Diagnostic Preparedness for Infectious Disease Outbreaks

Diagnostic preparedness for infectious disease outbreaks

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Diagnostics are crucial in mitigating the effect of disease outbreaks. Because diagnostic development and validation are time consuming, they should be carried out in anticipation of epidemics rather than in response to them. The diagnostic response to the 2014–15 Ebola epidemic, although ultimately effective, was slow and expensive. If a focused mechanism had existed with the technical and financial resources to drive its development ahead of the outbreak, point-of-care Ebola tests supporting a less costly and more mobile response could have been available early on in the diagnosis process. A new partnering model could drive rapid development of tests and surveillance strategies for novel pathogens that emerge in future outbreaks. We look at lessons learned from the Ebola outbreak and propose specific solutions to improve the speed of new assay development and ensure their effective deployment.

Published **Online**
May 31, 2017
http://dx.doi.org/10.1016/S0140-6736(17)31224-2

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Introduction

Many reforms and improvements have been proposed to improve epidemic preparedness in the wake of the 2014–15 Ebola epidemic.[1,2] One crucial response element that deserves increased attention is diagnostic preparedness for outbreak detection and control.

It took over 3 months to identify that an outbreak was percolating through rural Guinea and primed to cross international borders, leading to the largest Ebola outbreak in recorded history. It took a year for diagnostic capacity to be fully established,[3] largely because of the complexity and cost of the technology used. Fixed biocontainment laboratories using manual RT-PCR and staffed by expatriates with molecular experience cost US$2–3 million to establish and bring into operation.[4,5] The insufficient testing capacity, delays in testing and reporting, and poor distribution of testing centres for much of the epidemic helped fuel the outbreak's growth during 2014.[6] That these delays could occur with a disease whose epidemic potential has been shown in dozens of outbreaks over the past 40 years points to specific failures in diagnostic preparedness.

The low case reproduction numbers seen during the Ebola outbreak[7–10] suggest that modest improvements in transmission interruption can have a marked effect on disease control.[11] This was particularly shown by Chowell and colleagues[12] who estimated that diagnosing 60% of patients with Ebola within one day instead of five days could have dropped the population attack rate from 80% to nearly 0%.

In Monrovia, Liberia in 2015, the benefits of rapid detection and isolation on disease control were shown, with the average time to detection and isolation declining from 6·0 to 1·5 days accompanied by a fall in case reproduction numbers from five to zero.[13,14] Even after any future implementation of ring vaccination with an effective vaccine,[15] Ebola control will remain dependent on early diagnosis to interrupt transmission.

Framework for diagnostic preparedness

We have developed a framework for diagnostic preparedness and response comprising four pillars, from outbreak detection through to research and development, manufacturing and distribution, and then implementation of new diagnostic tools (figure). This framework maps the needs in diagnostic outbreak preparedness and response, and identifies 14 key factors to speed the response for known and unknown pathogens and thereby prevent future outbreaks from becoming epidemics. We also note that the diagnostic ecosystem for diagnostics research and development must be enabled by a number of cross-cutting systems, including ethically-managed specimen repositories, platforms for data sharing and connectivity, sustained and targeted financing, and pre-agreed regulatory approaches.

We propose to set up a dedicated diagnostic product development effort, coordinated by the Foundation for Innovative New Diagnostics (FIND) and based on collaborations with key diagnostic partners, which would work under the auspice of the Coalition for Epidemics and Preparedness Innovations (CEPI)[16,17] with the specific goal of ensuring that diagnostic outbreak needs are comprehensively addressed. Such a partnering model between CEPI, FIND, and other key diagnostics players such as Institut Pasteur (CEPIdx) would need to have a unified vision for achieving diagnostic preparedness and response.

Outbreak detection

Rapid outbreak recognition is most effectively achieved in the context of a functioning health system. However, even in weak health systems, surveillance capacity can be strengthened[18] by training of health-care workers to recognise disease risk syndromes, putting in place standard notification procedures and information systems, and training individuals with clear responsibility for managing the investigation and reporting of putative outbreaks.

Rapid pathogen identification requires pre-agreed logistical arrangements and financing for collection and shipping of samples to reference laboratories. Such plans should be incorporated into ongoing efforts to establish surveillance laboratory networks.[19]

Research and development

A clear lesson that was learned during the Ebola virus outbreak is that commercial test development during an

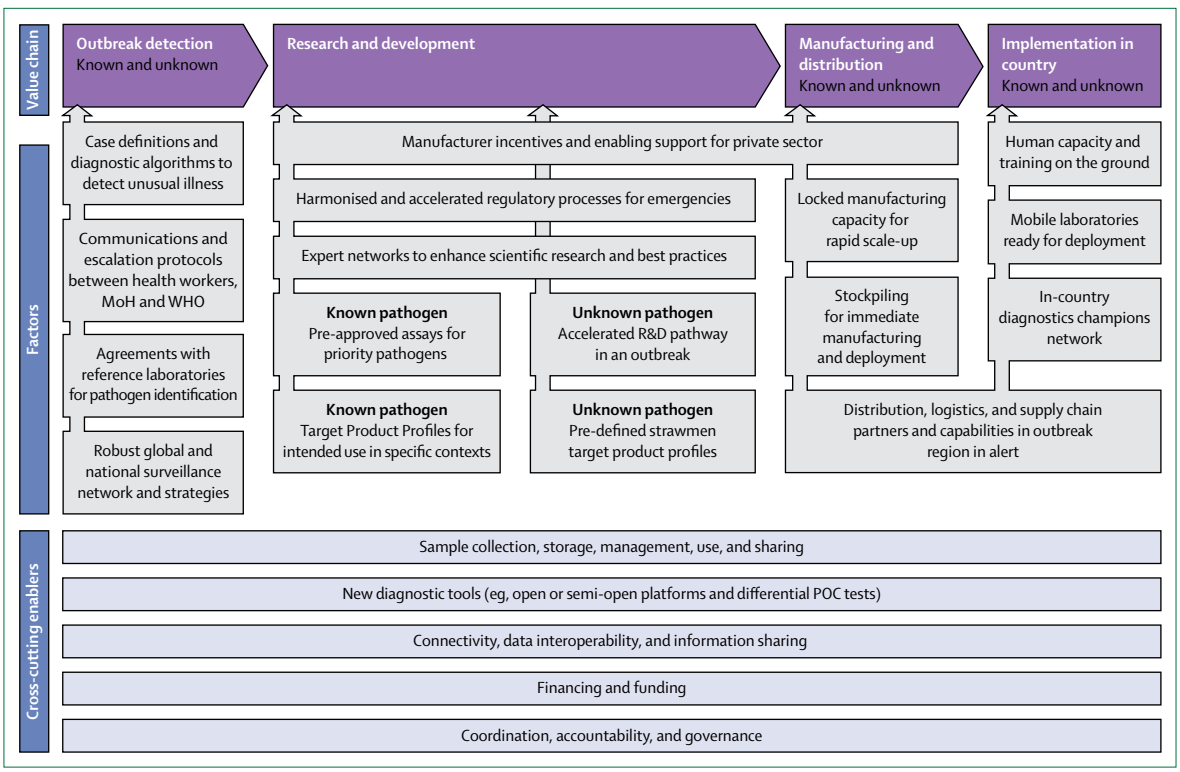

Figure: **Framework for diagnostic preparedness**
Map of the diagnostics preparedness value chain and phase-specific activities that are necessary for rapid outbreak detection and response, along with five necessary cross-cutting functions to enable progress. MoH=Ministry of Health. R&D=research and development. POC=point-of-care.

outbreak should be replaced by development before an outbreak. Such an effort will require public investment, as outbreak diagnostics do not produce a predictable return on investment. Substantial public funding was available for diagnostic development during the Ebola virus outbreak.[20] Most of the 70 active companies did not complete development, and only seven are Emergency Use approved by WHO,[21] stressing the need for technology assessment and funder coordination to ensure effective investment.

Another key take-away message is the importance of defining better sample ownership, sharing of access to samples, and prioritisation of research questions in anticipation of outbreaks. Access to well-characterised specimens is an obstacle to the rapid development and assessment of diagnostics across epidemics—this was aggravated by prevention of sample sharing due to local export restrictions in the case of Zika.[22] Standardised agreements for ethical collection and use of specimens, which are formalised with governments, are a necessity.

Eight of the 11 pathogens that have been prioritised in the WHO R&D Blueprint have inadequate diagnostics.[23,24] Moreover, when novel pathogens emerge, there will not be time for development of regulated diagnostics on custom-made platforms. A funded, shortened process should be established to shrink the time to get new, pathogen-specific assays developed and validated. Harnessing the power of diagnostic companies, working with academic groups and reference laboratories, is essential. Partners with expertise in molecular reagent development could be linked to public sector institutes charged to go from sequence data to lyophilised PCR reagents, with proven effectiveness, within days.

Manufacturing and distribution

Preparedness for an outbreak demands that diagnostic manufacturing and distribution capacity is established before an emergency happens. Many of the diagnostic biotech companies drawn to the high visibility of the outbreak to work on Ebola had little manufacturing and distribution capacity. Suppliers of tests should be pre-selected based on this capacity, or a mechanism developed to partner technologies of interest with companies that can provide manufacturing and distribution support. Incentives will be needed to ensure that logistical readiness for outbreak pathogen exists despite the competition to manufacture more profitable assays.

Implementation

Ultimately, the success of diagnostic preparedness efforts rests on local and international implementation capacity. Preparedness and response plans must take into account country-specific needs and be developed with local ownership. Human resources limitations are

common and there is an almost ubiquitous need for diagnostics training, including specimen collection, handling, and testing, and results reporting. Laboratory and equipment maintenance must also be planned and budgeted for.

Conclusion

The recent back-to-back occurrence of two viral epidemics that blossomed into public health emergencies of international concern has highlighted the need for improved capacity for diagnostic surveillance and patient management. Establishing a new partnering model to ensure effective surveillance–response approaches and diagnostic preparedness, in conjunction with WHO and other organisations, has the potential to radically change the international health response to infectious disease outbreaks.

The formation of CEPIdx would improve coordination, collaboration, and accountability for diagnostic preparedness. It would focus on the pragmatic issues that need to be addressed to achieve success, and leverage multi-disciplinary experts across research and development, clinical trials, ethics, sociology and anthropology, regulation, manufacturing, and product delivery. Additionally, it could play an instrumental role in designing and managing the finance and coordination mechanisms needed to overcome weak market forces.

We do not underestimate the challenge of radically improving diagnostic preparedness, but all of the elements outlined above are achievable through joint efforts. The efforts of CEPIdx would need to be complemented by dedicated action from regulatory bodies, governments, donors, expert working groups, the private sector, product development partnerships, non-governmental organisations, and the normative, organisational, and convening power of WHO.

The observations here reinforce existing WHO guidance documents,[25,26] but put a sharper focus on technology preparedness and the need for a managed research and development process toward improved diagnostics. As we come together to develop the global health infrastructure necessary to better face future infectious disease threats, the role of diagnostics must be considered foremost, and mechanisms established to carry out the logistical, financial, political, and technical work required to ensure diagnostic preparedness for the inevitable next outbreak.

Important first steps will be the development of a diagnostic roadmap, target product profiles, product development plans, and timelines, fitted within the context of broader outbreak readiness efforts, including the WHO R&D Blueprint and CEPI's vaccine development.

Declaration of interest

CB is President of Institut Pasteur, a non-profit research organisation that receives funding from multiple funders including industries, and is involved in infectious diseases surveillance and research on diagnostics and contributes to the identification of mechanisms, molecules, and methods that are useful for diagnosis discovery and development. J-AR is interim CEO, Coalitiation for Epidemic Preparedness Innovations (CEPI). MT declares grants and travel grants from GlaxoSmithKline and PATH's Malaria Vaccine Initiative, individual board fees from Optimus Foundation, institutional board fees from Novartis Institute of Tropical Diseases, pending grants from the Bill & Melinda Gates Foundation and MVI. and travel grants from MVI and Sanaria outside the area of the work discussed in this Viewpoint. All other authors declare no competing interests.

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