Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Virology

Zika crisis in Brazil: challenges in research and development

Lucas Secchim Ribeiro[1,2,4], Rafael Elias Marques[2,4], Amélia Maria Ribeiro de Jesus[3], Roque Pacheco de Almeida[3] and Mauro Martins Teixeira[2]

Infection with the Zika virus (ZIKV) usually causes a mild acute illness, but two major severe syndromes have been described during the epidemic in Brazil: microcephaly and the Guillain-Barré Syndrome. There is now much evidence to show that ZIKV can infect and damage neuronal cells *in vitro*. In experimental animals, ZIKV has significant neurotropism and can cause brain damage. At present, diagnosis is still a challenge in the field and there is no treatment available. Another major challenge is that one must devise therapies for pregnant women, at all stages of pregnancy. Devising adequate treatment for ZIKV infections represents a challenge that will only be met by the joint effort of the research community.

Addresses
[1] Department of Microbiology, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
[2] Immunopharmacology, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
[3] Laboratório de Biologia Molecular and Programa de Pós Graduação em Ciências da Saúde, Hospital Universitário, Universidade Federal de Sergipe, Aracaju, Brazil

Corresponding author: Teixeira, Mauro Martins (mmtex@icb.ufmg.br)
[4] These authors contributed equally to this work.

Current Opinion in Virology 2016, **18**:76–81

This review comes from a themed issue on **Antiviral strategies**

Edited by **Raymond F Schinazi** and **Erik de Clercq**

For a complete overview see the Issue and the Editorial

Available online 12th May 2016

http://dx.doi.org/10.1016/j.coviro.2016.04.002

Introduction

Zika virus (ZIKV) is an emerging flavivirus that has been associated to an alarming increase in microcephaly and congenital malformation in Brazil [1•]. Like most flaviviruses, such as Dengue virus (DENV) and Japanese encephalitis virus, ZIKV is an enveloped virus of 50 nm in diameter, composed of three structural proteins (C, prM and E) and a positive-strand RNA genome of approximately 11 kb. During infection, the viral genome is translated into the structural and non-structural (NS) proteins: NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5, which mediate viral replication and immune evasion [2,3]. The ZIKV structure is similar to other flavivirus structures except for 10 amino acids surrounding the Asn154 glycosylation site found in the envelope glycoproteins that compose the icosahedral shell. A carbohydrate associated to this aminoacid residue may be related to the binding of the virus to the host cells [4] (Figure 1).

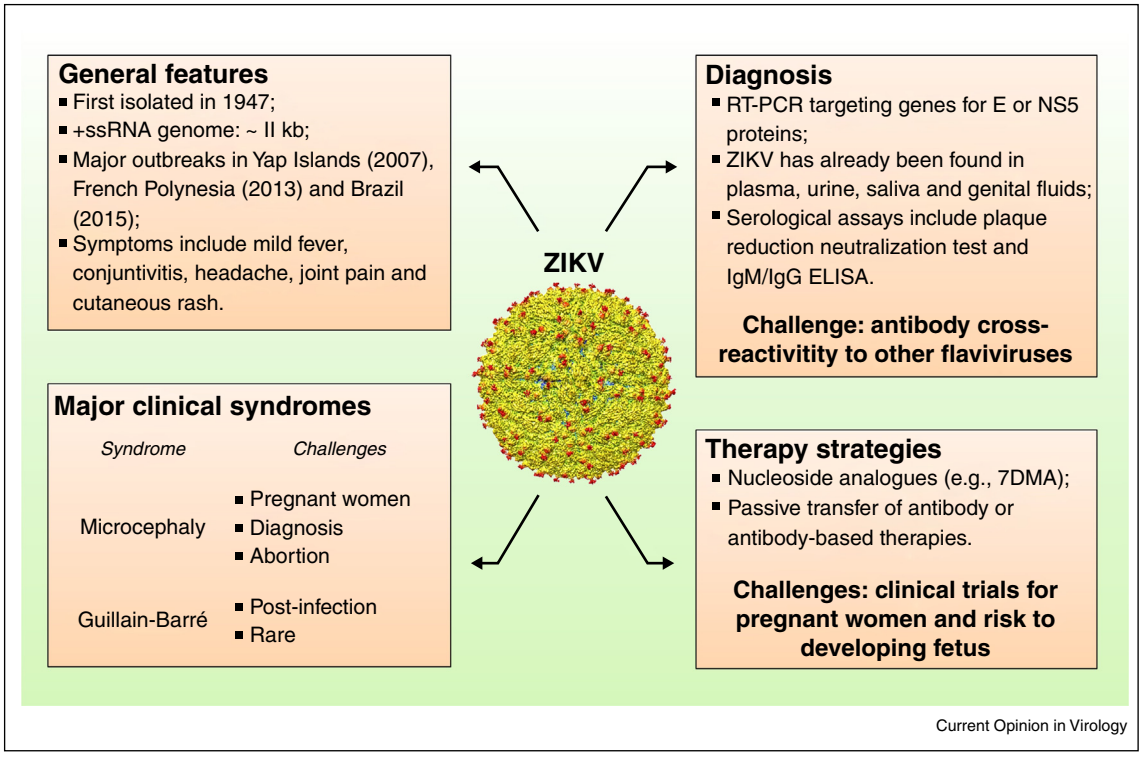
ZIKV was first isolated from a Rhesus monkey in the Zika Forest in Uganda in 1947 [5], and since then associated with the occurrence of a benign febrile disease in humans called Zika fever. For more than five decades, ZIKV caused sporadic outbreaks in countries such as Gabon, Nigeria, Senegal, Malaysia, Cambodia, Indonesia and Micronesia [6,7]. The surge of ZIKV in Brazil in May 2015 was preceded by an outbreak in French Polynesia in 2013, with more than 30,000 cases, and by the spread of ZIKV to new areas in the Pacific [8]. It has been hypothesized that the Football World Cup in 2014 facilitated ZIKV introduction in Brazil, as national delegations and tourists from countries in the Pacific visited northeast Brazil. Most tourists visited the state of Pernambuco, which presents the highest incidence of newborn microcephaly in Brazil, with 1722 suspected cases, 241 cases confirmed and 1214 still under investigation [9,10]. However, a recent study revealed an earlier entry date for the virus. Seven ZIKV genomes from Brazilian patients were compared to sequences from other outbreaks around the world. The molecular clock analysis showed the virus first came to Brazil in 2013, between May and December [11••]. Even though the Tahitian national team had visited and played in the state of Pernambuco during the Confederation Cup, it seems most likely that the ZIKV has arrived in Brazil through air travel [12].

The establishment of ZIKV in the tropical regions of the Americas is associated to the presence of the mosquito vector *Aedes aegypti* [13], although sexual transmission has also been found [14] but is unlikely to account for the majority of cases. There is neither a vaccine nor a specific treatment for ZIKV infections. The increasing association of ZIKV with neurological complications, in both newborns and adults, indicates the need for preventive and therapeutic measures for populations at risk, especially pregnant women.

Clinical and epidemiological findings

ZIKV infection was described as a benign disease in Africa, and the majority of cases in Brazil have a mild

Figure 1



ZIKV features and challenges in ZIKV research. General features of ZIKV biology and ZIKV infection are listed, together with major clinical syndromes observed during the epidemic in Brazil. The main challenges faced by the research community are the development of reliable diagnostic tests, and the development of an adequate treatment for pregnant women. The three-dimensional structure of ZIKV was adapted from Sirohi *et al*. (2016) [4].

presentation. Clinical presentation of ZIKV infection range varies, but most adult patients present mild fever for one or two days, pruritic descending macular or maculopapular rash, mild muscle and joint pain, and headache [15]. Other frequent clinical signs are conjunctivitis (50–90%), lymph node enlargement (40%) and in some cases, neurological disorders [1•]. For example, we have seen three patients admitted in the University Hospital, Aracaju, Sergipe presenting with mild fever for 2 days, followed by maculopapular rash, joint pain and headache. These patients also presented with abdominal clamps and diarrhea in the first two days after the onset of symptoms, which are not typically associated to ZIKV infection. Additionally, blood analysis indicated that two patients developed leukopenia, due to reduction in lymphocyte and neutrophil counts below 1000 cells/mm^3. Leukocyte counts returned to normal levels as patients recovered. All three patients were PCR+ positive for ZIKV and negative for Dengue and Chikungunya.

Two major syndromes have been associated with ZIKV infection and are of particular interest because of their severity: microcephaly and Guillain-Barré Syndrome (GBS), both discussed with greater detail further in the text. The ZIKV outbreak in Brazil is still expanding despite the intensification of mosquito control measures. Moreover, because of the lack of easily available diagnostic tests, the size of the epidemic is yet to be determined. For example, Sergipe state in the Northeast of Brazil had no previously reported cases of ZIKV infection, but saw an increase in incidence of microcephaly to 162 cases [16]. Whether these cases are associated to Zika infection is not known at present but do reflect the overall trend of the northeastern region of the country.

Microcephaly

The most threatening aspect of the ZIKV outbreak is the infection of pregnant women, due to the risk of newborn microcephaly and the risk of severe life-long limitations for the child and the family. In Brazil, the Zika virus was first reported in early 2015, during an outbreak in the northeastern region of the country [17]. A few months later, the Brazilian government published a report indicating an overwhelming increase in the number of babies born with microcephaly [18]. Although a causal association of ZIKV infection with microcephaly in newborns has not been firmly confirmed, ZIKV introduction in northeast Brazil is associated with an increase in congenital malformations in newborns in the same period. A total of 6776 suspected cases of microcephaly have been reported