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Familiar barriers still unresolved—a perspective on the Zika virus outbreak research response

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Research is an important component of an effective response to the increasing frequency of widespread infectious disease outbreaks. In turn, the ability to do such studies relies on willingness of partners in different regions to collaborate and the capacity to mount a rapid research response. The EU-funded ZIKAlliance Consortium has initiated a multicountry epidemiological, clinical, and laboratory research agenda to determine the incidence, risk factors, and outcomes of Zika virus infection in pregnant women and their children. We reviewed the timeline of patient cohort initiation in relation to the Zika virus epidemic and mapped key events regarding funding, regulatory approvals, and site preparation during this timeline. We then assessed barriers and delays that the international research team experienced through a systematic telephone interview. We have identified three major bottlenecks in the implementation of a swift response: the absence of a timeline for the funding process, delays in regulatory and ethical approval, and the challenging logistics of laboratory support, including diagnostics. These bottlenecks illustrate the clear and urgent need for implementing a strong and permanent global emerging infectious diseases research capacity that has structured funding, enables long-term partnerships, and develops basic clinical and laboratorial research and a response infrastructure that is ready to deploy.

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Introduction

In an overview published in 2017, Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases, highlighted the need for preparing for emerging infectious diseases.[1] The list of recommendations includes the development of capacity to do global (syndromic) surveillance to detect outbreaks, capacity to do basic and clinical–epidemiological research to understand key parameters of a new disease, and capacity to rapidly develop and test vaccines, diagnostics, and therapeutics. In this Personal View, we discuss some aspects from the research response to the emergence of the Zika virus epidemic in a consortium of research groups from Europe and the Americas, showing some of the practical challenges in emerging disease response.

After initial reports of an association between Zika virus infection and microcephaly and other congenital abnormalities by the Ministry of Health of Brazil in November, 2015, WHO declared a Public Health Emergency of International Concern on Feb 1, 2016, and called for urgent research into the causes, risk factors, diagnostics, and possible interventions for this infection, in parallel with a stepping up of international surveillance and control activities.[2,3] Following this alert, the ZIKAlliance Consortium and other research consortia started preparations for multicountry cohort studies to determine the incidence, risk factors, and outcomes of Zika virus infections in pregnant women and their children, and to investigate the unexplained geographical variability observed in the frequency of congenital abnormalities.[4,5] These multicountry cohort studies were done by bringing existing partnerships together, with the aim to respond quickly given the severe nature of the complications, the uncertainty of their prevalence, and the resulting questions faced by health-care providers and pregnant women and their families in the affected regions. Initially, researchers considered that the establishment of the necessary cohorts to address these essential questions would be straightforward, since the affected countries in the Latin American region (as a whole) have excellent clinical and laboratorial facilities, including expertise in arbovirus clinical research and diagnostics. However, to our surprise, the establishment of harmonised protocols took much longer (>8 months) than foreseen, the competitiveness for funding and lack of a central funding body for research involving countries worldwide triggered the development of several cohorts with varying sample sizes, and tracking of the Zika virus epidemics continues to be a major challenge since the availability of routine diagnostics for Zika virus is still restricted.[6,7]

In our view, the following three issues remain serious bottlenecks for a successful research response: the absence of a timeline for the funding process, delays for regulatory and ethical approvals, and the challenging logistics to provide appropriate laboratory support, including diagnostics.

Initiation of research response and the role of funding in cohort comparability

In the weeks and months that followed the initial Zika case reports (December, 2015–March, 2016), researchers urgently called for funding to be made available rapidly to respond to the ongoing epidemic and capture the upcoming arboviral transmission season starting in February, 2016. At the time, several European research initiatives were present in Brazil with their infrastructure in place, among them the International Research Consortium on Dengue Risk Assessment, Management and Surveillance,[8] doing observational clinical research on dengue virus infections in Recife, Fortaleza, and Rio de Janeiro. A global group of research funders, together in the Global Coalition for Emerging Disease Preparedness (GLOPID-R), met in January, 2016, to

For more on the **Global Coalition of Emerging Disease Preparedness** see http://www.glopid-r.org/zika-workshop-summary-now-available/

review possible needs for a coordinated action, but decided to leave the initiative to individual funding agencies such as the European Commission, the Wellcome Trust, the US National Institutes of Health (NIH), the Canadian International Development Research Center, and others. Because of this funding landscape, despite intentions by all organisations to advance the research response to this outbreak, initiatives for international collaborations were fragmented into different national or regional projects. To compensate for this fragmentation, efforts were made to bring together lead investigators of those different projects to harmonise their research protocols[9] and to agree to pool data from the larger cohort studies under the coordination of WHO, since almost all cohorts were likely to be underpowered. A review of the protocols of 32 cohort studies and 13 case-control studies warned of the obvious risk of bias in the different designs.[10]

The approaches to funding also differed: the European Commission Horizon 2020 Framework issued a separate call for proposals in February, 2016, with a fast-tracked deadline of April 28, 2016, whereas the NIH channelled funds into existing research projects operating in the Latin American region. The European projects were evaluated rapidly because of modifications to the existing administrative procedures. Grant contract negotiations started in July, 2016, and three projects involving cohort studies started in October, 2016.

For more on **European Commission research projects for Zika** see https://ec.europa.eu/research/health/index.cfm?pg=area&areaname=zika

Funds were made available soon thereafter, a substantially faster process than the regular funding schemes. However, since further administrative work was necessary before money could be distributed internationally and partners often cannot pre-finance research activities, the actual research activities could only start towards the end of 2016, and in many cases in the first half of 2017 (figure 1). Consequently, the peak of cases in many of the participating centres had already subsided, and the recruitment of Zika-virus-infected pregnant women took much longer and is still in progress.

Following initial discussions of Zika research cohorts at the GLOPID-R meeting in January, 2016, further harmonisation efforts for protocols and ethical approval were coordinated by WHO and the Pan American Health Organization (PAHO), culminating in a meeting in Mexico City, Mexico, in June, 2016. Initially, the harmonised protocols were planned to have expedited ethical approval by WHO in order to support the research sites, similarly to what was done during the Ebola crisis.[11] In September, 2016, these harmonised protocols entered the review process by WHO, but the internal process was too long to be able to inform the local institutional review board approval process that is needed. Therefore, the research sites submitted their cohort study protocols to local ethical and regulatory agencies without the backup of a formal WHO ethical approval, which according to partners most probably would have expedited the local reviews. Another consequence of the ethical approval by local agencies was that the heterogeneity between the protocols increased over time due to requested changes by local review boards.[10]

Some countries and institutions received ethical approval much faster than others. Obviously, research partners with less clinical research experience were slower to obtain approval compared with those with well developed research infrastructures. Poor research capacity or responsiveness often coincides with health systems under stress and, therefore, the countries hardest hit by an epidemic are often those where the obstacles to mount an effective research response are hardest to overcome.

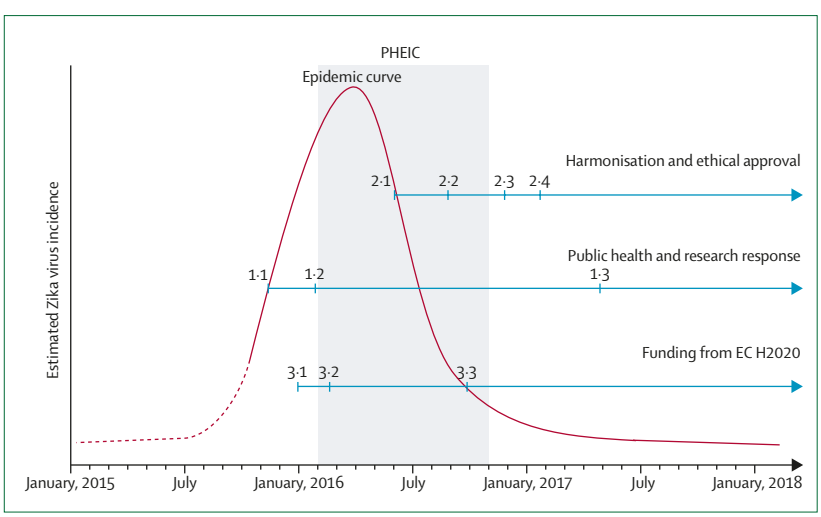

Figure 1: **Timeline of funding and harmonisation of protocols and regulatory approvals**
Schematic epidemic curve of the Zika virus epidemic, indicating critical steps in the initiation of the research response as follows: (1·1) Brazilian Minister Of Health declares public health emergency (November, 2016); (1·2) WHO declares PHEIC (February, 2016); (1·3) first pregnant woman enrolled in ZIKAlliance partner site; (2·1) WHO and Pan American Health Organization harmonisation meeting in Mexico (June, 2016); (2·2) protocols submitted for ethical approval at WHO (September, 2016); (2·3) harmonised protocols published and available on WHO website (December, 2016); (2·4) first ZIKAlliance partner obtains ethical approval for the pregnant women cohort (end of January, 2017); (3·1) EC Global Coalition for Emerging Disease Preparedness meeting (January 2016); (3·2) EC call for proposals is published (February, 2016); and (3·3) start of the EC-funded Zika projects (October, 2016). PHEIC=Public Health Emergency of International Concern. EC=European Commission. H2020=Horizon 2020.

Barriers to laboratory support for effective clinical research response

The ability to diagnose or rule out Zika cases, and hence assess the magnitude of an outbreak, is crucial to any outbreak response and research.[12] Sadly, diagnostics was also one of the weakest components of the Zika response. Biological diagnosis of Zika virus infection is difficult and relies on molecular detection of the virus (generally with RT-PCR), which is only possible during the short viraemic phase of Zika virus in the host, associated with moderate or low viral loads, so the detection window is short; and serological diagnosis, which is hampered by antigenic cross-reactivity with other flaviviruses, such as dengue. Also, the importance of laboratory protocols is often overlooked in clinical research studies. In a region with co-circulating arboviruses of the same family, serological diagnosis of Zika virus infection proved to be extremely challenging at the time and remains difficult

today.[7] Consequently, 2 years into the epidemic, we still do not have tools to reliably and quickly diagnose Zika virus infection during the first trimester of pregnancy in mothers or in children (at birth), which renders estimates of the association of Zika virus with congenital abnormalities still very imprecise. New commercial assays have become available, but their performance remains to be independently validated against robust fit-for-purpose panels.[13,14]

In addition, research efforts aiming to provide discriminatory serology have had some promising results, but not to the scale that would be directly applicable in clinical research practice.[15]

In view of these challenges, and as part of our research quality assurance approach, the ZIKAlliance Consortium included an assessment of the ability and performance of ten local laboratories linked to the 11 clinical sites involved in the ZIKAlliance cohort studies to perform the diagnostic protocols established for these research protocols.

External quality assurance panels (ie, set of samples with known content that are sent to participants for blind sample testing) were developed by two laboratories—Aix-Marseille University, Marseille, France prepared the panels, and Erasmus MC, Rotterdam, Netherlands organised the shipping of the panels and the collection and analysis of the results—and distributed for testing by local laboratories in Latin America, following the model of the European Emerging Viral Diseases Laboratory network.[16] However, instead of the intended rapid support to an extremely important endeavour, this preliminary exercise turned out to be a major hurdle, because of difficulties regarding shipping regulations, courier availability and cost, obtaining national and local permissions for sharing of samples, and availability and costs of reagents in the different institutions and countries (figure 2). Sites had difficulties in getting the required preparatory paperwork (ranging from 50–340 days) and import permits (5–77 days), in organising shipment (2–233 days, with no courier service available in some sites such as Cuba), and in the execution of the testing (4–288 days, for instance, affected by the political instabilities in Venezuela). Reasons for difficulty in executing the quality assurance test were shortage of reagents, lack of time, or need for more or clearer instructions. PAHO, which initially proposed to provide logistical assistance for the distribution of these external quality assurance panels and reagents in the Latin America region, did not support or develop an expedited process. Therefore, the basis of Zika virus surveillance as trigger for site activation in the region still remains clinical disease detection and reporting, which has numerous problems.[7] In addition, the ability to share reagents for validation has been restricted by ambiguity in the ramifications of the Nagoya protocol, which came into effect in mid-2015 and has been interpreted differently in different parts of the world.

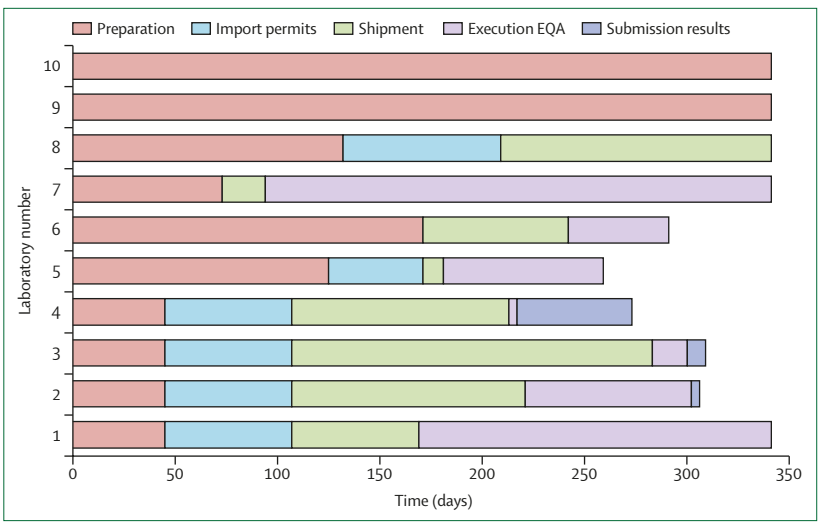

Figure 2: **Timeline of execution of laboratory diagnostic external quality assurance (EQA) scheme**
Figure shows time needed for the logistics of international distribution of EQA panels for ten laboratories in Latin America taking part in the ZIKAlliance Consortium. Preparation=preparation time for logistics, including preparing and collecting information and paperwork necessary for the submission of the request for import permits. Import permits=the process from submission of paperwork to relevant national authorities until obtaining the import permits. Shipment=time from first contact with courier for shipment of EQA panel (after obtaining permits) until delivery on site. Execution EQA=time from arrival of EQA panel on site until completion of the EQA. Results submission=time from completion of the EQA until submission of the results in the online electronic reporting system.

Conclusions

We have shown that, despite international goodwill in the face of a severe epidemic, organising the response to an emerging infectious disease outbreak remains extremely challenging. The need for a more rapid epidemiological, clinical, and laboratorial research response has now been identified many times, but sadly crucial constraints remain, despite major efforts to improve our multinational response capacity, such as the WHO research and development blueprint, GLOPID-R, and the Coalition for Epidemic Preparedness networks.[18] Although we applaud these initiatives, the reality is that a large and, potentially, even widening gap between vision and practical implementation still exists.

The issues we have highlighted in this Personal View are largely procedural and logistical, and generic to any disease outbreak research response. Leaving the resolution of these issues to isolated research teams at the time of an outbreak is a waste of everyone's time and effort, leading to major delays in outbreak response, and poor use of already scarce funding. What is required for such an impasse to change? At a global level, public health, researchers, and other decision makers need to agree on: the responsibilities and roles of international organisations and funding bodies in setting up the necessary pre-approvals to expedite shipment of essential materials; the servicing of laboratory equipment; and the biobanking, sample, and data sharing procedures. The delays in the procedures needed to obtain ethical clearance for protocols show the need for an agreement

For more on **ZIKAlliance cohort studies** see https://zikalliance.tghn.org/

For more on **WHO blueprint project** see http://www.who.int/blueprint/en/

For more on the **Coalition for Epidemic Preparedness networks** see http://cepi.net/

For more on the **Nagoya protocol** see https://www.cbd.int/abs/nagoya-protocol/signatories/default.shtml

on emergency committees to fully respond to the request in a few days, in case of outbreaks.

Furthermore, the need for a meaningful peacetime research response strategy is clear. This response strategy is defined as preparedness research between epidemics, leading to the development of a strong and permanent global emerging disease research capacity that has structured funding; secures and fosters long-term institutional partnerships; and develops basic epidemiological, clinical, legal, logistical, regulatory, and laboratorial research capacity; and response infrastructure that are ready to be deployed. In view of the many uncertainties regarding impact of emerging infections on pregnant women and neonates, such preparedness research should certainly include these groups.

Contributors

The plan for the manuscript was conceived during a face-to-face meeting of the clinical research partners and laboratory partners who listed all present progress and barriers to progress. MK, XdL, and TJ conceived the outline for the paper. MK had full access to all the data in the study and had final responsibility for the decision to submit for publication. MK and TJ prepared the first draft. MK drafted an interview with a list of questions to guide review of the individual's experiences when trying to do the cohort initiation. All partners read, amended, and approved the final version of the manuscript.

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Declaration of interests

We declare no conflicts of interest.

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