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Re-imagining the future of diagnosis of Neglected Tropical Diseases

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ABSTRACT

Neglected Tropical Diseases (NTDs) affect an estimated 1 billion people in 149 countries. The World Health Organization (WHO) prioritised 17 NTDs for control and elimination by 2020 and defined a Road Map to help countries reach these goals. Improved diagnostics for NTDs are essential for guiding treatment strategies at different thresholds of control, interruption of transmission, elimination and post-elimination surveillance. While substantial progress has been made in the last decade with chemotherapy, the same cannot be said of diagnostics, largely due to the perceived lack of a commercially viable market for NTD diagnostics.

New sample in-answer out nucleic acid amplification technologies that can be performed at the point-of-care offer improved performance over current technologies and the potential to test for multiple pathogens using a single specimen. Finding commonalities for different NTDs in terms of geographic overlap, sentinel populations and treatment strategy will allow NTD programs to leverage these innovations to build cost-effective multiplex surveillance platforms. Connectivity solutions linking data from diagnostic laboratories and POC test readers/devices provide opportunities for automated surveillance systems to make health systems more efficient, improving patient outcomes and assessing impact of interventions in real time. New models of public–private product development partnerships are critical in leveraging diagnostic innovation in other priority area for better diagnosis, control and elimination of NTDs.

1. Introduction

Neglected Tropical Diseases (NTDs) affect an estimated 1 billion people in 149 countries in the developing world and give rise to a myriad of adverse impacts, including anemia, blindness, cognitive impairment, and death [1,2]. The World Health Organization (WHO) prioritised 17 NTDs (Buruli ulcer, Chagas disease, cysticercosis, Dengue, drancunculiasis (Guinea worm disease), echinococcosis, endemic treponematoses (Yaws), foodborne trematode infections, human African trypanosomiasis (HAT), visceral leishmaniasis (VL), leprosy, lymphatic filariasis (LF), onchocerciasis, rabies, schistosomiasis, soil-transmitted helminthiases (STH), and trachoma) for control and elimination. These NTDs were selected on the basis that their transmission characteristics or treatment opportunities make them good candidates for control and elimination [3].

WHO, the Bill & Melinda Gates Foundation and 13 leading pharmaceutical companies, at a meeting in London in 2010, resolved to sustain, expand and extend programmes to ensure the necessary supply of drugs and other interventions to eradicate Guinea worm disease, eliminate LF, leprosy, HAT and blinding trachoma; and to control schistosomiasis, STH, Chagas disease, VL and onchocerciasis by 2020 [4]. The London Declaration ensured the donation of drugs for NTDs but diagnostics, critically needed for monitoring progress towards elimination and assessing the impact of special intervention, was not included in the Declaration as a priority.

In 2013, WHO defined a Road Map including five key interventions to help countries reach the 2020 goals [3]. These are: (i) preventive chemotherapy based on large-scale use of safe, single-dose medicines at regular intervals (i.e. mass drug administration, MDA); (ii) innovative and intensive case management; (iii) vector ecology and management; (iv) improvements in water, sanitation and hygiene in NTD-endemic areas; and (v) veterinary interventions to protect and improve human health [2,3]. While substantial progress has been made in the last decade with chemotherapy reaching a billion people in 2014 [5], the same cannot be said of diagnostics needed to guide chemotherapy and for surveillance, largely due to the perceived lack of a commercially viable market for NTD diagnostics.

Diagnostics are needed, with the exception of Guinea worm which is associated with unmistakable clinical features, to monitor and certify elimination of NTDs. Dowdle advocated for 'practical diagnostic tools of sufficient sensitivity and specificity to detect levels of infection that can lead to transmission' as an essential requirement for disease elimination or eradication [6]. The lack of a clear diagnostic strategy has resulted in limited surveillance data, with countries often using only

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using disease burden as a proxy for countrywide data. Solomon et al. suggested that country programs for control and elimination of NTDs demand improved diagnostic tools in order to "guide decisions on the required intensity, frequency, and duration of intervention and to conduct surveillance for re-emergency of infection after elimination" [7].

This article examines recent advances in diagnostic technologies driven by high profile, high burden diseases such as HIV and tuberculosis, emerging global health threats such as antimicrobial resistance and emergencies such as outbreaks of SARS, Ebola virus disease and Zika virus infections, and determines how these innovations can be leveraged to improve the diagnosis and surveillance of NTDs.

2. Investments in diagnostic innovation

Accurate diagnostic tests are commercially available for most infectious diseases. These tests are laboratory based and hence not widely accessible in the developing world, where laboratory infra-structure is often limited. The need for increasing access to diagnostics for patients with HIV and TB in the development world has led to major investments in more accessible diagnostic technologies that can be used at the point-of-care within the last decade.

2.1. Diagnostic innovations for HIV and tuberculosis

UNAIDS set 90–90–90 targets for HIV which call for 90% of those who are infected know their HIV status, 90% of those infected be put on treatment, and 90% of those on treatment achieve viral suppression [8]. Globally, countries are now at 50%, 37% and 25% respectively with regard to these targets [9]. To realize these targets, good performing diagnostic and monitoring tests that are widely accessible for populations in remote areas or marginalized from care are needed.

The diagnosis of TB traditionally depends on smear microscopy and chest radiography, both of which are insufficiently sensitive and specific. Culture is highly specific but requires up to 6 weeks for a result. Molecular methods are now used in developed countries, but the cost and requirement for laboratory infrastructure and skilled technical staff prevent their adoption in low-resource settings. Modeling studies show that if a test of 85% sensitivity and 97% specificity can be performed during a single patient visit and is widely implemented, 625,000 lives could be saved each year [10,11].

Investments in point-of-care (POC) technologies have resulted in a range of highly sensitive and specific HIV and TB molecular assays that can be performed in remote settings [12]. These tests are designed in a "sample-in answer-out" format, requiring minimal training, and providing a result in 1–2 h. Molecular platforms which can detect *Mycobacterium tuberculosis* and rifampicin resistance with high accuracy in just under 2 h have transformed TB diagnosis in both the developed and developing world. POC tests for CD4 enumeration have been commercially available for a few years now and have shortened delay in HIV treatment [13]. POC assays for HIV early infant diagnosis and viral load are currently under evaluation and will be implemented shortly. The expectations are that these tests will increase access to HIV viral load monitoring and early infant diagnosis with faster turn-around time for results to patients, increased linkage to care and reduced loss-to-follow up, and decreased risk of drug resistance.

2.2. Diagnostics for global health emergencies

Further investments in technological innovation are being driven by successive global health emergencies including SARS, flu, MERS CoV, Ebola virus disease and Zika virus infection. WHO calls for development of open platform technologies to accelerate the development, validation and production of vaccines, therapeutics, diagnostics and reagents for infectious diseases of epidemic potential as part of the WHO Blue Print for R&D preparedness [14]. At the 2015 G7 Ministers of Health meeting, there was consensus on "…continued financing, collaboration and coordination … through initiatives such as the WHO blueprint for R&D preparedness and the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)" [15].

The priority pathogens for the WHO Blue Print R&D include Crimean Congo Haemorrhagic Fever (CCHF), Filoviruses, Lassa, Severe Coronaviruses such as the Corona viruses that caused SARS and the Middle East Respiratory Syndrome (MERS CoV), Nipah virus, Rift Valley fever, Chikungunya, Zika and Severe fever with Thrombocytopenia Syndrome (SFTS), an emerging tick-borne infectious disease caused by the SFTS virus (SFTSV), a novel and highly pathogenic phlebovirus in the family Bunyaviridae. As a result of the call for open platform technologies, industry and public sector developers have initiated collaborations to work together to accelerate product development.

These open platform technologies are being developed by companies that have already developed highly accurate POC tests for HIV and TB. Many of these companies have also developed cartridges to detect Ebola and Zika viruses using the same platform. Some companies have already developed a broad menu of infectious diseases on the same platform. Advocacy and incentives, such as advance market commitment, would be needed for these companies to apply their technologies to NTDs. A review of emerging molecular technologies that have been developed and can be used in resource-limited settings has been published [16].

2.3. Antimicrobial resistance

Antimicrobial resistance (AMR) is one of the greatest public health challenges of this century with an estimated 25,000 deaths and over €1.5 billion a year in healthcare expenses and productivity losses in Europe alone [17–19]. In the United Kingdom AMR Strategy, two of the five AMR targets require the development of diagnostics that will rapidly identify infections that require antibiotics and of assays that can be used to identify and track patterns of antimicrobial resistance [18]. Rapid POC tests can also be used in drug trials to reduce the cost and length of trials, as target populations can be identified and recruited without expensive laboratory tests and procedures. Diagnostic technologies for AMR currently available and in the pipeline are described in a compendium prepared by the Oxford Centre for Evidence-based Medicine [20].

The challenge is to create a cost-effective, accurate, rapid, and easy-to-use test for bacterial infections that will allow health professionals worldwide to administer the right antibiotics at the right time or rule out antibiotic use by identifying viral infections. A number of initiatives to incentivise public and private sectors to develop rapid diagnostic tests and assays for AMR surveillance have been announced. The £10 million Longitude Prize is a prize fund for a diagnostic tool that can be used to rule out antibiotic use or help identify an effective antibiotic to treat a patient [21]. The Horizon 2020 prize of €1 million put forth by the European Commission is to incentivise better use of antibiotics for respiratory infections through the development of a rapid test that will allow healthcare providers to distinguish, at the point of care, between patients with respiratory tract infections that require antibiotics and those who can be managed safely without antibiotics [22]. The US National Institutes of Health has also offered a prize of up to $20 million to the first group(s) to develop a rapid, POC diagnostic test to be used by health care providers to identify highly resistant bacterial infections to promote responsible use of antibiotics [23].

Promising high throughput array technologies for pathogen detection coupled with detection of antimicrobial susceptibility patterns for AMR surveillance will be needed to guide patient management and improve our understanding of the emergence and spread of resistance. How can the NTD community leverage these investments in diagnostic innovation to improve patient management, disease control and surveillance towards the elimination of NTDs?