Infect Dis Ther
https://doi.org/10.1007/s40121-023-00815-z

COMMENTARY

Rapid Diagnostic Test Value and Implementation in Antimicrobial Stewardship Across Low-to-Middle and High-Income Countries: A Mixed-Methods Review

Luke S. P. Moore · Maria Virginia Villegas · Eric Wenzler · Timothy M. Rawson · Rita O. Oladele · Yohei Doi · Anucha Apisarnthanarak

Received: February 27, 2023 / Accepted: April 20, 2023

ABSTRACT

Despite technological advancements in infectious disease rapid diagnostic tests (RDTs) and use to direct therapy at the per-patient level, RDT utilisation in antimicrobial stewardship programmes (ASPs) is variable across low-to-middle income and high-income countries. Key insights from a panel of seven infectious disease experts from Colombia, Japan, Nigeria, Thailand, the UK, and the USA, combined with evidence from a literature review, were used to assess the value of RDTs in ASPs. From this, a value framework is proposed which aims to define the benefits of RDT use in ASPs, separate from per-patient benefits. Expert insights highlight that, to realise the value of RDTs within ASPs, effective implementation is key; actionable advice for choosing an RDT is proposed. Experts advocate the inclusion of RDTs in the World Health Organization Model List of

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40121-023-00815-z.

L. S. P. Moore (✉)
Clinical Infection Department, Chelsea and Westminster NHS Foundation Trust, 369 Fulham Road, London SW10 9NH, UK
e-mail: l.moore@imperial.ac.uk

L. S. P. Moore
Imperial College Healthcare NHS Trust, North West London Pathology, London, UK

L. S. P. Moore · T. M. Rawson
NIHR Health Protection Research Unit in Healthcare Associated Infections & Antimicrobial Resistance, Imperial College London, London, UK

M. V. Villegas
Grupo de Resistencia Antimicrobiana y Epidemiología Hospitalaria, Universidad El Bosque, Bogotá, Colombia

M. V. Villegas
Molecular Genetics and Antimicrobial Resistance Unit, International Center for Microbial Genomics, Universidad El Bosque, Bogotá, Colombia

E. Wenzler
College of Pharmacy, University of Illinois at Chicago, Chicago, IL, USA

T. M. Rawson
Centre for Antimicrobial Optimisation, Imperial College London, London, UK

R. O. Oladele
Department of Medical Microbiology and Parasitology, College of Medicine, University of Lagos, Lagos, Nigeria

Y. Doi
Department of Infectious Diseases, Fujita Health University School of Medicine, Toyoake, Aichi, Japan

Y. Doi
Department of Microbiology, Fujita Health University School of Medicine, Toyoake, Aichi, Japan

Published online: 01 June 2023

essential in vitro diagnostics and in iterative development of national action plans.

Keywords: Antimicrobial resistance; Antimicrobial stewardship; Antimicrobial stewardship programmes; High-, middle-, and low-income countries; Infectious disease RDT; Point-of-care testing; Rapid diagnostic tests

Key Summary Points

Rapid diagnostic test (RDT) utilisation in antimicrobial stewardship programmes (ASPs) is variable across low-to-middle income and high-income countries.

The 5P (programme support, preserve, practicable, population health, and precision) Value Framework is proposed to enable a wider analysis of the value of RDTs in an ASP beyond per-patient outcome measures.

Effective implementation across a range of resourcing, communication, education, logistic, and interfacing activities is key to maximise RDT adoption.

Experts advocate the inclusion of RDTs in the World Health Organization Model List of essential in vitro diagnostics and in iterative development of national action plans.

Y. Doi
Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

A. Apisarnthanarak
Research Group in Infectious Diseases Epidemiology and Prevention, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand

A. Apisarnthanarak
Division of Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand

INTRODUCTION

Infectious disease rapid diagnostic tests (RDTs) are fast and accurate medical tests used to identify infectious organisms and evaluate antimicrobial susceptibility [1]. RDTs are one of the most important tools the global community can use to preserve the value of antimicrobials [2, 3]. Generally, RDTs are undervalued, as their utility is viewed by their per-patient impact, rather than by the wider societal benefit of faster diagnosis and reduction in onward transmission of communicable diseases [4, 5]. In some way, the coronavirus disease 2019 pandemic has highlighted the global societal value of RDTs and raised awareness of the importance of diagnostic capabilities [6–8]. However, global use of RDTs as part of antimicrobial stewardship programmes (ASPs) remains low [9, 10].

Implementation and use of RDTs in ASPs is associated with multiple clinical benefits; similarly, ASPs play an important role in the effective implementation of RDTs [11]. Thus, ASPs must evolve alongside technological advancements of RDTs and be continually re-evaluated [12]. Goal 3 of the national action plan (NAP) for combating antibiotic-resistant bacteria in the USA calls for the development and use of rapid and innovative diagnostic tests for identification and characterisation of resistant bacteria [13]. Despite increasing recognition and emphasis of the importance of RDTs to ASPs, other NAPs do not include mandates to implement RDTs in ASPs. For example, the NAP for antimicrobial stewardship (AMS) in the UK acknowledges the need for RDTs but does not provide specific recommendations for their use [14].

Whilst the value of novel antimicrobials has recently begun to be reconsidered by recognising wider clinical, societal, and economic impacts [15], similar perspectives on valuing infectious disease RDTs are not as well developed. In this paper, the value of RDTs as part of an ASP, beyond per-patient clinical and cost outcomes, is triangulated through an expert working group (EWG) and synthesis of published literature. The reasons behind the potential underuse of RDTs in ASPs across low-

to-middle income countries (LMICs) and high-income countries (HICs) are also explored.

METHODS

A panel of seven experienced infectious disease physicians, translational pharmacists, academics, and microbiologists from Colombia, Japan, Nigeria, Thailand, the UK, and the USA was identified using a stratified snowball recruitment method. Snowball recruitment is a sampling method where one interviewee provides the name of at least one more potential interviewee. The subsequent interviewee then provides the name of at least one more potential interviewee, and so on [16]. Purposeful selection was used to establish an EWG with representation across low-to-middle and high-income resource settings as well as different global regions. Three experts represented LMICs, including Colombia, Nigeria, and Thailand, and four experts represented HICs including Japan, the UK (two experts), and the USA. Country income levels correspond to classifications determined by the World Bank [17].

A mixed-methods approach was used to capture experiential knowledge from the EWG as well as from published literature. During semi-structured one-on-one interviews, from 26 May 2022 to 12 August 2022, experts provided 'on-the-ground' opinions gained from implementing RDTs, treating patients with suspected infectious disease, and managing ASPs. Experts also guided the search strategy required for a targeted literature review (TLR) to evaluate the clinical and economic outcomes associated with RDT use as part of ASPs.

PubMed was searched from 24 June 2010 to 24 June 2022 using the search terms described in the 'Search Strategy and Selection Criteria' section (Table S1 in the supplementary material). Articles were reviewed using predefined inclusion and exclusion criteria (Table S2 in the supplementary material). Screening stages were conducted by a single expert reviewer, with a 10% check conducted by a second reviewer. Of note, articles were excluded if they did not present data in the context of an ASP or an AMS initiative, such as infectious disease physician support alone. The quality of evidence for outcomes selected for inclusion in this TLR was considered and is described in further detail in the supplementary material.

Results from the literature review were discussed by the EWG during a meeting on 9 September 2022, together with considerations for RDT implementation across a range of hospital settings and global regions. A meeting on 20 October 2022 validated the recommendations in this paper.

Compliance with Ethics Guidelines

This review does not contain any new data with human participants or animals performed by any of the authors.

Search Strategy and Selection Criteria

A combination of keywords was used: ("antimicrobial stewardship" OR "antimicrobial program*" OR stewardship OR program*) AND ("point-of-care testing" OR "rapid diagnostic test" OR "rapid diagnostic" OR "rapid test" OR "rapid antigen" OR "rapid assay" OR RDT); NOT ("immunisation program*" OR "immunization program*"). Non-human study participants and non-English literature were excluded. Grey literature searches were conducted using keyword website searching, including the European Congress of Clinical Microbiology & Infectious Diseases, IDWeek, American Society for Microbiology Microbe, and national Health Technology Assessment sites.

RESULTS AND DISCUSSION

To explore the value and impact of RDTs within an ASP, one must first consider the global definition of an RDT. The EWG agreed that a wide range of definitions exist for 'rapid', varying from 90 min up to 24 h. According to a Delphi Consensus in Asia–Pacific, RDTs should provide results within 4–6 h to determine treatment before administration of the second dose of an antimicrobial [18]. To accommodate a variety of

settings, where this is not possible delivery of results within 24 h may be acceptable [2].

"If we can do [an RDT] from a positive blood culture, get an answer from there in an hour or two, that's a day or two ahead of conventional microbiology… that's rapid."
Clinical Pharmacist in Infectious Diseases, USA

"Whenever you're thinking around the word rapid, you've got to add on front time for transport and back time for result generation onto an IT platform and transmission back to where it can be actioned."
Clinical Fellow in Infectious Diseases, UK

Members of the EWG from HICs noted that some non-molecular tests such as matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) and VITEK®2 may not be regarded as RDTs in some settings, since HICs have access to molecular RDTs that give results within several hours. Whilst 'rapidity' is important, the accuracy, performance, and information provided by the diagnostic test are equally vital characteristics. Moreover, although molecular RDTs add granularity to microorganism identification, they are not used in isolation, and further diagnostic tests are usually needed for phenotypic characterisation to guide antimicrobial prescription. Therefore, a global definition of RDT needs to encompass a multitude of RDT modalities, ever-improving turnaround times, and where the test is conducted [9].

The EWG proposes the following global definition of RDTs for use in ASPs: *Infectious disease RDTs include both microbial and host assays which can be conducted and actioned within a 24 h period that can substantially support ASPs*.

Whilst some regions may not consider biomarkers as RDTs, the EWG agreed that biomarkers of infection are key to both antimicrobial initiation and cessation decision nodes when turnaround time is appropriate. Biomarkers of infection, including C-reactive protein, erythrocyte sedimentation rate, and procalcitonin, help to determine host response and stratify risk of patients with infection. In some LMIC settings, use of RDTs is limited to evaluation of biomarkers.

WHY IS THE GLOBAL USE OF RDTS LOW?

The EWG agreed that global use of RDTs in infection-related management strategies could be increased, particularly the use of molecular RDTs in Africa and the Asia–Pacific region. The EWG outlined several barriers to RDT use across HICs and LMICs (Fig. 1).

Although some biomarkers like procalcitonin and C-reactive protein are included in the World Health Organization (WHO) Model List of essential in vitro diagnostics (EDLs), they are not mandated for use [19]. The LMIC representatives of the EWG advocated for the inclusion of non-molecular RDTs and other biomarkers in the WHO Model List of EDLs [19]. Furthermore, insufficient quality of evidence has resulted in a general lack of guidance from professional societies and guidelines. For example, the updated Infectious Diseases Society of America guidelines for AMS make a weak recommendation for ASPs to advocate RDTs for bloodstream infections (BSIs) as a result of moderate-quality evidence [20]. Additionally, RDTs are perceived as expensive compared to non-rapid laboratory-based diagnostic assays [21].

"In our day-to-day practice, it's almost exclusively culture based for the majority of infections."
Infectious Diseases Physician and Clinical Microbiologist, UK

"Right now, most of the RDTs need to be confirmed by conventional methods, which means additional time and costs."
Professor of Infectious Diseases, Japan

Providers tend to prioritise antimicrobial prescriptions over diagnostic testing, and such prescribing behaviours can be entrenched and resistant to change [22]. Generally, RDTs are complementary to conventional culture-based methods [23, 24]. RDTs help provide information more quickly and allow changes to be made sooner but do not yet replace traditional

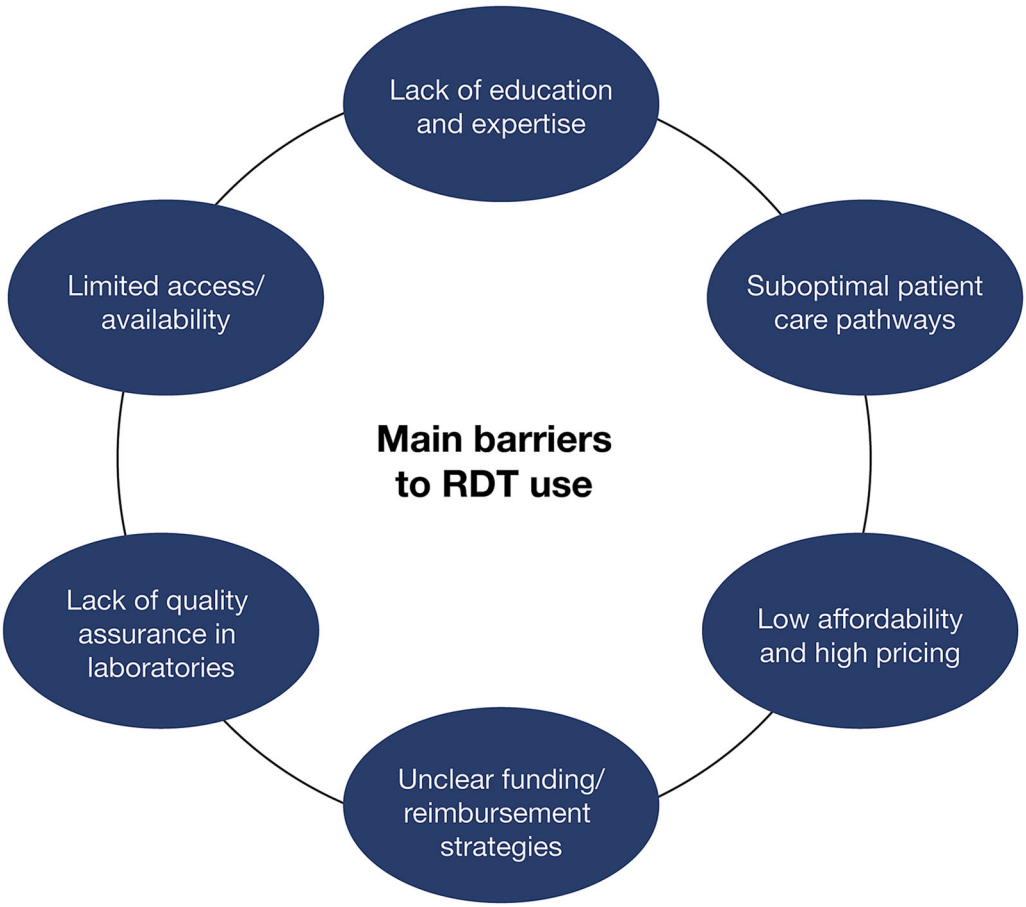

Fig. 1 Main barriers to use of RDTs, derived from EWG semi-structured interviews. *EWG* expert working group, *RDT* rapid diagnostic test

culture-based methods which are considered the 'gold standard' for detection of many infectious pathogens and crucial for determining antimicrobial susceptibility. Using both techniques requires more human resources and incurs additional costs.

> *"Due to the National Insurance programme [in Thailand], patients pay $1 and can be admitted to hospital for any treatment]; in that situation, the hospital tries to limit tests."*
> *Professor and Chief of Infectious Diseases, Thailand*

> *"The system we have [in Japan] where AMS activities are reimbursed is fairly unique. The national insurance pays us a fixed amount per patient to do AMS and we use that money to run the programmes. There is the possibility to pay for some [RDTs] out of this of funding. This could be a model for steady support for activities and testing [elsewhere]."*
> *Professor of Infectious Diseases, Japan*

> *"Patients pay out of pocket for healthcare [in Nigeria]. Cost affects availability. Clinicians tend to think that the patient needs to buy the drugs first… How do you know this [patient] needs this antibiotic? It's a behaviour that will need to change…"*
> *Associate Professor, Nigeria*

Reimbursement models differ significantly in each country, and these policies impact RDT use. Although overall costs are typically higher for molecular RDTs than for non-molecular RDTs, in 2020, state-based government insurance reimbursement rates for a molecular RDT were higher than for a non-molecular RDT in Georgia, USA [25]. The additional cost of

molecular testing may be offset by lower costs associated with appropriate prescribing and decreased time of performing cultures [25]. However, such cost savings are not commonly redirected to the laboratory that initially invested capital to purchase the RDT, resulting in disconnected cost silos.

WHAT VALUE DO RDTS BRING TO AMS?

The value of RDTs was explored via the TLR and discussed by the EWG. The following results summarise the data identified from the TLR. The searches retrieved 1829 articles and conference abstracts. Of these, 69 reported clinical and economic outcome data recorded in hospital or long-term care facility patients with suspected infection tested with any RDT as part of an ASP or an AMS initiative. Full details are shown in Fig. S1 in the supplementary material. Most data were from retrospective and observational studies (n = 39) and randomised controlled trials (RCTs) were scarce (n = 4) (Fig. S2 in the supplementary material). There was a gap in globally representative data, with most published research focused on the USA. Additionally, almost all studies reported RDT use for suspected BSIs. The overall quality of the evidence for outcomes selected for inclusion in this review was rated low using an objective assessment (see Tables S4–S7 in the supplementary material).

Reduced Mortality

Many studies identified in the TLR reported infection-related and all-cause mortality across a variety of time points including 7-, 15-, 28-, 30-, and 60-day mortality. Of these, four quasi-experimental studies and two retrospective studies demonstrated that RDTs plus ASPs were associated with improved all-cause 30-day mortality compared with conventional or standard-of-care interventions [26–31]. For example, MALDI-TOF combined with antimicrobial susceptibility testing (AST) intervention significantly decreased time to organism identification and was associated with a significant reduction in 30-day all-cause mortality (12.7% vs. 20.3%, p = 0.021), when retrospectively compared to conventional identification methods [27]. However, two RCTs and three quasi-experimental studies did not demonstrate an additional benefit of RDT use on 30-day mortality [32–36].

Improved AMS Metrics

AMS metrics may be indirectly positive for patients but not directly associated with clinical (morbidity or mortality) impact; outcomes related to AMS were highly variable across the literature review. Overall, studies demonstrated a reduction in time to optimal therapy [27, 29, 37–44] and time to effective therapy following an RDT plus an ASP [27,37, 40–44].

Five studies (one RCT [33], three retrospective studies [38, 45, 46], and one quasi-experimental study [47]) demonstrated significant reductions in time to de-escalation following RDT plus ASP intervention when compared to conventional diagnostic methods. Only three studies (one RCT [33] and two retrospective studies [38, 46]) demonstrated significant reductions in time to escalation following RDT plus ASP intervention. One quasi-experimental study [34] and one retrospective study [45] demonstrated a numerical reduction in time to escalation following RDT plus ASP, and both state that ASP intervention was only performed on weekdays.

Decreased Length of Stay

Twelve studies identified in the TLR showed that RDTs combined with ASPs were associated with significant decreases in hospitalisation and/or intensive care unit (ICU) length of stay (LOS) [27, 28, 35, 40, 42, 43, 46, 48–52]. In a retrospective study, use of Gram-negative blood culture test (BC-GN) plus an active ASP intervention was associated with a significant decrease in hospital LOS (7 vs. 9 days [interquartile range 5–15 vs. 4.5–21], p = 0.001), when compared to the preintervention group [46]. LOS was the most common economic

outcome identified in the targeted literature review; however, despite a general trend towards reduced LOS after RDT intervention in ASPs, most findings were not significant. This may be due to factors such as study design, e.g. an underpowered study; only looking at intensive care units where infection may not be the only issue governing LOS; or inappropriate population selection.

Other commonly reported economic outcomes included internal hospital costs and hospital readmission rates. Although economic outcomes were reported across most studies identified, only two were economic models [24,53]. Most data and methodology utilised could not demonstrate a direct economic benefit of RDT use, which may be due to the study design, e.g. if ASP metrics were not included as primary outcomes. Whilst some savings can be made by reducing antibiotic use, it was noted that RDTs are expensive to implement and use as an adjunct.

Cost-Effectiveness

In a cost-effectiveness analysis of competing strategies for the diagnosis of BSI alone or combined with an ASP, molecular RDTs were determined to be cost-effective for the diagnosis of patients with suspected BSI [24]. The economic model compared the cost-effectiveness of different strategies used for the identification of bacterial organisms and/or the presence of antibiotic resistance among these patients. MALDI-TOF plus an ASP was the most cost-effective strategy, resulting in savings of $29,205 per quality-adjusted life year (QALY) and preventing one death per 14 patients with suspected BSI, compared to conventional laboratory methods without an ASP (incremental cost-effectiveness ratio [ICER], − $29,205/QALY) [24]. Other cost-effective options included BC-GN plus an ASP (ICER, − $23,587/QALY) and polymerase chain reaction plus an ASP (ICER, − $19,833/QALY); RDT alone without ASP was not cost-effective [24].

Another study assessed the cost-effectiveness of treating malaria based on microscopy, RDT, or presumptive diagnosis as part of a malaria control programme in Uganda. Malaria RDTs (primarily histidine-rich protein II-based tests) were conducted in healthcare centres with no laboratory infrastructure [53]. Overall, malaria RDTs were the most cost-effective with the lowest ICER (US $5.0), compared to microscopy (US $9.61 per case correctly diagnosed and treated) [53]. Malaria RDTs were cost-effective in both low- and high-transmission settings [53].

The EWG noted that economic analyses are important and must consider the broader ASP in the local area. Cost benefits of RDT use are difficult to translate across settings, and most available economic evidence is not applicable to LMICs.

Nine studies identified in the TLR suggest that RDTs plus ASPs are associated with reduced hospital costs [30, 42, 43, 54–58]. One study evaluated total hospital costs following MALDI-TOF implementation and dedicated pharmacy stewardship personnel time [30]. Data used in the cost analysis were derived from patients; and factors considered included the cost of RDT implementation, the cost of pharmacist and microbiology technologist time, laboratory costs, and costs associated with LOS. As a result of MALDI-TOF implementation and ASP pharmacy stewardship, total hospital costs decreased by $2439 per BSI, giving an approximate annual cost saving of $2.34 million [30].

Overall, most studies in the TLR indicated that RDTs have a positive impact on AMS metrics, but not on clinical outcomes such as mortality. A wide variety of AMS metrics were reported, including time to optimal therapy, time to effective therapy, time to escalation, and time to de-escalation. Future studies, including RCTs, with more rigorous designs (e.g. higher statistical power, or with primary outcomes focused on key AMS metrics and clinical outcomes) are needed to better capture the impact and evaluate the value of RDTs in ASPs. Demonstrating outcomes not only at the individual level but also at the population level requires studies developed in collaboration with many stakeholder organisations, clinical and physician societies, and government groups [5].

VALUE BENEFITS OF RDT USE IN ASPS

Reflecting the themes derived above, to define the value of RDT use, the EWG proposed five aspects of value benefits of RDT use in an ASP, as part of the 5P (programme support, preserve, practicable, population health, and precision) framework (Table 1). The value framework for RDTs was modelled on the STEDI (spectrum, transmission, enablement, diversity, and insurance) principles, which were used as the evaluation framework for the de-linkage pilot in England, and re-valued infection therapies [59,60]. The proposed 5P framework will allow future wider analysis of the value of RDTs in an ASP beyond per-patient outcome measures.

Table 1 5P framework: value benefits of RDT use in an ASP

Value	Definition of benefit
Programme support	Enable specific ASP interventions and provision of meta-data for delineating ASP outcome KPIs
Preserve	Quantifiable changes in antimicrobial consumption, appropriateness of antimicrobial prescriptions, and potential antimicrobial resistance
Practicable	Impact on laboratory and clinical area sample flow (including logistics, information technology, and personnel) and patient flow (including admission avoidance, and length of stay) across LMIC and HIC settings
Population health	Quantifiable impact on population health through both impact on infection transmission and speed of return to work
Precision	Evaluable test performance characteristics which may supersede existing traditional laboratory 'gold standard' diagnostics

ASP antimicrobial stewardship programme, *HIC* high-income country, *KPI* key performance indicator, *LMIC* low- to middle-income country, *RDT* rapid diagnostic test

Across both HICs and LMICs, the EWG agreed that RDTs bring value to ASPs and aid in the fight against antimicrobial resistance and clinically challenging pathogens. Even where RDTs are not widely available, there is value seen in diagnostics in general as they aid surveillance and provide epidemiological data [61]. Beyond the clinical and economic value described in the literature, the EWG recognised a broader impact and value of RDT use in ASPs to a variety of stakeholders including hospitals, clinicians, patients, and wider society (Fig. 2).

EFFECTIVE IMPLEMENTATION IS KEY TO REALISE THE VALUE OF RDTS IN ASPS

In this section, opinions from the EWG were combined with supporting data from the literature.

> *"We have all these very nice gadgets and tools which we can implement. But we've learned from our experience in terms of trying to develop and implement technology that you can't force these into someone's decision-making pathway. They must be developed and designed to fit in with current processes in a way that isn't burdensome on the end user."*
> *Clinical Fellow in Infectious Diseases, UK*

To achieve optimal antimicrobial use, RDTs must be used to facilitate decision-making at various stages of the clinical pathway, i.e. antimicrobial initiation, on-treatment, and de-escalation [18]. Use of RDTs as part of bundled interventions that support decision-making is key. Generally, experts acknowledge molecular RDTs to be most valuable in the initiation phase of the patient care pathway (Fig. 3). Early, safe de-escalation of antimicrobials based on RDT results can also play an important role in ASPs by reducing antimicrobial consumption [34,38,45–47].

> *"[RDTs] bring a lot of clinical benefits of course because they can make a quick diagnosis, especially in the ICU. It's very important*

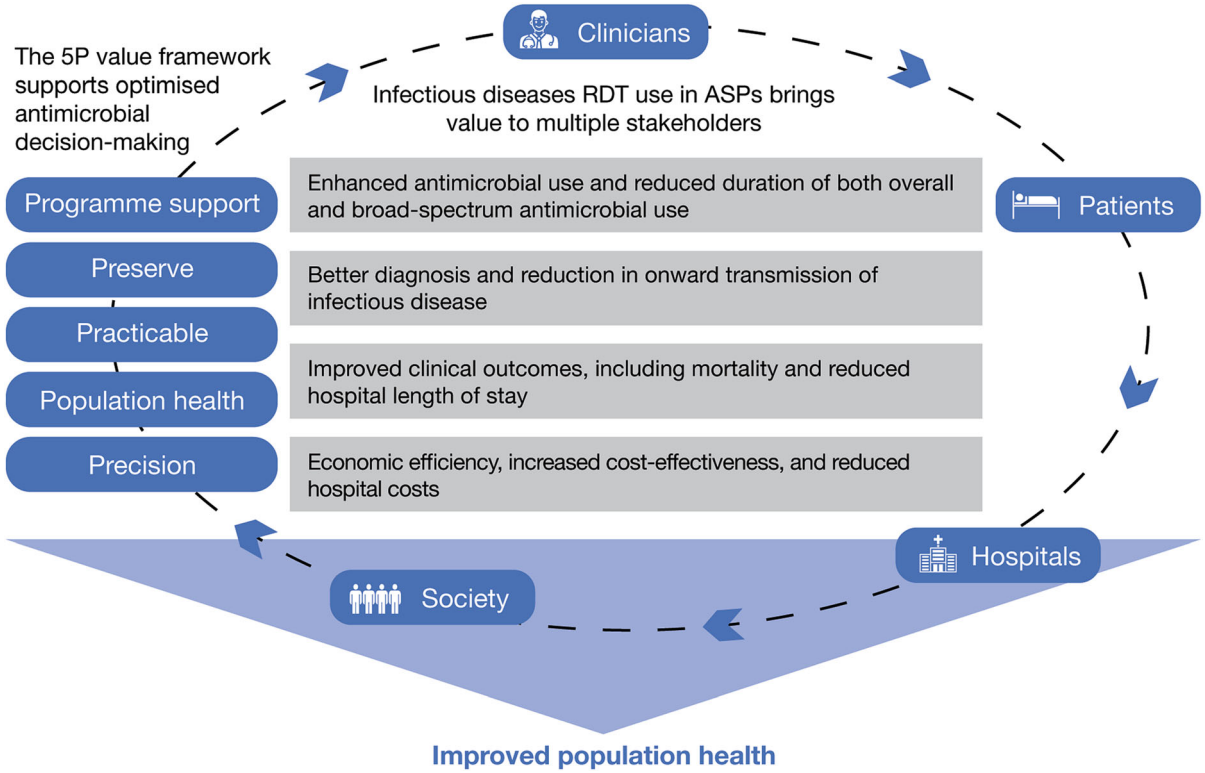

Fig. 2 The value of RDT use in ASPs to key stakeholders: hospitals, clinicians, patients, and society. *AMS* antimicrobial stewardship, *ASP* antimicrobial stewardship programme, *RDT* rapid diagnostic test

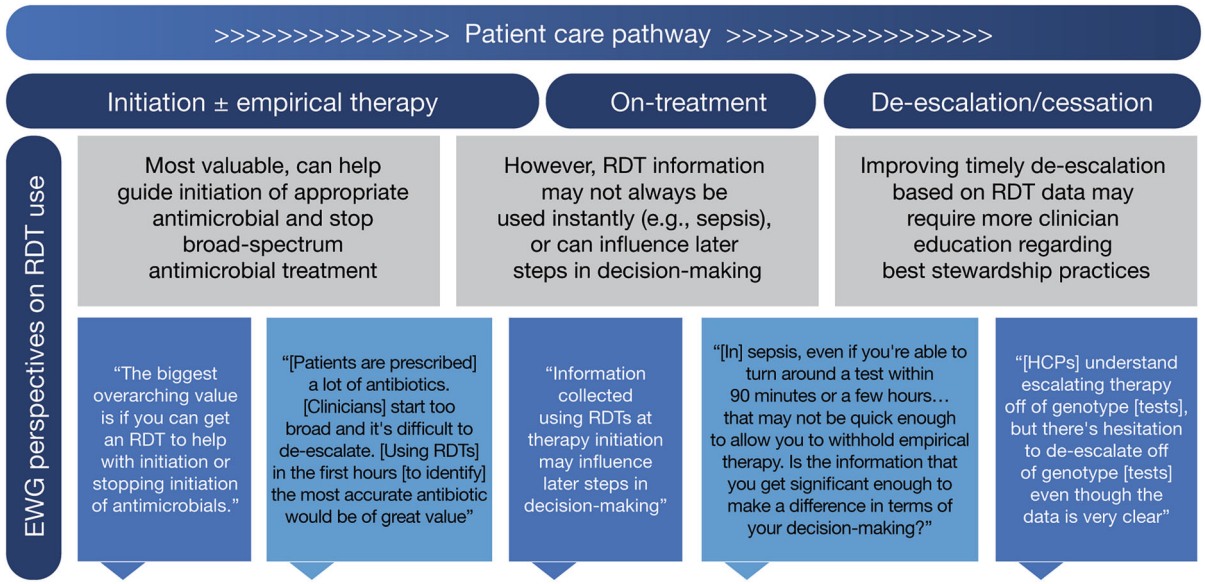

Fig. 3 EWG perspectives on RDT use across the patient care pathway. *EWG* expert working group, *HCP* healthcare professional, *RDT* rapid diagnostic test

to start with the right antibiotic, the right one will decrease mortality."
Scientific Advisor, Colombia

Implementation requires more than the provision of the test: it requires support and training, ensuring the test fits within the clinical decision-making pathway and ASP, and the provision of available resources including staff and laboratory capabilities. Successful implementation in both LMICs and HICs is dependent on five main aspects: communication, resources, justification, education, and behaviour.

Communication

Alongside physicians and pharmacists trained in infectious disease, the EWG recognised the importance of the microbiology laboratory and information technology staff in the implementation of RDTs within ASPs. Close communication between the laboratory and the ASP team results in savings which can offset the added RDT cost [51].

"If you implement an RDT [but] don't have the support staff from stewardship to do the active intervention, and [call] providers and translate outputs, you might as well not even have [that RDT]. That's where a lot of people struggle even if they can afford to bring in the test."
Clinical Pharmacist in Infectious Diseases, USA

Resources and Justification

The EWG reinforced that each region is affected by different economic development levels and infrastructure and therefore RDT implementation is specific to each setting. When considering resources, this should be based on prioritisation of areas of greatest ASP impact or improvement within that setting. Achieving this requires effective utilisation of hospital and laboratory data to help prioritise ASP goals.

"Our intensive care colleagues are really interested in these types of tools and there is a willingness to engage with them. It becomes a business case [to] demonstrate the benefit."
Infectious Diseases Physician and Clinical Microbiologist, UK

"Studies of cost-effectiveness [are needed] to try to show the administrators how important [RDTs] are [alongside] the ASP."
Scientific Advisor, Colombia

At the national level, country-specific economic models can help to justify and guide decision-making processes regarding RDT use. For example, a cost-effectiveness analysis conducted from a Brazilian Public Health System perspective, used data on direct medical costs to evaluate molecular RDTs to diagnose methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant Gram-negative bacteria (CRGNB), and vancomycin-resistant *Enterococcus* spp. (VRE) [62]. Although the model did not evaluate RDT use as part of ASPs, complementary use of molecular RDTs and conventional methods were shown to be more cost-effective than conventional methods alone for the detection of antimicrobial drug-resistant bacteria in BSI [62].

Education and Behaviour

More education and training of clinical teams outside infectious disease specialties is needed to increase awareness and optimal use of RDTs.

"Awareness should be driven among clinicians to know that [RDTs] are available. A lot of doctors were taught in medical school about biomarkers. They've never seen them. Their labs don't have them, so they don't request them, and they've forgotten about them."
Associate Professor, Nigeria

"I would say that education is key. Some [hospitals] have [RDTs], but [clinicians] try not to use them very often. Many physicians don't know how to use them."
Scientific Advisor, Colombia

"There is no expertise to help with the interpretation of the results with some diagnostics."
Professor and Chief of Infectious Diseases, Thailand

Diagnostic stewardship must be incorporated in ASPs to guide the use of RDTs in the patient pathway and to support interpretation of RDT results. ASP-supported interpretation of RDT results helps expediate antimicrobial therapy optimisation and decrease broad-spectrum antimicrobial use for several organisms. Some studies indicate that procalcitonin guidance can reduce duration of treatment and daily defined dose (DDD) and is associated with significant decreases in mortality [63,64].

RDT SELECTION AND IMPLEMENTATION

Here, the EWG outline approaches for RDT selection and implementation in ASPs. When deciding which RDTs should be implemented, ASP teams should consider the prevalent or problematic organisms within their hospital setting, as well the sensitivity and specificity of each test [23]. The EWG compiled a checklist to facilitate hospital RDT implementation in any hospital setting and geographical region (Table S3 in the supplementary material). Experts agreed on the imporance of considering existing interventions and processes that the candidate RDT can complement. Microbiologist-validated RDT instruments should be used, and laboratory staff should guide discussions on implementation of RDTs and new AST interpretive criteria [23, 65]. Test location, i.e. at point of care versus in the laboratory, impacts the governance of test use as well as internal and external quality assurance. Ultimately, this determines who runs the test, who pays for the test, and who oversees the quality assurance of the test [25].

The ASP team and microbiology laboratory must elucidate RDT processes within local protocols and algorithms, detailing what RDT to perform, where to send specimens, and how to respond to RDT results [25, 43]. Thus, total process efficiency is key to effective implementation. This includes end-to-end efficiency from the moment a test is ordered, through to specimen collection, testing in the lab, and communication of the result outside the lab that will impact or change patient care. If a hospital is expecting value from an RDT, the hospital must make sure there is nothing that negates that value in the workflow, such as process inefficiencies. To aid RDT selection in any hospital setting and geographical region, the EWG summarised the main implementation factors for each RDT, ordered by lowest to highest sophistication (Table 2).

The EWG agreed that robust RDT post-implementation follow-up processes are required to ensure adoption upon implementation. ASPs must document clinical and economic outcomes associated with each RDT and consequent impact on patient care [36, 65]; the 5P approach enables a whole-healthcare economy lens through which to make these evaluations. Hospitals and long-term healthcare facilities must establish key performance indicators (KPIs) to measure RDT effectiveness [18].

> *"It is important to tailor [KPIs] to what you can accomplish [in your setting]. For example, maybe you have overuse of vancomycin [in your setting] and that's your main target. [This] makes data a little easier to collect."*
> *Clinical Pharmacist in Infectious Diseases, USA*

Most hospitals focus on easily accessible pharmacy metrics, i.e. DDD, concordance with policy, concordance with AST results, and time to effective antimicrobial therapy. However, these KPIs can be harder to extract in some settings and the most appropriate KPI for each ASP is dependent on the capabilities on the resources of the setting. In hospitals with minimal ASPs, a focus for the laboratory could be turnaround time, whereas a setting with advanced ASP may be able to focus on hospital level outcomes and data collated for LOS and mortality. Moreover, KPIs must reflect effectiveness of RDTs against local data [18, 69]. The combination of passive guidance through evidence-based institutional guidelines, active monitoring, and feedback of prescribing patterns by ASP teams, as well as real-time data, can improve local antimicrobial management [47].

Table 2 RDT selection and implementation factors

Technology type	Global use[a]	Implementation factors
Biomarker e.g. procalcitonin, CRP, ESR	High	Biomarkers are useful in both HICs and LMICs. Procalcitonin suggests whether a patient has a bacterial infection versus a viral infection. Biomarkers can reduce antibiotic prescribing for respiratory infections but not for other issues like pharyngitis
Antigen test e.g. PBP2a, CrAg® LFA, Tb-LAM Ag	High	Lateral flow assays benefit both HICs and LMICs owing to their compact size and low upfront cost. PBP2a antigen testing can be used to detect methicillin resistance in *S. aureus* [66]. Some antigen tests can be provided near the patient. Most have high specificity rates and lower sensitivity rates, and therefore a high number of false negatives
Biochemical chromogenic assay e.g. RAPIDEC® Carba NP	Low	Carba NP can be useful in resource-limited regions or LMICs without access to or expertise in molecular RDTs. Carba NP is reliable for detection of carbapenemase activity from species of *Enterobacterales* and *Pseudomonas aeruginosa* [67]. Carba NP allows for fast screening and easy handling as well as optimal performance to detect carbapenemase-producing bacteria; however, subtle colour changes can be missed during analysis of results
Automated identification/AST e.g. VITEK®2, BD Phoenix™	High	Automated identification and antimicrobial susceptibility systems are accessible to both LMICs and HICs. VITEK®2 can be used for AST in combination with MALDI-TOF (for organism identification) in a centralised laboratory, resulting in significantly shorter LOS and significantly shorter length of antimicrobial therapy [48]. This technology is automated and compact. It can estimate resistance in Gram-negative and Gram-positive bacteria, and can detect ESBL-producing strains. The biggest advantage of this technology is its ability to provide phenotypic, as opposed to genotypic, information for which translation of resistance markers is needed
Mass spectrometry (MALDI-TOF) e.g. Vitek MS®, Microflex®	Intermediate	MALDI-TOF can be useful in resource-limited regions or LMICs. Generally, HICs have access to molecular RDTs producing results within several hours. The integration of MALDI-TOF MS with AST, and near-real-time AMS practices for patients with Gram-negative BSIs can significantly improve time to optimal therapy [42]. MALDI-TOF detects both bacterial and fungal microbes and is useful in settings with many uncommon infections. Direct analysis is performed on biological samples. For now, MALDI-TOF does not detect resistance mechanisms, but promising studies are emerging. Moreover, MALDI-TOF cannot provide susceptibility reports

Table 2 continued

Technology type	Global use[a]	Implementation factors
PCR e.g. Verigene® System, ePlex system, BIOFIRE® FilmArray® System	Intermediate	PCR is an established and useful technology in both HICs and LMICs, but high upfront costs can limit its use in more rural regions of LMICs. PCR is well suited to detect the presence or absence of resistance genes. However, PCR is less suited for detection of point mutations within target genes. Multiplex PCR can detect several resistance genes simultaneously. The VERIGENE® System, ePlex system, and BIOFIRE BCID2 can detect key Gram-negative resistance markers. Dependent on the platform, a comprehensive number of targets can be tested, including bacteria, viruses, and fungi. Panels can be used to provide pathogen-specific results. BIOFIRE® FilmArray® Pneumonia Plus tests for pneumonia and other lower respiratory tract infections
NMR e.g. T2MR, T2Candida	Low	NMR technologies are currently limited to some centres in HICs. Traditional blood cultures are the gold standard for the diagnosis of candidemia, but these take 2–3 days for results and require further species identification. T2MR has a short turnaround time of 8 h and supports safe early discontinuation of empiric antifungal therapy in ICU patients with suspected candidemia [68]. T2 systems have a rapid turnaround time and can use blood specimens directly. De-escalation is possible with negative results

AST antimicrobial susceptibility testing, *BCID2* blood culture identification 2, *BSI* bloodstream infection, *CRP* C-reactive protein, *ESBL* extended-spectrum beta-lactamase, *ESR* erythrocyte sedimentation rate, *EWG* expert working group, *HIC* high-income country, *ICU* intensive care unit, *LMIC* low-to-medium income country, *LOS* length of stay, *MALDI-TOF* matrix-assisted laser desorption/ionisation time-of-flight, *MS* mass spectrometry, *NMR* nuclear magnetic resonance, *PBP2a* penicillin-binding protein 2a, *PCR* polymerase chain reaction, *RDT* rapid diagnostic test, *T2MR* T2 magnetic resonance

[a]Global use is defined as use across HICs and LMICs and was determined by EWG feedback. High = $\geq$ 5 experts across HICs and LMICs reported use of RDTs in their setting; intermediate = three or four experts across HICs and LMICs reported use of RDTs in their setting; and low = $\leq$ 2 experts reported use of RDTs in their setting

FUTURE DIRECTIONS

The EWG discussed that, to realise the true impact of RDTs on ASPs, there needs to be investment in appropriately designed studies (e.g. ASP metrics as primary outcomes) which are adequately powered to evaluate this impact. The EWG have identified the following areas for focus: more robust clinical studies in a range of non-academic or community-based settings; larger studies that capture representative patients; targeted cost-effectiveness studies in a range of geographical locations; and studies to investigate the value of RDTs to ASPs and wider society.

LIMITATIONS AND STRENGTHS

This work has some limitations. Firstly, the EWG was represented by one expert per country across selected HICs and LMICs (except for the UK which was represented by two experts).

Although the EWG was recruited from a variety of geographical regions, within each region there remains a high degree of intercountry variability. Therefore, the views expressed in the EWG may not be representative of all possible issues around RDT use in ASPs in each country. Secondly, snowball recruitment for selecting group members may risk exclusion of experts with alternative views. This was mitigated by one-on-one interviews that enabled group members to provide independent opinions before validating a consensus during EWG meetings. Thirdly, the targeted literature review results are based on a single database (PubMed) and were developed to capture articles reporting clinical or economic data covering RDT use within an ASP, and therefore studies without programmes or AMS initiatives were not included. In addition, the majority of the literature identified in the TLR is based on evidence in HICs, which has implications for the applicability of findings to LMICs. The EWG are aware that additional studies exist investigating biomarkers as RDTs; however, biomarkers are often not identified as RDTs within the literature. All literature was limited to English language, thus excluding literature from non-English speaking regions.

CONCLUSION

Experts across HICs and LMICs agree that RDTs have significant potential to bring substantial value to patients, clinicians, ASPs, healthcare providers, and wider society. However, supporting published evidence, at least for perspectives beyond just the per-patient impact, remains sparse. Results from this review indicate that published evidence for the clinical and economic value of RDT use in ASPs is weighted towards BSIs in the USA; more evidence must be generated across other disease areas and regions. The use of RDTs is low across HICs and LMICs, and a lack of setting-specific clinical and economic outcome data is a key barrier to RDT uptake. A wider evidence base, combined with robust clinical and economic outcome data, is needed to drive uptake of RDTs. Moreover, effective implementation across a range of resourcing, communication, education, logistic, and interfacing activities is key to maximise RDT adoption. The EWG developed an evaluation framework through which the value of RDTs in an ASP may be more optimally realised than per-patient outcomes only. This paper is a call to action for global stakeholders (i.e. clinicians, laboratory staff, hospital administrators, payers, and policymakers) to:

- Raise awareness of RDTs available in their setting and maintain close communication with both the ASP team and the microbiology laboratory personnel.
- Provide and share practical support, training, and resources to facilitate uptake and effective implementation of RDTs in their setting.
- Encourage the use of RDTs in national reimbursement models, and provide recommendations on RDT use in NAPs and the WHO Model List of EDL.

ACKNOWLEDGEMENTS

Funding. The one-to-one interviews were funded by bioMérieux, Marcy-l'Étoile, France. The study sponsor funded the journal's Rapid Service Fee. The study sponsor had no role in study design, data collection, analysis, or preparation of the manuscript. No payments or honoraria were made to the authors in respect of manuscript preparation.

Medical Writing and Editorial Assistance. Writing and editorial support was provided by Anna L. McCormick, PhD, Cecilia R. F. Silva, MSci, and Rachael M. Kershaw, PhD from Prime Access (Prime Global) and funded by bioMérieux.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors contributed to the study design. Material preparation, data collection and analysis were performed by Anna L. McCormick, Cecilia R. F. Silva, and Rachael M. Kershaw in collaboration with Anucha Apisarnthanarak, Eric Wenzler, Luke S. P. Moore, Maria Virginia Villegas, Rita O. Oladele, Timothy M. Rawson and Yohei Doi. Medical writing support was provided by Cecilia R. F. Silva, Rachael M. Kershaw and Anna L. McCormick. All authors contributed to the development of the manuscript and approved the final manuscript.

Disclosures. Luke S. P. Moore has consulted for or received speaker fees from bioMerieux (2013–2022), Pfizer (2018–2022), Eumedica (2016–2022), Kent Pharma (2021), Umovis Lab (2020–2021), Shionogi (2021–2022), Pulmocide (2021), Sumitovant (2021–2022), and received research grants from the National Institute for Health Research (2013–2022), CW+ Charity (2018–2022), Infectopharm (2022), and LifeArc (2020–2022).Anucha Apisarnthanarak declares no competing interests.Eric Wenzler reports grants from Qiagen and Shionogi Inc (research grant paid to institution), and personal fees from Abbvie Inc, Ferring Pharmaceuticals, Qiagen, Melinta Therapeutics, Astellas Pharma and Venatorx Pharmaceuticals.Maria Virginia Villegas reports grants from Pfizer and bioMerieux, personal fees from Pfizer, MSD and bioMerieux and support for meetings from Pfizer and bioMerieux.Rita O. Oladele declares no competing interests.Timothy M. Rawson reports personal fees from bioMeriuex, Roche Diagnostics Ltd and Pfizer.Yohei Doi reports personal fees from Gilead Sciences, MSD, GSK, Shionogi, Meiji Seika Pharma, Moderna, bioMerieux, Chugai, FujiFilm, MSD and Eiken Chemical.

Compliance with Ethics Guidelines. This review does not contain any new data with human participants or animals performed by any of the authors.

Data Availability. The data supporting the content of this review is from publicly available sources. Some of the articles are from journal sites that require paid access and are not freely available.

REFERENCES

1. Beganovic M, McCreary EK, Mahoney MV, Dionne B, Green DA, Timbrook TT. Interplay between rapid diagnostic tests and antimicrobial stewardship programs among patients with bloodstream and other severe infections. J Appl Lab Med. 2019;3:601–16.

2. O'Neill J. Tackling Drug-resistant infections globally: final report and recommendations. 2016. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf. Accessed 14 May 2022.

3. World Health Organization. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit. 2019. https://apps.who.int/iris/handle/10665/329404. Accessed 18 May 2022.

4. Årdal C, Outterson K, Hoffman SJ, et al. International cooperation to improve access to and sustain effectiveness of antimicrobials. Lancet. 2016;387:296–307.

5. Miller MB, Atrzadeh F, Burnham CA, et al. Clinical utility of advanced microbiology testing tools. J Clin Microbiol. 2019;57:e00495–e519.

6. Álvarez-Moreno C, Valderrama-Beltrán S, Rodriguez-Morales AJ. Implications of antibiotic use during the COVID-19 pandemic: the example of associated antimicrobial resistance in Latin America. Antibiotics. 2021;10:328.

7. Callejas D, Echevarría JM, Carrero Y, Rodríguez-Morales AJ, Moreira R. The SARS-CoV-2 pandemic in Latin America: the need for multidisciplinary approaches. Curr Trop Med Rep. 2020;7:120–5.

8. Wachinger J, McMahon SA, Lohmann J, de Allegri M, Denkinger CM. Highly valued despite burdens: qualitative implementation research on rapid tests for hospital-based SARS-CoV-2 screening. SSM Qual Res Health. 2022;2: 100140.

9. Apisarnthanarak A, Kim HB, Moore L, et al. Rapid diagnostic testing for antimicrobial stewardship: utility in Asia Pacific. Infect Control Hosp Epidemiol. 2021;42(7):864–8.

10. White BP, Barber KE, Chastain DB. Variation among infectious diseases pharmacists for the treatment of *Staphylococcus aureus* bacteremia. J Pharm Pract. 2021. https://doi.org/10.1177/08971900211038864.

11. Lam SW, Bass SN. Advancing infectious diseases diagnostic testing and applications to antimicrobial therapy in the ICU. J Pharm Pract. 2019;32:327–38.

12. Minejima E, Wong-Beringer A. Implementation of rapid diagnostics with antimicrobial stewardship. Expert Rev Anti Infect Ther. 2016;14:1065–75.

13. Office of the Assistant Secretary for Planning and Evaluation. National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020–2025. United States: Assistant Secretary for Planning and Evaluation. 2020. https://aspe.hhs.gov/sites/default/files/migrated_legacy_files//196436/CARB-National-Action-Plan-2020-2025.pdf. Accessed 23 Nov 2022.

14. UK Government. Tackling antimicrobial resistance 2019 to 2024: the UK's 5-year national action plan. UK Government. 2019. https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024. Accessed 14 Nov 2022.

15. Boucher HW, File TM, Fowler VG, Jezek A, Rex JH, Outterson K. Antibiotic development incentives that reflect societal value of antibiotics. Clin Infect Dis. 2021;72:e420–1.

16. Kirchherr J, Charles K. Enhancing the sample diversity of snowball samples: recommendations from a research project on anti-dam movements in Southeast Asia. PLoS ONE. 2018;13: e0201710.

17. The World Bank. The world by income and region. 2021. https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html. Accessed 22 Mar 2023.

18. Apisarnthanarak A, Bin-Kim H, Moore LSP, et al. Utility and applicability of rapid diagnostic testing in antimicrobial stewardship in the Asia-Pacific region: a Delphi consensus. Clin Infect Dis. 2022;74:2067–76.

19. World Health Organization. The selection and use of essential in vitro diagnostics. 2021. https://www.who.int/publications/i/item/9789240019102. Accessed 14 Nov 2022.

20. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51–77.

21. National Institute for Health and Care Excellence. Rapid tests for group A streptococcal infections in people with a sore throat. NICE. 2019. www.nice.org.uk/guidance/dg38. Accessed 6 July 2022.

22. Hellyer TP, McAuley DF, Walsh TS, et al. Biomarker-guided antibiotic stewardship in suspected ventilator-associated pneumonia (VAPrapid2): a randomised controlled trial and process evaluation. Lancet Respir Med. 2020;8:182–91.

23. PAN American Health Organization. Recommendations for implementing antimicrobial stewardship programs in Latin America and the Caribbean: manual for public health decision-makers. Florida International University; 2018.

24. Pliakos EE, Andreatos N, Shehadeh F, Ziakas PD, Mylonakis E. The cost-effectiveness of rapid diagnostic testing for the diagnosis of bloodstream infections with or without antimicrobial stewardship. Clin Microbiol Rev. 2018;31:e00095-e117.

25. Thompson TZ, McMullen AR. Group A streptococcus testing in pediatrics: the move to point-of-care molecular testing. J Clin Microbiol. 2020;58: e01494-e1519.

26. Eby JC, Richey MM, Platts-Mills JA, Mathers AJ, Novicoff WM, Cox HL. A healthcare improvement intervention combining nucleic acid microarray testing with direct physician response for management of *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2018;66:64–71.

27. Huang AM, Newton D, Kunapuli A, et al. Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention

in adult patients with bacteremia and candidemia. Clin Infect Dis. 2013;57:1237–45.

28. Mahrous AJ, Thabit AK, Elarabi S, Fleisher J. Clinical impact of pharmacist-directed antimicrobial stewardship guidance following blood culture rapid diagnostic testing. J Hosp Infect. 2020;106:436–46.

29. Nagel JL, Huang AM, Kunapuli A, et al. Impact of antimicrobial stewardship intervention on coagulase-negative Staphylococcus blood cultures in conjunction with rapid diagnostic testing. J Clin Microbiol. 2014;52:2849–54.

30. Patel TS, Kaakeh R, Nagel JL, Newton DW, Stevenson JG. Cost analysis of implementing matrix-assisted laser desorption ionization-time of flight mass spectrometry plus real-time antimicrobial stewardship intervention for bloodstream infections. J Clin Microbiol. 2017;55:60–7.

31. Walker T, Dumadag S, Lee CJ, et al. Clinical impact of laboratory implementation of verigene BC-GN microarray-based assay for detection of gram-negative bacteria in positive blood cultures. J Clin Microbiol. 2016;54:1789–96.

32. Banerjee R, Komarow L, Virk A, et al. Randomized trial evaluating clinical impact of rapid identification and susceptibility testing for gram-negative bacteremia: RAPIDS-GN. Clin Infect Dis. 2021;73:e39–46.

33. Banerjee R, Teng CB, Cunningham SA, et al. Randomized trial of rapid multiplex polymerase chain reaction-based blood culture identification and susceptibility testing. Clin Infect Dis. 2015;61:1071–80.

34. Hogan CA, Ebunji B, Watz N, et al. Impact of rapid antimicrobial susceptibility testing in gram-negative rod bacteremia: a quasi-experimental study. J Clin Microbiol. 2020;58:e00360–e420.

35. Murri R, Taccari F, Spanu T, et al. A 72-h intervention for improvement of the rate of optimal antibiotic therapy in patients with bloodstream infections. Eur J Clin Microbiol Infect Dis. 2018;37:167–73.

36. Robinson ED, Stilwell AM, Attai AE, et al. Implementation of a rapid phenotypic susceptibility platform for gram-negative bloodstream infections with paired antimicrobial stewardship intervention: is the juice worth the squeeze? Clin Infect Dis. 2021;73:783–92.

37. Ehren K, Meißner A, Jazmati N, et al. Clinical impact of rapid species identification from positive blood cultures with same-day phenotypic antimicrobial susceptibility testing on the management and outcome of bloodstream infections. Clin Infect Dis. 2020;70:1285–93.

38. Gawrys GW, Tun K, Jackson CB, et al. The impact of rapid diagnostic testing, surveillance software, and clinical pharmacist staffing at a large community hospital in the management of Gram-negative bloodstream infections. Diagn Microbiol Infect Dis. 2020;98:115084.

39. Kim JH, Kim TS, Chang E, et al. Effectiveness of antimicrobial stewardship programmes based on rapid antibiotic susceptibility testing of haematological patients having high-risk factors for bacteraemia-related mortality: a post-hoc analysis of a randomised controlled trial. Int J Antimicrob Agents. 2022;60:106604.

40. Kunz Coyne AJ, Casapao AM, Isache C, Morales J, McCarter YS, Jankowski CA. Influence of antimicrobial stewardship and molecular rapid diagnostic tests on antimicrobial prescribing for extended-spectrum beta-lactamase- and carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* in bloodstream infection. Microbiol Spectr. 2021;9:e0046421.

41. Messacar K, Hurst AL, Child J, et al. Clinical impact and provider acceptability of real-time antimicrobial stewardship decision support for rapid diagnostics in children with positive blood culture results. J Pediatric Infect Dis Soc. 2017;6:267–74.

42. Perez KK, Olsen RJ, Musick WL, et al. Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs. Arch Pathol Lab Med. 2013;137:1247–54.

43. Perez KK, Olsen RJ, Musick WL, et al. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. J Infect. 2014;69:216–25.

44. Porter AM, Bland CM, Young HN, et al. Comparison of pharmacist-directed management of multiplex PCR blood culture results with conventional microbiology methods on effective and optimal therapy within a community hospital. Antimicrob Agents Chemother. 2019;63:e01575-e1618.

45. Neuner EA, Pallotta AM, Lam SW, et al. Experience with rapid microarray-based diagnostic technology and antimicrobial stewardship for patients with gram-positive bacteremia. Infect Control Hosp Epidemiol. 2016;37:1361–6.

46. Rivard KR, Athans V, Lam SW, et al. Impact of antimicrobial stewardship and rapid microarray testing on patients with Gram-negative bacteremia. Eur J Clin Microbiol Infect Dis. 2017;36:1879–87.

47. Bookstaver PB, Nimmich EB, Smith TJ, et al. Cumulative effect of an antimicrobial stewardship and rapid diagnostic testing bundle on early streamlining of antimicrobial therapy in gram-negative bloodstream infections. Antimicrob Agents Chemother. 2017;61:e00189–e217.

48. Cavalieri SJ, Kwon S, Vivekanandan R, et al. Effect of antimicrobial stewardship with rapid MALDI-TOF identification and Vitek 2 antimicrobial susceptibility testing on hospitalization outcome. Diagn Microbiol Infect Dis. 2019;95:208–11.

49. Gray ME, Cox HL, Donohue LE, Poulter MD, Eby JC, Mathers AJ. The effect of rapid diagnostic testing with infectious diseases fellow consultative intervention on the management of enterococcal bloodstream infection. Diagn Microbiol Infect Dis. 2018;92:319–24.

50. O'Donnell JN, Rhodes NJ, Miglis CM, et al. Impact of early antimicrobial stewardship intervention in patients with positive blood cultures: results from a randomized comparative study. Int J Antimicrob Agents. 2022;59:106490.

51. Pardo J, Klinker KP, Borgert SJ, Butler BM, Giglio PG, Rand KH. Clinical and economic impact of antimicrobial stewardship interventions with the Film Array blood culture identification panel. Diagn Microbiol Infect Dis. 2016;84:159–64.

52. Walsh TL, Bremmer DN, Moffa MA, et al. Impact of an antimicrobial stewardship program-bundled initiative utilizing accelerate Pheno™ system in the management of patients with aerobic gram-negative bacilli bacteremia. Infection. 2021;49:511–9.

53. Batwala V, Magnussen P, Hansen KS, Nuwaha F. Cost-effectiveness of malaria microscopy and rapid diagnostic tests versus presumptive diagnosis: implications for malaria control in Uganda. Malar J. 2011;10:372.

54. Box MJ, Sullivan EL, Ortwine KN, et al. Outcomes of rapid identification for gram-positive bacteremia in combination with antibiotic stewardship at a community-based hospital system. Pharmacotherapy. 2015;35:269–76.

55. Lockwood AM, Perez KK, Musick WL, et al. Integrating rapid diagnostics and antimicrobial stewardship in two community hospitals improved process measures and antibiotic adjustment time. Infect Control Hosp Epidemiol. 2016;37:425–32.

56. Macvane SH, Hurst JM, Boger MS, Gnann JW. Impact of a rapid multiplex polymerase chain reaction blood culture identification technology on outcomes in patients with vancomycin-resistant Enterococcal bacteremia. Infect Dis (Lond). 2016;48:732–7.

57. Macvane SH, Nolte FS. Benefits of adding a rapid PCR-based blood culture identification panel to an established antimicrobial stewardship program. J Clin Microbiol. 2016;54:2455–63.

58. Sango A, McCarter YS, Johnson D, Ferreira J, Guzman N, Jankowski CA. Stewardship approach for optimizing antimicrobial therapy through use of a rapid microarray assay on blood cultures positive for Enterococcus species. J Clin Microbiol. 2013;51:4008–11.

59. Colson AR, Morton A, Årdal C, et al. Antimicrobial resistance: is health technology assessment part of the solution or part of the problem? Value Health. 2021;24:1828–34.

60. National Institute for Health and Care Excellence. Models for the evaluation and purchase of antimicrobials [Online]. England: National Institute for Health and Care Excellence. 2022. https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials. Accessed 17 Nov 2022.

61. Timbrook TT, Olin KE, Spaulding U, Galvin BW, Cox CB. Epidemiology of antimicrobial resistance among blood and respiratory specimens in the united states using genotypic analysis from a cloud-based population surveillance network. Open Forum Infect Dis. 2022;9:ofac96.

62. Salvador BC, Lucchetta RC, Sarti FM, et al. Cost-effectiveness of molecular method diagnostic for rapid detection of antibiotic-resistant bacteria. Value Health Reg Issues. 2022;27:12–20.

63. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis. 2016;16:819–27.

64. Sathitakorn O, Jantarathaneewat K, Weber DJ, et al. The feasibility of procalcitonin and CPIS score to reduce inappropriate antibiotics use among severe-critically ill COVID-19 pneumonia patients: a pilot study. Am J Infect Control. 2022;50:581–4.

65. Centers for Disease Control and Prevention. The Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: Centers for Disease Control and Prevention. 2019. https://www.cdc.gov/antibiotic-use/core-elements/hospital.html. Accessed 23 May 2022.

66. Yu D, Stach L, Newland JG, Selvarangan R, Goldman J. Integrating a rapid diagnostic test and antimicrobial stewardship: optimizing discharge antibiotics in skin and soft tissue infections. Pediatr Infect Dis J. 2016;35:1362–4.

67. Bouslah Z. Carba NP test for the detection of carbapenemase-producing *Pseudomonas aeruginosa*. Med Mal Infect. 2020;50:466–79.

68. Gill CM, Kenney RM, Hencken L, et al. T2 Candida versus beta-D-glucan to facilitate antifungal discontinuation in the intensive care unit. Diagn Microbiol Infect Dis. 2019;95:162–5.

69. Mponponsuo K, Leal J, Spackman E, Somayaji R, Gregson D, Rennert-May E. Mathematical model of the cost-effectiveness of the BioFire FilmArray blood culture identification (BCID) panel molecular rapid diagnostic test compared with conventional methods for identification of *Escherichia coli* bloodstream infections. J Antimicrob Chemother. 2022;77:507–16.

Publisher's Note