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REVIEW

Diagnostics in a digital age: an opportunity to strengthen health systems and improve health outcomes

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Diagnostics play a critical role in clinical decision making, and in disease control and prevention. Rapid point-of-care (POC) tests for infectious diseases can improve access to diagnosis and patient management, but the quality of these tests vary, quality of testing is often not assured and there are few mechanisms to capture test results for surveillance when the testing is so decentralised. A new generation of POC molecular tests that are highly sensitive and specific, robust and easy to use are now available for deployment in low resource settings. Decentralisation of testing outside of the laboratory can put tremendous stress on the healthcare system and presents challenges for training and quality assurance. A feature of many of these POC molecular devices is that they are equipped with data transmission capacities. In a digital age, it is possible to link data from diagnostic laboratories and POC test readers and devices to provide data on testing coverage, disease trends and timely information for early warning of infectious disease outbreaks to inform design or optimisation of disease control and elimination programmes. Data connectivity also allows control programmes to monitor the quality of tests and testing, and optimise supply chain management; thus, increasing the efficiency of healthcare systems and improving patient outcomes.

Keywords: Connectivity, Diagnostics, Digital age, Point-of-care, Surveillance

Introduction

'*Without diagnostics, medicine is blind*.' Alain Merieux.

Diagnostics and laboratory services have been labelled as the Achilles heel of global health.[1] In the past, low quality diagnostics and ineffective laboratory services resulted in a mistrust of laboratory results, which in turn led to a decreasing demand for laboratory services and a low priority for funding.[2] The 2008 Maputo Declaration has called on governments, multilateral agencies, development partners, professional associations and academic institutions to address laboratory challenges that limit the scale-up of services for TB, malaria and HIV diagnosis and care. Together with the 2010 US Centers for Disease Control and Prevention's call to End the Neglect of laboratories, this has provided a major milestone on a pathway to place diagnostics and laboratory services as important pillars of a healthcare system.[3,4] Recent outbreaks of influenza, Middle East respiratory syndrome coronavirus (MERS-CoV) and Ebola virus disease illustrate the importance of diagnostics in outbreak investigations.[5–7] With rapid technological innovations in the last 10 years and donor investments in the development of improved diagnostics for infectious diseases of public health importance, it is time to re-examine the Achilles heel and explore the promises and challenges of diagnostics in a digital age.

The role of diagnostics

Accurate diagnostic tests play a key role in clinician trust and patient management. Diagnostic testing is traditionally considered as a tool to rule in or rule out a condition or infection when clinical presentation in a patient is non-specific. For diseases such as HIV and other sexually transmitted infections, most infections are asymptomatic but can cause serious long-term consequences. Diagnostics are used to screen for infection so that treatment can be given to prevent the development of long-term complications and to interrupt the chain of transmission to sexual partners or to the fetus in the case of pregnant women. A test for the human papillomavirus helps to determine risk of disease progression to cervical cancer. For pathogens that have developed antibiotic resistance, such as *Neisseria gonorrhoeae*, diagnostic testing is used to determine antibiotic susceptibility to ensure treatment efficacy. For HIV patients, a CD4 test result is used to determine if the patient is eligible for antiretroviral treatment and, for those on treatment, a viral load assay is used to determine treatment compliance and drug efficacy. A test of cure is used to determine when treatment can be stopped (Figure 1).

Beyond patient management, diagnostics play a critical role in various aspects of public health through disease prevention and control. Diagnostics are critical in surveillance, to monitor trends

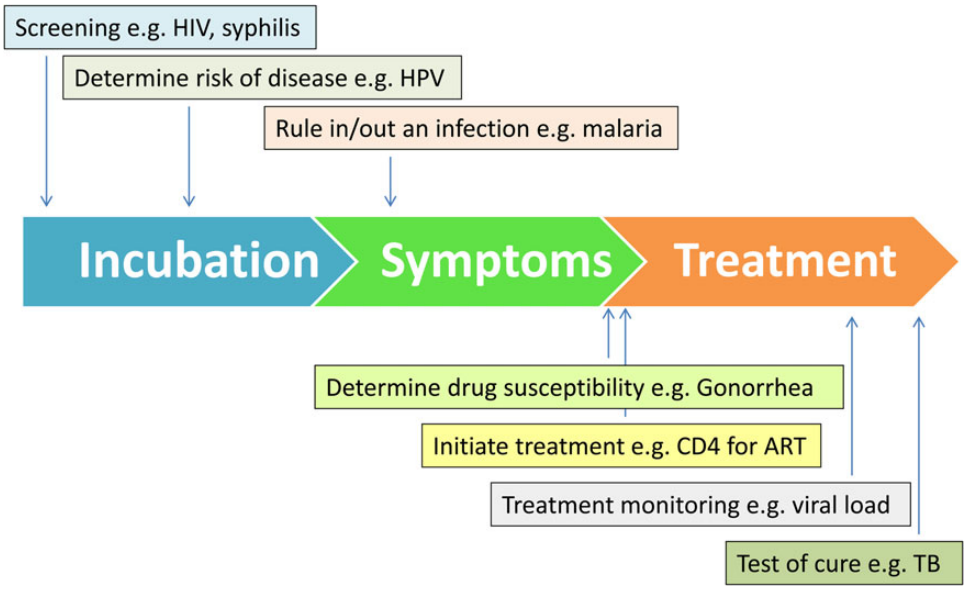

Figure 1. Role of diagnostics in clinical decision making. ART: antiretroviral treatment; HPV: human papillomavirus. This figure is available in black and white in print and in color at International Health online.

in disease and antimicrobial resistance and assess the impact of interventions.

Diagnostic tools 'of sufficient sensitivity and specificity to detect levels of infection that can lead to transmission' were identified as one of the three essential requirements for disease elimination or eradication.[8] WHO has set eradication or elimination targets for a number of neglected tropical diseases (NTDs), including Guinea worm, polio, yaws, trachoma, schistosomiasis, lymphatic filariasis, onchocerciasis, human African trypanosomiasis, Chagas' disease and visceral leishmaniasis (VL)[9] and the elimination of mother to child transmission (eMTCT) of HIV and syphilis. Mass drug administration (MDA) is the main control strategy for many of these diseases, resulting in the need for highly sensitive tests to detect the few remaining cases in areas of low transmission intensity after multiple rounds of MDA. Highly specific tests are then needed to certify elimination and maintain post-elimination surveillance. There is often little commercial interest in the development of diagnostics that are used mainly for surveillance because of the low return on investment.

For a NTD such as schistosomiasis, the Chinese national control programme has defined stages for schistosomiasis control as morbidity control (prevalence over 5% as defined by stool examination), infection control (prevalence of 1–5%), transmission control (prevalence lower than 1%), transmission interruption (no case detected in 5 years successively) and elimination (no case detected in the 5e years after transmission was interrupted). Diagnostics results are used to inform national and regional control policy, redirect resources and to transition to the next phase of the control and treatment strategy.[10] The WHO targets for eMTCT and WHO/UNAIDS 90-90-90 targets for HIV by 2020 also include diagnostic test coverage as indicators for efficiency of service delivery that help countries with setting a course to have an AIDS free generation and to end the HIV epidemic by 2030.

Recent technological advances in diagnostics

Diagnostic testing is usually performed in laboratories. In countries where the laboratory infrastructure is limited, WHO advocates for the use of a syndromic approach for patient management whereby patients are treated for all the major causes of that syndrome. This often leads to overtreatment and increases risk for the development of antimicrobial resistance. In the last decade, rapid point-of-care (POC) diagnostic tests fulfilling the ASSURED criteria (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable) have become commercially available and are widely used for infectious diseases such as malaria, HIV and syphilis.[11–15] These tests have allowed control programmes to increase access to testing, identify those who need to be put on treatment, optimise disease control and save lives. However, the quality of these tests varies, quality of testing is often not assured and there are few mechanisms to capture test results for surveillance when the testing is so decentralised.

Emerging diagnostic technologies to transform disease surveillance

A new generation of immunoassays, molecular and nanotechnology platforms has been developed in recent years that can improve patient management and disease surveillance. These platforms have superior performance and make use of optical readers, mobile phones and data transmission capabilities to improve reading of results and data transmission. Such technologies provide real-time results to inform patient management decisions. Data, linked to precise geographical locations using GPS, can be transmitted to a central database to inform disease control programmes or to monitor progress towards elimination.

Many of these assays can also yield quantitative results to give estimates of pathogen copy number or, in the case of HIV, to monitor treatment compliance or efficacy. These technology

platforms can also be used to detect multiple targets from a single specimen. For geographic areas with multiple diseases targeted for elimination, if surveillance is conducted in the same sentinel population, such as children under the age of 10 years, using the same specimen, such as a blood sample, exposure to multiple NTDs can be detected on a multiplex platform. This may be a more cost-effective means of conducting post-MDA surveillance than collecting specimens and testing for a single NTD at a time,[16,17] although cost-effectiveness of using these platforms for multiple NTDs remains to be demonstrated.

Increased sensitivity of detection using these advances has made it possible to have tests that detect antibodies from oral fluids. The use of these non-invasive specimens has made it possible to design HIV tests for self-testing or for home use.[18] The availability of self-testing at home has allowed testing to be de-stigmatised and should help countries with achieving the first 90 of the UNAIDS/WHO 90-90-90 targets.[19]

Bead-based immunoassays

Bead-based technologies are more versatile and potentially offer higher sensitivity compared to traditional solid phase immunoassays.[20] Instead of using enzymatic amplification of a colorimetric substrate, bead-based assays can use a range of labels, including laser or fluorescence to detect the binding of the secondary antibody to an antigen or antibody target. The beads are in solution, offering more sites for ligand binding compared to a solid phase support. Fluorescent intensities can yield quantitative results. Protein arrays offer the potential of quantification of the antigen target as a surrogate measure of bacterial, parasite or viral load to inform treatment strategies. Detection of multiple targets from the same pathogen can lead to increased efficiency over single-target assays. Detection of targets from multiple pathogens using a single specimen can offer substantial cost and sample savings over traditional ELISA measurements. The detection platforms are often equipped with data transmission capacities and allows near real-time surveillance of disease trends and monitoring the effect of special interventions.

Microfluidic immunoassays

Microfluidic devices offer many advantages, such as high throughput, short analysis time, small volume and high sensitivity, which make them an ideal immunoassay format for clinical diagnoses. The current microfluidic immunoassays have limited multiplexing capability compared to flow cytometric assays but are improving.

Immunoassays developed on a microfluidic platform that reproduce all the steps of a traditional ELISA in a miniaturised format are now available.[21] The microfluidic disc can fit into the palm of a hand and is rapid and inexpensive to manufacture. These platforms allow multiplexing, but have only been validated for antibody detection in blood samples. Antigen detection from urine or stool samples will require multistep specimen processing and/or purification or concentration before being put into the antigen-antibody reaction within the microfluidic channels. A recent publication showed that it is possible to use the power of smart phones to power a microfluidic immunoassay reaction by plugging the reaction chamber into a smart phone using a dongle.[22] Over 80 assays can be run before recharging is necessary. The results are interpreted and displayed on the phone and the data transmitted to a central database if required. A dual test to detect antibodies to HIV and syphilis has been designed on this platform and will have utility not only to improve access to prenatal screening but also to allow surveillance data for the dual elimination of MTCT of HIV and syphilis to be available in real time.[23]

Nanosensor assays

A growing number of promising diagnostic tools are based on nanotechnology. The application of nanomaterials to detect host or pathogen biomarkers has the potential to yield ultrasensitive assays. Quantum dots are fluorescent semiconductor nanoparticles typically between 10 and 100 atoms in diameter and the technology has been applied to the development of ultrasensitive tests for HIV and other viral infections.[24] It is also possible to use these technologies to combine pathogen detection and speciation with genetic analysis, such as detection of single nucleotide polymorphisms. Hence, they can be used for high throughput screening of drug mutation targets. Quantum wires are being used in the development of a fully automated diagnostic test for malaria infection, speciation and drug resistance status in less than 20 minutes.[25]

These nanosensors can ultimately be configured to a handheld PDA-type device or a thin plate about the size of a small business card containing a tiny nanowire sensor. Operationally, these tests are simple to use and give answers in less than 30 minutes. They can be used during a doctor's visit or at home by a patient, or early detection of bioterrorism in a community setting. Linking mobile connectivity and GPS will enable anonymised disease data to be sent to a data cloud for real-time surveillance.

Advocacy to apply these novel technologies to NTDs and antimicrobial resistance monitoring is an urgent priority. This requires precise engineering of nanomaterial surfaces as the interface between the nanomaterial and the specimen is where the reaction occurs.

POC molecular assays

Molecular assays offer superior diagnostic performance compared to the limit of detection of immunoassays. In the last two decades, nucleic acid amplification tests (NAATs) have become the 'gold' or reference standard to which the performance of other diagnostic tests is compared. Until recently, they have remained largely laboratory based and are expensive and inaccessible. A number of POC molecular assays, with or without amplification, are now on the horizon that may transform the delivery of health services.[26,27]

The first sample-in/answer-out real-time PCR platform that can be used wherever there is a source of electricity has been introduced for the diagnosis of TB and detection of rifampicin resistance.[28–30] The GeneXpert real-time PCR platform has a large menu of test targets; thus, allowing polyvalency to test for different pathogens. It requires minimal onsite expertise and provides a result in less than 2 hours. It has additional advantages of random access and remote quality control. However, the cartridges are expensive and not affordable or sustainable unless subsidised in most high burden countries. To maximise the impact of these novel technologies, it is critical that patient pathways be modified to take advantage of the speed to result and to find cost-efficient

means of implementation compared to traditional laboratory testing.[31]

Isothermal amplification platforms such as helicase dependent amplification (HDA), cross priming amplification (CPA), recombinase polymerase amplification (RPA) and loop-mediated amplification (LAMP) assays can be engineered into POC NAATs as there is no requirement for sophisticated equipment to perform thermal cycling. The details of these technologies have been described elsewhere.[27,32]

POC NAATs based on these technologies have largely been applied to high burden diseases such as HIV and TB, but other technologies, such as LAMP, have been developed and evaluated for the diagnosis of VL and HAT. In the case of VL, the LAMP assay for *Leishmania donovani* is highly sensitive and specific for the diagnosis of VL (using a blood sample), and for the diagnosis of post-kala azar dermal leishmaniasis (PKDL) (using a skin biopsy).[33] Diagnosis of PKDL will be important for the elimination agenda since patients with this condition are an important source of infection. In the case of HAT, the LAMP assay was shown to have a sensitivity of 87.3% (95% CI 80.9 to 91.8%) and a specificity of 92.8% (95% CI 86.4 to 96.3%) compared to a PCR reference standard.[34] Advocacy and investments are needed to apply these technologies to the control and elimination of NTDs.[35]

The promise of diagnostics in a digital age

In a digital age, data from social media and POC diagnostics in communities can be used to provide early warning for infectious disease outbreaks, and timely information to inform disease control and elimination programmes. The iSense project, an EPSRC IRC funded project in Early Warning Sensing systems in Infectious Diseases, aims to create low-cost latent sensing systems to analyse self-reported symptoms on the web, including social networks and micro-blogging sites (Twitter) and searches (Bing, Google). iSense will develop a new generation of early warning sensing systems to identify outbreaks of deadly infectious diseases, such as flu, methicillin-resistant staphylococcus aureus (MRSA) and HIV, by linking self-reported symptoms on the web to a new sensor-enabled disease surveillance infrastructure for an early warning sensing system for infectious diseases (http://www.i-sense.org.uk/research).

Improving surveillance

The simplest POC diagnostic tests that are widely used today are rapid diagnostics tests (RDTs) in a lateral flow format. These are read with the naked eye, which is subjective and prone to human error and may be further exacerbated by poor lighting in health posts. In addition, RDTs lack on-board quality control and are often used in remote areas where health workers receive minimal training. As a result, accuracy of RDTs performed in the field can be quite variable. This may adversely affect patient care and the accuracy of the data gathered for surveillance.

Digital imaging technology in electronic readers and smart phones can be used to capture and interpret RDT results and transmit data. Given the large number of brands of RDTs for HIV, malaria and syphilis, it would be ideal to have diagnostic test readers that could accommodate a variety of test technologies (e.g., lateral flow, immunofiltration) and formats (e.g., strips, cassettes of various sizes and shapes).

A number of RDT readers are already on the market and others are in the pipeline. Given the widespread adoption of smart phones in resource-limited settings, RDT readers using this technology have the potential to combine high-resolution test images with the computing capability required to run image analysis software and transmit data. The readers range in price depending on the technical complexity of the instrument and their compatibility with the type of RDTs.

Data collection for the eMTCT is difficult when testing is highly decentralised and data quality is difficult to verify. To track global progress towards elimination of MTCT of HIV and syphilis many challenges need to be addressed. Currently, data from antenatal screening need to be manually accessed from individual testing sites. Electronic readers for RDTs are able to capture and automatically transmit data and may, therefore, serve a critical purpose for strengthening data collection and surveillance in the context of monitoring and evaluation of dual elimination.[36,37]

Improving supply chain management

Real-time data monitoring via electronic readers could help to improve coordination of supply chain management by multiple partners. Operational data on stocks, device usage and condition can be uploaded via Wi-Fi or cellular networks and transmitted to central databases. By linking the data to supply chain management software, stock-outs can potentially be avoided and health system efficiency improved.

Opportunities to strengthen health systems and improve health outcomes

In recent years, RDTs have been introduced to increase HIV and syphilis screening in antenatal clinics, enabling same day testing and treatment of infected mothers to prevent adverse outcomes of pregnancy and fetal loss. The eMTCT targets to be achieved are 95% of pregnant women access antenatal care, 95% of pregnant women at antenatal care tested for HIV and syphilis, and 95% of those testing positive receive treatment. To achieve these targets, countries will need to have a system to track progress the capacity for ongoing surveillance once the elimination target is achieved.

Studies have shown that the introduction of rapid RDTs for syphilis for prenatal syphilis screening has strengthened health systems by improving access to diagnostics, health worker job satisfaction and reducing stillbirths and neonatal mortality. In Peru, the introduction of RDTs for prenatal screening has resulted in infected pregnant women being screened and treated in a single visit instead of 5–6 visits over 27 days.[38,39]

Challenges of new technologies

Assuring quality of POC lateral flow tests and devices

Decentralisation of testing outside of the laboratory can put tremendous stress on the healthcare system and presents challenges for training and quality assurance. When testing is decentralised, programme managers are often unable to monitor testing coverage and quality, making it difficult to identify problems of sub-standard testing and stock-outs in a timely manner.[40]

For POC molecular devices, requirements for instrument calibration, ongoing maintenance and frequency of failure, power usage and environmental sustainability should also be considered.

Data storage, transmission and governance

Creation of a central database to collect surveillance data from village antenatal clinics all the way through to national and global databases is needed. This involves obtaining consensus on where to host the data, what data to collect, who has access to the data and finding affordable software. Middleware solution that provides 'open access' will allow for rapid coordinated transmission of data to governments.

Technology is needed to ensure data is collected, transmitted and stored in a way that conforms to ethical and legal standards, maintaining patient privacy and confidentiality. These governance issues may be resolved by ensuring separate levels of access to operational data versus patient data. In addition, data storage should be in-line with country specific regulations. Further discussion needs to take place around data ownership.

An excellent example of a national database that informs critical programmatic decisions in real time is the Kenyan national Early Infant Diagnosis (EID) portal (www.nascop.org/eid), which has now been extended to cover HIV viral load and other diagnostics. This database is the result of a successful public–private partnership that involved the government of Kenya Ministry of Health, USAID/President's Emergency Plan for AIDS Relief (PEPFAR), the US CDC, The Clinton Health Access Initiative (CHAI), Hewlett Packard, Safaricom and Strathmore University. Hewlett Packard built a basic data centre at the National AIDS/STD Control Programme (NASCOP) and at testing laboratories for early infant diagnosis. Safaricom, the largest provider of mobile services in Kenya, set up a short code service for SMS. Strathmore University students built the application. PEPFAR, CDC and CHAI rolled out the EID programme countrywide. The result is a National EID portal running on a government data centre—hosting all the testing and program data entered from computers in laboratories equipped with Laboratory Information Systems (web-based applications). Over 2000 health facilities that provide EID services have access to all the data and test results over SMS, mobile web, web and email in near real time. Data analytics include sample transport tracking, volume of testing at each facility, test results, including the number of rejected samples and indeterminate results. Results are delivered via electronic and paper means (SMS printer, email, courier, web) and real time EID/prevention of MTCT programme analytics are available online by facility, and at regional and national levels.

Conclusion

The new generation of diagnostics equipped with digital technologies are transforming the field of clinical decision-making and disease control and prevention. Rapid POC tests for infectious diseases can improve access to diagnosis and patient management, but the quality of these tests varies, quality of testing is often not assured and there are few mechanisms to capture test results for surveillance when the testing is so decentralised. Electronic readers have the potential to provide fast, accurate, standardised RDT interpretation and real-time data reporting with a huge range of positive functions, including improving quality assurance, supply chain management and providing accurate timely data for surveillance. Although countries need to consider data governance and confidentiality issues, data connectivity allows control programmes to monitor the quality of tests and testing, and optimise supply chain management; thus, increasing the efficiency of healthcare systems and improving patient outcomes.

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