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Editorial

Zika virus: An emerging player in the global scenario

Virus Zika: un jugador emergente en el escenario global

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Zika virus (ZIKV) is a member of the family *Flaviviridae* with three lineages described to date: West African, East African, and a descendant Asian lineage responsible for the latest epidemic outbreaks in the Western Hemisphere.[1] The virus was first isolated in 1947 in samples taken from a sentinel rhesus monkey in the Zika forest of Uganda, and was subsequently recovered from *Aedes africanus* mosquitoes in the same forest. The first human cases were identified in Uganda and Tanzania in 1952 during a serosurvey study, which demonstrated the presence of neutralizing antibodies against ZIKV.[1,2] Throughout the 1950s, serosurveys demonstrated the presence of neutralizing antibodies to ZIKV in Egypt, Mozambique, Nigeria, Malaysia, Vietnam, and the Philippines. Although it was thought that ZIKV was confined to Africa, serological studies showed that ZIKV was widespread throughout Asia even before the 1980s.[2]

The first 3 cases of human infection were identified in Nigeria in 1953. During the following 57 years, only 13 additional cases of naturally acquired infection were reported.[2] It was not until 2007 when the first large outbreak of ZIKV in humans was reported on the Pacific island of Yap (Federated States of Micronesia). An estimated 73% of Yap residents older than 3 years were affected.[2,3] Given that there were no monkeys on the island, it seems likely that the virus was introduced by an infected person or an infected mosquito. Sporadic cases were subsequently detected in Asia and Africa until 2013, when French Polynesia experienced the largest ZIKV outbreak reported at the time, in which more than 32,000 persons were assessed for suspected infection. The virus spread to other Pacific islands, notably Easter Island, and in March 2015, Brazil reported autochthonous transmission of ZIKV, which then rapidly extended throughout South America and the Caribbean. On 1 February 2016, the WHO declared a Public Health Emergency of International Concern regarding clusters of cases of microcephaly and neurological disorders in areas affected by ZIKV. In March 2017, a total of 70 countries reported evidence of mosquito-borne transmission of ZIKV since 2015.[4] Furthermore, soon after the epidemics spread in Asia and Latin America, imported cases were identified in countries with no mosquito-borne transmission.[5]

The incubation period has not been well defined, although it is estimated to be around 3–10 days. Most individuals infected with ZIKV do not show signs or symptoms of infection. In contrast to dengue or chikungunya the onset of the disease is not abrupt. Symptomatic patients may present with mild fever, rash, conjunctivitis, arthralgia, myalgia, and headache. The most common neurological complication is Guillain–Barré syndrome (GBS). During the 2013–2014 ZIKV outbreak in French Polynesia, there was an increase in the number of cases of GBS, with an estimated incidence of 0.39 cases/1000 infected persons/year.[6] The odds of having had a recent ZIKV infection were more than 30 times higher in patients who had GBS than in those who did not.[7] The same phenomenon was detected in surveillance data and medical records during 2015–2016 in Brazil, as well as in other affected countries where the incidence of GBS was estimated to have increased 2–10 times during the epidemic period.[8] Other complications such as encephalitis, myelitis, haemorrhagic manifestations, and death are very rare.[1,9]

Diagnosis is based on molecular and serological tests. In patients presenting with a $\leq$7-day history of symptoms, the presence of ZIKV can be confirmed using nucleic acid tests such as RT-PCR. Given the non-specificity of the clinical picture and possible coinfection with other arboviruses, patients should also be tested for dengue and chikungunya. Nucleic acid tests are performed mainly with whole blood, serum, and urine. As for patients presenting $\geq$7 days after the onset of symptoms, serology (IgM detection) is the preferred method for diagnosis. Whenever possible, paired serum specimens should be collected at least 2–3 weeks apart. Recommended tests include enzyme immunoassay or immunofluorescence assay, together with neutralization techniques for confirmation (such as the plaque reduction neutralization test). It is important to remember that serology tests are subject to cross-reactivity, especially in patients with a previous history of flavivirus infection or previous immunization (yellow fever or dengue). In addition to serological tests, the ZIKV genome may be detected in urine and semen much later (up to 30 days in urine and even longer in semen).[10]

As in the case of other mosquito-borne arboviruses, the only specific treatment is symptomatic relief and supportive measures for severe cases. Treatment with nonsteroidal anti-inflammatory

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drugs or acetylsalicylic acid is discouraged, because of a theoretical risk of haemorrhaging, as occurs with other flaviviruses. Candidate vaccines are currently in the preclinical and clinical development stages and include those based on DNA, messenger RNA, inactivated and live-attenuated vaccines, and viral vectored vaccines.[11] However, the falling number of cases in previously affected areas could constitute a threat to vaccine development.

In contrast to the chikungunya epidemic that struck most of the American continent during 2013–2014, or the recurrent outbreaks of dengue after the 1970s in the Americas, South-East Asia, and Western Pacific, the recent epidemic of ZIKV is particularly worrying because it can be sexually transmitted and, more importantly, the effects on the foetus are sometimes devastating.

ZIKV is transmitted mainly by mosquitoes of the *Aedes* genus. In Africa, ZIKV is sustained in a sylvatic transmission cycle comprising nonhuman primates and forest-dwelling species of *Aedes* mosquito. In areas with nonhuman primates, ZIKV is probably maintained in human–mosquito–human cycles.[9] The urban–suburban cycle involves humans and *A. aegypti* (and to a lesser extent *A. albopictus*), which has been responsible for most of the ZIKV outbreaks. Both *A. aegypti* and *A. albopictus* have demonstrated low vector competence for the transmission of ZIKV, although the characteristics of *A. aegypti* that make it an efficacious vector are rapid development, behavioural plasticity, desiccation-resistant eggs, and a preference for urban environments. The insect feeds preferentially on humans and often bites multiple individuals in a single blood meal.[12] Other anthropophilic vectors, such as *Culex* mosquitoes, are unable to transmit ZIKV, with the result that the geographical extension and transmissibility of the virus are restricted.[13]

The other forms of non-vectorial transmission reported include sexual contagion, as well as vertical transmission, non-sexual person-to-person contact, and laboratory accidents. A potential risk for infection through blood transfusion has been identified in endemic regions.[1,9,14] ZIKV RNA is detected in semen as late as 93 or even 188 days after onset of symptoms,[15] and persistence of ZIKV RNA in the female genital tract has been identified after up to 11 days.[16] Contagion through sexual contact has been shown to be male to male,[17] male to female,[18] and female to male.[19] To date, ZIKV is the only flavivirus that has been sexually transmitted. Male-to-female sexual transmission has occurred as late as 32–41 days after the onset of symptoms.[18] The ability to be sexually transmitted could cause adverse foetal outcomes in women who are pregnant or women who become pregnant while the male partner is infective and/or lead to the emergence of new cases in non-endemic areas. Such a scenario could be more worrying in areas where there are competent vectors capable of initiating a transmission cycle.

Nevertheless, global concern over ZIKV stems from the relationship between ZIKV and microcephaly and adverse neurological outcomes in the foetuses and infants of infected mothers. This connection was first suspected in Brazil at the end of October 2015 because of an increase in the number of cases reported in Pernambuco State. Since then, 33 countries and territories have reported an increased incidence in GBS, and 31 have reported cases of microcephaly and other central nervous system malformations potentially associated with ZIKV.[4,20] The risk of birth defects is increased if infection is acquired before conception or during the first trimester and has been estimated to be 1–13% based on the outbreak in Bahia, Brazil.[21] Data from the US Zika Pregnancy Registry showed that the risk of birth defects was similar for symptomatic infections (6%; 10/167) and asymptomatic infections (6%; 16/271), although the highest rate (11%) was detected in women infected during the first trimester.[22] A recent expert review showed that the risk of congenital brain abnormalities could be 50 times higher in mothers who had acquired ZIKV infection while pregnant than in those who did not.[7] Of note, microcephaly may also develop in asymptomatic newborns with congenital ZIKV infection.[23] The various potential explanations for the unexpected central nervous system damage caused by ZIKV include strong tropism for neuronal progenitor cells,[24,25] nutritional deficits affecting newborns, pesticides, and immune interplay caused by prior infection with other flaviviruses.[1] It has been reported that a single mutation in the viral polyprotein (S139N) could be implicated in the neuropathogenesis of ZIKV infection. This mutation appeared before the 2013 outbreak in French Polynesia and was still present during the subsequent spread of ZIKV to the Americas.[26] Because of the risk of infection in the foetus and newborns, health recommendations for pregnant women stress avoidance of travel to risk areas, or when this is not possible, maximization of anti-mosquito precautions.

In this issue of EIMC, Diaz-Menéndez et al.[27] describe a retrospective analysis performed in a referral tropical medicine unit in Madrid, Spain on travellers returning from an area where ZIKV was endemic. The study population comprised returned travellers attended from 1st January to 30th April 2016 and who underwent screening for ZIKV infection. The diagnostic workup for ZIKV was carried out according to national protocols, and neuroultrasonography was performed in all pregnant women irrespective of their ZIKV infection status.

Most of the 184 patients screened were women (60%). Mean age was 37 years, 90% were from Central and South America, and 88% were travellers (business, traditional, or immigrant travellers). Dengue was diagnosed in 17 patients (9.2%) and chikungunya in two (1.1%). ZIKV infection was detected in 13 patients (7%) (by serology in eight cases, positive RT-PCR in organic fluids in seven, and by both techniques in two). Four infected patients were pregnant and another was the male sexual partner of a pregnant woman. At the time of writing, no adverse foetal outcomes were identified. Symptoms at the moment of evaluation were non-specific, thus reflecting the difficulty in making a diagnosis of the most common arboviruses based only on clinical grounds.

Diaz-Menéndez et al.[27] provide valuable information on the role of travellers as sentinels of actively circulating pathogens. Even during an active ZIKV outbreak, dengue virus infection was more common, thus reflecting the diverse origin of the patients. Real-time epidemiological information is critical for the evaluation of potentially exposed patients, as in the case of pregnant women infected by ZIKV. Moreover, since immigrants often travel despite the risks, this information could prove to be very helpful. Lastly, this study highlights the risk of autochthonous transmission of ZIKV: vectorial transmission is possible through *A. albopictus* feeding on viraemic patients, as well as through excretion of the virus in genital fluids during sexual intercourse.

The case reported by Oliveira Souto et al.[28] in this issue of EIMC highlights the potential long-term risk of infection with ZIKV through sexual transmission. The patient was a man in his 30s who sought medical attention two days after returning from a 15-day holiday in Venezuela. He developed a clinical picture suggestive of ZIKV infection, which was confirmed by RT-PCR in serum at day 3. A specific IgM and IgG response was also detected, and other concomitant arboviruses were ruled out. ZIKV RNA was not detected in follow-up serum (days 48 and 210) or urine samples (days 48, 93, and 213). However, ZIKV RNA was identified in semen samples at days 30, 48, and 93, although the sample was negative at day 201. Nevertheless, the virus was not isolated in culture at any point. The patient was diagnosed with prostatitis the month before his trip, during which he reported haematospermia and needed medical care by a urologist. Therefore, in this case, chronic prostate inflammation might have contributed to the prolonged period of viral excretion.

Given the ability of ZIKV to be sexually transmitted, the CDC and WHO recommend condoms or sexual abstinence of at least six months for the male partner of a pregnant woman or women of

childbearing age, even if he does not have symptoms. This period can be shortened to eight weeks when only the female partner visits the endemic area.

Could ZIKV become established in Spain? In theory, ZIKV could become established in Spain, because some of the necessary conditions for infection to occur are already present. There is a competent vector (*A. albopictus*), which is widely distributed, and there are imported cases with detectable viraemia. In addition, the nature of local social customs means that the interaction between vectors and humans is frequent in the months of greatest risk (May to November). Furthermore, sexually acquired infection might be the source of new cases. However, several factors hamper the occurrence of significant outbreaks. *A. albopictus* is a much less efficient vector than *A. aegypti* and is not widespread in areas that receive a significant number of potentially transmitting returned travellers (such as Madrid).[29] In countries such as France, a large number of ZIKV cases have been identified in returning travellers. Despite the fact that *A. albopictus* is well established in many parts of France, no autochthonous transmission has been detected.[30] Furthermore, the period of viraemia of ZIKV is short,[31] the level of ZIKV viraemia seems to be low,[31] and the Asian strain is not transmitted better than the African strain.[32] Consequently, significant outbreaks seem unlikely. In fact, viruses with more favourable conditions for transmission, such as dengue virus or chikungunya, have not led to autochthonous cases in recent years, despite the increase in imported cases. However, active clinical and vector surveillance remain important. The devastating consequences of ZIKV infection mean that early detection of cases and control of outbreaks are essential if we are to prevent the spread and establishment of this virus.

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