

Improving the development and deployment of rapid diagnostic tests in LMICs

Workshop report

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Executive summary

Key Context

Rapid diagnostic tests have great potential to improve both clinical care and disease surveillance in low and middle-income countries (LMICs). By identifying specific causes of infection (and in some cases antimicrobial resistance genes), such tests enable clinicians to prescribe the most appropriate treatment. This ensures that patients rapidly receive optimal treatment and prevents unnecessary use of antimicrobials, avoiding wastage and overuse that could cause antimicrobial resistance and increase healthcare costs.

In terms of surveillance, rapid diagnostic tests can play multiple roles. They can generate insight into local disease burdens and changing trends in disease and patterns of antimicrobial resistance, provide tools to identify and track emerging infections, and enable the impact of control and elimination programmes to be assessed.

However, despite much scientific and technological progress, and some notable successes, the potential of rapid diagnostic tests has yet to be fully realised in LMICs. In discussions and breakout sessions, workshop participants identified a range of barriers to their development and deployment, and potential ways they might be overcome.

Barriers

- **Insufficient prioritisation, globally and nationally:** Despite their great value, diagnostics are not given the attention they warrant, especially at a national level.
- **Financial barriers:** Diagnostics development for LMICs is commercially unattractive, deterring investment by major diagnostics companies. Smaller companies may struggle to obtain funding to scale-up production and establish sustainable businesses.
- **Challenging demands:** The requirements of diagnostic tools for use in LMICs are challenging. As well as needing to be affordable, they must also be robust enough to cope with difficult environmental conditions, easy to use, reliable and, ideally, accessible to remote populations.
- **Evaluation shortcomings:** Evaluations of diagnostic tools currently place too much emphasis on test performance in isolation, rather than in the context of local settings, specific patient pathways and health systems, and their impact on patient outcomes. This can encourage decision-makers to focus primarily on the costs of diagnostics rather than their quality and potential impact.
- **Complex and heterogeneous regulatory environments:** In some LMICs, regulatory processes may be weak or absent entirely, leading to the use of poor-quality or unvalidated tests and discouraging investment in the development of high-quality tools. Complex approvals processes, variation between countries and a desire for country-specific data are all major challenges to diagnostics developers.
- **Quality assurance:** The long-term reliability of rapid diagnostic tests is dependent on effective national quality assurance systems, which are lacking in many LMICs.
- **Performance issues with existing tests:** Some existing tests do not achieve claimed levels of performance, undermining confidence in their results and in diagnostics testing more generally.
- **Involvement of the private and public sectors:** In many LMICs, the private sector plays a major role in delivering healthcare services; its activities may be more challenging to influence and regulate than the public sector.
- **Insufficient focus on differential diagnosis:** Many rapid diagnostic tests focus on individual pathogens; negative results may therefore leave clinicians still unaware of the specific cause of symptoms and unsure of the most appropriate treatment.

Potential solutions

- **Enhancing the profile of diagnostics globally and nationally:** Diagnostics need to be given a higher priority globally, especially given their value in surveillance and control of antimicrobial resistance as well as in improved clinical care. A globally recognised 'Essential Diagnostics List' could be considered, to provide guidance to national decision-makers. This could include diagnostics for transmissible dangerous pathogens such as the Ebola virus or SARS-CoV. A global umbrella organisation could promote sharing of resources, information and expertise, act as a coordinating body, and undertake advocacy activities. At an individual country level, 'National Diagnostics Committees' could provide strategic leadership and expert advice, promote a greater emphasis on the quality of diagnostics rather than just their cost, and underpin greater regional coordination.
- **Economic incentivisation to overcome market failure:** Drawing upon experience in areas such as vaccines, innovative economic tools ('market pull' mechanisms) could be developed to encourage diagnostics developers to focus on LMICs.
- **Promoting locally driven, patient-focused development:** Diagnostics development needs to be more strongly rooted in local clinical needs and informed by the realities of local healthcare systems, patient journeys and cultural practices – hence less technology-driven and more needs-driven.
- **More coherent regulatory environment:** Rather than focus only on test performance, evaluation of diagnostics should link more closely to patient pathways, be based on comparisons with existing pathways, and focus more on patient outcomes, to generate stronger evidence for policymakers. Strengthened national regulatory systems are required to encourage the development of high-quality tests, with more focus on international standards and consistency in approach between countries. Greater regional cooperation is needed to harmonise regulatory approvals and to minimise the requirement for country-specific data sets.
- **Developing deployment 'packages':** Diagnostics need to be implemented as part of 'deployment packages' that consider diagnostic use within the context of patient pathways, and take account of factors such as healthcare worker training, communication with patients, integration with existing healthcare systems and reporting structures, and long-term quality assurance.
- **Strengthening quality assurance systems:** To ensure the long-term reliability of diagnostics testing technology, effective national quality assurance infrastructures are required, allied to agreed international standards. Such systems should also reassess rapid diagnostic tests already in use.
- **Engaging with the private sector:** The private sector is likely to play a key role in diagnostics deployment in many LMICs; efforts are needed to promote good diagnostics practice in the private sector and its involvement in national quality assurance processes.
- **Boosting local research, R&D and manufacturing:** Local development of tests should be encouraged, supported by international collaborations. Technology transfer and the development of local manufacturing capabilities provide opportunities to minimise production costs while also contributing to local economic development. In addition, continued support for research capacity building and regional research networks will provide an important foundation for understanding local pathogens and disease outbreaks, informing the development and implementation of diagnostic tests.
- **Developing more flexible diagnostic tools:** There is a growing need for diagnostics that are better able to support differential diagnosis (e.g. multiplex diagnostics, multi-use platforms) and 'upgradable' tools that can be rapidly updated in response to new knowledge about pathogens (e.g. new resistance genes).
- **Supporting surveillance:** Diagnostics are required that support surveillance activities, from disease burden assessments to monitoring of control and elimination programmes. It is also important that results from diagnostic tests in routine clinical practice feed into national health data systems, for example by exploiting built-in networking capabilities of diagnostic tools, mobile phone technologies or by integrating testing into national reporting systems.
- **Next-generation sequencing and disruptive technology:** Given its relative simplicity, wide applicability and the rapid speed of technical developments, next-generation sequencing is a credible near-term application in LMICs, particularly for surveillance. Its potential use in LMICs should be closely monitored and assessed.
- **Diagnostics for non-communicable diseases:** Although the workshop focused mainly on infectious diseases, LMICs will also need simple and affordable diagnostic tools for non-communicable diseases. Most of the issues discussed are relevant to the development of such diagnostics. Healthcare apps, with which diagnostics are becoming increasingly integrated, were discussed at another Academy workshop¹ and are not covered here.

1. World Health Organization (2014). Non-Communicable Diseases (NCD) Country Profiles, 2014. http://www.who.int/nmh/countries/zaf_en.pdf?ua=1

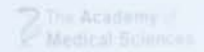
Welcome and introduction

Professor George Griffin FMedSci

Foreign Secretary, The Academy of Medical Sciences

Professor Sanjeev Krishna FMedSci (Workshop Chair)

Professor of Molecular Parasitology and Medicine, St George's, University of London



Workshop chair, Professor Sanjeev Krishna FMedSci, welcomes participants to the workshop on rapid diagnostic tests.

Introduction

Rapid diagnostic tests hold enormous promise in the battle against infectious disease in LMICs. Clinical examination is often insufficient to reveal specific causes of infection, as many pathogens elicit similar symptoms. Rapid tests to identify specific causes of infection can ensure that patients immediately receive the most appropriate treatment, benefiting them and avoiding wasteful use of antimicrobial resources.

Furthermore, more sophisticated tests can provide information on the likely susceptibility of pathogens to antimicrobial drugs, guiding the choice of treatment. Rapid diagnostic tests can also be used in screening programmes to identify asymptomatic infections, such as syphilis infections in pregnant women, enabling treatment to be given to prevent their spread.

As well as helping patients, rapid diagnostic tests have the potential to deliver major social and global benefits. By limiting unnecessary use of antibiotics or other antimicrobials, they can delay the development of antimicrobial resistance. They can also generate valuable surveillance data on disease burden and the distribution, spread and evolution of infectious organisms (including antimicrobial-resistant strains). Such information can inform local disease control measures and provide a means to assess the effectiveness of disease control programmes and interventions. Finally, rapid diagnostic tests also provide tools for identifying, tracking and controlling emerging infections.

Over recent decades, multiple diagnostic tests have been developed for many pathogens, including those primarily affecting LMICs. Good progress has been made in the implementation of rapid tests for several infections, including HIV, malaria and tuberculosis (TB), with growing use of the GeneXpert diagnostic platform². Nevertheless, rapid diagnostic tests have not been deployed as widely as might have been expected, and it is clear that they have yet to achieve their full potential (in both high-income countries and LMICs).

There are a multitude of emerging opportunities in diagnostic development, including improving existing diagnostics and developing new tools for infections for which suitable diagnostic tests are lacking. Scientific progress is offering the potential for new nucleic acid-based tests, while technological advances in areas such as microfluidics are underpinning smaller, easier to use tools with more sophisticated detection capabilities. Next-generation sequencing of whole pathogen genomes is emerging as a technology that could be widely employed, even in LMICs. In addition, advances in IT and telecommunications systems, including mobile phone-linked devices, are providing opportunities for rapid sharing, centralised storage and analysis of data.

Point-of-care tests could also help to address issues with laboratory infrastructure, which is poorly resourced in many LMICs. Being largely autonomous, point-of-care rapid tests can provide effective diagnostic services even in settings with limited laboratory facilities. While some rapid tests may still be best situated within a laboratory setting, some may obviate the need for a centralised service. Furthermore, rapid tests should provide standardised results, including those relating to markers of resistance, allowing them to be compared between different geographic settings.

Diagnostics are also securing more political attention. They are seen as critical to the battle against antimicrobial resistance, the global significance of which was illustrated by its discussion at the United Nations (UN) General Assembly in September 2016³. Diagnostics are also a core component of the World Health Organization's (WHO) Global Action Plan on Antimicrobial Resistance⁴. As well as their value in individual patient management, the potential importance of rapid diagnostics in disease surveillance, control of antimicrobial resistance, and the detection and control of emerging and re-emerging infections all provide support for their essential place in health care in LMICs.

Against this backdrop, a one-day workshop of key stakeholders from the UK and LMICs was held on 21 November 2016, jointly organised by the Academy of Medical Sciences and the InterAcademy Partnership for Health. The workshop examined a range of barriers that are limiting the development and deployment of rapid diagnostic tests, and discussed possible ways in which these barriers might be overcome. Discussions focused mainly on diagnostics for infectious diseases, although it was recognised that rapid diagnostic tests were also urgently needed for the detection and monitoring of non-communicable diseases.

This report is intended to provide a summary of the key themes that emerged during the workshop discussions. It reflects the views expressed by participants at the meeting and does not necessarily represent the views of all participants or of the Academy of Medical Sciences or the InterAcademy Partnership for Health.

The workshop was funded by the UK Government's Global Challenges Research Fund⁵ and was the second of six policy workshops co-organised by the Academy of Medical Sciences that aim to:

- Enable partners (primarily National Academies) in Official Development Assistance (ODA) eligible countries to consider how scientific evidence can help address key global health challenges.
- Build capacity in ODA countries for the provision of scientific advice.

Further information and reports from the programme of workshops can be found at www.acmedsci.ac.uk/GCRF

2. UNITAID (2015). UNITAID's Key Performance Indicators 2015. http://unitaid.org/images/kpi/2015/KPI_2015_WEB_v04.pdf

3. United Nations (2016). Draft Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance. www.un.org/pga/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf

4. WHO (2015). Global Action Plan on Antimicrobial Resistance. www.who.int/drugresistance/global_action_plan/en/

5. The Global Challenges Research Fund (GCRF) is a £1.5bn fund announced by the UK Government to support cutting-edge research that addresses the challenges faced by developing countries through:

Challenge-led disciplinary and interdisciplinary research.

Strengthening capacity for research and innovation within both the UK and developing countries.

Providing an agile response to emergencies where there is an urgent research need.

The GCRF is administered through delivery partners including the Research Councils and National Academies.



Diagnostics Landscape in LMICs

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- **Lack of access**
Although high-quality diagnostics are available for many infectious diseases, they are neither affordable nor accessible to patients in the developing world
- **Lack of investment**
Little industry interest in developing quality diagnostics for diseases prevalent in the developing world, due to a perceived lack of return for investment, and lack of investment by MOHs
- **Lack of regulatory oversight**
Tests are often sold and used without evidence of effectiveness, discouraging companies with quality products from competing
- **Lack of quality standards for test evaluations**
Claimed accuracy on product inserts often misleading



A keynote presentation from Professor Rosanna Peeling on the progress so far for the design and development of diagnostic tests suitable for use in LMICs.

Barriers

Insufficient prioritisation

Despite the widely recognised importance of rapid diagnostics, they are not receiving the attention they warrant. Notably, the UN General Assembly declaration, WHO Global Action Plan and O'Neill report⁶ all emphasise the key role to be played by diagnostics in the control of antimicrobial resistance, suggesting that they are increasingly a global priority, alongside drugs and vaccines.

In particular, national governments are typically not prioritising diagnostics development and implementation at a local level. The widespread use of HIV testing illustrates how global commitment can help to overcome technological and practical obstacles to the development and implementation of diagnostic tools.

However, a lack of political commitment can lead to a failure to implement proven approaches – such as in the case of rapid syphilis screening in antenatal care to prevent mother-to-child transmission⁷. Conversely, high-profile health emergencies, such as the Zika virus in South America, can catalyse the urgent development of rapid diagnostics⁸. Such responses are in contrast with the relatively slow progress made in the development of diagnostics for high-burden infections such as dengue. Politically driven responses also run the risk of diverting resources from other worthy causes or promoting less evidence-based approaches. participants identified a range of barriers to their development and deployment, and potential ways they might be overcome.

6. Review on Antimicrobial Resistance (2016). Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

7. Peeling RW & Mabey D (2016). Celebrating the Decline in Syphilis in Pregnancy: A Sobering Reminder of What's Left to Do. *The Lancet Global Health* 4(8): e503–4.

8. Reliefweb (2016). Brazil develops first rapid Zika detection test. <http://reliefweb.int/report/brazil/brazil-develops-first-rapid-zika-detection-test>

Financial barriers

Diagnostics for use in LMICs are not seen as commercially attractive, deterring private sector investment in diagnostics development. Despite important efforts by global philanthropic funders and agencies such as the Foundation for Innovative New Diagnostics (FIND), insufficient resources are being committed globally to the development of diagnostic tools for poverty-related diseases.

In general, more funding is available for earlier stages of diagnostic development (although developers may find it difficult to keep track of multiple diverse sources of international funding). Securing funding to commercialise a test or platform after successful proof-of-concept studies – overcoming the so-called ‘valley of death’ – can be particularly challenging. One risk is that innovative technology is acquired by larger commercial organisations and redirected away from applications in LMICs.

Challenging demands

A crucial factor in the relatively slow pace of diagnostics development and deployment in LMICs is the challenging demands made of diagnostic tests in such settings. Rapid point-of-care tests are needed that fulfill the ASSURED criteria – affordable, sensitive, specific, user-friendly, robust and reliable, equipment-free, and deliverable to those in need.

In practice, these criteria can be challenging to meet. The need for low-cost devices is paramount, but diagnostic tools for LMICs also need to cope with environmental challenges, such as heat, dust and high humidity, as well as unreliable electricity supplies and refrigeration facilities. Access may also be a constraint, as many members of a population may live large distances from a health centre with laboratory facilities. Speed is often a critical factor, as results need to be timely enough to influence clinical decision-making.

Hence, trade-offs are likely to be made between accuracy, affordability and access. The most sophisticated tools, maximising accuracy, may be suitable for some urban centres but are unlikely to be affordable or accessible to most of the population. Semi-urban populations might benefit from intermediate-level technology, which is more affordable at the expense of some accuracy. Finally, rural populations might be best served by simple, portable technology that is cheap but potentially less accurate.

Such trade-offs are not straightforward. HIV testing could be considered a success story, with 150 million tests being carried out in 2014; but assuming a 99% accuracy rate, this translates to more than one million inaccurate results⁹. On the other hand, a technology that achieves 100% accuracy but that is accessible to, say, only 30% of the population may have a significantly reduced impact than a less sensitive test accessible to much larger numbers. These kinds of issues highlight the importance of considering very carefully how diagnostic tests should be implemented and what their population impacts are when considering what performance characteristics are acceptable.

The implementation of point-of-care diagnostics also presents a number of practical challenges. Important factors include the availability not just of a test but also of the accessory materials (chemicals, swabs, gloves) required to use it safely, as well as the shelf-life of essential consumables. Ease of use is also critical, particularly as highly trained healthcare workers may not be available. In the private sector, cost may be a significant factor, as the patient must be willing to pay for the test.

Adoption will also depend on a multitude of ‘human factors’, such as healthcare workers’ knowledge of the test and the need for it, their attitudes to the test and their trust in its results, and its ‘fit’ with their clinical practice. Patient factors may also be significant, such as their acceptance of the need for testing, confidence in the result and willingness to allow healthcare workers to act on the results. For malaria diagnostics, there is at least some evidence that testing may be implemented without due consideration of effective communication between healthcare workers and patients, potentially affecting patients’ confidence in the system¹⁰.

9. WHO (2015). Consolidated Guidelines on HIV Testing Services. http://apps.who.int/iris/bitstream/10665/179870/1/9789241508926_eng.pdf?ua=1&ua=1

10. Altaras R, et al. (2016). How Do Patients and Health Workers Interact Around Malaria Rapid Diagnostic Testing, and How Are the Tests Experienced by Patients in Practice? A Qualitative Study in Western Uganda. *PLoS One* 11(8): e0159525.

A further set of constraints arise from the need for tests to integrate with local health system practices, including record keeping and data capture, healthcare worker training and reimbursement practices. Ideally, health systems need to have 'surge capacity' to detect and manage outbreaks of known or emerging infections, although this is highly challenging to implement.

Additional complexity is introduced by the need to consider a heterogeneous mix of clinical situations in which diagnostics could play a role. Clinicians may need to treat young children, pregnant women, or newborns, all with unique factors that influence consultation practice, choice of treatment and patient management.

The performance of tests can also be influenced by distinctive local features of pathogens or disease transmission. For malaria, for example, the possibility of mixed infections needs to be considered, while the desired performance of tests will vary with transmission rates. Although 'target product profiles' can be developed to guide diagnostics developers, these should be adaptable to local requirements and are therefore liable to change.

Evaluation shortcomings

The effectiveness of diagnostic tools is generally assessed in terms of their specificity and sensitivity. Although these are useful guides to how accurate a test might be, these criteria alone have significant shortcomings in terms of guiding policymaking on implementation. Initial studies are usually carried out on 'convenience' laboratory samples with comparisons to a laboratory gold standard (which may itself not be wholly reliable). With much diagnostics development carried out by small companies, field tests may be small, generating accuracy data of limited value.

Conceptually, the use of a diagnostic tool could be recommended based on two questions: Does its introduction have net benefits for the patient, and do these benefits have any additional costs or savings? Both these questions depend on rigorous comparisons with existing clinical practice and patient pathways¹¹. In particular, the value of a diagnostic tool is dependent not simply on its accuracy but on its ultimate impact on patient health, emphasising the importance of assessing patient outcomes.

Ideally, therefore, tests should be introduced if there is good evidence that they will have a more beneficial impact on patients' health than existing approaches. However, this evidence can be difficult to obtain. The appropriate designs for comparative studies may not be obvious, as potential benefits may vary significantly between different settings. Study designs should therefore aim for generalisability to allow for differences in pathogens and their management in different healthcare contexts.

This approach emphasises the importance of considering the evaluation of diagnostic tools not in isolation but in the context of patient journeys through healthcare systems, to determine how a diagnostic tool influences clinical decision-making and ultimately outcomes. Data on performance and the accuracy of diagnostics are therefore important but are not by themselves sufficient. A notable example is provided by a multicentre evaluation of the GeneXpert TB platform in Africa, which found that improved detection of TB did not translate into lower TB-related morbidity¹².

It is clearly impractical to evaluate a diagnostic tool in every conceivable situation, so it is also important to analyse data from evaluation studies to draw out general trends that might inform policymaking. Systematic reviews, such as those carried out by the Cochrane Library, can play an important role in this area, as well as in identifying gaps in knowledge¹³. Cochrane reviews can also communicate more clearly the expected impact of false results.

Decision models are commonly used to weigh up the benefits and harms and to assess the potential impact of new diagnostic tools. However, these have significant drawbacks as they address specific health and economic benefits in only a minority of cases and rarely consider the benefits of speedier diagnosis or enhanced population access.

11. Ferrante di Ruffano L, et al. (2012) Assessing the Value of Diagnostic Tests: A Framework for Designing and Evaluating Trials. *BMJ* 344:e686.

12. Theron G, et al. (2014). Feasibility, Accuracy and Clinical Effect of Point-of-Care Xpert MTB/RIF Testing for Tuberculosis in Primary-Care Settings in Africa: A Multicentre, Randomised Controlled Trial. *The Lancet* 383(9915): 424–35.

13. <http://www.cochranelibrary.com/topic/Diagnosis/>

Complex regulatory environment

The challenges of diagnostic test evaluation are compounded by the complex and disjointed regulatory environment for diagnostic development. A 2002 WHO study found that only around half of all countries surveyed had regulatory processes in place for in vitro diagnostic devices. The lack of effective regulatory oversight can result in the use of poorly performing or ineffective tests, which discourages diagnostic developers from investing in improving the quality of their products. Countries that lack an effective regulatory regime are heavily dependent on WHO's list of prequalified in vitro diagnostic products in individual disease areas.

On the other hand, with onerous regulatory systems, the time taken to obtain approval and then to achieve adoption is very long, resulting in a high attrition rate. A further challenge for diagnostics developers is the variation in regulatory practice between regions and individual countries. In particular, countries often require country-specific data in order to support implementation of diagnostic tools within a local setting.

There is a lack of standardisation in approaches to the evaluation of diagnostic devices, particularly for those targeting infections predominantly affecting LMICs; furthermore, standards developed for industrialised countries may not be appropriate to LMICs. This may have a significant impact on the quality of evidence generated on diagnostic performance¹⁴.

Inadequate quality assurance mechanisms

Even if diagnostic tests receive regulatory approval, it is important to ensure that they continue to deliver high-quality results once implemented. Some rapid diagnostic tests are located within laboratory settings. However, laboratories are often poorly resourced in LMICs, so long-term quality assurance processes may be inadequate. Although rapid point-of-care tests are often intended to be 'stand-alone', there is still a need for appropriate quality assurance systems to ensure that they continue to generate reliable results.

As well as the impact of an under-resourced national infrastructure, effective quality assurance is also hampered by a lack of internationally agreed quality standards. Without effective quality assurance, even high-quality diagnostic tools may generate unreliable results, potentially harming patients and undermining trust in specific technology and diagnostic testing more generally.

For example, the performance of diagnostic tests in practice may not match that claimed by manufacturers. A 2006 comparison of dengue immunodiagnosics found significant discrepancies between reported sensitivities and specificities and those actually achieved, with sensitivities in particular well below manufacturers' claims¹⁵. Workshop participants identified other situations in which tests had performed well below what was expected, including in a large population-based test-and-treat programme for HIV.

There are legitimate reasons why diagnostic tools may not work in the field as effectively as they do in highly controlled laboratory testing environments. Performance may be affected by harsh environmental conditions, storage of consumables may impair their quality, and equipment may not be handled correctly by trained staff. However, manufacturers' performance figures may be based on inadequately designed or performed evaluation studies, generating potentially misleading data.

Inadequate regulatory oversight and a lack of independent verification of manufacturers' data may lead to the use of tools of debatable value. Although the full extent of data reliability issues is hard to determine, misleading claims again have the potential to harm patients and undermine confidence in diagnostic tests. These issues further emphasise the importance of rigorously evaluating point-of-care devices in the specific environment in which they would be used.

14. Peeling RW, Smith PG & Bossuyt PM (2010). A Guide for Diagnostic Evaluations. *Nature Reviews Microbiology* 8 (12 Suppl.),S2–6.

15. Blacksell SD, et al. (2006). The Comparative Accuracy of 8 Commercial Rapid Immunochromatographic Assays for the Diagnosis of Acute Dengue Virus Infection. *Clinical Infectious Diseases* 42(8), 1127–34.

Public versus private sector

In many LMICs, the private sector plays an important role in the delivery of health care to significant numbers of people. The involvement of the private sector adds further complexity to the introduction of diagnostic testing, and raises additional challenges for regulation and quality assurance processes.

As the costs of private sector health care are generally borne by customers, their acceptance of the need for a diagnostic test and their willingness to pay are important factors in the adoption of testing.

Differential diagnosis

Sometimes, an accurate diagnosis can be made by a clinician on the basis of a patient's symptoms and health history. More usually, however, patients present with a set of symptoms, one of which might be a fever, with multiple possible causes. In the absence of a diagnostic test to identify specific causes of infection, clinicians generally adopt a syndromic approach, treating all possible causes of the infection, or use a 'likelihood model' and treat based on the most probable causes of infection, given local circumstances. Childhood fever in malaria-endemic regions of Africa, for example, would traditionally have been ascribed to malaria and treated with antimalarials. A major shortcoming of likelihood models is the impact of changing patterns of disease as a result of better disease control or the emergence of new infections, which makes treatment based on past experience less reliable.

Although empirical treatment is one pragmatic answer in the absence of diagnostic certainty, syndromic treatment and likelihood-based methods have significant drawbacks. In the case of syndromic treatment, patients may receive drugs they do not need, which may cause them harm, while overuse of antibiotics selects for resistance.

Diagnostics can reveal specific causes of infection, but they typically identify only one type of pathogen. With a negative test result, clinicians are likely to be left unclear about specific causes of infection and revert to syndromic or likelihood-based approaches. Notably, in some settings, the use of rapid diagnostic tests for malaria led to a drop in the use of antimalarials but a corresponding increase in the use of antibiotics, as non-malarial fever was assumed to be due to bacterial infection¹⁶.

From a clinical perspective, tools with the capacity to detect a range of possible causes of infection are therefore needed, to support differential diagnosis and rapid instigation of appropriate therapies.

16. D'Acromont V, et al. (2011). Reduction of Anti-Malarial Consumption After Rapid Diagnostic Tests Implementation in Dar es Salaam: A Before-After and Cluster Randomized Controlled Study. *Malaria Journal* 10:107.

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We are the independent body in the UK representing the diversity of medical science.
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Experts from low and middle income countries share barriers and solutions to the development and deployment of rapid diagnostic tests.

Potential solutions

Given these challenges, participants identified a range of possible solutions that could help accelerate the development of high-quality rapid diagnostic tools in LMICs and promote their implementation within health systems.

Enhancing the profile of diagnostics globally and nationally

Globally, diagnostics development needs to be given a higher profile and receive greater political impetus. Although diagnostics development is integral to the work of WHO and other global bodies, more support is needed for research on biomarker development, early product development and testing, and later-stage commercialisation. Alongside work on target product profiles to provide guidance to diagnostics developers¹⁷, WHO could consider developing an 'Essential Diagnostics List'¹⁸ akin to its Essential Medicines List to provide guidance to decision-makers.

17. Dittrich S, et al. (2016). Target Product Profile for a Diagnostic Assay to Differentiate Between Bacterial and Non-Bacterial Infections and Reduce Antimicrobial Overuse in Resource-Limited Settings: An Expert Consensus. *PLoS One* 11(8):e0161721.

18. Schroeder LF, et al. (2016) Time for a Model List of Essential Diagnostics. *The New England Journal of Medicine* 374(26):2511–4.

It was also suggested that a global umbrella body could facilitate diagnostics development in LMICs, for example by supporting the sharing of information, resources and expertise, promoting consistency in practice and international coordination, and undertaking advocacy activities. While it would be beneficial to engage with commercial organisations, it was recognised that they might be reluctant to share resources or technology.

At a country level, it was suggested that 'National Diagnostics Committees' could be established to provide strategic leadership and expert advice, and to act as a focal point for diagnostics development and implementation. Links between National Diagnostics Committees could underpin greater regional cooperation in diagnostics development, evaluation and regulation.

National Diagnostics Committees could also play a role in promoting diagnostic use within national healthcare systems. They could also emphasise the need for quality-driven rather than just cost-driven approaches to diagnostics, linked to effective evaluation mechanisms, regulatory processes and quality assurance systems.

Economic incentivisation to overcome market failure

The absence of an attractive return on investment makes many commercial organisations unwilling to invest in diagnostics development for use in LMICs. Building on the experience of other fields, such as vaccine development, innovative financial mechanisms could be established to make diagnostics development more commercially attractive. These could include mechanisms such as tiered pricing structures, subsidies, or advance purchase commitments.

Although public sector and philanthropic funding is available for early product development, more could be done to highlight funding opportunities and to enable developers to navigate a complex and diverse funding environment. To enable companies to overcome the so-called 'valley of death', more funding is required to support scale-up of manufacturing and distribution of proven technologies.

Locally driven patient-focused development

Although multiple diagnostics have been developed, there remains an urgent need for tools that better meet the needs of patients, clinicians and healthcare systems in LMICs. Future diagnostics development needs to have a stronger focus on the specific requirements of clinicians in particular LMIC settings, and needs to consider how diagnostic devices would integrate into potentially challenging local environments, taking into account existing patient pathways and healthcare systems, including reimbursement practices. Achieving this requires careful information gathering from the potential users of a new diagnostic.

As well as practical issues such as reliability in the face of environmental challenges, and the likelihood of an intermittent electricity supply and lack of refrigeration facilities, developers need to consider 'human factors'. These include clinicians' working practices and their trust in results, patients' attitudes to testing and their need for information, as well as other health systems factors such as training and the availability of essential accessories. This emphasis will ensure that diagnostics development is more needs-driven than technology-driven.

Enhanced regulatory environment

There is a need for a more coherent, internationally integrated regulatory framework for diagnostics, with a greater focus on outcomes rather than simply test performance. However, more stringent regulatory regimes should not present unnecessary obstacles to diagnostics developers.

Effective regulatory regimes would reduce the use of poor-quality tests, which have the potential to cause patient harm, waste resources and deter investment in the development of high-quality tests. There is a need for more consistent and higher-quality approaches to diagnostics evaluation, to generate information of greater value to decision-makers. These approaches could build on the groundwork carried out by bodies such as the TDR Diagnostics Evaluation Expert Panel¹⁹ and the Standards for Reporting Diagnostic Accuracy (STARD) guidelines²⁰.

Effective regulatory regimes would require developers to provide more evidence of how their products perform in real-life settings, including their impact on patient outcomes. To avoid adding unnecessarily to the regulatory burden on companies, regulatory processes need to be streamlined and efficient, and ideally coordinated between countries to avoid the need for duplicate studies and country-specific data sets. The development of internationally agreed evaluation standards and regional collaboration could reduce the regulatory burden on companies and accelerate the evaluation, licensing and implementation of high-quality tests.

More use of deployment ‘packages’

Consistent with the idea that rapid diagnostics use should be considered in the wider context of patient pathways and health system function, new diagnostic tools should be implemented within more broadly defined deployment ‘packages’. These would systematically consider key issues such as the practicalities of using the test in specific local settings, the type of healthcare worker likely to be administering the test and the training they would need, how the results would affect clinical decision-making and choice of treatment, communication with patients, reporting mechanisms and integration with existing healthcare systems, and sustainability, including maintaining the supply chain for all necessary materials and long-term quality assurance.

Strengthening quality assurance systems

Over the long term, diagnostics testing programmes require strong national quality assurance systems to guarantee the reliability of results. Rapid tests could be used in laboratory settings, which are poorly resourced in many LMICs and often lack effective quality assurance systems. Although it has been suggested that robust point-of-care tests could overcome such deficiencies, some degree of quality assurance will still be required to ensure the reliability of results. Of particular note is the safety of use which must be a key consideration given the highly dangerous nature of some pathogens.

The introduction of rapid diagnostic tests to larger numbers of facilities is likely to add further pressures to hard-pressed national quality assurance systems. Greater implementation of diagnostic tests should therefore go hand in hand with the strengthening of national quality assurance systems. There could be a need for clearly defined international standards, and potentially for regional cooperation, or for international collaborations to support the implementation of appropriate standards.

19. TDR Diagnostics Evaluation Expert Panel/Banoo S, et al. (2010). Evaluation of Diagnostic Tests for Infectious Diseases: General Principles. *Nature Reviews Microbiology* 8(12 Suppl.): S17–29.

20. Bossuyt PM, et al. (2015). STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies. *BMJ* 351:h5527.

Engaging with the private sector

Given the importance of the private sector in many LMICs, efforts should be made to ensure its activities complement those being introduced in the public sector. This could include regulatory oversight to promote the use of high-quality evidence-based approaches and to encourage participation in national quality assurance systems. Public education and awareness raising could empower patients to exert pressures on private providers to promote good practice.

Boosting local research, R&D and manufacturing capacity

High costs remain a significant obstacle to the use of many advanced diagnostic technologies. On the other hand, many LMICs have emerging R&D and technology sectors capable of developing and manufacturing sophisticated devices. Through international collaboration, it is therefore increasingly feasible to consider developing the capacity of countries to produce innovative diagnostics tools locally at relatively low cost. The development of such capacity would also generate economic benefits for the country concerned.

Furthermore, although countries often look to import established tools, LMICs are increasingly able to develop tools to meet their own needs. A greater willingness of countries to consider supporting 'home-grown' products could help to nurture sustainable local ventures. This approach would benefit from the kinds of enhanced evaluation and regulatory frameworks discussed above to ensure the quality of locally developed tools.

More generally, the indigenous science base and regional scientific collaborations provide an important foundation for understanding local pathogens and disease epidemiology, and for identifying and characterising emergent infections. Continued strengthening of the research infrastructure in LMICs through north-south collaborations will help to ensure rapid responses to emerging and re-emerging infections on the ground, and to support the development, testing and implementation of diagnostic tools tailored to local needs.

A stronger local science base could help to develop and exploit local resources, such as sample collections. Local scientific expertise could also inform the development of regulatory frameworks and quality assurance systems. Implementation research studies could also generate important data on effective deployment strategies and the impact of diagnostics.

More flexible diagnostic tools

While most diagnostics development has focused on individual pathogens, there is an increasing need for more flexible platforms or multifunctional tests to support differential diagnosis. These could include multiplex tests that detect multiple pathogens or platforms (such as cartridge-based systems) that support the use of different individual tests. There are also advantages to testing approaches that can be rapidly updated, for example to take account of pathogen evolution and changes in antimicrobial resistance.

WHO has recognised this issue, stimulating discussion on the development of open platforms, which could include diagnostics, for example to accelerate responses to disease outbreaks and emerging infections²¹. In 2013, WHO also floated the idea of a potential open point-of-care diagnostic platform (or platforms), which received a cautious welcome from industry²².

It was also suggested that funding agencies tend to consider individual pathogens or diseases in isolation, which may not reflect clinical realities. This can discourage the development of clinically useful solutions spanning several diseases, such as malaria and other potential causes of fever. A greater cross-disciplinary focus could lead to the development of more clinically useful tools.

21. http://www.who.int/csr/research-and-development/documents/eval_ideas-platform/en/

22. http://www.who.int/phi/Feed_back_from_Dx_industry.pdf

Developing surveillance capacities

Diagnostics will also need to be deployed nationally to support surveillance activities. As well as delivering estimates of disease burden, diagnostics provide a means for monitoring the emergence and spread of antimicrobial resistance. Diagnostics also have an important role to play in identifying and tracking emerging and re-emerging infections, and in assessing the effectiveness of control and elimination programmes.

It is important to ensure that the results generated by diagnostics use in routine clinical practice are captured and fed into national health data systems. Data collection could be based on the built-in networking capabilities of many diagnostic tools, use of mobile phone-enabled diagnostic technologies, or integration of testing into national reporting systems.

Next generation sequencing and disruptive technology

The costs of next generation DNA sequencing are falling rapidly, and whole genome sequencing of pathogens is being introduced in multiple countries, including many LMICs. Use of genome sequencing in the recent Ebola virus disease epidemic illustrated its great potential for identifying transmission chains and providing a clearer picture of the spread of the epidemic²³ and the evolution of the virus²⁴. Furthermore, the Ebola epidemic provided an opportunity to explore the use of pocket-sized 'nanopore' DNA sequencers in field situations.

Given the speed of developments, the richness of information obtained, and the relative simplicity of their use, nanopore or other next generation sequencers hold great potential for rapid analysis of pathogens once reliable and flexible ways are developed to isolate nucleic acids suitable for analysis from different sources. Their initial application is likely to be in surveillance but clinical applications are a realistic medium-term prospect²⁵. There is a need to monitor the development of this technology and its diagnostic applications, and to consider how it might be implemented in LMICs.

23. Folarin OA, et al. (2016). Ebola Virus Epidemiology and Evolution in Nigeria. *The Journal of Infectious Diseases* 214 (suppl.3): S102–9.

24. Holmes EC, et al. (2016). The Evolution of Ebola Virus: Insights from the 2013–2016 Epidemic. *Nature* 538(7624):193–200.

25. Pennisi E (2016). Genomics. Pocket DNA Sequencers Make Real-Time Diagnostics a Reality. *Science* 351(6275):800–1.



Session One: Drivers and core principles for RDTs in LMIC settings

Panel of diagnostics experts in different settings from LMICs

- Dr Firdausi Qadri, Bangladesh
- Dr Marcos Lopes de Miranda, Brazil
- Ms Olga R. Torres, Guatemala
- Professor Dr Rahmah Nordin FASc, Malaysia
- Professor Rajae El Aouadi, Morocco
- Professor Christian Happi, Nigeria

- Including comments from a newly graduated MChD
- Dr Ashton Rogers, Trinidad and Tobago



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Workshop participants came together to suggest solutions to some of the challenges around the deployment of rapid diagnostic tests in LMICs.

Conclusions

The workshop identified a range of barriers to the development and implementation of diagnostics for infectious diseases in LMICs and ways in which they might be overcome. Although the main focus of the workshop was on infectious disease, it was also recognised that LMICs need diagnostic tools for non-communicable diseases (NCDs).

The constraints on such tools, including the ASSURED criteria, will be similar to those for infectious disease diagnostics. Hence most of the issues discussed will also be relevant to NCD diagnostics.

The overarching conclusion was that there is unlikely to be a single 'silver bullet' diagnostic technology that will be suitable for all applications. Rather, there is likely to be a need for multiple tools tailored to specific purposes. This reinforces the need to consider precisely what role a diagnostic is expected to perform, in which setting, and in which population group. A further roundtable was hosted the following day where workshop participants from LMICs were invited to discuss how some of the solutions could be acted upon within their own countries. It is hoped that this context specific discussion will help inform lasting change to the development and deployment of rapid diagnostic tests in LMICs.

Appendix 1: Workshop steering committee

The organisation of this workshop was overseen by a joint steering committee:

Professor Sanjeev Krishna FMedSci

Professor of Molecular Parasitology and Professor of Medicine, St George's, University of London (Chair)

Dr Catharina Boehme

Chief Executive Officer, Foundation for Innovative New Diagnostics (FIND)

Professor Ajit Lalvani FMedSci

Chair of Infectious Diseases and Honorary Consultant Physician, Imperial College London

Professor Looi Lai-Meng FASc

Distinguished Professor, Department of Pathology, University of Malaya

Appendix 2: Participant list

Dr Emily Adams

Liverpool School of Tropical Medicine

Professor Rajae El Aouad

Hassan II Academy of Sciences and Technology, Morocco

Dr Matthew Bates

University of Zambia-University College London Medical School

Dr Eddie Blair

Integrated Medicines Ltd

Dr Catharina Boehme

Foundation for Innovative New Diagnostics (FIND)

Mr Mike Bond

MRC Technology

Professor Miguel Brito

Escola Superior de Tecnologia da Saúde de Lisboa

Dr Tim Brooks CBE

Public Health England

Dr Mark Carrington

University of Cambridge

Professor Timothy Coats

University of Leicester

Miss Marilia De Assis Alcoforado Costa

University of Dundee

Dr Lisa Crossman

University of East Anglia

Professor Jon Deeks

University of Birmingham

Dr Cheikh Tidiane Diagne

Institut Pasteur de Dakar

Ms Susan Dixon

GlaxoSmithKline

Dr Alexander Edwards

University of Reading

Ms Katharine Fox

Academy of Medical Sciences

Professor Sir Brian Greenwood CBE FMedSci

London School of Hygiene and Tropical Medicine

Professor George Griffin FMedSci

St George's, University of London

Professor Lisa Hall CBE

University of Cambridge

Professor Christian Happi

Redeemer's University, Nigeria

Dr Caroline Harris

Medical Research Council

Professor Richard Hayes FMedSci

London School of Hygiene and Tropical Medicine

Professor David Heymann CBE FMedSci

Public Health England

Dr Heidi Hopkins

London School of Hygiene and Tropical Medicine

Mr Jeremy Huddy

Imperial College London

Mr Alex Hulme

Academy of Medical Sciences

Mr Phil Jordan

Wellcome Trust

Professor Peter Kremsner

Universitätsklinikum Tübingen

Professor Sanjeev Krishna FMedSci

St George's, University of London

Professor Ajit Lalvani FMedSci

Imperial College London

Mr EL Law

Reszon Diagnostics International

Dr Nick Loman

University of Birmingham

Ms Catherine Luckin

Academy of Medical Sciences

Professor David Mabey CBE FMedSci

London School of Hygiene and Tropical Medicine

Dr Marcos Lopes de Miranda

State University of Rio de Janeiro, Brazil

Dr Jaime Montoya

Philippine Council for Health Research and Development

Professor Dr Rahmah Noordin FASc

Universiti Sains Malaysia

Dr Anne-Laure Page

Epicentre, MSF

Professor Julian Parkhill FRS FMedSci

Wellcome Trust Sanger Institute

Professor Catherine Peckham CBE FMedSci

University College London

Professor Rosanna Peeling

London School of Hygiene and Tropical Medicine

Dr Firdausi Qadri

International Centre for Diarrhoeal Disease and Research, Bangladesh

Dr Ashton Rogers

University of Trinidad and Tobago

Professor Sarah Rowland-Jones FMedSci

University of Oxford

Dr Tariq Sadiq

St George's, University of London

Ms Joy Ann Petronio Santos

University of the Philippines Manila

Dr Stephen Smith

University of York

Dr Henry Staines

St George's, University of London

Professor Molly Stevens FEng

Imperial College London

Dr James Tibenderana

Malaria Consortium, Uganda

Ms Olga R Torres

Kids' Lab and Centro de Investigación en Nutrición y Salud (CIENSA), Guatemala

Ms Elaine Warburton OBE

QuantuMDx

Professor Sue Welburn

University of Edinburgh

Professor Jimmy Whitworth FMedSci

London School of Hygiene and Tropical Medicine

Appendix 3: Workshop programme

- 08:30: Registration and refreshments**
- 09:00: Welcome and aims of the meeting**
Professor George Griffin FMedSci
Foreign Secretary, The Academy of Medical Sciences
- Professor Sanjeev Krishna FMedSci, Chair of workshop steering committee**
Professor of Molecular Parasitology and Professor of Medicine, St George's, University of London
- 09:15: Key note session**
- 09:15-09:40: Design and development of diagnostic tests suitable for use in LMICs: the progress so far**
Professor Rosanna Peeling
Chair of Diagnostics Research; Director of the International Diagnostics Centre, LSHTM
- 09:45-10:00: Methodological challenges in evaluating rapid diagnostic tests**
Professor Jon Deeks
Institute of Applied Health Research University of Birmingham, Professor of Biostatistics, Joint School Research Lead, Deputy Director of the Institute of Applied Health Research
- 5 minutes Q&A*
- 10:05: Refreshments break**
- 10:20: Session 1: Drivers and core principles for RDTs in LMIC settings**
- 10:20-10:40: Access, use and research gaps in RDT implementation**
Dr James Tibenderana
Development Director, Malaria Consortium
- 10 minutes Q&A*
- 10:50-12:15: Panel of diagnostics experts in different settings from LMICs**
Dr Firdausi Qadri
Director, Centre for Vaccine Sciences (CVS), International Centre for Diarrhoeal Disease and Research, Bangladesh
- Dr Marcos Lopes de Miranda**
Assistant Professor, State University of Rio de Janeiro, Brazil
- Ms Olga R Torres**
Kids' Lab Director and Senior Researcher, Centro de Investigación en Nutrición y Salud (CIENSA), Guatemala
- Professor Dr Rahmah Noordin FASc**
Professor, Universiti Sains Malaysia, Malaysia
- Professor Rajae El Aouad**
Resident Member, Hassan II Academy of Sciences and Technology, Morocco

Professor Christian Happi

Professor of Molecular Biology and Genomics, Redeemer's University, Nigeria

Including comments from a newly graduated high income country:

Dr Ashton Rogers

Assistant Professor, The University of Trinidad and Tobago

12:15: Lunch

13:15: Session 2: Innovative technologies and approaches

13:15-13:30: Development of diagnostics and collaboration with industry: challenges and opportunities

Professor Lisa Hall CBE

Professor of Analytical Biotechnology, Deputy Head of Department (Research), Department of Chemical Engineering and Biotechnology, University of Cambridge

13:30: Panel discussion: challenges and opportunities for diagnostics development

Professor Lisa Hall CBE

University of Cambridge

Ms Elaine Warburton OBE

Chief Executive Officer, QuantuMDx

Dr Nick Loman

Research Fellow, University of Birmingham

Ms Joy Ann Petronio Santos

University Researcher, University of the Philippines Manila

14:15: Refreshments break and Q&A with diagnostics developers

14:45: Session 3: Research and development of emerging and next generation rapid diagnostic tests for use in LMICs

14:45: Breakout session

What role does your assigned group have to play in contributing to the research and development of emerging and next generation rapid diagnostic tests for use in LMICs?

Introduction

The breakout session will focus on discussions around the evidence base according to what has been presented throughout the programme and through the expertise of the participants.

Red group: Investment and innovation**Group facilitator: Ms Elaine Warburton OBE**

What are the challenges to investment for innovative developments in RDTs in LMICs, including long-term investments and risk profiles for RDTs, and how can these be addressed?

Blue group: Access to diagnostics**Group facilitator: Dr James Tibenderana**

How can the research community help to overcome barriers to access of RDTs in LMICs, particularly costs, access to health care and lack of diagnostic tests optimised for pathogen subtypes common in LMICs?

Green group: Regulation and evaluation**Group facilitator: Professor Jon Deeks**

What is needed to tighten regulation requirements to improve the specificity, sensitivity and safety of diagnostic tests in LMICs?

White group: Industry and development**Group facilitator: Dr Catharina Boehme**

How can concerns over pricing and reimbursement, which result in time lag for development, be addressed in LMICs?

Yellow group: Infrastructure and capacity**Group facilitator: Professor George Griffin FMedSci**

How can the human resource capacity be strengthened to facilitate greater academic research into the development of diagnostics, to improve the evaluations of RDT performance, and to carry out cost-effectiveness studies that are directly relevant to local contexts?

15:45: Feedback from groups

16:45: Conclusions and next steps

Professor Sanjeev Krishna FMedSci, Chair of workshop steering committee

17:00: End



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