



Global health diagnostics: research, development and regulation

Workshop report

The Academy of Medical Sciences

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1. Background

This report provides a summary of a workshop held by the Academy of Medical Sciences on 'Global health diagnostics: research, development and regulation' on 3 December 2008 at the Wellcome Collection Conference Centre in London. The workshop aimed to:

- Raise awareness of the importance of diagnostics for tackling global health issues.
- Highlight the range of barriers to research, development and regulation of global health diagnostics.
- Highlight the latest research and development in the field.
- Identify areas where further activity may be required.

The meeting was chaired by Sir Andy Haines FMedSci, Director of the London School of Hygiene and Tropical Medicine, and included presentations and a panel discussion with key experts in the field. Presentations were given by: Professor Rosanna Peeling, London School of Hygiene and Tropical Medicine and UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR); Dr Helen Lee, University of Cambridge; and Mr Ian Boulton, TropMed Pharma Consulting Ltd. Three key topics were addressed:

- Research into novel diagnostics.
- Challenges to the evaluation and regulation of novel diagnostic tests.
- Perspectives from the private sector.

Panellists included: Professor David Mabey FMedSci, London School of Hygiene and Tropical Medicine; Mr Jean-François de Lavison, European Diagnostics Manufacturers' Association; and Dr Mark Perkins, Foundation for Innovative New Diagnostics (FIND). The meeting was attended by 60 invited guests representing academia, industry, medicine, publishing, research funders and other stakeholders. A full programme and delegate list is annexed.

The Academy of Medical Sciences is extremely grateful to speakers and attendees for their contributions to this event. This report captures some of the key issues and themes that arose from presentations and discussions on the day, including:

- Design and development of diagnostic tests suitable for use in low- and middle-income countries (LMIC).
- Access to diagnostics in LMIC.
- Use of diagnostic tests in practice.
- Regulation and evaluation of diagnostic tests.
- Challenges and opportunities for the diagnostics industry.

The report is intended for researchers, research funders, policymakers and other stakeholders.

2. Introduction

To date, efforts to address the burden of global health have largely focused on the development and delivery of therapeutic interventions, whilst the value of diagnostics has been somewhat overlooked. For instance, in 2004, global investment in diagnostics represented less than 1% of the total global spending in tackling malaria, compared to 37% for drug development and 24% for vaccines.¹

Yet results from diagnostic testing for infectious diseases guide the majority of healthcare decisions and are therefore critical to improving global health. In LMIC in particular, the deployment of accurate, affordable and safe diagnostic tests has the potential to revolutionise the diagnosis, monitoring and treatment of disease at the individual and population level. Specifically, the use of diagnostics facilitates:

- Screening for asymptomatic infections in at risk populations, such as HIV, Hepatitis C, syphilis and chlamydia.
- Evidence-based patient management (particularly for diseases with non-specific clinical symptoms and signs, such as fever).
- Disease surveillance and outbreak investigations.
- Evaluation of the effectiveness of interventions and certification of disease elimination.
- Detection and monitoring of drug-resistance.
- Facilitation of epidemiological studies to monitor disease burden and trends; and of clinical trials, such as drug and vaccine efficacy trials.

However, there are a number of barriers to the development and use of diagnostics for diseases of importance in LMIC, including:

- **A lack of investment and innovation**
The development of novel tests requires substantial investment and there are few incentives for the commercial sector to develop diagnostics of importance to LMIC.

Many diagnostic tests remain inappropriate to the infrastructure and contexts of LMIC.

- **A lack of access to diagnostic tests**
The high purchase costs of many diagnostic tests preclude access by the majority of patients in LMIC. Patients in LMIC also lack physical access to diagnostics since laboratory infrastructure is often limited and the majority of patients do not live in communities with laboratory diagnostic services.
- **A lack of regulatory control and quality standards for evaluation**
Many tests are sold and used without any evidence of clinical effectiveness due to the lack of regulatory standards, which can dissuade reputable companies with quality products from competing.
- **A lack of infrastructure and human resource capacity**
Existing infrastructure and capacity limits the delivery and integration of novel diagnostics into existing health systems.

As a result of these barriers, the availability of diagnostic testing in LMIC remains limited and many clinicians rely solely on the symptoms and clinical signs presenting in the patient. This can create difficulties, particularly for the management of illnesses that are caused by a range of pathogenic agents, and for latent or asymptomatic infections such as sexually transmitted infections (STIs). The syndromic approach to disease management can waste costly medicines, placing a further strain on budgets in resource-limited settings. Importantly, inappropriate treatment can also exert selection pressure on drug-resistant variants and, in some cases, can prevent treatment of the true cause of illness.

Many current diagnostic tools used in LMIC require repeat visits to a clinic, which presents further challenges. A substantial proportion of patients may not return for follow up visits, which can lead to the development of long term

¹ Malaria R&D Alliance (2005). *Malaria research and development, an assessment of global investment*. http://www.malariaalliance.org/pdfs/rd_report_complete.pdf

complications, and, in the case of infectious diseases such as tuberculosis (TB), HIV and STIs, can result in the continued transmission of the infectious agent to others. Appropriate diagnostics are often unavailable for the

testing of blood donors, which can increase the transmission of blood-borne viruses.

There is also little capacity for diagnosing and monitoring chronic non-communicable diseases (NCD) in LMIC settings.

Box 1 Background to diagnostic tests

Rapid diagnostic tests (RDTs) use samples such as urine or blood from a finger prick to give rapid visual results. Such tests provide particular promise for use in primary healthcare settings in LMIC since they are simple to use and can often be performed without specialist equipment or skilled personnel. RDTs mostly use immunochromatography to detect antigens or antibodies using a lateral flow or dipstick design; or visualise antigen-antibody complexes.²

Additional diagnostic tests utilised in LMIC include microscopy, bacterial culture, enzyme immunoassay, and nucleic acid amplification. Microscopy is frequently used to diagnose mycobacterial or parasitic infections such as TB and malaria, using sputum or blood samples. Culture remains the gold standard for bacterial diagnosis, but is rarely available in LMIC, and results are not available for several days. Antibody or antigen detection assays, such as enzyme immunoassays, are increasingly used to diagnose infectious diseases, in part, since tests are based on the antigen-antibody interaction and results can be obtained in hours rather than days or weeks. Assays can also be performed with relatively simple equipment.

Nucleic acid amplification tests, such as polymerase chain reaction (PCR), have high sensitivity and specificity and, particularly for the diagnosis of sexually transmitted infections, have the advantage of using non-invasive specimens such as urine. However, such tests are expensive, and require highly skilled personnel and specialised technical equipment.

3. Design and development of diagnostic tests

The design and development of diagnostic tests suitable for use in LMIC has to take account of a number of factors. At present the majority of tests are designed in high-income countries (HIC) and are not suitable to the local context of many LMIC. For instance, there may be no distilled water, a lack of refrigerators or freezers to store reagents and/or tests, and conditions of high humidity and temperature, which may affect the performance of tests designed for use in HIC. Many companies do not guarantee the results of rapid tests for tropical diseases, such as malaria, when they are stored at temperatures above 30°C, despite the fact that these tests are most frequently used in clinics where the ambient temperature exceeds this. Where tests are available, there may be difficulties in assuring test quality, sustainable adoption, and clinical impact, given the weak infrastructure in many LMIC health systems.

Further challenges are presented by the lack of equipment and infrastructure present at diagnostic test sites and laboratories. Distilled, deionised water and laboratory equipment are often required to prepare lyophilised reagents, yet assessments of diagnostic test sites in LMIC show that:

- 25% of sites do not have pipettes that measure volumes under 1ml.
- Over 50% of sites have no biosafety cabinet.
- 25% of sites have no distilled deionised water.
- Over 50% do not have air conditioning to reduce temperature.³

In addition, failure to store tests at the appropriate temperature can markedly affect quality.

In practice, the development of diagnostic tests is a multi-step process. Technology development, assay development, validation, clinical trials and regulatory approval are all required to develop an effective diagnostic test. Only once the final regulatory stage has been

completed can the test reach the market. In some cases, private companies can wait up to two years before regulatory approval is given for sale of a test in LMIC, creating significant delays in availability.

Commercial companies have a relatively poor track record of developing diagnostics aimed at LMIC, mostly due to the perceived limited market and lack of profitability. There are also barriers to the development of diagnostics within the public sector, including:

- Difficulties in obtaining funding for technology and assay development, and/or clinical trials of a diagnostics test.
- A focus on the number of research papers published within academia, which may disadvantage more applied diagnostics-focused research and development.
- The high investment costs associated with research into diagnostics to detect infectious agents such as HIV or TB, which require specialised laboratory containment facilities.
- Difficulty for small start-up or spin-out companies in obtaining funding for validation and verification of a new test following proof-of-concept studies. Delays in funding these studies can create a gap in the diagnostic development process.
- A lack of collaboration between academia and the diagnostics industry to translate research advances into practical diagnostic tests that can be manufactured on a large scale at low cost and high quality.

Nevertheless, point-of care, rapid diagnostic tests (RDTs) for a range of infectious diseases, such as malaria, HIV, syphilis and chlamydia have been successfully developed (see Box 2), and use of RDTs is growing in LMIC.

Key considerations in the design of RDTs are sensitivity and specificity, which define clinical effectiveness. Researchers face many challenges in optimising strategies that refine

³ Data presented by Dr Helen Lee at the Academy of Medical Sciences' workshop, *Global health diagnostics: research, development and regulation*.

these parameters. In recent years, studies have aimed to improve the sensitivity of RDTs through the amplification of detection signals. This has been effective, for example, at improving the sensitivity of tests that detect the surface antigen of Hepatitis B.

RDTs based on amplification of the relevant nucleic acid are also attractive, since their high sensitivity and specificity facilitates the detection of the pathogen in non-invasive specimens such as urine and saliva. At present however, currently available nucleic acid-amplification based tests are not feasible for use in LMIC, since most require multiple sample preparation steps: even the simplest test requires 7 individual steps. Expensive reagents, specialised laboratory infrastructure, complex equipment and training are also required. The interpretation of results can present challenges, since the nucleic acid of pathogens can remain in the body for several weeks following clearance of an infection. Notably, methods that use a single temperature for nucleic acid amplification, such as loop-mediated amplification, may be particularly

useful in LMIC. Such methods do not require sophisticated equipment for thermal cycling, and involve a simpler detection process that does not require specialised equipment and laboratory infrastructure. The advent of simpler preparation processes would make point-of-care nucleic acid tests more feasible in all settings.

In optimising the sensitivity of diagnostic tests, it is important to remain aware that greater sensitivity does not always translate into benefits for patients. In some cases, a less sensitive, but more rapid, test may actually result in treatment of a greater number of patients. For instance, tests based on nucleic acid amplification technology are highly sensitive, but results cannot be given to the patients at the same visit, requiring patients to return to the clinic for the appropriate treatment. Thus:

- Assuming that a nucleic acid amplification test has a sensitivity of 95%, but that only 70% of patients return to the clinic due to the delay in obtaining the test result, the appropriate treatment would be prescribed for **66.5% of patients**.

Box 2 Case Study: development of a rapid diagnostic test for Chlamydia

In LMIC there is a pressing need for RDTs to diagnose STIs. For instance, there are approximately 90 million new cases of *Chlamydia trachomatis* infection worldwide each year. Chlamydia is a major cause of infertility, but the infection is largely asymptomatic so few infected individuals are treated, despite the availability of cost-effective treatments. A novel RDT, developed by the Diagnostics Development Unit (DDU) at the University of Cambridge, requires no instrumentation and uses non-invasive samples, such as first-void urine collection, using a simple disposable device. Sample extraction takes less than one minute and results are obtained in 25 minutes via a colour change on a dipstick. An evaluation showed that the test has a sensitivity of 84% compared to the gold standard DNA amplification test, which surpasses the performance of currently available Chlamydia RDTs.⁴

A Chlamydia screening programme carried out in the Philippines using a new RDT identified that 28% of sex workers, and 6% of patients at obstetrics and gynaecology clinics, were infected. In antenatal clinics in Western Samoa, 29% of patients were found to be positive for Chlamydia.

Despite its clinical effectiveness, widespread use of this test in LMIC is lagging, in part, owing to cost. Greater adoption of affordable and high-performance RDTs and treatments is crucial to preventing spread of this STI.

⁴ Wisniewski CA et al. (2008). *Optimal method of collection of first-void urine for diagnosis of Chlamydia trachomatis infection in men*. Journal of Clinical Microbiology **46**(4), 1466-9, Mahilum-Tapay L et al. (2007). *New point of care Chlamydia rapid test - bridging the gap between diagnosis and treatment: performance evaluation study*. British Medical Journal **335** (7631), 1190-4.

- However, an RDT with a sensitivity of 80% that gives a rapid result whilst patients are on site - and thus assures that 100% of patients who test positive are treated - would result in **80% of patients** being managed appropriately. In this case, the provision of immediate treatment to infected patients would prevent the development of complications and interrupt the chain of transmission in a greater proportion of patients.⁵

In the future, tests that combine the detection of multiple analytes may become increasingly useful. The multiplex diagnostic system currently available to detect HIV, Hepatitis B virus and Hepatitis C virus is effective, and similar developments in RDTs that detect more than one pathogen would be particularly useful in LMIC. It should be noted, however, that such an approach might offer little incentive to the private sector, given the greater profit to be gained from supplying multiple individual RDTs.

⁵ Gift TL (1999). *The rapid test paradox: when fewer cases detected lead to more cases treated: a decision analysis of tests for Chlamydia trachomatis*. Sexually Transmitted Diseases **26(4)**, 232-40.

4. Access to diagnostics

The marked imbalance of resources available for the purchase and utilisation of diagnostic tests between LMIC and HIC has created substantial inequalities in access to diagnostics. In addition, since the majority of diagnostic tests are developed in HIC, many tests are optimised for pathogen subtypes that are common in HIC, rather than those prevalent in LMIC. For instance, the majority of commercially available tests for HIV have been optimised for subtype B, the most prevalent variant in the USA and Europe. The distribution of different HIV subtypes also varies markedly around Africa. Thus, to meet the needs of HIV diagnosis in LMIC, diagnostic tests need to be optimised for the detection of subtypes prevalent in particular regions.

Poor access to healthcare and a lack of affordable treatments compound the lack of tests available to detect strains and species of pathogens prevalent in LMIC. Individuals who are most at risk are often the least able to afford a diagnosis. It is for this reason that RDTs are especially effective in LMIC: the use of RDTs enables test results to be more closely linked to on-the-spot treatment, removing the need for patients to re-visit health services over weeks or months. The widespread use of RDTs could therefore revolutionise treatment provision and reduce morbidity and mortality in LMIC.

Currently, even in cases where individuals access health services, the proportion of

individuals that access treatment, and the proportion of individuals that are treated, are not always equivalent. This disparity is particularly evident for the treatment of STIs such as congenital syphilis. In 1999, there were approximately 4 million new cases of syphilis involving adults in sub-Saharan Africa alone, and it is estimated that around half a million babies die of syphilis in this region each year.⁶ Yet syphilis and its sequelae can be effectively managed, if the appropriate diagnosis is made. Estimates around the diagnostic provision for the prevention of congenital syphilis in LMIC indicate that:

- Approximately 75% of infected women access care at an antenatal clinic but only 50% access the clinic early in pregnancy (it is important that women are screened and treated before the end of the second trimester to avoid adverse outcomes of pregnancy from syphilis).
- Only a proportion of women - around 25% - are tested for syphilis owing to a lack of availability of the appropriate diagnostics.
- Many women do not return to the clinic, resulting in a further reduction in the proportion of infected women who are actually treated.⁷

It is estimated that the provision of affordable RDTs for syphilis would enable 75% of infected women to be treated, which would make a substantial impact on perinatal mortality due to congenital syphilis.

⁶ World Health Organization (2001). *Global prevalence and incidence of selected curable sexually transmitted infections: overview and estimates*. WHO, Geneva, World Health Organization (2005). *Projections of mortality and burden of disease to 2030*. WHO, Geneva.

⁷ Data presented by Professor Rosanna Peeling at the Academy of Medical Sciences' workshop, *Global health diagnostics: research, development and regulation*.

5. Use of diagnostic tests in practice

In practice, the accuracy of RDTs is dependent on many variables. In the case of RDTs for malaria, performance depends on the *Plasmodium* species that is present, the level of parasitaemia, and the sensitivity and specificity of the test.⁸ A recent study reported that the sensitivity and specificity of malaria RDTs varied considerably, both between high- and low-transmission areas, and according to the month of test, age of patient and presence/absence of fever during consultation.⁹

Importantly, false negative and false positive results can be obtained using poor quality RDTs. In addition, in high-transmission areas, the *Plasmodium falciparum*-specific protein histidine rich protein 2 (HRP2) from previous infections can persist in the bloodstream for several weeks, leading to a false positive result. Furthermore, RDTs for malaria that test for HRP2 do not detect malaria caused by other species. Thus appropriate use and interpretation of the results of diagnostic tests is critical.

False positive or negative results can greatly compromise the confidence of clinicians in using diagnostic test results to guide treatment. Manufacturers are often not required to supply validated specificity and sensitivity data in product inserts, which further exacerbates this mistrust, since claims of performance may be highly inflated (see section 6). Thus, even if a negative result is obtained, health workers may treat patients for the suspected disease to avoid a potential fatality, and possibly waste costly medicines. One study performed in Tanzania using an HRP2-specific RDT demonstrated that 54% of individuals testing negative for malaria were treated for malaria, despite the high sensitivity (94%) and specificity (89%) of the chosen RDT.¹⁰ In addition, the study showed that over 90% of prescriptions for antimalarial drugs in low or moderate transmission areas were given to patients with a negative test result,

suggesting that, in many cases, presumptive diagnosis could prevent treatment for the true cause of illness.

The lack of credible data in product inserts, and the lack of validation data available from field trials, present challenges to policy makers. It may not be clear which test is the most sensitive, specific and cost-effective, and decisions may therefore be guided by cost alone. This mistrust and lack of data underscores the need to improve quality assurance and regulatory processes to increase confidence in diagnostic tests and to ensure that procurement and clinical decisions are evidence-based (see section 6). Education, supervision and training of clinicians and health workers are important components of any RDT introduction programme, in addition to effective communication of data to decision makers.

An additional consideration is the need to take account of language variations between LMIC in leaflets and RDT packages. Health professionals and/or individual users rely primarily on product inserts for guidance, and it is the role of manufacturers and distributors to ensure that instructions for storage, preparation and interpretation are clear, and suitable for the local and national context.

Distribution of tests within LMIC can present further challenges. The extent to which RDTs are distributed depends largely on the regional incidence of disease, which can vary markedly between countries. In central and eastern Africa, HIV subtype A is the most prevalent, whereas in southern Africa, subtype C is the most prevalent, with CRF-02-AG the most prevalent in western Africa. Differences in the length of the diagnostic supply chain between LMIC will affect the storage facilities and health system infrastructure required, and existing capacity may be variable between and within different LMIC.

8 Ochola LB et al. (2006). *The reliability of diagnostic techniques in the diagnosis and management of malaria in the absence of a gold standard*. *Lancet Infectious Diseases* **6**, 582.

9 Abeku et al. (2008). *Determinants of the accuracy of rapid diagnostic tests in malaria case management: evidence from low and moderate transmission settings in the East Africa highlands*. *Malaria Journal* **7**, 202-212.

10 Reyburn H et al. (2007). *Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial*. *BMJ* **334(7590)**, 403.

6. Regulation and evaluation of diagnostic tests

The tightening of government regulatory requirements for drugs utilised in LMIC has done much to improve the quality and consistency of drug trial methodology, and assessments of efficacy and safety. However, at present, few national and international regulations exist for the evaluation of diagnostic tests important to LMIC and no single body has responsibility for assuring quality standards. Variations in quality standards are evident between RDTs that detect infectious diseases in LMIC, and manufacturers are able to make inflated claims of clinical effectiveness (see Box 3).

An independent evaluation of 8 of the 20 commercially available RDTs for dengue virus demonstrated that: only two tests had sensitivities over 50%; none accurately distinguished between primary and secondary dengue infections; and test performance deteriorated following storage for 3 months at high ambient temperatures.¹¹ Similar disparities between claims and actual sensitivities have been found for TB serology and Gonorrhoea diagnostic tests.

Inaccuracies can be improved through field trials and evaluations; these are crucial to

highlighting variations in performance between geographic regions, seasons and patients, in addition to identifying practical issues such as the storage conditions required, shelf life and user applicability. To date, a number of field studies have been carried out for RDTs, particularly for malaria, but methodologies, reference standards and study populations vary substantially. A range of factors affects the quality of trials, such as:

- Conduct of the test evaluation in the appropriate setting, with the target population for which the test is intended.
- Design of the evaluation according to the purpose of test use.
- Sample size.
- Blinding.
- The gold standard reference utilised in trials.

Large-scale trials and quality assurance studies of diagnostic tests need to be performed according to agreed guidelines in the appropriate context, to obtain reliable, high quality data. Consistent, effective methodologies combining tests in the laboratory and in clinical practice are required, alongside comparative analyses between

Box 3 Variations in global diagnostic regulatory standards

Of 85 countries that responded to a World Health Organization (WHO) questionnaire, just 48% regulate diagnostic tests for infectious diseases outside of tests used for blood screening. The data obtained highlight substantial variation in the regulation of RDTs around the world:

- The European and American regions showed the highest level of regulation, although clinical evaluations were not always included and marked variations were evident in the robustness of evaluations.

Further details provided by individual countries indicated that:

- 83% and 92% of respondent countries regulate HIV and Hepatitis diagnostics respectively, yet just 42% regulate diagnostics for STIs and only 13% of countries regulate diagnostics for TB and malaria.
- The costs associated with evaluations of diagnostic tests were markedly variable, ranging between USD2,000 to USD2,000,000.
- One particular evaluation assessed performance of the diagnostic test in just 15 patients.¹²

11 Blacksell *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.

12 World Health Organization (2006). *Diagnostics for tuberculosis: global demand and market potential. Annex: Regulation of in vitro diagnostics: a global perspective*. Geneva: WHO, reviewed in Peeling RW *et al.* (2006). *Rapid tests for sexually transmitted infections (STIs): the way forward*. *Sexually Transmitted Infections* 82(Suppl V), 1-6.

diagnostic tests. The use of standardised specimens or reagents, against which test quality can be compared, would enable quality testing of RDT batches, to account for any deterioration during transit.

To this end, WHO has partnered with FIND and other agencies to develop a three-tiered approach to test the accuracy and stability of RDTs for malaria, which includes:

- Product testing to demonstrate performance characteristics.
- Post-purchase batch testing.
- The use of positive controls at remote test sites to ensure that the 'delivered' and 'stored' product has retained the necessary qualities.¹³

Recent publications detailing guidelines for the design, conduct and reporting of diagnostic evaluation studies are a welcome advance.¹⁴

In part, the lack of quality assurance of diagnostic tests is due to the sheer number of RDTs available and the lack of human resource capacity, infrastructure and financial investment available for evaluation. For malaria alone, there are over 60 companies manufacturing more than 120 different RDTs. Greater capacity in human resources, equipment, raw materials and knowledge is urgently required at diagnostic reference laboratories, to enable test performance studies to be carried out in the country in which the diagnostic test will be used. The development of regional and international laboratory networks would

enable information to be shared effectively, and greater research capacity would facilitate studies into the cost-effectiveness of different tests, and communication of outcomes to decision-makers.

WHO/TDR is playing a crucial ongoing role in evaluating the performance of a range of available diagnostic tests including RDTs. WHO also launched a pre-qualification programme for diagnostics in 2008, which has three components for manufacturers: submission of a dossier of their product for review by an expert group; inspection of the manufacturing site for good manufacturing practice; and a laboratory evaluation of the performance and operational characteristics of the diagnostic test. The building of regulatory capacity and post-market surveillance are also subsequently required.¹⁵ Current priorities for the pre-qualification programme are tests for malaria and HIV.

Such strategies are important, since the continued use of inaccurate tests poses a threat to patient safety, and variation in test quality erodes confidence in test results and thus inhibits evidence-based treatment. Furthermore, the inclusion of unreliable tests on the market discourages reputable commercial companies from investing in the development of novel diagnostic tests. Given the enormous number of diagnostic tests available, WHO cannot perform all of the required evaluations alone and greater capacity for regulation and quality assurance will be required.

13 WHO, WHO/TDR and FIND (2008). *Initiative for quality assurance of malaria rapid diagnostic tests. Outline of product testing and associated protocols.* http://www.wpro.who.int/NR/rdonlyres/586DC848-8078-4DDD-85FD-9181E352BF14/0/ProductTestingOverview_final_280208.pdf

14 TDR Diagnostics Evaluation Expert Panel (2007). *Evaluation of diagnostic tests for infectious diseases: general principles.* Nature Reviews Microbiology Suppl S17-29. Peeling RW *et al.* (2007). *A guide to diagnostic evaluations.* Nature Reviews Microbiology Suppl S2-6.

15 http://www.who.int/diagnostics_laboratory/evaluations/en/

7. Challenges and opportunities for the diagnostics industry

Challenges to the diagnostics industry in the development of novel diagnostics important to LMIC include:

- The limited share of the global diagnostics market generated in LMIC, particularly sub-Saharan Africa, which accounts for approximately 0.35% of the global diagnostics market.
- Low profit margins owing to pressure to provide diagnostic products to LMIC at low cost.
- Difficulties in sustaining collaborations and partnerships between academia, industry and multilateral health initiatives.
- The plethora of counterfeit and ineffective diagnostic tests available on the market in LMIC, which discourages reputable companies from investing in the development of novel diagnostics.
- A lack of global pressure and advocacy to develop and regulate diagnostic tests relevant to LMIC.

Despite these barriers, there is substantial scope for greater development and use of diagnostics, especially RDTs in LMIC, given the appropriate financial support. For instance, estimates based on the WHO World Malaria Report 2008 highlight that approximately 152 million cases of malaria were clinically confirmed using RDTs or microscopy in 2006, compared to 82 million treatment courses prescribed.¹⁶ Additionally, whilst the majority of diagnoses were made using microscopy in 2006, RDT use has been steadily rising since 2000. The use of RDTs for malaria alone is estimated to have increased from 2.9 million RDTs in 2000 to 28.3 million in 2005.¹⁷

The significant rise in the use of more costly artemisinin-based combination therapy (ACT)

to treat malaria underscores the importance of making sure that scarce resources are spent only on necessary treatments. At present, the global coverage of diagnostic tests is approximately 10% - just 2% in sub-Saharan Africa. Thus, there are significant opportunities for growth in the markets of RDTs.

As has been the case in the development of therapeutic drugs to treat infectious diseases such as HIV, TB and malaria, there are opportunities for the diagnostics industry to collaborate with others to overcome obstacles to diagnostics research and development.

For instance:

- Greater global co-ordination between academia, funding bodies, the diagnostics industry, pharmaceutical industry and other stakeholders, together with FIND, would ensure that the development of RDTs follows a systematic and co-ordinated process.
- The development of global product development partnerships would accelerate the development of clinically effective diagnostics suitable for use in LMIC, similar to drug and vaccine development.
- Greater collaboration between academia and the diagnostics industry in HIC and LMIC would facilitate the development of diagnostics of benefit to both HIC and LMIC, for instance TB, STIs such as chlamydia, and NCD such as diabetes.
- The development of diagnostics and therapeutic drugs linked to the same disease would benefit both the company and patients in the relevant countries. Co-ordinated delivery of the diagnostic and treatment as a combined package might also facilitate more effective dissemination into the health system.

¹⁶ Data gathered from *World Malaria Report 2008*. Geneva, WHO, 2008; Roll Back Malaria (RBM) Commodity database.

¹⁷ <http://www.rollbackmalaria.org/gmap/1-3.html>,

¹⁷ http://www.wpro.who.int/NR/rdonlyres/A15EBA35-91E1-4D8F-9798-5352CEBC7395/0/20_May_2007_RDT_Forecast_report.pdf

Conclusions

To date, efforts to address the burden of infectious diseases in LMIC have largely focused on new therapeutic interventions, whilst the importance of diagnostics has been comparatively neglected. As a result, current diagnostic methodologies are often inappropriate to local needs and contexts of LMIC. Many diagnostic tests require skilled personnel, specialised equipment and expensive reagents, and take days or weeks to obtain a result, which can reduce the number of patients who are treated, and exacerbate the spread of disease.

Yet, results from diagnostic tests guide the majority of healthcare decisions and are therefore critical to addressing the health burden in LMIC. In particular, the advent of fast, accurate, point-of-care diagnostic tests holds significant promise to enable evidence-based diagnosis and treatment in primary healthcare settings. Appropriate diagnostic tests also facilitate: disease surveillance and screening; evaluation of the effectiveness of interventions; certification of disease elimination; detection of markers of drug resistance; and the facilitation of clinical trials and epidemiological studies - all of which are crucial to addressing the health burden in LMIC. Yet, despite the promise of rapid diagnostic tests (RDTs), and evidence of rising demand, there remain a number of barriers to the implementation of new diagnostics within LMIC health systems.

Investment and innovation

The limited share of the diagnostics market generated in LMIC and the large number of ineffective tests available can discourage reputable companies from investing in the development of novel diagnostic tests. Many diagnostics are designed in high-income countries and therefore fail to take account of the needs and priorities of LMIC, or the variations in prevalence of different pathogen strains or subtypes between countries. Greater investment would significantly benefit patients

by stimulating innovative developments in RDTs of importance to LMIC, particularly:

- The ability to function above 30°C and at high humidity.
- The ability to be stored for long periods without refrigeration.
- A reduction in requirement for multiple preparation steps.
- The ability to conduct the test without the need for local reagents/water and/or specialised laboratory equipment.
- The ability to detect multiple pathogens, or to distinguish between different pathogens and/or strains and subtypes.

Importantly, there has been a focus on developing RDTs for infectious diseases at the expense of tests for non-communicable diseases and this imbalance will need to be addressed in the coming years.

Access to diagnostics

A substantial proportion of patients in LMIC lack access to appropriate diagnostics, owing to the high purchase cost of many diagnostic tests, poor access to healthcare and a lack of diagnostic tests optimised for pathogen subtypes common in LMIC. Effective advocacy could play an important role in stimulating investment in research, development and delivery of affordable diagnostic tests appropriate to LMIC contexts.

In particular, enhanced access to RDTs resonates with recent calls for a revival of primary health care and the Alma Ata Declaration (1978),¹⁸ since RDTs facilitate diagnosis and treatment at the community level, without a need for extensive training and specialist equipment. Linking diagnosis to on-the-spot treatment removes the need for many patients to travel long distances to re-visit healthcare services over weeks or months.

Regulation and evaluation

Many RDTs are on the market despite a lack of specificity and/or sensitivity; their performance

¹⁸ http://www.who.int/hpr/NPH/docs/declaration_almaata.pdf

can vary widely between regions, seasons or patients. Insufficient evidence of accuracy, and inflated claims of test performance by manufacturers, can lead to misdiagnosis and adverse consequences, waste of precious resources, and mistrust of test results, which can all compromise patient safety and affect RDT cost-effectiveness. Decision-makers may base purchase decisions on cost alone in the absence of robust sensitivity or specificity data.

Effective communication between researchers, clinicians and decision makers in LMIC will be needed to overcome these obstacles. Moreover, improved regulation and quality assurance of RDTs would greatly enhance the quality, accuracy and consistency of diagnostic test performance, through a requirement for robust clinical trials and laboratory performance evaluations. At present the lack of regulation enables counterfeit and ineffective tests to reach the market - on the ground or via the Internet - and there is no requirement for manufacturers to provide data detailing the sensitivity and/or specificity of the test. This poses serious threats to public health.

There is a pressing need for regulatory policies that are proportionate and appropriate to the issues on the ground, and not over-prescriptive. Requirements for the future should include:

- Evaluations of RDTs in clinical practice using robust, consistent methodologies.
- Comparative analyses between tests using appropriate reference standards.
- Quality testing of RDT batches following delivery and storage.

A World Health Assembly resolution on the global regulation of diagnostic tests would provide a crucial policy framework for improvements in the quality of diagnostic tests sold and used around the world.

Advances in the accuracy and clinical effectiveness of diagnostic tests would enable a greater proportion of patients to be treated appropriately, which would interrupt the

transmission of infectious agents and reduce the burden of disease.

The development of a single body that represents researchers, clinicians, industry, funders, charities and stakeholders, and which holds responsibility for leading advocacy and/or the implementation of regulatory policy would also be a welcome advance.

Infrastructure and capacity

Underpinning all of the factors described above is a need to strengthen human resource capacity to facilitate greater academic research into the development of diagnostics, to improve evaluations of RDT performance, and to carry out cost-effectiveness studies that are directly relevant to local contexts. Investment in specialised equipment and infrastructure capacity in 'grassroots' services, such as diagnostics reference laboratories, are additional requirements. The role of community health workers in delivering diagnoses and treatments should be a key consideration, since the use of RDTs in primary care often does not require specialist knowledge or extensive training. The introduction of pioneering approaches that bring together mobile telephone and diagnostic technologies also hold promise in the future.

Advances in research, development and delivery of diagnostics require a greater focus on partnerships and collaborations. Innovative approaches that bring together academia, the diagnostics industry, the pharmaceutical industry and the clinical community - possibly in regional consortia - could catalyse developments in RDTs. North-South and South-South partnerships could play a crucial role in facilitating knowledge exchange, education, training and advances in research and development of RDTs. Collaboration between pharmaceutical and diagnostic companies would also link diagnosis and treatment of disease and thus lead to more accurate and effective patient care.

Key points

- The use of accurate, safe and affordable diagnostic tests has a critical role to play in addressing the health burden in LMIC. In particular, point-of-care diagnosis using rapid diagnostic tests that are appropriate to LMIC contexts could revolutionise diagnosis and treatment in primary healthcare settings. Research and development have a crucial role to play in the generation of appropriate diagnostics for both infectious and non-communicable diseases.
- Effective advocacy is needed to secure greater investment in: research, development and delivery of diagnostic tests; infrastructure; equipment; and human resource capacity.
- Clearer and more precise data are needed regarding the performance, quality, accuracy and cost-effectiveness of RDTs in relation to the LMIC contexts in which they are used.
- Clear communication of data to decision makers and health professionals is required to enable evidence-based treatment and policymaking, and to enhance confidence in the use and application of diagnostic tests.
- A tightening of regulatory requirements is needed, to improve the specificity, sensitivity and safety of diagnostic tests. A World Health Assembly resolution on global regulation of diagnostic tests would provide a crucial policy framework for such improvements.
- A single global body involving academia, clinicians, the diagnostics industry, pharmaceutical companies, funding bodies and stakeholders, would play an important role by providing leadership on behalf of the diagnostics community, and by contributing to the implementation of regulatory policy.

Annex 1: meeting programme

Global health diagnostics: research, development and regulation

Wednesday 3 December 2008

16:30 Registration

16:45 Opening remarks

Sir Andy Haines FMedSci

16:50 Regulation and evaluation of novel diagnostic tests

Professor Rosanna Peeling, Professor of Diagnostics, London School of Hygiene and Tropical Medicine and Research Co-Ordinator and Director, Diagnostics R&D, UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR)

17:20 Development and application of rapid tests for resource-limited settings

Dr Helen Lee, Principal Investigator and Head of Diagnostic Development Unit, University of Cambridge

17:50 A private sector perspective on R&D for global health diagnostics

Mr Ian Boulton, Managing Director, TropMed Pharma Consulting Ltd

18:20 Panel discussion

- Professor David Mabey FMedSci, Professor of Communicable Diseases, London School of Hygiene and Tropical Medicine
- Mr Jean-François de Lavison, President, European Diagnostics Manufacturers' Association
- Dr Mark Perkins, Chief Scientific Officer, Foundation for Innovative New Diagnostics

18:55 Closing remarks

19:00 End

Annex 2: delegate list

Dr Daniel Agranoff, Clinical Senior Lecturer
Imperial College London

Dr Till Bachmann, Chief Operating Officer
Division of Pathway Medicine, University of Edinburgh

Professor Jangu Banatvala CBE FMedSci, Emeritus
Professor of Clinical Virology
Guy's and St Thomas' School of Medicine

Dr Martha Betson, Post-Doctoral Research Assistant
Natural History Museum

Dr Eddie Blair, Managing Director
Integrated Medicines

Dr Laura Boothman, Policy Officer
Academy of Medical Sciences

Dr Meredith Bradbury
Technology Strategy Board

Professor Philip Butcher, Professor of Molecular
Medical Microbiology
St George's University of London

Dr Carmen Camino, Public Health Specialist
LATH

Dr Mark Carrington, Research Group Leader
University of Cambridge

Dr Chris Chamberlain, Biomarker Expert
Roche

Dr Jane Crawley
MRC Clinical Trials Unit

Dr Nicholas Dellaportas, Practice Manager
Cassidy Medical Centre, Hammersmith and Fulham PCT

Dr Helen Donoghue, Senior Lecturer
University College London

Mr Quinton Fivelman, Business Development Manager
London School of Hygiene and Tropical Medicine

Dr Robert Frost, Senior Policy Officer (FORUM)
Academy of Medical Sciences

Professor Diana Gibb, Professor of Paediatric
Infectious Diseases
MRC Clinical Trials Unit

Professor Peter Godfrey-Faussett, Professor of
International Health
London School of Hygiene and Tropical Medicine

Dr Clare Green
University College London

Dr Philip Green, Executive Assistant to the Director
Wellcome Trust

Professor Brian Greenwood CBE FRS FMedSci, Professor
of Clinical Tropical Medicine
London School of Hygiene and Tropical Medicine

Ms Pamela Hepple, Laboratory Specialist
Manson Unit, Médecins sans Frontières UK

Dr Richard Horton FMedSci, Editor
The Lancet

Dr Jim Huggett, Senior Research Fellow
University College London

Professor Anne Johnson FMedSci, Professor of Infectious
Disease Epidemiology and Head, Division of
Population Health
University College London

Ms Paula Kanikadan
PhD Student

Dr Mallika Kaviratne, Technical Officer
Malaria Consortium

Dr Zahra Khatami FRCPath, Consultant Biochemist
BHR Hospitals

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

Professor Ajit Lalvani, Wellcome Trust Senior Clinical
Research Fellow
Imperial College London

Professor Ronald Laskey FRS FMedSci, Honorary
Director, MRC Cancer Cell Unit
University of Cambridge, Vice-President
Academy of Medical Sciences

Dr Werner Leber
Academic General Practitioner
London School of Hygiene and Tropical Medicine

Dr Kathy Liddell, Fellow in Law University of Cambridge	Dr Hyaatun Sillem, Manager, International Activities Royal Academy of Engineering
Dr David Lynn, Head of Strategic Planning and Policy Wellcome Trust	Professor Peter Smith CBE FMedSci, Professor of Tropical Epidemiology London School of Hygiene and Tropical Medicine
Dr Georgie MacArthur, Policy Officer Academy of Medical Sciences	Dr Val Snewin, International Activities Manager Wellcome Trust
Dr Ruth McNerney, Senior Lecturer London School of Hygiene and Tropical Medicine	Mr Jose de Sousa Figueiredo, Post-Graduate Research Assistant Natural History Museum
Mr Peter Medway, Director of Operations IMC Worldwide	Dr David Thompson, Clinical Lecturer and Co-Director of the Oxford Centre for Monitoring and Diagnosis University of Oxford
Ms Stefanie Meredith, Formerly Director of Public Health Partnerships International Federation of Pharmaceutical Manufacturers and Associations	Alex Timusiine, MSc Student Institute of Child Health, University College London
Dr Helen Munn, Director, Medical Science Policy Academy of Medical Sciences	Professor Richard Trembath FMedSci, Professor of Medical Genetics Guys' Hospital
Dr Behzad Nadjm, Clinical Lecturer London School of Hygiene and Tropical Medicine	Professor Elizabeth Trimble CBE, Professor of Clinical Biochemistry Queen's University Belfast
Ms Katherine Nightingale, Assistant News Editor SciDev.Net	Professor Jonathan Weber FMedSci, Head, Division of Medicine Imperial College London
Dr Paul Newton, Director Wellcome Trust – Mahosot Hospital – Oxford University Tropical Medicine Research Collaboration	Dr Alison Webster, Director Infectious Diseases Medicine Development Centre GlaxoSmithKline
Ms Anne-Laure Page, Epidemiologist Epicentre, Médecins sans Frontières	Dr Jimmy Whitworth, Head of International Activities Wellcome Trust
Professor Geoffrey Pasvol, Professor of Infection and Tropical Medicine Imperial College London	Professor Roger Williams CBE FMedSci, Director University College London
Professor Catherine Peckham, Professor of Paediatric Epidemiology Institute of Child Health, University College London	Dr Penny Wilson, Diagnostic Specialist Technology Strategy Board
Sir Keith Peters FRS FMedSci, Emeritus Regius Professor of Physic GlaxoSmithKline	Dr Maria Zambon, Head Respiratory Virus Unit, Health Protection Agency
Ms Anita Ramesh, PhD Student London School of Hygiene and Tropical Medicine	Professor Alimuddin Zumla, Director, Centre for Infectious Diseases and International Health, University College London
Dr Steven Reid, Project Manager, CD4 Initiative Imperial College London	



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