Harmonisation of Zika virus research protocols to address key public health concerns

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Prior to 2013–14, Zika virus infection was described as a mild febrile illness with clinical symptoms.[1] However, the emergence of Zika virus in the Pacific and the Americas, the sharp increase in cases of Guillain-Barré syndrome (GBS), and the birth of babies with neurological complications such as microcephaly[2,3] in several countries led to the Declaration of a National Emergency in Public Health by the Brazilian Ministry of Health in November, 2015,[4] the Pan American Health Organization (PAHO) to issue an Epidemiological Alert on May 7, 2015,[5] and WHO to declare a public health emergency of international concern on Feb 1, 2016.[6] The emergency status was maintained in a recent meeting of the Emergency Committee on Zika virus.[7]

While the evidence linking Zika virus infection and GBS in adults and separately between microcephaly and other neurological conditions in the fetuses of pregnant women is strong and growing,[8,9] many key research and public health questions need to be addressed through comprehensive epidemiological studies to better understand the extent of Zika virus infection and the diseases Zika virus causes in humans and their offspring. WHO and PAHO have convened several meetings to discuss research needs and questions during which partners, diverse organisations, and institutions have identified research gaps and explicitly established research priorities to tackle key public health questions raised by this outbreak. To address these key public health concerns, numerous countries have expressed interest in conducting or are currently conducting clinical and epidemiological studies. Here we report on a large international and multidisciplinary collaborative effort to generate standardised clinical and epidemiological research protocols and questionnaires for Zika virus.

The global community has recognised the need for standardised investigations and data collection following the outbreaks of avian influenza (H5N1, H7N9) and during the H1N1 pandemic of 2009.[10] Since 2011, two international and well-represented networks (the International Severe Acute Respiratory and Emerging Infection Consortium [ISARIC] and the Consortium for the Standardization of Influenza Seroepidemiology [CONSISE]) have been working in collaboration with WHO towards the standardisation

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For **ISARIC** see https://isaric.tghn.org/

For **CONSISE** see https://consise.tghn.org/

	Study protocol to address public health question	Primary objectives of standardised protocol
What are the risk factors for microcephaly (and/or congenital Zika virus syndrome)?	Case-control study for microcephaly	Identify and quantify risk factors for microcephaly (and congenital Zika virus syndrome when clear definition is available)
What are the risk factors for Guillain-Barré syndrome?	Case-control study for Guillain-Barré syndrome	Identify and quantify risk factors for Guillain-Barré syndrome
What is the clinical presentation spectrum of Zika virus infection in pregnant women? What is the absolute risk of microcephaly and other birth defects by gestational age, rash, viraemia, and other co-factors?	Cohort study of pregnant women	Measure Zika virus infection in pregnant women Describe the clinical spectrum of Zika virus Infection in pregnant women Identify, describe, and quantify the spectrum of congenital deficiencies, including microcephaly, in the fetuses/newborns of Zika virus-infected women
What are the characteristics, grade of neurological impairment, evolution, complications, and mortality of newborns with microcephaly? What are the longer-term health consequences for infants with microcephaly or born from a mother with Zika virus?	Cohort study of newborns of pregnant women with documented Zika virus infection	Identify, describe, and quantify the spectrum of congenital deficiencies, including microcephaly, in the fetuses/newborns of Zika virus-infected women Follow-up of infants with microcephaly or born to mothers infected with Zika virus
What is the risk of sexual transmission of Zika virus?	Study of the persistence of Zika virus in body fluids	Measure Zika virus in different body fluids of confirmed Zika virus patients at different timepoints
What is the prevalence of Zika virus infection? What is the role of natural immunity particularly in the regions with previous outbreaks?	Zika virus seroprevalence study in the general population	Estimate seroprevalence of Zika virus in all age groups of the general population living in exposed and non-exposed areas
What is the natural history of Zika virus infection and the associated risk of severe complications and other outcomes in the context of co-circulating arboviruses?	Clinical characterisation protocol*	Analyse the full spectrum and frequency of disease manifestations associated with Zika virus across all age groups Identify clinical and/or simple laboratory parameters, which differentiate between Zika virus, chikungunya virus, and dengue virus Perform serial samples in a subgroup of patients infected with Zika virus to determine shedding profiles over time and in different body fluids

*Not discussed at the Mexico WHO/PAHO meeting in June, 2016, but added to the package of standardised protocols being developed to support member states for Zika virus research. This protocol was developed by the International Severe Acute Respiratory and Emerging Infection Consortium, the International Research Consortium of Dengue Risk Assessment, Management, and Surveillance, WHO, and partners, and its development is based on previous experience of developing and implementing clinical protocols/tools for pre-approval and preparedness of pandemics.

Table: **Seven study protocols, their objectives, and the public health questions each study will address**

of clinical, epidemiological, and laboratory methods used in outbreaks.

The process by which these standardised research protocols were generated is described in the appendix (p 1). Briefly, WHO, Institut Pasteur, and CONSISE used existing Zika virus and dengue research protocols provided by numerous institutions to generate six full research protocol drafts that harmonise (standardise) the key methodological aspects of each study design (table). A seventh protocol (clinical characterisation protocol for Zika virus infection in the context of co-circulating arboviruses) is also in development.

For the **existing Zika virus and dengue research protocols** see http://www.paho.org/zika-research/

The standardised research protocols have been shared with a number of international experts involved in Zika virus research. In June, 2016, a face-to-face meeting in Mexico City, Mexico, attended by more than 60 researchers and public health professionals from 14 countries across the Americas and Europe (see appendix pp 5–11 for agenda of meeting and list of participants) discussed in detail the research methodologies being proposed in the protocols and agreed on points for harmonisation (appendix p 2). Following feedback from this meeting with key international scientists and policy makers, the protocols were modified and are now freely available on the WHO, PAHO, and other partners' websites to anyone who would like to use them, under a Creative Commons license.

See **Online** for appendix

The protocols have been designed to maximise the likelihood that data and biological samples are systematically collected and shared rapidly in a format that can be easily aggregated, tabulated, and analysed across many different settings globally. We encourage any and all study centres to contribute to this effort regardless of resource availability or patient volume, but the ownership of the primary data remains firmly with the individual countries or sites.

For the **standardised research protocols** see http://origin.who.int/reproductivehealth/zika/zika-virus-research-agenda/en/

The data collected using these standardised protocols will be used to refine and update recommendations for prevention of Zika virus spread, surveillance, and case definitions for microcephaly (and other congenital abnormalities related to Zika virus infection), to help understand the spread, severity, spectrum, and impact on the community of Zika virus and to guide public health measures, particularly for pregnant women and couples planning a pregnancy.

The geographic scope of the current Zika virus outbreak is vast, extending throughout the Americas and the Caribbean and into parts of Africa and Asia. Use of standardised research protocols offers the possibility of individual participant data analysis of Zika virus cohort studies and will ensure results of the studies can be compared across regions and countries and can potentially improve the quality of observational studies, by identifying and minimising biases, and thus of public health recommendations.

Members of the Working Group on ZIKV Harmonized Research, in alphabetical order, are listed in the appendix. The opinions expressed herein do not necessarily reflect the opinions of the institutions with which the authors are affiliated. We declare no competing interests.

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