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EDITORIAL

### Editorial

## Zika virus: Growing guilt from association<sup>☆</sup>



## Virus de Zika: se expande su culpabilidad por asociación

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The Zika virus (ZIKV) is part of the *Flaviviridae* family and is transmitted by mosquitoes of the *Aedes* genus,<sup>1</sup> as is the case with other members of that family, including the dengue virus (DENV), the yellow fever virus (YFV), the Japanese encephalitis virus (JEV), and the Western Nile virus (WNV). The ZIKV genome consists of an RNA molecule (ribonucleic acid) that encodes for a polyprotein which, following processing, results in the production of three structural proteins (C, prM and E) and seven non-structural proteins (NS).<sup>2,3</sup> Studies about its molecular evolution point to three main ZIKV lineages: one from Asia and two from Africa.<sup>4,5</sup> Recent studies have shown that it has undergone several recombination events since it emerged in Uganda early in the 20th century, and then after it moved towards Western Africa and Asia.<sup>6</sup> Phylogenetic tree analyses have shown that the Surinam ZIKV strains belong to the Asian genotype and are intimately related to the strain that circulated in the French Polynesia in 2014, with which they share 99.7% of the genetic information and 99.9% of their identity in the amino acid sequences that make up the protein.<sup>7</sup>

The clinical picture caused by the ZIKV is similar to that of dengue fever and chikungunya. Patients present with fever, headache, arthralgia, myalgia and maculopapular rash, a whole complex of symptoms that renders a differential diagnosis difficult. This is compounded by the fact that a high proportion of ZIKV infections are asymptomatic, and many are associated only with a mild disease.<sup>8</sup> Although the ZIKV vector is the *Aedes* mosquito species, sexual transmission was suggested when ZIKV was detected in the semen of a patient

affected by the outbreak of the virus in the French Polynesia in 2013.<sup>9</sup> Potential ZIKV sexual transmission has been reported in three cases,<sup>10</sup> creating concern especially during gestation. The possibility of ZIKV transmission through blood transfusions has also been reported,<sup>11</sup> and the health authorities in Brazil have reported two cases of ZIKV transmission.<sup>12</sup>

On February 1st 2016, the World Health Organization declared the ZIKV expansion as a worldwide public health emergency.<sup>13</sup> Experts have declared a strong space and time association between ZIKV infection and an increase in congenital malformations and neurological complications. However, emphasis is made on the need for additional research in order to determine with scientific certainty the causal relationship between ZIKV and microcephaly, despite the strong suspicion of a relationship between ZIKV infection during pregnancy and microcephaly. An urgent appeal to coordinate international research work has been launched in an attempt to gain a better understanding of the disease and eventually pave the way for the development of a protective vaccine.

ZIKV expansion was reported in 2015 in Latin America and the Caribbean, particularly in Brazil where the number of cases in the latter part of the year were estimated at 440,000–1,300,000<sup>14,15</sup> with almost a twenty-fold increase in cases of neonates born with microcephaly associated with ZIKV infection during pregnancy.<sup>15–18</sup> A recent publication in the *New England Journal of Medicine* (NEJM) (February 9 2016)<sup>19</sup> refers to an association between ZIKV and microcephaly, reinforcing the suspicion of a causal relationship.

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The publication reports the case of a European citizen infected with the ZIKV in Brazil at 13 weeks of gestation, and includes ultrasound images with no foetal abnormalities at 14 and 20 weeks of gestation. However, between 29 and 32 weeks there were findings of intrauterine growth retardation, microcephaly, diffuse cerebral structures and calcifications in the brain.<sup>19</sup> The autopsy performed following the interruption of the pregnancy revealed a severely affected foetal brain, a relatively small brain mass (84 g), and absent gyri. Histopathological and molecular tests revealed numerous neuropathological findings, including in particular multifocal calcifications of the cerebral cortex and the subcortical white matter.<sup>19</sup>

However, pursuant to rigorous scientific research, the results are not absolute evidence that ZIKV causes microcephaly.<sup>20</sup> The causality criteria proposed by Robert Koch in 1891<sup>21</sup> require isolation of the causative agent and the reinfection event of a susceptible individual in order to reproduce the disease and isolate the causative agent. Given the devastating and intractable manifestations of the disease, it has been found difficult to apply Koch's criteria,<sup>20</sup> the recommendation being to use a combination of scientific and epidemiological evidence.

An association has also been found between ZIKV infection and the infrequent but very worrisome Guillain-Barré syndrome (GBS). This autoimmune syndrome has been reported in patients from French Polynesia and Brazil during ZIKV outbreaks,<sup>15,17,22</sup> although emphasis has been placed on the need for further research in order to understand the potential association. In Brazil, 1,708 cases of GBS were reported between January and November 2015, with increases ranging between 100% and 500% in several states where ZIKV and other flavivirus circulate, compared to 2014.<sup>23</sup> Case-control studies are under way in Brazil to determine the causes of this rise in GBS and confirm or rule out a causal relationship with ZIKV.

While waiting for the scientific research that may shed light on the basic mechanisms involved in ZIKV replication and that may eventually pave the way for developing primary prevention strategies and therapeutic interference of the viral infection, the public health infrastructure in the affected countries will have to face up to the challenge of controlling and eradicating the vector, implementing diagnostic procedures, strengthening contraceptive programmes and programmes for the prevention of sexually transmitted diseases, providing care to pregnant women and guaranteeing their right to interrupt pregnancy, among other related challenges.

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