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LETTER TO THE EDITOR

INTRODUCTION AND TRANSMISSION OF ZIKA VIRUS IN BRAZIL: NEW CHALLENGES FOR THE AMERICAS

Campinas, August 27, 2015

Dear Editor

In October 2014 an outbreak of a febrile rash illness of unknown etiology was identified in the State of *Rio Grande do Norte*, Northeastern Brazil, whose clinical manifestations were low fever or no fever, maculopapular rash, pruritus, arthralgia, and limb edema, lasting 4-7 days. In the following months, similar cases were identified in other States of the region. The initial diagnostic hypotheses of dengue, measles, rubella, enterovirus, and other arbovirus (including Chikungunya) were not confirmed. In early May 2015, Zika virus (ZIKV), an arbovirus which until then had not circulated in Brazil, was confirmed by RT-PCR tests in 15 of 45 samples from patients of two States: *Bahia* and *Rio Grande do Norte*. CAMPOS *et al.* (2015) reported seven confirmed cases of 24 tested samples and ZANLUCA *et al.* (2015) confirmed eight cases of 21 acute phase serum samples^{1,2}. In the following weeks, since the end of May, new autochthonous cases were laboratory confirmed in other States of the Northeastern region (*Alagoas*, *Ceará*, *Maranhão*, *Paraíba*, *Pernambuco*, *Piauí*), Northern region (*Pará*, *Roraima*) Southeastern region (*São Paulo* and *Rio de Janeiro*), and Southern region (*Paraná*), showing that the disease has already expanded throughout the Brazilian territory. These results represent not only the first human cases in Brazil, but also the first presumptive vector borne transmission of ZIKV in Continental America and, potentially, the epidemiological trigger for a worldwide epidemic. Previously imported cases of flavivirus infection have been identified in Europe³, and recently, a first “exported” case of ZIKV to Europe was reported in the new Brazilian scenario of ZIKV expansion⁴.

ZIKV infection was confirmed in different Brazilian States in a short period of time; some locations were separated by 2300 km away⁵ ZIKV circulation has occurred simultaneously to a dengue epidemic of large proportions in regions dense and chronically infested by *Aedes aegypti*. The confirmed circulation of Chikungunya virus in some regions of the Brazilian territory, as in other countries of South America and Caribe raises concerns about the implications of the new virus and its co-circulation with other arboviruses in the context of public health.

The ZIKV is an arbovirus of the genus *Flavivirus* belonging to the Flaviviridae family. It was first identified in 1947 in a rhesus monkey sentinel for yellow fever research conducted at the Zika forest in Uganda^{6,7}. The disease in humans has been well documented only from the 1960's, and by 2007, when less than 20 laboratory confirmed cases were described⁸. The ZIKV has been isolated from various species of *Aedes* mosquitos especially *Ae. africanus*, *Ae. aegypti* and *Ae. albopictus*, all potential vectors. Recent epidemics transmission has been attributed to *Ae. hensilli* and *Ae. Polynesiensis*^{9,10}. The sylvatic cycle of viruses is maintained by genus *Aedes* mosquitoes and non-human primates⁸ and, until recently human beings would be considered only casual hosts.

The geographical expansion of ZIKV transmission beyond Asia and Africa has possibly occurred after 2007, when an outbreak hit the Island of Yap, Micronesia, with an estimated infection of 73% of the population and 12% with clinical manifestations¹¹. Since then a spread of the virus to several Pacific islands has been observed, with autochthonous cases reported in New Caledonia, Cook Islands and Easter Island^{10,11}.

Special attention should be given to an outbreak in French Polynesia from October 2013 until early 2014 due to a large number of symptomatic patients (more than 29,000 people, or about 10% of the population) and the severe cases, particularly with neurological disorders (including 40 cases of Guillain-Barré syndrome (GBS) and 72 cases of various neurological syndromes), assigned to infection ZIKV¹⁰. However, it is noteworthy that a real causal relationship between ZIKV as the etiologic agent of neurological complications (especially those related to immune mechanisms) or neurological conditions resulting from potential association between ZIKV co-circulation and distinct virus serotypes Dengue (serotypes 1 and 3)¹¹ has not yet been well established.

The laboratory diagnosis of the ZIKV infection might require the identification by direct methods, such as viral isolation and RT-PCR since there is no serological testing available for specific IgM/IgG antibodies to ZIKV⁶. There are also specific limitations of serological studies resulting from the possible cross-reactivity with other flaviviruses, among which the dengue virus and yellow fever virus (wild and vaccine virus). This is a very probable scenario in South America and other regions of the world, where there is an endemic circulation of other pathogens like Japanese encephalitis virus and West Nile virus.

Transmission of Zika virus in Brazil has many concerns: social and ecological context in the Americas, particularly in Brazil favors the spread of arboviruses and the occurrence of severe cases associated with viral co-circulation; the current strategy to combat the vector in most areas seems ineffective; climate and environmental conditions are adequate to the vector activity; crowded cities with intense flow of travelers from around the world makes Brazil not only vulnerable to large outbreaks but also a point of dispersion of cases through the world. Moreover, the widespread presence of *Ae. albopictus* in the Americas brings concern that the vector becomes a ZIKV very efficient transmitter, further aggravating this complex epidemiological context. Nowadays, the high vector density in Brazil supports the simultaneous circulation of three arboviruses transmitted by *Ae. aegypti*: dengue, Chikungunya and Zika. However, this context shows that there is also risk of a potential introduction and/or expansion of other arboviruses, in not endemic areas in the Americas. The recent introduction of ZIKV raises many concerns to the Brazilian health authorities especially about the potential occurrence of severe

cases in the future. However, the recent report of a high number of cases presenting neurological syndromes, mostly compatible with GBS, in some Northeastern Brazilian States, has already brought a worrying impact on the health system, despite the fact that further epidemiological information are awaited from ongoing investigation⁵.

From this, questions as how to structure patient care to address difficulties on clinical and laboratory diagnosis and what will be the implications of co-circulation of ZIKV and other flaviviruses are only some of the too many questions to be answered. The apparent rapid expansion of ZIKV transmission area in Brazil should now be seen as an emergent public health challenge not only to the country, but to the Americas and, to some degree, also to the globe.

André Ricardo Ribas FREITAS(1,3)
Rodrigo Nogueira ANGERAMI(2,3)
Andrea Paula Bruno von ZUBEN(3)
Maria Rita DONALISIO(4)

(1) *Faculdade de Medicina São Leopoldo Mandic, Departamento de Medicina Social, Campinas, SP, Brasil.* E-mail: arrfreitas2010@gmail.com

(2) *Universidade Estadual de Campinas/Unicamp, Departamento de Infectologia, Hospital das Clínicas, Campinas, SP, Brasil.* E-mail: rodrigo.angerami@gmail.com

(3) *Departamento de Vigilância à Saúde, Município de Campinas, SP, Brasil.* E-mail: andreabrunovonzuben@gmail.com

(4) *Universidade Estadual de Campinas/Unicamp, Faculdade de Ciências Médicas, Departamento de Saúde Coletiva, Campinas, SP, Brasil.* E-mail: rita.donalisio@gmail.com

Correspondence to: Maria Rita Donalisio, Universidade Estadual de Campinas/Unicamp, Faculdade de Ciências Médicas, Departamento de Saúde Coletiva, Rua Tessalia Vieir de Camargo 126, 13083-997 Campinas, SP, Brasil. E-mail: rita.donalisio@gmail.com

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