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Zika Virus: An Update on Epidemiology, Pathology, Molecular Biology, and Animal Model

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Abstract

Zika virus (ZIKV) was first described in 1947, and became a health emergency problem in 2016 when its association with fetal microcephaly cases was confirmed by Centers for Disease Control and Prevention (CDC) in the United States. To date, ZIKV infection has been documented in 66 countries. ZIKV is recognized as a neurotropic virus and numerous diseases manifested in multiple neurological disorders have been described, mainly in countries that have been exposed to ZIKV after the 2007 outbreak in the Federated States of Micronesia. The most dramatic consequence of ZIKV infection documented is the abrupt increase in fetal microcephaly cases in Brazil. Here, we present an update of the published research progress in the past few months.

Keywords

Zika virus; epidemiology; pathology; transmission; animal model

INTRODUCTION

Although Zika virus (ZIKV) was described 70 years ago, it only became a public health problem at the end of 2015 when an outbreak in Brazil was associated with a significant increase of microcephaly cases in fetus and newborns. Since then, scientists all over the world are rushing to study the pathogenesis of ZIKV infection and understand the differences of infection between the first described strain African MR766, which only caused some mild symptoms, and the one identified in Asia at the Yap Island of the Federated States of Micronesia in 2007 and later in French Polynesia in 2013, which resembles the one in Brazil. New scientific information about ZIKV is available almost daily. Although a few great reviews have been recently published, important information has been described since then. Here we present an update review with the latest available information. Detailed reviews may be found elsewhere [Lazear and Diamond, 2016; Musso and Gubler, 2016; Petersen et al., 2016; Weaver et al., 2016].

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ZIKV INFECTION IN DIFFERENT GEOGRAPHIC AREAS

ZIKV was first isolated from a monkey in 1947 and then from an *Aedes africanus* in 1948 at the Zika Forest in Uganda [Dick, 1952, 1953; Dick et al., 1952]. The virus was subsequently detected in humans in other areas of Africa, and South and Southeast Asia in the following years [Smithburn, 1952, 1954; Macnamara, 1954; Smithburn et al., 1954a,b]. From 2007 to 2015, the outbreaks of ZIKV infection have been associated with different consequences in each region. In an outbreak in 2007, most of the population of Yap Island were infected by ZIKV but only mild symptoms including fever, headache, and skin rash previously described [Macnamara, 1954] were observed [Duffy et al., 2009]. When the virus reached French Polynesia in 2013 [Cao-Lormeau et al., 2014], there was an increase in cases of Guillain–Barré syndrome, an auto-immune disease that might cause temporary paralysis [Willison et al., 2016]. ZIKV was first detected in Brazil in early 2015. By the end of the year, a dramatic increase in cases of microcephaly in fetus and newborns were reported [Campos et al., 2015; Cardoso et al., 2015; Schuler-Faccini et al., 2016]. In February 2016, the World Health Organization (WHO) declared ZIKV infection as a Public Health Emergency of International Concern [Heymann et al., 2016], and in April 2016, the association between ZIKV infection and microcephaly was confirmed by the United States Centers for Disease Control and Prevention (CDC) [Rasmussen et al., 2016].

Neurological Diseases Associated With ZIKV Infection: Microcephaly

ZIKV has mainly been associated with a number of neurological disorders including Guillain–Barré syndrome [Oehler et al., 2014; Araujo et al., 2016; Cao-Lormeau et al., 2016; Malkki, 2016; Roze et al., 2016; Watrin et al., 2016] and acute disseminated encephalomyelitis (ADEM) [Ferreira, 2016] in adults, and with a drastic increase of microcephaly cases in fetus and newborns [Broutet et al., 2016; Cauchemez et al., 2016; Schuler-Faccini et al., 2016]. Microcephaly is characterized by a decrease in the head circumference of the fetus or baby. In Brazil, the cut off for term newborns is set at 32 cm after December 2015 [Victora et al., 2016]. Before the ZIKV epidemic in Brazil, numerous well-known infectious agents including toxoplasmosis, *Treponema pallidum*, varicella-zoster, parvovirus B19, rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV) infections have been associated with cases of microcephaly [Neu et al., 2015]. ZIKV has now been suggested as a new cause for the outbreak of microcephaly cases in Brazil since October 2015 [Rasmussen et al., 2016]. The raw numbers for microcephaly that are indeed caused by ZIKV but not by aforementioned other etiologies are still controversial. Clinical re-evaluation of the early diagnosed cases and the molecular detection of ZIKV have expressively cut down the initial numbers of cases [Victora et al., 2016] though it remained possible that some of these cases were false negative. However, the number of cases confirmed as microcephaly between the end of 2015 and the beginning of 2016 remains at least five times higher than the number of annual cases reported before 2015 [Victora et al., 2016].

ZIKV was specifically detected in the brain tissue of a fetus with microcephaly, whose mother was probably infected around gestational week 13th in Brazil [Mlakar et al., 2016]. The virus was also identified in the amniotic fluid collected at gestational week 28th in two

other patients, whose babies were diagnosed with microcephaly [Calvet et al., 2016a]. No correlation has been found between the gestational time of infection and the severity of the microcephaly [Brasil et al., 2016]. Besides Brazil, a few other countries have detected ZIKV in fetus/newborn with microcephaly or central nervous system anomalies [Driggers et al., 2016; WHO, 2016]. ZIKV has also been associated with the death of a few patients but none was related to microcephaly [Arzuza-Ortega et al., 2016; Sarmiento-Ospina et al., 2016].

One of the first studies showing ZIKV infection of neurons and astrocytes in mice was published in 1971 [Bell et al., 1971]. ZIKV productive infection of human neural progenitor cells (hNPC) has recently been shown [Tang et al., 2016]. ZIKV-infected hNPC had reduced cellular proliferation as a result of activated caspase-3 and cell cycle arrest [Tang et al., 2016]. In a separate study, it was also reported that ZIKV infection induced cell death in human neural stem cells (hNSC) derived from human induced pluripotent stem cells (hiPSC) [Garcez et al., 2016]. ZIKV-infected hNSCs generated abnormal neurospheres compared with the non-infected hNSCs; and that apoptotic nuclei were detected in the ZIKV-infected neurospheres [Garcez et al., 2016]. Additionally, hiPSC-derived brain organoids exposed to ZIKV had a 40% reduction in the growth area compared with non-exposed ones. These cytopathic effects were not observed with DENV-2 infection [Garcez et al., 2016].

In an elegant study, forebrain organoids from hiPSCs mimicking human cortical development were generated in 3D cell culture using a mini-bioreactor spinΩ [Qian et al., 2016]. Following exposure to ZIKV, there was a decrease in the size of the organoid with a thinner ventricular zone-like layer. An increase in cell death, decrease of neural progenitor cells proliferation, and increase of the lumen size in the ventricular structures were also observed. These observed phenotypes resembled the characteristics of microcephaly [Qian et al., 2016]. A tropism of ZIKV for neural progenitor cells was also observed when different stages of hiPSCs mimicking first and second gestational trimesters were tested. There was an increase in the infected cells indicating productive infection and spread of the virus in the culture. Interestingly, no difference of phenotype between ZIKV strains from African or Asian lineages was observed [Qian et al., 2016]. It is unclear whether the Brazil strain would behave the same as the other lineages. This important model should be valuable for exploring ZIKV infection with close biological relevance, and useful for drug screening [Qian et al., 2016].

It remains unclear how ZIKV is able to cross the placenta barriers. In one study, it was shown that primary human trophoblast (PHT) cells from full-term placentas were resistant to infection of ZIKV when the African and Asian lineage were used. Since PHT cells constitutively release interferon (IFN)-III/IFNλ1, this might avoid ZIKV infection. Although the mechanism is still unknown, it has been suggested that ZIKV evasion of IFN-III signaling and the placenta barrier bypass might depend on the gestational stage [Bayer et al., 2016]. On the other hand, IgM against ZIKV has been detected in 97% of the cerebrospinal fluid (CSF) samples, and in 90% of the serum from 31 evaluated newborns with microcephaly, indicating that the fetus/newborn might be infected in the central nervous system [Cordeiro et al., 2016].

Structural Characteristics for ZIKV Lineages

Two ZIKV lineages have been described so far, African and Asian. The strains isolated from samples in Brazil between 2015 and 2016 resembled those of Asian strains, particularly the French Polynesia strain [Baronti et al., 2014; Brasil et al., 2016; Faria et al., 2016; Giovanetti et al., 2016]. ZIKV is an arbovirus of the *Flaviviridae* family, *Flavivirus* genus, which also includes Dengue virus (DENV-1 to DENV-4), West Nile virus (WNV), Japanese encephalitis virus (JEV), and Yellow fever virus (YFV) [Musso and Gubler, 2016].

The ZIKV genome consists of one complete open reading frame (ORF) of less than 11 kb, and, as other flaviviruses, encodes three structural proteins: capsid, envelope glycoprotein (E) and membrane (M) or pre-membrane (prM), and seven non-structures proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 [Lindenbach and Rice, 2003]. Its recently described 3.8 Å structure has revealed an important difference from those of other flaviviruses in the amino acids around Asn154 in the E protein [Sirohi et al., 2016]. Within this glycoprotein, ZIKV has a glycosylation site at Asn154 [Sirohi et al., 2016] while DENV has two glycosylation sites at Asn67 and Asn153, which influence viral assembly and exit, and infectivity, respectively [Johnson et al., 1994; Mondotte et al., 2007], and WNV has an glycosylation site at Asn154, which has been associated with neurotropism [Beasley et al., 2005]. It is possible that modifications at the glycosylation sites might be associated with the differences of tropism, infectivity, fitness, and pathogenicity among different strains of ZIKV. Some glycosylation sites were absent in a few African strains; however, passage of the virus might have caused the alterations, making it difficult to track when the modifications had occurred in the earlier isolated strains [Wang et al., 2016]. A detailed analysis comparing the available ZIKV isolates showed a 59 amino acid variation between the Asian and African lineages, where around 10% of the variations are located in the prM region [Wang et al., 2016].

Among the NS proteins, NS1, which also contains N-glycosylation sites, is essential for the replication and late infection of flaviviruses [Muller and Young, 2013]. Structural differences in the ZIKV NS1 has been discovered recently revealing different electrostatic potentials among ZIKV, DENV, and WNV, which might help clarify the differences in the pathogenesis among these viruses, as well as among different ZIKV strains [Song et al., 2016]. A mutation region in NS1 was observed in some isolates from Brazil compared with other Asian strains but the biological implication was unclear [Wang et al., 2016]. Another unique characteristic of the ZIKV structure is its stability in a wide range of temperatures ranging from 4 to 40°C [Kostyuchenko et al., 2016].

ZIKV TRANSMISSION

The main route for ZIKV transmission to a human is through a mosquito bite with *Aedes aegypti* and *Aedes albopictus* as the most common vectors. Two different cycles have been described: the first transmission cycle is restricted to non-human primates designated sylvatic; and the second transmission cycle is through the human-mosquito-human cycle-(urban cycle) [Petersen et al., 2016; Weaver et al., 2016]. Recently, ZIKV has been detected in marmosets and capuchin-monkeys, most of which have been kept as pets, in Brazil [Favoretto et al., 2016].

Additional transmission routes have recently been described. Following the ZIKV outbreak in South America, autochthonous transmission not facilitated by mosquito has been described in Brazil and Colombia [Zanluca et al., 2015; Camacho et al., 2016] including a person with HIV [Calvet et al., 2016b]. Sexual transmission of ZIKV through vaginal, oral, and anal sex has also been reported and the virus was detected in saliva, urine, and semen samples [D'Ortenzio et al., 2016; Hills et al., 2016; McCarthy, 2016]. In Italy, import of ZIKV from Thailand through sexual transmission was described in a case [Venturi et al., 2016]. Additionally, blood transfusion transmission from an asymptomatic donor was reported in Brazil [Cunha et al., 2016]. Thus, extreme cautions should be taken for women who plan for a pregnancy.

ZIKV RECEPTORS

AXL, a receptor tyrosine kinase, which is also known as ARK, JTK11, or Tyro7, has been described as a main possible receptor for ZIKV entry in hNSCs [Nowakowski et al., 2016]. AXL is highly expressed in human radial glia cells, astrocytes, and endothelial cells [Nowakowski et al., 2016]. ZIKV entry of cells is also mediated by DC-SIGN and Tyro3 [Hamel et al., 2015]. Some cell types such as dermal fibroblasts, epidermal keratinocytes, and dendritic cells were described as permissive to ZIKV infection though the infection might be inhibited by types I and II IFNs [Hamel et al., 2015]. ZIKV infection triggers the innate antiviral response in skin fibroblasts with upregulation of Toll-like receptor 3 (TLR3) transcription but no change of interferon 3 (IRF3) gene expression [Hamel et al., 2015]. Other upregulated genes included retinoic acid-inducible gene 1 (RIG-I), Melanoma Differentiation-Associated protein 5 (MDA5), and Chemokine (C-C Motif) Ligand 5 (CCL5) [Hamel et al., 2015]. Interesting, ZIKV infection also induced an autophagy program, which might promote viral replication in permissive cells [Hamel et al., 2015].

ANIMAL MODELS

A mouse model for ZIKV has recently been reported [Lazear et al., 2016]. In this model, mice lacking IFN-α and -β signaling developed neurological disease and died as a consequence of ZIKV infection. High viral loads in the brain, spinal cord, and testes were detected compared to the wild-type mice. The lethal ZIKV infection was detected in adult mice lacking the capacity to either respond to or induce IFN-α/β (Ifnar1$^{-/-}$, Irf3$^{-/-}$ Irf5$^{-/-}$ Ift7$^{-/-}$ triple knockout), and in AG129 mice (Ifnar1 and Ifngr1 deficient) [Lazear et al., 2016]. Although, AG129 mice are deficient in IFN-α, -β, and -γ receptors, the humoral and cellular T cell responses are intact. A separate study also showed a deadly ZIKV infection in young and adult AG129 mice. It was noted that the cytopathic effect was observed in the brain but not in other organs [Aliota et al., 2016].

The importance of developing a valid animal model cannot be denied; however, the results from an animal model may not always be extrapolated to humans, and the correlations of infection in the model and in humans should be carefully analyzed. This is particularly true for ZIKV because the natural reservoirs for the ZIKV are humans, non-human primates and mosquitoes, which makes precise modeling of natural transmission and infection difficult. Furthermore, the anatomy of mouse is quite different from that of human. For example, the

mouse placenta structure is distinct from that of human, thus, limiting the use of a mouse model for studying the infection and transmission of ZIKV across the placenta barriers in human.

PERSPECTIVES AND FUTURE DIRECTIONS

In the early studies with ZIKV following its initial discovery, most of the mice and even some monkeys infected by ZIKV had only mild symptoms. For almost 70 years, ZIKV was not associated with serious health problems in humans until it reached the Pacific Islands and South America. Even in this scenario, Brazil is the only country that is presenting a dramatic number of microcephaly cases despite ZIKV infection has been detected in 66 countries up to this day [WHO, 2016]. While there are differences between the African and Asian lineages, countries impacted by the Asian lineage also have had different outcomes ranging from low fever, Guillain–Barré syndrome to microcephaly. The development of the 3D model mimicking different stages of the central nervous system should help clarify the pathological features manifested in different geographic regions [Qian et al., 2016].

The dramatic differences could be related with the geographic areas affected, which present different climate, temperature, and population. Even inside Brazil, the distribution is also not clear-cut with most of the cases restricted to a limited area in the Northeast region [Faria et al., 2016]. A study showed that both *Aedes aegypti* and *Aedes albopictus* were susceptible to ZIKV infection but they also depended on the mosquito population in each region or country [Chouin-Carneiro et al., 2016]. Importantly, the study indicated that both mosquitoes were not competent vectors as expected. It was pointed out that there was no data available on ZIKV isolated from any *Aedes* mosquitoes from Brazil since the focus had been on humans so far [Chouin-Carneiro et al., 2016].

Another fact that cannot be ignored is the presence of other flaviviruses in the affected regions. Co-infections with DENV and CHIKV have been described in Brazil and New Caledonia [Dupont-Rouzeyrol et al., 2015; Pessoa et al., 2016] but synergetic effect has not been noticed in the patients. However, the idea that a pre-infection with another flavivirus might cause a worsen scenario for ZIKV infection should not be ruled out. A better understanding of the diseases associated with ZIKV will become possible when all the information about the distribution of *Aedes* mosquitoes, the differences in climate and season in the affected regions, geographic distribution [Messina et al., 2016; Rodriguez-Morales et al., 2016], precise mechanism of transmission, functional consequences of genetic variations among different strains, and the gestational stage(s) affected by infection become available.

References

Aliota MT, Caine EA, Walker EC, Larkin KE, Camacho E, Osorio JE. Characterization of lethal Zika virus infection in AG129 mice. PLoS Negl Trop Dis. 2016; 10:e0004682. [PubMed: 27093158]

Araujo LM, Ferreira ML, Nascimento OJ. Guillain–Barre syndrome associated with the Zika virus outbreak in Brazil. Arq Neuropsiquiatr. 2016; 74:253–255. [PubMed: 27050856]

Arzuza-Ortega L, Polo A, Perez-Tatis G, Lopez-Garcia H, Parra E, Pardo-Herrera LC, Rico-Turca AM, Villamil-Gomez W, Rodriguez-Morales AJ. Fatal sickle cell disease and Zika virus infection in girl from Colombia. Emerg Infect Dis. 2016; 22:925–927. [PubMed: 27089120]

Baronti C, Piorkowski G, Charrel RN, Boubis L, Leparc-Goffart I, de Lamballerie X. Complete coding sequence of Zika virus from a French Polynesia outbreak in 2013. Genome Announc. 2014; 2:e00500–e00514. [PubMed: 24903869]

Bayer A, Lennemann NJ, Ouyang Y, Bramley JC, Morosky S, Marques ET Jr, Cherry S, Sadovsky Y, Coyne CB. Type III interferons produced by human placental trophoblasts confer protection against Zika virus infection. Cell Host Microbe. 2016 pii: S1931-3128(16)30100-7.

Beasley DW, Whiteman MC, Zhang S, Huang CY, Schneider BS, Smith DR, Gromowski GD, Higgs S, Kinney RM, Barrett AD. Envelope protein glycosylation status influences mouse neuroinvasion phenotype of genetic lineage 1 West Nile virus strains. J Virol. 2005; 79:8339–8347. [PubMed: 15956579]

Bell TM, Field EJ, Narang HK. Zika virus infection of the central nervous system of mice. Arch Gesamte Virusforsch. 1971; 35:183–193. [PubMed: 5002906]

Brasil P, Calvet GA, Siqueira AM, Wakimoto M, de Sequeira PC, Nobre A, de Quintana MS, Mendonca MC, Lupi O, de Souza RV, Romero C, Zogbi H, da Bressan CS, Alves SS, Lourenco-de-Oliveira R, Nogueira RM, Carvalho MS, de Filippis AM, Jaenisch T. Zika virus outbreak in Rio de Janeiro, Brazil: Clinical characterization, epidemiological and virological aspects. PLoS Negl Trop Dis. 2016; 10:e0004636. [PubMed: 27070912]

Broutet N, Krauer F, Riesen M, Khalakdina A, Almiron M, Aldighieri S, Espinal M, Low N, Dye C. Zika virus as a cause of neurologic disorders. N Engl J Med. 2016:1506–1509. [PubMed: 26959308]

Calvet G, Aguiar RS, Melo AS, Sampaio SA, de Filippis I, Fabri A, Araujo ES, de Sequeira PC, de Mendonca MC, de Oliveira L, Tschoeke DA, Schrago CG, Thompson FL, Brasil P, Dos Santos FB, Nogueira RM, Tanuri A, de Filippis AM. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: A case study. Lancet Infect Dis. 2016a pii: S1473-3099(16)00095-5.

Calvet GA, Filippis AM, Mendonca MC, Sequeira PC, Siqueira AM, Veloso VG, Nogueira RM, Brasil P. First detection of autochthonous Zika virus transmission in a HIV-infected patient in Rio de Janeiro, Brazil. J Clin Virol. 2016b; 74:1–3. [PubMed: 26615388]

Camacho E, Paternina-Gomez M, Blanco PJ, Osorio JE, Aliota MT. Detection of Autochthonous Zika virus transmission in Sincelejo, Colombia. Emerg Infect Dis. 2016; 22:927–929. [PubMed: 27089253]

Campos GS, Bandeira AC, Sardi SI. Zika virus outbreak, Bahia, Brazil. Emerg Infect Dis. 2015; 21:1885–1886. [PubMed: 26401719]

Cao-Lormeau VM, Blake A, Mons S, Lastere S, Roche C, Vanhomwegen J, Dub T, Baudouin L, Teissier A, Larre P, Vial AL, Decam C, Choumet V, Halstead SK, Willison HJ, Musset L, Manuguerra JC, Despres P, Fournier E, Mallet HP, Musso D, Fontanet A, Neil J, Ghawche F. Guillain–Barre Syndrome outbreak associated with Zika virus infection in French Polynesia: A case-control study. Lancet. 2016; 387:1531–1539. [PubMed: 26948433]

Cao-Lormeau VM, Roche C, Teissier A, Robin E, Berry AL, Mallet HP, Sall AA, Musso D. Zika virus, French Polynesia, South Pacific, 2013. Emerg Infect Dis. 2014; 20:1085–1086. [PubMed: 24856001]

Cardoso CW, Paploski IA, Kikuti M, Rodrigues MS, Silva MM, Campos GS, Sardi SI, Kitron U, Reis MG, Ribeiro GS. Outbreak of exanthematous illness associated with Zika, Chi-kungunya, and Dengue viruses, Salvador, Brazil. Emerg Infect Dis. 2015; 21:2274–2276. [PubMed: 26584464]

Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, Salje H, Van Kerkhove MD, Abadie V, Garel C, Fontanet A, Mallet HP. Association between Zika virus and microcephaly in French Polynesia, 2013–15: A retrospective study. Lancet. 2016

Chouin-Carneiro T, Vega-Rua A, Vazeille M, Yebakima A, Girod R, Goindin D, Dupont-Rouzeyrol M, Lourenco-de-Oliveira R, Failloux AB. Differential susceptibilities of *Aedes aegypti* and *Aedes albopictus* from the Americas to Zika virus. PLoS Negl Trop Dis. 2016; 10:e0004543. [PubMed: 26938868]

Cordeiro MT, Pena LJ, Brito CA, Gil LH, Marques ET. Positive IgM for Zika virus in the cerebrospinal fluid of 30 neonates with microcephaly in Brazil. Lancet. 2016

Cunha MS, Esposito DL, Rocco IM, Maeda AY, Vasami FG, Nogueira JS, de Souza RP, Suzuki A, Addas-Carvalho M, de Barjas-Castro ML, Resende MR, Stucchi RS, de Boin IF, Katz G, Angerami RN, da Fonseca BA. First complete genome sequence of Zika virus (Flaviviridae, Flavivirus) from an autochthonous transmission in Brazil. Genome Announc. 2016:4.

D'Ortenzio E, Matheron S, de Lamballerie X, Hubert B, Piorkowski G, Maquart M, Descamps D, Damond F, Yazdanpanah Y, Leparc-Goffart I. Evidence of sexual transmission of Zika virus. N Engl J Med. 2016 in press.

Dick GW. Zika virus. II. Pathogenicity and physical properties. Trans R Soc Trop Med Hyg. 1952; 46:521–534. [PubMed: 12995441]

Dick GW. Epidemiological notes on some viruses isolated in Uganda; Yellow fever, Rift Valley fever, Bwamba fever, West Nile, Mengo, Semliki forest, Bunyamwera, Ntaya, Uganda S and Zika viruses. Trans R Soc Trop Med Hyg. 1953; 47:13–48. [PubMed: 13077697]

Dick GW, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological specificity. Trans R Soc Trop Med Hyg. 1952; 46:509–520. [PubMed: 12995440]

Driggers RW, Ho CY, Korhonen EM, Kuivanen S, Jaaskelainen AJ, Smura T, Rosenberg A, Hill DA, DeBiasi RL, Vezina G, Timofeev J, Rodriguez FJ, Levanov L, Razak J, Iyengar P, Hennenfent A, Kennedy R, Lanciotti R, du Plessis A, Vapalahti O. Zika virus infection with prolonged maternal viremia and FBrain abnormalities. N Engl J Med. 2016 in press.

Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, Pretrick M, Marfel M, Holzbauer S, Dubray C, Guillaumot L, Griggs A, Bel M, Lambert AJ, Laven J, Kosoy O, Panella A, Biggerstaff BJ, Fischer M, Hayes EB. Zika Virus infection with prolonged maternal viremia and fetal brain abnormalities. N Engl J Med. 2009; 360:2536–2543. [PubMed: 19516034]

Dupont-Rouzeyrol M, O'Connor O, Calvez E, Daures M, John M, Grangeon JP, Gourinat AC. Co-infection with Zika and dengue viruses in 2 patients, New Caledonia, 2014. Emerg Infect Dis. 2015; 21:381–382. [PubMed: 25625687]

Faria NR, do Azevedo RS, Kraemer MU, Souza R, Cunha MS, Hill SC, Theze J, Bonsall MB, Bowden TA, Rissanen I, Rocco IM, Nogueira JS, Maeda AY, Vasami FG, Macedo FL, Suzuki A, Rodrigues SG, Cruz AC, Nunes BT, Medeiros DB, Rodrigues DS, Nunes Queiroz AL, da Silva EV, Henriques DF, Travassos da Rosa ES, de Oliveira CS, Martins LC, Vasconcelos HB, Casseb LM, de Simith DB, Messina JP, Abade L, Lourenco J, Alcantara LC, de Lima MM, Giovanetti M, Hay SI, de Oliveira RS, da Lemos PS, de Oliveira LF, de Lima CP, da Silva SP, de Vasconcelos JM, Franco L, Cardoso JF, Vianez-Junior JL, Mir D, Bello G, Delatorre E, Khan K, Creatore M, Coelho GE, de Oliveira WK, Tesh R, Pybus OG, Nunes MR, Vasconcelos PF. Zika virus in the Americas: Early epidemiological and genetic findings. Science. 2016; 352:345–349. [PubMed: 27013429]

Favoretto S, Araujo D, Oliveira D, Duarte N, Mesquita F, Zanotto P, Durigon E. First detection of Zika virus in neotropical primates in Brazil: A possible new reservoir. BioRxiv The preprint server for biology. 2016

Ferreira, MLB. Neurologic Manifestations of Arboviruses in the Epidemic in Pernambuco. Brazil. AAN 68th Annual Meeting Abstract; 2016.

Garcez PP, Loiola EC, Madeiro da Costa R, Higa LM, Trindade P, Delvecchio R, Nascimento JM, Brindeiro R, Tanuri A, Rehen SK. Zika virus impairs growth in human neuro-spheres and brain organoids. Science. 2016 pii: aaf6116.

Giovanetti M, Faria NR, Nunes MR, de Vasconcelos JM, Lourenco J, Rodrigues SG, Vianez JL Jr, da Silva SP, Lemos PS, Tavares FN, Martin DP, do Rosario MS, Siqueira I, Ciccozzi M, Pybus OG, de Oliveira T, Alcantara LCJ. Zika virus complete genome from Salvador, Bahia, Brazil. Infect Genet Evol. 2016

Hamel R, Dejarnac O, Wichit S, Ekchariyawat P, Neyret A, Luplertlop N, Perera-Lecoin M, Surasombatpattana P, Talignani L, Thomas F, Cao-Lormeau VM, Choumet V, Briant L, Despres P, Amara A, Yssel H, Misse D. Biology of Zika virus infection in human skin cells. J Virol. 2015; 89:8880–8896. [PubMed: 26085147]

Heymann DL, Hodgson A, Sall AA, Freedman DO, Staples JE, Althabe F, Baruah K, Mahmud G, Kandun N, Vasconcelos PF, Bino S, Menon KU. Zika virus and microcephaly: Why is this situation a PHEIC? Lancet. 2016; 387:719–721. [PubMed: 26876373]

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. [PubMed: 26937739]

Johnson AJ, Guirakhoo F, Roehrig JT. The envelope glycoproteins of dengue 1 and dengue 2 viruses grown in mosquito cells differ in their utilization of potential glycosylation sites. Virology. 1994; 203:241–249. [PubMed: 8053148]

Kostyuchenko VA, Lim EX, Zhang S, Fibriansah G, Ng TS, Ooi JS, Shi J, Lok SM. Structure of the thermally stable Zika virus. Nature. 2016 in press.

Lazear HM, Diamond MS. Zika virus: New clinical syndromes and its emergence in the western hemisphere. J Virol. 2016 pii: JVI.00252-16.

Lazear HM, Govero J, Smith AM, Platt DJ, Fernandez E, Miner JJ, Diamond MS. A mouse model of Zika virus pathogenesis. Cell Host Microbe. 2016 pii: S1931-3128(16)30102-0.

Lindenbach BD, Rice CM. Molecular biology of flaviviruses. Adv Virus Res. 2003; 59:23–61. [PubMed: 14696326]

Macnamara FN. Zika virus: A report on three cases of human infection during an epidemic of jaundice in Nigeria. Trans R Soc Trop Med Hyg. 1954; 48:139–145. [PubMed: 13157159]

Malkki H. CNS infections: Zika virus infection could trigger Guillain–Barre syndrome. Nat Rev Neurol. 2016; 12:187. [PubMed: 26988905]

McCarthy M. Zika virus was transmitted by sexual contact in Texas, health officials report. BMJ. 2016; 352:i720. [PubMed: 26848011]

Messina JP, Kraemer MU, Brady OJ, Pigott DM, Shearer FM, Weiss DJ, Golding N, Ruktanonchai CW, Gething PW, Cohn E, Brownstein JS, Khan K, Tatem AJ, Jaenisch T, Murray CJ, Marinho F, Scott TW, Hay SI. Mapping global environmental suitability for Zika virus. Elife. 2016:5.

Mlakar J, Korva M, Tul N, Popovic M, Poljsak-Prijatelj M, Mraz J, Kolenc M, Resman Rus K, Vesnaver Vipotnik T, Fabjan Vodusek V, Vizjak A, Pizem J, Petrovec M, Avsic Zupanc T. Zika virus associated with microcephaly. N Engl J Med. 2016; 374:951–958. [PubMed: 26862926]

Mondotte JA, Lozach PY, Amara A, Gamarnik AV. Essential role of dengue virus envelope protein N glycosylation at aspara-gine-67 during viral propagation. J Virol. 2007; 81:7136–7148. [PubMed: 17459925]

Muller DA, Young PR. The flavivirus NS1 protein: Molecular and structural biology, immunology, role in pathogenesis and application as a diagnostic biomarker. Antiviral Res. 2013; 98:192–208. [PubMed: 23523765]

Musso D, Gubler DJ. Zika virus. Clin Microbiol Rev. 2016; 29:487–524. [PubMed: 27029595]

Neu N, Duchon J, Zachariah P. TORCH infections. Clin Perinatol. 2015; 42:77–103. [PubMed: 25677998]

Nowakowski TJ, Pollen AA, Di Lullo E, Sandoval-Espinosa C, Bershteyn M, Kriegstein AR. Expression analysis highlights AXL as a candidate Zika virus entry receptor in neural stem cells. Cell Stem Cell. 2016 pii: S1934-5909(16)00118-1.

Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, Baudouin L, Mallet H, Musso D, Ghawche F. Zika virus infection complicated by Guillain–Barre syndrome-case report, .French Polynesia, December 2013. Euro Surveill. 2014:19.

Pessoa R, Patriota JV, Lourdes de Souza M, Felix AC, Mamede N, Sanabani SS. Investigation into an outbreak of dengue-like illness in pernambuco, Brazil, revealed a cocirculation of Zika, Chikungunya, and Dengue virus type 1. Medicine (Baltimore). 2016; 95:e3201. [PubMed: 27015222]

Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Med. 2016; 374:1552–1563. [PubMed: 27028561]

Qian X, Nguyen HN, Song MM, Hadiono C, Ogden SC, Hammack C, Yao B, Hamersky GR, Jacob F, Zhong C, Yoon K-J, Jeang W, Lin L, Li Y, Thakor J, Berg DA, Zhang C, Kang E, Chickering M, Nauen D, Ho C-Y, Wen Z, Christian KM, Shi P-Y, Maher BJ, Wu H, Jin P, Tang H, Song H, Ming G-l. Brain-region-specific organoids using minibioreactors for modeling ZIKV exposure. Cell. 2016; 165:1–17.

Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects—Reviewing the evidence for causality. N Engl J Med. 2016 in press.

Rodriguez-Morales AJ, Garcia-Loaiza CJ, Galindo-Marquez ML, Sabogal-Roman JA, Marin-Loaiza S, Lozada-Riascos CO, Diaz-Quijano FA. Zika infection GIS-based mapping suggest high transmission activity in the border area of La Guajira, Colombia, a northeastern coast Caribbean department, 2015–2016: Implications for public health, migration and travel. Travel Med Infect Dis. 2016 pii: S1477-8939(16)30010-2.

Roze B, Najioullah F, Ferge JL, Apetse K, Brouste Y, Cesaire R, Fagour C, Fagour L, Hochedez P, Jeannin S, Joux J, Mehdaoui H, Valentino R, Signate A, Cabie A, Group GBSZW. Zika virus detection in urine from patients with Guillain-Barre syndrome on Martinique, January 2016. Euro Surveill. 2016:21.

Sarmiento-Ospina A, Vasquez-Serna H, Jimenez-Canizales CE, Villamil-Gomez WE, Rodriguez-Morales AJ. Zika virus associated deaths in Colombia. Lancet Infect Dis. 2016 pii: S1473-3099(16) 30006-8.

Schuler-Faccini L, Ribeiro EM, Feitosa IM, Horovitz DD, Cavalcanti DP, Pessoa A, Doriqui MJ, Neri JI, Neto JM, Wanderley HY, Cernach M, El-Husny AS, Pone MV, Serao CL, Sanseverino MT. Brazilian Medical Genetics Society-Zika Embryopathy Task F. Possible association between Zika virus infection and Microcephaly—Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016; 65:59–62. [PubMed: 26820244]

Sirohi D, Chen Z, Sun L, Klose T, Pierson TC, Rossmann MG, Kuhn RJ. The 3.8 A resolution cryo-EM structure of Zika virus. Science. 2016; 352:467–470. [PubMed: 27033547]

Smithburn KC. Neutralizing antibodies against certain recently isolated viruses in the sera of human beings residing in East Africa. J Immunol. 1952; 69:223–234. [PubMed: 14946416]

Smithburn KC. Neutralizing antibodies against arthropod-borne viruses in the sera of long-time residents of Malaya and Borneo. Am J Hyg. 1954; 59:157–163. [PubMed: 13138582]

Smithburn KC, Kerr JA, Gatne PB. Neutralizing antibodies against certain viruses in the sera of residents of India. J Immunol. 1954a; 72:248–257. [PubMed: 13163397]

Smithburn KC, Taylor RM, Rizk F, Kader A. Immunity to certain arthropod-borne viruses among indigenous residents of Egypt. Am J Trop Med Hyg. 1954b; 3:9–18. [PubMed: 13114587]

Song H, Qi J, Haywood J, Shi Y, Gao GF. Zika virus NS1 structure reveals diversity of electrostatic surfaces among flavi-viruses. Nat Struct Mol Biol. 2016 in press.

Tang H, Hammack C, Ogden SC, Wen Z, Qian X, Li Y, Yao B, Shin J, Zhang F, Lee EM, Christian KM, Didier RA, Jin P, Song H, Ming GL. Zika virus infects human cortical neural progenitors and attenuates their growth. Cell Stem Cell. 2016 pii: S1934-5909(16)00106-5.

Venturi G, Zammarchi L, Fortuna C, Remoli ME, Benedetti E, Fiorentini C, Trotta M, Rizzo C, Mantella A, Rezza G, Bartoloni A. An autochthonous case of Zika due to possible sexual transmission, Florence, Italy, 2014. Euro Surveill. 2016:21.

Victora CG, Schuler-Faccini L, Matijasevich A, Ribeiro E, Pessoa A, Barros FC. Microcephaly in Brazil: How to interpret reported numbers? Lancet. 2016; 387:621–624. [PubMed: 26864961]

Wang L, Valderramos SG, Wu A, Ouyang S, Li C, Brasil P, Bonaldo M, Coates T, Nielsen-Saines K, Jiang T, Aliyari R, Cheng G. From mosquitos to humans: Genetic evolution of Zika virus. Cell Host Microbe. 2016 pii: S1931-3128(16)30142-1.

Watrin L, Ghawche F, Larre P, Neau JP, Mathis S, Fournier E. Guillain-Barre syndrome (42 cases) occurring during a Zika virus outbreak in French Polynesia. Medicine (Baltimore). 2016; 95:e3257. [PubMed: 27057874]

Weaver SC, Costa F, Garcia-Blanco MA, Ko AI, Ribeiro GS, Saade G, Shi PY, Vasilakis N. Zika virus: History, emergence, biology, and prospects for control. Antiviral Res. 2016; 130:69–80. [PubMed: 26996139]

WHO. World Health Organization. Zika situation report: Zika virus, Microcephaly and Guillain-Barré syndrome. 2016 Apr 21. http://apps.who.int/iris/bitstream/10665/205505/1/zikasitrep_21Apr2016_eng.pdf?ua=1

Willison HJ, Jacobs BC, van Doorn PA. Guillain–Barre syndrome. Lancet. 2016 pii: S0140-6736(16)00339-1.

Zanluca C, Melo VC, Mosimann AL, Santos GI, Santos CN, Luz K. First report of autochthonous transmission of Zika virus in Brazil. Mem Inst Oswaldo Cruz. 2015; 110:569–572. [PubMed: 26061233]