

Commentary

Rapid diagnostic testing for antimicrobial stewardship: Utility in Asia Pacific

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Abstract

Rapid diagnostic testing (RDT) can provide prompt, accurate identification of infectious organisms and be a key component of antimicrobial stewardship (AMS) programs. However, their use is less widespread in Asia Pacific than western countries. Cost can be prohibitive, particularly in less resource-replete settings. A selective approach is required, possibly focusing on the initiation of antimicrobials, for differentiating bacterial versus viral infections and identifying locally relevant tropical diseases. Across Asia Pacific, more data are needed on RDT use within AMS, focusing on the impact on antimicrobial usage, patient morbidity and mortality, and cost effectiveness. Moreover, in the absence of formal guidelines, regional consensus statements to guide clinical practice are warranted. These will provide a regionally relevant definition for RDT; greater consensus on its role in managing infections; advice on implementation and overcoming barriers; and guidance on optimizing human resource capacity. By addressing these issues, the outcomes of AMS programs should improve.

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Rapid diagnostic testing (RDT) methods offer prompt, accurate identification of infectious organisms and assessment of antimicrobial susceptibility.¹ RDTs could therefore be a valuable component of the coordinated interventions that comprise multimodal antimicrobial stewardship (AMS) programs.^{2–4}

Despite the increasing availability and scope of these methods, there is currently no global or regional consensus on what constitutes an RDT. Indeed, even the definition of 'rapid' within this context has not yet been standardized. A 2017 meta-analysis included any appropriate diagnostic tests that could provide results within 24 hours.⁵ However, throughput times have continued to decrease, and a more stringent definition may now be warranted.

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Ideally, RDTs should possibly provide results to the clinician within 4–6 hours. However, in settings where this is not possible, delivery of results within 24 hours may be acceptable. A preferred RDT can yield results to guide treatment before the second dose of antimicrobial is administered. Multiple technologies may fit within this definition, including peptide nucleic acid fluorescent in situ hybridization (FISH), matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry, polymerase chain reaction (PCR), nanoparticle probe technology, lateral-flow enzyme-linked immunoassays (ELISA or LFA), nuclear magnetic resonance, and computed tomography.^{1,4,6}

The definition of an RDT should be independent of where the test is conducted, which might be near the patient (possibly at the bedside) or further away (an offsite laboratory), depending on the specific technology used. Also, although multiple technical platforms could potentially be considered RDTs, any definition should incorporate the identification not just of bacterial organisms but also nonbacterial pathogens, to help reduce unnecessary antimicrobial

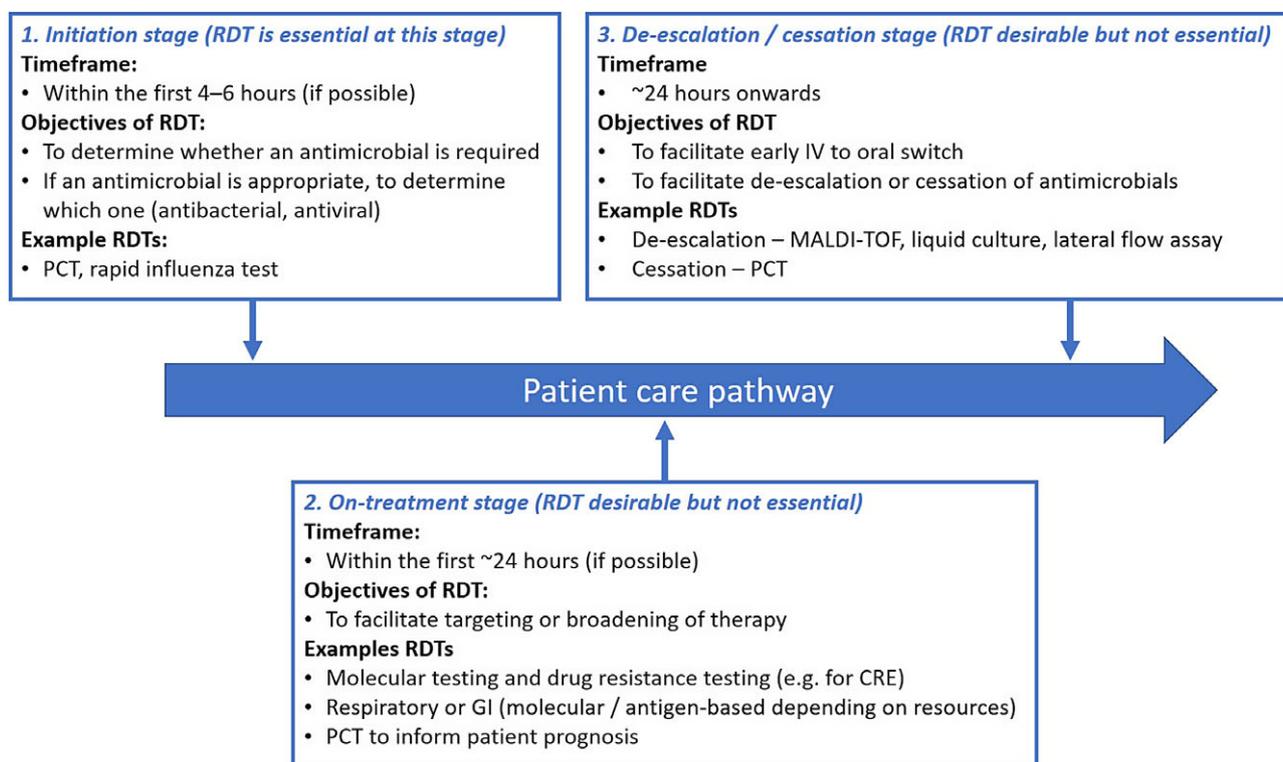


Fig. 1. Impact of RDT on AMS at different time points during the patient journey. Note. AMS, antimicrobial stewardship; CRE, carbapenem-resistant Enterobacteriaceae; GI, gastrointestinal; IV, intravenous; MALDI-TOF, matrix-assisted laser desorption/ionization–time of flight; PCT, procalcitonin; RDT, rapid diagnostic testing.

usage. Furthermore, RDT implementation must be tailored to the specific setting, particularly in the Asia Pacific region, which encompasses countries with wide-ranging economic development levels and many different infective pathogens. Other relevant factors include high specificity and the cost-effectiveness of the technology.

Within an AMS framework, the key advantage of RDT is the facilitation of rational use of antimicrobials in general, and of antibacterials in particular. In considering the patient pathway, RDTs may potentially impact 3 key antimicrobial decision nodes: at initiation, on treatment, and for de-escalation or cessation of treatment (Fig. 1). RDTs are particularly essential at initiation, whereas at other stages they might be considered as desirable rather than essential, because ‘nonrapid’ diagnostic tests are more affordable (particularly in less resource-replete settings).

In addition to facilitating AMS, RDT can improve individual patient outcomes. A recent meta-analysis by Timbrook et al⁵ identified 31 studies that compared conventional microbiological methods with molecular RDT in patients with bloodstream infections (BSIs). Their analysis revealed that mortality risk was significantly reduced with RDT versus conventional laboratory techniques (odds ratio [OR], 0.66; 95% confidence interval [CI], 0.54–0.80). RDT was also associated with reductions in time to effective therapy and length of hospital stay (LOS).⁵

Further stratification showed that significant mortality benefit was evident when RDTs were coupled with an AMS program (OR, 0.64; 95% CI, 0.51–0.79) but was lost in the absence of AMS (OR, 0.72; 95% CI, 0.46–1.12). This finding suggests that appropriate team members within AMS programs play a key role in interpreting and acting on RDT data. Ideally, these teams should include members from multiple specialties (eg, infectious disease physicians, clinical pharmacy specialists, microbiologists, nurses,

infection control professionals, information system specialists, and hospital epidemiologists).¹ However, bringing together such broad expertise may be a significant challenge in low- and middle-income countries (LMICs) in Asia Pacific. A recent Korean analysis estimated that the human resource requirement for AMS activities for hospitalized patients requiring antibiotic treatment was ~1.2 full-time equivalents per 100 beds,⁷ a substantial commitment. Notably, most studies included in the aforementioned Timbrook meta-analysis were observational and quasi-experimental, and more data are needed from randomized controlled trials comparing RDT with conventional laboratory methods.^{1,5} Furthermore, fewer studies have analyzed the use of RDT in patients with non-BSI infections,¹ and high-quality trials are required in these other disease settings (eg, respiratory tract, gastrointestinal, and central nervous system [CNS] infections).

Many novel RDT methods are associated with elevated capital and consumable costs, and financial outlays may also be required for hiring and training personnel to operate the equipment and interpret the results. There might also be additional challenges around service logistics (eg, all hours vs working hours only; in-batch vs on-demand testing), and these might have a substantial impact on the effectiveness of an AMS program.

The availability of resources is therefore essential, and cost-effectiveness analyses will be crucial to determining the value of RDTs in clinical practice. Such analyses may be particularly pertinent in LMICs, including those in the Asia Pacific region, where budgets are often constrained. In the BSI meta-analysis, financial measures were not assessed, although the decrease in LOS suggested potential for reduced cost.⁵ Relatively few cost-effectiveness analyses of RDT have been performed, and most did not adopt a whole-healthcare-economy perspective. A US study of MALDI-TOF for

rapid identification of BSI organisms, alongside a dedicated AMS program, demonstrated a decrease in total hospital costs of >US \$2,000 per infection.⁸ This decrease was driven primarily by decreased LOS in the intensive care unit.⁸ In addition, a comprehensive analysis of various RDT platforms demonstrated that cost-effectiveness improvements were particularly significant when combined with AMS, with savings of up to US\$30,000 per quality-adjusted life year.⁹

Current guidelines for implementing AMS from the Infectious Diseases Society of America encourage the use of RDT in selected patients with BSIs or acute respiratory infections.² More pertinently to much of the Asia Pacific region, a recent AMS tool kit for LMICs developed by the World Health Organization (WHO) highlighted the importance of cost-effective RDTs. Specifically, the WHO document noted that, “There is a great need for affordable, sensitive, specific and rapid diagnostic tests that provide prescribers with quality-assured information about whether or not a patient has a bacterial infection, and which antibiotics the causative bacteria are susceptible to.”³ Nonetheless, there are significant challenges in meeting this aspiration in Asia Pacific.

Current status and challenges in implementing RDT and AMS in Asia Pacific

The use of RDT as part of AMS programs is not as widespread in Asia Pacific as it is in North America or western Europe. Nonetheless, in high-income countries (HICs) within the region, RDT is increasingly becoming part of standard practice, for example, based on microbiology, antigen testing, biochemistry (particularly procalcitonin [PCT]), and some molecular methods. In a survey of AMS programs in Korean hospitals, almost all had access to some rapid testing (particularly for influenza viruses).¹⁰ The situation in LMICs in Asia Pacific is more variable, but some RDTs are available in at least some centers.

Realistically, cost is likely to remain prohibitive in many institutions, particularly in LMICs, and a selective approach will be required. Here, resources may be most effectively deployed by focusing on RDTs that assist with the ‘initiation’ stage of antimicrobial use (Fig. 1), in particular, for differentiating bacterial versus viral infection (eg, PCT, influenza panels, CNS panels, SARS-CoV-2 testing) and for identifying tropical diseases relevant to specific countries or local areas (eg, malaria, dengue, tuberculosis).

Across the Asia Pacific region, data on the use of RDT are lacking. Indeed, of the 31 studies included in the 2017 BSI meta-analysis,⁵ only 2 were from this region: 1 performed in the Republic of Korea¹¹ and 1 from Japan.¹² A small number of studies have followed, particularly in Japan,^{13,14} and analyses from less resource-replete Asian settings have now started to appear in the literature. For example, a recent study demonstrated the utility of a multiplex PCR system for diagnosing CNS infections in a tertiary-care center in India.¹⁵ In addition, a randomized controlled trial in Vietnam compared rapid pathogen identification using MALDI-TOF versus conventional methods.¹⁶ However, this study demonstrated no difference in the proportion of patients on optimal antimicrobial therapy within 24 or 48 hours of positive culture. No concomitant AMS program was in place within the trial centers,¹⁶ suggesting that such initiatives may be as crucial to the effectiveness of RDT in LMICs as they are in HICs.

In addition, to the best of our knowledge, no published data are available on the cost effectiveness of RDT methods in the Asia Pacific region, although studies are ongoing and results are

Table 1. Key challenges to overcome in implementing RDT and AMS in Asia Pacific

| Key challenges |
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| <ul style="list-style-type: none"> • Insufficient funding of, and insufficient access to, some or all RDT technologies |
| <ul style="list-style-type: none"> • Inability of some RDT platforms to accommodate the full range of relevant organisms, particularly where these differ from North America and Europe (eg, tropical diseases) |
| <ul style="list-style-type: none"> • A lack of microbiology laboratories with sufficient internal expertise and/or external quality assurance |
| <ul style="list-style-type: none"> • Suboptimal patient care pathways and reporting structures that hinder the process of obtaining rapid test results and subsequent implementation of findings |
| <ul style="list-style-type: none"> • A lack of guideline recommendations and general guidance from professional societies, which compounds the lack of awareness and education among physicians regarding RDT and AMS outside of hospital intensive care and infectious disease departments |

Note. AMS, antimicrobial stewardship; RDT, rapid diagnostic testing.

expected soon. Such data are essential if the potential advantages of these techniques are to be realized. Hence, overall, there remains a need for further trials of RDT technologies in Asia Pacific, ideally conducted within the context of AMS programs. Key analyses should include their impact on antimicrobial usage patterns, patient morbidity and mortality, time to effective therapy, LOS and cost effectiveness.

Furthermore, there is a pressing need to improve guidance on developing appropriate AMS programs in Asia Pacific, including direction on the necessary human resources and the requirement for sustainable funding models, applicable both in hospitals and in community settings. Such guidance has already been developed for resource-replete countries of western Europe and North America.^{17,18} However, considerations may be different in Asia Pacific, particularly in LMICs, and should be defined in detail.

Beyond these issues, many other challenges in the Asia Pacific region are likely to be at least somewhat specific to individual countries and territories (Table 1).^{3,19} They include challenges related to technological access and expertise, clinical guidance, and care pathways.

Impact of the SARS-CoV-2 pandemic on RDT and AMS in Asia Pacific

The SARS-CoV-2 pandemic has had a substantial impact on healthcare provision across the region, drawing resources away from other services including AMS programs. Furthermore, although SARS-CoV-2 is infrequently associated with respiratory bacterial and fungal coinfection, broad-spectrum empirical antimicrobials are often used.^{20,21} Thus, appropriate AMS activities are urgently required.

However, the pandemic has also driven an increased focus on (and uptake of) diagnostic methods that provide rapid and accurate results, particularly PCT, PCR, and molecular testing. More generally, the pandemic has substantially raised overall awareness of infectious diseases among healthcare stakeholders, including clinicians, payers, policy makers, and the public.

As long as ‘COVID fatigue’ can be overcome, this enhanced awareness creates an opportunity for a renewed discussion among these stakeholders about the broad value of RDT and AMS.

To maximize the impact of such dialog, there should be an increased focus on generating local data that support the use of RDT, including antibiotic usage patterns, clinical outcomes, and cost-effectiveness analyses.

The need for guidance: Creating consensus on RDT practices in Asia Pacific

Greater consensus is needed regarding the role of RDT technologies in managing infection in Asia Pacific and regarding the value of RDT in optimizing antimicrobial use within local, national, and regional AMS programs. In the absence of formal guidelines, we are currently developing consensus-based statements to guide clinical practice on the role of RDT in AMS.

These consensus statements will provide a working definition for RDT that is meaningful and appropriate to Asia Pacific settings. We will recommend an inventory of RDTs appropriate for both HICs and LMICs, and current barriers to the use of RDT in these settings will be discussed, together with possible solutions. The consensus statements will provide guidance on implementation of RDTs within current patient pathways (ideally based on point-of-care testing), as well as advice for practice on how to organize and build capacity of faculty and staff for implementing RDT.

The consensus statements will target not only infectious diseases specialists but also other physicians (eg, surgeons, intensive care physicians and general practitioners) and nonphysician healthcare professionals (eg, nurses and pharmacists) routinely managing infections in Asia Pacific to ensure that this guidance reaches a multidisciplinary audience.

Beyond these efforts, it takes a village to devise, implement, and monitor AMS strategies effectively and successfully. Thus, all stakeholders in Asia Pacific need to recognize the utility and potential benefits of RDT in AMS and take action to incorporate RDT to assist AMS efforts wherever it may be beneficial. Greater data collection on the use of RDT that focuses on antimicrobial usage patterns, patient mortality, and cost-effectiveness will improve outcomes of AMS programs across the region.

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