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Diagnostics for Development

2014-05-30 08:00:59

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Having been left in the long grass for several years while donors, activists, governments and public health experts focused on the question of access to vital medicines, the issue of diagnosis is today at the very top of the global health agenda. The rise of diagnosis as a global health issue has tracked its reformulation into a question of access to diagnostic devices. A new wave of point of care, rapid detection, low-cost diagnostic devices has emerged as a multi-faceted solution to the poverty of laboratory infrastructures in resource poor settings, the high costs of treatment that follow from over-diagnosis, the burden of morbidity generated by diagnostic error and, increasingly, the imperative to monitor and evaluate

the “impact” of globally funded public health programs. Tiny, modest-looking technologies, such as the new immunochromatographic rapid test for sleeping sickness that detects antibodies against *Trypanosoma brucei gambiense* in 15 minutes, are imbued with the promise of healthier, more economical and more equitable futures. Bilateral donors, philanthropic organisations, ministries of health, university researchers, and frontline health workers are all working hard to turn those promises into a reality.

But how much work can the diagnostic device itself do? This question was at the heart of a workshop on ‘Diagnostics, Disease & Development’ that was hosted at the University of Edinburgh on 30th January 2014. The workshop brought together stakeholders from academia, civil society activism, private industry and non-profit product development partnerships to address the opportunities and challenges afforded by the rapid development, proliferation and roll-out of new diagnostics for development.

The rationale behind the experimental format was simple. While the social scientists and civil society activists who participated in the event wanted to learn more about the specificities of the “partnership”-based product development approach that increasingly dominates this sector and the constraints imposed by the institutional contexts, funding structures and regulatory environments in which those designing, developing and implementing new devices must operate; representatives from industry were keen to find out more about the health systems and care environments in which their devices will ultimately need to work. The focus on new diagnostics as the solution to problems of diagnosis has seen extraordinary progress in the development of affordable technologies. But these technologies have been accompanied by unanticipated challenges, obstacles and complications: in the global regulation of rapidly expanding markets, the integration of new diagnostics with existing health system infrastructures, and the unforeseen technological glitches that occur in difficult environments. These emerging challenges highlight the urgent need for cross-sector dialogue about the wider implications of and opportunities for new diagnostics in fragile health systems.

Partnership

The opening panel on “innovation networks and institutional configurations” highlighted the significance of partnership as both a buzzword and an actual constellation of relationships. Marcus Lovell Smith from Diagnostics for All highlighted some of the challenges accompanying the ‘non-profit’ partnership model for technology development. Non-profits avoid the major bias affecting Big Pharma, as they are not

required to make product choices based on profit margins. But he pointed to the constant pressure on non-profit organisations to raise capital. All but one of the five speakers depended on “soft funding” for their product development work. As Roger Peck pointed out in the case of PATH – this means they have to find $300 million dollars in “partnership” funding every year to ensure the stable employment of 1200 people employed across projects in 70 countries.

Many of the product development partnerships (PDPs) share funding streams, with the key funders – Gates Foundation, DFID and NIH – emphasising the development of ‘novel’ products that reduce complexity and enable implementation in low resource settings. A common language of ‘transformative innovations’ (Roger Peck) and ‘transformational improvement’ (Peter Jeffries) across the PDP presentations pointed to the weight of expectation currently being placed on new diagnostic devices, and also perhaps to certain biases within that funding environment. Nonetheless presentations on the everyday activities of product development revealed a multiplicity of relationships and institutional arrangements, and challenged the social scientists present to produce more fine-grained analyses of what partnership means in practice.

What and who, Caroline Jones asked, are diagnostic devices actually for? She noted the shifting goals for malaria diagnosis, whereby an earlier clinical goal – to identify infected persons for treatment – has become a mere add-on to a larger public health goal – evaluating the implementation and impact of malaria control programmes, in line with global control and elimination targets. Joseph Ndung’u described the perceived need to monitor impact of public health programs to be a driving force behind the development of new diagnostics for Neglected Tropical Diseases. A presentation from Annie Wilkinson described the biosecurity concerns that have framed diagnosis interventions for lassa fever in Sierra Leone. Chris Lowe explained that the mHealthcare phone applications his team were designing target the ‘worried well’ in a bid to identify illnesses sooner and bring down mounting health costs, raising questions about the ways in which new diagnostic devices might both create as well as respond to perceived needs. The expanding remit for diagnostic technologies is likely to have important consequences for national health systems as they attempt to integrate new testing regimes and data streams without complementary increases in budgetary support.

Jennifer Cohn from Medecins Sans Frontieres argued that the significant variability in the price that ministries of health pay for diagnostic devices indicates considerable leeway in device pricing. For example the cost of an HIV viral load test in Kenya is £11.50, in Thailand the same test costs $44.07. Diagnostics, Cohn argued, have a long way to go in terms of access by comparison with pharmaceuticals. Rather than demanding more

regulation MSF's agenda is to provide greater transparency, with the goal of assisting governments in negotiating down pricing. This provoked strong disagreement from Chris Lowe, who felt that the substantial R&D costs involved in diagnostics were being played down. Cohn's key point was that access to information could prevent market failure in contexts of greatest need. Where the devices supported by PDPs fall on MSF's pricing spectrum was unclear, and it is significant that this moral debate about the role of business in public health involved the representatives from civil society and commercial industry rather than public-private partnerships.

Indeed the tension between collaboration and competition emerged as a major theme that was crystallised in a discussion about whether we should design single or multiplex devices. On the one hand multiplex devices afford opportunities for cross-subsidy. Joseph Ndung'u underscored FIND's approach to diagnostic development which seeks out 'technology platforms' applicable to more than one disease. In this way products developed for profitable diseases like malaria or TB have their applications explored for non-commercial diseases. Here he cited two examples of cross over products – the iLED microscope and the LAMP test – which, while initially devised for TB – are now being used to diagnose the neglected tropical disease Human African Trypanosomiasis. Establishing a good relationship with the manufacturer is a key component of this FIND strategy. On the other hand it was noted that while the Bill and Melinda Gates Foundation would ideally like to see the development of universal do-it-all diagnostic device there is in fact no appetite for this kind of device from industry quarters as it would kill off competition in the market.

The Point of Care

The question of single versus multiplex surfaced again in the session on "point of care challenges". Clare Chandler's extensive field research on rapid diagnostic tests for malaria in Tanzania suggests that they have had very little impact on treatment practices, partly because a negative result for malaria still effectively leaves the patient undiagnosed. For many of the participants from industry this example pointed to the importance of the multiplex test that would enable health workers to diagnose for multiple common diseases at the same time. It also points to the potential proliferation of infrastructure around supposedly self-contained diagnostic devices, as the ability to diagnose for one disease necessitates the diagnosis of further diseases.

Caroline Jones suggested that presuming the need to diagnose at all costs was problematic and would take us to a place where 'if we can't

diagnose it, it doesn't exist'. In her opinion this stance would risk pitting technology against a clinician's skill, and a holistic approach to healthcare against the simplistic imperative to administer drugs. Caroline Jones also reminded us that it was only in 1993 that the WHO took the decision to treat all fevers as 'malaria' and that this regimen of presumptive treatment often replaced nuanced local distinctions between types of fevers. Behaviour change can be successful, she suggested, but by the time it has been achieved it might no longer be desirable.

Crucial here are issues of trust, both in relationships between patient and clinician and clinician and test. Diagnostic tests are only useful in case management if they are acted on and this depends on the health worker trusting the result. Joseph Ndung'u and Lars Gredsted of the Wellcome Trust both suggested that the reliability of health devices (in this instance HAT RDTs and DDT bed nets) could be double-checked with supplementary tests. Indeed FIND are currently involved in the development of positive control wells that will enable health workers to test the accuracy of devices on site. But might this safeguard potentially undermine rather than strengthen user trust in the original device?

Regulatory Environments

The issue of trust emerged again in relation to global regulatory frameworks. David Mabey pointed out that the WHO simply cannot keep up with the current pace of diagnostic development. Where in the pharmaceutical industry only four or five new drugs require pre-qualification in a given year hundreds of new diagnostic devices are coming onto the market annually. This has the potential to both reduce the quality of devices and trust in those devices by health workers. David Mabey discussed a new International Centre for Diagnostics set up at LSHTM by Professor Rosanna Peeling that is working with partners to try to harmonise the regulation of diagnostic tests globally. This raises important questions about the kinds of institutional networks and partnerships that will enable effective regulation in a rapidly growing market. Equally important is the fact that medical equipment does not usually need to undergo the same levels of testing and qualification to meet country level requirements as pharmaceuticals. This means that either country level guidelines/laws need to change or governments are even more dependent on global regulation and pre-qualification systems. At a regulatory level the varying capacity of national and regional authorities to operationalise effective safeguards reminds us of the broader system requirements needed to support new point of care diagnostics.

Hidden Infrastructures

'Health systems integration' was the theme of the third and last panel. Ian Harper described the roll out of cartridge-based Gene Xpert machines for the diagnosis of multi-drug resistant tuberculosis in Nepal. Intended to improve the accuracy and speed of diagnosis, the $25,000 machines encountered numerous operational challenges in the field. Breakdowns were common and frequent power outages added to diagnosis times. The machines generated an increase in positively diagnosed TB cases – cases which had not been budgeted for in the national treatment budget; and there was no room in the national database for categorising the additional cases picked up by the machines.

Interestingly, while GeneXpert is feted as a point of care TB diagnostic, the presentations by Ian Harper and Jennifer Cohn drew attention to the substantial infrastructure demands the machines place on existing laboratories – the machines require a dependable electricity supply, a working computer, careful infection control and a skilled operator. Indeed the discrepancy between the skillsets of existing lab techs and the lab techs needed to operate the machines has seen the introduction of financial incentives for technicians to conduct the tests in Nepal, raising further questions about the overall cost-burden of such devices and their post-donor sustainability.

The limitations of GeneXpert brought the discussion full circle to the implications of potential multi-platform monopolies for health system capacity. Cepheid, the company that manufactures GeneXpert is currently planning the development of cartridges to test for multiple diseases. The need to integrate new tests into existing infrastructure or to create new supportive infrastructure for new diagnostic tests marks them out as uniquely different to pharmaceuticals, which can be switched in and out of health systems. Instead, having built the required infrastructure for diagnostics, it is much less likely that a diagnostic device will be easily superseded by an improved or cheaper device. The infrastructure foundations give the test a semi-permanence, which may have cost and efficacy repercussions for the national health system later down the line.

The case studies of new diagnostic devices discussed at the workshop suggest that point of care devices do not substitute for laboratory infrastructure or negate the need for it. Instead they might actually require entirely new types of infrastructure being built up around new, potentially 'infrastructure-lite' tests: solar, cool chain, mobile technologies to geospatially capture diagnoses. In this scenario new tests are not removing the need for infrastructure but may in fact be replacing it with

more platform-less physical infrastructures that require more sophisticated technological platforms.

Concluding remarks: Product Profiles

Can diagnosis be contained in a single device? Where a policy and investment focus has increasingly narrowed diagnosis down to diagnostics, this workshop drew attention to the infrastructures, institutions, and practices that make up the diagnostic process.

Taking the concept of the diagnostic process, which was introduced at the workshop by Nora Engel, as a starting point we suggest that this process might be expanded backwards from the point of care to include a focus on the funding structures, regulatory environments, partnership agreements and lab bench collaborations that enable and direct the flow of product development; and outwards to the health system infrastructures, logistics and complexity of point of care interactions that new devices must necessarily entangle with.

One very practical way to think through the implications of expanding the parameters of diagnosis in such a way is to focus on the role of Target Product Profiles. Target product profiles are a central part of the early product development cycle across the medical device industry. At present TPPs focus on technical specifications and are usually written with assistance from a variety of technical and scientific experts, which rarely resonate directly with ‘end users’: people seeking treatment. More than anything it is the TPP that defines the parameters of the device and the responsibility of the developers, often cutting the network at the sidelines of scientific evidence and capacity. This workshop highlighted the impossibility of divorcing technology from context: perfectly functional technologies are rendered useless if they are not trusted, test results are renegotiated, new devices necessitate new infrastructures, regulatory frameworks struggle to keep up with product development. What if these insights, often garnered from social science research, were used to expand the remit of the target product profile in ways that afforded improved health system integration? What might a socio-technical product profile that tracks needs, limitations and opportunities through institutional arrangements, point of care processes and health system infrastructures look like?

Workshop Organisers

Alice Street *is a social anthropologist whose works explores issues related to health institutions, personhood, biomedical technology and management in Papua New Guinea and India.*

Emma Michelle Taylor *is a research fellow on the ERC-funded project* 'Investigating Networks of Zoonosis Innovation' (INZI)*. Her research explores issues of health policy, healthcare financing, development coordination and aid effectiveness in Sub-Saharan Africa*

James Smith *is Professor of African and Development Studies at the University of Edinburgh. He is Acting director of the* Centre of African Studies *& Director of the* Global Development Academy*. He has published widely on the relationship between scientific research, technological innovation and international development. He has recently been awarded a* European Research Council *Advanced Investigator Grant for a project entitled* INZI (Investigating Networks of Zoonosis Innovation)*.*

Ian Harper *is a trained medical practitioner who has worked in hospital medicine and general practice in the UK. For three and a half years he managed a tuberculosis control project in Nepal, and for two years worked with NGOs throughout India in supporting community health programmes. He is the recipient of a Wellcome Trust Senior Investigator Grant for the project:* Understanding TB Control: Technologies, Ethics and Programmes

Workshop Contributors

Joseph Ndung'u is the head of the HAT and Other Neglected Diseases diagnostics programme at FIND in Geneva. He has a degree in Veterinary Medicine and Surgery (BVM) from the University of Nairobi and a PhD in immunopathology of HAT from the University of Glasgow's Veterinary School. He is a Visiting Professor of the University of Glasgow and a Corresponding Fellow of the Royal Society of Edinburgh (CorrFRSE).

Chris Lowe is Professor of Biotechnology in the University of Cambridge and a Fellow of Trinity College, the Royal Academy of Engineering, the Institute of Physics and the Royal Society of Chemistry.His principal research interests cover areas of healthcare biotechnology including biopharmaceuticals, diagnostics and sensors, ageing and medical microbiology.

Marcus Lovell Smith is the CEO of Diagnostics For All. Prior to this, Marcus has directly founded and run businesses in environmental services, real estate, utility metering technology, and broadband wireless. Most recently he ran Sensable Technologies (haptics and 3D software)

and Microbia Inc (industrial biotechnology). He has worked at several of the major US investment banks. He has an MA in chemistry from Oxford and the Gibbs Prize in Chemistry.

Roger Peck is a technical officer in PATH's Technology Solutions Global Program, where he is responsible for laboratory-based tasks and activities related to the design, development, and evaluation of diagnostic tests suitable for use in low-resource settings. He also manages relationships with private-sector collaborators during research and development, product development, technology transfer, and clinical evaluation of diagnostic tests. Mr. Peck has over 18 years of experience developing rapid diagnostic tests.

Peter Jeffries is the CEO of GalvMed. He sat on the board of GALVmed from the formal creation of the charity in 2006 until 2012. He trained as a veterinarian before working in Zambia, Kenya, France and the US.

David Mabey is a physician specialising in Infectious and Tropical Diseases. In recent years he has become particularly interested in the development and evaluation of new point-of-care diagnostics for infectious diseases and worked with Rosanna Peeling to establish the International Diagnostics Centre at the School in 2012.

Christine Amongi Acup is a postdoctoral researcher at the Division of Pathway and Infection Medicine, University of Edinburgh, researching and working with African trypanosomiasis. Christine joined the sleeping sickness group in 2006, which is dedicated to molecular epidemiology of sleeping sickness in Uganda.

Clare Chandler is a medical anthropologist who has worked at the interface with global health since 2004, researching social aspects of malaria, health care delivery, public, private and community health care access, diagnostics, use of medicines and pharmacovigilance in low-resource settings, primarily in Tanzania and Uganda, as well as in West Africa. Clare is experienced in interdisciplinary research, following her training in both anthropology and epidemiology with a series of studies working with clinicians, economists and epidemiologists to develop and evaluate interventions to improve access to better quality health care, including several cluster randomised trials. She is concerned with improving evaluation methodology, including re-shaping questions around global health intervention and impact and she is committed to strengthening the quality of social science in global health research.

Nora Engel is an assistant professor of global health at Maastricht University. Her work focuses on innovation dynamics in global health challenges (such as tuberculosis) and on the sociology of diagnostics and

innovations at the point-of-care in India and South Africa.

Jennifer Cohn is the medical coordinator of MSF's Access Campaign, based in Geneva. She has worked with MSF on HIV policy and medical support in Kenya, Uganda and Malawi. She is also an assistant professor of Infectious Diseases at the University of Pennsylvania School of Medicine and has provided clinical care to people living with HIV, HCV and TB in the US and Kenya for the past 6 years. She has experience in conducting operational research and served as the PI on two recent operational research projects focused on HIV care in Kenya. She is published in peer-reviewed journals including Science, the Lancet and JAIDS. Jennifer received her MD and did her infectious diseases sub-specialty training at University of Pennsylvania School of Medicine and her MPH at Johns Hopkins University.

Caroline Jones is a senior social scientist at the KEMRI-Wellcome Trust Reseach Programme in Kenya. She has a PhD in anthropology and 20 years of experience working in sub-Saharan Africa on treatment seeking and the provision of health care for malaria. More recently the focus of her research has shifted to the implementation and sustainability of public health interventions, focusing on the relationship between the production of data and its use in decision making for policy and practice. A key role in her current position is to contribute to building Kenyan and regional expertise to develop and lead such research.

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Diagnostics Workshop Report – Final

AMA citation
Street A, Taylor E, Smith J, Harper I. Diagnostics for Development. *Somatosphere*. 2014. Available at: http://somatosphere.net/2014/05/diagnostics-for-development.html. Accessed May 30, 2014.

APA citation
Street, Alice, Taylor, Emma Michelle, Smith, James & Harper, Ian. (2014). *Diagnostics for Development*. Retrieved May 30, 2014, from Somatosphere Web site: http://somatosphere.net/2014/05/diagnostics-for-development.html

Chicago citation
Street, Alice, Emma Michelle Taylor, James Smith and Ian Harper. 2014.

Diagnostics for Development. Somatosphere. http://somatosphere.net/2014/05/diagnostics-for-development.html (accessed May 30, 2014).

Harvard citation
Street, A, Taylor, E, Smith, J & Harper, I 2014, *Diagnostics for Development*, Somatosphere. Retrieved May 30, 2014, from <http://somatosphere.net/2014/05/diagnostics-for-development.html>

MLA citation
Street, Alice, Emma Michelle Taylor, James Smith and Ian Harper. "Diagnostics for Development." 30 May. 2014. Somatosphere. Accessed 30 May. 2014.<http://somatosphere.net/2014/05/diagnostics-for-development.html>