International Journal of Infectious Diseases 45 (2016) 92–94

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Editorial

Zika virus outbreak and the case for building effective and sustainable rapid diagnostics laboratory capacity globally

Keywords:
Zika virus
Emerging pathogens
laboratory
diagnostics
surveillance
public health

New and re-emerging pathogens with epidemic potential have threatened global health security for the past century.[1] As with the recent Ebola Virus Disease (EVD) epidemic, the Zika Virus (ZIKV) outbreak has yet again surprised and overwhelmed the international health community with an unexpected event for which it might have been better prepared.

ZIKV was first identified in Uganda in 1947, was also found in Gabon in 2007 and may be endemic in much of tropical Africa without receiving much attention.[2] The current ZIKV epidemic facing the Americas,[3] was declared a "Public Health Emergency of International Concern (PHEIC)" by the World Health Organization on 1st February 2016.[4,5] Preceding the declaration of a Global Public Health Emergency by 4 days was the release of the United Nations report "Protecting Humanity from Future Health Crises. Report of the High-level Panel on the Global Response to Health Crises (UN 26 Jan 2016)".[6] The report recommends that countries be able to "If deemed necessary, diagnostic teams must be deployed to investigate unusual cases. These teams must also have access to laboratory capacities to test samples and to provide rapid test results."[6] This is simply not realistic for the major part of the UN member countries.

The ZIKV outbreak has spread further into South- and Central America, into the Caribbean and will most likely spread into Southern United States in areas where *Aedes spp* mosquitoes are present.[7] There is also a risk of ZIKV introduction into Southern Europe where *Ae. albopictus* mosquitoes are present.[8] The WHO "Zika strategic response framework and joint operations plan, January-June 2016" describes the current global distribution, the spread and nature of ZIKV infection as well as its potential association with microcephaly and neurological complications.[7] The report also highlights a clear need for accurate and scalable surveillance methods, and emphasizes the need to increase the capacity to diagnose ZIKA in infected countries, for improving data collection, surveillance and vector control, and 6 Million USD has been allocated to research. However the plan expects national authorities to establish laboratory testing.

The present ZIKV outbreak again exposes an unprepared global public health system.

Surveillance of infections is based on reporting cases of illness, often syndromic reporting of CNS or pulmonary infections among others, but unspecified brief febrile illnesses are rarely reported, even in pregnant women. In addition, assigning a possible diagnosis to syndromic surveillance requires suitable laboratory tests to be readily available for the causative agent and require a considerable laboratory capacity. During the first six months of the Ebola virus disease (EVD) epidemic in West Africa, the weak diagnostic laboratory capacity in the affected countries was an important factor in the rapid spread of the outbreak.[9] As a result of intense international efforts, over 27 laboratories were established to provide rapid in-country testing for Ebola virus. These laboratories included both mobile and temporary laboratories equipped to do molecular diagnostic testing and several laboratories to provide local genomic sequencing of the virus to help in contact tracing. However, since the laboratories were mostly run by Non Governmental Organizations and volunteers from overseas public health laboratories, most of these efforts provided only a temporary solution, rather than a long-term sustainable solution. Furthermore these laboratories were focused on a single, known infection.

The greatest laboratory need for epidemiological surveillance and clinical management for the ongoing ZIKV outbreak in Brazil and Latin America is for an easy to use, robust, affordable, rapid, sensitive, and specific diagnostic test for ZIKV. The current estimates of the number of infections is 134,460 suspected cases, 2,765 confirmed and 12 fatal outcomes, constantly rising.[10] Current diagnostic tests for ZIKV are limited;[11] the current gold standard test is RT-PCR but this remains unavailable to most clinics due to the associated cost and a shortage of trained personnel. The urgent need for new methods for diagnostics that are scalable, accurate and accessible were highlighted in the recent WHO report.[7] While the WHO has called for strengthening of national capabilities, most national public health reference laboratories, where they exist, do not have the equipment or expertise to identify unknown pathogens in clinical samples, or in many cases even to look for the many known pathogens that may be uncommon to their own geographical area.

In the present ZIKV outbreak, it is difficult to fully understand how the infection could spread for over a decade in Asia and the Pacific without being picked up by ongoing surveillance programs.

http://dx.doi.org/10.1016/j.ijid.2016.02.1007

Obvious questions arise: Have genetic changes resulted in a more pathogenic virus where previous exposure does not provide protective immunity? After all, ZIKV associated microcephaly, Guillain-Barré and retinitis have not been reported from Asia or Africa. Are similar viruses circulating in Asia and Africa providing a certain degree of cross protection, alleviating the symptoms whereas the population in the Americas is immunologically naïve?[2] Has the virus changed to become better adapted to the *Aedes spp* mosquito making transmission more efficient? At present we simply don't know, but many scientists around the world have recognized the urgency with which we need to answer these questions and studies are ongoing.

The public health community has over the past twenty years expanded syndromic surveillance to less traditional approaches including data mining, analysis of internet search trends as well as monitoring the consumption of certain drugs as indicators of potential outbreaks etc.[12] However, without proper and rapid laboratory back up, syndromic surveillance cannot provide a full solution to the problem and thus will delay the implementation of informed public health measures. We have previously highlighted the constant threat of new emerging viruses to Africa and the lack of laboratory infrastructure in Africa to allow the monitoring of the existence and spread of new infectious diseases threats like the Middle East Respiratory Syndrome, MERS,[13] and re-emerging ones like Ebola Virus Disease.[9] Despite this, there appears to be a lack of awareness of this urgent but unmet need.

There is now a call for a reorganization of the WHO to be better able to cope with outbreaks.[14] While this is a welcome initiative, we fear that again emphasis will be placed on surveillance and reporting and not on laboratory capacity. The call for upgrading national capacity in detecting and analyzing new or emerging pathogens is in principle correct, but it must be realized that the capacity to perform the required analysis looking for new, so far unknown pathogens, or known but unexpected pathogens and analyzing the vast amount of data from genomic studies, can at present be done in a very few places. As examples Nipah virus and SARS was identified by the CDC and MERS by the Erasmus Medical Center, Netherlands not national laboratories.[15–17] Except for a very limited number of countries, only academic centers have the capacity to perform this type of analysis. However academic centers are invariably funded by research grants and it is thus not certain that the appropriate samples will reach such laboratories and again not certain that the right analysis will be performed and in time – it has to fit into the research strategy and is thus haphazard.

To adequately address the global concern over preparedness to identify the next emerging global infectious disease threat, countries require high level laboratory capacity with the capacity to undertake diagnostics and genomics, allowing the identification of new or emerging pathogens, as well as molecular analysis to allow the identification of antimicrobial resistance. The recent study of HIV resistance to tenofovir showed an alarming spread of tenofovir resistance, which again illustrate that the development of infrastructure and surveillance without proper laboratory backup – in this case drug susceptibility testing of HIV – will result in long-term failure of the interventions.[18] This also applies to surveillance of MDR- and XDR TB, without susceptibility testing new drugs cannot be introduced in patient care.[19] This need exceeds what is possible to establish in most countries even industrialized countries. The international community must consider the longevity of their support. Investment in human resources from affected or potentially affected countries have started with the Ebola crisis but this efforts seem not to be sustained because when the danger disappears so does the interest of the donors.

Sub-Saharan African countries have suffered from recurrent outbreaks of new and emerging infectious diseases. Regional public health laboratory networks established by WHO AFRO and its Member States, along with their technical partners, undertake the reporting of these outbreaks. However much of sub-Saharan Africa have weak health systems, inadequate resources, and poor capacity to identify and respond quickly and effectively to disease outbreaks, making them very vulnerable to the devastating effects of most infectious diseases epidemics. The scale and overwhelming effects of the recent EVD epidemic in West Africa clearly demonstrates this. This situation is compounded by lack of preparedness and capacity to conduct comprehensive and well-coordinated research in response to such disease threats.

The establishment of high quality laboratory capacity will require careful review of existing structures and capacity, mapping of the current diagnostic capacity of national reference laboratories for all the 47 Member States in AFRO,[20,21] most probably sharing reference laboratory facilities between several countries Opportunities now presented by Europe-Africa initiatives like the European & Developing Countries Clinical Trials Partnership (EDCTP) must be seized.[22]

It is important that investments into developing laboratory capacity within countries are tailored towards moving away from the age-old single pathogen screening approach. Advances in molecular biology,[23,24] and other technologies,[25] now allow for rapid screening for multiple pathogens and their antibiotic sensitivity patterns and reporting them within hours.[26,27] There is also a need to establish sentinel regional centres in each continent, which can provide high level laboratory support and analysis to national governments and international organizations.

Such centers should be established with additional support from industry and international donors comparable to The Global Fund to Fight AIDS, Tuberculosis and Malaria and instruments for sharing data with industry established. The centers should also have the responsibility for safely and rapidly transporting samples, so that an interesting sample from for instance South Sudan is just a phone call away from being picked up on location, transported and analyzed no matter whether it is a HIV or TB treatment failure or fever of unknown origin with respiratory symptoms.

This would fill current gaps in surveillance and diagnostic capabilities to monitor the introductions of new or re-merging pathogens with epidemic potential into a community. Calls for the creation by the World Health Organization (WHO) of a new "Centre for Emergency Preparedness and Response" that has real command and control capacity and has the personnel and laboratory resources it needs to respond should be supported strongly since coordination and surveillance is critical to preventing another disastrous epidemic like EVD. However we fear that without support from industry funding will be inadequate. We hope that the ZIKV outbreak will turn out to be storm in a teacup.

Author declarations: All authors have an academic interest in laboratory diagnostics and infectious diseases. Authors declare no conflicts of interest.

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29 February 2016
Accepted 29 February 2016