and more data are required.

Use case 3: severity test for higher-skilled HCWs

Table 6. Summary of revisions to the use case — severity test for higher-skilled HCWs

Proposed use case		Breakout group revisions
What	Severity test for higher-skilled HCWs	■ Test is highly prognostic (i.e. in addition to picking up severe disease, the test would identify patients who may appear clinically stable but who are at risk of deterioration).
Who	High-skilled HCWs	■ No revisions.
Why	To provide more confidence in decisions to treat in outpatient care, admit or refer	■ Must add value to what is already in place (e.g. clinical skill, algorithms, and tests and monitoring devices). For uptake, it must fit easily into the algorithms already in place.
Where	Hospital OPD, EDs, select PHC facilities (depends on country)	■ A prognostic biomarker would however be quite valuable to highly skilled providers working in remote, less well-resourced facilities, however, the number of sites meeting these criteria needs to be considered. At many facilities, however, alternative diagnostics are available (e.g. vital signs, more sophisticated algorithms in use, CBC, glucose, lactate, etc.) and therefore the 'need' for an HRB test may be less acute. ■ Consider further stratification based on the resources available at the facilities where the HCWs work, as health facility tiers mean different things in different contexts (district, regional, tertiary level hospitals), the level of care available would influence the outcomes.
Target Pop.	Not specified	■ Suggested that in higher skilled providers, the test would apply to patients with some clinical uncertainty.
Priority	Low	■ This group prioritized use case 4, a similar test but for lower skilled HCWs, over this use case, agreeing with the FGs. The group felt that higher-skilled HCW have better clinical skills, and are better able to identify clinical signs of severity and to assess risk, allowing for better implementation of algorithms like ETAT or IMCI. Additionally, they are also likely to have access to other tests and vital sign measurements to support these assessments. Thus, the group considered HRB tests for severity to be more valuable at the community level where the skills are lower, and where many of the deaths occur. ■ Additionally, they noted that at the community level, an ideal severity HRB would not only pick up patients 'early' but would also serve to backstop HCWs with limited ability to assess standard clinical signs of severity, and where other tools are not available to support prognostic decision making. ■ Overall, the group felt that there was great value in identifying patients, especially at lowest levels, who are not severely ill in the moment but are likely to progress, for referral decisions and early recognition of sepsis, etc.
Timing	Near-term	■ Likely a longer-term opportunity in light of current lack of data on how well biomarkers can identify severity early on, in the population of interest (e.g. outpatients, patients presenting to an emergency department).

Evidence base and applicability of existing and pipeline HRBs to this use case

The group noted that nearly all of the studies of prognostic HRBs come from hospital settings in high income countries, looking at severely ill patients in intensive care units. Given the lack of evidence that was relevant to the use case (outpatients who may need escalation of care), the group did not comment extensively on any specific biomarkers, but spent more time defining some of the key characteristics for these tests, most importantly the HRB test must provide actionable data, in a clinically relevant time frame (i.e. early enough for interventions that can have an impact on patient outcomes). In LRS, referrals often take time, for example, by the time referral to a tertiary hospital is completed, patients are often extremely ill which reduces the potential to successfully assess impact outcomes. They stressed that it is not useful to predict mortality when patients are already quite sick and going to die, there is little utility in a "death marker" for this use case, although, there may be value for such a test in inpatient settings (e.g. post discharge care planning; resource allocations).

Table 7: Technology summary — severity test for higher-skilled HCWs, completed by participants

HRB tests	How well does this HRB test address the problem vs. other tech or interventions? (e.g. implementation of ETAT, vital signs)	Would you implement the HRB test largely alone or with key interventions?	Caveats, essential test characteristics or implementation considers	If you think other interventions address this problem better than HRB tests, then describe here
ALL TESTS	■ Only addresses patients who look well but will progress to worse outcomes.	■ Needs to complement tests that are already being use in situ and pathogen-specific tests could be used where available and relevant.	■ Diagnostic information to increase prognostic specificity in a population that likely escalate towards a need for admission. ■ Must add value to existing diagnostic information (e.g. vital sign devices, etc.) ■ Actionable results that impact outcome (mortality, AMR, surrogate outcomes depending on context (i.e. length of stay, delivery of organ support, etc.) ■ Studies to date have primarily been done at hospital level rather than lower level where the max impact will be.	■ Development of machine learning algorithms incorporating various clinical data. ■ Focus training on common causes of AFI at OPD to maximize impact.

Use case 4: severity test for lower-skilled HCWs

Table 8. Summary of revisions to the use case — severity test for lower-skilled HCWs

Proposed use case		Breakout group revisions
What	Severity test for lower-skilled HCWs	■ Similar to use case 3, the test should focus on early detection of severity - in a timeframe that allows for referral to be completed - in addition to the presence of severe disease.
Who	CHWs and minimally skilled primary care providers	■ Additional detail and stratification would be helpful because the treatments, referrals available can be very heterogeneous for "primary" level. The health workers' skill may be less important than their scope of practice and setting, as less skilled health workers would receive appropriate training and supervision to support implementation.
Why	To identify patients who need referral, and reduce delays in linkage to care	■ The emphasis should be on "early" detection/identification of severe disease, as opposed to just detection of severe disease. The group noted potential high impact of being able to detect even a proportion of those children and babies who appear well, but where severe disease could be prevented through early referral. They note that very sick children with overt signs most likely will be picked up with existing algorithms and danger signs, but the "grey area" is where the test could have substantial value.
Where	Community or primary level	■ Suggest adding additional detail on treatments and referrals available (as above).
Target Pop.	Not specified	■ The group suggested focusing on certain populations where mortality is highest, for example within reproductive, maternal, neonatal, and child health (RMNCH) programming. It was noted that newborn babies are a particular area of high mortality, both the first 28 days and late newborn period. Pregnant women were also mentioned. ■ There was discussion about the importance of malnutrition, genetic factors, past history, co-infection/co-morbidities; and how, depending on the biomarker, they could impact biomarker levels, and as a result some patients might need to be excluded from the severity HRB algorithm, or their biomarker levels would need to be interpreted differently from the general population. ■ Even in diseases like malaria where we have good RDTs for diagnosing the pathogen, they pointed out the value in early identification of severe malaria.
Priority	Medium	■ The group felt the use case should be high priority, and this sentiment was shared broadly among the meeting participants.
Timing	Long-term	■ While the group discussed existing biomarkers briefly, they pointed to a lack of data on biomarkers' ability to predict severity and death in a population that is reflective of this use case. The optimal biomarker would identify impending severity with enough time for action, and work universally across patients independently of underlying conditions and risk factors. Since there is no evidence for HRBs that can do this today, this therefore is likely a longer-term opportunity.

Evidence base and applicability of existing and pipeline HRBs to this use case

Two types of markers were discussed:

- Existing markers that are largely inflammatory or hematology based
- Newer markers (e.g. vascular) that are more generalizable across patients with varying underlying conditions and diseases.

The group noted that for the **existing HRBs**, (e.g. CRP, PCT, specific components of the hematology tests), there is minimal data on how well they predict severity and death. While abnormal results for these biomarkers may indicate the need for early therapy (e.g. antibiotics), they are not necessarily predictive of outcomes. Overall, clinical trials are needed to establish performance linked to outcomes, followed by trials on use to inform triage, referral and antibiotic use compared to the standard of care (e.g. IMCI). This is needed for existing biomarkers as well as those in the pipeline and was flagged as a gap effectively precluding any near-term implementation of severity biomarkers.

CRP and PCT are familiar and commonly used, so they may be worth evaluating and are far simpler than hematology tests because they provide a single variable, rather than a WBC. If they were predictive, cutoffs would need to be set, and it would likely be difficult to set one number because these inflammatory markers tend to be dependent on clinical context and patient factors and would therefore require complex algorithms to support their use and interpretation.

Thus, the group felt it may be preferable to focus on some of the newer biomarkers that may reliably perform risk stratification in a variety of underlying conditions (e.g. HIV infections, in malnourished, patients with underlying disease), ultimately predicting clinical trajectory independent of these conditions. While a test like this would be included in an algorithm, it would not require such a highly complex and nuanced algorithm to support its use and interpretation.

The group also discussed the importance of severity markers in the context of other technologies and interventions. The predictive value of HRB tests should be compared to other approaches to stratifying risk and prioritizing resources, for example some conditions that increase risk of severe disease (e.g. malnutrition, anemia) can be measured with existing tools (e.g. MUAC tape) that are already included in IMCI algorithms. Other risk factors for poor outcomes, such as anemia, are currently included in IMCI, but are not well implemented. Introducing technologies such as hemoglobinometers might improve detection of anemia, and subsequent management of these higher risk patients. Overall, those tools that are most predictive of severe disease (i.e. able to identify those patients becoming critically ill, in a relevant timeframe for action) are those that should be prioritized.

Table 9. Technology summary — severity test for lower-skilled HCWs, completed by participants

HRB test	How well does this HRB test address the problem vs. other tech or interventions? (e.g. iCCM IMCI, RR/SpO2)	Would you implement the HRB test largely alone or with key interventions?
Existing: PCT, CRP, Hematology POCT.	■ CRP/PCT widely used but need for clinical data as there is a lack of clinical trials that look at their performance as predictors of severity/death. ■ Need data to inform choice of cutoff values. ■ These are most useful to guide patient treatment. Hematology markers need more granularity to be useful so maybe not a good fit for this use case. ■ Need for clinical trials to produce data on the performance of these biomarkers to predict severity early on in the disease. There is no data and especially no clinical outcome data to inform the choice of best biomarker candidate at this point.	■ CRP: Need to integrate in an algorithm to increase performance.
In development: sTREM RDT Inflammatix,	■ sTREM or other vascular markers may work better then CRP on their own, as CRP would need to be integrated in a complex algorithm for interpretation. ■ Vascular markers are a good choice for a common biomarker that can be used for febrile newborn, children and adults.	■ For markers in development, need to think of value for money and will this be integrated in existing algorithm/ processes/interventions or replace them?

ANNEX II.
MEETING PRE-READS

Please refer to the pre-read materials on **FIND** and **Unitaid**'s websites

- **Focus group report: Centering the needs of health care providers diagnosing and managing acute febrile illness**
  Refer to pre-reads page 5 to 51.

- **Host biomarkers for fever: recent progress and future challenges**
  Refer to pre-reads page 52 to 95.

- **Host biomarkers for fever: market challenges**
  Refer to pre-reads page 96 to 118.