Diagnostics: An essential tool to combat the ongoing pandemic of antimicrobial resistance

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Diagnostics can play a key role in ensuring that existing and future antimicrobials are used rationally and appropriately to prevent the development and spread of antimicrobial resistance (AMR). This can only be achieved through the development and use of affordable diagnostics, especially for low- and middle-income countries. This article looks at the role of diagnostics in preventing AMR, the priorities for developing new diagnostic tools for rational antimicrobial use and for surveillance, and how this impacts on cancer treatment.

The World Health Organization (WHO) has declared antimicrobial resistance (AMR) to be one of the top 10 global health threats facing humanity *(1)*. By any rational scale, we are in the midst of an AMR pandemic; according to recent estimates, 4.95 million deaths were associated with bacterial AMR globally in 2019, 1.27 million of which were directly attributable to resistance *(2)*. The incidence of AMR is projected to increase over time, with annual cases of multidrug-resistant (MDR) bloodstream infections and pneumonia predicted to rise from 5.4 million in 2020 to 8.3 million by 2040 *(3)*. There is an urgent need to ensure that existing and future antimicrobials are used rationally and appropriately to prevent the further development and spread of AMR *(4)*. This can only be achieved through the development and use of affordable diagnostics.

In addition to guiding treatment decisions, diagnostics are also central to AMR surveillance. Accurate tracking of the spread of AMR locally and nationally is important to guide decision-making at every level of a health system from primary care management to national public health measures.

However, the availability of diagnostic tests needed for antimicrobial stewardship (AMS) and AMR surveillance is limited *(5)*. This is especially true for tests suitable for use in low- and middle-income countries (LMICs), where the burden of AMR is highest *(2)*. With drug-resistant infections on the rise, and the list of available treatments decreasing, there is an urgent need for investment in diagnostics to prevent the further development of AMR and to protect new antimicrobials in development. Gaps and priorities for AMR diagnostic development are summarized below and in Figure 1.

Role of diagnostics in preventing AMR

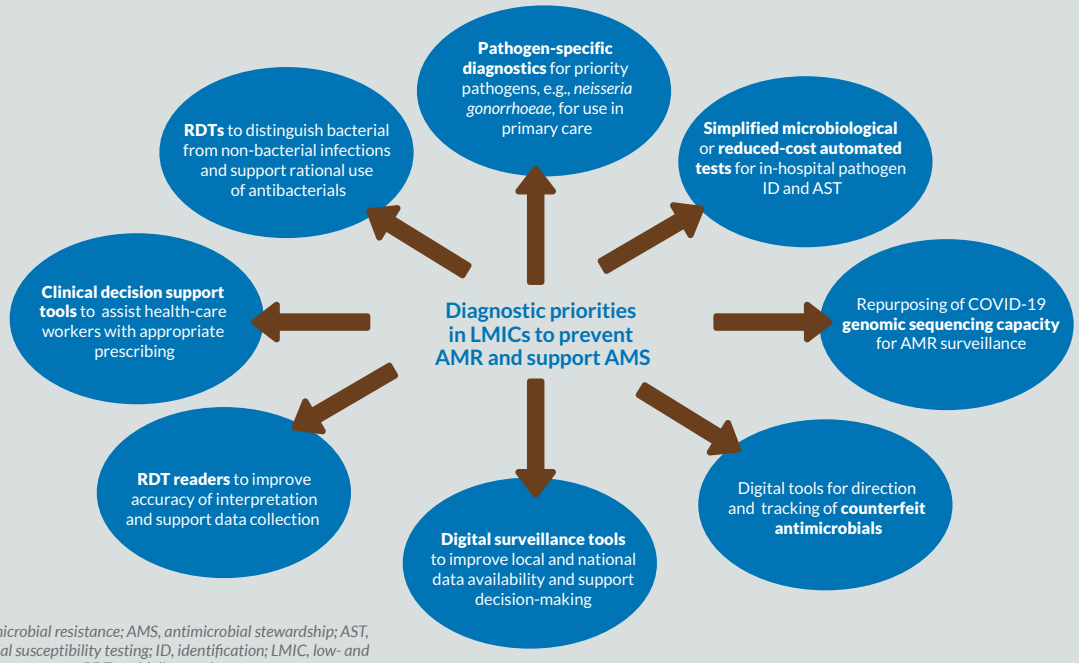
Empiric prescription frequently leads to misuse or overuse of antibiotics, which drives AMR development. Appropriate use of antibiotics requires an evidence-based approach based on the causative pathogen. Diagnostic tools that can determine the nature of the infection, for example, whether it is bacterial or viral, or identify the specific pathogen, are essential to reducing misuse and decreasing the overall demand for antimicrobials. Furthermore, in patients with antimicrobial-resistant infections, determining the resistance profile of a pathogen is key to selecting the most appropriate antibiotic, optimizing patient outcomes, and preventing the further development and spread of resistance. Diagnostics that can determine the susceptibility of an infection-causing pathogen to different antimicrobial agents form the core of this approach.

Gaps and priorities for AMR diagnostic development

Diagnostics to ensure rational use of antibiotics

Acute febrile illnesses (AFI), particularly in young children, represent a major global disease burden *(6)*. Determining the cause of the illness is often challenging, as signs and symptoms tend to be highly non-specific, with considerable overlap between bacterial and non-bacterial causes *(7)*. The emergence of SARS-CoV-2 has also confounded differential diagnoses. In many LMICs, diagnosis is further complicated by the presence of endemic malaria and dengue fever as possible causative agents *(7,8)*. Furthermore, diagnosis of AFI in LMICs often takes place at the community level, where health-care workers may have limited access to diagnostic tools, as well as training and experience. As such, misuse and overuse of antimicrobials in patients with AFI is common *(9)*.

Figure 1: Gaps and priorities for AMR diagnostic development



AMR, antimicrobial resistance; AMS, antimicrobial stewardship; AST, antimicrobial susceptibility testing; ID, identification; LMIC, low- and middle-income country; RDT, rapid diagnostic test

Rapid diagnostic tests (RDTs) are easy-to-use diagnostics that are affordable, have short turnaround times, and can be used at the point of care (POC). RDTs can play a key role in evidence-based prescribing at the community level. The widespread implementation of malaria RDTs, for example, has substantially reduced the consumption of antimalarial drugs *(10)*. A rapid POC diagnostic that can differentiate bacterial from non-bacterial infections would enable health-care workers to move beyond empirical treatment of AFI *(6,11)*. To date, however, development of such a test has proven challenging. Although tests that measure host biomarkers, such as C-reactive protein and procalcitonin, are often used in clinical practice to indicate a bacterial infection, studies suggest that these biomarkers perform poorly in LMICs, since they may also be elevated in common non-bacterial diseases, including malaria, severe dengue fever and COVID-19 *(6,12–15)*.

Support for health-care workers in diagnosing, treating and managing AFI and other infections is provided through guidelines such as the Integrated Management of Childhood Illness (IMCI), a tool developed by WHO and UNICEF that consists of numerous clinical algorithms and training materials for the diagnosis and management of illness in children under five years of age. Digitized versions of such tools, known as electronic clinical decision-support algorithms (eCDA), can combine an individual's health information with the health-care worker's knowledge and clinical protocols to assist with treatment decisions *(16)*, and have been shown to increase adherence to clinical guidelines *(17)*. When POC diagnostic tests are included in the algorithms, eCDA can lead to reduced over-prescription of antibiotics *(18)*. Approaches comprising validated, evidence-based eCDAs combined with POC diagnostics would provide a powerful tool to prevent AMR.

Another disease area in which enhanced diagnostics are urgently needed to support AMS is sexually transmitted infections (STIs) *(19)*. Gonorrhoea, caused by the bacterium *Neisseria gonorrhoeae*, is the second most common bacterial STI, with an estimated annual global burden of 87 million cases *(20)*. The bacterium has progressively developed resistance to the majority of available antibiotics, with failures to last-line treatment reported in several countries *(21)*. Currently, a syndromic approach to the diagnosis of STIs has been used, especially in LMICs, to decide the treatment course *(22)*. However, with increasing rates of AMR, there is a need to move away from the currently used syndromic approach to the use of specific diagnostics to ensure targeted antibiotic treatment. Although molecular tests for *N. gonorrhoeae* are available, they require significant infrastructure, resources and equipment, and are not suitable for use in LMICs *(19)*. Diagnostic tests for *N. gonorrhoeae* that can be used at the primary care level in LMICs are urgently needed *(19,22)*.

Treatment of MDR infections requires identification of the causative pathogen and determination of its antimicrobial susceptibility or resistance profile. In high-income settings, this can be achieved with nucleic acid-based molecular testing such as polymerase chain reaction (PCR) tests. However, in low-

income settings, cost and resource constraints limit the use of such tests.

Severely ill, hospitalized patients with MDR bloodstream infections or pneumonia, including adults and neonates, harbour a large proportion of the burden of MDR *(3)*, and the bacteria responsible for the majority of these infections are classed as "critical" or "high" in the WHO priority pathogen list for the development of new antibiotics *(23)*. Many patients acquire these infections whilst hospitalized *(24)*. There is a need for simplified microbiological diagnostic technologies, such as blood culture systems, or price reductions for existing automated systems, to support rational use of antibiotics in people with MDR infections in LMICs. A single test that can quickly detect these critical pathogens and perform antibiotic susceptibility testing at the hospital level in LMICs could significantly improve outcomes for hospitalized patients and reduce the spread of MDR organisms.

AMR surveillance and data collection

The WHO Global AMR and Use Surveillance System (GLASS) fosters global surveillance of AMR and antimicrobial consumption to inform AMR containment strategies *(25)*. A key component of GLASS is surveillance at the national level. However, AMR data from LMICs are limited, in part because databases are fragmented across different health-care centres such as hospitals, universities and the private sector, and across veterinary and agricultural sources *(26,27)*. Digital platforms that can aggregate AMR data from these numerous sources could help to build capacity for surveillance at all levels. In particular, robust local surveillance would enable better use of actionable data at the hospital level, allowing early detection and response to outbreaks of health-care-associated MDR infections, and can be used to inform local empiric treatment guidelines. Notably, capacity for genomic sequencing in many LMICs has been substantially increased in response to the COVID-19 pandemic, as it is required to track the emergence of new SARS-CoV-2 variants. This capacity has enormous potential to be repurposed for the surveillance of drug-resistant pathogens. Before sequencing can be routinely implemented, a large body of work remains to fully elucidate and characterize the phenotypic and genotypic AMR profiles of infection-causing bacteria.

In the meantime, low-cost tests such as RDTs also have the potential to reduce antimicrobial consumption, however, they present challenges for data collection. Results from RDTs, if collected at all, are commonly filed on paper, from which collation and interpretation may be more challenging, leading to a high risk of error and loss of data *(28)*. This can be prevented through the use of digital readers, which can enhance the accuracy of the interpretation of the RDT results, as well as transmitting the results to local and national databases. Cost and technological requirements often prohibit their use in LMICs, but devices with limited hardware requirements, for example, smartphone apps that utilize the camera for photographic analysis, are under development and could represent a giant leap in data management *(28)*.

AMR diagnostics and cancer

Empiric antibiotics are frequently prescribed to patients with cancer, especially those undergoing immunosuppressive chemotherapies, since any delay in treatment can lead to poor outcomes *(30)*. Because time is of the essence, and the differential diagnosis of possible infecting pathogens is often wide, broad-spectrum antibiotics are frequently given. While logical, this approach may foster AMR, which is of consequence both to the individual under treatment, who often undergoes multiple rounds of chemotherapy and antimicrobial treatment for infectious complications, and the community at large. In the absence of AMR surveillance data in LMICs, empiric treatment guidelines may not be adequate enough to successfully treat the infection. Diagnostics for AMR may be of particular value in this population to ensure appropriate treatment and prevent further development of resistance. In LMICs, where the burden of AMR is already high, the incidence of cancer is rising *(31)*. AMR diagnostics appropriate for use in LMICs will therefore become increasingly important for cancer management.

Conclusions

Diagnostics are an essential component of AMS programmes, yet numerous gaps in the availability of AMR diagnostics exist. Investment in development of diagnostics must be urgently accelerated to prevent further development of AMR and to protect the efficacy of existing and future antimicrobials. ■

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