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Highlights

- The diagnostic gap hides the true extent of AMR in Africa.
- Conventional laboratory diagnostics are unlikely to bridge this gap.
- Various point-of-care (POC) assays for AMR applications are in development.
- Implementation strategies for POC assays are needed to close the diagnostic gap.

Point-of-Care Diagnostics for Infection and Antimicrobial Resistance in Sub-Saharan Africa – A Narrative Review

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ABSTRACT

Introduction

Sub-Saharan African (SSA) countries are severely impacted by antimicrobial resistance (AMR). Due to gaps in access to diagnostics in SSA the true extent of AMR remains unknown. This diagnostic gap affects patient management and leads to significant antimicrobial overuse. This review explores how point-of-care (POC) testing for pathogen identification and AMR may be used to close the diagnostic gap in SSA countries.

Methods

A narrative review exploring current clinical practice and novel developments in the field of point-of-care (POC) testing for infectious diseases and AMR.

Findings

POC assays for identification of various pathogens have been successfully rolled out in SSA countries. While implementation studies have mostly highlighted impressive test performance of POC assays, there is limited data on effect of implementation on clinical outcomes and cost-effectiveness. We did not encounter local studies of host-directed POC assays relevant to AMR. Novel POC assays using real-time PCR, isothermal amplification, microfluidics and other technologies are in various stages of development.

Discussion

Available literature shows that POC testing for AMR applications is implementable in SSA and holds the potential to reduce the diagnostic gap. Implementation will require effective regulatory pathways, incorporation of POC testing in clinical and laboratory guidelines, and adequate value capture in existing health financing models.

INTRODUCTION

Communicable diseases are the foremost cause of morbidity and mortality in sub-Saharan Africa (SSA).[1] This trend is mainly driven by the pandemics of HIV, tuberculosis, malaria, and COVID-19, neglected tropical diseases, and pneumonia and diarrhoeal disease in children.[2–4] The rising incidence of antimicrobial resistant (AMR) bacterial infections threatens to compound this already significant burden. A recent survey estimated that in 2019, the four global regions most heavily affected by AMR were all in SSA.[5]

While estimates of the impact of AMR in SSA are alarming, they are likely to constitute a considerable underestimate. The limited access to laboratory diagnostics across SSA

constitutes a crucial “diagnostic gap”.[6] This gap is not only due to shortages of infrastructure and equipment but also due to limitations of human resources and expertise.[6] Aetiological diagnosis of infection and antimicrobial sensitivity pattern therefore remains relatively rare in SSA.[7]

Low- and middle-income countries (LMICs) on other continents share Africa’s limitations; more than half of the global population having little or no access to diagnostics.[8] This diagnostic gap is most keenly felt at the primary health care level, where less than 20% of LMIC populations have access to the simplest diagnostic tests.[8] High poverty levels and long travel distance to healthcare facilities limits the potential for patients to return for follow-up appointments to receive results and treatment, especially in rural areas, driving need for syndromic or empiric management of infection. Access to point-of-care (POC) or near-POC rapid diagnostic tests (RDTs) in LMICs, especially those incorporating detection of antimicrobial sensitivities could be a significant advance in health systems strengthening in SSA.

Health systems, infection burden, and access to diagnostics remain heterogeneous across SSA. In this review, we will explore the current use of POC diagnostics in infectious diseases in SSA and discuss their relevance to and impact on AMR. We subsequently discuss novel POC and near-POC tools related to AMR.

METHODS

A comprehensive literature search was conducted in the PubMed and Google Scholar online databases. Grey literature from the World Health Organisation and assay manufacturers was included on an *ad hoc* basis. Literature was searched by two researchers with a background in clinical infectious diseases and one researcher with a microbiological background. The search was performed using relevant keywords and Medical Subject Headings (MeSH) and was separated with Boolean operators [AND] and [OR].

CURRENTLY AVAILABLE POINT-OF-CARE TESTS

POC tests (POCT) may allow for screening and prognostication in infection management and bolster antimicrobial stewardship (AMS) in rural settings. POCT for specific pathogens such as malaria and tuberculosis are good rule-in tests to steward antimicrobials while POCT for biomarkers of bacterial infection have good negative predictive value (NPV) useful in withholding unnecessary antimicrobials. In this section, we will discuss POC diagnostics for endemic infections, evidence for their impact on prevention of antimicrobial overuse, and thereafter, on clinical utility of biomarkers for bacterial infection and the evidence of their impact on antimicrobial prescription practices. Much of the evidence originates from South Africa. The infectious diseases burden as well as the health infrastructure in this country are discussed separately (supplementary materials 1).

Malaria - Rapid diagnostic tests (RDTs)

Lateral flow POC RDTs for malarial antigens performed on whole blood at the bedside have become widely used in resource-limited settings targeting various malarial antigens, most commonly the histidine-rich protein 2 (HRP2), specific to *Plasmodium falciparum* (Kavanaugh et al., 2021a). While confirmatory microscopy after a positive RDT is recommended, RDTs themselves do not require laboratory infrastructure (Kavanaugh et al., 2021b). Accuracy of malaria RDTs exceed the prespecified target of 75% panel detection score set by the World Health Organization (WHO) (Cunningham et al., 2019).

Introduction of RDTs has significantly improved the speed and rate of malaria diagnosis while substantially reducing unnecessary prescription of antimalarials in high-burden countries (Odaga et al., 2014). However, overtreatment with antimalarials still occurs, mainly due to lack of local access to test kits, empiric treatment in the private sector, and widespread over-the-counter sale of antimalarials in the retail sector (Ochodo et al., 2016). Unfortunately, according to a systematic review of studies performed mostly in SSA, introduction of malaria RDTs has led to increased rates of empiric antibiotic treatment from 53% to 59% (Hopkins et al., 2017). This counterintuitive finding may be explained by increased rates of empiric antibiotic prescribing in patients with febrile illness and a negative malaria RDT result.

Tuberculosis – nucleic acid amplification tests (NAAT)

The nucleic-acid amplification test (NAAT) Xpert® MTB/RIF (Cepheid, Sunnyvale, CA) and related assays have improved *Mycobacterium tuberculosis* (MTB) detection rates over sputum microscopy for pulmonary tuberculosis (Penn-nicholson et al., 2021; Steingart et al., 2014). The rpoB gene targets encode targets both highly specific to MTB and those

containing predictable mutations involved in rifampicin-resistance, a key marker for multidrug resistance (Lawn & Nicol, 2011). Recently, a new generation NAAT, Xpert® MTB/RIF Ultra has demonstrated improved sensitivity at the expense of only marginally reduced specificity compared to Xpert® MTB/RIF (Zifodya et al., 2021). Application of NAATs to other sample types is currently being introduced (Chen et al., 2020; Lacourse et al., 2018).

Sputum-based NAAT testing is at the heart of current WHO diagnostic algorithms for pulmonary tuberculosis (World Health Organization, 2019a). A cluster-RCT showed its near-POC utility inside clinical ward environments, reducing time to diagnosis (Lessells et al., 2017; Pooran et al., n.d.). NAAT testing has not found an overall reduction of mortality in tuberculosis patients, but all-cause mortality has been reduced in HIV/TB co-infected patients after its introduction (Haraka F, Kakolwa M, Schumacher SG, Nathavitharana RR, Denkinger CM, Gagneux S, Reither K, 2021). Early identification of MTB in cases of pneumonia using NAAT testing has been shown to lead to early and appropriate initiation of TB treatment, with improved patient and public health outcomes (Centers for Disease Control and Prevention, 2000; Sorsa et al., 2020). However, we could not identify studies exploring the impact of NAAT on prescription of antibiotics in general.

Tuberculosis – Urine lipoarabinomannan (LAM)

Lipoarabinomannan (LAM) is a cell wall glycolipid of MTB and a key virulence factor involved in the interaction between the pathogen and macrophages (Lawn, 2012). Lateral flow tests for urine-LAM has high specificity for the detection of MTB, although false-positive results exist due to LAM's presence in the cell walls of non-tuberculous mycobacteria (Qvist et al., 2014) and Nocardia spp (Dheda et al., 2010). Newer generation urine-LAM assays have

improved sensitivity while retaining comparable specificity (Sossen et al., 2020). Urine-LAM detection is recommended by WHO for the detection of MTB in HIV-positive populations in advanced disease, as indicated by the CD4+ T-lymphocyte count (CD4 count), any severe illness, or signs and symptoms of tuberculosis (World Health Organization, 2019b).

The urine-LAM test is a true POCT with potential to improve clinical outcomes in hospitalised patients with advanced HIV. Use of urine-LAM was associated with reduced early mortality in one RCT and a trend towards improved survival in another (Gupta-Wright et al., 2018; Peter et al., 2016). In both RCTs, urine-LAM testing shortened time to diagnosis and substantially increased the prescription rate of TB treatment. The impact of urine-LAM testing on overall antibiotic prescribing is unclear. One cohort study of patients with smear-negative TB and advanced HIV infection found that 90.4% of patients with a positive urine-LAM still received antibiotics not directed at MTB, but did not include a comparator group (Mthiyane et al., 2019).

Cryptococcosis – Cryptococcal antigen (CrAg) testing

Lateral flow cryptococcal antigen (CrAg) tests target Cryptococcal serotype A and D (*C. neoformans*) and B and C (*C. gatti*) capsular polysaccharide antigens. CrAg tests can be performed on both serum/plasma and cerebrospinal fluid, and are highly sensitive and specific for the diagnosis of cryptococcal antigenemia and cryptococcal meningitis. They show significant improvement in detection rates over conventional laboratory-based microscopy and staining methods (Dominic et al., 2009). Current WHO guidelines recommend CrAg testing on serum/plasma in HIV-positive patients with CD4 count ≤100 cells/mm^3. In the South African public sector, the NHLS has introduced reflex CrAg testing in

response to a low CD4 count (World Health Organization, 2018). Point-of-care CrAg assays have been successfully implemented in a pilot study in South Africa (Wake et al., 2018).

Routine CrAg testing has clear clinical impact, as treatment of cryptococcal antigenemia with fluconazole guided by routine CrAg testing is associated with decreased mortality due to cryptococcal disease, but not all-cause mortality in patients with advanced HIV (Awotiwon et al., 2018; Faini et al., 2019; Meya et al., 2010, 2019; Parkes-ratanshi et al., 2011). We have found no data pertaining to the effect of CrAg testing on antibiotic prescribing, but expect that it may prove beneficial in leading to cessation of antibiotics in patients presenting with meningitis.

Other rapid tests

A range of other RDTs in current use may guide antibiotic therapy. *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 antigen testing are available in some resource-limited settings, but uptake of these rapid tests has been limited. For example, South African guidelines do not recommend the use of pneumococcal antigen testing in community acquired pneumonia (CAP), and recommend legionella antigen testing in severe cases only, to guide selection and duration of antibiotic treatment (Boyles et al., 2017). COVID-19 saw an unprecedented development and uptake of rapid testing of SARS-CoV-2 Ag RDTs with good diagnostic performance (Brümmer et al., 2021). Reliable RDTs for viral pneumonia could significantly impact antimicrobial stewardship, yet clinical experience during the COVID-19 pandemic highlights how, even when a diagnosis of viral pneumonia is made, significant overuse of antibiotics still occurs (Langford et al., 2021).

Dipstick urinalysis is an important stewardship tool in near universal use across South Africa, and is in many ways the archetypal RDT for stewardship, yet remains underutilized despite its ability to prevent unnecessary antibiotic use in African settings (Sundvall & Gunnarsson, 2009). In addition, dipstick urinalysis can be used to detect endemic infections such as schistosomiasis, an important differential diagnosis for urinary symptoms including haematuria, which is unresponsive to empiric antibiotic treatment for UTI, while being responsible for significant morbidity in South African and SSA. Dipstick urinalysis or simple microscopy methods are highly sensitive tools for the detection of Schistosoma haematobium ova in urine and may differentiate between bacterial UTI and schistosomiasis at POC (Meents & Boyles, 2010). In addition, the urine dipstick leucocyte esterase test has also been repurposed for use on CSF to rapidly detect the presence of CSF pleocytosis, enables rapid identification of cases of probable bacterial meningitis at the point of care. A meta-analysis has demonstrated a high degree of sensitivity and specificity for CSF dipstick leucocyte esterase testing when compared to traditional laboratory CSF analysis (Bortcosh et al., 2017).

The impact of rapid tests for endemic infections on antibiotic use

In summary, the implementation of RDTs for endemic infections has led to improved rates of targeted antimicrobial treatment. However, limited available data suggests that this does not necessarily translate to reductions in the rate of untargeted antibiotic prescription. In the case of malaria, rollout of malaria RDTs leads to increased antibiotic prescriptions with agents that are not expected to be active against pathogens that mimic malaria-like febrile

illness (Hopkins et al., 2017), which are mostly viral in origin (D'Acremont et al., 2014; Bonko et al., 2019).

For POCT implementations in patients with advanced HIV, the likelihood of simultaneous opportunistic infections complicates the assessment of effect on antibiotic prescribing. In these patients, guideline indications for antibiotic prophylaxis exist, and studies have shown that an enhanced prophylaxis package (anti-TB, antifungal medication, and a 5-day course of azithromycin) conveyed further mortality benefit (Hakim et al., 2017). In addition, empirical antibiotics may sometimes be used as a diagnostic tool in symptomatic patients without microbiological confirmation, despite questionable diagnostic accuracy (Divala et al., 2020).

As rapid tests for specific pathogens may increase rates of pathogen-directed treatment but increase or have little effect on the overall rates of empirical antibiotic prescribing, biomarkers for bacterial infection have been implemented at POC in an attempt to reduce antibiotic misuse.

C-reactive protein

C-reactive protein (CRP) is a hepatocyte-derived acute phase reactant produced in response to stimulation by interleukin-6, functioning as an opsonin and activator of complement through the classical pathway (Black et al., 2004). It is elevated during infection and/or tissue injury and rapidly normalizes when the pathophysiological process is interrupted (Ansar & Ghosh, 2013a). Increased CRP is a poor rule-in test for bacterial infection, as it is also raised in fungal and viral infections including SARS-CoV-2, malignancy, and other inflammatory processes (Ansar & Ghosh, 2013b). However, low CRP levels have good NPV

for bacterial infections. CRP-guided management safely reduced antibiotic initiation by 7% [95% CI: 4-10%] according to one meta-analysis of 5 RCTs of adult outpatients with respiratory tract infections (Petel et al., 2018). In 4 studies of neonates, serial CRP-guided early cessation of antibiotics lead to a reduction in treatment duration of 1.15 to 1.45 days without increased risk of mortality or relapse of infection (Petel et al., 2018). Other meta-analyses have raised caution about the use of CRP in neonatal populations with suspected sepsis based on insufficient sensitivity (Brown et al., 2019), but have confirmed the utility of CRP in adults with respiratory tract infections in reducing antibiotic prescriptions without adversely affecting patient outcomes (Aabenhus et al., 2014a). Unfortunately COVID-19 patients frequently have elevated CRP in the absence of bacterial infection (van Berkel et al., 2020).

There is a paucity of data on the clinical value of CRP in SSA. Particular concerns exist in patients with tuberculosis and advanced HIV. In a cohort of mostly HIV-positive individuals attending outpatient care at a South African clinic, CRP had a 96% NPV for the diagnosis of tuberculosis (Wilson et al., 2011). Similar promising results have been demonstrated in other settings in SSA (Olsson et al., 2019). However, in HIV-positive inpatients with symptoms of respiratory tract infection, CRP cannot discriminate between bacterial pneumonia, pulmonary tuberculosis, or Pneumocystis jirovecii pneumonia (Mendelson et al., 2018; Schleicher et al., 2005). Two recent systematic reviews have attempted to summarize the available evidence on CRP in LMICs but the heterogeneity and small selection of studies precluded a formal meta-analysis of diagnostic accuracy (Escadafal et al., 2020a; van Griensven et al., 2020a). The available data does support reduction in antibiotic prescribing using CRP-based criteria as possible and likely to be cost-effective in LMICs (Escadafal et al., 2020a).

Procalcitonin (PCT)

Procalcitonin (PCT) is produced by thyroid C cells and upregulated in bacteraemia via cytokine stimulation (IL-1, IL-6, TNF-α) (Meisner, 2002). PCT production is downregulated by IFN-γ, produced by most viral infections (Linscheid et al., 2003). PCT-guided antibiotic therapy in hospitalised adults with acute respiratory tract infection decreases mortality and length of antibiotic therapy in high-income countries (Schuetz P et al., 2017). In adult intensive care patients with suspected sepsis, PCT-guided cessation of antibiotics reduces the number of antibiotic days with non-inferior clinical outcomes (Bouadma et al., 2010; de Jong et al., 2016). In suspected neonatal and paediatric sepsis, PCT has moderate accuracy in the diagnosis of sepsis and may be used as part of composite clinical decision rules for the diagnosis of sepsis (Kuppermann et al., 2019; Pontrelli et al., 2017). PCT has limited sensitivity and specificity for the diagnosis of bacterial infections in outpatient settings (A. et al., 2007). Like CRP, elevated PCT may occur as part of severe COVID-19 without bacterial co-infection (Pink et al., 2021; van Berkel et al., 2020; Heer et al., 2021).

In SSA, PCT has shown diagnostic value in the diagnosis of bacterial infection in surgical inpatients (Chomba et al., 2020; Wineberg et al., 2020) and as a rule-out test for bacterial meningitis (Bottieau et al., 2019). In four studies of children with acute presumed infectious illness in SSA, PCT had an area under the curve of more than 0.80 for the diagnosis of bacterial infection (van Griensven et al., 2020b). Published data on use of PCT in neonatal settings in SSA demonstrate implementability but are limited and inconclusive.

Utility of CRP and PCT at the point-of-care

Data on cost-effectiveness of CRP and PCT in LMIC is scarce. At current prices, laboratory-based PCT-guided antibiotic treatment has been found to be cost-effective in high-income countries but is likely to be cost-prohibitive in LMICs (Geraerds et al., 2021; Kip et al., 2018; Westwood et al., 2015). We did not encounter cost-effectiveness analyses for PCT from LMIC. For CRP, this data is limited to two studies from Laos and Vietnam, in which CRP was assessed as highly cost-effective, with an incremental cost effectiveness ratio of US$ 94 per DALY averted (Escadafal et al., 2020b).

Several POCT for measurement of CRP and PCT, either qualitative, semi-quantitative, or quantitative, have been used in clinical or research settings (Aabenhus et al., 2014b; van Griensven et al., 2020b). Turn-around times are short (<30 minutes), and pricing ranges from US$ 0.5-17, significantly lower than quantitative chemistry assays for these biomarkers (van Griensven et al., 2020b). Validation and implementation studies for these tests in SSA are urgently needed. A recent pragmatic RCT on real-world implementation of POC CRP testing in Vietnam has shown encouraging results, but such trials have not been performed in SSA to date. (Ho et al., 2023)

NOVEL POINT-OF-CARE TESTING MODALITIES FOR AMR

Reliable culture-based diagnostics are insufficiently available in large parts of SSA (Fonjungo et al., 2017). There therefore exists a clear need for a POCT to identify bacterial infection and AMR (Van Hecke et al., 2019). Xpert® MTB/RIF was the first molecular test for AMR implemented in SSA (World Health Organization, 2013). The GeneXpert platform now

supports other molecular cartridge-based tests relevant to AMR, including MRSA, *C. difficile*, and carbapenemase genes and could be leveraged to develop laboratory capacity for AMR detection and surveillance. The cost of these and similar assays, and specificity limited to a small number of resistance markers, makes them more suited for in-hospital screening and less for implementation in LMICs (Shanmugakani et al., 2020). The withdrawal of the portable battery-operated GeneXpert® Omni, specifically designed for remote and resource-limited settings, signals a move away from POC implementation of GeneXpert® assays (Branigan & Time for $5 Coalition, 2021). The WHO target product profile specifications for AMR diagnostics acknowledges the need for an affordable platform suitable for use in laboratories in level 1 or 2 health-care facilities, although they fall short of specifying use directly at POC or a requirement for instrument-free designs (World Health Organization, 2020).

A few other commercial platforms for molecular identification of AMR from clinical specimens exist, but few are suitable for use in SSA (Shanmugakani et al., 2020). The implementation cost, especially in rural settings where sample volumes are lower, remains high (Hsiang et al., 2016). The Truenat® platform, a chip-based real-time PCR system, may be more affordable, marketing a substantial test menu of viral and bacterial targets, but lacks GeneXpert's broad network of expertise and instrument placement (Lee et al., 2019; Molbio Diagnostics, n.d.). The PROMPT® (portable, rapid, on-cartridge magnetofluidic purification, and testing) assay can detect *N. gonorrhoeae* and the ciprofloxacin resistance mutation in *gyrA* in clinical samples within minutes, and is designed for quick (<15 min) versatile POC implementation using a small-footprint instrument with minimal power requirements (Trick et al., 2021; Stone, 2021). In determining the major marker of

ciprofloxacin resistance which does vary by region (Młynarczyk-Bonikowska et al., 2020), the test could prevent empirical use of broader spectrum cephalosporins. The need to link specific mutations or genes to a predicted phenotype remains the major limitation of molecular assays.

Contrasting real-time PCR-based platforms, isothermal amplification techniques may hold additional promise in LMIC, as they do not require complex thermal cyclers and the endpoint can be visualised with the naked eye. Isothermal PCR has been incorporated into microfluidic devices with rapid detection of AMR targets (Kaprou et al., 2021). However, multiplexing of isothermal reactions is complex, and they are prone to contamination. They also require well isolated nucleic acid as a starting point (Shanmugakani et al., 2020).

Phenotypic antimicrobial sensitivity usually requires a centralised laboratory (World Health Organization, 2019b). Novel microfluidics enable phenotypic assessment of sensitivity by automated observation of a single cell's division rate in the presence of antibiotics. This drastically reduces the platform size and enables rapid detection. For example, Accelerate Pheno® and Gradientech® benchtop systems enable rapid pathogen identification and susceptibility testing. While theoretically implementable at near-POC these assays still require pathogen isolation from initial blood culture (Bhalodi et al., 2021; Wistrand-Yuen et al., 2020). Microfluid technologies can be performed from a primary sample, but are usually pathogen- or sample type-specific. The fASTest® assay could enable detection and susceptibility testing for E. coli in urine within 30 minutes at the POC (Baltekin et al., 2017). Similarly, the benchtop Astrego® system bypasses the need for a culture step and may provide susceptibility results for several pathogens directly from urine within 2-3 hours (Toosky et al., 2020).

Development of true POCT for the detection of AMR or to support AMS is still in an early stage (Shanmugakani et al., 2020; Smith & Kirby, 2019; Vasala et al., 2020). As a stimulus for research and development, the Longitude Prize funds the development of accurate, rapid and affordable POCT to address AMR. There are currently 53 contenders for the prize, with products in various stages of development. These assays, as well as their key characteristics, are displayed in Table 1.

Novel host-directed POCT have recently been brought to market. The instrument-free Woundchek® detects the bacterial enzyme protease, a marker of infection in wounds, and could prevent antibiotic prescription for non-infected wounds (Woundcheck, n.d.). FebriDx® is a self-contained blood collection device and lateral flow assay for the detection of CRP and Myxovirus resistance protein A, a marker of viral infection, which has a high NPV for bacterial infection (99% [95%CI 93-100%]) (Shapiro et al., 2018). Several other tests are in various stages of development (Table 1).

DISCUSSION AND SOLUTIONS

From development to use - Considerations regarding uptake

Licensing requirements: Novel diagnostics often do not attract widespread use, for complex reasons. Regulatory frameworks for licensing requires demonstration of assay validity and diagnostic accuracy, but not clinical studies required for licensing of therapeutics.[9] Consequently, the clinical diagnostic relevance and cost-effectiveness of a diagnostic assay may remain unclear even after its introduction.[9] This problem could be addressed by strengthening of licensing regulations for diagnostic testing. The International Medical Device Regulators Forum provides guidance that could help countries establish and strengthen regulatory oversight for licencing purposes.[10,11] The South African Health Products Registration Authority (SAHPRA) requires provision of supporting clinical data in licencing applications, while recognising the challenges associated with collecting such data.[12]

Development lag: Development of novel AMR diagnostics tends to lag behind drug development. For example, development of point mutation assays for drug resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) for HIV treatment only underwent clinical evaluation when NNRTI-based regimens were being phased out.[13] Similarly, the Xpert MTB/XDR cartridge contains targets for resistance to aminoglycoside injectables, which has since lost relevance having been replaced by newer oral drugs.[14] A common design feature of novel POCT for drug susceptibility is the specific targeting of one or several compounds. Novel diagnostic technology in AMR should focus on enabling assay adaptivity both to accommodate advances in drug development as well as pathogen evolution.

Further lag may be introduced downstream in the development pipeline, particularly at the point of implementation research. Implementation studies provide valuable insight into potential facilitators and barriers to uptake, and serve to introduce techniques to end-users. The example of CRP POCT is illustrative in this regard. Our search did not yield any research on such testing in SSA countries, which stands in stark contrast with its relatively common use in primary care in European countries. Research of the available literature on implementation research confirms that sub-Saharan African data on POCT implementation is sorely lacking.[7,15]

Cost-effectiveness: The health economic evidence on POCT generally favours the introduction to replace traditional laboratory based tests.[16] Pragmatic RCTs in which the impact of POCT on waiting time reductions and costs are scarce in SSA, but when performed, they provide a crucial evidence base for the introduction of POCT in discrete care pathways.[17] Trial research has guided widespread implementation of urine-LAM and CrAg testing in the diagnostic work-up of advanced HIV in several countries in SSA. Despite this evidence, the lack of mechanisms for reimbursement for POCT is a major impediment to its clinical uptake.[18] In an ideal scenario, POCT are offered as part of an integrated healthcare service, their use guided by guidelines and local protocols as part of a comprehensive care package. In reality however, patient pay mostly out of pocket for healthcare services in SSA. As the direct costs of POCT may be high, and the downstream benefits in terms of cost not always apparent to the individual patient, patients may be reluctant to pay for such testing.[19]

In order to increase uptake, financing models must adequately capture the value of POCT, ideally without charging end users. Models of integration of AMR-related POCT into discrete

care pathways (such as febrile illness) should be applied to evaluate the real-world clinical impact and cost-effectiveness of diagnostic tools for AMR. Such studies should take into account that the impact of POCT on cost may be expected to increase over time. POCTs to guide antibiotic treatment may be more expensive than standard of care if cost of the POCT is high and that of the antibiotics is low,[20] highlighting one of the challenges to POCT adoption especially in settings where patients have to pay out of pocket for diagnostic tests. However, rising AMR has resulted in the need for novel antibiotic compounds which have become substantially more expensive, making POCT development more cost appealing.[21]

From use to impact - How rapid tests (fail to) change management

Our review of existing POCTs illustrates how the introduction of a diagnostic test does not necessarily translate into impact on clinical outcomes. When a POCT does lead to a change in prescribing practice, this change may not always be anticipated or desired, exemplified by increasing antibiotic prescribing following introduction of malaria RDTs. This illustrates that careful consideration of potential unexpected effects of introduction of POCT on patient management need to be considered during the implementation process.

Coupling antimicrobial stewardship to diagnostic stewardship: To solidify the link between POCT introduction and treatment selection in AMR, antimicrobial and diagnostic stewardship should be firmly coupled. It has been suggested that this requires antibiotic prescribing based on the results of an RDT wherever possible.[22] In SSA, the rational antibiotic prescription based on RDT results is commonplace in tuberculosis and cryptococcal meningitis. Sputum NAAT for tuberculosis, urine-LAM, and cryptococcal antigen screening form a comprehensive package of care for individuals with advanced HIV

disease in WHO HIV treatment guidelines.[23] Such pathways could be adopted for other indications, as has been proposed for febrile illness in malaria-endemic areas.[24]

Combining POCTs: The combination of two or more POCT in decision algorithms supported by guidelines could represent another important method to insure rapid testing meaningfully impacts on clinical management and patient outcomes. Combining POCTs for endemic diseases with biomarker tests may avoid inappropriate antibiotic prescribing. An example would be combining a malaria POC RDT, with POC CRP or PCT. In this scenario, the malaria RDT would be performed first, and treatment initiated if positive. The result of the biomarker could then be used to decide on either inpatient or outpatient treatment.[24] In case of a negative malaria RDT, a CRP or PCT POCT could then be used to guide the initiation, and duration, of antibiotic therapy.[25]

Laboratory infrastructure optimisation and reflex testing: Given the current limited repertoire of diagnostics suitable for POCT in SSA countries, attention should be directed to the optimisation of existing laboratory-based diagnostic pathways. The introduction of centralised and decentralised referral strategies in several resource-limited settings has resulted in improved access to diagnostic modalities and reduction of turn-around times.[26] Separation of sample processing and incubation, which is performed at the peripheral laboratory, from identification and susceptibility testing of positive samples, which is performed centrally, may also improve laboratory efficiency.[27] However, strengthening and optimisation of laboratory systems for clinical detection and surveillance of AMR lacks emphasis in many National Action Plans in SSA.[28]

Clinical decision algorithms: The use of CRP and malaria RDTs as input to electronic clinical decision algorithms (eCDA) is a budding area of research. Many eCDA are based on

guidelines such as the WHO integrated management of childhood illness and are often developed iteratively, enabling continuous finetuning and adaptation of algorithms to local circumstances.[29] Algorithms have been applied to various clinical scenarios, with some showing efficacy on clinical endpoints.[30] Two algorithms for application in febrile illness in children decrease antibiotic prescription rates, while improving patient outcomes.[29]

Author contributions

MM and LEH conceptualised the review. CMC created the overview of novel AMR-related diagnostics in the table. CMM and OL discussed health economic considerations related to POC testing. CMC and FC provided discussion on novel AMR-diagnostics. OM and CB provided input on implementation of POC testing in the regional context. LEH and MM drafted the manuscript. All authors provided feedback on the manuscript and approved the final manuscript version.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Approval Statement

This narrative review does not require ethical approval in accordance with international and South African standards for Good Clinical Practice.

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Table 1 Stimulus responsive materials that change shape on binding with pathogens

Organisation	Test name	Target	Infection syndrome	Sample type	Technology	Testing modality	Platform	Point-of-care	Time to result	Potential role in AMS/AMR	Website
Biomarker tests											
AgPlus	Not specified	Host response/biomarker (not specified)	Multiple	Fingerprick blood	Electrochemical senors	Cartridge-based	Portable reader	Yes	Not specified	Differentiate bacterial from viral infection. Reduce antibiobiotic prescription	https://www.agplusdiagnostics.com (website removed as at 27 May 2022)
Attomarker	Not specified	Host response/biomarker (CRP, others)	Multiple	Blood	Gold nanoparticle-antibody/antigen array	Single-use chip read by a smartphone camera	Single-use chip read by a smartphone camera	Yes	5 min	Differentiate bacterial from viral infection. Reduce antibiobiotic prescription	https://www.attomarker.com/ (accessed 9 January 2023)
Commonwealth Testing Limited (CT-Dx)	Not specified	Biomarker (not specified)	Multiple	Not specified	No information provided	Self-contained device	Instrument-free	Not specified	5 min	Differentiate bacterial from viral infection. Reduce anti	http://www.ct-dx.com/ (website removed as at 9 January 2023)

										biobiotic prescription	
Engineering for All	ReVDx	Host reponse / biomarker (white cell count / full blood culture)	Sepsis	Finger prick blood	Information not provided	Multi-channel technology	Portable device	Yes	Not specified	Differentiate bacterial from viral infection. Reduce antibiobiotic prescription	https://revdxmedical.com/ (accessed 9 January 2023)
Global Access Diagnostics	Not specified	Host response / biomarker (neutrophil protease)	UTI	Not specified	Immunoassay	Lateral flow assay	Information not provided	Not specified	Not specified	Not enough information provided	https://www.globalaccessdx.com/ (accessed 9 January 2023)
Burnet Institute	Going against the flow	Host response / biomarker (CD64)	BSI, sepsis	Not specified	Information not provided	Lateral flow assay	Information not provided	Not specified	Not specified	Not enough information	https://burnet.edu.au/ (accessed 9 January 2023)
Inflammatix, Inc	HostDx Fever	Host response / biomarker (not specified)	Multiple	Not specified	Isothermal amplification	Information not provided	Information not provided	Not specified	Not specified	Differentiate bacterial from viral infection. Reduce antibiobiotic prescripti	https://inflammatix.com/ (accessed 9 January 2023)

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Lumos Diagnostics	FebriDx	Host reponse / biomarker (MxA and CRP)	RTI	Finger prick blood	Not specified	Self-contained blood collection device and lateral flow assay	Instrument-free	Yes	10 min	Diffrentiate between viral and bacterial infection with specific viral infection marker (MxA)	https://www.febridx.com/
PEAS Institute	Not specified	Host response / biomarker (not specified)	Multiple	Not specified	Colorimetric detection of host response biomarkers	Information not provided	Information not provided	Not specified	1 minute	Not enough information	https://www.peasinstitut.se/ (website not in operation as at 9 January 2023)
Rizab Health Inc.	CytoTracker	Host reponse / biomarker (white cell count and differential)	Sepsis	Finger prick blood	Microfluidic cytometry	Portable pocket-sized reader		Yes	Not specified	Differentiate bacterial from viral infection. Reduce antibiobiotic prescription	https://www.rizlabhealth.com/ (accessed 9 January 2023)
SpotSense	Not specified	Host response / biom	Neonatal se	Saliva	Information not provided	Lateral flow assay	Instrument-fre	Yes	Not specifi	Monitor disease cour	https://spotsense.in/ (website removed as at 9 January 2023)

		arker (CRP, PCT, IL-8)	psis				e		ed	se/response to therapy	
Pathogen detection with or without AST											
3i Diagnostics	Biospectrix	Pathogen detection	Multiple	Multiple	Differential mechanical cell lysis to separate bacterial cells from host cells followed by infrared spectral profiling	Cartridge-based	Information not provided	Not specified	<30 min	Early targeted antibiotics	https://www.3idx.com/ (accessed 9 January 2023)
AMR @ University of Bredford	Not specified	Pathogen detection	Multiple	Not specified	Stimulus responsive materials that change shape on binding with pathogens	Information not provided	Information not provided	Yes	<30 min	Not enough information provided	https://www.polymerbiomaterials.com (website not in operation as at 23 May 2022)
Astrego Diagnostics (Sysmex)	Captiver UTI-panel, others in develo	Pathogen detection, AST	UTI, BSI	Not specified	Trapping and monitoring of single bacterial cells in	Microfluidics chip	Desktop instrument	Near-care	<1 hour for ID, 2-6 hours for	Targeted antibiotics	https://astrego.se/ (accessed 9 January 2023)

	pment				real-time using imaging				AST		
BiosparQ	BiosparQ	Pathogen detection	UTI	Not specified	Single cell MALDI-TOF (DigiTOF)	Unclear	Standalone instrument	Near-care	<30 min	Pathogen-directed antibiotics, detection of mixed growth (differentiation between infection and contamination)	https://npkdesign.com/project/biosparq/ (accessed 9 January 2023)
Coris BioConcept	Not specified	Pathogen detection, detection of carbapenemases	Multiple	Not specified	Immunoassays and others	Microfluidics chip and lateral flow assays	Information not provided	Microfluidics: not specified; lateral flow assays: no	Not specified	Targeted antibiotics according to resistance mechanism	https://www.corisbio.com/ (accessed 9 January 2023)
Commonwealth Scientific and Industrial Research	Not specified	Pathogen detection, AST, host response/	UTI, BSI	Not specified	Detection of volatile and non-volatile orga	Information not provided	Sensor platform	Yes	Not specified	Not enough information provided	https://www.csiro.au/ (accessed 9 January 2023)

Organisation (CSIRO) & Macquarie University		biomarker			nic compounds						
eProfiler Solutions Pvt. Ltd.		Pathogen detection	Not specified	Not specified	Electronic molecule fingerprinting	Lab-on-a-chip	Portable device	Not specified	5 min	Not enough information provided	https://hold.eprofilersolutions.com/ (website removed as at 9 Jaunary 2023)
Encompass Consortium	PART-ICLE	Pathogen detection, AST	BSI	Not specified	Flow-cytometry-assisted antimicrobial susceptibility testin (FAST)	Information not provided	Information not provided	Yes	Not specified	Not enough information provided	Not found
Foundation for Neglected Disease Research	Not specified	Pathogen detection, host response	Multiple	Fingerprick blood	Protein electrophoresis of host and pathogen proteins, and pH-based separation of viral and bacterial proteins	Strip	Information not provided	Yes	Not specified	Differential viral from bacterial infection	https://www.fndr.in/programs.html (website removed as at 9 January 2023)

FluoretiQ	NANOPLEX, SCFI	Pathogen detection, AST	UTI	Not specified	Molecular probes	Not specified	Not specified	Yes	15 min	Not enough information provided	https://www.fluoretiq.com/ (accessed 9 January 2023)
Fraunhofer	Not specified	Pathogen detection, AST	UTI	Urine	Photonics	Disposable chip	Information not provided	Yes	Not specified	Not enough information provided	https://www.fraunhofer.co.uk/ (accessed 9 January 2023)
ID Genomics	Not specified	Pathogen detection, AST	UTI, BSI	Not specified	Genetic barcodes	Information not provided	Information not provided	Not specified	Not specified	Not enough information provided	http://www.idgenomics.com/ (website removed as at 26 May 2022)
Light AI	Strepic	Pathogen detection (Streptococcus)	Pharyngitis	Not specified	Information not provided	Information not provided	Information not provided	Yes	<1 min	Prevent antibiotic prescription for non-streptococcal pharyngitis	http://yesbiotechnology.com/ (website removed as at 26 May 2022)
Llusern Schientific	UTI Test	Pathogen detection, resistance detection	UTI	Urine	Nucleic acid detection (loop-mediated amplication)	Assay tube	Lodestar DX reader	Yes	<20 min	Targeted antibiotics	https://llusern.co.uk/ (accessed 9 January 2023)
Not specified	MAD NAAT	Pathogen detection	Multiple	Not specified	Isothermal strand displacement	Self-contained automated	Instrument-free	Yes	<10 min	Not enough information prov	Not provided

					amplification with lateral flow detection	disposable device				ided	
Module Innovations	Usense	Pathogen detection (four species)	UTI	Urine	Colorimetric detection	Credit card-sized cartridge	Instrument-free	Yes	30-60 min	Not enough information provided	http://moduleinnovations.com/ (accessed 9 January 2023)
Nano Dx	Septiflo	Pathogen detection and gram profiling	BSI	Plasma	Information not provided	Colour indicator and semi-quantitation with colour score chart	Information not provided	Yes	<10 min	Targeted antibiotics (gram negative vs. gram positive cover)	https://nanodiagnostics.com/ (website removed as at 9 January 2023)
Nostics B.V.	Not specified	Infection and pathogen detection	UTI, STI	Urine	Raman spectroscopy, nanosurfaces, artificial intelligence	Information not provided	Portable device	Yes	15 min	Pathogen-targeted antibiotics	https://nostics.com/ (accessed 9 January 2023)
ODx Innovations Ltd.	Not specified	UTI pathogens detection, AST	UTI	Not specified	Information not provided	Information not provided	Information not provided	Yes	30 min	Not enough information provided	http://www.odxinnovations.com/ (website removed as at 27 May 2022)
OhMedics	Not specified	Pathogen detection, AST	Multiple	Not specified	Bioelectronics	Wearable technology	Not specified	Yes	Minutes	Not enough information prov	https://www.ohmedics.co.uk/ (accessed 9 January 2023)

										ided	
OmiX Labs	Not specified	Pathogen detection, AST	UTI, BSI	Not specified	Rapid molecular amplification	Information not provided	Information not provided	Not specified	Not specified	Not enough information provided	http://omixdx.com/ (website removed as at 27 May 2022)
PhAST	Not specified	Pathogen detection, AST	UTI	Not specified	Single cell imaging	Information not provided	Information not provided	Not specified	<30 min	Not enough information provided	http://www.phastdiagnostics.com/ (website not found as at 26 May 2022)
pOgO Intelligent Solutions	Not specified	Pathogen detection, AST	Multiple	Not specified	Electrophotography	Information not provided	Information not provided	Not specified	Not specified	Not enough information provided	Not provided
Precise Research	Not specified	Pathogen detection (N. gonorrhoea and Mycoplasma), resistance detection	STI	Not specified	Information not provided	Information not provided	Information not provided	Not specified	30 min	Targeted antibiotics	http://preciseresearch.co.uk/ (website removed as at 27 May 2022)
ZonMw	RAPDIF	Pathogen detection	BSI	Not specified	PCR	Information not provided	Information not provided	Laboratory	Not specified	Reduce empirical antibiotic prescription in children pres	https://www.zonmw.nl/en/research-and-results/infectious-diseases-and-antimicrobial-resistance/award-for-rapdif/ (accessed 9 January 2023)

										enting with fever in malaria endemic areas	
RADIR	Syringe Integrated Total Analysis System (SiTAS)	Pathogen detection, AST, host response/ biomarker	Multiple	Not specified	Biosensor	Information not provided	Information not provided	Yes	Minutes to hours	Not enough information provided	Not provided
University of Bath, Bristol Royal University Hospital for Children and Queen Victoria Hospital	SmartWound PREDICT, SmartWound RESOLVE	Pathogen detection	Wound infection	Wound fluid	Fluorescent dye detection of bacterial and fungal toxins	PREDICT: Dressing applied to wound, RESOLVE:wound swab	Portable fluorometer	Yes	Not specified	Discriminate colonisation from infection, targeted antimicrobials	https://www.smartwound.co.uk/ (accessed 9 January 2023)
Spectral Platforms	Inspector-01	Pathogen detection (30 species)	BSI	Blood	Information not provided	Information not provided	Tabletop instrument	Not specified	<20 min	Targeted antibiotics	https://spectralplatforms.com/ (accessed 9 January 2023)
Test & Treat	U-treat	Pathogen detection, AST	UTI	Urine	ATP bioluminescence	Sample tube with added antib	Desktop reader	Near-care	Pathogen detecti	Detect bacterial infection. Dire	https://www.tandtreat.com/u-treat/ (website removed as at 9 January 2023)

						iotics discs			on: 30 min AST: further 90 min	cted anti biotics	
University of Bristol and Vitamica Ltd.	Not specified	Pathogen detection, AST	UTI	Urine	Detects nanoscale fluctuations in bacteria from urine samples treated with antibiotics	Information not provided	Information not provided	Information not provided	Not specified	Targeted antibiotics	https://www.vitamica.co.uk/ (Website not in operation as at 23 May 2022)
University of Plymouth		Pathogen detection, AST	Multiple	Not specified	Microwave-assisted nucleic acid release and detection	Information not provided	Tabletop instrument	Yes	5 min	Not enough information provided	https://www.plymouth.ac.uk/research/microbial-diagnostics-and-infection-control-research-group (accessed 9 January 2023)
Valetude Primus	Not specified	Pathogen detection and gram profiling	Multiple	Blood	Spot immunomagnetic enrichment	Information not provided	Information not provided	Yes	Not specified	Targeted antibiotics (gram negative vs. gram positive cove	http://www.valetudeprimus.com/ (website removed as at 26 May 2022)

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Woundchek Laboratories	Woundchek Bacterial Status	Pathogen detection	Chronic wound infection	Wound fluid	Detection of bacterial protease as a marker of virulence	Card-based immunoassay	Instrument-free	Yes	10-20 min	Prevent overtreatment of chronic wounds with antibiotics	https://www.woundchek.com/bacterial-status.html (accessed 9 January 2023)
Antimicrobial susceptibility testing and resistance detection											
Adiuvo Diagnostics	Not specified	AST	Infection with *P. aeruginosa*	Multiple	Measurement of autofluorescence	Microfluidics chip	Information not provided	Yes	<4-6 hours	Early targeted antibiotcs	https://www.adiuvodiagnostics.com/ (accessed 9 January 2023)
BioAmp Diagnostics	Not specified	Resistance detection	UTI	Urine	Colorimetric biochemical test with signal amplification	Information not provided	Information not provided	Yes	Not specified	Broaden spectrum of antibiotics according to resistance mechanism	https://bioampdx.com/ (accessed 9 January 2023)
Gradientech	QuickMIC	AST	BSI	Positive blood culture	MIC determination by live cell imaging across a microfluidi	Cassette prefilled with 12 antibiotics. Separate gram nega	Standalone instrument	Laboratory	2-4 hours	Targeted early antibiotics, MIC-guided antibtioti	https://gradientech.se/ (accessed 9 Januart 2023)

					c antibiotic concentration gradient	tive and gram positive case ttes				c selection	
University of Strathclyde	Microplate	AST	Multiple	Not specified	Electrochemical senors	Low-cost, commercial screen-printed electrode	Information not provided	Not specified	<45 min	Targeted antibiotics	https://www.strath.ac.uk/workwithus/innovationindustryengagement/casestudies/microplate/ (accessed 9 January 2023)
Molsid	PYTHIA	Resistance detection	Multiple	Multiple (clinical samples)	Fluorescent detection of bacterial resistance enzymes		Dedicated fluorescence reader	Yes	30-60 min	Targeted antibiotics	https://molsid.com/rapid-diagnostics-of-antimicrobial-resistance/ (accessed 9 January 2023)
Prismatix	Not specified	AST	UTI	Not specified	Photonic crystal biosensors	Information not provided	Information not provided	Not specified	Not specified	Not enough information provided	Not provided
Welnovate Biosolutions	Not specified	AST	Multiple	Not specified	Detects changes in bacterial metabolic activity on exposure to antibiotics	Information not provided	Information not provided	Not specified	<1 hour	Not enough information provided	http://www.weinnovatebiosolutions.com/ (website removed as at 26 May 2022)
Wheeler Microf	Not specifi	AST	Multiple	Not sp	Digital micro	Not specified	Not specifi	Yes	Not sp	Not enough	https://microfluidics.utoronto.ca/ (accessed 9 January 2023)

luidics Laboratory	ed			ecified	fluidics		ed		ecified	information provided	
Other											
IMSPEX Diagnostics Ltd.	BreathSpec	Infection	RTI	Breath	Analysis of volatile organic compounds	Breath analyser	Standalone gas flow unit	Yes	Not specified	Differentiate bacterial from viral infection. Reduce antibiotic prescription	https://breathspec.com/ (accessed 9 January 2023)
Not specified	Not specified	No test information provided	Multiple	Not specified	Capture of volatile organic compounds emitted by bacteria	Information not provided	Information not provided	Not specified	10 min	Not enough information provided	Not provided
Quick Count UK	Quick Count	Ratio of red: white cell count	RTI, sepsis	Finger prick blood, fluid	Cell separation and microscopy	Information not provided	Cartridge read by a smartphone microscope	Yes	<5 min	Differentiate bacterial from viral infection. Reduce antibiotic prescription	http://www.quickcount.co.uk/ (website removed as at 9 January 2023)
Sonavi Labs	Felix	Disease pathology	RTI	N/A	Artificial intelligence analy	Digital smart stethosco	N/A	Yes	N/A	Accurate diagnosis of	https://sonavilabs.com/ (accessed 9 January 2023)

					sis of breath sounds	pe with smartphone interface				lower respiratory tract infection and appropriate therapy	