INTRODUCTION OPEN

Expanding the role of diagnostic and prognostic tools for infectious diseases in resource-poor settings

Azra C. Ghani[1], Deborah Hay Burgess[2], Alison Reynolds[1] & Christine Rousseau[3]

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The life-saving impact of new diagnostic and prognostic technologies that aim to reduce the burden of infectious diseases is often not well understood. Although the potential benefits of other interventions such as drugs and vaccines can be estimated by simply counting the numbers treated and multiplying that by the effect size of the intervention, understanding the role that diagnostics can have requires more complex analyses. As for other interventions, the performance of the tool is important. Few, if any, diagnostic tools have 100% sensitivity and specificity or a perfect quantitative range. However, unlike drugs or vaccines, the impact of the diagnostic depends on the actions taken after the diagnostic or prognostic test result. First, the tests may not always be run or interpreted correctly because they are often used by staff with minimal training. This may further reduce performance, depending on the level of the health-care setting in which the test is used. This has been clearly demonstrated by a South African study[1] in which several HIV rapid diagnostic test procedures were observed and only 3.4% were found to have been performed in full compliance with procedure, suggesting that there is a potential for high rates of misdiagnoses. Second, the clinician or health-care worker must interpret the results and make the appropriate clinical decision. In the case of Cepheid Gene Xpert and malaria rapid diagnostic tests, for example, studies have shown that even when the test gives the correct result, treatment is often provided empirically[2,3]. Third, the clinical decision needs to be realized. This will depend on the availability of appropriate treatment facilities and drug stocks. Crucially, the combination and timing of these processes can affect the onward transmission of infectious diseases at the population level and hence have an impact on the control of epidemics or progress towards elimination of endemic diseases.

This complexity adds to the controversy in assessing the value of diagnostics and often delays the already long process of discovery, development and delivery of new technologies for global infectious diseases. This was addressed in the 2006 Nature Publishing Group supplement *Improved Diagnostic Technologies for the Developing World*, which used modelling techniques to define the value of new diagnostic tools for resource poor settings[4]. Over the subsequent 10 years there has been encouraging progress in the development and use of new diagnostics, but many gaps remain. By way of a response, this collection presents new modelling work that addresses the potential impact of diagnostic tools both at the individual and population level.

This work could not have come at a more crucial time. Over the past decade there has been a shift in the epidemiology of infectious diseases, with dramatic reductions in burden, which was catalysed by the Millennium Development Goals and the associated increase in global health funding[5]. This has been accompanied by a shift from control of diseases in centralized health-care settings to prevention and early treatment. Accompanying this changing epidemiology, diagnostics are increasingly demanded and used in novel health-care paradigms. Technological advances have supported this shift. For example, the reach of centralized laboratory testing can be extended through the use of specimen collection and stabilization technologies in combination with sample transport systems; such as the use of dried blood spots for HIV levels, malaria parasite detection and serology[6–8]. In addition, new portable and integrated technologies can allow testing at primary health facilities, providing greater access to care and adoption[9]. This was first quantified in a seminal study from Mozambique where point-of-care CD4 technologies with same-day results enabled a near doubling of patients on treatment, owing to the reduction in loss to follow-up that normally occurs when patients wait several weeks for results from centralized laboratory testing[10]. For chronic conditions such as HIV, self-testing is also being considered as a method to improve testing coverage and ultimately linkage to care[11]. Rapid results and ease of use are clearly key characteristics that are affected by the treatment paradigm or patient flow. For example, the balance may be shifted towards sensitivity over specificity if the reason for testing is to determine onward referral rather than immediate treatment. For reasons such as these, the target product specification for a diagnostic in these settings is likely to differ to that in centralized health-care settings.

As reported in the 2006 supplement, modelling can be a useful tool to capture the health impact that improved diagnostics can have on global health efforts. However, although the decision-analytic approach previously adopted was appropriate to estimate the impact of a diagnostic at the point of care on health outcomes such as cases, deaths and disability-adjusted life years (DALYs), in the wider contexts it is also important to capture the effect of the diagnostic on onward transmission. Transmission dynamic models are well developed for such a purpose and are increasingly used to guide product development and public-health decision-making for a wide range of diseases. However, the integration of diagnostics into such models is often overlooked. To fill this gap, the Diagnostics Modelling Consortium funded by the Bill and Melinda Gates Foundation was formed in 2013 to catalyse the incorporation of diagnostics into transmission dynamic models across key global health diseases, including HIV, tuberculosis, pneumonia, malaria and neglected tropical diseases. The Consortium and its partners brought together not only modelling groups, but also those involved in diagnostics development and disease

[1] MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College London, Norfolk Place, London W2 1PG, UK. [2]Principal, Kimataifa Diagnostics and Devices Consulting, 17319 15th Drive SE, Mill Creek, Washington 98012. Seattle, USA. [3]Bill and Melinda Gates Foundation, 500 5th Avenue North, Seattle, Washington 98109, USA. Correspondence should be addressed to A. C. G. e-mail: a.ghani@imperial.ac.uk.

Table 1 | Levels of laboratory testing available for public health programmes in different levels of the health system. Adapted from ref. 12.

Health-care level	Description	Appropriate diagnostic or prognostic tools
0	Informal – 'under the tree'	• First point of care with a community health worker – tool must be simple to use and not require special storage • Prognostic tools particularly relevant for rapid referral
1	Primary – health post and centres	• Simple diagnostic techniques, including collection of dried blood spots and rapid or dipstick tests
2	District – district hospital	• Act as referral centre for specimens sent from level 1 • Include dedicated laboratory space, trained technicians and reagents • Can manage a more extensive test menu for diagnosis and treatment
3	Regional or provincial – referral hospitals or part of regional or provincial health bureau	• Laboratory facilities sufficient to perform complete menu testing for HIV/AIDs, tuberculosis and malaria as well as many other diseases • Typically include level 2 laboratories
4	National or multicountry – reference laboratories for one or more countries	• Strengthen laboratory capacity for all diseases of concern and provide molecular and esoteric testing that cannot be performed in level 2 laboratories, for example nucleic acid assays, HIV drug resistance studies and tuberculosis drug susceptibility studies

specialists who could define the strategic needs within these priority disease areas. Over an 18-month period the groups worked together to define the questions that, when answered, would best inform diagnostic product and prognostic tool development, and to extend existing models to address these questions. At the same time, the group sought to share experiences and lessons learned across the disease areas.

Two themes emerged in the subsequent work. The first was the importance of considering the patient flow for use of both diagnostic and prognostic tools in the wider community. The papers by Floyd *et al.* and Arinaminpathy and Dowdy describe the importance of capturing individuals in the wider community who do not promptly seek care. Floyd *et al.* assess the potential impact of a new prognostic device — pulse oximetry — for pneumonia, and find that simple medical devices that increase early prognosis of severe pneumonia could have a substantial public health impact as well as being highly cost-effective, provided subsequent access to oxygen treatment is available. Arinaminpathy and Dowdy also consider this issue, but more broadly, for tuberculosis, arguing that the evaluation of new diagnostics needs to take into account not only the sensitivity and specificity of the diagnostic itself, but also the impact that it can have on patient behaviour and care seeking.

Similarly, the Working Group on Modelling of Antiretroviral Therapy Monitoring Strategies in sub-Saharan Africa explore the potential public health impact and cost-effectiveness of using viral load measurement to differentiate levels of care so that those with a lesser need visit the clinic less often, thereby freeing health-care capacity for those in greater need. Despite the limitations associated with viral load testing using dried blood spots (and noting that point-of-care tests may become available in the future), they find that such an approach is cost-effective. In the second HIV article, Sharma *et al.* present a systematic review of the methods that have been used to improve coverage of HIV testing. They find that compared with facility-based testing, community testing and counselling is a model that identifies HIV-infected individuals at an earlier stage of infection (higher CD4 counts). In addition, they find that mobile and self-testing are even more effective in reaching key population groups, including men, young people and those at higher risk.

Efforts have been made to standardize the settings where diagnostic technologies can be used, given the range of levels that exist — from centralized laboratories to minimally-resourced settings. During a meeting in January 2008 held in Maputo, Mozambique, the World Health Organization brought together key stakeholders who were charged with making recommendations on laboratory standardization and harmonization[12]. This group defined four tiers of the laboratory system (see Table 1), as well as level 0 or 'under the tree' — an informal site where diagnostics can and should be used. As patients flow through these levels, a range of different technologies will probably be used to meet their needs, and it will therefore be important to optimize the tools' placement and use based on potential impact. Now that technologies are available that can integrate into each laboratory setting, next-generation modelling efforts will need to address optimal placement.

The second theme was the use of new diagnostic technologies to target interventions with the purpose of disease elimination. This comes at a time when new global commitments for the elimination of diseases have been made, including a call in 2007 by Bill and Melinda Gates to move towards malaria eradication[13] (and subsequent inclusion of elimination goals in the World Health Organization Global Technical Strategy[14]) alongside the elimination goals set out for neglected tropical diseases under the London Declaration[15]. Diagnostic needs for elimination pose new challenges. First, as the disease declines to low levels, identifying remaining foci of infection is important. For this, diagnostic tools need to be sufficiently sensitive to detect the remaining reservoir of infection. However, as the end point is reached, and in the subsequent maintenance phase, identifying infected individuals becomes crucial. For this, highly sensitive and rapid diagnostic tests are required. In both the elimination and the maintenance phase, diagnostics have a crucial role in the overall surveillance strategy, providing the first indication of potential for re-emergence. However, for many diseases appropriate diagnostics for this phase are not yet developed, with major challenges remaining in relating the different biomarkers to disease status. For example, although substantial progress has been made in moving towards the elimination of onchocerciasis in West Africa, current diagnostic tools — such as skin-snips to detect micro-filariae and nodule palpation to identify foci of transmission — are unlikely to identify very low levels of infection and thus may have insufficient sensitivity to prevent resurgence[16]. Hence, for diseases such as this it is likely that a combination of diagnostic tests will need to be used, each targeted to the appropriate stage of transmission.

These issues are addressed in two related articles on *Plasmodium falciparum* malaria. Wu *et al.* undertake an extensive review of the relationship between current diagnostic tools used in endemic settings. They find that current rapid diagnostic tests detect only 41% of infections detected by high-sensitivity polymerase chain reaction (PCR) techniques, indicating that a substantial number of infections will be missed if this diagnostic is used in the field and implying that a large infectious reservoir remains. Slater *et al.* continue this theme to estimate the target product specifications for new diagnostic tests that aim to reduce onward transmission. They find that increasing the sensitivity of the current rapid diagnostic test tenfold could detect 83% of the infectious reservoir. Applying this strategy to settings in sub-Saharan Africa and Asia, the authors demonstrate that increase in sensitivity could widen the areas in which mass screen-and-treat programmes and targeted mass drug administration could succeed in interrupting transmission.

Medley *et al.* take a similar approach to assessing the role of diagnostics for visceral leishmaniasis — concentrating on the potential for elimination in the Indian subcontinent. They find that shortening the time from health seeking to diagnosis could dramatically reduce incidence, especially if a diagnostic can be developed that is able to detect infected individuals before the onset of clinical kala-azar. The study also highlights the importance of bringing modellers and scientists together to develop diagnostic tools early on in the development process. Given the overall poor understanding of the aetiology and transmission biology of pathogens such as *Leishmania*, modelling can help to identify key parameters for which further data are needed. In turn, the data collected can be used to refine the models in subsequent iterations, potentially speeding up the process of diagnostic development.

Finally, while the work of the Consortium was underway, the world experienced the unprecedented spread of Ebola virus disease across West Africa. During the subsequent global health response it became apparent that the reliance on PCR-based diagnostics resulted in significant delays in diagnosis. Nouvellet *et al.* review the development of rapid diagnostic tests for Ebola virus disease over the past year and use modelling to explore the potential benefits of such tests. Their results demonstrate the key role of rapid diagnostics

to guide individual treatment decisions, while also reducing the potential scale of future epidemics.

Although the outputs of the Diagnostics Modelling Consortium presented in this supplement clearly demonstrate the impact and cost-effectiveness of new diagnostic approaches for multiple diseases of global health significance, the impact of diagnostics remains overlooked. The results can be grave, ranging from overestimation of the impact of interventions when perfect diagnosis is assumed to ignoring the potential role of a diagnostic tool to facilitate lower-cost approaches to treatment. This supplement pulls together a range of articles that highlight the importance of considering the individual- and population-level aspects of the use of diagnostics, encouraging a shift in mindset for all infectious-disease modelling moving forward. In addition, the interdisciplinary nature of this work should not be underestimated. Bringing together the key scientific, clinical and strategic perspectives is imperative from the start of any effort to develop and use technology. Modelling, even at its best, is only a way to describe and quantify our thoughts. To truly determine the impact of diagnostics technologies, they must be evaluated in the field. Only then can we place the appropriate diagnostic and prognostic tools in the right settings to achieve our global health goals.

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1. Strategic Evaluation, Advisory and Development Consulting. *Analysis of POCT/VCT Performed at South African Primary Health Care Clinics* (SEAD, 2011).
2. McNerney, R. & Zumla, A. Impact of the Xpert MTB/RIF diagnostic test for tuberculosis in countries with a high burden of disease. *Curr. Opin. Pulm. Med.* **21,** 304–308 (2015).
3. Rao, V. B., Schellenberg, D. & Ghani, A. C. Overcoming health systems barriers to successful malaria treatment. *Trends Parasitol.* **29,** 164–180 (2013).
4. Hay Burgess, D. C., Wasserman, J. & Dahl, C. A. Global health diagnostics. *Nature* **444** (Suppl 1), 1–2 (2006).
5. United Nations. *The Millenium Development Goals Report* (United Nations, 2015).
6. Smit, P. W. *et al.* Systematic review of the use of dried blood spots for monitoring HIV viral load and for early infant diagnosis. *PLoS ONE* **9,** e86461 (2014).
7. Corran, P. H. *et al.* Dried blood spots as a source of anti-malarial antibodies for epidemiological studies. *Malar. J.* **7,** 195 (2008).
8. Tran, T. M. *et al.* A nested real-time PCR assay for the quantification of *Plasmodium falciparum* DNA extracted from dried blood spots. *Malar. J.* **13,** 393 (2014).
9. Fonjungo, P. N. *et al.* Access and quality of HIV-related point-of-care diagnostic testing in global health programs. *Clin. Infect. Dis.* http://dx.doi.org/10.1093/cid/civ866 (2015).
10. Jani, I. V. *et al.* Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: an observational cohort study. *Lancet* **378,** 1572–1579 (2011).
11. Choko, A. T. *et al.* Uptake, accuracy, safety, and linkage into care over two years of promoting annual self-testing for HIV in Blantyre, Malawi: a community-based prospective study. *PLoS Med.* **12**, e1001873 (2015).
12. World Health Organisation. *Consultation on Technical and Operational Recommendations for Clinical Laboratory Testing, Harmonization and Standardization: Report from the Maputo Meeting* (WHO, 2008).
13. Bill and Melinda Gates Foundation. *Melinda French Gates — Malaria Forum Keynote Address* http://www.gatesfoundation.org/media-center/speeches/2007/10/melinda-french-gates-malaria-forum (Bill and Melinda Gates Foundation, 2007).
14. World Health Organisation. *Global Technical Strategy for Malaria 2016–2030* (WHO, 2015).
15. World Health Organisation. *Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases: a Roadmap for Implementation* (WHO, 2012).
16. Vlaminck, J., Fischer, P. U. & Weil, G. J. Diagnostic Tools for Onchocerciasis Elimination Programs. *Trends Parasitol.* http://dx.doi.org/10.1016/j.pt.2015.06.007 (2015).

COMPETING FINANCIAL INTERESTS

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ADDITIONAL INFORMATION