Unitaid
SAVE LIVES FASTER

# Landscape of rapid diagnostic tests for severe bacterial infections in Advanced HIV Disease

unitaid.org

# Introduction

## Unitaid is an international organization that accelerates the introduction of health products in Low- and Middle-Income Countries (LMICs) to prevent, diagnose and treat HIV/AIDS, tuberculosis, and malaria more quickly, affordably, and effectively.

Our work also covers maternal, newborn and child health, as well as pandemic response. Over the past 15 years, Unitaid has led the way in identifying promising health innovations, demonstrating their utility, effectiveness, and impact in low-resource settings, and laying the foundations for governments and partners to make them available at scale.

Unitaid plays this important role in the market-shaping and introduction of numerous innovative medicines and health products, working through an extensive network of partners, including governments, NGOs and civil society, researchers, and academic institutions, among others. With a new ambitious 2023 - 2027 strategy (available here), Unitaid aims to continue driving equitable access to innovative health products as a core function. In addition, the new Unitaid strategy prioritizes improvement of health outcomes for people living with HIV (PLHIV) through investing in health products/innovations that deliver better health benefits for prevention, diagnosis and treatment of HIV and associated co-infections, especially at primary care level to support the creation of systemic conditions for sustainable equitable access, and partnerships.

Rapid Diagnostic Tests (RDTs) are often facilitators of quick diagnosis and linkage to appropriate care and treatment at primary care facilities in resource limited settings, where majority of the PLHIV first present for care. This Rapid Diagnostic Test for Severe Bacterial Infections in Advanced HIV Disease Landscape Report intends to inform potential opportunities to improve the management of severe bacterial infections in advanced HIV disease, acknowledging diagnostic tests' foundational role.

This landscaping exercise builds on the WHO's 2021 Scoping Consultation on Severe Bacterial Infections in Advanced HIV Disease. *(1)* Severe bacterial infections (SBIs) represent a significant cause of morbidity and mortality among PLHIV. Unitaid has invested in the introduction of a WHO recommended package of care for advanced HIV disease management, primarily for diagnostics and treatment for tuberculosis (TB) disease and cryptococcal infections, the two leading causes of death among PLHIV. Severe Bacterial infections are another important cause of morbidity and mortality; this report explores the potential for on-market RDTs to improve the diagnosis and management of SBIs in adults and children with Advanced HIV Disease (AHD).

**Figure 1. Guiding questions for landscaping**

Specifically, this report considers whether any RDTs should also be considered for inclusion in the care package for advanced HIV. The approach considered several related, sub-questions, iteratively. (Figure 1)

## Methods

This exploratory landscape report was prepared primarily by reviewing information in the public domain, including policymaker and partner reports, webinars, and peer-reviewed publications. Extensive stakeholder discussions supplemented this desk review.

Given the multitude of bacterial infections that can cause disease, the landscaping approach simultaneously considers i) available rapid diagnostic tests; and ii) their potential clinical impact. Thus, the first step was identifying the highest-priority bacterial infections causing severe disease in AHD populations. Three common severe disease syndromes were considered: meningitis, sepsis (i.e. suspected bacteremia), and severe lower respiratory tract infection (bacterial pneumonia). The report focuses on the most common causative bacterial pathogens within these syndromes.

A high-level technology scan was undertaken to compile an initial list of on-market RDTs. It was not intended to be exhaustive but rather to identify the major pathogens where bacterial RDTs existed. This involved review of existing reports, AMR diagnostic landscapes *(2)* and test directories *(3)*, targeted literature searches, and extensive expert input.

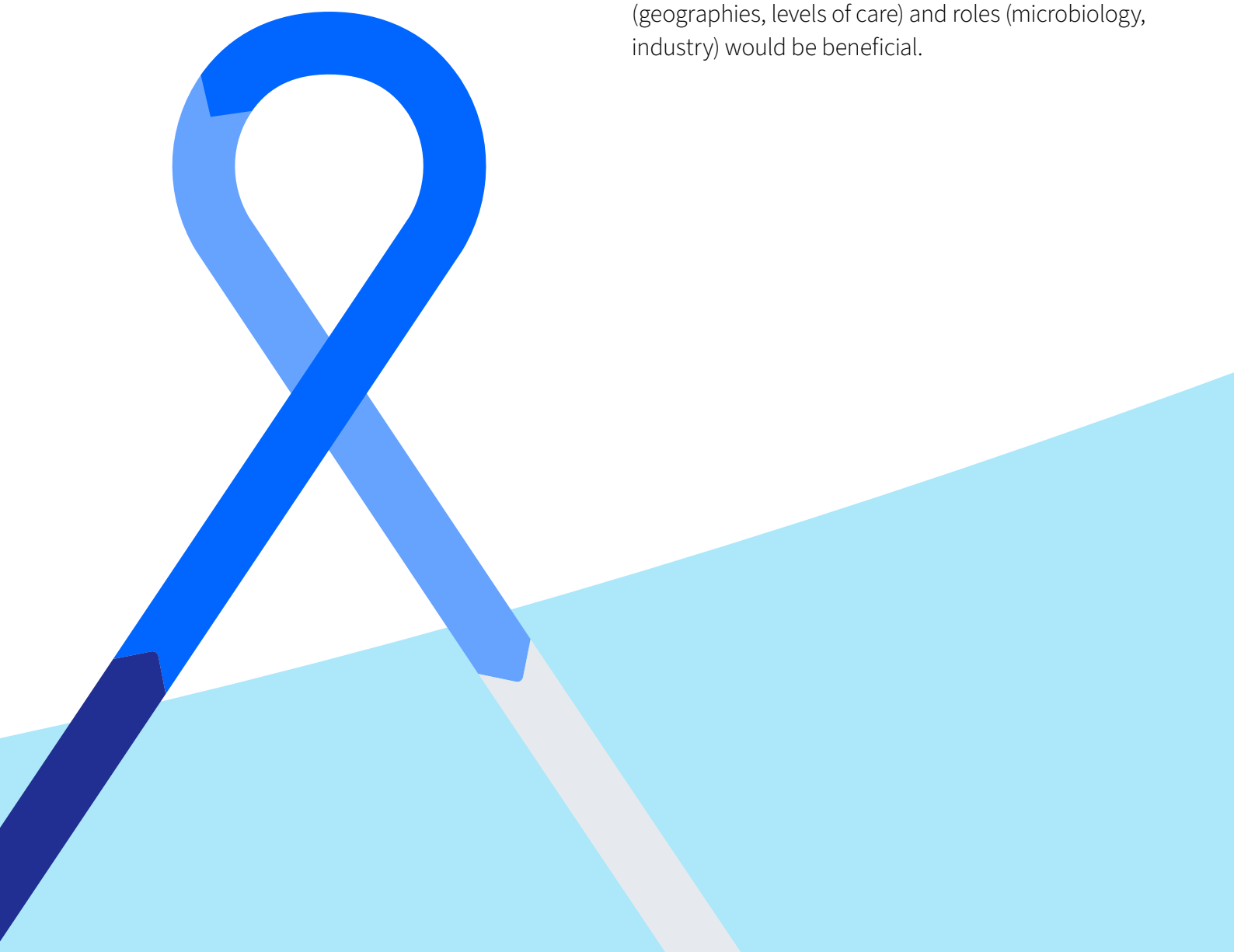
Unitaid's priorities influence the technology scope. Because Unitaid is actively supporting AHD packages of care the focus is near-term, on-market RDTs. Additionally, ensuring access to HIV care in the community and at the lowest levels of the health system is a priority, requiring a focus on tests that can be implemented where AHD patients present for care, in other words, in a rapid diagnostic test format, i.e., akin to an HIV RDT, TB-LAM or a cryptococcal antigen (CrAG) test. While the primary focus is pathogen specific RDTs, host response biomarker tests are also considered because they are available in RDT formats.

Simultaneously, over 40 clinicians (see Annex), researchers, program managers, and microbiologists were consulted on a variety of topics including:

- Appreciating the varied potential use cases for SBI RDTs in AHD, based on AHD patient points of contact with the health system and corresponding health system capabilities and understanding of some of the key clinical questions and decisions being made by providers at this level.
- Challenges in SBI disease diagnosis and management.
- The potential impact that any given test would have on clinical practice and patient management. Only tests with some likelihood of changing management were researched further.
- Priorities for strengthening SBI diagnosis and management in AHD.

Using the Unitaid framework, the market shortcomings analysis focuses on gaps in innovation and availability because few RDTs exist. Several potential opportunities for advancing SBI management in AHD were developed and discussed with experts to identify priorities. The opportunities are not specific to Unitaid, but are a general set of recommendations meant to stimulate further discussion of this complex, yet important public health priority.

There are several important limitations of this report. First, we focus on four globally relevant bacteria contributing to severe disease in AHD patients. However, it is important to appreciate the imprecision around this data and the dynamic nature of bacterial epidemiology. The limited published knowledge and data on SBIs in AHD, as well as the inherent complexity of the topic, lends itself to heavy reliance on expert consultation. The selection of experts introduces bias, as the interviewees included many academics and clinicians practicing at tertiary care level in high burden African settings. Validating the findings with clinicians and experts in other settings (geographies, levels of care) and roles (microbiology, industry) would be beneficial.



We also did not contact manufacturers to get their input on this area, as high-priority RDTs for bacterial infections were not identified through the landscaping process. This review also focuses on the near-term agenda – i.e. available RDTs, it did not consider RDTs that are still in development, or other technology platforms (e.g. POC/near POC multiplex PCR panels, simplified blood culture platforms).

# Public health challenges:

## Diagnosing severe bacterial infections in patients with advanced HIV

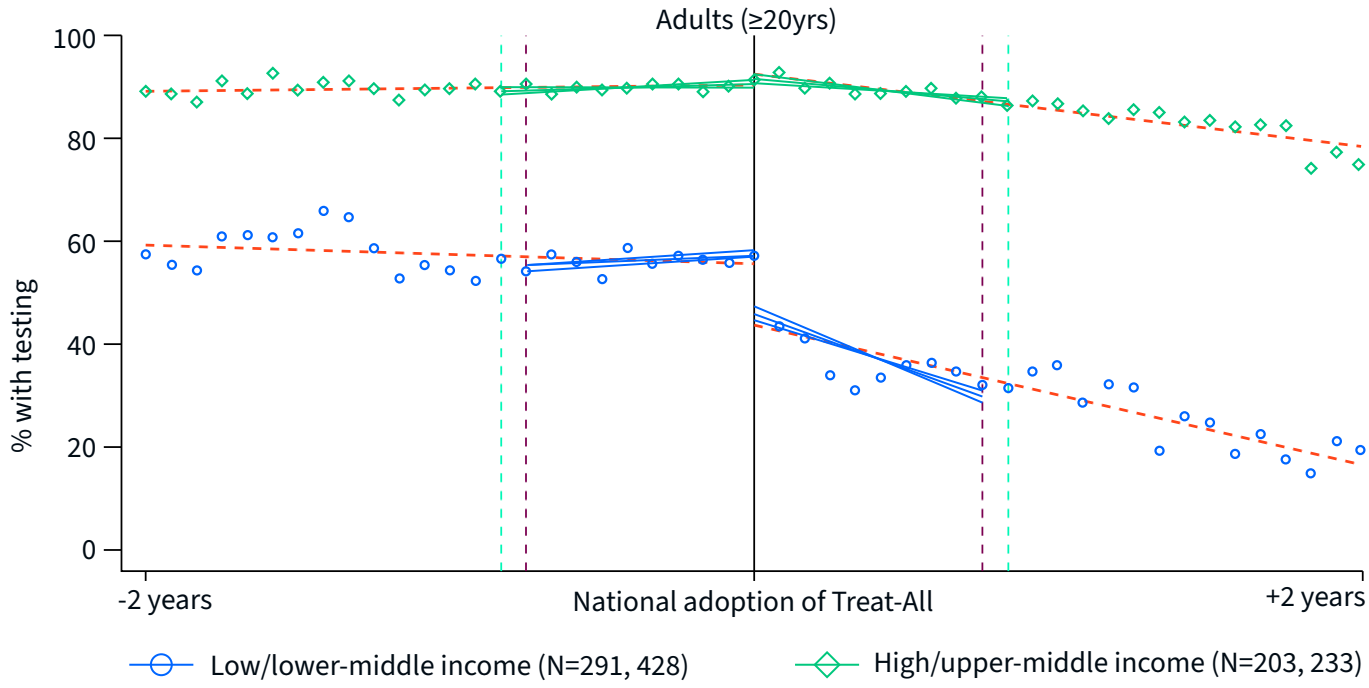
# This section reviews:

- The AHD burden, at a high-level;
- the complexity and challenges of diagnosing SBIs in AHD;
- the available global guidance pertaining to SBIs in AHD; and
- the clinical capacity and context where AHD patients present to care.

## Advanced HIV Disease

For adults, adolescents and children 5 years and older, AHD is defined as having a CD4 count below 200 cells/mm^3 and/or WHO stage 3 or 4 disease at presentation to care. *(4)* All children under five years of age, who are not already receiving ART are considered to have AHD at presentation. Because young untreated children living with HIV have an increased risk of severe disease and mortality regardless of their clinical staging or CD4 percentages, they are considered to have AHD until they have been on treatment for a year and are clinically stable *(5)*.

**Figure 2. Pre-ART CD4 testing before and after adoption of WHO Treat-All policy**




Source: Brazier, et al. *(6)*

## AHD burden

Broadly, the AHD population comprises: undiagnosed PLHIV with advanced immuno-suppression; newly diagnosed PLHIV who may be engaged in care, but not yet stable on ART; PLHIV on ART who are not virologically suppressed; and ART experienced people who have interrupted care.

PLHIV with AHD are at risk of early mortality prior to and even after starting ART. Because many AHD patients lack clinical symptoms CD4 count is the preferred way to diagnose advanced HIV in PLHIV over age five, and the entry point for WHO Package of care for AHD. However, access to CD4 remains limited, for example, over 30% of eligible patients lack access to CD4 *(7)*. (Figure 2) Consequently, many patients who would benefit from focused interventions for AHD (e.g. preventing, screening, and treating opportunistic infections) are not being identified. *(6)*

A country's AHD burden depends on several factors, including HIV prevalence, and the strength of the HIV testing, treatment, and care retention programmes. One recent study estimated that 4.3 million adults lived with advanced HIV, ~12% of HIV infected adults *(8)*. (Figure 3) There are no estimates for children, although the proportion of children with AHD is likely greater than the proportion in adults, because children are less likely to be on treatment than adults, and those on treatment are less likely to be virally suppressed. HIV mortality is disproportionate among children, who comprise 4% of the PLHIV and 15% of deaths.

The AHD burden has decreased since the scale-up of ART; however, it has not decreased as much as anticipated: up to a third of individuals entering and cycling back into HIV care have AHD. This number has changed little in the past decade *(9)*, and it may have increased due to service disruptions during the COVID-19 pandemic. In settings with high ART coverage, the proportion of ART-experienced adults with AHD is high *(10)*, suggesting that the burden is likely to persist without significant improvement in care retention. Data on children is scarce. Pediatricians in high-burden countries note improvement due to the ART and infant diagnosis scale-up. Currently, the AHD burden comprises babies missed by weak spots in vertical transmission programs presenting for the first time with illness during the first year of life and older children and adolescents who have interrupted care.

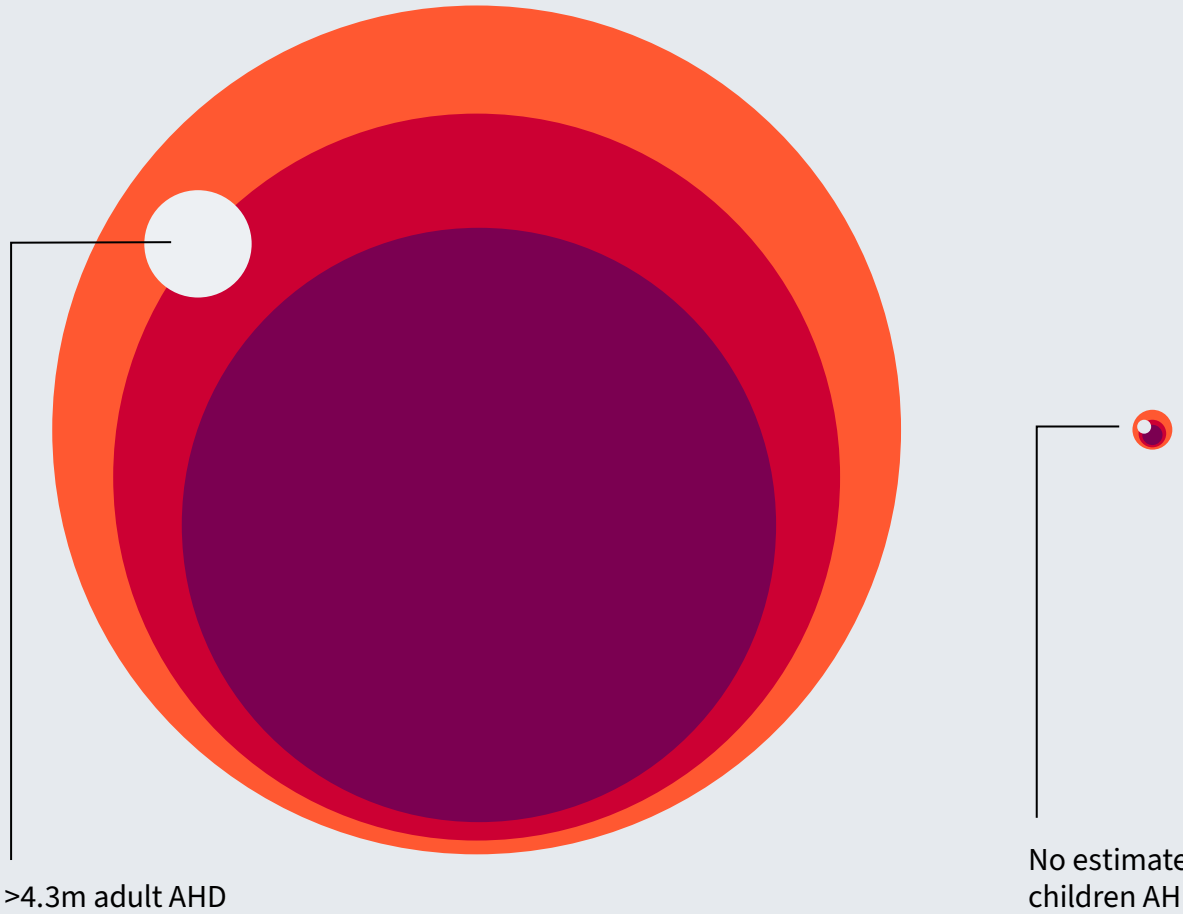
**Figure 3. 2021 Estimate of adults and children living with HIV, number on treatment and virally suppressed, and proportion with AHD.**

## Adults – in 2021:

- 36.7m Adults living with HIV
- 27.9m On treatment
- 25.7m Virally suppressed

## Children – in 2021:

- 1.7m children living with HIV
- .9m On treatment
- .7m Virally suppressed

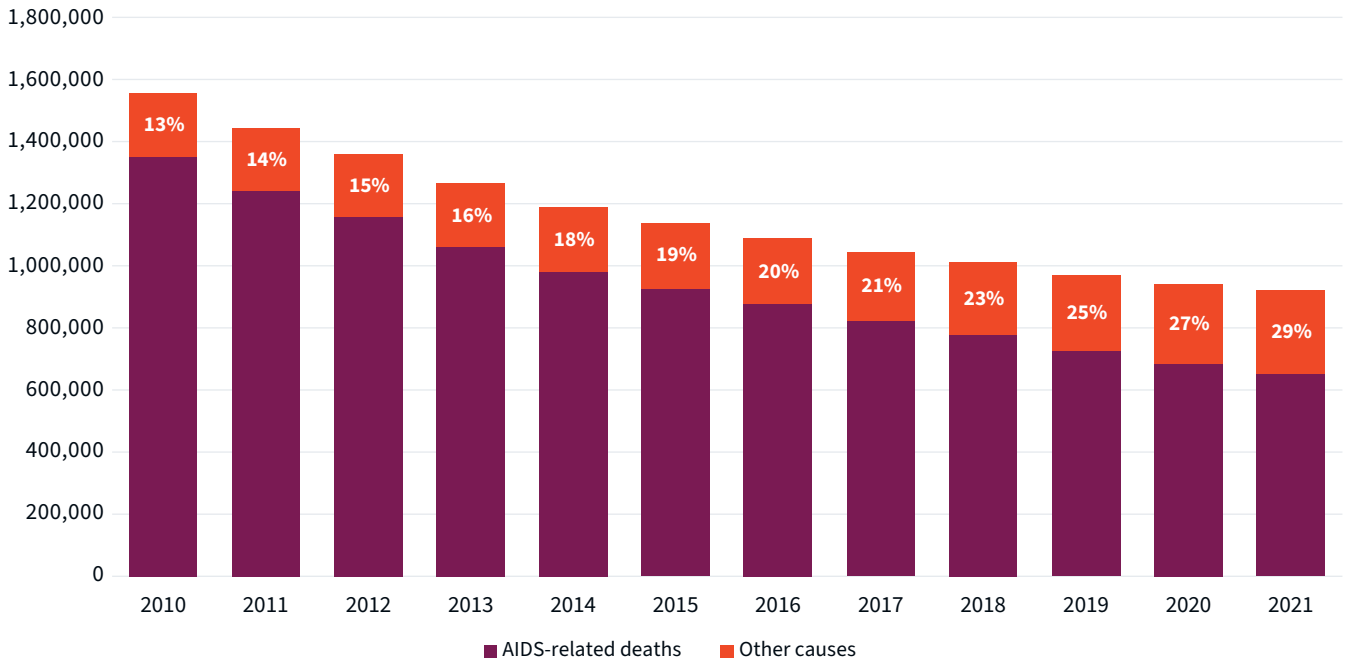



Source: UNAIDS; adult AHD estimate from *Rajasingham, R et al 2022.*

## AHD increases the risk of severe disease and mortality from infectious causes, including bacterial infections

Mortality from infectious causes in AHD is exceptionally high (Figure 4) and remains high during the first 3-6 months of ART. One 2019/2020 study documented that HIV-infected adults hospitalized with fever have three times the mortality risk compared to un-infected. *(11)* For children, a 2016-2019 Mozambiquan study reported 19% mortality for HIV-infected children with culture-confirmed community-acquired bacteremia. *(12)* After TB (in adults and children) and cryptococcal meningitis (in adults), severe bacterial infections are a leading cause of HIV-related hospitalization and death. *(13) (14)*

### Figure 4. Deaths to people living with HIV, by cause, global, 2010-2021




Source: UNAIDS, November 2022

## The complexity of severe bacterial infection diagnosis and management in AHD

Diagnosing and appropriately treating a severe bacterial infection is complex for clinicians worldwide. Over one-thousand bacterial pathogens can cause disease in humans *(15)*, and it is not possible to confirm a diagnosis for all bacterial infections, given the technical limitations of even the most advanced diagnostics for bacterial infections in well-resourced settings. Moreover, treatment decisions are often urgent, as a severely ill patient can deteriorate in a matter of hours, and few bacteriology test results are available in a timeframe that aligns with the initial treatment decisions. (See box below: Bacteriology testing)

LMIC clinicians contend with high bacterial disease burdens, and knowing the most common pathogens that cause a particular clinical syndrome is the starting place for selecting an appropriate treatment. However, LMICs have limited information on bacterial (and other) pathogens' prevalence and susceptibility to antibiotics. This critical epidemiologic information differs by geography and population. For example, resistance patterns between countries in the same region *(16)* can differ, or children may be more susceptible to some infections than adults. Bacterial disease prevalence also shifts over time; for example, the scale-up of ART and vaccinations (e.g., for *Haemophilus influenzae type b*, pneumococcus) influences the overall bacterial disease burden and the mix of pathogens causing severe disease. *(17) (18)*

Additional factors challenge SBI diagnosis and broaden the differential in AHD. First, among the many potential infectious causes of severe disease, there is a high degree of symptom overlap, and AHD patients may not present typically. For example, elevated white blood cell counts are often used to signal bacterial infection instead of viral; however, in AHD, severe immune suppression makes these counts unreliable signals of bacterial infection. Second, co-infection is more common in AHD than in immune-competent patients. While having one pathogen confirmed will greatly assist patient management, it is important also to explore other potential causes, as failure to identify and treat concurrent illness can be rapidly fatal in AHD.

Considering the major clinical syndromes associated with severe bacterial infection and the most common causative agents is helpful (Tables 1 and 2). Experts suggest that a few bacterial pathogens contribute most to severe disease syndromes in AHD: invasive *non-typhoidal salmonella, Streptococcus pneumoniae, Escherichia coli, Staphylococcus aureus*. Other bacteria and infections, including regionally relevant ones, may also contribute to hospitalization and mortality in AHD patients. Because there is limited testing, the etiology of these infections is insufficiently characterized.

Given the broad differential and lack of testing, clinicians consult empiric treatment guidelines. Ideally, these guidelines reflect current pathogen epidemiology and resistance in the community. However, in low resource care settings, representative surveillance data is often outdated or unavailable. As a result, the treatment approach is often trial and error, and there is a tendency to over-treat than to undertreat (e.g., use of broad vs. narrow-spectrum antibiotics, simultaneous treatment for multiple potential causes etc.).

Increasing antimicrobial resistance in LMICs is another diagnostic challenge for clinicians and likely contributes to AHD mortality. (See box below: Antimicrobial resistance) Even though HIV infection has no direct effect on infection or colonization with resistant bacteria, PLHIV are more likely to be colonized or infected by resistant bacterial strains, as they have many risk factors (e.g. frequent exposure to antibiotics and health systems contact, especially admissions). *(11)* Experts interviewed for this report expressed concern about long hospitalizations and the potential for hospital-acquired bacterial infections, which are frequently drug-resistant, in their AHD patients. As the proportion of ART-experienced AHD patients increases, the risk of resistant infections is likely to grow as well.

**Table 1. Adults: most common bacterial pathogens and non-bacterial causes of severe disease syndromes in AHD patients.**

| Syndrome | Bacterial etiologies<br>*most common in bold, less common in [brackets] | Other etiologies<br>*most common in bold, less common in [brackets] | Source |
|---|---|---|---|
| Meningitis | ***Streptococcus pneumoniae;*** *Neisseria meningitides; Haemophilus influenzae, Escherichia coli, Listeria monocytogenes, Treponema Pallidum*<br>*[Streptococcus agalactiae (Group B), Rickettsia, Leptospira, Staphylococcus aureus, Non-typhi Salmonella]* | **Crypto**<br>**TB**<br>Viruses (enteroviruses, HIV, herpes, mumps)<br>Parasites (less acute, more chronic) | M Bremer (2021),<br>SAHCS Guidelines (2022), K Gaskell (2015) |
| LRTI / Pneumonia | ***Streptococcus pneumoniae;*** *Haemophilus influenzae, Staphylococcus aureus*<br>*[Moraxella catarrhalis, Klebsiella pneumonaie, Pseudomonas aeruginosa; mycoplasma pneumoniae; Legionella pneumophilia, Chlamydia pneumonia]* | **TB**<br>**PJP**<br>Viruses (influenza, monkeypox, COVID etc.)<br>other fungi | SAHCS Guidelines (2022), K Gaskell (2015) |
| Sepsis / blood stream infection | **Invasive non-typhoidal salmonella, *Streptococcus pneumoniae, Escherichia coli, Staphylococcus aureus*** | TB, Many other fungal, parasitic, and viral infections. | K Gaskell (2015) |

**Table 2. Children: most common bacterial pathogens and non-bacterial causes of severe disease syndromes in AHD patients.**

| Syndrome | Bacterial etiologies<br>*most common in bold, less common in [brackets] | Other etiologies<br>*most common in bold, less common in [brackets] | Source |
|---|---|---|---|
| Meningitis | ***Streptococcus pneumoniae;*** *Neisseria meningitides; Haemophilus influenzae, invasive non-typhoidal Salmonella*<br>*0-1 month: Streptococcus agalactiae (Group B), E coli; Listeria monocytogenes, Streptococcus pneumoniae* | Crypto (over 5); cerebral toxoplasmosis<br>**TB**<br>Viruses (enteroviruses, herpes, arboviruses)<br>Cerebral malaria, parasites | WHO AWaRe, (2022) - which is not HIV specific |
| LRTI / Pneumonia | ***Streptococcus pneumoniae;*** *(most common CAP after 1st-week life) Haemophilus influenzae,* ***Staphylococcus aureus***<br>*Moraxella catarrhalis, Enterobacterales*<br>*Atypical pathogens (more frequent in >5 years) Mycoplasma pneumoniae* | **TB**<br>**PJP (infants)**<br>**Viruses** (PERCH study, RSV, influenza, COVID-19, Parainfluenza virus, Adenovirus, Rhinovirus, CMV COVID etc.)<br>other fungi | WHO STOP AIDS (2020) |

**Table 2. Children: most common bacterial pathogens and non-bacterial causes of severe disease syndromes in AHD patients. (continued)**

| Syndrome | Bacterial etiologies<br>*most common in bold, less common in [brackets] | Other etiologies<br>*most common in bold, less common in [brackets] | Source |
|---|---|---|---|
| Sepsis / blood stream infection | ***Streptococcus pneumoniae, Staphylococcus aureus,*** Invasive non-typhoidal *Salmonella,* ***Salmonella,*** *Escherichia coli*<br>WHO AWaRe (general population)<br>Neonatal: *Escherichia coli, Staphylococcus aureus, Klebsiella spp.*<br>Children > 28 days: Gram-negative *(Escherichia coli, Klebsiella spp.)* *Salmonella* Typhi & Paratyphi, Invasive non-typhoidal *Salmonella, Streptococcus pneumoniae, Steptococcus pyogenes, Staphylococcus aureus, Neisseria meningitides; Haemophilus influenzae* | TB, Many other fungal, parasitic, and viral infections. | WHO STOP AIDS (2020)<br>K Gaskell (2015)<br>WHO AWaRe, (2022) - which is not HIV specific |

## *Bacteriology testing*

Microbiological culture is the "gold standard" for diagnosing most severe bacterial infections, yet it is imperfect. For example, even in well-resourced, optimal conditions, only ~10% of blood cultures yield any microbial isolate, and some of the isolates identified are contaminants (i.e. they are not causing disease). Factors contributing to low positivity are biologic (e.g. low bacteria load in the sample) and more operational (e.g., inadequate blood volumes, patients receiving antibiotics prior to blood draw which reduces yield, mishandling of samples, etc.)

When a blood culture becomes positive, it triggers additional testing, initially to identify the bacterial pathogen and then to further test for antimicrobial susceptibility, which informs the appropriate susceptibility-matched antibiotic treatment. Preliminary culture results are only available after 48-72 hours, and antibiotic susceptibility information follows. While newer automated and faster systems can reduce the timelines for culture results (e.g. improve time to results by ~12 hours), these platforms are typically only available in referral centers in low resource settings.

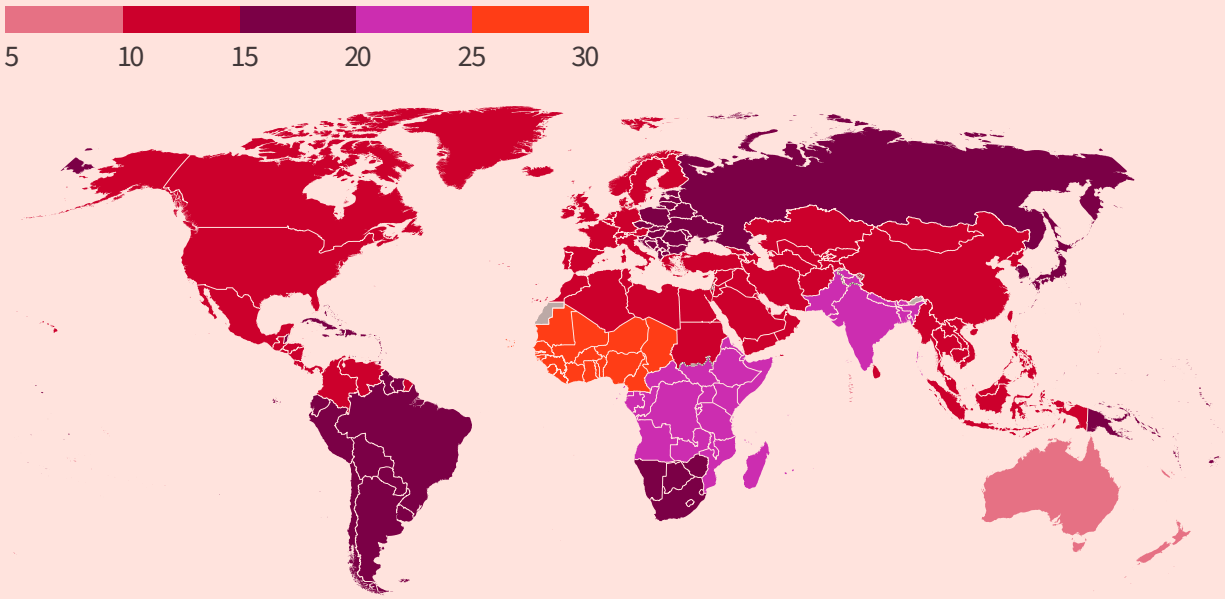
Additionally, blood culture yields a set of information that must be carefully interpreted. For example, advanced microbiological and clinical skills are needed to appreciate whether the bacteria is causing the illness, is a contaminant, or is the result of the bacterial colonization that is not contributing to the current disease process.

Nucleic acid testing for specific pathogens and some resistance markers are increasingly coming to market. Many require culture to be performed first, but a few may be performed directly on the specimen (e.g. blood, CSF). These are often multiplex syndromic panels. They are expensive and the panels of tests may not address the common infections in AHD nor common pathogens in low resource settings. Additionally, although bacterial culture is imperfect, further progress in direct testing from blood performance, turnaround time, and affordability of novel techniques are necessary for routine LMIC use. *(19)*

## *Antimicrobial resistance*

The burden of AMR and its contribution to mortality in LMICs is poorly understood, given insufficient data on the prevalence of bacterial infections and resistance, although many efforts are underway to improve the data (e.g., the Fleming Fund initiatives to improve AMR surveillance, Mortality from Bacterial Infections Resistant to Antibiotics study). Recent modeling suggests that globally, AMR is directly responsible for over 1 million deaths each year and is associated with 5 million. *(20)* Deaths attributable to AMR are highest in many countries with high HIV and AHD burdens (Figure 5. Estimated global burden of antimicrobial resistance; deaths attributable to pathogen-drug resistance per 100,000 people in 2019). The recently published MAAP project review found that only five of the 15 pathogens prioritized for antibiotic resistance testing were consistently tested in LMICs, and that all five had higher-than-expected resistance prevalence. Moreover, access to 'reserve' antibiotics that are needed to treat these resistant infections, was lower than expected. *(21)* Antibiotic resistance exacerbates the negative impact SBIs have on PLHIV, as these infections become more difficult to treat, lengthening hospital stays and requiring increasingly costly antibiotics that are often not available in LMICs. *(21)*

**Figure 5. Estimated global burden of antimicrobial resistance; deaths attributable to pathogen-drug resistance per 100k people in 2019.**




Source: UNAIDS, November 2022

## Global guidance for severe bacterial infections and advanced HIV

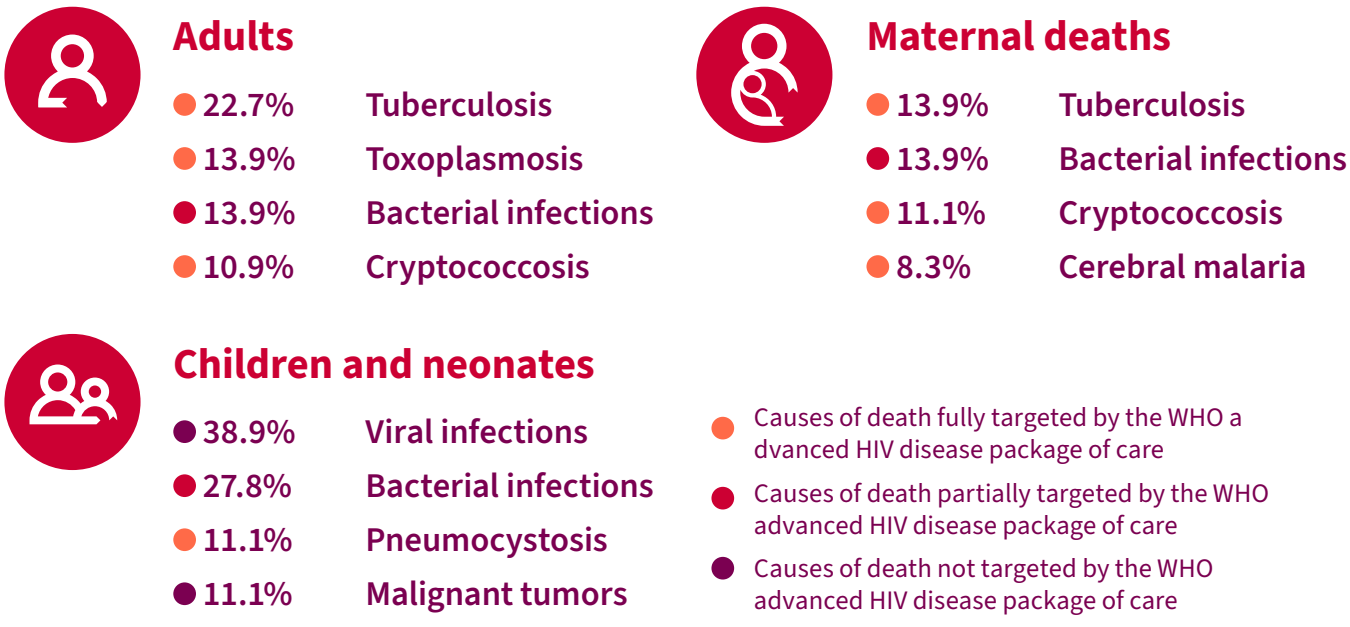
### HIV guidance

The WHO Global Health Sector Strategy has a strong focus on the reduction of AIDS-related deaths as well as disaggregating the causes of death. The development and implementation of guidance to reduce AIDS-related deaths to zero by 2030 is thus a critical area of focus. *(26)*

ART is essential in preventing the severe immune compromise that increases risk of SBIs. Other SBI prevention components of the HIV response include vaccines (e.g. *Haemophilus influenzae* type b, pneumococcus) for PLHIV and cotrimoxazole prophylaxis, which primarily prevents pneumocystis pneumonia[1] and toxoplasmosis, and may have some activity against malaria, bacterial infections, and inflammation more generally. *(27)* Despite recommendations, experts suggest that there are many implementation challenges that limit coverage of vaccination and cotrimoxazole in PLHIV *(28)*.

Since 2017, the WHO recommends that a package of screening, prophylaxis, rapid ART initiation and intensified adherence interventions be offered to everyone living with HIV presenting with advanced disease. This AHD package of care only partially addresses bacterial infections (Figure 6), by preventing bacterial infection through ART and cotrimoxazole prophylaxis. *(4) (29)* Whether AHD patients would benefit from additional antibiotic prophylaxis (i.e., azithromycin) is also debated and awaits more evidence. *(1)*

**Figure 6. Major causes of death in PLHIV in Mozambique and Brazil and coverage of WHO package of care for AHD.**




Source: Letang et al. *(14)*

1 Alternatively referred to as PCP or PJP, caused by Pneumocystis jirovecii fungus

## General guidance on bacterial infections

Healthcare workers seeing PLHIV with possible bacterial infection rely on general training and clinical practice guidelines that at a basic level do not differ from general population bacterial illness guidelines. At a high level, the approach is to assess the severity and risk for poor outcomes and need for referral, and to decide if the patient would benefit from an available antibiotic or supportive therapies. The relevant guidance depends primarily on where the patient presents, the provider, and the patient's symptoms. For example, lower skilled providers at outpatient or first level referral hospitals may refer to WHO's Integrated Management of Childhood Illness; or Integrated Management of Adolescent and Adult Illness guidelines. *(30) (31)*Medical doctors may consult society guidelines for some syndromes, e.g., lower respiratory tract infections, or the Southern African HIV Clinicians Society guidelines for hospitalized adults with advanced HIV disease. *(32)*

Until recently, global guidance for the management of bacterial infections was incorporated into these general practice guidelines. In December 2022, the WHO released WHO AWaRe (Access, Watch, Reserve) antibiotic book, its first guidance for bacterial infections and antibiotics. *(35)* Mostly, the guidance does not differ between immunocompetent patients and PLHIV; there are a few HIV-specific recommendations and considerations.

The AWaRe antibiotic book is an extension of the WHO's Model Lists of Essential Medicines (EML), providing evidence-based guidance for treating common infections in adults and children at the primary and hospital levels based. While the choice of antibiotic is a formal WHO recommendation, many aspects of diagnosis and management (e.g., dose, duration), are best practice because there is insufficient evidence and clinical trials for many of the infections. The guideline fills a major void in translating the WHO EML into clinical practice guidelines, as many LMICs lack antibiotic prescribing guidance. WHO is currently rolling out the guidance, including its availability as a mobile application to ease updating, local customization, and end-user access. Optimally, MoHs will adapt these guidelines based on the specificities of the health system, local epidemiology, and antimicrobial resistance patterns.

Notably, the AWaRe guidelines, do not recommend any bacterial pathogen testing at the outpatient level for pneumonia, sepsis,[2] and meningitis syndromes, and testing suggestions for inpatients are limited, largely to microbiological culture and sensitivity, when available. At hospital level, other tests mentioned in the guidelines that "might be considered" to identify a bacterial infection include white blood cell counts, c-reactive protein, and procalcitonin.

While the WHO AWaRe guideline developers considered the role of diagnostics in each clinical condition (i.e., consulted with the Essential Diagnostics List at WHO, conducted literature reviews, and considered expert), the lack of available diagnostic tools and evidence resulted in few recommendations for specific tests. Moreover, where tests are recommended, it is notable that the diagnostics are imperfect and have been around for decades with little advancement or innovation to support clinical decision making.

2 The AWaRe guidance does mention that Widal serology is not a reliable method for diagnosing enteric fever.

**Table 3. WHO AWaRe bacterial diagnostics recommendation (inpatients)**

| Syndrome | Diagnostics recommended |
|---|---|
| Meningitis | Microbiology and culture of cerebrospinal fluid (CSF)<br>Cryptococcal antigen in CSF and blood<br>Blood cultures<br>TB molecular WHO recommended rapid diagnostic test (mWRD) in CSF<br>Several other tests are suggested (e.g., full blood count, blood lactate, blood glucose, CRP/ PCT) |
| Sepsis/ Suspected bacteremia | Blood cultures (2 sets). Consider additional microscopic examination and cultures depending on the most likely source of infection (e.g., sputum, CSF, stool, abscess fluid, urine).<br>The guidelines suggest considering white blood count, CRP, and/or PCT for identification of bacterial infection, and to guide antibiotic therapy.<br>Several other tests are essential to identify organ dysfunction. |
| Sepsis/ Suspected bacteremia – neonates and children | Blood, urine, and CSF culture.<br>Consider additional microscopic examination and cultures depending on the most likely source of infection (e.g., urine, CSF, stool, abscess fluid).<br>The guidelines suggest considering white blood count, CRP, and/or PCT for identification of bacterial infection, and to guide antibiotic therapy. Several other tests are essential to identify organ dysfunction. |
| LRTI/ Pneumonia | For mild disease: no tests recommended.<br>For severe disease: blood culture suggested, sputum microscopy and culture, urinary antigen RDTs for *Legionella pneumophilia* and *Streptococcus pneumoniae*. Based on local availability, the following may support differentiation of bacterial and viral causes: CRP and/or PCT; white blood cell count.<br>Consider the following tests (depending on season/epidemiology):<br>• TB molecular WHO-recommended rapid diagnostic test on sputum; TB LF-LAM in AHD),<br>• Nucleic acid amplification test for influenza viruses depending on epidemiologic situation.<br>• SARS-Co-V-2 antigen or nucleic acid amplification test depending on the epidemiologic situation |

Source: The WHO AWaRe antibiotic book *(35)*
CSF: cerebrospinal fluid; CRP: c-reactive protein; PCT: procalcitonin; TB: tuberculosis; LF-LAM: lateral flow urine lipoarabinomannan assay; mWRD: molecular WHO-recommended rapid diagnostic test; and WBC: white blood cell.

## Entry points for AHD care

Program experts and published literature indicates that AHD impacts the entire health system, including primary care facilities as well as HIV treatment centers *(36)*. AHD patients could present through four different visit types:

1. Outpatient: HIV/ART clinic routine visit
2. Outpatient: HIV/ART clinic acute visit
3. Outpatient: OPD/ED acute visit
4. Hospital: inpatient visit

This section reviews the clinical encounters at each of these visit types, as the clinical skills, infrastructure, resources, and typical scope of practice where AHD patients present for care influence the capacity to diagnose and manage SBIs in AHD. (Figure 7). For example, nurses and clinical officers typically staff outpatient clinics where both testing and the selection of antibiotics is limited to the most common infections. Medical doctors are usually available at first-level referral hospital emergency departments and inpatient wards.

**Figure 7. Overview of resources typically available where AHD patients may present for care**

**Outpatient**

### Primary care

- 1000's of sites, some caring for >1000 patients
- HIV/ART clinic: caring for ~50% of PLHIV, including AHD
- General outpatient department: sick visits
- Nurse, clinical officer
- No lab, only RDTs
- No Lumbar puncture

**Inpatient**

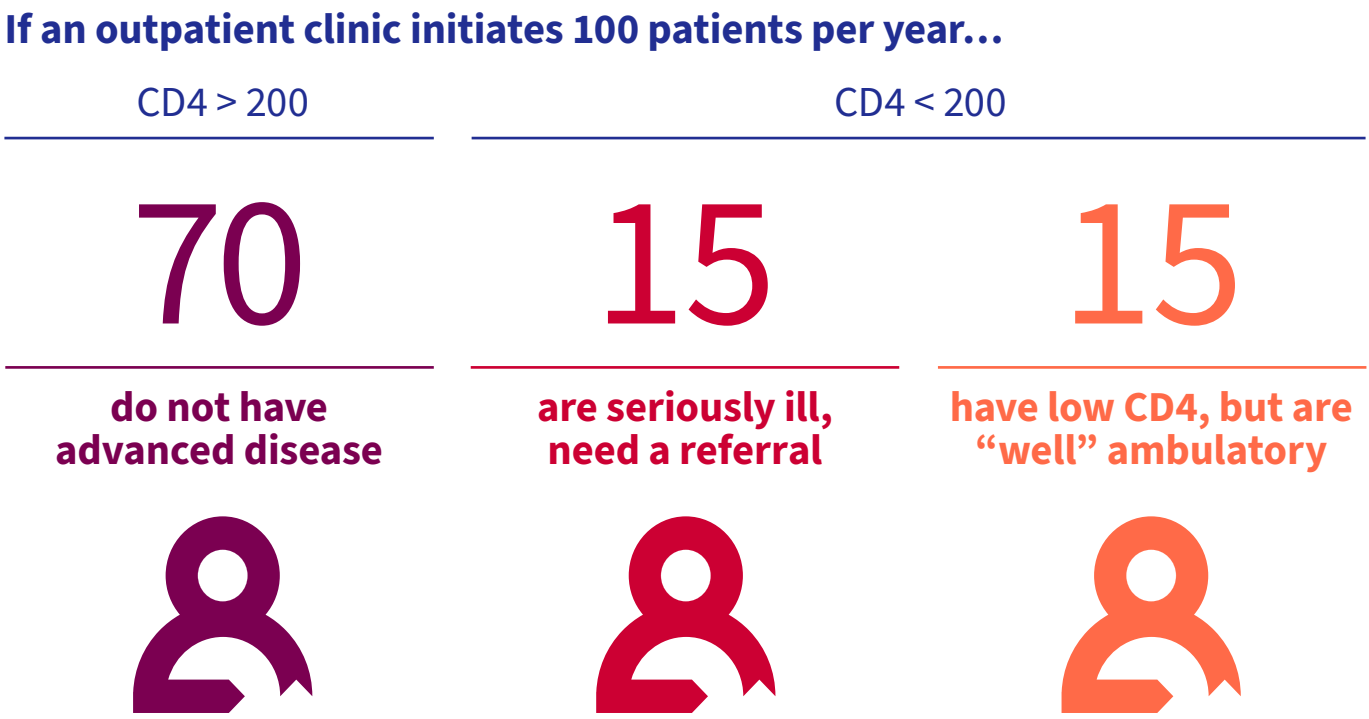
### First-level referral hospital

- Outpatient HIV/ART clinic
- OPD/Emergency
- Inpatient wards
- Nurse, clinical officers, medical doctors
- Small lab: CSF microscopy (lumbar puncture).
- Likely no culture/AST available or reliably used in practice

### Outpatient visits

An **ART/HIV clinic** may see both well and sick patients. While the proportion will vary from site to site, approximately 30% of patients presenting to care at an HIV/ART clinic will have AHD. *(9)* Experts suggest that approximately half of these patients will be seriously ill, the other half are ambulatory and largely asymptomatic *(37)* (i.e. 15% of total patients) (Figure 8).

**Figure 8. Illustrative example of proportion of patients with AHD at an outpatient clinic initiating 100 patients each year**




Source: Analysis of data and estimates from Carmona, S. et al *(9)*, Hakim, J. et al *(37)*, and stakeholder interviews

For **"well" AHD patients** presenting to an ART/HIV clinic, the health worker's objective regarding SBIs is to rule out an infection by confirming the lack of signs or symptoms, provide cotrimoxazole prophylaxis, and initiate ART or provide refills and monitor those already on ART. At presentation, experts suggest that a low CD4 result prompts the provider to screen for TB and cryptococcus infection using diagnostic tools and AHD guidelines. While providers also screen for common bacterial infections, e.g., pneumonia, there is scope for strengthening the evidence and tools for bacterial infection.

For **seriously unwell AHD patients** who seek care at the HIV/ART clinic, the health worker will consider the potentially rapid deterioration (i.e., hours) from possible severe bacterial infections and need to act quickly.

As outlined in the WHO's recent policy brief on care for seriously unwell patients with AHD *(38)*, the encounter with respect to SBIs focuses on:

1. Quickly assessing severity, and the need to make a referral to a higher-level facility and to provide prereferral treatments. The severity assessment is based primarily on clinical assessment of danger signs, there are no tests at the outpatient level to support triage decision-making, although a low CD4 count suggests a higher risk and should prompt a rapid referral/admission decision.
2. Deciding if the patient needs an available antibiotic. In the outpatient setting, the options are usually limited to oral first-line treatments and sometimes a pre-referral antibiotic treatment. Bacterial infections are clinically diagnosed, healthcare workers rely on history and symptoms using syndromic management guidelines, and there are no tests to support decision-making around bacterial infection at the outpatient level. While several RDTs may be available to help "rule in" other infections (Table 4), in an AHD patient, even if a non-bacterial infection is confirmed, the healthcare worker might still consider co-infection, especially in a patient whose immune system is compromised.

**Table 4. Diagnostic tools that may be available to HCW in outpatient settings**

| Category | Non-bacterial tests | | | Bacterial tests | | | Triage/ severity |
|---|---|---|---|---|---|---|---|
| **Syndrome** | **Pneumonia** | **Fever/ Sepsis** | **Meningitis** | **Pneumonia** | **Fever/ Sepsis** | **Meningitis** | |
| Tests | Viral Influenza, COVID, TB LF-LAM<br><br>*HIV RDT, CD4 RDT* | Malaria RDT, TB LF-LAM<br><br>*HIV RDT, CD4 RDT* | CrAg test, TB LF-LAM<br><br>*HIV RDT, CD4 RDT* | Respiratory rate counter (in children) | | | HIV RDT CD4 Pulse oximetry, MUAC tape, Hb, etc. |

TB: tuberculosis; LF-LAM: lateral flow urine lipoarabinomannan assay; CrAg: rapid Cryptococcal antigen test; MUAC: mid-upper arm circumference; Hb: Hemoglobin.

Note: Italicized tests, if available, would also inform clinical decision-making/differential diagnosis

**Seriously unwell AHD patients** may also seek care at health facilities' **general outpatient or emergency departments.** The encounter is similar to the HIV/ART clinic sick visit, however, the health worker seeing the patient may not be aware of the patient's HIV status, or if they are, they may not have access to their CD4 or viral load test results.

## Inpatients

First-level referral hospital staffing will include nurses, clinical officers, and medical doctors. There may not be any specialists or pediatricians. First-level hospital laboratories are small and basic; culture and sensitivity testing are generally unavailable or if available, are seldom used. *(21)* Lumbar puncture should be possible at this level, although, in practice, experts report that it is inconsistently implemented.

For AHD patients presenting to first-level referral hospitals with signs of severe disease suggestive of possible bacterial infection, the initial goal is to stabilize the patient, and then to tailor treatments. Providers will assess severity, focus of the infection (if any) and immediately commence broad-spectrum antibiotics and treatments for a broad range of pathogens potentially contributing to severe disease (e.g. malaria, pneumocystis). Optimally, the empiric antibiotic provides coverage for the most likely bacterial pathogens, informed partly by knowledge of local pathogen and resistance prevalence.

If laboratory testing is available, the antibiotic treatment will be reassessed based on any results as they become available (noting that culture usually takes 48-72 hours). However, in the absence of testing, clinicians rely on the patient's clinical response to empiric treatment to decide whether to continue with the initial antibiotic, change antibiotics (e.g., add coverage for less common pathogens, use a narrower spectrum antibiotic if a diagnosis is confirmed, or if resistance is expected escalate to a higher class of antibiotic), or to stop antibiotics if alternative diagnosis is confirmed and co-infection unlikely. Switching to oral antibiotics as soon as possible is often a priority given limited nursing staff for intravenous antibiotic administration and high rates of hospital acquired infections associated with intravenous administration.

# Access gaps:

Data on access to diagnostics for bacterial infections is limited, there are no systems for monitoring access to diagnostics for severe bacterial infections in the general population or in PLHIV. At the outpatient level, there are no recommended tests for bacterial diagnosis (i.e., bacterial infections are clinically diagnosed, and antibiotics empirically prescribed). Therefore, the focus below is on the inpatient setting.

### Individual severe bacterial infection diagnostic access gap

Neither culture nor NAAT are available and routinely used in LMICs outside the highest-level referral hospitals. For example, a recent study considered the 50,000 laboratories comprising the laboratory network in 14 African countries. Only 1.3% conduct bacteriology testing, many at very low volumes, and only a fraction of those have the capability to evaluate antimicrobial resistance. Moreover, in 8 of the 14 countries, this bacteriology service is geographically accessible (reachable within one hour by foot or car) to less than half of the population. *(21)* Quality is suboptimal, including high rates of contamination and gaps in capturing essential patient information (e.g. syndrome, prior antibiotic use, hospital vs community-acquired infection,) that are essential for results interpretation and use.

As a result, beyond a few tests mentioned above (e.g., malaria parasites, CrAg, rapid molecular TB tests) infections causing severe disease and inpatient admission are seldom diagnostically confirmed. *(24)* Very frequently, a patient receives a clinical diagnosis that is imprecise (e.g. “AHD” or “Meningitis”); additional investigation of the causes of severe disease or mortality *(23)* is seldom available.

Even though there are efforts, such as the Flemming Fund’s support for AMR surveillance, to strengthen bacteriology and AMR monitoring in LMICs, the process is complex and timelines are long. (See box below: Efforts to strengthen bacteriology testing in LMICs) These efforts also focus first on the highest-level referral hospitals. Since most advanced HIV patients present at lower levels of the health system (i.e. primary care and first level referral hospitals), they are not expected to benefit from these efforts to strengthen bacterial infection diagnosis in the near to medium term.

## Population-level diagnostics access gap

At the population level, the lack of bacteriology testing in a country impairs empiric management of bacterial infections. There are two issues:

1. Low awareness of the prevalence of pathogens, including bacteria, contributing to severe disease. This occurs both in the general population, but also in AHD patients. PLHIV, especially those with AHD, are likely to have similar infections to the general population but also have opportunistic infections. As discussed above, beyond TB and Cryptococcus, there is very little data on the contribution of other pathogens to severe disease. As a result, clinical suspicion of infection is low, leading to mortality. (24)
2. Secondly, empiric treatments may not be effective, partly because the common pathogens are not known (especially in AHD), but also, because the absence of local information on common resistance patterns means that the recommended and available antibiotics may not be effective.

All clinicians rely on empiric treatment for treating suspected bacterial infections at all levels of the health care system, including in outpatient settings where diagnostics are not available and the inpatient setting, where diagnostic tests may be available, but timelines are too long given the urgency of treating severe disease.

Empiric treatment guidelines are developed using knowledge of the most common bacteria contributing to various clinical syndromes, and information on resistance patterns. While high-level information is available globally (e.g. WHO EML, AWaRe antibiotic book), this data must be customized locally, with information about the local frequency of specific infections and local antibiotic susceptibility data.

National institutions, and some large hospitals, typically collect and compile data from cultures to inform the national essential medicines list and the empiric treatment guidelines. These guidelines should be reviewed every couple of years, using surveillance data that is continuously generated, i.e. results collected from laboratories performing culture and antibacterial sensitivity testing. When these labs are not performing culture, there are not enough samples to inform the knowledge base on common infections, or to detect resistance patterns.

As a result, management of SBIs is compromised. Instead of selecting treatments based on awareness of the most likely causative pathogens and the most effective antibiotics for these, the approach is trial and error with a tendency to treat for multiple infections simultaneously and to escalate to broader spectrum antibiotics (if available).

## Impact of diagnostics access gaps

No doubt, the individual and population level lack of diagnostics for bacterial infections contributes to high mortality in AHD. For the individual patient, clinicians are working blind, guessing whether bacteria, another organism, or both, are causing illness. The lack of access to testing, and the technical limitations of bacteriology tests, results in reliance on clinical diagnosis alone, which is insufficiently sensitive for many life-threatening infectious diseases. *(14) (24)*

A recent postmortem study on the cause of death in PLHIV found that in half of the deaths knowing the etiology of the condition could have prolonged survival or cured the patient. *(14)*

In severe disease, rapid initiation of effective empiric treatment improves the chances of patient survival and reduces length of hospital stay and associated costs. Optimally the empiric antibiotic choice is informed by local knowledge of common pathogens and resistance. Current AMR data from LMICs, albeit incomplete, suggests high levels of resistance, implying that many of the commonly used treatments are ineffective for resistant pathogens. For example, a recent study across 14 African countries noted a low use of "reserve" antibiotics, despite data suggesting the resistance patterns warrant greater use of these antibiotics. *(21)* Thus, beyond improving survival for individual patients, access to diagnosis can break the on-going cycle of poor management and outcomes, due to poor understanding of the causative agents, limiting delivery of optimal therapies. *(25) (14)* Since AHD patients are more prone to resistant infections and rapid deterioration if effective treatment is delayed, it is plausible that their lack of access to bacterial diagnostics and effective antibiotics contributes to excess mortality in PLHIV.

### *Efforts to strengthen bacteriology testing in LMICs*

With increasing AMR, there are several efforts to improve microbiology services in LMICs (e.g. Fleming Fund); however, these have long timelines:

- Culture and antimicrobial susceptibility testing strengthening will first focus on surveillance and patient management at national and regional referral facilities. Efforts to improve microbiology services have long timelines - considering many challenges, among them:
  - sustainable funding, i.e. Global Fund has only recently announced AMR surveillance can be included in grants.
  - infrastructure: lack of physical space and temperature control for microbiology laboratories;
  - supply chain: maintaining stock of reagents and supplies required to perform culture, identification and susceptibility testing can be challenging, especially given short shelf lives and the multiplicity of supplies needed.
  - implementation concerns: quality assurance, training for laboratory, clinical, and pharmacy staff to ensure microbiology results can inform practice.
- NAAT tests, while arguably easier to implement, are prohibitively expensive. Moreover, for NAAT implementation at lower-level hospitals, some of the same supply chain, infrastructure, and expertise/ workforce-related challenges faced by culture/ID/AST would also need to be overcome.

# Technology landscape

This section considers the landscape of on-market RDTs for diagnosing priority pathogens causing SBI in AHD and the potential utility and impact of these RDTs in AHD. Findings about the potential utility and impact of these RDTs was informed largely by expert input, which included over 40 discussions.

To frame this analysis, it is helpful to consider the key diagnostic questions and challenges related to severe bacterial infection in AHD patients, by setting and visit type. (Table 5. Overview of potential use cases for SBI RDTs in AHD patients, by setting and visit type).

Experts suggest that tests informing inpatient SBI diagnosis and management are the greatest priority. Guiding antibiotic use in outpatient AHD patients. Severity assessment in outpatient and inpatient AHD patients may be valuable but are lower priority.

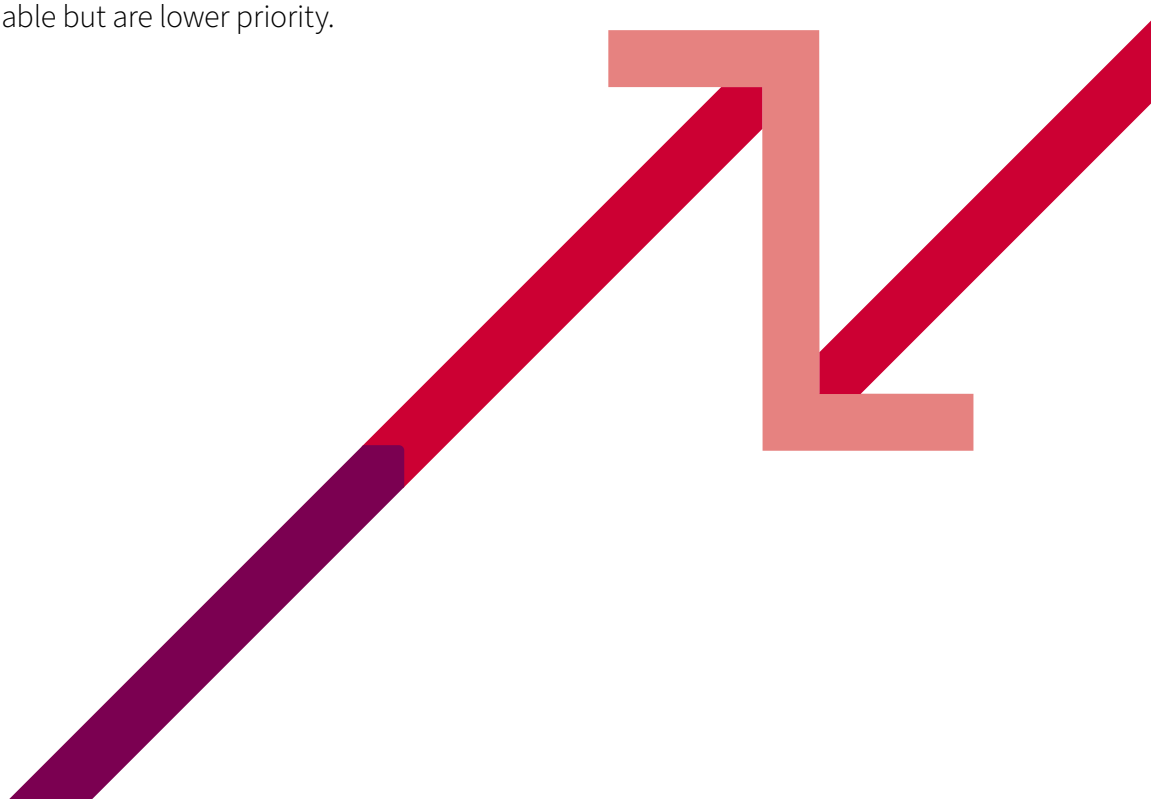


**Table 5. Overview of potential use cases for SBI RDTs in AHD patients, by setting and visit type**

## HIV/ART Clinic

| | Routine, well | Sick/acute care |
|---|---|---|
| *Level of concern for SBI* | **Limited in the absence of any symptoms or signs. Half AHD patients are well** | **High, depending on symptoms/signs, CD4, treatment status, VL** |
| *Key clinical questions concerning bacterial infection* | Minimal, perhaps risk of impending severe disease (i.e. either falling sick, or IRIS,) which would be informed by CD4, treatment status, & VL | • Need for admission: admit or treat as an outpatient, level of follow-up.<br>• Antibiotic use: would the patient benefit from an available antibiotic? if so, which? Decision partly informed by simple tests as available, (e.g., CD4, CrAg, TB , malaria RDT) yet co-infection is possible. |

## Potential RDT use cases

**Impending severity / need for closer follow-up**

**Host response (within an algorithm):**

- Assessing the need for referral/admission.
- Mild illness: guiding the decision to provide an antibiotic or not; treat mild illness before it progresses.

**Pathogen-specific**

- Guiding a decision about antibiotic choice/duration etc. and need for referral.

## OPD/ED

### Sick/acute care

**Moderate to high, based on symptoms, signs, history. May not know HIV and ART status, nor CD4/VL.**

- Need for admission: assess severity → admit or treat as an outpatient, level of follow-up.
- Antibiotic use: would the patient benefit from an available antibiotic? If so, which? Decision partly informed by HIV status & treatment status; as well as other simple tests as available, (e.g., CD4, CrAg, TB, malaria RDT) yet co-infection is possible.

**HIV RDT: HIV status**

**Host response (within an algorithm):**

- Assessing the need for referral/admission.
- Guiding the decision to provide an antibiotic or not

**Pathogen-specific**

- Guiding a decision about antibiotic choice/ duration etc.

## Inpatient

### Admitted for severe disease

**High. Can test for HIV; but may not have CD4/VL information.**

- Assess severity/prognosis
- Would the patient benefit from an available antibiotic?
  - — If so, which will be effective for the most likely causative pathogens?
- Would the patient benefit from other treatments for non-bacterial causes (viral/fungal/parasite)?
- What other therapies (oxygen, nutrition, hydration, nebulizer etc.) would help in this condition?
- How likely is co-infection?
- Is it possible to narrow the antibiotic safely?
- Discontinue the antibiotic?
- Need to escalate because of resistance?

**HIV RDT: HIV status**

**Host response:**

- Assessing prognosis.
- Guiding the decision to provide an antibiotic.
- Monitoring response to treatment.

**Pathogen-specific**

- Guiding a decision about antibiotic need, selection, duration, need to escalate (if local susceptibility is known) etc.
- Need for additional therapies (oxygen, hydration, etc.)

## RDT landscape for priority pathogens causing SBI in AHD

Two categories of tests might be considered in bacterial infection in AHD, pathogen-detecting RDTs and host response biomarker-based RDTs, these are discussed below.

### Pathogen detecting RDTs.

This landscaping exercise found few RDTs are available for the priority pathogens, i.e., *Streptococcus pneumoniae*, invasive non-typhoidal *Salmonella, Escherichia coli,* and Staphylococcus aureus. Only the antigen-detecting *Streptococcus pneumoniae* RDT is available and indicated for use in LRTI (urine samples) and meningitis (CSF). No RDTs were identified for invasive non-typhodial *Salmonealla, E. coli* or *S. aureus*.

Several well-known IVD companies sell antigen-detecting *Streptococcus pneumoniae* RDTs. (Table 6) These tests are based on detecting the c polysaccharide a component of the pneumococcal cell wall excreted in urine, found in all serotypes. Several are basic rapid tests, while some use fluorescence detection technology requiring an RDT reader. Performance of these tests varies, although it is most sensitive in severe disease. For example, one study found ~72% sensitivity for a common test (BinaxNOW) but suggested that sensitivity varies by the pneumococcal serotype (range, 33-100%). As the various pneumococcal conjugate vaccines (e.g. PCV7, PCV13) are rolled out, pneumococcal disease in a population reduces, but the circulating serotype mix may change. *(39)*

**Table 6. On-market RDTs for *Streptococcus pneumoniae***

| Primary syndrome | Pathogen | RDT name | Company |
|---|---|---|---|
| LRTI/Meningitis | *Streptococcus pneumoniae* | BIOSYNEX S. PNEUMONIAE | Biosynex |
| LRTI/Meningitis | *Streptococcus pneumoniae* | BinaxNOW™ S. pneumoniae Antigen Card<br>pPneumoniae | Abbott |
| LRTI | *Streptococcus pneumoniae* | Standard Q S. pneumoniae Ag (urine) | SD Biosensor (SD Biosensor, Inc.) |
| LRTI | *Streptococcus pneumoniae* | Standard F (FIA) | SD Biosensor (SD Biosensor, Inc.) |
| LRTI/Meningitis | *Streptococcus pneumoniae* | Sophia (FIA) | Quidel |
| LRTI/Meningitis | *Streptococcus pneumoniae* | Unigold | Trinity Biotech |
| LRTI/Meningitis | *Streptococcus pneumoniae* | Nadal Streptococcus Penumoniae Test | nal von miden |
| LRTI/Meningitis | *Streptococcus pneumoniae* | Rapid Viditest | Vida |
| LRTI | *Streptococcus pneumoniae* | ImmuView S. pneumonia + legionella | SSI Diagnostica |
| LRTI/Meningitis | *Streptococcus pneumoniae* | Biospedia's PenumoSpeed (urine & CSF) | BioSpeedia |

### Host response biomarker based RDTs.

Host response biomarker based RDTs can be used to support diagnosis of infections (e.g. elevated levels may suggest illness caused by bacteria) and to assess severity and inform prognosis, e.g. risk for severe disease and death. These RDTs typically detect molecules of the human response to infection (e.g. inflammation, immune system responses, activation of common severe disease pathways, changes in how an organ metabolizes substances). The presence and levels of these biomarkers must then be related to the presence and type of infection (e.g. bacterial, viral, fungal) or to severity. Unitaid has previously explored these tests through its fever diagnosis landscaping and in a 2020 Biomarker Consultation co-hosted with FIND *(40)*.

On market tests are predominantly CRP and PCT, both acute inflammatory markers, that are not specific to any disease. Thus, they are not diagnostic themselves but used as a piece of the clinical picture (i.e. would likely need a supporting algorithm for lower-skilled providers). Elevated levels indicate "something is going on" that needs attention, but they do not provide specific information on the cause (e.g. malaria will elevate CRP as does bacterial infection).

Commercial quantitative laboratory tests and POC tests exist for both. CRP is more amenable to an RDT format, as PCT testing is usually performed on serum or plasma, requiring a pre-processing step, and often it is device-based. While CRP RDTs may sell for $1-3/test, PCT tests tend to be several times as expensive.

While device-based formats are usually quantitative, in the rapid test format host response biomarker-based tests are either semi-quantitative (multiple bands corresponding to different levels) or qualitative tests (binary result based on levels exceeding a particular threshold). Studies are required to find the optimal cut off point, depending on the use case and decision to be taken. Depending on their use then, the on market RDTs with the appropriate cutoffs may or may not be commercially available.

Previous landscaping exercises have identified many CRP RDTs, for example: in 2017 FIND identified 36 products, 14 with a CE Mark. While 25 did not require a reader, 11employed a reader. As of early April 2023, FIND's newly launched AMR test directory includes 12 point-of-care CRP tests.[1] There are fewer on-market PCT tests, for example, FIND found only 20 POC tests in 2017, and there are currently 23 PCT tests in FINDs AMR test directory.

New biomarkers are being studied for a variety of risk stratification use cases in LMICs *(41) (42) (43)*. For example, one effort aims to identify incipient severe disease using markers of endothelial and immune activation that perform regardless of the cause (sTREM-1 and Ang2). *(44)* After limited yet favorable results in HIV-infected populations, results from a larger cohort (n=1000) of febrile adults and children in Mozambique (in and outpatients) are expected by mid-2023.

1 https://www.finddx.org/tools-and-resources/dxconnect/test-directories/amr-test-directory/ (Accessed 4 April 2023)

## Potential utility of on-market pathogen detecting RDTs to address priority diagnostics access gaps

### *Streptococcus pneumoniae* antigen test

For the prioritized AHD bacterial pathogens the only relevant on-market RDT is the *Streptococcus pneumoniae* antigen test. Globally, the test is not recommended for children, because of high rates of pneumococcal colonization, but it could be used in adults with lower respiratory tract infections or meningitis. A study of Kenyan adults with respiratory illness confirmed urinary antigen performance in LMICs, where both colonization and HIV are more prevalent and could affect performance. The study reported 67% sensitivity (although the number of positives in the sample size was limited) and 98% specificity, which is similar to findings in developed countries. *(45)*

In terms of clinical impact, there is little experience with the test in LMICs, and experience from high resource settings is mixed. A recent UK article suggests that the yield of the test is low (<10%) in severely ill patients, and that positive results infrequently resulted in use of targeted antibiotics. *(46)* The 2022 WHO AWaRe guidelines state the test is "not routinely needed but suggested in severe cases."

For AHD, few clinicians interviewed for this report in LMICs had experience with the test, but most did not expect it would change management. For outpatients, it is not considered practical to implement, given existing workloads and the low expected yield of the test, i.e., few would test positive.

For admitted patients with severe pneumonias, the test's performance implies use as a 'rule in' test (i.e. sensitivity is too low to rule out *Streptococcus pneumoniae)*, a positive result prompting use of a narrow-spectrum antibiotic. A negative result would not be used to exclude *S. pneumoniae*. In practice, for immunocompetent patients, clinicians reported that a positive test would prompt a switch to narrow-spectrum antibiotics.

In AHD patients, LMIC clinicians differed in opinions about whether this test would change management. Depending on the patient's condition, most clinicians would continue a broad-spectrum antibiotic to cover additional potential infections. Only a few clinicians interviewed, concerned about stewardship, would switch to a narrower-spectrum antibiotic in an AHD patient. Overall, while there may be scope for scaling up this test in pneumonia for stewardship and pneumococcus prevalence purposes, (especially in otherwise healthy patients), its clinical impact for the individual patient is likely limited in AHD populations.

A second use of the test is in meningitis: performing the test on CSF samples to diagnose meningitis caused by *Streptococcus pneumoniae*. Only a few experts interviewed for this report had experience with it, but their experience is favorable. Literature also suggests high performance of antigen tests in CSF, 99.5% sensitivity and 98.2% specificity. *(47)*

How a test would be implemented requires more study, for example how does the RDT complement microscopic examination of CSF? Which other tests, such as urine dipsticks, biomarker RDTs for viral versus bacterial differentiation, *Neisseria Meningitis*, TB LAM, CrAG, syphilis, might be considered as well to support the meningitis etiology investigations *(48) (49) (50) (51)*. Given that CSF analysis typically occurs where a laboratory and basic microscopy skills are available, do additional RDTs simplify the work up and add value? While this approach could be explored in meningitis cases generally, the potential clinical impact in AHD needs further consideration. For AHD patients with meningitis, cryptococcal and tuberculosis etiologies dominate, and the relative contribution of *S. pneumoniae* infections to "other" meningitis etiologies is unknown, so the yield of the test would be important to consider. Also, even if one bacterial infection is ruled out, clinicians are likely to continue broad spectrum antibiotics for other possible bacterial causes, so the value may be diminished without additional testing. The likelihood of co-infection also suggests additional testing would be needed.

### Other pathogen RDTs

Expert opinion on the utility of a pneumococcus antigen test is illustrative of sentiments about pathogen specific RDTs in AHD more broadly: generally speaking, when asked about the potential impact of a pathogen specific RDT on management of a hospitalized AHD patient, adult or child, most experts felt it was minimal, primarily due to high frequency of coinfection, possible colonization, and needing resistance and susceptibility information. In other words, most clinicians would not stop a broad-spectrum antibiotic in AHD patient who is admitted with a severe syndrome, even if an RDT allowed them to 'rule-in' a pathogen, they would continue the antibiotics because patients with low CD4 can have multiple infections at once and the presence of the pathogen does not mean it is causing the illness. If clinicians were to narrow antibiotics, it would not be for a large proportion of patients. Additionally, resistance patterns also vary, in some settings like the eastern Democratic Republic of Congo, resistance is so common that it is imperative to also know susceptibility as well. *(52)*

## Potential utility of on-market host response biomarker based RDTs to address priority diagnostics access gaps

There are two commonly discussed use cases for host response biomarker tests, to guide antibiotic decision making and to prognosticate. For simplicity, we describe the use cases separately here but in reality, they are not so dichotomous. The first use case contemplates using elevated biomarker results to suggest the patient has a bacterial infection and requires antibiotic. The second use case suggests that the elevated biomarker is indicative of severe disease. In this situation, absent an apparent cause of illness, a clinician is likely to provide an antibiotic while trying to stabilize the patient and investigate the cause of infection.

### Host response biomarker RDTs to guide antibiotic decision-making

In some common syndromes, especially respiratory illness, inflammatory biomarkers like CRP, PCT can provide information useful in deciding about whether a patient may benefit from antibiotics. Elevated values are suggestive of bacterial infection. Increasingly, these markers are studied and recommended for antibiotic stewardship in respiratory infection in adult immunocompetent patients, guiding clinicians to withhold antibiotics when PCT/CRP levels are below a certain threshold.

The WHO AWaRe (2022) antibiotic book notes the use of CRP, PCT, and white blood cell count to support decision making about antibiotic therapy in sepsis, meningitis, and severe pneumonia syndromes. *(35)* However, the guidance is not particularly specific regarding their use, there are no thresholds suggested, requiring the user to have the skills needed to interpret the values given the patient's condition.

There are several concerns about using these tests in AHD patients. First, these markers are imperfect. While SBIs are likely to elevate CRP and PCT values, HIV itself may alter these markers as can many other common infections, including those requiring specific treatments (e.g. malaria, TB). For example, a South African study in PLHIV admitted for lower respiratory tract infection found that while CRP and PCT values were elevated, differentiating between common causes, i.e. pneumocystis, tuberculosis and bacterial pneumonia, was not possible, and as such, the test provided little additional value in guiding antibiotic treatments. *(53)* Most clinicians interviewed agreed with this assessment.

Moreover, in AHD, severe immune compromise dampens the immune response, and these markers may not be elevated; therefore, without more definitive evidence, in the absence of a highly elevated c-reactive protein or procalcitonin levels, clinicians are not likely to rule out bacterial illness and will continue broad spectrum antibiotics.

Despite these shortcomings, several LMIC based specialists (e.g. HIV, Infectious Disease, and pediatric specialists) interviewed for this report use these markers routinely, considering them "one piece of the picture." However, it is challenging to translate this knowledge and reasoning into algorithms with appropriate cut offs for broader use by clinicians lacking this advanced training and experience, which prevents widespread implementation.

### Host response biomarker RDT for risk stratification and prognosis

Discussions and research for this report elucidated several different risk stratification or prognostic applications for host response biomarker based RDTs in AHD.

First, in the outpatient, primary care setting a HRB RDT such as CRP or PCT could support health workers to identify severely ill patients who need referral. In general, a test that helps frontline health workers confidently risk stratify patients for outpatient treatment or referral/admission would be beneficial. However, HIV experts contributing to this report felt that delayed presentation to health care [e.g. due to stigma, reluctance to (re-)engage in care) was a greater challenge than health care worker failure to identify and refer patients with severe disease using danger signs and basic clinical indicators. Thus, it is unclear if this use would complement or be redundant of clinical assessment skills and CD4 count in PLHIV.

The second possible application of a HRB RDT is at the hospital or inpatient setting. Because clinical assessment skills are typically higher in these settings, clinicians felt that the incremental value of a CRP or PCT in the initial assessment of a sick AHD patients was insufficient to justify wide use.

Also in a hospital setting, serial biomarker testing, usually PCT, is used to supplement clinical assessment of a patient's response to treatment. However, in LMICs and AHD the latter was not considered to be a high priority use case.

The last use case relates to initiating ART. Given the high rates of death in early ART there is ongoing research on using markers like CRP (sometimes in combination with other signs or POC tests for anemia) to risk stratify patients who are at risk of mortality, TB or SBIs *(54)*. Early in the HIV epidemic when CD4 coverage was low and affordability a major challenge, CRP was suggested as a potential indicator of disease progression *(55)*; more recently studies have shown the utility of CRP in screening for TB in PLHIV. Currently WHO recommends CRP (with a low cuttoff of 5mg/L) for TB screening. *(56)*. Today, with access, albeit imperfect, to CD4 testing, the added value of biomarker tests for risk stratification is unclear. One recent study of patients with CD4<350 and without TB from Uganda suggests that elevated CRP could be used to flag patients needing a closer work up, additional monitoring, additional screening for TB and opportunistic infections as they begin ART. *(57)* Pragmatically, several questions remain around 1) optimal thresholds for this use case; 2) feasibility of implementation by health care workers already seeking simplicity; and 3) whether it adds value if a current CD4 result is available. Unitaid is currently funding interventions to increase access to TB diagnostic tests, including point of care CRP screening tests, in locations where they are not available, and with a focus on key and vulnerable populations with limited access to TB diagnosis. Single tests and/or combinations of screening tests will be utilized with the aim of increasing the identification of people with presumptive TB eligible to undertake confirmatory tests.

### Technology landscape conclusion

Overall, there are no available RDTs that would have a compelling direct impact on severe bacterial infection outcomes in AHD populations. However, slightly beyond this report's focus are some applications that may improve outcomes for PLHIV. Specifically:

- **CRP RDTs might improve risk stratification in people initiating ART,**
- **A bundle of pathogen and biomarker RDTs, alongside other rapid tests (e.g. for fungal and tuberculosis infections), combined with support for conducting lumber puncture, might be combined to improve meningitis diagnosis.**

Both would benefit from additional research and work up to better appreciate the degree of added value compared to existing approaches; as well as an assessment of implementation feasibility.

Research uncovered a few additional RDTs for bacterial infections besides the priority SBIs infections (See Annex). However, considering the high number of possible causative organisms, no one RDT would be practical to implement. Additional information on the organisms contributing most to severe bacterial disease and severe disease overall in PLHIV would inform any decisions about the value of these tests.

Another challenge highlighted by this review is that on-market tests are imperfect, lacking in sensitivity or specificity. In part, biology explains the lack of RDTs for bacterial infections. Even in sophisticated reference laboratories, the causes of bacterial infection are not always identified. Sampling is a challenge, often, the site of infection (e.g. lung) is not accessible for sampling. Other sites, like the nasal pharynx, are challenging because people are colonized with bacteria that the test may detect, even though these bacteria are not causing infection. Additionally, for the priority pathogens, the number of bacteria present in a sample can be extremely low. For example, for *S. pneumoniae, S. aureus*, and non-typhoidal *Salmonella* there may be as few as a one pathogen in 1 mL of blood, making it statistically challenging to directly detect an organism. In addition, the rapid test platform is generally less sensitive than laboratory methods that often rely on bacterial growth or amplification. Technically speaking, it has proven extremely difficult to achieve the performance necessary to influence the clinical management of a severely ill patient within a clinically relevant timeframe.

# Market shortcomings and challenges

There are important needs in diagnosing SBIs in AHD for which adequate diagnostics do not exist. Where products do exist, there is a lack of evidence supporting their use, and products may need adapting for the specific use indication. The lack of tests reflects the substantial technical challenges associated with developing these tests, as well as limited market incentives to develop tests for bacterial infections generally and in AHD specifically.

This section first considers the shared market challenges limiting access to bacteriology tests, and then the specific current and anticipated challenges associated with the lack of SBI RDTs and HRB RDTs, and finally, challenges relating to population-level bacteriology testing.

### Shared challenges for bacterial infection diagnostics

From a developer's perspective, the costs to develop diagnostics for bacterial infections are high, the revenues uncertain, and timelines long. Trials are time-consuming and costly, partly because the gold standard, high-quality culture, is not widely available, especially in LMICs. Typically, multiple sites are needed to identify an adequate number of cases for a trial, and finding sites with sufficient microbiological expertise and capacity is challenging. Moreover, given the shortcomings in existing diagnostics (low yield, sensitivity, inaccessibility of sampling the site of infection), trial design can be complex, requiring "composite" reference standards that combine microbiology results and expert clinician adjudication.

From a revenue perspective, the potential need, by use case, has not been quantified. Funding for these tests is uncertain; there are no large donors supporting routine bacterial infection testing. Bacteriology tests are generally funded out of pocket by patients and through domestic funding for laboratories, and hence, the service is usually underfunded. At the individual patient level, the financial incentive to test is low, as it is often cheaper to treat presumptively than to test and then treat. While knowing the causative pathogen is sometimes vital for the patient because it directs a particular treatment, many benefits are more subtle. For example, a bacteriology test may result in a change to a more effective antibiotic if the empiric choice was ineffective, which may be life-saving. However, the test result could indicate discontinuation or de-escalation of treatment, which reduces side effect risk, or potential colonization with drug-resistant organisms, but these are hard to appreciate. In this case, the benefits largely accrue at a population level and are not well captured in current cost-benefit analyses. Additionally, the aggregate bacteria test results

provide information on the bacteria prevalence in the population, data that are essential at the population level to inform EMLs and empiric treatment guidelines.

## Pathogen-specific RDTs: minimal product availability for priority SBIs

The market incentives to develop RDTs for SBIs are diminished by high costs and long timelines (as above), and importantly the lack of knowledge around which bacterial pathogen test would have the greatest uptake and market. In AHD, SBIs have only recently been prioritized, given their high contribution to hospitalization and mortality *(13)*. However, the specific pathogens causing these severe bacterial infections, and their resistance profiles, is insufficiently characterized, making it difficult to prioritize investment in any particular pathogen test.

The use cases are undefined, as are estimates of need and market size (e.g., estimates of the number of patients hospitalized with particular syndromes are not available). With resistance increasing, the value of pathogen-specific tests that do not provide resistance information may also be diminished unless coupled with robust local empiric treatment guidance.

Additionally, given the number of potential bacteria that could cause illness in AHD and practical limits on the number of RDTs that can be performed from a cost and human resources perspective, a multiplex or a flexible test platform like culture may have greater commercial and public health appeal.

### HRB RDTs: existing imperfect tests lack evidence to support use in SBI

While host response biomarker RDTs exist, the evidence base required to support widespread use for SBI management in AHD does not exist. Additionally, the tests may need further development (i.e. identifying thresholds for clinical use) depending on the use case.

From an evidence perspective, existing biomarker-based tests are imperfect, and while highly skilled physicians use them to refine their clinical assessment, additional guidance and algorithms are needed to inform broader use. These algorithms must take many factors into consideration and are time-consuming to develop and to validate in LMICs. Moreover, they likely need local customization based on common diseases (e.g. malaria, dengue, helminths) that influence biomarker values.

Only recently has work commenced to articulate the use cases for these tests, and work to date has largely focused on outpatient febrile illness and TB. Their potential role in care for PLHIV has not been articulated nor prioritized, making it difficult for developers to appreciate the potential market opportunity or for policymakers and donors to appreciate the public health impact. Better articulation and prioritization would help inform decision-making.

Once a use case is established, the relevant thresholds for acting on the test result must be elucidated and validated. If not already commercially available, tests with these thresholds must be developed in RDT format, with a binary or semiquantitative readout.

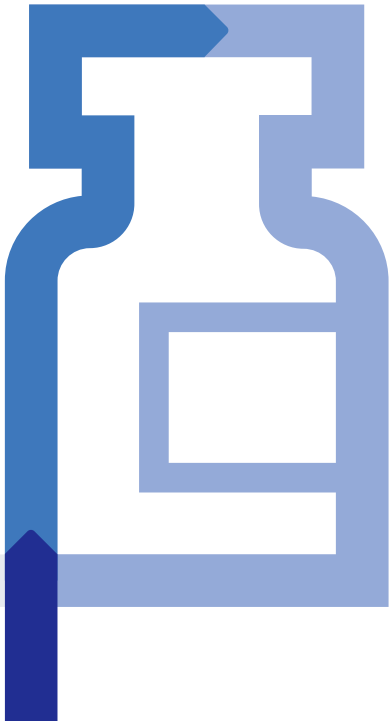
## Anticipated market challenges: supporting adoption and use

For new SBI diagnostics to impact patient outcomes, providers long accustomed to treating empirically with antibiotics need to change behavior. While many clinicians prioritize knowing more about the etiology of infections, today there is no "culture" of using diagnostics for patient management. Behavior change will be needed to ensure clinicians know when to request tests, are confident in test quality and interpretation (e.g. colonization, risk of co-infection), and act on the results. Outcomes data, education, and monitoring would likely be required to support uptake. In the absence of such behavior change programming to support test uptake, diagnostics developers will be reluctant to develop necessary tests.

## Lack of bacteriology knowledge contributes to population level gaps in access to effective treatment

At the population level, lack of bacteriology testing means there is little knowledge of the most common infections in the population. This limits confidence in empiric treatment guidelines: the guidelines recommend antibiotics thought to cover the most common causes of a syndrome, however, when sufficient representative data is not locally available, the guidelines may not reflect the local disease burden and resistance patterns, and the suggested treatments may not be effective.

There are several reasons for limited bacteriology testing: existing bacteriology diagnostics are poorly adapted to LMIC settings, they are unaffordable, and uptake is limited. Additionally, the approach to standardizing, quality controlling, and translating bacteriology results into empiric treatment recommendations requires strengthening.



Specifically, available technologies (e.g. culture, identification, and susceptibility testing) for diagnosing bacterial infection are poorly adapted to low resource settings: they require highly skilled staff, dedicated dust-free, climate-controlled space, and a multiplicity of reagents and consumables. While some newer technologies automate or simplify some aspects of the process, they tend to be expensive (e.g., automated culture platforms, molecular pathogen identification platforms, chromogenic media).

Even where bacteriology is available, it is underutilized for several reasons. First, even if the clinician wanted to test, patients cannot afford the testing, and MoH and donors do not adequately prioritize and fund microbiology. When few people use a laboratory service, technicians lose their skills, quality becomes compromised, and stock-outs are unaddressed. The problem becomes circular, i.e., clinicians stop requesting tests, and labs stop performing them. As noted above, poor uptake of tests is a disincentive to potential test developers.

Finally, a process for routinely compiling and quality-controlling bacteriology results (including key clinical information) is needed. Because bacteriology testing is so limited and often only available from selected severely ill patients, considerations around representativeness and sample size are important. Thus, an expert committee (e.g., infectious disease doctors, microbiologists, pharmacists) is needed to interpret available data and consider global recommendations (e.g. the WHO EML, AwARe, published literature) to make local EMLs and empiric treatment recommendations. Specific frameworks and approaches to this process for settings with limited capacity for culture and sensitivity testing are being revisited in light of increasing concern about antimicrobial resistance. *(58)*

# Opportunities for intervention

This section provides an initial view of opportunities to address market shortcomings in order to increase availability and access to SBI diagnostics. While pathogen and host response RDTs are considered, given the population level gaps, opportunities related to bacterial diagnostics and optimizing antibiotic use are also considered. The opportunities are not specific to Unitaid's mandate and business model; they are illustrative, representing a range of interventions that different global health actors could undertake.

### Defining needs, use cases, and potential demand

Current blind spots in understanding severe disease etiology in AHD hinder the prioritization of potential approaches to improving the diagnosis and management of SBIs. A better appreciation for the distribution of disease, including bacterial pathogen prevalence and resistance patterns, as well as the relative contribution of fungal, viral, and parasitic pathogens to severe disease syndromes in AHD is needed. This knowledge, along with an appreciation for how a test (i.e. confirming or excluding a pathogen) would change management, could inform the prioritization of pathogen-specific diagnostics.

Use cases for host response biomarker RDTs need additional definition as well in order to prioritize investment in their further development, including the development of algorithms to support their use.

### Supporting bacterial diagnostics R&D

R&D support for fit-for-purpose bacterial diagnostics can benefit both the AHD and general patient populations more broadly. Support may include direct funding for developers or access to sample banks and facilitation of trials. The studies above can inform investment priorities (i.e., single disease RDTs, multiplex tests, culture-based diagnostics) but an overarching need is finding technologies and pragmatic approaches that make bacteriology more accessible to laboratory workers and clinicians with limited training.

In the near term, to advance host-response biomarker RDT development and introduction, trials in relevant populations are needed to inform the relevant biomarker thresholds and to develop algorithms specific to each use case.

## Demand realization and incentivizing future innovation in bacterial diagnostics

While policymakers and clinicians value increasing etiological diagnosis of severe disease and its importance to patient management, and to increasing the precision of disease management, when resources are limited, it can be difficult to fund testing unless there is a direct, quantifiable impact (e.g., on mortality or cost). New methods for valuing diagnostic tests that improve disease management and have a population-level impact are needed to support favorable cost-benefit assessments.

Investing in and advocating for improved bacteriology services will signal to the market the increasing importance of this neglected area. Where currently available, funding and increased clinician awareness for appropriate bacteriology testing are needed, coupled with support to ensure testing quality and interpretation of results. In the future, as simplified culture systems and POC NAAT become available, their introduction needs to be supported holistically. Ensuring that the empiric guidelines match the local disease epidemiology is also critical, and support is needed for schemes that regularly update local EMLs and guidelines, drawing on global guidance and locally available data (albeit incomplete in the near term).

## A syndrome-based cross-cutting approach to diagnostics in severe disease

In high-burden HIV settings, AHD patients comprise a substantial proportion of the severe disease burden. Therefore, a patient- and health-worker-centered approach would focus on each of the main severe disease syndromes (e.g., sepsis, meningitis, severe pneumonia). In this approach, diagnostics would focus on the major bacteria and other pathogens (including tuberculosis and malaria) contributing to the syndrome. The goal would be to optimize management, including strengthening diagnosis, ensuring empiric treatment matches epidemiology, and optimizing supportive therapies (e.g., oxygen, fluids). For example, in meningitis, the approach would include supporting lumbar puncture implementation, bundling a few rapid tests to improve etiological diagnosis, and ensuring treatment access. In sepsis, specific supportive treatments such as fluids can be life-saving or life-threatening, depending on the etiology. To impact AHD, such an approach would need to cover major OIs, in addition to SBIs. However, from a market perspective, a syndrome-based approach may have wider population applicability and a greater market impact than an HIV focused intervention.

## Other considerations

**Explore COVID-19 advances.** Longer term, an approach that involves simple multiplex POC molecular testing for common infections coupled with localized and up-to-date empiric treatment guidelines could be promising. While existing multiplex NAATs for bacterial infections have yet to achieve optimal sensitivity, are too expensive, and are poorly suited to LMIC conditions, it is timely to take stock of pandemic-related technology advances and consider the potential public health impact and market opportunity of affordable syndromic panels covering major SBIs impacting AHD and general populations. Past efforts to prioritize pathogens for syndromic panels should be leveraged (e.g. MAP-Dx *(59)* ) and the data generated through the epidemiological studies (recommended above) would validate and refine these prioritizations.

**Link with other initiatives.** SBI diagnosis and severe disease in HIV patients is an exceptionally complex and cross-cutting topic that touches on many different health initiatives. (Figure 9). The crosscutting nature of this area also suggests there is scope for synergies and leveraging other investments. In particular, supporting the implementation of WHO AWaRe antibiotic book and the increasing interest in AMR diagnostics could be impactful for AHD.

**Figure 9. SBI diagnosis in AHD - a cross-cutting topic that touches on many health initiatives**

# Conclusion

## Severe bacterial infection mortality risk in advanced HIV disease is high, and especially concerning as HIV patients are vulnerable to resistant infections. With resistance increasing, it is essential to balance rational use with increased access to effective antimicrobials.

However, improving SBI diagnosis and management in AHD is challenging, given the broad differential, lack of fit-for-purpose diagnostics, and exceptional lack of data. As a result, policymakers and providers are working blind, lacking the information to act on severe bacterial infections.

The strengths of HIV programmes (e.g. laboratory networks, skilled providers, strong monitoring systems) present an opportunity to strengthen the diagnosis and management of SBIs in AHD starting with developing a stronger evidence base and simplified tools that can be used at the lowest levels of the health care system.

# Works cited

1. World Health Organization. *Report from the scoping consultation on severe bacterial infections among people with advanced HIV disease: virtual meeting, 23 November 2021.* Geneva : World Health Organization, 2022.
2. *Landscape of diagnostics against antibacterial resistance, gaps and priorities.* Geneva : World Health Organization, 2019.
3. FIND. AMR Test Directory. [Online] 2023. https://www.finddx.org/tools-and-resources/dxconnect/test-directories/amr-test-directory/.
4. World Health Organization. *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach.* Geneva : World Health Organization, 2021.
5. *Priorities for Decreasing Morbidity and Mortality in Children With Advanced HIV Disease.* Frigati L, Archary M, Rabie H, Penazzato M, Ford N. s.l. : Clin Infect Dis., 2018 Mar 4, Vols. 66(suppl_2):S147-S151.
6. *Effects of National Adoption of Treat-All Guidelines on Pre-Antiretroviral Therapy (ART) CD4 Testing and Viral Load Monitoring After ART initiation: A Regression Discontinuity Analysis.* Brazier E, Tymejczyk O, Zaniewski E, Egger M, Wools-Kaloustian K, Yiannoutsos CT, Jaquet A, Althoff KN, Lee JS, Caro-Vega Y, Luz PM, Tanuma J, Niyongabo T, Nash D. s.l. : Clin Infect Dis, 2021 Sep 15, Vols. 73(6):e1273-e1281.
7. Clinton Health Access Initiative. *The Road to zero: Report on the implementation of teh Advanced HIV Disease Package of Care in low- and middle-income countries.* s.l. : Clinton Health Access Initiative, 2022.
8. *The global burden of HIV-associated cryptococcal infection in adults in 2020: a modelling analysis.* Rajasingham R, Govender NP, Jordan A, Loyse A, Shroufi A, Denning DW, Meya DB, Chiller TM, Boulware DR. s.l. : Lancet Infect Dis., 2022 Dec, Vols. 22(12):1748-1755.
9. *Persistent High Burden of Advanced HIV Disease Among Patients Seeking Care in South Africa's National HIV Program: Data From a Nationwide Laboratory Cohort.* Carmona S, Bor J, Nattey C, Maughan-Brown B, Maskew M, Fox MP, Glencross DK, Ford N, MacLeod WB. s.l. : Clin Infect Dis, 2018 Mar 4, Vols. 66(suppl_2):S111-S117.
10. *The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa.* Osler M, Hilderbrand K, Goemaere E, Ford N, Smith M, Meintjes G, Kruger J, Govender NP, Boulle A. s.l. : Clin Infect Dis., 2018 Mar 4, Vols. 66(suppl_2):S118-S125.
11. *High mortality in adult patients with HIV admitted with fever to hospitals in Malawi, Mozambique and Zimbabwe - results from the FIEBRE study.* Ioana D Olaru, Marta Valente, Sara Ajanovic, Justina M Bramugy, Sham Lal, Mabvuto Chimenya, Edward W Green, Nicholas A Feasey, David Mabey, Quique Bassat, Katharina Kranzer, Heidi Hopkins. s.l. : Poster presented at ASTMH; November 2021; virtual meeting.
12. *Community-acquired bacteremia among HIV-infected and HIV-exposed uninfected children hospitalized with fever in Mozambique.* Kenga DB, Gebretsadik T, Simbine S, Maússe FE, Charles P, Zaqueu E, Fernando HF, Manjate A, Sacarlal J, Moon TD. s.l. : Int J Infect Dis., 2021 Aug, Vols. 109:99-107.

**13.** *Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis.* Ford N, Shubber Z, Meintjes G, Grinsztejn B, Eholie S, Mills EJ, Davies MA, Vitoria M, Penazzato M, Nsanzimana S, Frigati L, O'Brien D, Ellman T, Ajose O, Calmy A, Doherty M. s.l. : Lancet HIV, 2015 Oct, Vols. 2(10):e438-44.

**14.** *Minimally Invasive Tissue Sampling: A Tool to Guide Efforts to Reduce AIDS-Related Mortality in Resource-Limited Settings.* Letang E, Rakislova N, Martinez MJ, Carlos Hurtado J, Carrilho C, Bene R, Mandomando I, Quintó L, Nhampossa T, Chicamba V, Luis E, Ismail MR, Fernandes F, Lorenzoni C, Ferreira L, Freire M, Teresa Rodrigo-Calvo M, Guerrero J, Munguambe K, Maixenchs M, Nav. s.l. : Clin Infect Dis., 2021 Dec 15, Vols. 73(Suppl_5):S343-S350.

**15.** *A comprehensive list of bacterial pathogens infecting humans.* Bartlett A, Padfield D, Lear L, Bendall R, Vos M. s.l. : Microbiology (Reading), 2022 Dec, Vol. 168(12).

**16.** *Introduction to the Site-specific Etiologic Results From the Pneumonia Etiology Research for Child Health (PERCH) Study.* Deloria Knoll M, Prosperi C, Baggett HC, Brooks WA, Feikin DR, Hammitt LL, Howie SRC, Kotloff KL, Madhi SA, Murdoch DR, Scott JAG, Thea DM, O'Brien KL. s.l. : Pediatr Infect Dis J, 2021 Sep 1, Vols. 40(9S):S1-S6.

**17.** *The Etiology of Pneumonia in HIV-infected Zambian Children: Findings From the Pneumonia Etiology Research for Child Health (PERCH) Study.* Seidenberg P, Mwananyanda L, Chipeta J, Kwenda G, Mulindwa JM, Mwansa J, Mwenechanya M, Wa Somwe S, Feikin DR, Haddix M, Hammitt LL, Higdon MM, Murdoch DR, Prosperi C, O'Brien KL, Deloria Knoll M, Thea DM. s.l. : Pediatr Infect Dis J., 2021 Sep 1, Vols. 40(9S):S50-S58.

**18.** *The Etiology of Pneumonia in HIV-1-infected South African Children in the Era of Antiretroviral Treatment: Findings From the Pneumonia Etiology Research for Child Health (PERCH) Study.* Moore DP, Baillie VL, Mudau A, Wadula J, Adams T, Mangera S, Verwey C, Sipambo N, Liberty A, Prosperi C, Higdon MM, Haddix M, Hammitt LL, Feikin DR, O'Brien KL, Deloria Knoll M, Murdoch DR, Simões EAF, Madhi SA. s.l. : Pediatr Infect Dis J., 2021 Sep 1, Vols. 40(9S):S69-S78.

**19.** *Diagnosis of Bloodstream Infections: An Evolution of Technologies towards Accurate and Rapid Identification and Antibiotic Susceptibility Testing.* Tjandra KC, Ram-Mohan N, Abe R, Hashemi MM, Lee JH, Chin SM, Roshardt MA, Liao JC, Wong PK, Yang S. Basel : Antibiotics, 2022, Vol. 2022 Apr 12;11(4):511.

**20.** *Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis.* Antimicrobial Resistance Collaborators. s.l. : Lancet, 2022 Feb 12, Vols. 399(10325):629-655.

**21.** Mapping AMR & AMU Partnership. *Incomplete antimicrobial resistance (AMR) data in Africa: The crisis within the crisis.* Addis Ababa : ASLM, 2022.

**22.** Elliot, Oli, Smith, Alan and and Jack, Andrew. Antibiotic resistance kills over 1mn people a year, says study. *Financial times.* 19, 2022, 1.

**23.** *The DReAMM project: Initial results from Tanzania.* The DREAMM Consortium. Berlin / Virtual : The 11th IAS Conference on HIV Science, 18-21 July 2021.

**24.** *Clinico-pathological discrepancies in the diagnosis of causes of death in adults in Mozambique: A retrospective observational study.* Ordi J, Castillo P, Garcia-Basteiro AL, Moraleda C, Fernandes F, Quintó L, Hurtado JC, Letang E, Lovane L, Jordao D, Navarro M, Bene R,

Nhampossa T, Ismail MR, Lorenzoni C, Guisseve A, Rakislova N, Varo R, Marimon L, Sanz A, Cossa A, Mandomando I, Maixenc. s.l. : PLoS One, 2019 Sep 6, Vol. 14(9):e0220657.

**25.** *A Longitudinal, Observational Study of Etiology and Long-Term Outcomes of Sepsis in Malawi Revealing the Key Role of Disseminated Tuberculosis.* Lewis JM, Mphasa M, Keyala L, Banda R, Smith EL, Duggan J, Brooks T, Catton M, Mallewa J, Katha G, Gordon SB, Faragher B, Gordon MA, Rylance J, Feasey NA. s.l. : Clin Infect Dis., 2022 May 30, Vols. 74(10):1840-1849.

**26.** World Health Organization. *Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030.* Geneva : World Health Organization, 2022.

**27.** *Cotrimoxazole reduces systemic inflammation in HIV infection by altering the gut microbiome and immune activation.* Bourke CD, Gough EK, Pimundu G, Shonhai A, Berejena C, Terry L, Baumard L, Choudhry N, Karmali Y, Bwakura-Dangarembizi M, Musiime V, Lutaakome J, Kekitiinwa A, Mutasa K, Szubert AJ, Spyer MJ, Deayton JR, Glass M, Geum HM, Pardieu C, Gibb DM, Klein N, Eden. s.l. : Sci Transl Med., 2019 Apr 3, Vol. 11(486):eaav0537.

**28.** *Mixed methods systematic review and metasummary about barriers and facilitators for the implementation of cotrimoxazole and isoniazid-Preventive therapies for people living with HIV.* Müller P, Velez Lapão L. s.l. : PLoS One., 2022 , Vol. Mar 1;17(3):e0251612.

**29.** World Health Organization. *Providing care to people with advanced HIV disease who are seriously ill: policy brief.* Geneva : World Health Organization, 2023.

**30.** *Integrated management of childhood illness - Chart booklet.* Geneva : World Health Organization, 2014.

**31.** *Integrated management of adolescent and adult illness (IMAI) district clinician manual: Hospital care for adolescents and adults.* Geneva : World Health Organization, 2011.

**32.** Southern African HIV Clinicians Society. *Guidelines for hospitalised adults with advanced HIV disease.* Johannesburg : Southern African HIV Clinicians Society, 2022.

**33.** World Health Organization. *Updated guideline: paediatric emergency triage, assessment and treatment.* Geneva : World Health Organization, 2016.

**34.** *Pocket book of hospital care for children: Second edition.* Geneva : World Health Organization, 2013.

**35.** *The WHO AWaRe (Access, Watch, Reserve) antibiotic book.* Geneva : World Health Organization, 2022.

**36.** *Proportions of CD4 test results indicating advanced HIV disease remain consistently high at primary health care facilities across four high HIV burden countries.* Lamp K, McGovern S, Fong Y, Atem CD, Nfetam JBE, Nzuobontane D, Bollinger T, Jani I, Sitoe N, Kiyaga C, Senyama G, Mangwendeza PM, Mtapuri-Zinyowera S, Doi N, Peter T, Sacks JA, Vojnov L. s.l. : PLoS One., 2020 Jan 7, Vol. 15(1):e0226987.

**37.** *Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa.* Hakim J, Musiime V, Szubert AJ, Mallewa J, Siika A, Agutu C, Walker S, Pett SL, Bwakura-Dangarembizi M, Lugemwa A, Kaunda S, Karoney M, Musoro G, Kabahenda S, Nathoo K, Maitland K, Griffiths A, Thomason MJ, Kityo C, Mugyenyi P, Prendergast AJ, Walker AS,. s.l. : N Engl J Med., 2017, Vols. Jul 20;377(3):233-245.

**38.** World Health Organization. *Providing care to people with advanced HIV disease who are seriously ill: policy brief.* Geneva : World Health Organization, 2023.

**39.** *The Alere BinaxNOW Pneumococcal Urinary Antigen Test: Diagnostic Sensitivity for Adult Pneumococcal Pneumonia and Relationship to Specific Serotypes. Shoji H, Domenech A, Simonetti AF, González A, García-Somoza D, Cubero M, Martí S, Maeda M, Tubau F, Liñares J, Domínguez MA, Carratalà J, Ardanuy C. s.l. : J Clin Microbiol., 2018 Jan 24, Vols. 56(2):e00787-17.*

**40.** Unitaid and FIND. *Biomarkers for acute febrile illness at the point-of-care in low-resource settings: Meeting report.* Geneva : Unitaid and FIND, 2021.

**41.** *alAnticipating the future: prognostic tools as a complementary strategy to improve care for patients with febrile illnesses in resource-limited settings.* Chandna A, Osborn J, Bassat Q, et al. s.l. : BMJ Global Health, 2021, Vol. 6:e006057.

**42.** *Febrile Illness Evaluation in a Broad Range of Endemicities (FIEBRE): protocol for a multisite prospective observational study of the causes of fever in Africa and Asia.* Hopkins H, Bassat Q, Chandler CI, Crump JA, Feasey NA, Ferrand RA, Kranzer K, Lalloo DG, Mayxay M, Newton PN, Mabey D and Consortium., FIEBRE. s.l. : BMJ Open, 2020 Jul 21, Vol. 10(7):e035632.

**43.** *Prediction of disease severity in young children presenting with acute febrile illness in resource-limited settings: a protocol for a prospective observational study.* Chandna A, Aderie EM, Ahmad R, Arguni E, Ashley EA, Cope T, Dat VQ, Day NPJ, Dondorp AM, Illanes V, De Jesus J, Jimenez C, Kain K, Suy K, Koshiaris C, Lasry E, Mayxay M, Mondal D, Perera R, Pongvongsa T, Rattanavong S, Rekart M, Richard-Greenblatt M, Shom. s.l. : BMJ Open, 2021 Jan 25, Vol. 11(1):e045826.

**44.** *Prognostic Accuracy of Soluble Triggering Receptor Expressed on Myeloid Cells (sTREM-1)-based Algorithms in Febrile Adults Presenting to Tanzanian Outpatient Clinics.* Richard-Greenblatt M, Boillat-Blanco N, Zhong K, Mbarack Z, Samaka J, Mlaganile T, Kazimoto T, D'acremont V, Kain KC. s.l. : Clin Infect Dis. , 2020 Mar 17, Vols. 70(7):1304-1312.

**45.** *Evaluation of urine pneumococcal antigen test performance among adults in Western Kenya.* Hampton LM, Bigogo G, Jagero G, da Gloria Carvalho M, Pimenta F, Junghae M, Breiman RF, Whitney CG, Feikin DR, Conklin LM. s.l. : Diagn Microbiol Infect Dis, 2016 Aug, Vols. 85(4):405-8.

**46.** *Urinary antigen testing for pneumococcal pneumonia: is there evidence to make its use uncommon in clinical practice?* Hyams C, Williams OM, Williams P. s.l. : ERJ Open Res, 2020 Jan 10, Vols. 6(1):00223-2019.

**47.** *Diagnostic accuracy of rapid antigen tests in cerebrospinal fluid for pneumococcal meningitis: a systematic review and meta-analysis.* Someko H, Okazaki Y, Tsujimoto Y, Ishikane M, Kubo K, Kakehashi T. s.l. : Clin Microbiol Infect., 2023 Mar, Vols. 29(3):310-319.

**48.** *Microbial aspects and potential markers for differentiation between bacterial and viral meningitis among adult patients.* Alnomasy SF, Alotaibi BS, Mujamammi AH, Hassan EA, Ali ME. s.l. : PLoS One., 2021 Jun 11, Vol. 16(6):e0251518.

**49.** *Utility of the urine reagent strip leucocyte esterase assay for the diagnosis of meningitis in resource-limited settings: meta-analysis.* Bortcosh W, Siedner M, Carroll RW. s.l. : Trop Med Int Health., 2017 Sep, Vols. 22(9):1072-1080.

**50.** *Fujifilm SILVAMP TB LAM Assay on Cerebrospinal Fluid for the Detection of Tuberculous Meningitis in Adults With Human Immunodeficiency Virus.* Quinn CM, Kagimu E, Okirworth M, Bangdiwala AS, Mugumya G, Ramachandran PS, Wilson MR, Meya DB, Cresswell FV, Bahr NC, Boulware DR. s.l. : Clin Infect Dis, 2021 Nov 2, Vols. 73(9):e3428-e3434.

**51.** *Next generation rapid diagnostic tests for meningitis diagnosis.* Feagins AR, Ronveaux O, Taha MK, Caugant DA, Smith V, Fernandez K, Glennie L, Fox LM, Wang X. s.l. : J Infect, 2020 Nov, Vols. 81(5):712-718.

**52.** *Global burden of antimicrobial resistance: essential pieces of a global puzzle.* Mukwege D, Mitangala P, Byabene A, Busha E, Van Laethem Y, Vandenberg O. s.l. : Lancet, 2022 Jun 25, Vol. 399(10344):2348.

**53.** *C-reactive protein and procalcitonin to discriminate between tuberculosis, Pneumocystis jirovecii pneumonia, and bacterial pneumonia in HIV-infected inpatients meeting WHO criteria for seriously ill: a prospective cohort study.* Mendelson F, Griesel R, Tiffin N, Rangaka M, Boulle A, Mendelson M, Maartens G. s.l. : BMC Infect Dis., 2018 Aug 14, Vol. 18(1):399.

**54.** *Predictive value of C-reactive protein for tuberculosis, bloodstream infection or death among HIV-infected individuals with chronic, non-specific symptoms and negative sputum smear microscopy.* Bedell RA, van Lettow M, Meaney C, Corbett EL, Chan AK, Heyderman RS, Anderson ST, Åkesson A, Kumwenda M, Zachariah R, Harries AD, Ramsay AR. s.l. : Trop Med Int Health., 2018 Mar, Vols. 23(3):254-262.

**55.** *C-reactive protein independently predicts HIV-related outcomes among women and children in a resource-poor setting.* Drain PK, Kupka R, Msamanga GI, Urassa W, Mugusi F, Fawzi WW. s.l. : AIDS, 2007 Oct 1, Vols. 21(15):2067-75.

**56.** World Health Organization. *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease.* Geneva : World Health Organization, 2021.

**57.** *Point-of-care C-reactive protein and risk of early mortality among adults initiating antiretroviral therapy.* Chaisson LH, Semitala FC, Asege L, Mwebe S, Katende J, Nakaye M, Andama AO, Marquez C, Atuhumuza E, Kamya M, Cattamanchi A, Yoon C. s.l. : AIDS, 2019 Apr 1, Vols. 33(5):895-902.

**58.** *Surveillance strategies using routine microbiology for antimicrobial resistance in low- and middle-income countries.* Lim C, Ashley EA, Hamers RL, Turner P, Kesteman T, Akech S, Corso A, Mayxay M, Okeke IN, Limmathurotsakul D, van Doorn HR. s.l. : Clin Microbiol Infect., 2021 Oct, Vols. 27(10):1391-1399.

**59.** *Prioritising pathogens for the management of severe febrile patients to improve clinical care in low- and middle-income countries.* Osborn J, Roberts T, Guillen E, Bernal O, Roddy P, Ongarello S, Sprecher A, Page AL, Ribeiro I, Piriou E, Tamrat A, de la Tour R, Rao VB, Flevaud L, Jensen T, McIver L, Kelly C, Dittrich S. s.l. : BMC Infect Dis, 2020 Feb 10, Vol. 20(1):117.

**60.** *Maximizing access to achieve appropriate human antimicrobial use in low-income and middle-income countries.* Mendelson, M, et al. 10014, Jan 9, 2016, Lancet, Vol. 387.

**61.** *Antimicrobial resistance in Africa: a systematic reivew.* Tadesse, TB, et al. 1, Sept 11, 2017, BMC Infectious Disease, Vol. 17.

**62.** *Ad hoc consultation on rapid methods for antimicrobial susceptibility testing at point-of-care in lower-a nd middel-income countries.* World Health Organization. Geneva : s.n., 2014.

**63.** *Access to effective antimicrobials: a worldwide challenge.* Laxminarayan, R, et al. 10014, Jan 9, 2016, Lancet, Vol. 387.

# Acknowledgments

Jennifer Daily prepared this report, with input from Pamela Nawaggi and Carmen Perez Casas

of Unitaid. The research was completed in the last quarter of 2022 and the first quarter of 2023. Additionally, several reviewers provided valuable suggestions including: Ajay Rangaraj, WHO, Nathan Ford, WHO. Internally (Unitaid): Kelsey Barrett, Cherise Scott, Anisa Ghadrshenas.

# Abbreviations and acronyms

| | |
|---|---|
| **AHD** | Advanced HIV Disease |
| **AMR** | Antimicrobial resistance |
| **ART** | Antiretroviral therapy |
| **AST** | Cntimicrobial susceptibility testing |
| **CrAg** | cryptococcal antigen |
| **CRP** | C-reactive protein |
| **CSF** | Cerebrospinal fluid |
| **ED** | Emergency department / casualty |
| **EDL** | Essential Diagnostics List |
| **EML** | Essential medicines list |
| **Hib** | *Haemophilus influenzae* type B |
| **HIV** | Human immunodeficiency virus |
| **ID** | Identification (as in culture) |
| **IMCI** | Integrated management of childhood illness |
| **IVD** | In vitro diagnostic |
| **LF-LAM** | Lateral flow urine lipoarabinomannan assay |
| **LMIC** | Low- and middle-income countries |
| **LP** | Lumbar puncture |
| **LRTI** | Lower respiratory tract infection |
| **MoH** | Ministry of Health |
| **mWRD** | Molecular WHO-recommended rapid diagnostic test |
| **NAAT** | Nucleic acid amplification test |
| **OI** | Opportunistic infection |
| **OPD** | Outpatient department |
| **PCR** | Polymerase chain reaction |
| **PCT** | Procalcitonin |
| **PJP** | Pneumocystis pneumonia caused by *Pneumocystis jirovecii*, also abbreviated as PCP |
| **PLHIV** | People living with HIV |
| **PMTCT** | Prevention of mother-to-child transmission |
| **POC** | Point of care |
| **PCV** | Pneumococcal conjugate vaccine |
| **RDT** | Rapid diagnostic test |
| **SBI** | Severe bacterial infection |
| **TB** | Tuberculosis |
| **TB LF-LAM** | Tuberculosis lateral flow urine lipoarabinomannan assay |
| **VL** | Viral load |
| **WBC** | White blood cell |
| **WHO** | World Health Organization |

# Annex

## Interviewees

| | |
|---|---|
| **Ajay Rangaraj** | WHO, AHD |
| **Allan Mayi** | EGPAF, Project manager/clinician on AHD |
| **Ana Moore** | CHAI |
| **Angela Loyse** | CNS infections |
| **Anne von Gotberg** | NICD |
| **Barry Longwe** | EGPAF, Malawi programme, clinican, participated in WHO scoping |
| **Cassandra Kelly-Cirino** | FIND, Director of Disease |
| **Dan Shodell** | BMGF, AHD focal point |
| **David Moore** | Pedes/PERCH/South Africa |
| **Dr Anne-Marie** | Pedes ID in Kenya |
| **Dr Felistas Makokha** | Pedes, ID/HIV Kenya |
| **Dr James Wagude** | Adult, HIV specialist Kenya |
| **Emi Okamoto** | CHAI |
| **Fabiola Gordillo Gomez** | MSF, Microbiologist |
| **Fernando Pascual Martinez** | GARDP |
| **Francois Venter** | ezintsha |
| **Dr Freddy Mangana** | MSF |
| **Gina Gitau** | EGPAF Clinician Kenya |
| **Graeme Meintjes** | UCT |
| **Halima Dawood** | Head of Medicine at Greys' Hospital, Pietermaritzburg, KZN. She works with adults and HIV patients and is part of the working group for the Essential Drugs List. |
| **Helena Rabie** | Pedes research |
| **Ioana-Diana Olaru** | Heidi Hopkins colleague |
| **Irene Muku** | DnDi, former head Kenya HIV program |
| **Jane Cunningham** | MSF Access, Clinician/ID |
| **Jennifer Cohn** | GARDP |

| | |
|---|---|
| **John Crump** | Academic, ID |
| **Julia Tuttle** | CHAI |
| **Karen Heichman** | BMGF, Diagnostics focal point |
| **Laura Broyles** | Former US CDC; ID doc |
| **Lisa Frigati** | Pedes research |
| **Lydia Mpango** | EGPAF Clinician eSwatini |
| **Mark Mendleson** | UCT, ID Clinician, AMR |
| **Martina Penazzato** | WHO pedes |
| **Megan Knox** | CHAI supply person |
| **Mike Sharland** | Academic, Chair of the Antibiotic Working Group for the The World Health Organization's Essential Medicines List (WHO EML) |
| **Nada Malou** | MSF, microbiologist, AMR |
| **Nandita Sughandi** | Pedes research/ICAP |
| **Nathen Ford** | WHO, AHD |
| **Nicholas Feasey** | Academic (SBIs etiology AHD) |
| **Rob Heyderman** | Academic, UCL (SBIs etiology AHD) |
| **Rosie Burton** | MSF Clinican/ID |
| **Sabine Dittrich** | FIND/MapDx tech person |
| **Steve Aston** | Researcher pneumonia/ID clinician (UK, Malawi) |
| **Stijn Deborggraeve** | MSF Access, Lab focus |
| **Susan Meiring** | Medical officer, NICD South Africa |
| **Terri Roberts** | EGPAF |
| **Vanessa Quan** | Medical officer, NICD South Africa |
| **Zee Ndlovu** | MSF, Lab advisor |

# Annex

## High-level list of on-market RDTs for priority pathogens

**Table A1. *Streptococcus pneumoniae* RDTs**

| Primary syndrome | RDT name | Company | Sample |
|---|---|---|---|
| LRTI/Meningitis | BIOSYNEX S. PNEUMONIAE | Biosynex | Urine, CSF |
| LRTI/Meningitis | BinaxNOW™ S. pneumoniae Antigen Card | Abbott | Urine, CSF |
| LRTI | Standard Q S. pneumoniae Ag (urine) | SD Biosensor | Urine |
| LRTI | Standard F (FIA) | SD Biosensor | |
| LRTI/Meningitis | Sophia (FIA) | Quidel | Urine, CSF |
| LRTI/Meningitis | Unigold | Trinity Biotech | Urine, CFS |
| LRTI/Meningitis | Nadal Streptococcus Penumoniae Test | nal von miden | Urine, CFS |
| LRTI/Meningitis | Rapid Viditest | Vida | Urine, CFS |
| LRTI | ImmuView S. pneumonia + legionella | SSI Diagnostica | Urine |

## Table A2. Priority pathogen RDT search results

| Primary syndrome | Pathogen | RDT name |
|---|---|---|
| Sepsis/meningitis | *Escherichia coli* | *No tests found* |
| Meningitis/LRTI/sepsis | *Staphylococcus aureus* | *No tests found* |
| Sepsis | *Non-typhoidal Salmonella* | *No tests found* |

## Table A3. Lower priority pathogen RDTs

| Primary syndrome | Pathogen | RDT name | Company | Sample |
|---|---|---|---|---|
| Meningitis | *Neisseria meningitis* (groups A, C, Y, W and X) | MeningoSpeed | Biospedia | CSF |
| Meningitis | *Neisseria meningitis* (groups A, C, Y, W and X) | CERMES Duplix Dipstick | CERMES/ Institute Pasteur | CSF |
| Meningitis | *Neisseria meningitis* (group X) | NmX Dipstick | Pasteur | CSF |
| LRTI | *Legionella pneumophila* | BIOSYNEX LEGIONELLA PNEUMOPHILA BSS | Biosynex | Urine |
| LRTI | *Legionella pneumophila* | BinaxNow Legionella Urinary Antigen Card | Abbott | Urine |
| Pharyngitis | *Streptococcus* group A | STREPTATEST® | Biosynex | Throat swabs |
| Pharyngitis | *Streptococcus* group A | BIOSYNEX STREP A | Biosynex | Throat swabs |
| Pharyngitis | *Streptococcus* group A | *Various: Sofia, FIA Test Pack, Siosynex* | *various* | Throat swabs |

**Table A3. Lower priority pathogen RDTs (continued)**

| Primary syndrome | Pathogen | RDT name | Company | Sample |
|---|---|---|---|---|
| Enteric fever | *Salmonella Typhi* | Salmonella Typhi Antigen Rapid Test Cassette | Biozek | Stool |
| Enteric fever | *Salmonella Typhi* | S. Tyhpi Antigen Rapid Test | Healgen (Orient Gene) | Stool |
| Enteric fever | *Salmonella Typhi* | Strong Step Salmonella Antigen Rapid Test | Nanjing liming biological | |
| GI | *Shigella* | Nadal Shigella Dysenteriae | nal von miden | |
| GI | *Salmonella* Sps | Nadal Salmonella Test cassette | nal von miden | |
| GI | *Helicobacter pylori* | Rapid Hp StAR | Thermo Fisher | Stool |
| GI | *Helicobacter pylori* | RapiRun H. Pylori antibody detection kit | Otsuka Pharmaceutical | Stool |
| GI | *Campylobacter antigens* (C. jejuni and C. coli) | ImmunoCard Stat CAMPY | Meridian | Stool |
| GI | *Clostridium difficile (*TcdA and TcdB) | C Diff Quik Chek Complete | Abbott | Stool |

**Table A3. Lower priority pathogen RDTs (continued)**

| Primary syndrome | Pathogen | RDT name | Company | Sample |
|---|---|---|---|---|
| GI | *Clostridium difficile* (TcdA and TcdB) | Xpect Clostridium Difficile Toxin A/B test | Thermo Fisher | Stool |
| GI | *Clostridium difficile* (TcdA and TcdB) | ImmunoCard Toxins A&B | Meridian | Stool |
| Enteric fever | *Salmonella Typhi* | Nadal Salmonella Typhi Test cassette | nal von miden | |
| Enteric fever | *Salmonella Typhi* | Rapid salmonella typhi Antigen Test | Xiamen Boson Biotech | |
| STI | *Treponema pallidum* | Various: Determine, VisiTect, Syphicheck, First response. | Various | blood |

## Table A4. Host response biomarker RDTs

| Primary syndrome | Pathogen | RDT name | Company | Sample |
|---|---|---|---|---|
| Bacterial (vs viral) | CRP | Various | Many | Blood |
| Bacterial (vs viral) | PCT | Various | Many | Blood (often serum) |
| UTI | Bacteriuria and pyuria (somatic cells in urine) | Accutest Uriscreen | JANT | Urine |
| Bacterial (vs viral) | MxA & CRP | FebriDx | | Blood |
| Sepsis | Severity markers | Various, in development | | Blood |
| UTI | Bacterial cells (various) | RapidBac (? in development) | Silver Lake Research | Urine |
| Meningitis bacterial vs. viral | Glucose; protein; WBC etc | Various | Many | CSF |

## Table A5. Latex agglutination tests (lab required)

| Primary syndrome | Pathogen | RDT name | Company | Sample |
|---|---|---|---|---|
| Meningitis | Streptococcus group B, Haemophilus influenzae type B, Streptococcus pneumoniae, Neisseria meningitidis groups A, C, Y or W, or W, Neisseria meningitidis group B/ Escherichia coli K1. | Wellcogen Haemophilus influenzae b Rapid latex Aggluniation test | Thermo Fisher | CSF, serum, urine (blood cultures) |
| Meningitis | Streptococcus group B, Haemophilus influenzae type b, Streptococcus pneumoniae, Neisseria meningitidis groups A, C, Y or W, Escherichia coli K1. | Pastorex meningitis | BioRad | CSF, serum, urine (blood cultures) |
| Meningitis | Streptococcus group B, Haemophilus influenzae type b, Streptococcus pneumoniae, Neisseria meningitidis groups A, B, C, Y or W, Escherichia coli K1. | BD Directigen Meningitis Latex Test System | BD | CSF, serum, urine (blood cultures) |

**Unitaid Secretariat**

Unitaid — Global Health Campus
Chemin du Pommier 40, 5th floor
1218 Grand-Saconnex
Geneva, Switzerland

**unitaid.org**