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Zika virus infection in pregnant women and their children: A review

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ABSTRACT

Zika virus (ZIKV) is an arthropod-borne virus (arbovirus) transmitted primarily by *Aedes* mosquitoes. ZIKV can be transmitted to humans by non-vector borne mechanisms such as sexual intercourse, maternal-foetal transmission or blood transfusion. In 2015, ZIKV emerged in the Americas, and spread to 87 countries and territories with autochthonous transmission, distributed across four of the six WHO regions. Most ZIKV infections in pregnancy are asymptomatic, but mother to child transmission of the virus can occur in 20 to 30% of cases and cause severe foetal and child defects. Children exposed to ZIKV while in utero might develop a pattern of structural anomalies and functional disabilities secondary to central nervous system damage, known as congenital Zika syndrome, and whose most common clinical feature is microcephaly. Normocephalic children born to mothers with ZIKV infection in pregnancy, and with no observable Zika-associated birth defects, may also present with later neurodevelopmental delay or post-natal microcephaly. Screening and detection of ZIKV infection in pregnancy is essential, because most women with ZIKV infection are asymptomatic and clinical manifestations are non-specific. However, the diagnosis of ZIKV infection poses multiple challenges due to limited resources and scarce laboratory capabilities in most affected areas, the narrow window of time that the virus persists in the bloodstream, the large proportion of asymptomatic infections, and the cross-reactivity with other flaviviruses such as Dengue virus (DENV). Molecular methods (RT-PCR) are the most reliable tool to confirm ZIKV infection, as serodiagnosis requires confirmation with neutralization tests in case of inconclusive or positive serology results. Prenatal ultrasound assessment is essential for monitoring foetal development and early detection of possible severe anomalies. A mid- and long-term follow-up of children exposed to ZIKV while in utero is necessary to promptly detect clinical manifestations of possible neurological impairment.

Tweetable abstract: Zika virus infection during pregnancy is a cause of pregnancy loss and disability in children. Protection against mosquito bites, access to sexual and reproductive health services, prompt screening and detection of ZIKV infection in pregnancy, and prenatal ultrasound monitoring are key control strategies whilst a vaccine is not available.

What is Zika virus?

Zika virus (ZIKV) is an RNA arthropod-borne virus (arbovirus) from the *Flavivirus* genus and the *Flaviviridae* family [1,2]. Other viruses of clinical importance in the family are Dengue virus (DENV), West Nile virus (WNV) and Yellow Fever virus (YFV) [2]. In 1947, scientists conducting routine surveillance for YFV in the Zika forest in Uganda isolated the ZIKV in samples taken from a captive, sentinel rhesus monkey [1]. Antibodies anti-ZIKV were detected in serosurvey studies in different animals which could act as their hosts, that included monkey species in Africa and Asia, bats, goats, rodents, and sheep [1]. This sylvatic cycle involving nonhuman primates and mosquitoes is likely maintained in Africa,

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while in other countries ZIKV has adapted to humans as their own reservoir, following a human-mosquito-human cycle [1].

Epidemiology

In 1952, the first human cases of ZIKV infection were detected in Uganda and the United Republic of Tanzania in a study demonstrating the presence of neutralizing antibodies against ZIKV in sera, but cases remained sporadic for half century [1]. The complete genome of ZIKV strain was sequenced in 2006 from an infected patient in Thailand [3]. The first human outbreak was reported in 2007 on the Western Pacific island of Yap (Federated States of Micronesia), and it was the first time ZIKV was reported outside Africa or Asia [4]. The outbreak was characterized by presence of rash, arthralgia, and conjunctivitis [4]. A larger epidemic in the South Pacific French Polynesia followed in 2013–14, where 30,000 symptomatic infections were estimated to have occurred [4], and where the first severe complications and non-vector-borne transmission were reported [5]. Smaller outbreaks followed in 2014 in New Caledonia, the Cook Islands and Easter Island; and in 2015 in Vanuatu, the Solomon Islands, Samoa and Fiji [1]. In February 2015, ZIKV emerged in the Americas spreading to twelve countries and territories by the end of the year [1]. The potential link between maternal ZIKV infection and a congenital syndrome was suggested in September 2015 after an unusual and rapid increase in the number of cases of microcephaly, a twenty-fold increase in microcephaly rates compared with previous years, among newborns in Pernambuco state, North-eastern Brazil [5,6]. Similar clusters of microcephaly were also observed retrospectively in French Polynesia during the 2013–14 outbreak [5]. These studies also suggested an increase in severe neurological complications in adults with ZIKV infection, presenting with Guillain-Barré syndrome (GBS) [7]. Massive autochthonous circulation of the virus was reported in the Americas, and in February 2016 the World Health Organization (WHO) declared the ZIKV-related microcephaly clusters and other neurologic disorders as a Public Health Emergency of International Concern (PHEIC) [7]. ZIKV joined a group of tropical diseases that disproportionally affected maternal, foetal and reproductive health. The last WHO epidemiological update on ZIKV, dating of July 2019, reported that there were still 87 countries and territories with autochthonous ZIKV transmission, distributed across four of the six WHO regions (African, Americas, South-East Asia, and Western Pacific Regions) [8]. The re-emergence of ZIKV across the Americas was linked to changes in land use due to urbanization, changing of agricultural practices and deforestation [9]. Currently, ZIKV is endemic in all tropical areas of the world, similarly to DENV; and nearly half of the global population lives in areas at risk of ZIKV infection [10].

ZIKV mechanisms of transmission

The primary mode of transmission is vectorial, through the injection of infectious saliva via the bite of *Aedes* mosquitoes, specially *Aedes aegypti* [1]. ZIKV can also be transmitted by several Aedes mosquitoes, such as *Aedes hensilii, Aedes polynesiensis, and Aedes albopictus* [1]. Non vector transmission of ZIKV infection can occur vertically (mother-to-child transmission), sexually (both from symptomatic and asymptomatic individuals), by transfusion, via bone marrow or organ transplantation [1]. While infective ZIKV particles have been detected in breast milk samples, lactation has not been confirmed as a mode of transmission [11,12]. The WHO still recommends breastfeeding, as benefits outweigh the potential risks of the milk borne transmission of ZIKV [12].

Clinical features of ZIKV infection on pregnant women

In the general population, most ZIKV infections are asymptomatic (75–80%), and symptomatic infections are generally mild [13,14]. After an incubation period of three to fourteen days, the most frequent symptoms include an itchy macular or papular rash (90%), mild fever (65%), arthralgia (65%), non-purulent conjunctivitis (55%), myalgia (48%), headache (45%), oedema (19%), and vomiting (10%) [14]. If symptomatic, infection is clinically self-limited in most occasions, however, it may eventually result in serious neurological complications such as meningoencephalitis, myelitis, and GBS. GBS is a post-infection autoimmune polyneuropathy characterized by an acute onset flaccid paralysis presumed to be triggered by an exaggerated immune response after infection [15]. It is estimated to occur in 1.23% of infections in the general population [15]. GBS has a mortality rate of 5%, and 20% of the affected patients usually remain with significant disability [16]. GBS mortality increases to 10–35% if the affected individual is a pregnant woman [17]. The clinical features of ZIKV infection are similar in pregnant compared to non-pregnant women [11], though symptomatic infections seem to be more frequent during pregnancy. In a cohort study in the USA (n = 599), 36% of pregnant women with confirmed or probable ZIKV infection presented with symptoms [18], and in a prospective study in Spain, 75% of women with confirmed infection, and 48% of women with probable infection, compared to 18% of negative cases, reported Zika-like symptoms [19]. Of note, data from Brazil and Colombia showed higher rates of symptomatic ZIKV infections among women of reproductive age compared to men of same age, suggesting an increased susceptibility to ZIKV infection among women [20,21]. However, it is unknown whether behavioural factors or sexual transmission mechanisms may explain this difference in the risk of ZIKV infection [20,21].

ZIKV infection and the placenta

The pathogenesis of the mother-to-child transmission of ZIKV infection is driven by the inflammation of the placenta (placentitis), including multiplication of placental macrophages (Hofbauer cells) that facilitate viral transfer from the placenta to the foetal brain [22-24]. Similar to DENV, the infection of the placenta with ZIKV may lead to hypoperfusion, foetal loss, and neonatal infection [22]. ZIKV infects and replicates in primary human placental macrophages and cytotrophoblasts [25,26]. Active replication of the ZIKV in the placenta has been demonstrated to occur in mice models, and infective viruses have been found in human pregnancy losses, and in brain tissues of human foetuses with microcephaly [22,24,27]. Different routes for ZIKV to cross the placental barrier have been suggested, as ZIKV infects numerous primary cell types [24-26]. ZIKV is the only vertically transmitted flavivirus with the potential to infect brain cortical progenitor cells interfering with cell migration [22]. A systematic review aiming to characterize changes in placentas infected with ZIKV found histopathological features which were non-specific and similar to those described in other placental infections [28]. These features included chronic placentitis, villitis, increased number of Hofbauer cells, irregular fibrin deposits, increased mononuclear cells in villous stroma, villous immaturity, oedema, hypervascularization, stromal fibrosis, calcifications, and focal necrosis of syncytiotrophoblasts [28].

ZIKV vertical transmission can occur and cause severe foetal defects involving particularly the brain and the eye [29]. Recent estimates, based on prospective studies and case reports, have calculated a vertical transmission rate of 20–30%, irrespective of the trimester when maternal infection occurred [13,30]. The risk of maternal-foetal transmission, foetal loss or foetal abnormalities is

not related either to the presence or the severity of maternal symptoms [30]. In clinical practice, determining the risk of maternal-foetal transmission remains challenging because of the transience of ZIKV-RNA in amniotic and newborn fluids, and the low sensitivity of techniques to detect newborn's specific IgMs [30]. Though testing of amniotic fluid provides additional evidence for maternal diagnosis of ZIKV infection, frequency of Zika-associated birth defects are similar among women with ZIKV-RNA detected in amniotic fluid or other non-amniotic fluid specimens [31].

Impact of ZIKV infection on maternal and infant health

Microcephaly and congenital Zika syndrome

Microcephaly was the first birth anomaly reported in infants born to mothers with ZIKV infection [18]. It is defined as a head circumference (HC) of two standard deviations (SD) below the mean or below the third percentile according to sex and gestational age; and severe microcephaly is a HC of less than 3 SD below the mean on reference charts (Intergrowth 21st standards) [30,32]. Brain abnormalities associated to ZIKV can, however, occur in the absence of microcephaly, which makes neuroimaging key in foetal diagnosis [18]. The most common neuroimaging anomalies detected in a study with 71 infants with prenatal ZIKV infection in Rio de Janeiro included structural abnormalities such as calcifications (especially in the cortico-subcortical white-matter junction), cortex malformations, ventriculomegaly and reduced brain volumes followed by brainstem hypoplasia, cerebellar hypoplasia and dysgenesis of the corpus callosum [33]. Other foetal and birth severe brain abnormalities described in ZIKV affected children are cerebellar hypoplasia, lissencephaly with hydrocephalus, and foetal akinesia deformation sequence (arthrogryposis) [11]. ZIKV-associated brain anomalies are caused by disruption in brain development during gestation with subsequent skull collapse and neuronal and glial migration disorder [11].

The spectrum of ZIKV infection in foetuses and infants extends beyond microcephaly, which is observed at birth in 80% of children with congenital Zika syndrome (CZS) [5,29], to a pattern of structural anomalies and functional disabilities secondary to CNS damage [11,34]. CZS is defined as a spectrum of birth defects including foetal brain disruption sequence, brain anomalies, ocular anomalies, congenital contractures, intrauterine growth restriction, seizures, pyramidal or extrapyramidal abnormalities and neurodevelopmental delay [11]. Foetuses of women infected with ZIKV during pregnancy have a 5 to 14% risk of developing CZS, and a 4 to 6% risk of presenting with ZIKV-associated microcephaly [11,18,29,35-38]. The risk of developing CZS is the highest in the first trimester of pregnancy (8–15%), compared to second and third trimesters (4–5%) [11,14,18,39]. Both symptomatic and asymptomatic ZIKV infections in pregnancy have been reported to cause ZIKV-related birth anomalies. The national birth defects surveillance system in Costa Rica reported that 64% of all infants with Zika-associated anomalies were born to women who reported Zika-like symptoms, thus, 36% of these children were born to asymptomatic women [40].

Absence of clinical and radiologic anomalies at birth indicative of ZIKV does not exclude the eventual occurrence of later neurodevelopmental impairment including body tone anomalies, seizures, hearing loss, visual impairment, dysphagia or neurodevelopmental delay [11,29]. CZS shares common characteristics with most TORCH pathogens, such as presenting with a mild illness in the infected mother, potential vertical transmission, development of several foetal anomalies, and that maternal therapy may not ameliorate consequences on the foetus [41]. While many characteristics of the CZS, such as cognitive, sensory and motor disabilities are similar to those of other congenital infections, there are distinct manifestations of the syndrome [11,34]. Unique features include severe microcephaly with partially collapsed skull, subcortical calcifications, specific ocular lesions, congenital contractures, and hypertonia [11,34]. Ocular lesions found in CZS comprise microphthalmia, coloboma, cataract, posterior anomalies, chorioretinal atrophy, focal pigmentary mottling and optic nerve hypoplasia/atrophy [30]. Though these anomalies might be observed in other congenital infections, their presence in CZS is particularly common. [11,42]. As children with CZS get older, further neurodevelopmental problems have been recognized; still, the full spectrum and risks of CZS remain unknown [11,29] and the broad range of neurological impairment might be life-long [43].

Pregnancy loss and perinatal outcomes

ZIKV in pregnancy is also associated with poor pregnancy outcomes such as miscarriage, intrauterine growth restriction, stillbirths and perinatal death [22,35,44,45]. While the first and second trimesters of pregnancy represent the highest foetal risk [37,46], ZIKV infections occurring later in pregnancy have also been linked with adverse outcomes including intrauterine growth restriction and foetal loss [35,47]. Data from several studies showed an overall rate of foetal loss of 1–4% among pregnant women with confirmed ZIKV infection [11,38], and 3 to 22% risk of perinatal death in Zika-affected pregnancies [48]. A study in Brazil reported a four-fold excess neonatal mortality in infants born to ZIKV positive mothers compared to negative cases [49].

Impact of ZIKV in pregnancy beyond early infancy

Children exposed to ZIKV in utero, normocephalic with no observable defects at birth, may present with later cognitive and language neurodevelopmental delay [19,39,50-52]. It has been estimated that up to 40% of children with prenatal ZIKV exposure may develop any type of neurodevelopmental delay [52,53]. A study by Massaroni et al. showed a neurodevelopmental delay of 15% in the first year of age among in-utero exposed children, while by the second year, this percentage increased up to 50% of children [54]. The language function seems to be the most affected domain in ZIKV exposed children [19,39,50-52]. In the USA, among one-year-old children born to mothers with confirmed or possible ZIKV infection in pregnancy, 6% had a Zika-associated birth defect, 9% had more than one neurodevelopmental anomaly, and 1% presented both [29]. Given that most children, apparently healthy at birth, might not have had full developmental evaluations during infancy and childhood, these percentages might be higher [29]. HC growth deceleration (postnatal microcephaly) has been reported in exposed infants born with a normal HC at birth [5,29]. Postnatal-onset microcephaly is estimated to occur in 1% of children born to mothers with ZIKV infection in pregnancy [29].

ZIKV control

Screening and diagnosis

ZIKV screening is based on two main approaches: the detection of viral RNA by nucleic acid amplification testing (NAAT), which main method is Real-Time Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR); and the detection of antibodies (IgMs and IgGs) against ZIKV by serological assays (enzyme-linked immunosorbent assay -ELISA- tests) with confirmation by microneutralization assays or plaque reduction neutralization test (PRNT) [55]. qRT-PCR is the most reliable method to confirm ZIKV infection, though the narrow window of detection in blood samples of 3–14 days after symptom onset represents a

limitation in the diagnosis [56]; also it requires extensive sample preparation, expensive equipment, and technical expertise [57]. The window of detection by molecular methods can be considerable extended with the use of urine samples, for more than 10 days after symptom onset [56,58]. Additionally, prolonged viremias of up to 70 days of duration have been described in serum and plasma samples during pregnancy [56]. Testing multiple specimen types, such as urine, plasma, and whole blood is recommended to improve RNA detection [59]. A positive qRT-PCR confirms the infection, but a negative result does not exclude it, due to the time that ZIKV-RNA can be detected in blood or urine samples by molecular methods [30]. The combined sensitivity of serum and urine qRT-PCR testing within the first 14 days of onset of illness allows capturing of nearly 75% of serologically confirmed infections [60]. Currently, ZIKV laboratory diagnosis is mostly based on molecular detection, because of the high cross-reactivity to several flaviviruses [60], and high false positive rates of serological assays [57]. Of note, loop-mediated isothermal amplification (LAMP) techniques are considered a point-of-care alternative for their rapidity, low cost, high sensitivity, and high specificity [57], particularly for low-resource settings with lesser laboratory capacities in place.

Main serological tests for the diagnosis of ZIKV infection include ELISA for the detection of antibodies IgM and IgG against ZIKV [30]. Additionally, other serological methods such as immunofluorescence assays (IFA), immunoblots and (chemiluminescent) microsphere immunoassays (CMIA) are also being used [61,62]. Generally, a positive IgM indicates a recent infection, while a positive IgG result indicates a past flavivirus infection (presumptive positive infection of ZIKV or other flaviviruses) [63]. Confirmation by pathogen-specific microneutralization or PRNT is recommended [30,60], though it is not generally used for clinical management, because it is usually only available in highly specialized laboratories, or for research purposes [13].

ZIKV testing represents a challenge, particularly in an epidemic context due to limited resources and scarce laboratory capabilities in many affected areas [30], the narrow window of time that the virus persists in the bloodstream, the large proportion of asymptomatic infections, and the cross-reactivity with other flaviviruses, especially with DENV serotypes [43]. However, laboratory confirmation of ZIKV infection in pregnancy is essential, because most women with ZIKV infection are asymptomatic and even among those presenting symptoms these are non-specific [30]. According to the CDC, ZIKV testing is recommended for symptomatic pregnant women with possible ZIKV exposure (residence in, or history of travel to, an area with mosquito-borne ZIKV transmission; or reporting unprotected sex with a partner who has travelled to, or resides, in an area with ZIKV transmission), asymptomatic pregnant women with possible exposure, and any pregnant women presenting with foetal anomalies detected by ultrasound scan (USS) and possible previous exposure to ZIKV [30]. Testing of pregnant women with possible exposure to ZIKV is recommended as early as possible during pregnancy, and up to 12 weeks after travel to affected areas or symptoms' onset [30,60]. The CDC recommends molecular ZIKV diagnosis three times during pregnancy, however, due to resource constrains in most affected areas, effective implementation of this recommendation differs by countries and regions [30,63,64]. Exclusive serologic testing is not recommended due to inherent limitations of the test and potential false negative results [63,64]. For symptomatic pregnant women, the CDC recommends concurrent diagnosis for ZIKV along with DENV and CHIKV, by NAAT and IgM testing on serum samples [2,63].

Clinical management and treatment

ZIKV infection is generally a mild illness and the most important part of antenatal management is prenatal detection of foetal abnormalities. In cases where a pregnant woman is confirmed or suspected to have been exposed to ZIKV, serial prenatal USS examinations are recommended to assess the anatomy of the foetus, particularly the CNS, foetal growth, and amniotic fluid volume. The International Society of Ultrasound Obstetrics and Gynaecology (ISUOG) recommends detailed monthly USS including a specialized neurosonography in cases with suspected foetal brain abnormalities. If not available, in endemic areas, women should receive at least routine USS examinations as part of standard prenatal care [65]. Foetal USS findings associated with maternal ZIKV infection include microcephaly, intracranial calcifications, ventriculomegaly, abnormalities of cortical development and of the corpus callosum, hypoplasia of the cerebellum and limb abnormalities [66]. A recent systematic review showed a prenatal detection rate of CZS by USS of 83% in infected women, though the interval between maternal infection and the appearance of USS abnormalities ranged between 7 and 23 weeks [66]. This means that, in most countries, diagnosis may extend beyond the time limit for legal termination of pregnancy [66]. CNS magnetic resonance imaging (MRI) after 30 weeks allows for a better evaluation of the cortical gyration and development, and should be considered [30]. Routine amniocentesis is not recommended, because ZIKV-RNA virus may be present only transiently, and a negative result cannot rule out congenital ZIKV infection [67]. Moreover, the predictive value of a positive result for ZIKV infection in amniotic fluid in the absence of USS abnormalities has not been well defined [66]. In cases of foetal defects after maternal exposure to ZIKV, the decision to perform an amniocentesis to detect ZIKV infection, and to rule out other genetic or infectious pathologies should be discussed with the patient [30]. There is no specific antiviral treatment for ZIKV infection [1]. Therapeutic options are palliative, based on treatment of specific symptoms, paracetamol for fever, headache, and myalgia, antihistamines for pruritic rash, hydration, and rest [68]. Non-steroidal anti-inflammatory drugs should be avoided because of the risks of haemorrhagic complications [68]. The search for efficient antivirals remains a challenge [68].

Preventive measures

Strategies to prevent ZIKV infection include prevention of mosquito bites and vector-control strategies, considering that *Aedes* mosquitoes are more active in the daytime [11]. Measures to prevent mosquito bites comprise using bed-nets, screens on doors and windows [69], using insect repellents (DEET -N,N-diethyl-*meta*-toluamide- applied to exposed skin, and permethrin-treated clothing) [69,70], staying indoors in early morning and before sunset, emptying and cleaning containers that can hold standing water, remaining in air-conditioned locations [67], and wearing long-sleeved shirts and long pants [71]. Insect repellents containing DEET have been recommended by the CDC for its use in pregnancy to prevent WNV, Lyme disease, and ZIKV in pregnancy, due to its proved safety [72,73]. The WHO guidelines for the prevention of sexual transmission of ZIKV in areas with ongoing transmission include a full range of contraceptives and counselling to make an informed choice about whether and when to get pregnant, and to avoid possible adverse outcomes of ZIKV during gestation [74]. Recommendations for pregnant women not residing in areas with ZIKV transmission are to avoid travelling to risk areas [30,74]. Yet, when there is a need to travel, ZIKV preventive measures are similar to those recommended for pregnant women residing in ZIKV transmission areas [11,30,69,75,76].

Pregnant women's views about ZIKV

Gender inequality in roles and responsibilities lead to women to have a greater risk for acquiring ZIKV infection and suffering the

consequences of the disease [77]. The additional implications for maternal, sexual and reproductive health make the understanding of women's experiences, knowledge, perceptions, and attitudes towards ZIKV certainly crucial [77]. A multidimensional approach that considers healthcare services, gender issues, and environmental factors, is key to comprehend the repercussions of ZIKV infection on affected populations [77]. During the ZIKV epidemic in 2015–16, the international media coverage and circulation of misinformation shaped communities' perceptions and behaviours regarding ZIKV disease [6]. Images of infants with congenital malformations touched the global community, leading to perceptions of fear and concerns about the development of the foetus and the eventual quality of life among mothers both affected or potentially exposed to ZIKV [6]. Mental health of women diagnosed with ZIKV during pregnancy, and of mothers of children with CZS was a matter of concern reported in several studies where increased levels of stress, anxiety and poor emotional health were reported [78–80].

In 2017, in Brazil, knowledge about ZIKV among pregnant women infected with ZIKV was restricted to the little information they received through the TV and the Internet; healthcare services were rarely the primary source of information [81]. In Peru, a study showed that pregnant women with ZIKV infection lacked information about ZIKV-associated neurological disorders, sexual transmission of the virus or ways to prevent the infection [82]. Similarly, other studies also reported knowledge gaps on ZIKV being a sexually transmitted infection, both among pregnant women living in areas with ZIKV transmission [83-89], and pregnant travellers [90-92]. Psychosocial support has been pointed out necessary when ZIKV results are given to pregnant women and likewise throughout antenatal care and infant follow-up. Also in non-endemic areas, pregnant migrants and travellers to ZIKV areas have been reported to face the collateral effects of the epidemic and having suffered from stigma and discrimination when they returned from their home-countries [93].

Vaccines against ZIKV

As of September 2020, there were at least 20 vaccine candidates for ZIKV under clinical evaluation in phase I clinical trials, one trial in phase II, and more than 75 candidates in preclinical stages [94]. Most of the trials are being conducted in non-endemic countries, mainly in the USA and in Europe [94]. The only study in phase II (VRC5283) was performed in flavivirus endemic and non-endemic areas, including several sites in Central and South America [94], and assessed the efficacy of a three-dose regimen (0,4,8 weeks) in non-pregnant adults and adolescents [94]. Vaccine candidates under clinical development include purified inactivated virus, live attenuated virus, DNA, mRNA, subunit, and viral vectors vaccines [95]. Based on modelling analyses, a large ZIKV epidemic would be expected to occur in the next 10–15 years, a reason why it is critical to advance towards phase III trials that would make possible an approved vaccine for prevention of ZIKV in the upcoming years [94].

Research priorities on ZIKV vaccines should include the establishment of correlates of protection, determination of ZIKV vaccine-induced immune responses, evaluation of vaccine immunogenicity and efficacy in several populations (pregnant women, children, elderly people, populations of different ethnicities, genders, and socio-economic statuses) [96]. However, a major barrier for evaluation of ZIKV vaccines is the current context of reduced incidence after the ZIKV epidemic, which limits the plans for clinical development through phase II and III clinical trials [95,96]. Some issues would also need to be considered such the ethical implications of study design of vaccine trials in pregnant women living in areas with ZIKV transmission within an epidemic context [93], and strategies to effectively enrol pregnant women in ZIKV vaccine trials, as willingness to participate in previous hypothetical ZIKV vaccine trials has been reported to be low [97].

Summary

ZIKV infection entails severe consequences on maternal, child and reproductive health. Maternal-foetal transmission occurs in a high percentage of infected women , and is associated with high risk of foetal loss, structural and functional anomalies including microcephaly, and long-term neurodevelopmental sequelae. Screening for ZIKV in exposed pregnant women is essential as most infections are asymptomatic and clinical manifestations are non-specific. Prenatal ultrasound assessment is recommended for monitoring and early detection of possible ZIKV-associated foetal anomalies. A mid- and long-term follow-up of children exposed to ZIKV while in utero is crucial to promptly detect any clinical manifestations of possible neurological impairment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Musso D, Gubler DJ. Zika Virus. Clin Microbiol Rev 2016;29(3):487–524. https://doi.org/10.1128/CMR.00072-15.
[2] Plourde AR, Bloch EM. A literature review of Zika virus. Emerg Infect Dis 2016;22(7):1185–92. https://doi.org/10.3201/eid2207.151990.
[3] Nitatpattana N, Chaiyo K, Rajakam S, Poolam K, Chansiprasert K, Pesirikan N, et al. Complete genome sequence of a Zika virus strain isolated from the serum of an infected patient in Thailand in 2006. Genome Announc. 2018;6(10). https://doi.org/10.1128/genomeA.00121-18.
[4] Hayes EB. Zika virus outside Africa. Emerg Infect Dis 2009;15:1347–50. https://doi.org/10.3201/eid1509.090442.
[5] Baud D, Gubler DJ, Schaub B, Lanteri MC, Musso D. An update on Zika virus infection. Lancet (London, England) 2017;390(10107):2099–109. https://doi.org/10.1016/S0140-6736(17)31450-2.
[6] Albuquerque MdeFPM. de; Souza WV de, Araujo TVB, Braga MC, Miranda Filho D deB, Ximenes RA de A, de Melo Filho DA, Brito CAAde, Valongueiro S, Melo APL de, et al. The microcephaly epidemic and Zika virus: building knowledge in epidemiology. Cad. Saude Publica 2018, 34, e00069018, https://dx.doi.org/10.1590/0102-311X00069018.
[7] Ikejezie Juniorcaius, Shapiro Craig N, Kim Jisoo, Chiu Monica, Almiron Maria, Ugarte Ciro, et al. Zika virus transmission - Region of the Americas, May 15, 2015-December 15, 2016. MMWR Morb Mortal Wkly Rep 2017;66(12):329–34. https://doi.org/10.15585/mmwr.mm6612a4.
[8] WHO. Zika epidemiology update July 2019. July 2019. Accessible at: https://www.who.int/emergencies/diseases/zika/zika-epidemiology-update-july-2019.pdf?ua=1.
[9] Weinstein Joshua S, Leslie Timothy F, von Fricken Michael E. Spatial Associations between land use and infectious disease: Zika virus in Colombia. Int J Environ Res Public Health 2020;17(4):1127. https://doi.org/10.3390/ijerph17041127.
[10] Castanha Priscila M S, Marques Ernesto T A. Vaccine development during global epidemics: the Zika experience. Lancet Infect Dis 2020;20(9):998–9. https://doi.org/10.1016/S1473-3099(20)30360-1.
[11] Longo Dan L, Musso Didier, Ko Albert I, Baud David. Zika virus infection - After the pandemic. N Engl J Med 2019;381(15):1444–57. https://doi.org/10.1056/NEJMra1808246.
[12] Sampieri CL, Montero H, Breastfeeding in the time of Zika: a systematic literature review. PeerJ 2019, 7, e6452, https://dx.doi.org/10.7717/peerj.6452.
[13] Masmejan S, Musso D, Vouga M, Pomar L, Dashraath P, Stojanov M, Panchaud A, Baud, D. Zika Virus. Pathog. (Basel, Switzerland) 2020, 9, https://dx.doi.org/10.3390/pathogens9110898.
[14] Rasmussen SA, Jamieson DJ. Teratogen update: Zika virus and pregnancy. Birth defects Res 2020;112:1139–49.
[15] Barbi L, Coelho AVC, Alencar LCA de, Crovella S. Prevalence of Guillain-Barré syndrome among Zika virus infected cases: a systematic review and meta-analysis. Brazilian J Infect Dis Off Publ Brazilian Soc Infect Dis 2018, 22, 137–141, https://dx.doi.org/10.1016/j.bjid.2018.02.005.
[16] Blázquez A-B, Saiz J-C. Neurological manifestations of Zika virus infection. World J Virol 2016;5:135–43. https://doi.org/10.5501/wjv.v5.i4.135.

[17] Pacheco LD, Saad AF, Hankins GDV, Chiosi G, Saade G. Guillain-Barré syndrome in pregnancy. Obstet Gynecol 2016;128:1105–10. https://doi.org/10.1097/AOG.0000000000001716.
[18] Reynolds MR, Jones AM, Petersen EE, Lee EH, Rice ME, Bingham A, Ellington SR, Evert N, Reagan-Steiner S, Oduyebo T, et al. Vital Signs: Update on Zika Virus-Associated Birth Defects and Evaluation of All U.S. Infants with Congenital Zika Virus Exposure - U.S. Zika Pregnancy Registry, 2016. MMWR Morb Mortal Wkly Rep 2017, 66, 366–373, https://dx.doi.org/10.15585/mmwr.mm6613e1.
[19] Marbán-Castro Elena, Goncé Anna, Fumadó Victoria, Martínez Miguel J, López Marta, García-Otero Laura, et al. Zika virus infection in pregnant travellers and impact on childhood neurodevelopment in the first two years of life: a prospective observational study. Travel Med Infect Dis 2021;40:101985. https://doi.org/10.1016/j.tmaid.2021.101985.
[20] Coelho Flavio Codeço, Durovni Betina, Saraceni Valeria, Lemos Cristina, Codeco Claudia Torres, Camargo Sabrina, et al. Higher incidence of Zika in adult women than adult men in Rio de Janeiro suggests a significant contribution of sexual transmission from men to women. Int J Infect Dis IJID Off Publ Int Soc Infect Dis 2016;51:128–32. https://doi.org/10.1016/j.ijid.2016.08.023.
[21] Pacheco Oscar, Beltrán Mauricio, Nelson Christina A, Valencia Diana, Tolosa Natalia, Farr Sherry L, et al. Zika virus disease in Colombia - Preliminary report. N Engl J Med 2020;383(6):e44. https://doi.org/10.1056/NEJMoa1604037.
[22] Evans-Gilbert Tracy. Vertically transmitted chikungunya, Zika and dengue virus infections: The pathogenesis from mother to fetus and the implications of co-infections and vaccine development. Int J Pediatr Adolesc Med 2020;7(3):107–11. https://doi.org/10.1016/j.ijpam.2019.05.004.
[23] Rosenberg AZ, Yu W, Hill DA, Reyes CA, Schwartz DA. Placental Pathology of Zika Virus: Viral infection of the placenta Induces Villous Stromal Macrophage (Hofbauer Cell) proliferation and hyperplasia. Arch Pathol Lab Med 2017;141:43–8. https://doi.org/10.5858/arpa.2016-0401-OA.
[24] Coyne Carolyn B, Lazear Helen M. Zika virus — Reigniting the TORCH. Nat Rev Microbiol 2016;14(11):707–15. https://doi.org/10.1038/nrmicro.2016.125.
[25] Quicke Kendra M, Bowen James R, Johnson Erica L, McDonald Circe E, Ma Huailiang, O'Neal Justin T, et al. Zika virus infects human placental macrophages. Cell Host Microbe 2016;20(1):83–90. https://doi.org/10.1016/j.chom.2016.05.015.
[26] Martines RB, Bhatnagar J, de Oliveira Ramos AM, Davi HPF, Iglezias SD, Kanamura CT, Keating MK, Hale G, Silva-Flannery L, Muehlenbachs A, et al. Pathology of congenital Zika syndrome in Brazil: a case series. Lancet (London, England) 2016, 388, 898–904, https://dx.doi.org/10.1016/S0140-6736(16)30883-2.
[27] Goncé A, Martínez MJ, Marbán-Castro E, Saco A, Soler A, Alvarez-Mora MI, et al. Spontaneous abortion associated with Zika virus infection and persistent viremia. Emerg Infect Dis 2018;24:933–5.
[28] Venceslau Emanuella Meneses, Guida José Paulo, Amaral Eliana, Modena José Luis Proença, Costa Maria Laura. Characterization of placental infection by Zika virus in humans: A review of the literature. Rev Bras Ginecol e Obstet Rev da Fed Bras das Soc Ginecol e Obstet 2020;42(09):577–85. https://doi.org/10.1055/s-0040-1712126.
[29] Rice ME, Galang RR, Roth NM, Ellington SR, Moore CA, Valencia-Prado M, Ellis EM, Tufa AJ, Taulung LA, Alfred JM, et al. Vital Signs: Zika-Associated Birth Defects and Neurodevelopmental Abnormalities Possibly Associated with Congenital Zika Virus Infection - U.S. Territories and Freely Associated States, 2018. MMWR. Morb. Mortal. Wkly. Rep. 2018, 67, 858–867, https://dx.doi.org/10.15585/mmwr.mm6731e1.
[30] Pomar Léo, Musso Didier, Malinger Gustavo, Vouga Manon, Panchaud Alice, Baud David. Zika virus during pregnancy: From maternal exposure to congenital Zika virus syndrome. Prenat Diagn 2019;39(6):420–30. https://doi.org/10.1002/pd.v39.610.1002/pd.5446.
[31] Mercado Marcela, Ailes Elizabeth C, Daza Marcela, Tong Van T, Osorio Johana, Valencia Diana, et al. Zika virus detection in amniotic fluid and Zika-associated birth defects. Am J Obstet Gynecol 2020;222(6):610.e1–610.e13. https://doi.org/10.1016/j.ajog.2020.01.009.
[32] DeSilva M, Munoz FM, Sell E, Marshall H, Tse Kawai A, Kachikis A, et al. Congenital microcephaly: Case definition & guidelines for data collection, analysis, and presentation of safety data after maternal immunisation. Vaccine 2017;35:6472–82. https://doi.org/10.1016/j.vaccine.2017.01.044.
[33] Pool Kara-Lee, Adachi Kristina, Karnezis Stellios, Salamon Noriko, Romero Tahmineh, Nielsen-Saines Karin, et al. Association between neonatal neuroimaging and clinical outcomes in Zika-Exposed infants From Rio de Janeiro, Brazil. JAMA Netw Open 2019;2(7):e198124. https://doi.org/10.1001/jamanetworkopen.2019.8124.
[34] Moore Cynthia A, Staples J Erin, Dobyns William B, Pessoa André, Ventura Camila V, Fonseca Eduardo Borges da, et al. Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. JAMA Pediatr 2017;171(3):288. https://doi.org/10.1001/jamapediatrics.2016.3982.
[35] Brasil Patrícia, Pereira José P, Moreira M Elisabeth, Ribeiro Nogueira Rita M, Damasceno Luana, Wakimoto Mayumi, et al. Zika Virus infection in pregnant women in Rio de Janeiro. N Engl J Med 2016;375(24):2321–34. https://doi.org/10.1056/NEJMoa1602412.
[36] Pomar L, Vouga M, Lambert V, Pomar C, Hcini N, Jolivet A, et al. Maternal-fetal transmission and adverse perinatal outcomes in pregnant women infected with Zika virus: Prospective cohort study in French Guiana. Bmj, 2018. 363: p. k4431.
[37] Honein Margaret A, Dawson April L, Petersen Emily E, Jones Abbey M, Lee Ellen H, Yazdy Mahsa M, et al. Birth defects among fetuses and infants of US women with evidence of possible Zika virus infection during pregnancy. JAMA 2017;317(1):59. https://doi.org/10.1001/jama.2016.19006.
[38] Hoen Bruno, Schaub Bruno, Funk Anna L, Ardillon Vanessa, Boullard Manon, Cabié André, et al. Pregnancy outcomes after ZIKV infection in french territories in the Americas. N Engl J Med 2018;378(11):985–94. https://doi.org/10.1056/NEJMoa1709481.
[39] Mulkey Sarah B, Arroyave-Wessel Margarita, Peyton Colleen, Bulas Dorothy I, Fourzali Yamil, Jiang JiJi, et al. Neurodevelopmental abnormalities in children with in utero Zika virus exposure without congenital Zika syndrome. JAMA Pediatr 2020;174(3):269. https://doi.org/10.1001/jamapediatrics.2019.5204.
[40] Benavides-Lara Adriana, la Paz Barboza-Arguello María de, González-Elizondo Mauricio, Hernández-deMezerville Marcela, Brenes-Chacón Helena, Ramírez-Rojas Melissa, et al. Zika Virus-associated birth defects, Costa Rica, 2016–2018. Emerg Infect Dis 2021;27(2). https://doi.org/10.3201/eid2702.202047.
[41] Mehrjardi MZ, Is Zika Virus an Emerging TORCH Agent? An Invited Commentary. Virology (Auckl). 2017, 8, 1178122X17708993, https://dx.doi.org/10.1177/1178122X17708993.
[42] Li Hongda, Saucedo-Cuevas Laura, Shresta Sujan, Gleeson Joseph G. The neurobiology of Zika virus. Neuron 2016;92(5):949–58. https://doi.org/10.1016/j.neuron.2016.11.031.
[43] Lowe Rachel, Barcellos Christovam, Brasil Patrícia, Cruz Oswaldo, Honório Nildimar, Kuper Hannah, et al. The Zika virus epidemic in Brazil: From discovery to future implications. Int J Environ Res Public Health 2018;15(1):96. https://doi.org/10.3390/ijerph15010096.
[44] van der Eijk AA, van Genderen PJ, Verdijk RM, Reusken CB, Mögling R, van Kampen JJA, et al. Miscarriage associated with Zika virus infection. N Engl J Med 2016;375:1002–4.
[45] Kleber de Oliveira W, Cortez-Escalante J, De Oliveira WTGH, do Carmo GMI, Henriques CMP, Coelho GE, Araujo de Franca GV. Increase in Reported Prevalence of Microcephaly in Infants Born to Women Living in Areas with Confirmed Zika Virus Transmission During the First Trimester of Pregnancy - Brazil, 2015. MMWR. Morb. Mortal. Wkly. Rep. 2016, 65, 242–247, https://dx.doi.org/10.15585/mmwr.mm6509e2.
[46] Pomar L, Malinger G, Benoist G, Carles G, Ville Y, Rousset D, et al. Association between Zika virus and fetopathy: A prospective cohort study in French Guiana. Ultrasound Obstet Gynecol 2017;49(6):729–36. https://doi.org/10.1002/uog.17404.
[47] Alvarado-Socarras Jorge L, Idrovo Álvaro J, Contreras-García Gustavo A, Rodriguez-Morales Alfonso J, Audcent Tobey A, Mogollon-Mendoza Adriana C, et al. Congenital microcephaly: A diagnostic challenge during Zika epidemics. Travel Med Infect Dis 2018;23:14–20. https://doi.org/10.1016/j.tmaid.2018.02.002.
[48] Leisher Susannah Hopkins, Balalian Arin A, Reinebrant Hanna, Shiau Stephanie, Flenady Vicki, Kuhn Louise, et al. Systematic review: fetal death reporting and risk in Zika-affected pregnancies. Trop Med Int Health 2021;26(2):133–45. https://doi.org/10.1111/tmi.v26.210.1111/tmi.13522.
[49] França Giovanny V A, Schuler-Faccini Lavinia, Oliveira Wanderson K, Henriques Claudio M P, Carmo Eduardo H, Pedi Vaneide D, et al. Congenital Zika virus syndrome in Brazil: A case series of the first 1501 livebirths with complete investigation. Lancet (London, England) 2016;388(10047):891–7. https://doi.org/10.1016/S0140-6736(16)30902-3.
[50] Faiçal Adriana Virginia, de Oliveira Juliana Cabral, Oliveira João Vitor Vieira, de Almeida Breno Lima, Agra Iluska Andrade, Alcantara Luiz Carlos Junior, et al. Neurodevelopmental delay in normocephalic children with in utero exposure to Zika virus. BMJ Paediatr Open 2019;3(1):e000486. https://doi.org/10.1136/bmjpo-2019-000486.
[51] Nielsen-Saines Karin, Brasil Patrícia, Kerin Tara, Vasconcelos Zilton, Gabaglia Claudia Raja, Damasceno Luana, et al. Delayed childhood neurodevelopment and neurosensory alterations in the second year of life in a prospective cohort of ZIKV-exposed children. Nat Med 2019;25(8):1213–7. https://doi.org/10.1038/s41591-019-0496-1.
[52] Lopes Moreira ME, Nielsen-Saines K, Brasil P, Kerin T, Damasceno L, Pone M, Carvalho LMA, Pone SM, Vasconcelos Z, Ribeiro IP, et al. Neurodevelopment in Infants Exposed to Zika Virus In Utero. N. Engl. J. Med. 2018, 379, 2377–2379.
[53] Valdes Viviane, Zorrilla Carmen D, Gabard-Durnam Laurel, Muler-Mendez Natalia, Rahman Zarin Ibnat, Rivera Diego, et al. Cognitive development of infants exposed to the Zika virus in Puerto Rico. JAMA Netw Open 2019;2(10):e1914061. https://doi.org/10.1001/jamanetworkopen.2019.14061.
[54] Peçanha Pedro Massaroni, Gomes Junior Saint Clair, Pone Sheila Moura, Pone Marcos Vinicius da Silva, Vasconcelos Zilton, Zin Andrea, et al. Neurodevelopment of children exposed intra-uterus by Zika virus: A case series. PLoS ONE 2020;15(2):e0229434. https://doi.org/10.1371/journal.pone.0229434.
[55] Jääskeläinen AJ, Korhonen EM, Huhtamo E, Lappalainen M, Vapalahti O, Kallio-Kokko H. Validation of serological and molecular methods for diagnosis of Zika virus infections. J Virol Methods 2019;263:68–74. https://doi.org/10.1016/j.jviromet.2018.10.011.
[56] Voermans Jolanda JC, Pas, Suzan D, van der Linden Anne, GeurtsvanKessel Corine, Koopmans Marion, van der Eijk Annemiek, et al. Whole-blood testing for diagnosis of acute Zika virus infections in routine diagnostic setting. Emerg Infect Dis 2019;25(7):1394–6. https://doi.org/10.3201/eid2507.182000.
[57] Silva Severino Jefferson Ribeiro da, Pardee Keith, Pena Lindomar. Loop-mediated isothermal amplification (LAMP) for the diagnosis of Zika virus. A Review. Viruses 2019;12(1):19. https://doi.org/10.3390/v12010019.

[58] Gourinat Ann-Claire, O'Connor Olivia, Calvez Elodie, Goarant Cyrille, Dupont-Rouzeyrol Myrielle. Detection of Zika virus in urine. Emerg Infect Dis 2015;21 (1):84–6. https://doi.org/10.3201/eid2101.140894.
[59] Rossini Giada, Gaibani Paolo, Vocale Caterina, Cagarelli Roberto, Landini Maria Paola. Comparison of Zika virus (ZIKV) RNA detection in plasma, whole blood and urine - Case series of travel-associated ZIKV infection imported to Italy, 2016. J Infect 2017;75(3):242–5. https://doi.org/10.1016/j.jinf.2017.05.021.
[60] Munoz-Jordan JL. Diagnosis of Zika virus infections: Challenges and opportunities. J Infect Dis 2017;216:S951–6. https://doi.org/10.1093/infdis/jix502.
[61] Sharma Vikrant, Sharma Manisha, Dhull Divya, Sharma Yashika, Kaushik Sulochana, Kaushik Samander. Zika virus: An emerging challenge to public health worldwide. Can J Microbiol 2020;66(2):87–98. https://doi.org/10.1139/cjm-2019-0331.
[62] Van den Bossche Dorien, Michiels Johan, Cnops Lieselotte, Foque Nikki, Meersman Kathleen, Huits Ralph, et al. Challenges in diagnosing Zika-experiences from a reference laboratory in a non-endemic setting. Eur J Clin Microbiol Infect Dis 2019;38(4):771–8. https://doi.org/10.1007/s10096-019-03472-8.
[63] Sharp Tyler M, Fischer Marc, Muñoz-Jordán Jorge L, Paz-Bailey Gabriela, Staples J Erin, Gregory Christopher J, et al. Dengue and Zika virus diagnostic testing for patients with a clinically compatible illness and risk for infection with both viruses. MMWR Recomm Reports Morb Mortal Wkly Report Recomm Rep 2019;68(1):1–10. https://doi.org/10.15585/mmwr.rr6801a1.
[64] Adebanjo Tolulope, Godfred-Cato Shana, Viens Laura, Fischer Marc, Staples J Erin, Kuhnert-Tallman Wendi, et al. Update: Interim guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection - United States, October 2017. MMWR Morb Mortal Wkly Rep 2017;66(41):1089–99. https://doi.org/10.15585/mmwr.mm6641a1.
[65] Papageorghiou AT, Thilaganathan B, Bilardo CM, Ngu A, Malinger G, Herrera M, et al. ISUOG Interim Guidance on ultrasound for Zika virus infection in pregnancy: information for healthcare professionals. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol 2016;47(4):530–2. https://doi.org/10.1002/uog.15896.
[66] Viens LJ, Fleck-Derderian S, Baez-Santiago MA, Oduyebo T, Broussard CS, Khan S, Jones AM, Meaney-Delman D. Role of Prenatal Ultrasonography and Amniocentesis in the Diagnosis of Congenital Zika Syndrome: A Systematic Review. Obstet Gynecol 2020, 135, 1185–1197, https://dx.doi.org/10.1097/AOG.0000000000003829.
[67] Management of Patients in the Context of Zika Virus: ACOG COMMITTEE OPINION SUMMARY, Number 784. Obstet. Gynecol. 2019, 134, 655–657, https://dx.doi.org/10.1097/AOG.0000000000003400.
[68] da Silva S, Oliveira Silva Martins D, Jardim ACG, A Review of the Ongoing Research on Zika Virus Treatment. Viruses 2018, 10, https://dx.doi.org/10.3390/v10050255.
[69] Rather IA, Kumar S, Bajpai VK, Lim J, Park Y-H. Prevention and control strategies to counter ZIKA epidemic. Front Microbiol 2017;8:305. https://doi.org/10.3389/fmicb.2017.00305.
[70] Centers for Disease Control and Prevention. Yellow Book, 2020. Chapter 3. Environmental Hazards & Other Noninfectious Health Risks. Mosquitoes, Ticks & Other Arthropods. https://wwwnc.cdc.gov/travel/yellowbook/2020/noninfectious-health-risks/mosquitoes-ti.
[71] Rabaan Ali A, Bazzi Ali M, Al-Ahmed Shamsah H, Al-Ghaith Mohamed H, Al-Tawfiq Jaffar A. Overview of Zika infection, epidemiology, transmission and control measures. J Infect Public Health 2017;10(2):141–9. https://doi.org/10.1016/j.jiph.2016.05.007.
[72] Wylie BJ, Hauptman M, Woolf AD, Goldman RH. Insect Repellants during pregnancy in the era of the Zika virus. Obstet Gynecol 2016;128:1111–5. https://doi.org/10.1097/AOG.0000000000001685.
[73] Mytton OT, McGready R, Lee SJ, Roberts CH, Ashley EA, Carrara VI, Thwai KL, Jay MP, Wiangambun T, Singhasivanon P, et al. Safety of benzyl benzoate lotion and permethrin in pregnancy: A retrospective matched cohort study. BJOG 2007, 114, 582–587, https://dx.doi.org/10.1111/j.1471-0528.2007.01290.x.
[74] WHO guidelines for the prevention of sexual transmission of Zika virus. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
[75] Hills SL, Russell K, Hennessey M, Williams C, Oster AM, Fischer M, Mead P. Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission - Continental United States, 2016. MMWR. Morb. Mortal. Wkly. Rep. 2016, 65, 215–216, https://dx.doi.org/10.15585/mmwr.mm6508e2.
[76] Vouga M, Chiu Y-C, Pomar L, de Meyer SV, Masmejan S, Genton B, Musso D, Baud D, Stojanov M. Dengue, Zika and chikungunya during pregnancy: pre- and post-travel advice and clinical management. J. Travel Med. 2019, 26, https://dx.doi.org/10.1093/jtm/taz077.
[77] Forero-Martínez Luz J, Murad Rocío, Calderón-Jaramillo Mariana, Rivillas-García Juan C. Zika and women's sexual and reproductive health: Critical first steps to understand the role of gender in the Colombian epidemic. Int J Gynaecol Obstet 2020;148(S2):15–9. https://doi.org/10.1002/ijgo.v148.s210.1002/ijgo.13043.
[78] Horan H, Cheyney M, Nako E. Bovbjerg, M. Maternal stress and the ZIKV epidemic in Puerto Rico. Crit Public Health 2020, 1–11, https://dx.doi.org/10.1080/09581596.2020.1808189.
[79] Freitas, P.S.S.; Soares, G.B.; Mocelin, H.J.S.; Lamonato, L.C.X.L.; Sales, C.M.M.; Linde-Arias, A.R.; Bussinger, E.C.A.; Maciel, E.L.N. How do mothers feel? Life with children with congenital Zika syndrome. Int. J. Gynaecol. Obstet. 2020, 148 Suppl, 20–28, https://dx.doi.org/10.1002/ijgo.13044.
[80] Romero-Acosta, K.; Marbán-Castro, E.; Arroyo, K.; Arrieta, G.; Mattar, S. Perceptions and Emotional State of Mothers of Children with and without Microcephaly after the Zika Virus Epidemic in Rural Caribbean Colombia. Behav. Sci. (Basel, Switzerland) 2020, 10 https://dx.doi.org/10.3390/bs10100147.
[81] Sousa CA de, Mendes D do CO, Mufato LF, Queirós P de S. Zikavírus: knowledge, perceptions, and care practices of infected pregnant women. Rev Gauch Enferm 2018, 39, e20180025, https://dx.doi.org/10.1590/1983-1447.2018.20180025.
[82] Weldon Caroline T, Riley-Powell Amy R, Aguerre Ines M, Celis Nacimento Rosa A, Morrison Amy C, Oberhelman Richard A, et al. "Zika is everywhere": A qualitative exploration of knowledge, attitudes and practices towards Zika virus among women of reproductive age in Iquitos, Peru. PLoS Negl. Trop. Dis. 2018;12(8):e0006708. https://doi.org/10.1371/journal.pntd.000670810.1371/journal.pntd.0006708.s001.
[83] Johns Hopkins University. Monitoring Outcomes for Zika Prevention Knowledge and Behaviors in Dominican Republic, El Salvador, Guatemala and Honduras SMS MONITORING SURVEY: FINAL REPORT. 2017. Accessible at: https://www.zikacommunicationnetwork.org/sites/d.
[84] Gurman Tilly, Ballard Sara Anne, Villanueva Lorenzo Florentina, Luis Desirée, Hunter Gabrielle, Maloney Sean, et al. The role of gender in Zika prevention behaviors in the Dominican Republic: Findings and programmatic implications from a qualitative study. PLoS Negl Trop Dis 2020;14(3):e0007994. https://doi.org/10.1371/journal.pntd.0007994.
[85] Nelson EJ, Luetke MC, Kianersi S, Willis E, Rosenberg M. Knowledge and perceptions of Zika virus transmission in the community of Puerto Plata Dominican Republic. BMC Infect Dis 2019;19:339. https://doi.org/10.1186/s12879-019-3952-0.
[86] Abu-Rish EY, Elayeh ER, Browning MJ. Travelers to U.S.: Zika Virus Knowledge, Attitudes, and Determinants of Practices in the Middle East-Insights for Future Awareness Campaigns. Int. J. Environ. Res. Public Health 2019, 16, https://dx.doi.org/10.3390/ijerph16142517.
[87] Mendoza Carolina, Jaramillo Gloria-Isabel, Ant Thomas H, Power Grace M, Jones Robert T, Quintero Juliana, et al. An investigation into the knowledge, perceptions and role of personal protective technologies in Zika prevention in Colombia. PLoS Negl Trop Dis 2020;14(1):e0007970. https://doi.org/10.1371/journal.pntd.0007970.
[88] PASMO, Population Services International, U.S. Agency for International Development. PSI Zika Omnibus study results, LAC region. 2017. Accessible at https://www.zikacommunicationnetwork.org/resources/psi-zika-omnibus-study-results-lac-region-january-2017
[89] Chandrasekaran N, Marotta M, Taldone S, Curry C. Perceptions of community risk and travel during pregnancy in an Area of Zika transmission. Cureus 2017;9:. https://doi.org/10.7759/cureus.1516e1516.
[90] Rodriguez Miguel, Lord Ayla, Sanabia Carolina C, Silverio Abigail, Chuang Meleen, Dolan Siobhan M. Understanding Zika virus as an STI: Findings from a qualitative study of pregnant women in the Bronx. Sex Transm Infect 2020;96 (2):80–4. https://doi.org/10.1136/sextrans-2019-054093.
[91] Marbán-Castro Elena, Villén-Gonzalvo Ana, Enguita-Fernàndez Cristina, Marín-Cos Anna, Menéndez Clara, Maixenchs Maria, et al. Fear and stigma: Perceptions of Zika virus among pregnant women in Spain. Int J Environ Res Public Health 2020;17(18):6643. https://doi.org/10.3390/ijerph17186643.
[92] Castanha Priscila MS, Marques Ernesto TA. A glimmer of hope: recent updates and future challenges in Zika vaccine development. Viruses 2020;12(12):1371. https://doi.org/10.3390/v12121371.
[93] Garg Himanshu, Mehmetoglu-Gurbuz Tugba, Joshi Anjali. Recent advances in Zika virus vaccines. Viruses 2018;10(11):631. https://doi.org/10.3390/v10110631.
[94] Poland Gregory A, Kennedy Richard B, Ovsyannikova Inna G, Palacios Ricardo, Ho Paulo Lee, Kalil Jorge. Development of vaccines against Zika virus. Lancet Infect Dis 2018;18(7):e211–9. https://doi.org/10.1016/S1473-3099(18)30063-X.
[95] Vannice Kirsten S, Cassetti M Cristina, Eisinger Robert W, Hombach Joachim, Knezevic Ivana, Marston Hilary D, et al. Demonstrating vaccine effectiveness during a waning epidemic: A WHO/NIH meeting report on approaches to development and licensure of Zika vaccine candidates. Vaccine 2019;37 (6):863–8. https://doi.org/10.1016/j.vaccine.2018.12.040.
[96] Wilder-Smith Annelies, Vannice Kirsten, Durbin Anna, Hombach Joachim, Thomas Stephen J, Thevarjan Irani, et al. Zika vaccines and therapeutics: landscape analysis and challenges ahead. BMC Med. 2018;16(1). https://doi.org/10.1186/s12916-018-1067-x.
[97] Marbán-Castro Elena, Villén-Gonzalvo Ana, Enguita-Fernàndez Cristina, Romero-Acosta Kelly Carolina, Marín-Cos Anna, Arrieta Germán J, et al. Acceptability of a hypothetical zika vaccine among women from Colombia and Spain exposed to zikv: A qualitative study. Vaccines 2020;8(4):580. https://doi.org/10.3390/vaccines8040580.