

Zika virus and microcephaly in Brazil: a scientific agenda



Since 1981, the Brazilian population has had dengue fever epidemics and all control efforts have been unsuccessful.¹ In 2014, chikungunya fever was reported for the first time in the country.² In 2015, the occurrence of Zika virus was also reported,³ along with an increase of microcephaly and brain damage in newborn babies.^{4,5} The mosquito *Aedes aegypti* is the most conventional vector of these three viral infections and is widely disseminated in a great part of urban Brazil. Brazilian public health authorities declared a National Public Health Emergency on Nov 11, 2015, and intensified the vector control campaign to tackle the epidemic.⁶ A few months later, on Feb 1, 2016, in view of the spread of the Zika virus in several Latin American and Caribbean countries, the report of cases in North American and European citizens upon return from those countries, and concerns about reported clusters of microcephaly and other neurological disorders, WHO declared a Public Health Emergency of International Concern.⁷

In Brazil, Federal and State governments and scientific agencies are implementing initiatives to increase knowledge about this unexpected, unknown, and terrifying situation. Countrywide, scientists from different disciplines are working on the problem and its potentially devastating consequences. Nationally, two coordination activities should be highlighted: a task force set up by Fundação Oswaldo Cruz (FIOCRUZ), a scientific organisation attached to the Ministry of Health, and the Scientific Working Group on Zika Virus at the Ministry of Science Technology and Innovation.

To achieve better chances of success, a strategic plan for governmental action must be put forward, around six central components:

(1) To enlarge the basis of evidence of infection, diseases, and potential outcomes

Despite being known for several decades, Zika virus is a neglected subject, possibly because of its mild effects and its limited geographical expansion.⁸ Even though Zika virus is circulating in Brazil and most of the Latin American and Caribbean countries, scientific knowledge about its determinants and outcomes is emerging only slowly and is so far insufficient. Despite the existing evidence,^{5,9} a causal association of microcephaly and

brain damage observed in newborn babies has not been conclusively established. However, the weakness of other competing explanations makes Zika virus the most likely culprit. There is no doubt that criteria used for diagnosis of microcephaly are not the best,¹⁰ and insufficient knowledge about the previous incidence of microcephaly is partly responsible for the observed misunderstandings. In February, 2016, a retrospective review of microcephaly data from the northeast of Brazil showed undetected seasonal peaks of microcephaly dating back, at least, to 2012, and a trend towards an increased number of severe cases starting in 2013.¹¹ The variation is congruent with the *A aegypti* seasonal distribution pattern but started before the first detection of Zika virus in Brazil. To build up a robust basis of evidence, a large prospective multicentre cohort study is needed with a sound protocol involving women with and without Zika virus infection during pregnancy. The creation of a multidisciplinary team, including well-trained clinicians, epidemiologists, neonatologists, geneticists, neurologists, pathologists, radiologists, obstetricians, and anthropologists, among others, will make it possible to generate, share, and analyse a large amount of data. This strategy will allow quick clarification of several unknown aspects related to Zika virus, microcephaly, and brain damage (eg, magnitude of the association, potentially modifying factors, pathogenesis, patients perception, health-care delivery, etc).

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(2) To develop a fast and reliable immunologically based serological test

Currently, diagnosis of Zika virus relies on the molecular detection of viral RNA, which is present only in a brief period of viraemia. Because the clinical picture is non-specific, most cases remain undiagnosed, hindering the association between the presence of microcephaly and a previous infection by Zika virus. It is essential to have reliable and more sensitive and specific serological tests, without or with minimal cross-reactivity with other infections, particularly, dengue fever, yellow fever, and other flaviviruses.

(3) To control infestation by *A aegypti* with the aim of reducing infection and illness

A aegypti is the main transmitter of dengue virus and also seems to be the primary vector of chikungunya and Zika viruses in degraded urban contexts. In the context of Zika virus, other mechanisms of potential transmission can occur because the virus has been detected in other body fluids such as semen, saliva, and urine. The control of *A aegypti* breeding has been a national priority in Brazil, despite its lack of success.¹ Objectively, the aim is to minimise the occurrence of infection by the three arboviruses by decreasing the density of vectors to below a theoretical threshold that is, as of yet, empirically unknown. Studies need to assess the efficacy of new proposed ways of vector control: social participation, environmental management, mosquitoes infected with *Wolbachia*, transgenic mosquitoes, larval control methods, and global positioning system monitoring of adult mosquitoes or infected patients. Potentially, integration of some of these methods to enhance their capabilities and, in the middle and long term, improvements in the urban environment, are necessary measures to be taken to reach a sustainable transmission control.¹

(4) To define protocols for treatment of acute cases (in particular pregnant women) and prevention of the consequences of severe and disabling congenital malformations

There is no proven treatment for Zika virus, and any novel treatments will need to be safe for pregnant women. Furthermore, more knowledge is needed to understand how to best address newborn babies with severe and disabling congenital malformations.

(5) To start the groundwork for vaccine development, prospecting and evaluating possible technological strategies

In view of difficulties in controlling the mosquito vector and the absence of other forms of treatment and prevention, the development of a vaccine against Zika virus seems to be essential for long-term control of the disease. However, the insufficient information about the immunological mechanisms involved in Zika virus infection and previous experience with dengue virus are reasons for scepticism about the probability of a vaccine being developed soon.

(6) To reprogramme the health-care system as a consequence of the epidemic

Issues related to the magnitude of this emerging problem, its projection for the next years, and new patterns, needs, and demands for health care must be investigated. To cope with this new situation, it will be fundamental to define appropriate resources, training, capacity building, and adequate financing.

International cooperation, funding, a great level of coordination, and a major effort of regulatory agencies and review boards to speed regulatory questions related to the flow of biological samples and laboratory consumables are necessary steps to increase the chances of success and to develop effective solutions within a reasonable timeframe.

Brazil and other Latin American and Caribbean countries, particularly the urban poor populations, are facing an enormous challenge.¹² The Brazilian Government, public health institutions, research funding agencies, universities and research institutes, professional and scientific communities, and civil society must stand together and consider this an invaluable opportunity to show the ability to tackle one, from several yet to come, emerging health problems.¹³

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