Epidemiology and neurological complications of infection by the Zika virus: a new emerging neurotropic virus

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Introduction. The current epidemic outbreak due to Zika virus began in 2015 and since then it has been reported in 31 countries and territories in America. The epidemiological and clinical aspects related to infection by Zika virus are reviewed.

Development. Since 2007, 55 countries in America, Asia, Africa and Oceania have detected local transmission of the virus. This epidemic has affected almost 1.5 million people in Brazil. 80% of the cases are asymptomatic. The symptoms of Zika virus disease include fever, maculopapular rash, arthralgia and non-purulent conjunctivitis. The symptoms are usually self-limiting and last one week. An increase in the incidence of cases of microcephaly, retinal lesions and Guillain-Barré syndrome associated with the Zika virus has been reported. Zika-associated Guillain-Barré syndrome in Polynesia is a pure motor axonal variant. The RNA of the Zika virus has been identified in samples of brain tissue, placenta and amniotic liquid of children with microcephaly and in the still-born infants of women infected by Zika during pregnancy. The reverse transcription polymerase chain reaction test is recommended to detect viral RNA, and serological tests (IgM ELISA and neutralising antibodies) should be conducted to confirm infection by Zika. The differential diagnosis includes infection by the dengue and chikungunya viruses.

Conclusions. Knowledge about the pathogenic mechanisms involved in infection due to Zika virus and its long-term consequences in adults and newborn infants is still limited.

Key words. Epidemic outbreak. Flavivirus. Guillain-Barré. Microcephalia. Zika virus. Zika virus disease.

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Introduction

In 2015, a new almost unknown virus, called Zika, appeared on a global scale in epidemic proportions. Zika virus is an arbovirus belonging to the family *Flaviviridae,* genus *Flavivirus,* which includes other flaviviruses, such as the dengue, yellow fever or West Nile viruses. Zika virus is currently spreading throughout America and causing a great deal of concern due to the large number of cases, countries and areas affected, in addition to the recently reported neurological complications it is accompanied by.

The aim of this article is to review the, in some cases preliminary, clinical and epidemiological data available regarding the present Zika virus epidemic.

Epidemiology

Zika virus was first isolated in 1947 in a *rhesus* macaque monkey in the Zika forest in Entebbe, Uganda [1]. The monkey was a sentinel animal with fever located in a cage in a platform in a tree, and which was part of a yellow fever research programme sponsored by the Rockefeller foundation. The serum of the primate was inoculated in a mouse brain and approximately 10 days later the rodents developed the disease. This was how a filterable transmissible agent that was named Zika virus was isolated [2]. The virus was later isolated from the mosquito *Aedes africanus* in the same forest. In 1956 the transmission of Zika virus by *A. aegypti* mosquitoes to monkeys and rodents was confirmed [3].

The first symptomatic case was reported in Nigeria in 1954 [4]. Nevertheless, phylogenetic studies have estimated that Zika virus first appeared in East Africa around the year 1920 (confidence interval: 1892-1947) [5]. Serological studies conducted in Uganda in 1952 detected a seropositivity rate of 6% in humans [6]. In the late 1960s, the seropositivity for Zika virus in Kenya was 50%, although there were notable differences from one geographical area to another [7]. In the 1970s, Zika virus was again isolated in human beings in Nigeria; in one study, 40% of the subjects analysed had neutralising antibodies against the virus [8,9]. The cases reported in Nigeria involved children aged between 1 and 3 years who presented fever, headache and general malaise. Over the next two decades several dozens

of sporadic cases of infection by Zika virus were detected in different countries in Africa (Uganda, Tanzania, Sierra Leona, Central African Republic, Egypt, Senegal and Nigeria) [10-13].

The virus was first detected in Asia in *A. aegypti* mosquitoes in Malaysia in the late 1970s [14,15]. Phylogenetic studies, however, have dated the transmission of Zika virus from East Africa to south-east Asia as occurring around 1945 (confidence interval: 1920-1960) [16]. A study conducted in the 1980s with 71 volunteers in Lombok, Indonesia, detected the virus in 13% of them [17]. Cases were later reported in India, Thailand, Philippines, Indonesia and Vietnam [2].

From south-east Asia, the virus moved eastwards again. In 2007 the first great Zika virus epidemic occurred on the island of Yap in Micronesia [18]. An epidemic outbreak was reported in which the population presented fever, exanthema, painful joints and conjunctivitis. Although some patients presented positive immunoglobulin M (IgM) for dengue virus, it soon become apparent that it was a new viral infection, and RNA of Zika virus was detected in the infected subjects. Up until that time only isolated cases of Zika virus disease had been reported [1,9,10,12,19]. But in Yap state, it was estimated that 73% of the population under 3 years of age could have been infected by the virus [18].

In 2013 there was a new epidemic in French Polynesia; at least 28,000 people (11% of the population) presented the infection in the first four months [20]. The strain causing the epidemic outbreak was phylogenetically related to the strains that caused the outbreaks in south-east Asia (Cambodia, 2010), which suggested an independent introduction from Asia to Polynesia. Hence, the expansion of the Asian lineage of Zika virus was confirmed [21]. From then on, the virus spread quickly throughout the whole of the Pacific area [22] and new cases were discovered in the Cook Islands, New Caledonia and Easter Island [23-25].

In 2015, the World Health Organisation (WHO) communicated for the first time the local transmission of Zika virus in the American continent and autochthonous cases were identified in Brazil. The first infected subjects were detected in Salvador de Bahía in early 2015, and in May Brazil officially announced an epidemic outbreak due to Zika virus [26]. The epidemic was of such a magnitude that the Brazilian Ministry of Health estimated that between half a million and 1.5 million cases of infection by Zika virus had been registered. To illustrate the importance of the current epidemic, in 2015 Brazil reported half a million cases of dengue and 9,300 cases of infection by chikungunya to the Pan-American Health Organisation [27].

Since then, the epidemic has affected most of America. After Brazil, it spread rapidly to Colombia (October 2015), Surinam (November 2015), Guatemala, Mexico, Venezuela, Paraguay and Panama. Today, at least 31 countries in America report active transmission of the virus [28,29].

Transmission to the American continent seems to have had its origin in the islands of the Pacific. Phylogenetic analyses of the region coding for the NS5 protein, the capsid protein and the entire coding region have confirmed that the American strains belong to an Asian genotype [30]. In 2015 autochthonous cases of infection by Zika virus were also reported in Samoa, Salomon Islands, New Caledonia, Fiji and Vanuatu [29].

Zika virus came to the attention of the mass media after the Brazilian government officially released information about a dramatic increase in the incidence of microcephalia within the context of the epidemic. In February 2016, WHO declared the Zika virus epidemic a Public Health Emergency of International Concern, due to the spread to other countries of Latin America and the rising number of cases of microcephalia and Guillain-Barré syndrome (GBS) detected. In 2015 and during the first two months of 2016, 41 countries have reported an autochthonous transmission of Zika virus at a local level. The latest countries to report recent cases of Zika are Laos and Philippines.

A new epidemic outbreak was detected in Cape Verde and Gabon; between October 2015 and January 2016 more than 7,500 cases of Zika virus disease were reported in Cape Verde. Preliminary studies suggest that it is a new strain of the African lineage [31].

Several dozens of cases of infection have been identified in travellers and tourists returning from endemic zones to Europe and the United States, including pregnant women. Likewise, cases of local transmission have been reported in Italy, France, Argentine, New Zealand and the United States in the absence of any insect vector, probably due to sexual contact.

The virus. Modes of transmission

Zika virus is an arbovirus that has a sigle chain of RNA that contains 10,794 nucleotides that code for 3,419 amino acids. Its genome was sequenced in 2006 [32]. The organisation of the Zika genome is similar to that of other flaviviruses (5'-C-prM-E-NS1-NS2A-

NS2B-NS3-NS4-NS4B-NS5-3') and codes for the structural proteins C, M and E, as well as a series of non-structural proteins needed for their replication and assembly [32]. At present, two dozen genomes of the virus are available in GenBank, including the complete genomic sequence of Zika virus isolated from a Brazilian patient who received a blood transfusion from an asymptomatic donor [33].

The arthropod vector is the mosquito of the genus *Aedes,* and transmission can be both sylvatic and urban. It is unknown whether primates can be a reservoir during the human transmission cycle. Zika virus is transmitted to human beings through the bites of infected mosquitoes. The virus has been isolated from *A. aegypti, A. africanus, A. luteocephalus, A. apicoargenteus, A. vittatus* and *A. furcifer* mosquitoes [14,34]. *A. aegypti* is the main vector and it is widely distributed throughout tropical regions around the world. *A. polynesiensis* can favour transmission of the virus in Polynesia. *A. hensilii* was the principle mosquito detected in the epidemic in the Yap islands in 2007, although the virus was not isolated from that mosquito.Entomological and laboratory studies have shown that *A. albopictus* is susceptible to infection by the virus in the laboratory, although the rate of transmission was low [35].

From the evolutionary point of view, it is thought that this arbovirus adapted itself to a human cycle about 5,000 years ago, when the African communities became sedentary and began to accumulate deposits of water. The *Aedes,* which up until then were arboreal mosquitoes, adapted themselves to a domestic and peridomestic cycle, and started to lay their eggs in human containers.

The extrinsic incubation period in mosquitoes has been estimated at 10 days. In the original laboratory studies, it was observed that the concentration of virus in mosquitoes fed artificially diminished to undetectable levels in the 10 days following feeding, increased at day 15 and remained high from days 20 to 60 [3].

During outbreaks, human beings become the primary host in which amplification of the virus takes place. It is transmitted to the mosquito during the process of biting and sucking human blood, it reproduces inside the vector without affecting it and remains inside the insect throughout its entire life cycle. The virus will be transmitted again to another person, who will act as a reservoir, the next time the mosquito bites. *A. aegypti* is the vector involved in the current outbreak in America; it is found in many rural and urban areas, and can also transmit the dengue and chikungunya viruses.

Other modes of transmission of Zika virus without the mediation of an insect vector have been reported: sexual contact [36-38], intrauterine transmission that causes congenital infection, perinatal transmission from the viremic mother to the newborn [39], blood transfusion [40] and as a result of laboratory exposure [28]. These observations, based on isolated clinical cases, give rise to a certain amount of concern. It is possible that, once the virus has been introduced into an area where there is no vectorial transmission, the infection may persist in the absence of the insect vector. Transmission by means of organ and tissue transplants has still not been demonstrated, although this is something that might occur in the future.

The sexual transmission of Zika virus has been confirmed, and several cases of sexual transmission from males to females have been reported [36-38]. The cases are similar and involve males who acquired the infection in an endemic zone and on returning had sexual intercourse with their spouses, who, in turn, developed the classical symptoms of the infection two weeks after having sex. Several males presented prostatitis y haematospermia.

Viral RNA has been detected in semen using reverse transcription polymerase chain reaction (RT-PCR). In the outbreak in Polynesia, it was observed that the virus was capable of remaining in semen for several weeks, whereas in blood the RT-PCR had become negative [37]. Zika RNA has been detected in semen up to 62 days after the onset of the disease [41]. The viral load in semen can be 100,000 times higher than that seen in blood or urine two weeks after the first symptoms, which can favour the sexual transmission of the virus [42].

Screening for Zika virus was implemented in Polynesia for blood donors after the epidemic outbreak in 2013. Approximately 3% of asymptomatic donors had an acute infection due to Zika virus when they were giving blood [22,40].

Zika virus RNA has been detected in the milk of two mothers with a confirmed infection. Yet no viruses with a capacity to replicate in cell cultures have been identified to date [39]. There are currently no documented cases of infection by Zika virus transmitted via breastfeeding [43].

Clinical manifestations

The virus is thought to replicate in dendritic cells close to the inoculation starting point, and from there it goes on to the lymph nodes and the blood. The infection is usually asymptomatic and self-lim-

Table I. Common causes of microcephalia.

Genetic causes	Autosomal recessive microcephalia		
	Aicardi-Goutières syndrome		
	Chromosomal trisomies		
	Rett syndrome		
	X-linked microcephalia		
	Craniosynostosis		
Environmental causes	Maternal exposure to drugs and toxic substances	Alcohol, cocaine, drugs	
		Antiepileptic drugs	
		Intoxication by mercury or lead	
		Radiation	
		Exposure to other chemical and toxic products	
	Infectious	Viral infections	German measles
			Cytomegalovirus
			Herpes simplex and varicella zoster viruses
			Human immunodeficiency virus
			Arbovirus: chikungunya
		Toxoplasmosis, syphilis and other infections	
	Others: foetal malnutrition, placental insufficiency		

iting in 80% of subjects. In the remaining cases, the symptoms are usually mild and last from 3 to 7 days. Infections that present clinical manifestations are accompanied by headache, febricula or fever below 38.5 °C, mild to moderate pain in muscles and joints, pruritic maculopapular exanthema and non-purulent conjunctivitis. Less frequently, retro-orbital pain, anorexia, nausea, vomiting, abdominal upsets and diarrhoea have been reported. The fever generally lasts a couple of days and is accompanied by exanthema from the first or second day on. The exanthema and conjunctive hyperaemia are usually more pronounced in comparison to infection by dengue or chikungunya. Arthralgia may persist for several weeks in some patients [1,2,4,29].

Severe forms of infection are rare, although some deaths have been reported in Brazil. Neurological complications (microcephalia and GBS) have been associated to greater disability.

Neurological manifestations

There are clinical and epidemiological data that link the increased incidence of microcephalia and/or GBS with the recent Zika virus epidemic [44]. Certain neurological complications are known to be linked with other flaviviruses and cases of GBS associated to infections by dengue, West Nile or chikungunya viruses [45].

Microcephalia

In September 2015, the Brazilian Ministry of Health detected a marked increase in the number of cases of microcephalia in the north-eastern states of Brazil (above all in Pernambuco) and an official microcephalia register was set up. Until the end of February 2016, there have been 6,158 cases of microcephalia and 157 deaths in 21 states in Brazil. The incidence is 20 times higher than that registered in preceding years, and today stands at 99.7/100,000 live births. However, the number of cases of microcephalia directly related to infection by Zika virus is not known [31].

According to WHO, a case of microcephalia is defined by a fronto-occipital circumference of the head of a newborn infant or foetus that is equal to or greater than two standard deviations below the mean for the same gestational age and sex. Even though there are a number of genetic and environmental causes of microcephalia (Table I), epidemiological evidence suggests the existence of a link between the current infection by Zika virus and cases of microcephalia.

In November 2015, Zika virus RNA was first identified in the amniotic fluid of two pregnant women whose foetuses presented microcephalia in Paraíba state (Brazil). Both expectant mothers presented a possible infection by Zika in gestational weeks 18 and 19. The ultrasound scan performed at week 20 detected cerebral calcifications and another ultrasound scan at week 28 confirmed the diagnosis of microcephalia [46]. At week 28, the RT-PCR was negative in serum and urine in both mothers and positive in the amniotic fluid: the viral load was 10,000 times higher than that observed in blood during the acute exanthema phase [29]. Later reports informed of the presence of Zika virus RNA in the blood and tissues of a newborn infant with microcephalia who died several minutes after birth [29].

In November 2015, reports from French Polynesia informed of an unusual increase in the number of cases of microcephalia and other malformations of the nervous system (18 cases, 50% with microcephalia) during the epidemic over the period 2014-2015 [31]. In the current outbreak in Brazil, Zika virus RNA has been identified in samples from children with microcephalia (brain tissue, placenta and amniotic fluid) and in the still-born children of women infected during pregnancy.

Some of the notable consequences of infection by Zika virus during pregnancy include: foetal death, delayed intrauterine growth with or without microcephalia, cerebral calcifications and other lesions involving the central nervous system, macular hypoplasia, anomalies in the volume of amniotic fluid (oligohydramnios), placental insufficiency and alterations in the umbilical and cerebral arterial flow [47].

A recent Brazilian study evaluated 35 cases of children with microcephalia whose mothers had had exanthema during pregnancy suggestive of Zika virus infection. 75% of the mothers had the rash during the first or second trimester of the pregnancy. The transfontanellar brain ultrasound and computerised tomography scans detected cerebral calcifications in the brain parenchyma, the basal ganglia and the periventricular region, cortical atrophy and dilatation of the cerebral ventricles. A third of the children had neuronal migration anomalies, such as pachygyria or lissencephalia. 40% presented hypertonia; 20%, hyperreflexia; 15% had clubfoot and arthrogryposis; and 10%, convulsions [44].

A necropsy study conducted on the foetus of a Slovakian woman who was infected by Zika virus at week 13 of pregnancy in the north-east of Brazil has also been published. The autopsy performed on the foetus revealed an atrophied brain, the absence of convolutions, dilatation of the lateral ventricles, dystrophic calcifications in the cerebral cortex and white matter of the frontal, parietal and occipital lobes, hypoplasia of the brain stem and spinal cord, and Wallerian degeneration of the spinal tracts [48].

The histopathological study revealed granular, filamentous calcifications with a neuronal morphology in the cortex and the white matter, diffuse astrogliosis and occasional perivascular infiltrates with predominance of T-cells. Immunofluorescence studies showed granular intracytoplasmic reactions in the destroyed neuronal structures. Particles from Zika virus were viewed using electron microscopy, and virus RNA was isolated in the brain, but not in other organs. The histopathological examination of the placenta revealed focal calcifications in the villi and decidua, but an absence of any inflammatory process. The phylogenetic study of the genomic sequences of the virus retrieved from the foetal brain was similar (99.7%) to that found in other patients infected in French Polynesia in 2013 and in São Paulo, Brazil, in 2015 [48].

This case is important because the association between infection by Zika virus and foetal brain anomalies was confirmed after finding the virus in the brain using an electron microscope. The mechanism involved in the neurotropism of Zika virus remains unclear. Nevertheless, dense particles consistent with Zika virus have been observed in the damaged endoplasmic reticulum. The histopathological study performed on the foetus detected folded structures that were very similar to the remains of replication complexes that are characteristic of flaviviruses, which points to a replication of Zika virus in the brain. The electron microscope findings suggest a persistence of Zika virus in the foetal brain, perhaps due to the fact that the central nervous system is an immunological sanctuary. It is as yet unknown whether the ocular region or the gonads can behave in a similar manner, as occurs in the case of infection by Ebola virus [49,50]. In this study, the number of copies in the foetal brain was higher than that observed in the serum of patients infected by Zika virus, but similar to that found in samples of semen [16,51].

Guillain-Barré syndrome

During the epidemic outbreak in French Polynesia, at least 74 patients presented neurological or immune-mediated syndromes after suffering a viral infection consistent with Zika virus. Altogether 42 cases of GBS were reported, 37 of which had presented a viral infection in previous days. The incidence of GBS was 20 times higher than expected for the population of Polynesia [31]. The mean incidence in historical series in Micronesia was five cases per year. Yet during the Zika outbreak there were more than 40 cases, a number 20 times higher than could be expected [52].

In Brazil an increase of 20% in the number of cases of GBS was reported during 2015, in comparison to previous years. In the north-eastern states of Brazil, 121 cases of GBS accompanied by a preceding exanthema were reported between January and July 2015. 62% of the 42 cases of GBS declared in the state of Bahía up until July 2015 had symptoms consistent with an infection by Zika virus in the previous days [31].

Table II. Immune-mediated syndromes reported in infections by flavivirus.

Acute disseminated encephalomyelitis	
Cerebellitis and cerebellar syndrome	
Neuromyelitis optica	
Transverse myelitis	
Guillain-Barré syndrome	
Miller Fisher syndrome	
Brachial neuritis	
Mononeuropathies	Optic neuritis
	Oculomotor paralysis of third cranial nerve
	Paralysis of the abducens nerve
	Facial palsy
	Paralysis of the phrenic nerve
	Neuropathy of the long thoracic nerve
Post-viral chronic fatigue syndrome	

In the first months of 2016, Colombia, El Salvador, Surinam and Venezuela have reported an unusual increase in the number of cases of GBS. In previous years Colombia registered an annual average of 223 cases of GBS; in contrast, 201 cases have been reported in nine weeks from December 2015 to mid-February 2016. In El Salvador 118 cases of GBS were recorded between December and the first week of January 2016. Data are available for only 22 patients in El Salvador, and half of them had presented exanthema in the two weeks prior to the onset of GBS [31].

A formal analysis of the outbreak in Polynesia by means of a case-control study has shown a strong association between GBS and the cases of infection by Zika virus that were registered [53]. In this study, cases of GBS were compared to two control groups: a) patients admitted to hospital with a non-febrile disease, paired by age, sex and residence; and b) patients with Zika virus disease without any neurological symptoms, paired by age. No differences were observed in the frequency of a previous history of dengue in the cases and controls. 98% of the patients with GBS gave positive for IgM (93%) or IgG antibodies, and 100% for neutralising antibodies against Zika virus, whereas only 56% were positive in the control group. 88% had suffered transient viral symptoms during a mean of six days prior to the onset of the neurological symptoms. The neurophysiological findings were compatible with an acute motor axonal neuropathy. Nerve conduction studies showed prolonged distal latencies and a pronounced reduction in distal motor action potential. The amplitude and conduction speed of the sensitive nerve action potentials were normal [53]. Whether or not other variants of GBS, such as acute demyelinating polyradiculoneuropathy, can occur remains unknown.

93% of the subjects with GBS presented an increase in proteins in cerebrospinal fluid, with a mean concentration of 1.47 g/L, while the number of cells observed was 4/mm^3. The clinical features developed quickly, and the mean duration of the onset of symptoms and plateau phases were six and four days, respectively. Bilateral facial palsy was observed in 60% and dysphagia was seen in 45% of the individuals. 38% of the patients had to be admitted to an intensive care unit and almost a third of them required assisted respiration with mechanical ventilation; none of the patients died. Three months after discharge, 60% were able to walk unaided [53].

In this study antiganglioside antibodies were detected by means of the ELISA technique in 31% of the subjects (anti-GA1 antibodies in 19%), and by glycoarray assay in 46%. Conversely, hardly any characteristic anti-ganglioside antibodies for acute motor axonal neuropathy were detected [53]. The relevance or pathogenetic role of these antibodies in post-Zika GBS remains unclear.

Other immune-mediated syndromes reported include acute disseminated encephalomyelitis, acute myelitis, facial palsy and Miller Fisher syndrome (Table II). Acute encephalitis has also been described. One recently reported case involved an adolescent female who suffered acute myelitis due to Zika virus on the island of Guadalupe. The resonance scan showed areas of hypersignal in the cervical (C4-C7) and thoracic spinal cord (T5-T8). A large concentration of Zika virus RNA was detected in serum, urine and cerebrospinal fluid. The presence of Zika virus in the cerebrospinal fluid seems to confirm its neurotropic nature [54]. Other flaviviruses, such as dengue, Japanese encephalitis or West Nile viruses, can cause encephalitis and transverse myelitis [45].

Neuro-ophthalmological manifestations

Alterations of the macula, macular pigmentation stains, loss of foveal light reflex and neuroretinal at-

rophy have been reported in newborn infants with microcephalia whose mothers underwent infection during pregnancy. The most common ophthalmic anomalies are focal pigmentation stains in the retina and chorioretinal atrophy [55-57], with a predilection for the posterior pole, especially the macula, followed by anomalies affecting the optic nerve (hypoplasia).

Hypoplasia of the optic nerve has also been reported in intrauterine infection by cytomegalovirus. Likewise, West Nile virus can cause chorioretinal alterations when there is maternofoetal transmission.

Diagnosis

Confirmation of suspected cases

The presumptive diagnosis of Zika virus disease must be considered in any subject who resides or comes from an endemic area and who presents a febrile syndrome with exanthema, painful joints and conjunctivitis. Infection by Zika virus is confirmed on detecting virus RNA by means of the TR-PCR technique in samples of serum during the first 5-7 days of the disease. Likewise, IgM antibodies should be determined using the ELISA technique and a neutralising antibodies detection test (plaque reduction neutralisation test) in samples obtained within the first four days following the onset of clinical symptoms. Performance of a cross-reactivity test against other flaviviruses, such as the dengue virus, is recommended as the presence of both infections or a previous history of having suffered dengue fever is not rare.

Zika virus can be detected in saliva, and this can be useful when blood extraction is complicated, as in the case of children or newborn infants [58]. Yet, the detection of RNA can be negative in saliva and positive in blood. Zika virus RNA can be detected in urine for a longer period of time than in blood. In the outbreak in New Caledonia, viral RNA was detected in urine three weeks later, once viremia was at undetectable levels [59].

The IgM ELISA technique is relatively sensitive and specific to detect infections by arbovirus. But the IgM antibodies against Zika virus present cross-reactivity with other flaviviruses, such as the dengue virus or that of yellow fever. For this reason it is wise to conduct cross-neutralisation tests for each virus. The detection of the NS1 antigen is useful in the diagnosis of dengue. A false positive for the dengue NS1 antigen has recently been reported in a patient affected by Zika virus [60].

Table III. Differential diagnosis of infection by Zika virus.

Other infections by arbovirus	Dengue
	Chikungunya
	Yellow fever
	O'nyong-nyong virus
	Ross river virus
	Barmah forest virus
	Sindbis virus
Other viral infections	German measles
	Measles
	Parvovirus
	Adenovirus
	Enterovirus
Bacterial infections	Group A streptococcus
	Rickettsiosis
Malaria	

The differential diagnosis includes a number of bacterial and viral infections, including infection by other arboviruses that are endemic in tropical regions, such as dengue and chikungunya, which can cause similar clinical symptoms (Table III).

Expectant mothers and newborn infants

A series of special diagnostic recommendations have been drawn up for high-risk populations, such as pregnant mothers and newborn infants [61,62]. Recommended techniques include RT-PCR and neutralising antibody detection tests, and IgM-ELISA in serum from the mother.

The RT-PCR test for detecting Zika virus RNA can be performed in the amniotic fluid via amniocentesis, although its sensitivity and precision when it comes to determining a congenital infection have not been evaluated. A positive RT-PCR in the amniotic fluid is suggestive of an intrauterine infection by Zika virus, but its predictive value for predicting microcephalia or other foetal abnormalities is unknown [61]. Amniocentesis is not recommended in pregnant women before week 14 of gestation.

Table IV. Foetal microcephalia related to Zika virus.

Case definition	Foetal microcephalia with a molecular or epidemiological association linked to Zika virus in the absence of other causes of microcephalia
Definition of molecular or epidemiological association linked to Zika virus	Pregnant female with confirmed Zika virus disease, or
	Pregnant female who has had sexual contact with a confirmed case, or
	Pregnant female with a previous history of signs and symptoms consistent with infection by Zika virus who lives/travels in an area in which there is active transmission of the virus during pregnancy, or
	Presence of Zika virus in amniotic fluid, identified by means of amniocentesis and RT-PCR, or
	Presence of Zika virus in foetal brain tissue, identified *post mortem* by means of RT-PRC
	Absence of other causes of microcephalia

RT-PCR: reverse transcription polymerase chain reaction.

Table V. Recommendations for the diagnosis of neonatal infection by Zika virus.

Newborn infants	Serum sample obtained from the umbilical cord or blood of the newborn infant within the first two days following birth	Detection of viral RNA by means of RT-PCR
		IgM and neutralising antibodies against Zika virus
		IgM and neutralising antibodies against the dengue virus
	Cerebrospinal fluid	Detection of viral RNA by means of RT-PCR
		IgM and neutralising antibodies against Zika virus
		IgM and neutralising antibodies against the dengue virus
	Histopathological analysis of placenta/umbilical cord	Immunohistochemical analysis in fixed tissue
		RT-PCR for Zika virus in fixed and frozen tissue
Analysis in serum of the pregnant mother	Detection of viral RNA by means of RT-PCR	
	IgM and neutralising antibodies against Zika virus	
	IgM and neutralising antibodies against the dengue virus	

IgM: immunoglobulin M; RNA: ribonucleic acid; RT-PCR: reverse transcription polymerase chain reaction.

A newborn infant is considered to be suffering from a congenital infection due to Zika virus if viral RNA or antigen is identified in any sample, including the placenta, umbilical cord and amniotic fluid. Anti-Zika IgM neutralising antibody titres should be four times higher than the titres of neutralising antibodies against dengue virus, either in serum or in cerebrospinal fluid. If the titres of neutralising antibodies are less than four times the titres against dengue, the result is considered inconclusive. The diagnostic criteria of congenital infection by Zika virus are summarised in Table IV.

The recommendations for the diagnosis of neonatal infection in newborns in which there is evidence of maternal infection by Zika virus are outlined in Table V. Detection testing for the virus is recommended in every newborn infant born to mothers who have travelled or lived in areas with Zika virus transmission during their pregnancy and who present microcephalia or intracranial calcifications. Children born to mothers with positive or undetermined tests for Zika virus should also undergo these analyses [62].

Diagnosis of Guillain-Barré syndrome associated to Zika virus

The WHO has drawn up a guide to identifying and treating cases of GBS associated to infection by Zika virus [63]. The use of the Brighton criteria [64] is recommended to define the degree of certainty in the diagnosis of GBS (Table VI). The diagnosis of GBS is based on compatible clinical features and supportive findings in cerebrospinal fluid and an electromyogram [63].

Treatment

There is no specific antiviral treatment for Zika virus. Treatment is merely symptomatic and palliative. Rest, adequate hydration and the use of analgesics and antipyretics (acetaminophen) is recommended when necessary. Since it can sometimes be difficult to distinguish this infection from that caused by the dengue virus, the use of acetylsalicylic acid and nonsteroidal antiinflammatory drugs should be avoided in order to prevent the risk of haemorrhage. Neither is there any effective antiviral treatment to treat pregnant patients who acquire infection by Zika virus.

The treatment of GBS is based on the use of intravenous immunoglobulins and/or plasmapheresis. Clinical and ventilation support measures may be necessary in the more severe forms of GBS.

Prevention

Today there is no vaccine available to prevent infection by Zika virus.The use of mosquito netting in doors and windows, air conditioning systems, and

wearing long-sleeved clothes and trousers is recommended. Garments and footwear should be treated with permethrin. In the same way, the use of insect repellents is advised in outdoor environments.

Pregnant women living in endemic areas can become infected by Zika virus in any trimester of pregnancy and should therefore avoid being bitten by mosquitoes as far as possible. At present there is no evidence to suggest that pregnant women are more susceptible to the virus. The US Center for Disease Control currently recommends that pregnant women should postpone their trips to areas with active transmission of the virus [65,66].

Likewise, the US Center for Disease Control has drawn up a series of provisional guidelines on prevention of the sexual transmission of Zika virus. Males who reside in or have travelled to areas of active transmission of Zika virus and whose partner is pregnant are advised to use barrier methods (condoms) or to refrain from sexual activity during the pregnancy. Similar advice is given to couples living in areas of active transmission of the virus, since most of the infections are asymptomatic [67].

At present, WHO recommends continuing with breastfeeding, since the benefits of lactation in the first six months of life exceed the risks of a hypothetical (as yet unproven) maternal transmission of the virus via the mother's milk [68]. Blood and sperm banks must establish precautionary measures to prevent contagion via blood products and semen.

Table VI. Brighton criteria [64] used in the identification of the cases of Guillain-Barré syndrome (GBS).

	Levels of diagnostic certainty		
	1	2	3
a. Bilateral, flaccid and distal paralysis of the limbs	+	+	+
b. Tendon reflexes absent or diminished	+	+	+
c. Monophasic disease; interval between onset of symptoms and maximum weakness between 12 hours and 28 days; later stabilisation	+	+	+
d. No other cause of the paralysis identified	+	+	+
e. Albuminocytological dissociation [a]	+	+ or *f*	
f. Neurophysiological findings consistent with GBS	+	+ or *e*	

[a] High levels of proteins in the cerebrospinal fluid above the normal reference value; leukocytes < 50/μL.

Conclusions, questions and priorities

Infection by Zika virus occurs in tropical areas in which *A. aegypti* is endemic. Today, any country or region on Earth where *Aedes* exist is a zone where a new epidemic outbreak caused by Zika virus can potentially occur. In these vulnerable regions entomological surveillance should be stepped up. Areas at risk include the United States and the Mediterranean region, where the virus could be introduced by tourists or migratory movements [69], although transmission by sexual contact or blood transfusions is also possible [70]. *A. albopictus* has spread in many areas of the planet and represents a potential vector of virus transmission.

A. aegypti is, in addition, the biological vector of other viral diseases, such as dengue or chikungunya. We do not know whether other previous or coexisting viral infections, like dengue, can have an aggravating effect. Likewise, it remains unknown whether previous infection by Zika could offer protection against new infections by the same virus.

The introduction of Zika virus into Brazil and its rapid diffusion throughout the American continent is a consequence of the process of globalisation with international travel and the shipment of goods around the world, as well as the ability of *Aedes* mosquitoes to transmit and disseminate the Asian lineage of Zika virus.

Little is known about the pathogenic mechanisms involved, the genetic and environmental susceptibility factors, and the consequences of infection by Zika virus in human beings. Likewise, knowledge about the long-term complications in adults and newborn infants, as well as whether there is an additional risk in patients with chronic and autoimmune diseases, is scant.

The long-term effects of the virus on gonadal functioning have still to be determined, and further data are needed on the true prevalence of Zika infection in semen. Female-to-male transmission has not yet been reported, although it cannot be ruled out. Moreover, studies are needed to determine whether perinatal infection by Zika virus can affect development of the gonads in male foetuses [71].

The detection of cases of GBS and microcephalia associated to infection by Zika virus, if the causal relationship is finally confirmed, may represent an increase in the severity of clinical infection by Zika. Case-control studies are needed to assess the degree of neurovirulence of the virus. The true incidence of other neurological syndromes, such as transverse myelitis or mononeuropathies, is unknown.

As things stand today, our knowledge about the real magnitude of the problem of microcephalia as-

sociated to Zika virus is very limited. We do not know the period of time during pregnancy in which the virus can cause foetal anomalies. Expectant mothers can suffer from GBS, which can further complicate pregnancy [72]. Diagnostic tools are also limited, since the detection of RNA by means of RT-PCR is reduced to the period of viremia. Further problems arise from the current shortage of commercially available serological techniques and the frequent crossed reactivity with other flaviviruses in the same endemic regions. It therefore becomes difficult to determine retrospectively whether an expectant mother has been infected by Zika virus. There is an urgent need for the implementation of more sensitive diagnostic tests.

The work being done by international organisations, such as the WHO and the Pan American Health Organisation, is commendable. At present, the WHO is developing a programme that includes coordination, epidemiological surveillance, assistance, vector control, commitment with the community and hazard communication, and global, regional and local research programmes. A number of different emergency committees have been set up to draw up guidelines regarding the diagnosis and management of this new disease, and will be updated in the next few months. Likewise, priority must also be given to research programmes carried out with the aim of developing vaccines and specific antiviral drugs against Zika virus.

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Epidemiología y complicaciones neurológicas de la infección por el virus del Zika: un nuevo virus neurotropo emergente

Introducción. El actual brote epidémico por virus Zika se inició en 2015 y en la actualidad afecta a 31 países y territorios en América. Se revisan los aspectos epidemiológicos y clínicos asociados con la infección por virus Zika.

Desarrollo. Desde 2007, 55 países de América, Asia, África y Oceanía han detectado transmisión local del virus. La actual epidemia ha afectado a casi 1,5 millones de personas en Brasil. El 80% de los casos son asintomáticos. La enfermedad por virus Zika cursa con fiebre, exantema maculopapular, artralgias y conjuntivitis no purulenta. Los síntomas suelen ser autolimitados y duran una semana. Se ha descrito un aumento de la incidencia de los casos de microcefalia, lesiones retinianas y síndrome de Guillain-Barré asociados con el virus Zika. El síndrome de Guillain-Barré asociado al Zika en la Polinesia es una variante axonal motora pura. El ARN del virus Zika se ha identificado en muestras de tejido cerebral, placenta y líquido amniótico de niños con microcefalia y en pérdidas fetales de mujeres infectadas por Zika durante el embarazo. Se recomienda realizar la prueba de reacción en cadena de la polimerasa mediante transcriptasa inversa para detectar ARN vírico y pruebas serológicas (IgM ELISA y anticuerpos neutralizantes) para confirmar una infección por Zika. El diagnóstico diferencial incluye la infección por virus dengue y chikungunya.

Conclusiones. Existe un conocimiento limitado sobre los mecanismos patogénicos implicados y las consecuencias a largo plazo de la infección por virus Zika en adultos y recién nacidos.

Palabras clave. Enfermedad por virus Zika. Epidemiología. Flavivirus. Guillain-Barré. Microcefalia. Virus Zika.