Outcomes Research & AMR

Bringing Value to the Care Pathway: The Rising Role of Rapid Diagnostics

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Preamble

Antimicrobial use is the primary driver of antimicrobial resistance (AMR). According to a seminal study of antibiotic use in US hospitals, up to 50% of antibiotic use may be inappropriate, and antibiotics represent about 30% of hospitals' pharmacy budgets (Delitt 2007). In addition, despite the implementation of countries' national action plans (NAPs) to reduce antibiotic use, antibiotic consumption has increased, especially in low- and middle-income countries (LMICs), over the past 10 years (Browne 2021, Hamers 2018).

Diagnostics are an essential tool for antimicrobial stewardship and clinical decisions. The techniques that are still widely used for the isolation of bacteria and the identification of antibiotic resistance, however, are time-consuming. Many methodologies require the culturing of microorganisms, which can take several days; thus, empirical therapy is initiated before and antibiotic choice is optimized after culture results are available (Burnham 2017). Diagnostic molecular methods, which can provide results quickly, are already available, but costs have been one of the major barriers to their use (Doern 2018).

The field of outcomes research, as introduced in the previous paper, presents a significant opportunity to encourage uptake of rapid diagnostics and antimicrobial susceptibility tests for infectious diseases, improve patient care and patients' satisfaction with healthcare, revolutionize healthcare reform and reimbursement, and improve access to results-oriented healthcare in resource-limited settings. In this policy brief, alongside two case studies on sepsis and fungal infections, we will discuss the contribution of rapid diagnostics to patient management and the control of infectious disease and AMR, consider hurdles and opportunities posed by the use of outcomes research to clarify the value—economic, clinical, and societal—of rapid diagnostics, and offer a set of recommendations for applying outcomes research to the study, use, and policy of rapid diagnostics in healthcare.

Introduction

Diagnostics are a critical component in antimicrobial stewardship programs (ASPs), and various methodologies already play an important part in clinical settings. Effective ASPs include both avoiding unnecessary antibiotic use and, at the same time, prescribing the right antibiotics where and when they are needed. Ideally, clinical diagnosis and identification of resistant bacteria should be cheap enough to be deployed in community practices, accurate enough to distinguish pathogenic bacteria from commensal bacteria and from viruses, and rapid enough to support clinical decisions in acute-care settings. Rapid and accurate identification of bacteria can come with a reduction in antibiotic use, hospital days, patients' disability, and mortality, thus providing overall substantial savings to health systems (Giacomini 2021). However, the typical cost of $50 to $200 for molecular testing is a significant cost barrier for many healthcare systems, especially when current research frameworks might not fully capture or measure the benefits of their adoption on the full patient care pathway both during and after hospitalization. Additionally, although non-conventional methods, such as matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectroscopy (MS), have several advantages, including low cost per sample processed, the overall yearly system maintenance and expertise needed are very high, making them challenging candidates for point-of-care (POC) use (Patel 2017).

As we have seen during the spread of SARS-CoV-2, when investments were poured into the development of fast diagnostics to identify the virus, as well as molecular methods to detect its mutations, technological advances can be made quickly in a crisis. The same enthusiasm could be applied to AMR. Diagnostics are necessary to direct antimicrobial therapy and initiate infection control measures where appropriate. Yet, without serious commitment, we are unlikely to see significant changes in AMR-associated morbidity and mortality over the next decade.

Access to rapid diagnostic testing is an issue not only of test access and affordability, but also of available funding and resources to carry out implementation, training, and ongoing evaluation.

Rapid diagnostics for infectious diseases and AMR

Rapid diagnostics represent an improvement over the non-rapid, yet still widely used, conventional techniques of culture-based testing and microscopy. Traditional detection of microorganisms is based on the phenotypic characteristics, macroscopic and microscopic analysis (including staining), and the growth of the microorganisms in culture. The phenotypic methods for the detection of pathogens are relatively affordable and widely available. With rapid diagnostics, though, time to results may be significantly reduced from days to minutes, and appropriate treatment based on pathogen identification and susceptibility can be started before an infection spreads or becomes more complicated (Beganovic & Wieczorkiewicz 2020, Cottam 2014, Kaprou 2021). Molecular-based tests such as polymerase chain reaction (PCR)-based assays can provide results within a very short timeframe, which can help support antimicrobial stewardship. Moreover, PCR-based assays have the potential to be used as POC diagnostics (Rentschler 2021). A brief overview of rapid diagnostic methods is described in Table 1.

The implementation of rapid diagnostics, particularly in hospitals, requires significant engagement and ongoing evaluation from healthcare providers and the microbiology laboratory, particularly in making the economic and outcomes-associated value of the diagnostic apparent to hospital leadership (Wenzler 2018). Hospitals often face a circular issue, whereby they must choose which rapid diagnostic is worth the cost and training based on which pathogens they are likely to treat, yet they may lack the surveillance information to make the choice because they have little access to data-generating rapid diagnostics. After a test is chosen and implemented and after clinical and microbiology staff receive education on its use, ongoing metrics to evaluate outcomes—time to treatment, time to antimicrobial de-escalation or stop, time to infectious diseases consult, time to clinical or microbiological cure, time to discharge, and 30-day readmission and mortality rate, etc.—are essential to implement along with the test (Moore 2022).

Table 1. Uses and advantages of common rapid diagnostic tests

Type	Uses	Advantages
Phenotypic **Examples:** • Automated platforms for microbial identification and/or susceptibility testing	Automated phenotypic diagnostics mimic manual phenotypic methods (e.g., broth microdilution, agar dilution) by measuring the growth of a microbe or its response to the presence of antimicrobials, but integrate and automate sample preparation, incubation, detection, and interpretation of plated isolates.	• Reduced time spent in manually setting up broth microdilution and gram staining • In some cases where short culture methods are validated, testing can be performed on isolates early in the growth phase, reducing turnaround time
Molecular **Examples:** • Nucleic acid amplification (e.g. PCR) • Isothermal DNA amplification and DNA microarray • Microfluidics and "lab on a chip" • PNA-FISH • WGS	Molecular tests detect genetic sequences to identify microbial species and/or resistance markers from bacterial isolates or clinical samples.	• High sensitivity and specificity • Ability to quickly distinguish bacterial from viral infections, often providing results in less than 1 hour • Ease of transport and/or accessibility at the point of care • Ability to identify many different pathogens at once with the use of syndromic panels • No requirement for culture techniques • No requirement for isolate purification in some cases
Biochemical **Examples:** • Rapid antigen detection • Antibody detection (e.g., ELISA, or enzyme-linked immunoassay)	Rapid antigen tests detect protein fragments specific to a pathogen present in a sample, whereas antibody tests detect proteins produced by the host in response to an infection with a specific pathogen.	• Ability to identify pathogens that may be difficult or impossible to culture • Useful and accessible at the point of care • Fast provision of results, often in under an hour • Ease of reading and interpreting a visual display
Mass spectrometry **Examples:** • MALDI-TOF	MALDI-TOF uses lasers and a matrix (a small particle that distributes the laser's energy to surrounding proteins that have been extracted from a bacterial cell) and identifies molecules by their mass and speed in the time-of-flight chamber.	• Ability to rapidly identify a broad range of isolates at the species level • Detection of mechanisms of resistance

Note: The data in Table 1 are from The Academy of Medical Sciences 2016, Apisarnthanarak 2021, Beganovic & Wieczorkiewicz 2020, Ferreyra 2022, Fong 2021, Li 2017, Goff 2014, Kaprou 2021, Moore 2022, Ostrowsky 2017, Shanmugakani 2020, Timbrook & Wenzler 2019, Vasala 2020, and Wieser 2012.

MALDI-TOF: Matrix-assisted laser desorption/ionization time-of-flight; DNA: Deoxyribonucleic acid; PCR: Polymerase chain reaction; ELISA: Enzyme-linked immunosorbent assay; PNA-FISH: Peptide nucleic acid fluorescence in-situ hybridization; WGS: Whole Genome Sequencing.

Global access and implementation challenges of rapid tests

The World Health Organization (WHO) identifies the ideal criteria for diagnostic tests as REASSURED: real-time connectivity, ease of specimen collection, affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free or simple, and deliverable to end users (Otoo & Schlappi 2022). These standards, and the likelihood of their being applied, take on different meanings across different contexts, economies, and priorities.

Culture methods are the standard technique for identifying microbial pathogens from patient isolates, especially in LMICs, and cultures have the advantage of being mostly non–pathogen-specific. However, some bacterial organisms may take up to 4 days to grow, fungal colonies can take longer than a month, and many organisms, such as mycobacteria and *Chlamydia* species, are extremely difficult to culture (Okeke 2020).

Many currently available rapid diagnostics might not be affordable or accessible, especially in resource-limited settings, where their purpose and intent might differ from how they are used in high-income regions. While specific aid and research programs, such as the Fleming Fund and SPIDAAR (Surveillance Partnership to Improve Data for Action on Antimicrobial Resistance), have focused on improving laboratory capacity and consequently the collection of AMR surveillance data across LMICs, the integration of rapid and even culture-based diagnostics to inform appropriate antimicrobial use—for example, rapid and POC tests to identify the causes of fevers in young children—has received less attention and funding (Pokharel 2019). Furthermore, in many LMICs, tests are often paid out of pocket by patients, making them largely unaffordable (Fleming 2021, Yadav 2021).

Access to rapid diagnostic testing is an issue not only of test access and affordability, but also of available funding and resources to carry out implementation, training, and ongoing evaluation. Questions of access in tropical, remote, and low-income environments must also include the logistical challenges of heat and humidity, a possible lack of refrigeration, and electrical grid instability (Academy of Medical Sciences 2016).

Hospital-based rapid diagnostics, in contrast to tests offered in primary care settings, tend to be more frequently available in LMICs. Depending on the health system and the availability of diagnostics across public and private facilities, however, patients may need to pay out of pocket for necessary tests. (Academy of Medical Sciences 2016, Ferreyra 2022).

The lack of sufficient outcomes data and their effective translation into interventions is hampering the routine uptake of diagnostics in clinical practice, as diagnostic tests are still considered an economic burden compared to the short-term and long-term value and cost-savings they could offer to health systems.

Outcomes research and the value case for rapid diagnostics

OR plays an important role in making the value case for rapid diagnostics or for the availability of diagnostic testing in public hospitals. The choice to use a particular diagnostic is often presented solely as a matter of evaluating the technical capacity of the test such as the in vitro performance, rapidity, usability, and specificity and sensitivity within a laboratory setting. Yet an OR framework, if used in the context of the diagnostic intervention, can add additional information on value, and short- and long-term patient outcomes (Academy of Medical Sciences 2016). Additionally data on the economic and clinical value of diagnostic tests have largely been limited to single-center studies. A systematic review and meta-analysis in the US suggested that molecular rapid diagnostic tests for bloodstream infections were associated with better patients' outcomes, lower mortality risks, and shorter hospital stays when used in association with antimicrobial stewardship.

Even if clinicians can easily describe the value of tests for patient care, the dearth of large meta-analyses and analyses that clearly elucidate value as outcomes achieved relative to cost has led to weak recommendations that are challenging to be built in a healthcare system's case for investment in rapid diagnostics (Timbrook 2017). A study of rapid diagnostic availability in the Asia-Pacific region recommends that, because of the diversity in economic status and growth across countries, tests must be adaptable to and useful for different stages of patient care to be considered cost-effective, yet the lack of data that can be used to form recommendations presents a roadblock to defining value in these instances (Apisarnthanarak 2021).

The Infectious Diseases Society of America (IDSA) has recently called on the research community to design better studies to capture the clinical and economic benefits of the use of diagnostics, including describing the cost-effectiveness of increased uptake of diagnostics in AMR (Trevas 2021). Although evidence to support the cost-effectiveness of rapid diagnostics is increasing, a standard protocol does not exist for key components of good OR studies, as we discussed in the previous paper. The lack of sufficient outcomes data and their effective translation into interventions is hampering the routine uptake of diagnostics in clinical practice, as diagnostic tests are still considered an economic burden compared to the short-term and long-term value and cost-savings they could offer to health systems. In turn, poor uptake is a disincentive to companies investing in diagnostic R&D. What cannot be overstated is that a lack of OR and outcomes measurement hampers healthcare reform at all levels (Porter 2016).

Focus Box 1 — The value case of interventions according to NICE

The National Institute for Health and Care Excellence (NICE) in England is an independent public body responsible for providing recommendations on clinical guidelines, including the use of diagnostics, to improve outcomes for patients. It focuses on interventions that have been proven to be both clinically effective and cost-effective (NICE).

NICE will review the clinical evidence of an intervention in parallel with the economic evidence to evaluate its cost-effectiveness. A cost-effectiveness analysis measures one single health outcome, for example "a life year saved," "a death averted," or "a patient-year free of symptoms," and assesses the cost per unit of outcome based on relevant prices. The main type of cost-effectiveness analysis that NICE uses is a cost-utility analysis. Such an analysis evaluates the quality of life and length of life gained because of an intervention, or QALYs (quality-adjusted life years). QALYs, as defined in "Outcomes Research & AMR- Defining the value of healthcare interventions in antimicrobial resistance" (CIDRAP 2023), is an outcome measure obtained by adjusting the length of life gained as a result of an intervention to reflect the quality of life, by weighting each estimated year gained with a quality of life score. QALY is an outcome measure comparable between different populations and disease areas.

Additionally, according to NICE cost-effectiveness, immediate costs as well as immediate health benefits of an intervention have a higher value. Thus, an intervention that accumulates health benefits over a long time might still not be cost-effective if it has a high upfront cost. Sometimes ICER (incremental cost-effectiveness ratio) is considered when the most cost-effective intervention is also the most expensive. Although there is no accepted threshold, increased costs should match an increase in clinical effectiveness of the intervention. Cost-effective interventions have a preferred ICER of less than £20,000 ($25,700 US) per QALY gained. An ICER above £20,000 but still below £30,000 ($38,600) may still be acceptable, if the intervention is innovative and brings a significant change in the current standard of care (Garbi 2020, NICE).

NICE has also developed a structured approach to the assessment of new technologies, including therapeutics, diagnostics and medical procedures, entering the market, called Health Technology Assessment (HTA). NICE's HTA is regarded has one of the most transparent and robust assessments leading to quick access to new treatments for patients. It uses a cost-per-QALY and threshold approach that has led the UK to maintain a stable expenditure for health, equal to 12% over the past years, though with limitations and bias against rare and less treatable diseases (Anderson 2022, OECD 2022).

The need for a common outcomes research framework

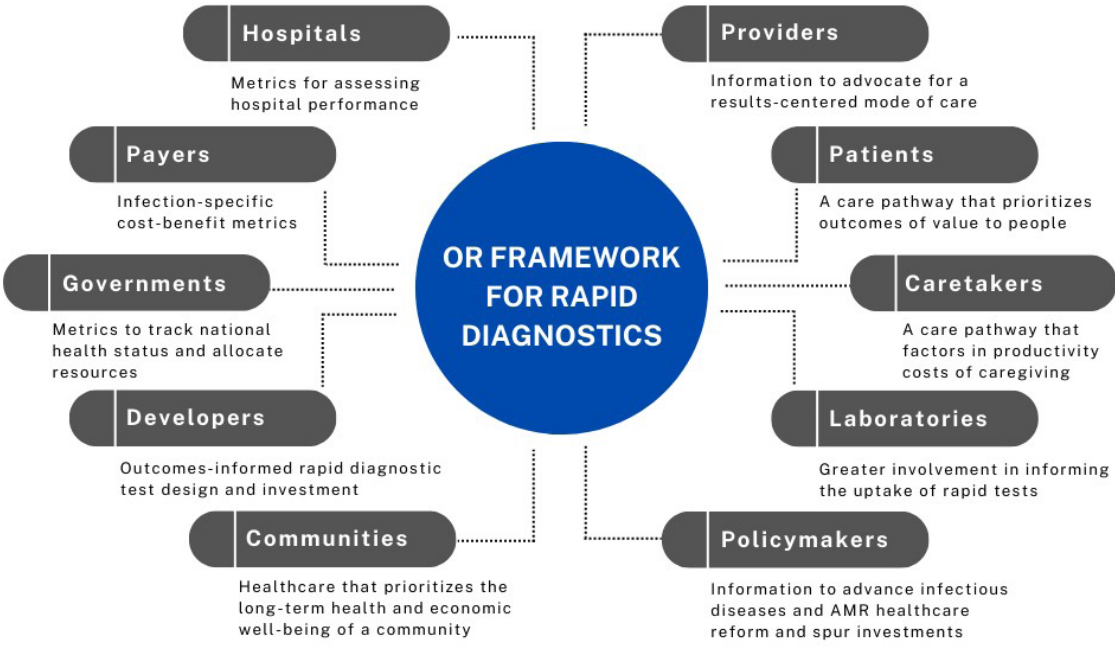
To date we were unable to identify a common framework to be used to design OR projects, which makes it very challenging to compare results and outcomes from various research groups. Alternatively, there are examples for which outcomes and cost analysis are systematically used in developing and implementing clinical guidelines (see Focus Box 1) or for new diagnostics entering clinical practice. They focus on using the wealth of existing data on target population, setting, comparator diagnostic tests and pathways, length of analysis (short-term or long-term), health outcomes, resource and incremental costs, and affordability and reimbursement. Studies that follow such recommendations will depend extensively on available data about new or in-development diagnostics and on the national regulations that enable data reporting on the performance of medical devices and tests (van der Pol 2021).

Antimicrobial stewardship has traditionally defined quality care as clinicians' compliance with appropriate use of tests and antimicrobials, an approach that places emphasis on process measures over outcome and value measures.

Data from rapid diagnostics uptake and use have also been viewed through this process-oriented lens, a limitation that has done little to encourage their uptake and an accurate view of the value they bring to the whole cycle of patient care (Figure 1) (Porter 2016). If OR were to truly elucidate the value of rapid diagnostics, it would mean measuring outcomes by infection type or patient population, rather than by the diagnostic procedure itself, thus considering the test an integral part of the full cycle of care for a particular infection (Porter 2014). Much of what an OR approach can bring to the uptake of rapid diagnostics is the clear definition of value (outcomes relative to cost) in a way that informs decision-making.

OR has made headway in defining value in the fields of chronic disease and injury, in which the patient care pathway appears to be longer and its phases (acute phase, recovery, long-term quality of life) better defined than in infectious diseases and AMR.

Figure 1. Outcomes Research Framework: Who Benefits?



Similar OR methods, however, can change the framework in which decisions about rapid diagnostics are made. A seminal framework on OR argues for the development of a set of outcomes for major medical conditions, clear methods for collecting data and performing risk adjustments, and maintaining a focus on outcomes that prioritize patient function rather than clinical cure (Porter 2016). Implicit in a results-oriented and functional outcomes focus is the fact that patients are not only a legitimate, but a necessary, part of the process of determining and using outcomes metrics (Porter 2014).

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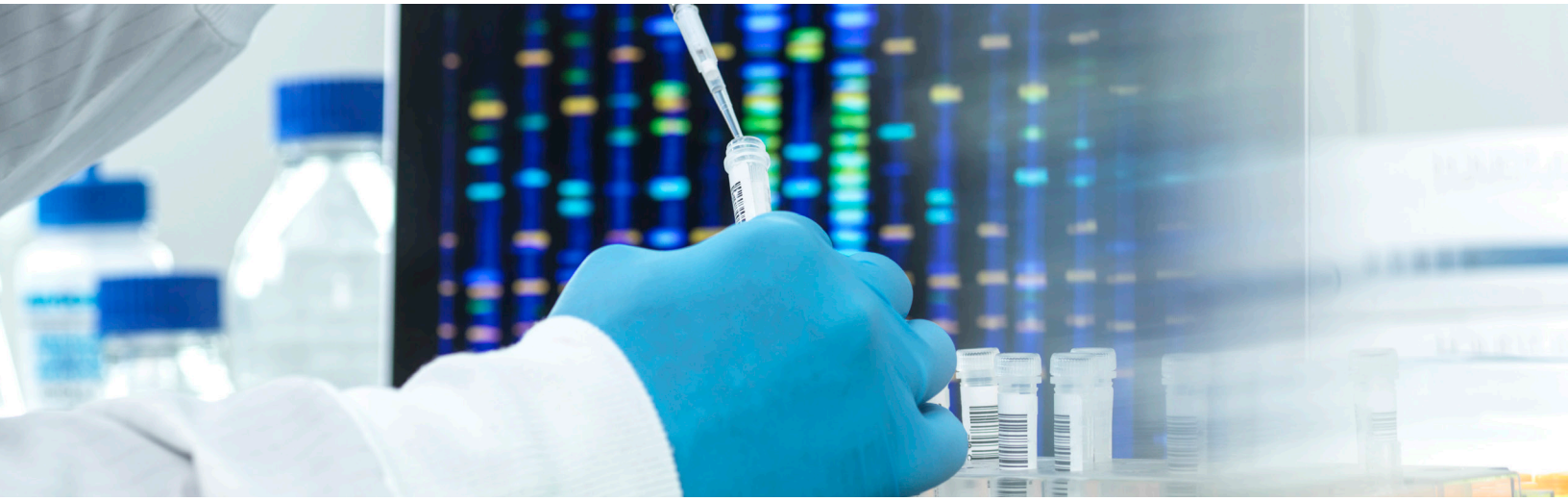
Capturing patients' perspectives in outcomes research

The shift in health systems toward providing healthcare with a patient-centered approach has seen the development and use of additional tools specifically designed with a focus on patients. For instance, PROMs (patient-reported outcome measures) and PREMs (patient-reported experience measures) are also important tools for OR (OECD 2019) and for evaluating the quality of care delivered by health systems and programs. PROMs measure the health outcomes experienced by a patient and the overall quality life and function as a result of a treatment or intervention. They are validated self-reporting instruments that capture patients' views and opinions to assess their health status and wellbeing. This allows patients to be heard and helps clinicians measure the effectiveness of an intervention from a patient perspective. For instance, a therapy, although clinically successful, might lead to severe side effects and thus poor patient compliance. The measurement of PROMs enables investigators and clinicians to assess the all-round effectiveness of medical interventions, including the patients' functional status, satisfaction with the intervention, and quality of life after the intervention (OECD 2019, Manary 2013).

On the other hand, to identify where improvements in patient experience are needed and evaluate how successful efforts to change the patient journey have been, one meaningful way to capture what exactly happens during a care episode is to analyze PREMs (Dawson 2010). Similar to PROMs, PREMs are questionnaire-based instruments that require patients to report on the quality of care received. Both PROMs and PREMs can be used to measure the effectiveness of an intervention, inform clinical decision-making, and identify areas for improvement (Manary 2013).

PROMs and PREMs may not be suitable as stand-alone tools, as they may not capture the full impact of an intervention or the true costs and benefits of an intervention. Nevertheless, if added to a well-rounded OR framework, PROMs and PREMs can help clarify the value of diagnostics. We have identified only two countries that routinely use PROMs and PREMs within their health systems, namely the National Health System in the United Kingdom and the Consumer Assessment of Health Providers and Services (CAHPS) program in the United States (Bull 2022).



Recommendations for outcomes research in building the value case for rapid diagnostics

Analyses that better incorporate OR have the potential to expand access to life-saving rapid diagnostics where they can do the most good. A system of more accurately estimating the value of rapid diagnostics over time using outcomes data and case studies is urgently needed. It would give healthcare administrators and clinicians the information they require to make truly informed decisions and should begin with the following recommendations:

Develop a standardized method for applying OR to rapid diagnostics in managing infectious diseases and AMR.

OR can begin to be applied to making a value case for rapid diagnostics in infectious diseases only if some agreement is formed about the outcomes, processes, and costs to be measured. Ultimately, the data should answer the question: "Are we improving patients' outcomes?" A standardized method should involve the development of a minimum set of outcomes for infections or medical conditions that is syndrome- and setting-specific and accounts for available resources, a clear methodology for collecting data, a means of assessing and adjusting for risk among different patient populations, a method of assessing costs and outcomes relative to costs across the entire patient care pathway, and the inclusions of patient perspectives as outcomes and value are defined and used to provide changes in testing and decision-making about care. In a Harvard Business School presentation, Michael Porter, PhD, MBA, affirms, "Ultimately, universal reporting of standardized measures will be the strongest driver in value improvement." (Porter 2014)

Develop a framework for integrating OR into the entire diagnostics pathway, from development to communication of results.

Considerations to be integrated in the research and development of antimicrobials, economic modeling and OR that links potential outcomes and costs should play a role in the development and validation of diagnostic tests. If infectious disease and AMR prevention and management is to be truly results-oriented and patient-centered, not to mention attractive to healthcare systems that must make the initial financial investment, then global funders of diagnostic development must invest in development frameworks that illuminate value for cost. As OR for rapid diagnostics

grows more robust and begins to produce data for decision-making and changes in care pathways, it must also ensure that results are communicated to patients and the public, who must be involved in informed decision-making about their care. Any framework for integrating OR into the diagnostics pathway should include a parallel path toward transparency of costs, results, and value.

Undertake context-informed implementation.

As exemplified in the case studies, comparable methods can lead to different outcomes and cost-effectiveness when applied to different health systems. It is clear that what appears beneficial in a health model might not be in a different system. This suggests the need for ad hoc interventions tested on different health model systems before wider implementation.

Incorporate training and safety.

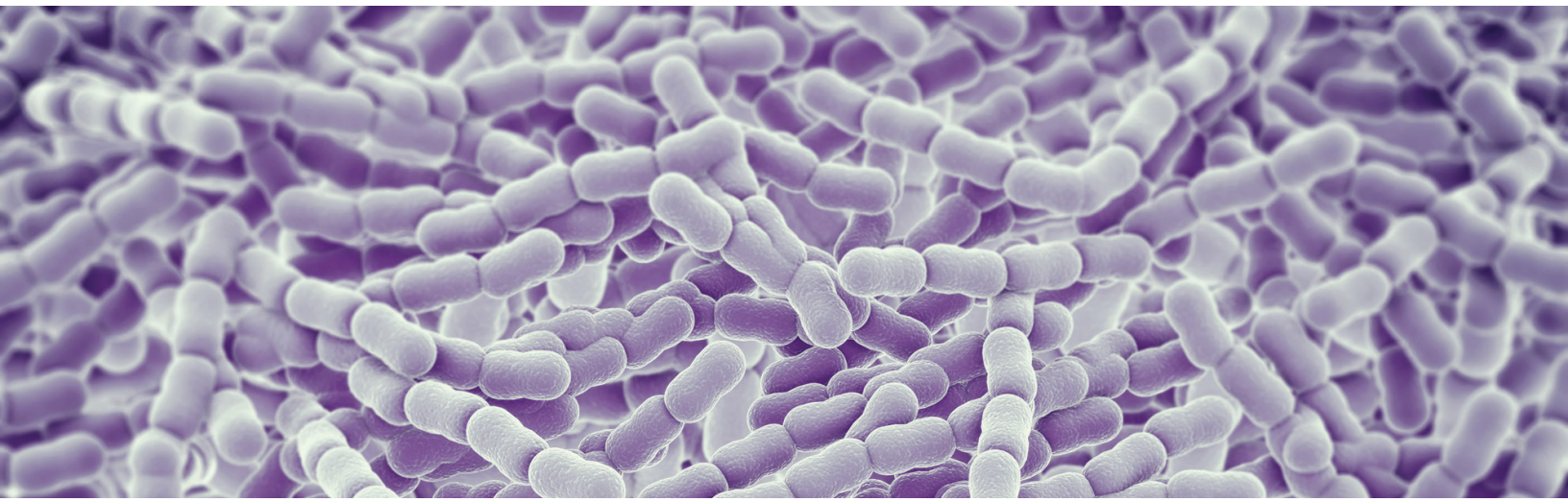
Many rapid and automated diagnostic tests require significant training in their use and interpretation, yet they are often easier to use than conventional methods, such as microscopy and culture. Additionally, rapid diagnostics may improve the safety of laboratory professionals, who may be performing conventional tests in an environment that cannot meet the biosecurity requirements for them. Costs incurred and saved related to training and safety should be a key element of OR and cost-effectiveness analyses.

Emphasize long-term OR.

Long-term OR models and studies—especially when rapid diagnostics incur high initial costs or when a rapid and conventional diagnostic are similar in cost—can help to identify situations in which initially cost-effective strategies are dominated by alternatives over time. For example, a conventional test may appear cost-effective in a month-long model as it outperforms a more expensive rapid test, yet a 5-year model that incorporates hospital stays, the sequelae of adverse events from inappropriate treatment, and the entire patient care pathway may reveal that the initially more expensive test was the most cost-effective over time. Once OR is integrated along the patient care pathway, it can be combined more efficiently with cost data to find opportunities for improving value and patients' experiences, processes, and the streamlined uptake of innovative tests.

Diversity of contextual clinical, social, and economic factors must be taken into account when making decisions about the integration or expansion of rapid diagnostic testing in hospital settings. Further case studies on sepsis (Appendix 1) and fungal infections (Appendix 2) highlight how OR can help to lay the groundwork for evidence-based choices that may have wide-ranging benefits for patients and healthcare systems.

Analyses that better incorporate OR have the potential to expand access to life-saving rapid diagnostics.



APPENDIX 1

Case Study: Cost-effectiveness of the use of rapid diagnostics for sepsis in different health contexts

Sepsis: An urgent global health issue

In 2017, the World Health Assembly passed a resolution with the aim of improving the prevention, diagnosis, and management of sepsis (Reinhart 2017). Sepsis poses a significant health and economic burden globally. It is defined as a life-threatening organ dysfunction caused by an infection. An estimated 11 million people die every year out of 50 million cases of sepsis (Rudd 2020). According to the same study, sepsis incidence fell by 37% and mortality decreased by nearly 53% from 1990 to 2017 (Rudd 2020). However, the highest burden remains in LMICs, where inadequate infection prevention and control and limited access to clean water and sanitation contribute to infectious disease spread (Keeley 2021). Experts have called for urgent investments to develop efficient, cheap, and reliable diagnostics and therapies applicable to all countries.

An estimated 10% or more of sepsis cases are due to AMR (Buchman 2020). Given the close relationship between these two global health issues, efforts to reduce sepsis should go hand in hand with ASPs (Reinhart 2017). The dilemma lies around the use of empirical antibiotic treatment, which should be phased out, given the AMR burden, and the effective management of sepsis, which requires urgent antimicrobial therapy to increase patients' survival. Standard clinical guidelines include broad-spectrum antibiotics given within 3 hours and later adjusted following identification of the causative agent and antibiotic susceptibility pattern (Burrell 2016). Given the high burden of sepsis, AMR, and associated risks for patients and communities over the irrational use of antimicrobials, understanding the cost-effectiveness of interventions—and, especially, the use of diagnostic methods for quick identification of pathogens and their drug susceptibility—is essential.

Most types of microorganisms can cause sepsis, including bacteria, fungi, viruses, and parasites. The most common culprits include bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* spp. and *Neisseria meningitidis* (Reinhart 2017). AMR can cause treatment to fail and increase the risk of death. Data from Europe have found *S aureus*, including methicillin-resistant *S aureus* (MRSA), to be the most common cause of sepsis. The estimated mortality rate associated with MRSA is about 50% higher than that for patients affected by methicillin-susceptible *S aureus* (European Sepsis Alliance).

The global cost of sepsis

A systematic review published in 2022 estimated high costs associated with treating sepsis. Total sepsis-related healthcare expenditure was lowest in Greece at €58 million ($61 million) and highest in the US at €51 billion ($54 billion) with a median sepsis-related healthcare expenditure of about €15 billion globally ($16 billion). This is likely a conservative estimate, since most of the data were extrapolated from the United States, Europe, Australia, and a few countries in Asia and Latin America (Torio 2016, van den Berg 2022). Additionally, a study conducted in Africa estimated that 5.29 million to 8.73 million disability-adjusted life-years (DALYs) are lost annually in sub-Saharan Africa to neonatal sepsis, which translates to an annual economic burden of $10 billion to $469 billion, according to the value of statistical life (Ranjeva 2018). With scarce data availability from various economic regions, the total global healthcare costs of sepsis are difficult to estimate and could be significantly higher than the figures above, making sepsis a critical priority not only in economic terms but also in unnecessary lives lost.

Current diagnostic pathways for sepsis

Treatment for sepsis should be started as soon as possible after a patient's consultation if sepsis is suspected. Several systematic reviews and observational studies suggest that delayed treatment increases mortality, and therapy should be initiated within 3 hours (Evans 2021). The gold-standard method for diagnosing the likely causative agent of sepsis is blood culture, and although the objective would be to start a targeted therapy, given the lag of time for the culture results to arrive, clinicians must initiate empirical therapy before microbiology results are obtained (Sterling 2015). The use of blood biomarkers can improve sepsis care and guide treatment. In this context, the blood marker procalcitonin has been shown to be useful for disease prognosis and stratification of patients (Gregoriano 2020).

Rapid molecular testing could speed up the confirmation of diagnosis to a few hours rather than several days, and thus the development of rapid POC tests has gained particular attention in recent years. Additionally, early identification of AMR is critical for the successful management of sepsis patients, especially in high-AMR settings. Recent data support a close relationship between neonatal sepsis morbidity and mortality and AMR, especially in LMICs. In some cases, half of the pathogens causing neonatal bacterial infections are resistant to first-line antibiotics such as penicillin and gentamicin and to second-line drugs such as third-generation cephalosporins (Le Doare 2015, Folgori 2017). Given the urgency and high costs associated with sepsis, identifying tests that are reliable, quick, and cost-effective is urgent.

Recent systematic reviews identified several studies that specifically addressed the use of rapid diagnostic tests for sepsis while also evaluating their cost-effectiveness (Higgins 2020, Rojas-Garcia 2022). Most of these studies,

however, were conducted in high-income countries. The lack of specific data for LMICs adds to the challenge of identifying suitable diagnostic tools that could be deployed in high-burden and resource-limited areas. In addition, most of the economic evaluations did not consider the long-term effect of sepsis morbidity and mortality, terminating data collation after 30 days. Costs were mostly calculated from the hospital point of view, foregoing potential costs borne by the community. Additionally, most studies calculated cost per case, and savings and did not compare the diagnostic tests with alternatives. Not all models included AMR, as it can be difficult to quantify its impact. The general assumption is that better diagnosis translates into appropriate treatment and less antibiotic misuse, leading to better health outcomes and shorter hospital stays.

Better antibiotic management also reduces the rates of AMR, at least within hospitals. These assumptions are backed by multiple studies. However, taking into consideration that AMR is also influenced by other factors, such as antibiotic use in other sectors beyond the hospitals' doors, a reduction of antibiotic use in hospital settings cannot always be correlated to AMR reduction overall. There is also no standard protocol used for cost analysis, and it is generally difficult, since savings and cost effectiveness can be calculated using varying formulas to compare studies. Additionally, cost savings and cost-effectiveness might be perceived differently in different health systems (e.g., insurance vs non-insurance models). Economic evaluations of health interventions pose a particular challenge for reporting. Additionally, guidelines need to be consolidated, updated, and made more user-friendly (Rojas-Garcia 2022).

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) report attempted to standardize economic analysis (Husereau 2013). This report consolidates previous health economic evaluation guidelines efforts into one reporting guidance; however, not all research groups use this protocol in their studies. Additionally, there is no clear guidance on how to incorporate CHEERS into OR studies, considering that an economic evaluation should take into account not only the cost saved but also the clinical outcomes and the overall effects of the intervention on patients and communities.

Given the high burden of sepsis, AMR, and associated risks for patients and communities, it is essential to understand the cost-effectiveness of interventions—especially, the use of diagnostic methods for quick identification of pathogens and their drug susceptibility.

Comparing cost analysis: The influence of contexts and health systems on outcomes

Given all these challenges, one solution cannot be applied to all contexts or health systems. This is why OR applied to different contexts can play a key role in establishing which methodologies are the most effective and efficient.

In Table 2 we look at examples of the use of molecular methods versus standard diagnostic techniques (such as blood cultures) applied to different contexts and health systems. This does not represent an exhaustive list of all major economic analyses performed to date on sepsis diagnosis. Rather, it uses a sample of studies to illustrate how differing results, despite the use of comparable diagnostic techniques, were obtained in diverse health systems.

Table 2. Cost analysis of rapid diagnostic tests for sepsis in different settings

Study	Country	Study type, perspective, follow up, and population	Diagnostic method used	Cost analysis
Shehadeh et al (2019) **Decision analysis model to evaluate the cost-effectiveness of the addition of molecular methods to blood cultures in patients with sepsis**	Canada, US, and Saudi Arabia	• Retrospective multi-center study • Hospital • Not specified • Not specified	• Molecular tests • Blood culture	• The use of molecular methods was cost-saving in all cases when the length of hospital stay differed by 2 and 4 days between patients receiving appropriate and inappropriate antimicrobial therapy • When the length of stay was the same, the use of molecular methods was more cost-effective for a willing to pay less than $3,000 per death averted.
Alvarez et al (2012) **Use of RT-PCR to diagnose sepsis**	Spain	• Individual sampling model • Healthcare center • 6 months • Adults	• PCR • Broad-spectrum antibiotic	• Control-group expenses amounted to €42,198 ($46,298 US), versus €32,228 ($35,359 US) in the intervention group. • Average saving was €9,970 ($10,938 US) per patient. • Mortality rate was similar in both groups.

Pliakos et al (2018) **Cost effectiveness of rapid diagnostic testing in bloodstream infections**	US	• Decision tree • Hospital • Projected life expectancy of the patients (death considered only in the first 30 days after admission) • Adults	• MALDI-TOF • Molecular methods • Traditional culture	• MALDI-TOF analysis with ASP was found to be the most cost-effective strategy, resulting in savings of $29,205 per QALY and preventing 1 death in 14 patients compared to conventional laboratory methods without an ASP. • Other options to consider: PCR with an ASP scored $19,833 savings per QALY, and PCR without an ASP reached $21,039 per QALY; blood culture nanotechnology microarray system for gram-positive bacteria (BC-GN) with ASP scored $23,587 per QALY. • Rapid diagnostics methods plus ASP are the most cost-effective overall.
Dixon et al (2021) **The RAPIDO trial evaluating the cost-effectiveness of MALDI-TOF versus standard blood culture alone in the diagnosis of sepsis**	UK	• Randomized multicenter controlled trial • Hospital • 28 days • Adults	• Traditional culture and identification of causative agent • Traditional culture + MALDI-TOF	• Prices per patient were lower by £126 ($146 US) using MALDI-TOF, but mortality at day 28 was slightly higher in this group (proportion of patients alive in the MALDI-TOF arm was 81.4% versus 82.3% in the control group). • The probability of cost-effectiveness of MALDI-TOF was less than 0.5 at cost-effectiveness thresholds between £20,000 ($24,000 US) and £50,000 ($60,000 US). • MALDI-TOF was not found to be cost-effective when compared to traditional methods using this short-term perspective; high-throughput MALDI-TOF could become cost-effective. • Further research should explore mortality outcomes between the use of MALDI-TOF and conventional diagnosis on a larger and systematic scale to really capture the full benefits of the diagnostic tool.

Penno et al (2015) **Using POCT in low-resource settings**	Ethiopia, The Gambia, Papua New Guinea, the Philippines	• Decision tree • Hospital • Not specified • Adults and children	• POCT • Clinical assessment	• POCT was generally more cost-effective ($1.10 less) per patient compared to traditional clinical assessment. • Survival was unchanged between traditional methods and POCT when tests' specificities were taken into account. • Varying sensitivity affected costs of POCT use, but higher sensitivity of POCT correlated to lower patient mortality. • When ceftriaxone was used, the two tests had cost parity at a specificity of 0.73 and a sensitivity of 0.84.
Cambau et al (2017) **EVAMICA open-label, cluster-randomized, interventional crossover trial evaluating the use of molecular methods versus culture techniques to detect pathogens in blood**	France	• Decision tree • Hospital • 30 days • Adults	• Molecular methods • Traditional culture	• Molecular detection of pathogens in the blood gave a higher microbial diagnosis rate than with conventional culture methods. • Molecular methods gave results faster, with bacteremia and fungemia diagnosed in less than 24 hours without an increase in hospital costs. • Molecular tests were an average of €1,000 ($1,097 US) per patient. • There were no significant differences between classical and molecular methods relating to clinical investigations and number of days with treatment. • Median total costs for molecular methods were €14,826 ($16,266 US), versus €17,828 ($19,560 US) for traditional methods. • The cost difference even in disease sub-groups was not significant.

Note: The data in Table 3 are from: Alvarez 2012, Cambau 2017, Dixon 2018, Penno 2015, Pliakos 2018, and Shehadeh 2019.
MALDI-TOF: Matrix-assisted laser desorption/ionization time-of-flight; QALY: Quality-adjusted life year; PCR: Polymerase chain reaction; POCT: Point-of-care test; RT-PCT: Real-time polymerase chain reaction

Conclusion

Numerous studies have found that the use of molecular methods or traditional methods combined with MALDI-TOF and antimicrobial stewardship were beneficial both in terms of improving patient outcomes and in being cost-effective for the hospitals in which they were tested. All the studies presented above used different protocols, and results might be difficult to compare even among hospitals within the same region. Results are context-specific, and organizational changes and larger systematic trials might be needed to exploit the full benefits of a new method. The standardization of outcomes research protocols, in this sense, might be useful to better define criticalities and must-have characteristics of a health system for the optimal implementation of AMR interventions. Extending the analysis to also include perspective beyond the hospitals will be also needed to measure the full impact, also in terms of cost-effectiveness, in the community.

Standardized outcomes research protocols can be used to define must-have characteristics of a health system for the optimal implementation of AMR interventions. Analysis in the community, beyond the hospital setting is needed to measure the full impact.

APPENDIX 2

Case Study: Guatemala's Diagnostic Laboratory Hub Reduces Mortality, Unnecessary Antimicrobial Use, and Costs Associated with Serious Fungal Infections in People Living with HIV

The risk of invasive fungal infections in Latin America

Approximately 2 million people die of fungal infections globally every year (Denning 2022). Invasive fungal infections (IFIs) and antifungal resistance present a significant risk to people living in areas in which pathogenic fungi are endemic and are a particular threat to people living with HIV, uncontrolled diabetes, and/or cancer. Cryptococcal meningitis causes about 20% of AIDS-related deaths around the world despite global advances in improving HIV/AIDS care and prevention, and, in 2020, about 152,000 cases of cryptococcal meningitis and 112,000 deaths occurred globally (Burry 2022). The availability of diagnostic tests to identify fungal infections quickly and accurately is crucial to ensuring that people receive appropriate healthcare and to prevent AMR (Salmanton-García 2023). Among immunocompromised people, particularly those with advanced HIV disease, opportunistic fungal infections—notably, cryptococcal meningitis, histoplasmosis, *Pneumocystis* pneumonia, and pulmonary aspergillosis—are a leading cause of morbidity and death (Lakoh 2022).

In Latin America, *Histoplasma* is the most prevalent endemic mycoses that can cause systemic disease, such as disseminated histoplasmosis, which is often fatal if left undiagnosed and untreated. Histoplasmosis is usually not reportable at the national level, even though it is associated with a high death rate in people with HIV. For instance, in endemic regions of Brazil, the death rate from disseminated histoplasmosis is 42% to 53%, and more than 40% of hospitalized people with HIV also have *Histoplasma* infections (Pasqualotto 2023).

Rapid and conventional diagnostics for invasive fungal infections

The WHO includes several fungal infection tests on its list of essential diagnostics, including *Aspergillus* antibody and antigen tests, and, for people living with HIV, cryptococcal antigen tests, rapid immunoassays for *Histoplasma* antigen detection, and *Pneumocystis jirovecii* nucleic acid tests (Denning 2022, WHO 2021). However, despite the fact that fungal infections cause about 2 million deaths globally every year, national infectious diseases surveillance programs often do not collect information on fungal disease or antifungal use, and the WHO does not currently have a global fungal infection surveillance program (Pathadka 2022).

Table 3 outlines common conventional and rapid diagnostics used to detect invasive fungal infections.

Table 3. Rapid and conventional diagnostics for common serious fungal infections

Indication	Rapid	Conventional
Cryptococcus species	• Cryptococcal antigen testing (*Cryptococcus* lateral flow assay, *Cryptococcus* latex agglutination, beta-d-glucan) • MALDI-TOF • DNA whole-genome sequencing • PCR	• Lumbar puncture • Microscopy using, for example, China/India ink, acridine orange, Giemsa, potassium hydroxide, or calcofluor white staining • Culture (e.g., Sabouraud dextrose agar, potato dextrose agar) • Automated assays
Histoplasma capsulatum	• *Histoplasma* antigen testing • Antibody testing, including ELISA • Real-time PCR	• Microscopy using, for example, Giemsa, periodic-acid Schiff, Grocott-Gomori's methenamine silver, lactophenol cotton blue, or potassium hydroxide staining • Culture (e.g., Sabouraud dextrose agar, potato dextrose agar) • MRI and CT
Pneumocystis jirovecii	• Quantitative PCR	• Microscopy using, for example, Grocott-Gomori's methenamine silver, calcofluor white, Giemsa, or toluidine blue staining • MRI and chest radiography
Aspergillus species	• Antibody testing • *Aspergillus* galactomannan antigen testing • PCR	• Microscopy using, for example, calcofluor white or lactophenol cotton blue staining • Culture (e.g., Sabouraud dextrose agar, malt extract agar)
Candida species	• Antibody detection testing, including ELISA • PCR	• Microscopy using, for example, Gram staining • Culture (e.g., Sabouraud dextrose agar) • Automated assays
Mucorales	• PCR	• Microscopy using, for example, Grocott-Gomori's methenamine silver, periodic-acid Schiff, lactophenol cotton blue, or hematoxylin and eosin staining. • Culture (e.g., Sabouraud dextrose agar, potato dextrose agar)

Note: The data in Table 4 are from: Caceres et al., 2021; Lakoh et al., 2022; Medina et al., 2021a; Medina et al., 2021b; Medina et al., 2022a; Medina et al., 2022b; PAHO, 2020; Salmanton-García et al., 2023; Samayoa et al., 2019; and WHO, 2021.

MALDI-TOF: Matrix-assisted laser desorption/ionization time-of-flight; DNA: Deoxyribonucleic acid; PCR: Polymerase chain reaction; ELISA: Enzyme-linked immunosorbent assay; MRI: Magnetic resonance imaging; CT: Computed tomography

Invasive Fungal Infections: Diagnostic, Treatment, and Economic Challenges

Because rapid fungal diagnostics are often not available, affordable, or recommended as part of national guidelines, many fungal diseases are misdiagnosed. A study across Ghana, India, and Vietnam found that more than half of patients with ongoing pulmonary symptoms following treatment for tuberculosis had aspergillosis (Denning 2022). Regional endemicity of fungal diseases may also affect awareness and testing. In the United States, coccidioidomycosis (valley fever), which is endemic in parts of the West, is often misdiagnosed as other lung diseases, especially when it occurs in travelers seeking healthcare in non-endemic regions. No rapid test for valley fever exists, and approximately 60% to 80% of infected people receive antibiotic treatment for their symptoms (US CDC 2021).

Financial barriers also limit the availability of fungal diagnostic tests. A 2023 study across 40 Asia-Pacific nations found that countries with a low per-capita gross domestic product (< $3,000) less frequently had laboratories equipped with higher-cost microscopy staining such as China/India ink, MALDI-TOF, DNA sequencing, *Aspergillus* antibody tests, and enzyme-linked immunosorbent assay (ELISA) for antigen detection (Salmanton-García 2023). A 2022 study of diagnostic capacity for fungal infections in people living with HIV across 48 African countries found a low availability of antigen testing, lumbar puncture, and China/India ink staining for *Cryptococcus*, urine antigen testing for *Histoplasma*, and *Pneumocystis jirovecii* microscopy or PCR testing. Fungal culture was widely available across all but 8 countries (Lakoh 2022).

A program to assess the implementation of rapid antigen assays for *Histoplasma* and *Cryptococcus* infections in people living with HIV in Honduras, Nicaragua, and Panama from 2015 to 2019 found that rapid tests had a high sensitivity for detecting positive cases and may present a cost-effective way to significantly reduce mortality and morbidity in endemic areas (Caceres 2021). The Histoplasmosis Porto Alegre manifesto notes that *Histoplasma* antigen tests have demonstrated sensitivity and specificity greater than 90%, require less training than traditional microscopy or histopathology methods, are commercially available, and can be validated easily. Most important, the use of comparatively rapid antigen tests with a high sensitivity has demonstrated improved survival in patients with disseminated histoplasmosis. A Brazilian study found reductions in mortality from 26.9% to 14.3% when an antigen test was the first diagnostic used to detect positive *Histoplasma* infections (Pasqualotto 2023). In its 2020 guidelines for diagnosing and treating disseminated histoplasmosis in people living with HIV, the Pan American Health Organization recommends diagnosis via antigen testing of urine samples (PAHO 2020).

Guatemala's Diagnostic Laboratory Hub for invasive fungal infections in people with HIV

In 2016, the Asociación de Salud Integral in Guatemala, in partnership with the Global Action Fund for Fungal Infections (GAFFI), implemented a countrywide strategy to increase laboratory capacity, microbiology training, and access to rapid diagnostics and affordable antifungal treatment for invasive fungal infections, with the primary goal of reducing deaths in people living with HIV. Guatemala is home to approximately 46,000 people living with HIV—the most with HIV and advanced HIV disease in any Central American country—yet only about 36% of those people are receiving antiretroviral therapy (GAFFI 2018, Medina 2020).

Initial implementation of the project involved establishing a network of 13 hospital-based HIV care units called Red de Infecciones Fúngicas (FUNGIRed) and forming a Diagnostic Laboratory Hub along with a diagnostics- and training-centered workflow that ensured the availability of test results within 24 to 48 hours. Crucial to the program's effectiveness was the establishment of a pathway through which couriers would deliver samples from hospitals to the Diagnostic Laboratory Hub at an HIV unit in the Hospital General San Juan de Dios in Guatemala City (GAFFI 2018).

Public healthcare for people living with HIV in Guatemala is provided by hospital-based units that have very little ability to perform conventional or rapid diagnostic tests onsite, and 12 of the FUNGIRed units were located in rural areas (Medina 2020). During discussions in preparation to launch FUNGIRed in 2015, providers who work with people living with HIV described the need for a system to rapidly detect opportunistic infections cost-effectively, increase capacity for fungal disease screening in at-risk people, and improve clinician and microbiologist education on diverse diagnostic testing techniques (Samayoa 2019).

Techniques provided by the Diagnostic Laboratory Hub include mycobacterial smear, isolator blood culture, in-house PCR for tuberculosis and histoplasmosis, ELISA for *Histoplasma* in urine samples, lateral-flow cryptococcal antigen assays, molecular detection via PCR for *Pneumocystis jirovecii* pneumonia, and *Aspergillus* antibody testing (GAFFI 2018, Medina 2020). The program also instituted universal screening for tuberculosis, non-tuberculosis mycobacterial infections, histoplasmosis, and cryptococcal infections regardless of CD4 cell count, and a 2022 study found that each unit screened up to 26 patients per month (Medina 2022a). In 2017, more than half of patients with an opportunistic infection tested through the program were found to have fungal infections, including 141 people with disseminated histoplasmosis, 84 with cryptococcal infections, and 10 patients who had histoplasmosis and tuberculosis co-infections (GAFFI 2018).

Informatics and workflow techniques also contributed to the cost-effectiveness of the Diagnostic Laboratory Hub and its capacity to quickly diagnose and treat life-threatening infections. Tools to track samples and patient outcomes, along with a rapid courier transport system, allowed tests to be performed quickly and cheaply and enabled a faster time to appropriate treatment (Medina 2022a).

The Diagnostic Laboratory Hub and its associated education and workflows have been found to improve training on rapid diagnostic methodologies and suspicion for fungal infection, enhance quality control of sample handling, and reduce costs per test, especially when automated or rapid tests are able to accommodate multiple samples (Medina 2020). For instance, a 2021 study found that costs amounted to about $7.50 per cryptococcal antigen test and $13 for

histoplasmosis testing, an expense the authors called reasonable given the seriousness of infection (Medina 2021a). Rapid treatment with fluconazole following a positive cryptococcal antigen test costs approximately $2—although the price and availability of fluconazole can fluctuate widely in Latin America—compared with the greater than $2,000 cost of treating cryptococcal meningitis if diagnosis and treatment is not made quickly (Medina 2022).

Please see Table 4 for more information on the sensitivity of *Histoplasma* and *Cryptococcus* rapid and conventional testing performed by the Diagnostic Laboratory Hub.

Table 4. Performance of *Histoplasma* and *Cryptococcus* diagnostics used in Guatemala's Diagnostic Laboratory Hub

Study	Patients Screened	*Histoplasma* (+)	*Cryptococcus* (+)	Diagnostic Tests Used
Samayoa B et al (2019)	1,953	99	59	• PCR: 56.5% sensitivity for histoplasmosis • Urine antigen: 75% sensitivity for histoplasmosis and 94.4% sensitivity for disseminated histoplasmosis in samples diagnosed by a positive antigen test and/or a positive isolator blood culture • Cryptococcal antigen: 100% sensitivity • Culture: 39.6% sensitivity for *Cryptococcus*
Medina N et al (2020)	4,245	271	170	• Urine antigen: 72.3% for histoplasmosis and 94% sensitivity for disseminated histoplasmosis, and 35.1% of cases were only detected via urine antigen • Isolator blood culture: 36.3% sensitivity for histoplasmosis • Culture of respiratory samples: 8.5% sensitivity for histoplasmosis • PCR on mostly sputum samples: 62.7% sensitivity for histoplasmosis, and 23.6% of cases were only detected via PCR. • Cryptococcal antigen lateral flow assay: 97% sensitivity, and 18 of 55 cryptococcal meningitis cases using cerebrospinal fluid were only detected via antigen testing.

Note: The data in Table 4 are from: Medina et al., 2020; and Samayoa et al., 2019.

PCR: Polymerase chain reaction

During the first 3 years of the Diagnostic Laboratory Hub (2017–2019), Guatemala observed a 111% increase in the number of serious fungal infections diagnosed in people living with HIV, along with an 8% reduction in deaths. The authors attribute the decreases in fungal infection mortality to rapid diagnosis, as the availability and type of treatments in the country remained unchanged. During the same period, the Diagnostic Laboratory Hub ruled out serious fungal infections in more than 2,100 people living with HIV, which saved costs related to empirical therapy and enabled better HIV-focused care (GAFFI 2018, GAFFI 2022).

In an interview about the Diagnostic Laboratory Hub, Eduardo Arathoon, MD, managing director of the Hospital General San Juan de Dios, said, "This diagnostic and educational program has been transformational for patients with HIV in Guatemala—inspiring confidence in our healthcare workers, providing rapid diagnostic answers in complex medical cases and saving lives." (University of Manchester 2021).

Not only has the project saved lives and avoided unnecessary antimicrobial therapy, but it has also demonstrated that rapid testing is a cost-effective strategy for addressing serious fungal infections, with a lower cost per sample processed (e.g., $13 for a more-sensitive *Histoplasma* antigen test versus $22 for a less-sensitive blood isolator culture) and prevention of inappropriate antifungal or anti-tuberculosis medication use (Medina 2020). The hub also continues to gather epidemiologic data to advocate for better testing and treatment availability, along with evidence-informed diagnostic investment, for fungal diseases in immunocompromised people across Latin America.

Conclusion

Prompt and accurate diagnosis and treatment of invasive fungal infections is imperative to lowering deaths in immunocompromised people. Rapid antigen tests for *Cryptococcus* and *Histoplasma* have shown significant promise in detecting invasive and disseminated infection in a cost-effective manner, and the main barriers to their use involve the development of programs to increase access to testing. Outcomes research focused on the introduction and availability of testing in endemic areas or areas where people may be particularly at risk of invasive fungal infections may provide information to encourage not only programs that increase access to rapid diagnostic testing, but also the development of national guidelines to encourage rapid fungal diagnostic use.

Prompt and accurate diagnosis and treatment of invasive fungal infections is imperative to lowering deaths in immunocompromised people.

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