Postnatal Zika Virus Infection

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Contributor: Jessica Raper

Although the Zika virus (ZIKV) typically causes mild or no symptoms in adults, during the 2015−2016 outbreak, ZIKV infection in pregnancy resulted in birth defects and neurodevelopmental disorders; however, little is known about the potential impact of ZIKV infection during infancy and early childhood. Considering the neurotropism of ZIKV and the rapidly-developing postnatal brain, it is important to understand how infection during infancy may disrupt neurodevelopment. Emerging clinical evidence supports the hypothesis that ZIKV infection during infancy can result in negative neurologic consequences. However, clinical data regarding postnatal ZIKV infection in children are limited; as such, animal models play an important role in understanding the potential complications of ZIKV infection related to the vulnerable developing brain. Preclinical data provide insight into the potential behavioral, cognitive, and motor domains that clinical studies should examine in pediatric populations exposed to ZIKV during infancy.

Keywords: flavivirus ; MRI ; emotion ; social ; cognition ; rhesus macaque ; pediatric ; postnatal ; neonatal

1. Introduction

Zika virus (ZIKV) is a neurotropic flavivirus that is primarily transmitted by the bite of an *Aedes* genus mosquito, but it has also been transmitted through sexual contact, blood transfusions, organ transplantation, and from mother to fetus during gestation[1][2]. Although vaccine clinical trials are currently under investigation[3], there are currently no licensed vaccines to prevent or targeted therapeutics to treat ZIKV infection. The main preventative measure is the avoidance of mosquito bites, from which it is difficult to ensure 100% protection.

Despite being first isolated in 1947, ZIKV was relatively unknown to the public for 70 years because it typically resulted in asymptomatic or mild symptoms in the majority of adults [4][5]. However, during the 2015−2016 outbreak in Brazil, it was discovered that ZIKV infection during pregnancy could result in birth defects, leading to the declaration of a global health emergency [6][7][8][9][10][11][12][13]. ZIKV spread rapidly across the Americas, and infections have now been reported in 91 countries and territories[13][14]. While ZIKV incidence no longer constitutes a current epidemic, continued infections occur, and ZIKV has adapted to persistent endemic transmission[15]. In fact, in a recent serologic study, 9% of children aged 1–4 years were ZIKV seropositive in Indonesia, highlighting the widespread transmission in young children living in endemic areas[16]. ZIKV is transmitted primarily by the bite of an *Aedes* genus mosquito, but also via sex, blood transfusions, organ transplantation, and from mother to fetus.

The passage of ZIKV into the brain, and its ability to induce pathological changes have been reported since the late 1950s[17][18][19]. During the 2015−2016 outbreak, it was discovered that ZIKV could infect neural stem cells and neural progenitor cells, causing their eventual apoptosis[20]. Data from fetal human brain development suggests that radial glia and intermediate progenitors are particularly susceptible to ZIKV infection[21][22][23]. Recent evidence also suggests an interaction between ZIKV-infected microglia and altered neural progenitor cell differentiation and proliferation[24]. Congenital infection with ZIKV occurs throughout gestation, with resultant microcephaly and other brain malformations[21][25][5][26][27] that are thought to be the consequence of the ZIKV infection of neural progenitor cells, as well as the activation of innate immune responses[28]. Congenital ZIKV syndrome is a pattern of birth defects that includes severe microcephaly, the thinning of the cerebral cortex with subcortical calcifications, macular scarring and retinal mottling, congenital contractures, and hypertonicity[29]. Infants with congenital ZIKV syndrome can develop seizures, hearing and vision problems, feeding difficulties, and gross motor abnormalities[30]. While microcephaly is probably the most salient feature of congenital ZIKV syndrome, it does not occur in all cases of prenatal exposure. In fact, a prospective study of 216 toddlers with prenatal ZIKV exposure reported microcephaly in only eight (3.7%) of the cases[31]. Although some studies report that head circumference at birth corresponds with abnormal posture and motor skills during infancy[32][33], a recent report found no correlation between head size at birth and gross motor function at 24 months of age[34]. In fact, Nielsen-Saines and colleagues found that, despite few cases of microcephaly, one third of children with prenatal ZIKV exposure had below-average cognitive, language or motor scores on the Bayley-III evaluation[31]. Thus, one cannot assume that infants born without microcephaly or obvious signs of congenital ZIKV syndrome will experience normal development. Language,

motor, and cognitive functions gradually develop over years in early childhood, which coincides with the prolonged maturation of the brain areas that are important for these skills[35][36]. Considering this protracted development, reports of infants prenatally infected with ZIKV exhibiting the postnatal onset of microcephaly, neurologic dysfunction, and neurodevelopmental abnormalities[10][12][37][38] further highlight the potential of ZIKV to cause ongoing damage after birth.

2. Clinical Evidence of Postnatal Zika Virus Infection

Postnatally, the brain matures exponentially, particularly in the temporal, prefrontal and parietal regions that are important for social, emotional, and executive functions, including learning, attention, and memory throughout the first two years of age in humans [35][39][40][41][42][43][44][45][46]. This highly dynamic period of postnatal brain development presents a time of great vulnerability. Prolonged synaptic proliferation and neuronal maturation during postnatal development not only contribute to learning and periods of plasticity, but also allow for environmental factors to affect the maturation of both the brain and behavior[40][47][48]. Considering the neurotropism of ZIKV, can infection during infancy disrupt this crucial period of neurodevelopment?

The evidence shows that infants and children can acquire ZIKV infection postnatally, through mosquito bites and, possibly, breast milk[49]. Children account for 10−31% of ZIKV infections in various studies[50][51][52]. However, the data on ZIKV in children are still sparse; many studies include a wide age range in their pediatric population (1 month to 18 years), and few include significant numbers of children infected with ZIKV at <1 year of age [53][54][55][56][57][58][59][60]. Acute neurologic complications of ZIKV infection in children have been described, including Guillian-Barre Syndrome, polyneuropathy, encephalitis, demyelinating disease, and inflammatory diseases of the central nervous system (CNS)[58][59][61]. A meta-analysis of pediatric ZIKV infection found that these cases are primarily mild, and most present with a fever and rash[56], but severe neurologic complications and death have also been reported [59][62][63][64].

Beyond the acute infection period, there have been few studies of neurodevelopment following postnatal ZIKV infection. A notable recent study of the neurologic outcomes of ZIKV included six children who were infected postnatally, one of whom was 10 months old at the time of infection and developed severe CNS involvement[65]. Additionally, a prospective study of 60 children with postnatal ZIKV infection between 1 and 12 months of age found that 15% had adverse neurologic, hearing or eye examinations at 20−30 months of age. An additional 12.8% received an alert score in the hearing domain. For those without abnormal neurologic, eye, or hearing outcomes, there was also a positive correlation between their age at ZIKV infection and their percentile score on the Personal–Social domain, as assessed by the Escala Abreviada de Desarrollo (EAD-1), meaning that the infants who were infected later performed better. These data suggest that the neurotropism of ZIKV can lead to adverse neurodevelopmental consequences for vulnerable young brains, but the full extent of this impact is still largely unknown. There is, at present, no compelling evidence to suggest either for or against the severity of symptoms during acute infection being predictive of neurodevelopmental outcomes. As with congenital ZIKV infection in which adverse neurodevelopment has been reported in children without overt birth defects, one might speculate that mild or asymptomatic postnatal ZIKV infection in children has the potential to be associated with subsequent neurodevelopmental deficits.

References

1. Dias, Í.K.R.; Sobreira, C.L.D.S.; Martins, R.M.G.; Santana, K.F.S.; Lopes, M.D.S.V.; Joventino, E.S.; Viana, M.C.A. Zika virus: A review of the main aspects of this type of arbovirosis. Rev. Soc. Bras. Med. Trop. 2018, 51, 261–269.
2. Caswell, R.J.; Manavi, K. Emerging sexually transmitted viral infections: 2. Review of Zika virus disease. Int. J. STD AIDS 2018, 29, 1238–1246.
3. Castanha, P.M.S.; Marques, E.T.A. A Glimmer of Hope: Recent Updates and Future Challenges in Zika Vaccine Development. Viruses 2020, 12, 1371.
4. Dick, G.W.; Kitchen, S.F.; Haddow, A.J. Zika virus. I. Isolations and serological specficity. Trans. R. Soc. Trop. Med. Hyg. 1952, 46, 509–520.
5. Smithburn, K.C. Neutralizing antibodies against certain recently isolated viruses in the sera of human beings residing in East Africa. J. Immunol. 1952, 69, 223–234.
6. Brasil, P.; Pereira, J.P.J.; Moreira, M.E.; Ribeiro Nogueira, R.M.; Damasceno, L.; Wakimoto, M.; Rabello, R.S.; Valderramos, S.G.; Halai, U.A.; Salles, T.S.; et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro. N. Engl. J. Med. 2016, 375, 2321–2334.

7. Ioos, S.; Mallet, H.P.; Leparc Goffart, I.; Gauthier, V.; Cardoso, T.; Herida, M. Current Zika virus epidemiology and recent epidemics. Med. Mal. Infect. 2014, 44, 302–307.
8. Kleber de Oliveira, W.; Cortez-Escalante, J.; De Oliveira, W.T.; do Carmo, G.M.; Henriques, C.M.; Coelho, G.E.; Araújo de França, G.V. 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.
9. Mlakar, J.; Korva, M.; Tul, N.; Popović, M.; Poljšak-Prijatelj, M.; Mraz, J.; Kolenc, M.; Resman Rus, K.; Vesnaver Vipotnik, T.; Fabjan Vodušek, V.; et al. Zika Virus Associated with Microcephaly. N. Engl. J. Med. 2016, 374, 951–958.
10. Rice, M.E.; Galang, R.R.; Roth, N.M.; Ellington, S.R.; Moore, C.A.; Valencia-Prado, M.; Ellis, E.M.; Tufa, A.J.; Taulung, L.A.; Alfred, J.M.; 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.
11. Van der Linden, H.; Carvalho, M.D.; van der Linden, V.; Lacerda, K.M.; Pessoa, A.; Carneiro, M.L.; Cordeiro, M.T.; Valente, K.D. Epilepsy Profile in Infants with Congenital Zika Virus Infection. N. Engl. J. Med. 2018, 379, 891–892.
12. Van der Linden, V.; Pessoa, A.; Dobyns, W.; Barkovich, A.J.; Junior, H.V.; Filho, E.L.; Ribeiro, E.M.; Leal, M.C.; Coimbra, P.P.; Aragao, M.F.; et al. Description of 13 Infants Born During October 2015–January 2016 with Congenital Zika Virus Infection Without Microcephaly at Birth—Brazil. MMWR Morb. Mortal. Wkly. Rep. 2016, 65, 1343–1348.
13. WHO. Zika Virus. Available online: http://www.who.int/news-room/fact-sheets/detail/zika-virus (accessed on 3 October 2020).
14. Center for Disease Control Zika Travel Information. Available online: https://wwwnc.cdc.gov/travel/page/zika-information (accessed on 3 October 2020).
15. Ruchusatsawat, K.; Wongjaroen, P.; Posanacharoen, A.; Rodriguez-Barraquer, I.; Sangkitporn, S.; Cummings, D.A.T.; Salje, H. Long-term circulation of Zika virus in Thailand: An observational study. Lancet Infect. Dis. 2019, 19, 439–446.
16. Sasmono, R.T.; Dhenni, R.; Yohan, B.; Pronyk, P.; Hadinegoro, S.R.; Soepardi, E.J.; Ma'roef, C.N.; Satari, H.I.; Menzies, H.; Hawley, W.A.; et al. Zika Virus Seropositivity in 1–4-Year-Old Children, Indonesia, 2014. Emerg. Infect. Dis. 2018, 24, 1740–1743.
17. Dick, G.W.A. Zika virus. II. Pathogenicity and physical properties. Trans. R. Soc. Trop. Med. Hyg. 1952, 46, 521–534.
18. Haddow, A.J.; Williams, M.C.; Woodall, J.P.; Simpson, D.I.H.; Goma, L.K.H. Twelve isolations of Zika virus from Aedes (Stegomyia) africanus (Theobald) taken in and above a Uganda forest. Bull. World Health Organ. 1964, 31, 57–69.
19. Weinbren, M.P.; Williams, M.C. Zika virus: Further isolations in the Zika area, and some studies on the strains isolated. Trans. R. Soc. Trop. Med. Hyg. 1958, 52, 263–268.
20. Dang, J.; Tiwari, S.K.; Lichinchi, G.; Qin, Y.; Patil, V.S.; Eroshkin, A.M.; Rana, T.M. Zika Virus Depletes Neural Progenitors in Human Cerebral Organoids through Activation of the Innate Immune Receptor TLR3. Cell Stem Cell 2016, 19, 258–265.
21. Cugola, F.R.; Fernandes, I.R.; Russo, F.B.; Freitas, B.C.; Dias, J.L.; Guimarães, K.P.; Benazzato, C.; Almeida, N.; Pignatari, G.C.; Romero, S.; et al. The Brazilian Zika virus strain causes birth defects in experimental models. Nature 2016, 534, 267–271.
22. Liang, Q.; Luo, Z.; Zeng, J.; Chen, W.; Foo, S.S.; Lee, S.A.; Ge, J.; Wang, S.; Goldman, S.A.; Zlokovic, B.V.; et al. Zika Virus NS4A and NS4B Proteins Deregulate Akt-mTOR Signaling in Human Fetal Neural Stem Cells to Inhibit Neurogenesis and Induce Autophagy. Cell Stem Cell 2016, 19, 663–671.
23. Onorati, M.; Li, Z.; Liu, F.; Sousa, A.M.M.; Nakagawa, N.; Li, M.; Dell'Anno, M.T.; Gulden, F.O.; Pochareddy, S.; Tebbenkamp, A.T.N.; et al. Zika Virus Disrupts Phospho-TBK1 Localization and Mitosis in Human Neuroepithelial Stem Cells and Radial Glia. Cell Rep. 2016, 16, 2576–2592.
24. Wang, J.; Liu, J.; Zhou, R.; Ding, X.; Zhang, Q.; Zhang, C.; Li, L. Zika virus infected primary microglia impairs NPCs proliferation and differentiation. Biochem. Biophys. Res. Commun. 2018, 497, 619–625.
25. Franca, G.V.; Schuler-Faccini, L.; Oliveira, W.K.; Henriques, C.M.; Carmo, E.H.; Pedi, V.D.; Nunes, M.L.; Castro, M.C.; Serruya, S.; Silveira, M.F.; et al. Congenital Zika virus syndrome in Brazil: A case series of the first 1501 livebirths with complete investigation. Lancet 2016, 388, 891–897.
26. Malkki, H. CNS infections: Mouse studies confirm the link between Zika virus infection and microcephaly. Nat. Rev. Neurol. 2016, 12, 369.
27. Rasmussen, S.A.; Jamieson, D.J.; Honein, M.A.; Petersen, L.R. Zika Virus and Birth Defects—Reviewing the Evidence for Causality. N. Engl. J. Med. 2016, 374, 1981–1987.

28. Wen, Z.; Song, H.; Ming, G.L. How does Zika virus cause microcephaly? Genes Dev. 2017, 31, 849–861.
29. Moore, C.A.; Staples, J.E.; Dobyns, W.B.; Pessoa, A.; Ventura, C.V.; Fonseca, E.B.; Ribeiro, E.M.; Ventura, L.O.; Neto, N.N.; Arena, J.F.; et al. Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians. JAMA Pediatr. 2017, 171, 288–295.
30. Satterfield-Nash, A.; Kotzky, K.; Allen, J.; Bertolli, J.; Moore, C.A.; Pereira, I.O.; Pessoa, A.; Melo, F.; Santelli, A.C.F.E.S.; Boyle, C.A.; et al. Health and Development at Age 19–24 Months of 19 Children Who Were Born with Microcephaly and Laboratory Evidence of Congenital Zika Virus Infection During the 2015 Zika Virus Outbreak—Brazil, 2017. MMWR Morb. Mortal. Wkly. Rep. 2017, 66, 1347–1351.
31. Nielsen-Saines, K.; Brasil, P.; Kerin, T.; Vasconcelos, Z.; Gabaglia, C.R.; Damasceno, L.; Pone, M.; Abreu de Carvalho, L.M.; Pone, S.M.; Zin, A.A.; 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, 1213–1217.
32. Einspieler, C.; Utsch, F.; Brasil, P.; Aizawa, C.Y.P.; Peyton, C.; Hasue, R.H.; Genovesi, F.F.; Damasceno, L.; Moreira, M.E.; Adachi, K.; et al. Association of infants exposed to prenatal Zika virus infection with their clinical, neurologic, and developmental status evaluated via the general movement assessment tool. JAMA Netw. Open 2019, 2, 187235.
33. Melo, A.; Gama, G.L.; Da Silva Júnior, R.A.; De Assunção, P.L.; Tavares, J.S.; Da Silva, M.B.; Costa, K.N.F.S.; Vânia, M.L.; Evangelista, M.A.; De Amorim, M.M.R. Motor function in children with congenital Zika syndrome. Dev. Med. Child Neurol. 2019, 62, 221–226.
34. Frota, L.M.D.C.P.; Sampaio, R.F.; Miranda, J.L.; Brasil, R.M.C.; Gontijo, A.P.B.; Mambrini, J.V.M.; Brandão, M.B.; Mancini, M.C. Children with congenital Zika syndrome: Symptoms, comorbidities and gross motor development at 24 months of age. Heliyon 2020, 6, 04130.
35. Deoni, S.C.; O'Muircheartaigh, J.; Elison, J.T.; Walker, L.; Doernberg, E.; Waskiewicz, N.; Dirks, H.; Piryatinsky, I.; Dean, D.C., III; Jumbe, N.L. White matter maturation profiles through early childhood predict general cognitive ability. Brain Struct. Funct. 2016, 221, 1189–1203.
36. Girault, J.B.; Cornea, E.; Goldman, B.D.; Knickmeyer, R.C.; Styner, M.; Gilmore, J.H. White matter microstructural development and cognitive ability in the first 2 years of life. Hum. Brain Mapp. 2019, 40, 1195–1210.
37. Aragao, M.; Holanda, A.C.; Brainer-Lima, A.M.; Petribu, N.C.L.; Castillo, M.; van der Linden, V.; Serpa, S.C.; Tenorio, A.G.; Travassos, P.T.C.; Cordeiro, M.T.; et al. Nonmicrocephalic Infants with Congenital Zika Syndrome Suspected Only after Neuroimaging Evaluation Compared with Those with Microcephaly at Birth and Postnatally: How Large Is the Zika Virus "Iceberg"? AJNR Am. J. Neuroradiol. 2017, 38, 1427–1434.
38. Mulkey, S.B.; Arroyave-Wessel, M.; Peyton, C.; Bulas, D.I.; Fourzali, Y.; Jiang, J.; Russo, S.; McCarter, R.; Msall, M.E.; du Plessis, A.J.; et al. Neurodevelopmental Abnormalities in Children with In Utero Zika Virus Exposure without Congenital Zika Syndrome. JAMA Pediatr. 2020, 174, 269–276.
39. Dean, D.C., 3rd; O'Muircheartaigh, J.; Dirks, H.; Waskiewicz, N.; Lehman, K.; Walker, L.; Han, M.; Deoni, S.C. Modeling healthy male white matter and myelin development: 3 through 60months of age. Neuroimage 2014, 84, 742–752.
40. Gao, W.; Alcauter, S.; Elton, A.; Hernandez-Castillo, C.R.; Smith, J.K.; Ramirez, J.; Lin, W. Functional Network Development During the First Year: Relative Sequence and Socioeconomic Correlations. Cereb. Cortex 2015, 25, 2919–2928.
41. Gao, W.; Zhu, H.; Giovanello, K.S.; Smith, J.K.; Shen, D.; Gilmore, J.H.; Lin, W. Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. Proc. Natl. Acad. Sci. USA 2009, 106, 6790–6795.
42. Geng, X.; Gouttard, S.; Sharma, A.; Gu, H.; Styner, M.; Lin, W.; Gerig, G.; Gilmore, J.H. Quantitative tract-based white matter development from birth to age 2years. Neuroimage 2012, 61, 542–557.
43. Knickmeyer, R.C.; Gouttard, S.; Kang, C.; Evans, D.; Wilber, K.; Smith, J.K.; Hamer, R.M.; Lin, W.; Gerig, G.; Gilmore, J.H. A structural MRI study of human brain development from birth to 2 years. J. Neurosci. 2008, 28, 12176–12182.
44. Lin, W.; Zhu, Q.; Gao, W.; Chen, Y.; Toh, C.H.; Styner, M.; Gerig, G.; Smith, J.K.; Biswal, B.; Gilmore, J.H. Functional connectivity MR imaging reveals cortical functional connectivity in the developing brain. AJNR Am. J. Neuroradiol. 2008, 29, 1883–1889.
45. O'Muircheartaigh, J.; Dean, D.C., III; Ginestet, C.E.; Walker, L.; Waskiewicz, N.; Lehman, K.; Dirks, H.P., I; Deoni, S.C. White matter development and early cognition in babies and toddlers. Hum. Brain Mapp. 2014, 35, 4475–4487.
46. Gilmore, J.H.; Shi, F.; Woolson, S.L.; Knickmeyer, R.C.; Short, S.J.; Lin, W.; Zhu, H.; Hamer, R.M.; Styner, M.; Shen, D. Longitudinal development of cortical and subcortical gray matter from birth to 2 years. Cereb. Cortex 2012, 22, 2478–2485.

47. Howell, B.R.; Sanchez, M.M. Understanding behavioral effects of early life stress using the reactive scope and allostatic load models. Dev. Psychopathol. 2011, 23, 1001–1016.

48. Sánchez, M.M.; Ladd, C.O.; Plotsky, P.M. Early adverse experience as a developmental risk factor for later psychopathology: Evidence from rodent and primate models. Dev. Psychopathol. 2001, 13, 419–449.

49. Blohm, G.M.; Lednicky, J.A.; Márquez, M.; White, S.K.; Loeb, J.C.; Pacheco, C.A.; Nolan, D.J.; Paisie, T.; Salemi, M.; Rodríguez-Morales, A.J.; et al. Evidence for Mother-to-Child Transmission of Zika Virus Through Breast Milk. Clin. Infect. Dis. 2018, 66, 1120–1121.

50. Brito, C.A.; Brito, C.C.; Oliveira, A.C.; Rocha, M.; Atanásio, C.; Asfora, C.; Matos, J.D.; Lima, A.S.; Albuquerque, M.F. Zika in Pernambuco: Rewriting the first outbreak. Rev. Soc. Bras. Med. Trop. 2016, 49, 553–558.

51. Hall, V.; Walker, W.L.; Lindsey, N.P.; Lehman, J.A.; Kolsin, J.; Landry, K.; Rabe, I.B.; Hills, S.L.; Fischer, M.; Staples, J.E.; et al. Update: Noncongenital Zika Virus Disease Cases—50 U.S. States and the District of Columbia, 2016. MMWR Morb. Mortal. Wkly. Rep. 2018, 67, 265–269.

52. Pacheco, O.; Beltrán, M.; Nelson, C.A.; Valencia, D.; Tolosa, N.; Farr, S.L.; Padilla, A.V.; Tong, V.T.; Cuevas, E.L.; Espinosa-Bode, A.; et al. Zika Virus Disease in Colombia—Preliminary Report. N. Engl. J. Med. 2016, 383, 44.

53. Goodman, A.B.; Dziuban, E.J.; Powell, K.; Bitsko, R.H.; Langley, G.; Lindsey, N.; Franks, J.L.; Russell, K.; Dasgupta, S.; Barfield, W.D.; et al. Characteristics of Children Aged <18 Years with Zika Virus Disease Acquired Postnatally—U.S. States, January 2015–July 2016. MMWR Morb. Mortal. Wkly. Rep. 2016, 65, 1082–1085.

54. Ho, Z.J.M.; Hapuarachchi, H.P.; Barkham, T.; Chow, A.; Ng, L.C.; Lee, J.M.V.; Leo, Y.S.; Prem, K.; Lim, Y.H.G.; de Sessions, P.F.; et al. Outbreak of Zika virus infection in Singapore: An epidemiological, entomological, virological, and clinical analysis. Lancet Infect. Dis. 2017, 17, 813–821.

55. Lindsey, N.P.; Porse, C.C.; Potts, E.; Hyun, J.; Sandhu, K.; Schiffman, E.; Cervantes, K.B.; White, J.L.; Mason, K.; Owens, K.; et al. Zika Virus Disease Enhanced Surveillance Working Group. Postnatally Acquired Zika Virus Disease Among Children, United States, 2016–2017. Clin. Infect. Dis. 2020, 70, 227–231.

56. Ramond, A.; Lobkowicz, L.; Clemente, N.S.; Vaughan, A.; Turchi, M.D.; Wilder-Smith, A.; Brickley, E.B. Postnatal symptomatic Zika virus infections in children and adolescents: A systematic review. PLoS Negl. Trop. Dis. 2020, 14, 0008612.

57. Read, J.S.; Torres-Velasquez, B.; Lorenzi, O.; Rivera Sanchez, A.; Torres-Torres, S.; Rivera, L.V.; Capre-Franceschi, S.M.; Garcia-Gubern, C.; Munoz-Jordan, J.; Santiago, G.A.; et al. Symptomatic Zika Virus Infection in Infants, Children, and Adolescents Living in Puerto Rico. JAMA Pediatr. 2018, 172, 686–693.

58. Salgado, D.M.; Vega, R.; Rodríguez, J.A.; Niño, Á.; Rodríguez, R.; Ortiz, Á.; DeLaura, I.; Bosch, I.; Narváez, C.F. Clinical, laboratory and immune aspects of Zika virus-associated encephalitis in children. Int. J. Infect. Dis. 2020, 90, 104–110.

59. Tolosa, N.; Tinker, S.C.; Pacheco, O.; Valencia, D.; Botero, D.S.; Tong, V.T.; Mercado, M.; Gilboa, S.M.; Gonzalez, M.; Nelson, C.A.; et al. Zika Virus Disease in Children in Colombia, August 2015 to May 2016. Paediatr. Perinat. Epidemiol. 2017, 31, 537–545.

60. Burger-Calderon, R.; Bustos Carrillo, F.; Gresh, L.; Ojeda, S.; Sanchez, N.; Plazaola, M.; Katzelnick, L.; Mercado, B.L.; Monterrey, J.C.; Elizondo, D.; et al. Age-dependent manifestations and case definitions of paediatric Zika: A prospective cohort study. Lancet Infect. Dis. 2020, 20, 371–380.

61. Cano, M.; Esquivel, R. Infección por virus Zika en el Hospital del Niño “Dr José Renán Esquivel” (Panamá): Revisión de casos de desde su introducción en Latinoamérica. Pediátr. Panamá 2018, 47, 15–19.

62. Arzuza-Ortega, L.; Polo, A.; Pérez-Tatis, G.; López-García, H.; Parra, E.; Pardo-Herrera, L.C.; Rico-Turca, A.M.; Villamil-Gómez, W.; Rodríguez-Morales, A.J. Fatal Sickle Cell Disease and Zika Virus Infection in Girl from Colombia. Emerg. Infect. Dis. 2016, 22, 925–927.

63. Azevedo, R.S.; Araujo, M.T.; Martins Filho, A.J.; Oliveira, C.S.; Nunes, B.T.; Cruz, A.C.; Nascimento, A.G.; Medeiros, R.C.; Caldas, C.A.; Araujo, F.C.; et al. Zika virus epidemic in Brazil. I. Fatal disease in adults: Clinical and laboratorial aspects. J. Clin. Virol. 2016, 85, 56–64.

64. Sarmiento-Ospina, A.; Vasquez-Serna, H.; Jimenez-Canizales, C.E.; Villamil-Gomez, W.E.; Rodriguez-Morales, A.J. Zika virus associated deaths in Colombia. Lancet Infect. Dis. 2016, 16, 523–524.

65. Lannuzel, A.; Fergé, J.L.; Lobjois, Q.; Signate, A.; Rozé, B.; Tressières, B.; Madec, Y.; Poullain, P.; Herrmann, C.; Najioullah, F.; et al. Long-term outcome in neuroZika: When biological diagnosis matters. Neurology 2019, 92, 2406–2420.