Review Article

Zika Virus from the Perspective of Observational Studies: a Review

Tayyab Saleem[1], Hashaam Akhtar[2], Syed Babar Jamal[3], Fizza Maryam[3], *Muhammad Faheem[3]

[1]School of Science, Monash University, Subang Jaya, Malaysia
[2]Yusra Institute of Pharmaceutical Sciences, Yusra Medical and Dental College, Islamabad, Pakistan
[3]Department of Biological Sciences, National University of Medical Sciences, Rawalpindi, Pakistan

*__Corresponding author:__ Dr Muhammad Faheem, E-mail: muhammad.faheem@numspak.edu.pk; faheem08@live.com

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Abstract

Background: Since 1952 when Zika Virus (ZIKV): a *Flavivirus*, was first discovered in humans, it has not received enough scientific research compared to some of the other members of the family Flaviviridae; like Dengue Virus (DENV). However, this has not stopped the virus from infecting the human population globally. In particular, the global spread of ZIKV has led to a surge in observational studies.

Methods: Regarding recently published ZIKV-related literature, we are not aware of any reviews strictly focusing on ZIKV from the perspective of observational studies. Therefore, we reviewed recently published observational studies exploring the global spread of ZIKV and its association with Congenital ZIKV Infection (CZI) and clinical manifestations in adults. Online databases including google scholar, PubMed and Elsevier were used for retrieving relevant studies.

Results: ZIKV cases have been reported in different parts of the world, with certain regions reporting more cases than the rest, like Brazil. ZIKV causes a wide spectrum of diseases and disorders including microcephaly, developmental disorders, and Guillain-Barre syndrome to name a few. Furthermore, CZI in neonates mainly manifests into neurological disorders and diseases, whereas ZIKV in adults' targets various organs.

Conclusion: ZIKV poses a serious threat to human population and observational studies provide a different perspective on the damaging capabilities of ZIKV in real-life settings. Moreover, there are gaps in the literature regarding ZIKV-related-complications that future experimental studies need to address. These complications include in-utero transmission, Guillain-Barre syndrome, cross-reactivity, sexual transmission, along with its persistence in the male reproductive tract.

Keywords: Zika virus; Arbovirus; Flavivirus; Congenital zika infection

Introduction

Zika Virus (ZIKV) is a mosquito-borne *Flavivirus* first discovered in 1947 in Uganda in monkeys (1). And then, shortly after, in humans in 1952 in the United Republic of Tanzania and Uganda. Importantly, ZIKV was isolated in Gabon from the Asian tiger mosquito *Aedes albopictus* (2), which is a rapidly expanding *Aedes* species living in close contact with urban human populations. It typically bites during the daytime but showcases its peak activity at dusk and dawn (3). At present, ZIKV has received far less attention in the literature than other mosquito-borne flaviviruses like Dengue Virus (DENV). Nevertheless, it is considered an emerging virus because of its global spread during the last decade. Furthermore, ZIKV cases have been reported in people from different walks of life, including laboratory personnel getting infected while conducting experimental studies on the virus (4). Moreover, its pathogenic potential is reminiscent of that of DENV. According to the reported ZIKV cases, Zika Virus Infection (ZVI) causes various symptoms and complications in both younger (including neonates) and older patients. They range from general ones like

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fever, myalgia, and conjunctivitis to more specific ones, like Guillain-Barre Syndrome (GBS) and Central Nervous System (CNS) complications like microcephaly in neonates.

Along with cases of ZVI, the number of observational studies on ZVI from around the world have surged in recent years. Therefore, using these observational studies, we provide a new perspective on ZIKV. The literature we review here provides new insight into the following topics: 1) ZIKV spread around the world, 2) Congenital ZIKV Infection (CZI), and 3) Clinical manifestations of ZVI in adults. We also discuss the gaps in knowledge about the ZVI and what areas future research should explore.

Materials and Methods

Observational studies published in recent years reporting the global spread of ZIKV, as well as its health implications on human population were searched for on multiple online databases including google scholar, Elsevier and PubMed. Studies that fit this description were included in this review.

Results

Background of ZVI in humans

Mode of entry

ZIKV enters the human body through the epidermis or dermis after the bite of the *Aedes* mosquito (Fig. 1). At this point, the host defense system is mainly under the control of skin fibroblast cells and epidermal keratinocytes. However, ZIKV deceives them quickly as they behave highly permissive toward the ZVI (4). As a result, viral RNA copies rapidly increase, and viral replication occurs in skin fibroblasts causing the virus to dominate (5). As ZIKV concentrates on its replication, it initiates apoptosis in numerous epidermal keratinocytes to deceive antiviral immune responses. As a result, immune cells divert their attention towards disseminating dying cells and ZIKV proliferates. Type I and III interferons are critical antiviral immune responses in keratinocytes, but their stimuli are kept inactive in ZVI. Therefore, the dendritic or other immune cells in the dermal or epidermal regions implement no initial resistance (5, 6).

Pathogenesis

According to ZIKV pathogenesis, summarized in Fig. 1, after replication the virus either starts showing its effects on the skin or causes fever, myalgia, or conjunctivitis. The adaptive immune system controls these pathological conditions and produces protective antibodies against them. Nevertheless, ZVI has many unanswered questions including its in-utero or transplacental transmission and teratogenic effects on the fetus in the form of, for example, microcephaly. Moreover, the association between GBS and ZVI is not well-understood. In GBS demyelination of nerve cells occurs, causing muscle weakness in adults, also leading to tingling of limbs or even paralysis (7, 8). This uncovering disturbs signal transduction within the body and creates a neurological complication. The gathering of T-cells, macrophages, leukocytes, and other inflammatory cells near the blood brain barrier is seen in ZVI (9), which is dangerous for the integrity of BBB, and in this infectious atmosphere the virus can slip through the loose junctions of BBB (10, 11) (Fig. 2). Also, there is a need to understand the increased pathogenicity of ZIKV by cross-reacting with anti-DENV antibodies. If ZIKV threatens to infect the human body in the presence of DENV antibodies, the antibodies tend to cross-react with ZIKV triggering the phenomenon of antibody-dependent enhancement (ADE) (12). After binding of the antibody-antigen complex to the FcγR receptor, it facilitates the viral entry through the cell membrane and viral replication occurs (12). Sexual transmission of ZIKV is another question to answer, since the transmission of ZIKV is possible through sexual fluids, but the mechanism is still unknown.

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Immune Response

Viral envelope proteins mediate the entry of Flaviviruses while several host surface receptors or attachment factors facilitate the viral entry. The receptors mediating ZIKV entry are DC-SIGN, AXL, Tyro3, and TIM-1 (13). TIM-1 may act as an attachment factor and facilitate viral entry by accumulating virions on the cell surface and enabling their contact with AXL (14, 15). After entering host cells and replicating, ZIKV has to protect itself from being recognized as PAMPs (Pathogen Associated Molecular Pattern), which can trigger an immune response instantly. Pattern recognition receptors like RIG-I, MDA-5 and TLR3 are active in ZIKV PAMP recognition, in which TLR3 is considered the pioneer in initiating immune response (16). PRRs, including TLR3 and TLR7, initiate specific pathways that lead to the expression of various cytokines including type I interferons (17). The expression and role of type III interferons are still unknown in ZVI. In contrast, transcription levels of IRF 7 rise during the infection, which is a precursor for initiating expression of interferon stimulating genes after attaching to the promoter region of its genes, i.e., interferon-stimulated response element (ISRE).

The exact mechanism by which TLR3 generates antiviral responses in ZVI is still unknown. However, the activation of these receptors in CNS regions can be harmful. It may leave lifelong complications like microcephaly in infected individuals (18). Numerous interferon (IFN) stimulated genes like OAS2, MX1 and ISG15 are also unregulated during a ZVI. In addition to this, CXCR3 ligands also play an essential role in recruiting T-cells and other leukocytes to the site of infection and boosting immune response (19). Interferons share downstream pathways among themselves and other proinflammatory cytokines, which creates a sense of cytokine redundancy against invading viruses and list them among the first line of defense antivirals. Experiments have shown that the production of type I and type II IFNs are not limited to IRF3 pathway activation, and other unknown corridors of activation and expression also exist (20).

Autophagosome-like vesicles are present in infected fibroblasts during ZVI, but the protein degraded in these autophagosomes is reused by ingenious viruses for their replication and proliferation (21, 22). Thus, though autophagy promotes viral replication in ZVI, it also evades the antiviral immune response by either limiting the replicating process within mammalian cells or by providing additional amenities for membrane structures (23, 24). However, the exact mechanisms by which ZIKV controls the host cells for its replication are yet to be determined.

ZIKV: Findings from observational studies

Using "Observational Studies" as an umbrella term, we have reviewed different case reports, cross-sectional studies, cohort studies, case-control studies and case series in this review concerning the ZVI. The findings from these studies are distributed into three sections to help establish their relevance to the following topics: a) The global spread of ZIKV, b) Association between ZVI during pregnancy and congenital disabilities and c) ZVI in adults.

Global spread

Cases of ZVI have been reported by numerous countries worldwide, especially in recent years. However, in terms of observational studies, the amount and nature of literature produced vary from country to country, with Brazil contributing the most (26). However, it is imperative to highlight ZIKV-related findings from different parts of the world to understand the extent of its spread (Fig. 3).

In one such study from Costa Rica, ZIKV spread in the region through sexual transmission was investigated, since the impact of sexual contact patterns and their alteration on ZIKV spread has not yet been explored. Nevertheless, by way of deleting sexual contacts in a heterosexual network model, the study showed that deleting sexual contacts can curb

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the spread of ZIKV. Study results also showed that females were infected more by ZIKV than males (27).

Among countries that have underreported the spread of ZIKV, Mali is one of them. Therefore, to better understand the extent to which ZIKV exists in Mali, a serological survey was conducted in two ecoclimatic regions (warm semiarid and tropical savannah). Samples were collected from 637 blood donors in 2013 and later in 2016 from 793 asymptomatic volunteers aged above 15. Results showed an overall seroprevalence of 12%, which increased with age, but gender did not play a role in the prevalence of ZIKV. Moreover, the same study detected an undiscovered outbreak from the latter part of the 1990s in 18% of the participants in the warm semiarid region using immunological markers. On the other hand, ZIKV only reached endemic proportions annually in the tropical savannah, with only 2.5 % of the population infected (28).

Furthermore, in seroprevalence studies, the population of Vietnam was evaluated for seroprevalence of ZIKV antibodies during and following the ZIKV epidemic of 2016. The number of collected serum samples was 879 in total from 801 participants between 2017 (January) and 2018 (July). Moreover, the area surrounding the district of Krong Bruk, where the samples from random participants were collected, showed ZIKV presence. Also, the prevalence of ZIKV antibodies had been around 1.1% since at least 2016, suggesting a low protective immunity towards ZIKV in the region, while a limited circulation and seroprevalence also hinted at a limited outbreak among the population (29).

Mexico has also been a target region for observational studies to better understand the natural history of ZIKV in the region, namely the city of Tapachula in the Mexican state of Chiapas, generally considered hyperendemic for Dengue Virus (DENV). The ZIKV outbreak in Mexico around 2016 was followed by the recording of the frequency of ZVI, Chikungunya and DENV cases from 2016–2018. ZIKV frequency increased and then decreased, but DENV kept on increasing throughout the study (30). Other investigated ZIKV outbreaks worldwide include the 2016 outbreak in Puerto Rico by Williamson et al. (31) where the participants in the study were all ZIKV-positive blood donors. Furthermore, the study estimated that ZIKV infected 21% of the population of Puerto Rico during the outbreak.

Congenital Zika Infection

Congenital disabilities associated with CZI are the most studied area in terms of observational studies, compared with other aspects of the ZVI. To better understand the frequency of CZIs, a surveillance study by Morris et al. (26) evaluated Congenital ZIKV Syndrome (CZS) occurrence in the Caribbean and the whole of Latin America from outbreaks between 2015–2017. The study relied on surveillance reports for infectious diseases to measure two main factors: CZS cases per 1,000 births and CZS cases per 1,000 births to women infected with ZIKV during pregnancy. The study also investigated whether these reports were complete or errors in reporting occurred. Forty-seven countries contributed data from Central and South America, the Caribbean, and Mexico. Pan American Health Organization (PAHO)/World Health Organization (WHO) epidemiology reports were used in the study to assess the presence of CZS. By the start of 2018, all 47 countries reported 548,623 cases suspected for ZIKV and 239, 063 confirmed cases to PAHO/WHO, with 80 percent of the patients reported from 25 countries being suspected cases of ZIKV. Confirmed CZS cases were 3,617, reported by 25 countries, with Brazil making up 82% of these cases (2,952) and Colombia 7% (248 cases). For the CZS cases per 1,000 births, Brazil and Caribbean communities of St. Martin, Puerto Rico, Martinique, Grenada, and Guadeloupe reported the highest prevalence of CZS with more than 0.5 per 1,000 births.

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On the other hand, incomplete reports and underreporting started to appear when analyzing the data for CZS births per 1,000 births to ZIKV-infected pregnant women, with Venezuela, in particular, being responsible for massive CZS underreporting.

According to the same study, by counting CZS cases concerning total births instead of absolute numbers, the disease burden can be better illustrated. Furthermore, the study concluded that data enumerating the pregnant women infected with ZIKV is helpful for identifying any inaccuracies in the reporting of CZS cases (26).

Brazil

Brazil reported the most CZS cases during the outbreaks of 2015–2017 (26). Consequently, the need for understanding the association between ZVI during pregnancy and cross-reactive immunity to other viruses of the same family arose. Therefore, numerous observational studies focusing on these topics have surfaced recently. One of these studies aimed to study pregnant women infected by ZIKV during the 2015–2016 outbreak, who gave birth to microcephalic infants. A total of 50 women participated and underwent serological testing. As a result, they all showed immunity toward DENV but still gave birth to microcephalic infants (32).

Before the 2015 ZIKV outbreak in Brazil, reports of microcephaly were rare, and ZIKV exposure during pregnancy has been reported as one of its significant causes. Moreover, the role of inflammation is not well understood during the pathogenesis of microcephaly, as this could prove to be of assistance in deriving therapeutic strategies. Vinhaes et al. (34), in a case-control study, tried to shed some light on this phenomenon. A total of 50 participants took part in the study (14 normocephalic and 22 microcephalic newborns exposed to ZIKV, and 14 newborns that were healthy and not exposed to ZIKV). The selected participants were also part of a previous surveillance of neonates for CZI, conducted in 2016 (33). Therefore, plasma samples from these subgroups were measured for inflammatory biomarkers. In summary, the inflammation level did not increase due to microcephaly (34).

Moreover, in terms of microcephaly caused by CZI, the impact of ZIKV exposure during twin pregnancies is not well understood. Sobhani et al. (35) explored this concept in a prospective cohort study. The study involved 244 pregnancies (out of which only 5 were twin pregnancies) with maternal ZIKV. The selected 4 out of 5 twin pregnancies did not have any co-infection and participated in the study. The researchers evaluated placental, maternal, and neonatal samples by PCR testing. Three out of 8 neonates showed abnormal outcomes, and after a long-term follow-up on six of the infants only three showed any abnormalities caused by ZIKV. Besides, infant outcomes and placental findings also hinted at a discordance between co-twins exposed to ZIKV during pregnancy. Therefore, the researchers concluded that it is necessary to evaluate each twin separately for vertical transmission of ZIKV.

Along with microcephaly, prenatal ZIKV exposure and other adverse pregnancy outcomes including small-for-gestational-age, low birth weight, prematurity, and fetal death have also been studied. For example, in a study by Clemente et al. (36), a total of 574 pregnant women were tested for ZIKV during the outbreak of 2015–2017. In addition, collection of urine samples from the women and the infants upon birth and RT-PCR tests were conducted. In total, 44 women tested positive for ZIKV during pregnancy. As for the 409 neonates tested during the first ten days following birth, 19 tested positive. In conclusion, ZIKV exposure during pregnancy did not contribute to an increased risk of adverse outcomes like small-for-gestational-age, low birth weight, prematurity or fetal death. However, it was discovered that compared to ZIKV-negative neonate, the risk of developing microcephaly and disproportionate microcephaly was five-

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fold and ten-fold higher in ZIKV-positive infants, respectively.

As established, CZI is associated with microcephaly, but to further explore this phenomenon, Coutinho et al. (37) conducted the largest Brazilian cohort study of ZVI during pregnancy. They investigated adverse pregnancy outcomes associated with maternal ZVI. The participating pregnant women were symptomatic, and the study also included their infants. In addition, researchers performed prenatal and early neonatal screening. ZVI had occurred in the participants during the ZIKV outbreak in Brazil from 2015–2016. Moreover, the total number of infected pregnant women enrolled in the study was 511 (confirmed ZVI through PCR), as well as 513 fetuses as two were twins. Pregnancy losses and/or congenital disabilities associated with ZIKV happened in only 42 infected mothers. Microcephaly or any other CNS malformations were detected in 1 stillbirth out of 4 in total, and in 19 live births out of 489. Also, it was found that fetal abnormalities were 14 times more likely to manifest when the mothers contracted ZVI before reaching the gestational age of 11 weeks. The study concluded that ZIKV leads to short-term adverse pregnancy outcomes less often than previous reports have shown. However, in the long term, although the 470 livebirths showed no signs of Microcephaly or any other neurological deformity within three months of their birth, a considerable number presented with subclinical findings related to eye, CNS imaging, and neurological symptoms.

Regarding improved diagnosis of CZS, there are also suggestions for measuring the degree of musculoskeletal alterations in the patients. These alterations are highly prevalent in CZS patients and can be categorized into Type 1: low incidence of musculoskeletal complications, Type II: progressive deformities, and Type III: most severe and prevalent deformities present simultaneously. Furthermore, this can allow orthopedic surgeons to treat their patients according to the severity of their condition (38).

Even though CZI is associated with Microcephaly, it is also imperative to pay equal attention to screening normocephalic asymptomatic births for CZI. A study conducted in Salvador, Brazil, explored this concept during the 2016 microcephaly outbreak. The study used 151 newborns comprising both normocephalic (119 in total) and microcephalic newborns (32 in total) suspected of CZI. Moreover, using serological tests (to check for IgG and IgM antiglobulin) and quantitative reverse transcriptase-polymerase chain reaction (RT-qPCR), presence of ZIKV was confirmed. As a result, 17 normocephalic newborns were detected with CZI, proving that asymptomatic neonates can also have CZI. Thus, emphasizing the need for prenatal and neonatal screening, especially in endemic regions, for ZIKV (33).

Along with screening normocephalic births for CZI, it is equally important to understand the impact of intrauterine ZIKV exposure on asymptomatic children later in life. This was investigated by Abtibol-Bernardino et al. (39) in a case series study where the researchers looked for minor neurological disorders caused by ZIKV exposure later in life. The study included 26 participants (25–42 months age range), all non-microcephalic children, who had underwent intrauterine exposure to ZIKV. They were subjected to neurological examination and the BSID-III test (Bayley Scales-III) which assessed their cognition, language, and motor performance. In total, 64.5% (17/26 children) performed satisfyingly, however, the language domain was impaired the most in eight children. At the same time, five children had severe neurological impairment (epilepsy, spastic hemiparesis, autism, and progressive sensorineural hearing loss). In total, the majority of the children showcased mild alteration. In another study of a similar nature, 194 normocephalic neonates had undergone prenatal exposure to ZIKV and were then investigated for neurological defects within 3 and 24 months of their birth. Bayley Scales of Infant and Toddler Development Screening Test-3rd

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Edition was used to perform the investigation and scores for the cognitive domain were in the typical range. However, the slower development of communication skills hinted at delayed neurodevelopment in older age (40).

In contrast, signs of CNS infection have also been studied in children with non-congenital ZVI. Like in the study by Bentes et al. (41), where 11 children with non-congenital ZVI participated and ZIKV RNA was detected using real-time RT-PCR tests in cerebrospinal fluid samples. Upon follow-up assessment of the patients, one-quarter of the subjects required antiepileptic medication, whereas two of the participants went on to experience delay-in-development/learning difficulties.

Other parts of the world

With Brazil contributing the most in the way of observational studies concerning CZI, still, there are significant findings from other parts of the world that need equal attention. Nevertheless, some of the conclusions we review here support and add to the findings made in Brazilian studies regarding CZI.

At this point, the global spread of CZIs has been established (26). Even in Southeast Asia, where ZIKV spread has not received any coverage since at least 2017, the Lao People's Democratic Republic reported their very first case of CZI-related microcephaly in 2020 (42). Regardless, Southeast Asia as a whole, dating back to 1997 until 2015, has not reported enough data concerning the ZIKV-and-related adverse pregnancy outcomes. In the case of Thailand however, between 1997–2015 prevention of perinatal transmission of HIV and HBV was studied. The samples from the study were stored and later used by Ngo-Giang-Huong et al. (43) in an unmatched case-control study to explore the relationship between adverse outcomes of pregnancy and the presence of ZIKV antibodies in the subjects. The participants included a case group of pregnant women and a control group without adverse pregnancy outcomes, and their infants. All the women had either HIV or HBV. None in the case group had ZIKV IgM, and the same was true for their live-born neonates. As for ZIKV IgG, prevalence in the case group averaged at 29% (24% case, 34% control). Furthermore, the authors did not report any ZIKV-related infections in the neonates, or ZIKV-related adverse pregnancy outcomes in any of the women who participated in this 18-yearlong study. The study further suggested that ZIKV immunity is common among pregnant women in Thailand.

The ZIKV epidemic in Colombia during 2015–2017 has also contributed to the literature on CZI. Various aspects were studied, like the brain or eye defects found in neonates born to mothers with laboratory confirmed ZIKV infection between the 2015 and 2016 outbreaks. Moreover, these defects were found more common during the outbreak than shortly before or after it (44). One of the studies also investigated the link between the epidemic prevalence of CNS defects/ microcephaly cases and CZI based on the biological specimens accumulated from maternal and infant/fetal sources. It was discovered that out of 858 reported cases of CNS defects and/or microcephaly, 503 (58%) could be attributed to CZI, but the strength of evidence fluctuated from limited to strong (45). However, according to a preliminary report from 2016 on the Colombian ZIKV epidemic, it was reported that the ZVI during the third trimester of pregnancy did not cause any structural deformities in fetuses. These observations were based on the data collected from different types of patients infected by ZIKV, including a subgroup of pregnant women. According to the same report, ZVD was reported twice as much in females than in males, aligning with previous findings from Brazilian studies (46).

Apart from the immediate manifestation of CZI shortly after birth, studies in Brazil reported asymptomatic births with CZI which developed a broad spectrum of neurological disorders later in life. Similar observational studies have been conducted in other countries

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as well. In one of these studies, conducted in response to the ZIKV outbreak in French territories in the Americas in 2016, the effects of in-utero exposure to ZIKV on children's neurodevelopment in their early childhood was studied. Compared to other aspects of CZI, this topic is less understood, with most of the literature focusing on congenital disabilities. The study involved toddlers (24 months old) born normocephalic during the 2016 ZIKV outbreak, and the researchers, between June 2018 and August 2019, assessed their neurodevelopment. The assessment involved the use of Ages and Stages Questionnaire-III (ASQ) to measure communication, gross motor, fine motor, problem-solving, and personal-social skills as the five dimensions of overall development, as well as the Modified Checklist for Autism on Toddlers (M-CHAT) to observe behavior, and the French MacArthur Inventory Scales (IFDC) for the acquisition of French language. The results were collected and reported by the parent for the 156 toddlers who underwent in-utero exposure and for the 79 who did not. It was found that 24 (15.4%) of the ZIKV-exposed toddlers and 20 (25.3%) without the ZIKV exposure scored below the reference ranges in their ASQ results. However, the overall difference in neurodevelopment was minimal between toddlers exposed to ZIKV and those who weren't at 24 months of age (47).

CZS encompasses a broad spectrum of developmental disorders in children. These include mobility, postural control, and social skills. Many observational studies have hinted at the development of these disorders either at birth or soon after. However, very few studies have attempted to develop possible forms of therapy to help cure these disorders. In a case report from Norway, first of its nature, researchers focused on a single child with CZS at the age of 17-18 months and observed the impact of intensive physical therapy intervention for six weeks, at home. According to the findings presented by the study, among other measures adopted to evaluate the outcome, mobility, postural control, and social skills of the child were improved due to physical therapy, but further research is required to validate these findings (48).

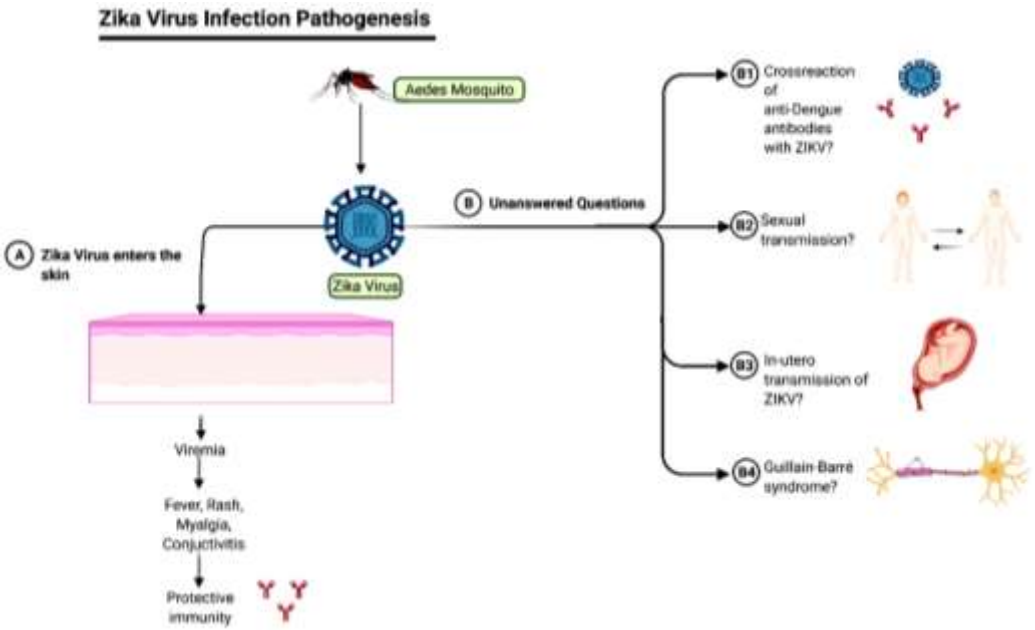

Fig. 1. Pathogenesis of ZIKV in humans and the unanswered questions surrounding it. Adapted from "The Role of ILC2s in Asthma Pathogenesis", by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates

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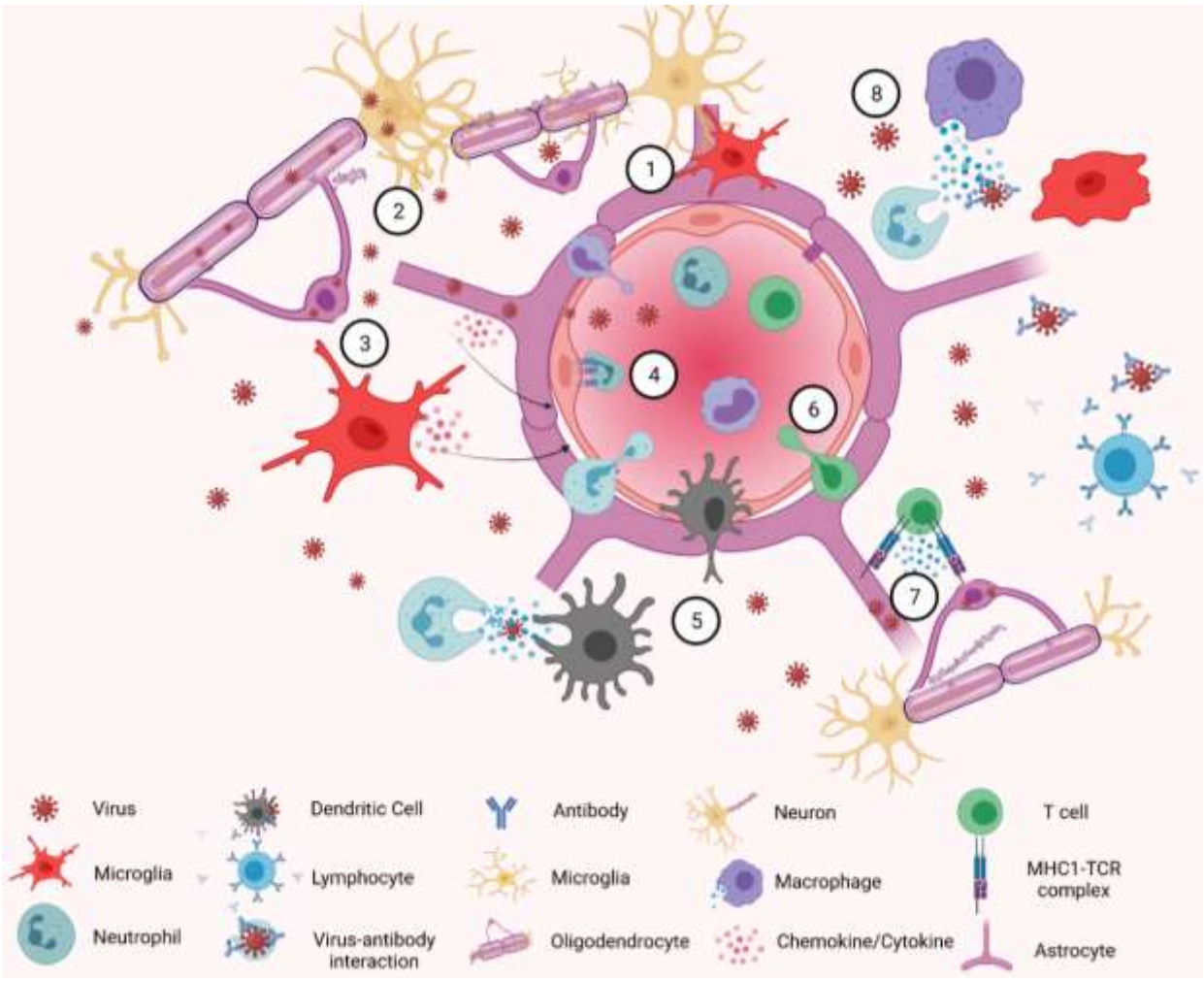

Fig. 2. Immune response during viral entry and infection of CNS: CNS is covered by BBB and other immune cells for protection against pathogenic microbes. With the BBB in a resting state (1), viruses can enter the CNS by infecting peripheral nerves and traveling by anterograde axonal transport into the CNS, by infecting host immune cells in the periphery and using these cells as "Trojan horses" to carry them across the BBB, or by directly infecting BBB endothelial cells (2). Viral PAMPs then activate microglia, astrocytes, and oligodendrocytes (3). Microglia and astrocytes produce a range of antiviral/proinflammatory cytokines, including type-I IFNs, IL-6, TNF-α, IL-12, IL-1α, and IL-1β (3). Astrocytes also produce MMP-3 and MMP-12, resulting in the up-regulation of adhesion molecules on endothelial cells (3). Interactions between adhesion molecules and neutrophils contribute to BBB breakdown via the production of MMP-9 and the disassembly of the tight junctions (4). DCs are seen in the CNS within several days and migrate to draining lymph nodes where they activate and expand virus-specific T cells (5). Chemokines produced by astrocytes are responsible for recruiting virus-specific CD4+ and CD8+ T cells and ASCs to the CNS (6). CD8+ T cells produce IFN-γ and lytic molecules, including granzyme B and perforin, to eliminate the virus from astrocytes, while IFN-γ controls viral replication in oligodendrocytes (7). Virus-specific antibodies control virus replication in cells such as neurons via complement–independent, non-cytolytic mechanisms. These antibodies inhibit virus budding and replication, viral RNA transcription, and cell-to-cell virus spread (25). Adapted from "Blood Brain Barrier (Transverse)", by BioRender.com (2023). Retrieved from https://app.biorender. com/biorender-templates

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Fig. 3. Global spread of ZIKV according to reviewed observational studies. Adapted from "Global Presence (World Map)", by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates

ZIKV in adults

Compared to CZI, ZVI is also prevalent in adults and in most cases its symptoms are more apparent and abundant compared to younger patients. Therefore, revision of the current definition of Paediatric ZIKV provided by WHO and Pan American Health Organization (PAHO) is needed as age is an essential factor to consider when describing the clinical implications of ZIKV. Furthermore, diagnosing ZIKV in children is more challenging as the symptoms are mild and often non-specific. Therefore, attending clinicians might need to perform molecular and serological tests to confirm the diagnosis of ZIKV (49).

Like CZI, ZVI in adults has been investigated more in Brazil than in any other country. These investigations have focused on the effects of ZIKV on different parts of the human body, like the male reproductive system, specifically, the seminal fluid. This is because ZIKV can be transmitted sexually but how the virus persists in the male reproductive tract is not yet well understood. Therefore, this was investigated in a case study during the 2016 ZIKV epidemic in Brazil involving a 33-year-old semen donor. The donor was followed before, during, and after the ZVI. After the infection, there was delayed damage in the form of reduced progressive motility and concentration of the sperm. Also, eight months after the virus became undetectable in the body fluids, the rapid directional motility of the sperm remained reduced. However, the complete clearance of ZIKV from semen could not be achieved and is a matter of concern, something to be investigated by future studies (50).

Guillain-Barré Syndrome (GBS) is another way in which ZVI manifests itself in adults. However, the association between ZVI and GBS is unknown. During the ZIKV outbreaks in Brazil, a rise in GBS cases was recorded and as a response, an observational cohort study was conducted by Leonhard et al. (51) which recruited 71 (36 females and one child aged 9) GBS patients between December 2014 and February 2017. The median age of the patients was 46, with a total of 48 patients confirmed with a recent arbovirus infection (25 of them for ZIKV). It was found that most of the patients with a recent arbovirus infection had a sen-

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sorimotor, demyelinating GBS. Furthermore, an observational study by Ferreira et al. (52), conducted during Brazil's 2015–2016 ZIKV outbreak, established a similar association between ZIKV and GBS. The study investigated neurological disorders caused by ZIKV and other arboviruses, individually and by dual infection. A total of 201 adults participated (median age: 48), with 106 females. In conclusion, a wide variety of neurological diseases were caused by ZIKV, including GBS, which also overlapped with other arboviruses like Chikungunya.

Among findings from other countries, cross-reactivity of ZIKV antibodies with DENV is another topic not completely understood. However, in a case report from the United States, a school-aged female child returning from the Dominican Republic presented with symptoms including vomiting, fever, abdominal pain, and hypovolemic shock. The death of the child occurred in less than 24 hours following hospitalization. She had an early acute first DENV infection, confirmed by performing PCR on serum, plasma, and spinal fluid samples. Moreover, no IgG antibodies were present against DENV nonstructural protein 1 (NS1) for any of the four known serotypes of DENV. However, immunity toward a previous ZVI existed due to antibodies against the ZIKV NS1 envelope. Therefore, the researchers came to believe that perhaps the presence of immunity towards ZIKV triggered the Antibody-dependent enhancement (ADE) phenomenon, as it has been reported in the past that ZIKV antibodies tend to cross-react with DENV. Therefore, this was the first case of such nature in the United States where ZIKV immunity probably contributed to the triggering of the ADE phenomenon, eventually leading to the fatality of the patient (53). With that in mind, there are also reports of ZIKV vaccination boosting pre-existing immunity towards flaviviruses, as demonstrated when tested on a DENV-experienced individual, and protecting against DENV and ZIKV (54).

Regarding the association between ZVI and different diseases, a connection was established between Acute Anterior Uveitis (inflammation of the middle layer of the eye) and an acute systemic ZVI in a study conducted in the French West Indies in Guadeloupe in the 2016 ZIKV outbreak. An ophthalmic investigation was performed in 62 adults with red-eye who had tested positive for ZVI through serology. Half of the patients who presented with red-eye and a ZIKV-positive profile had anterior uveitis. The uveitis was mainly associated with a rise in intraocular pressure and was bilateral. Therefore, the study suggested that patients with red-eye who test positive for acute systemic ZVI should undergo an ophthalmic examination to diagnose them with hypertensive anterior uveitis (55).

Discussion

ZIKV is a major threat to public health in various countries around the world (26–31). The virus itself is transmitted to humans through the *Aedes* mosquito (4). ZIKV penetrates the skin (4-6), causing a wide variety of symptoms, disorders, and diseases. These range from general symptoms like fever, rash, myalgia and conjunctivitis, to name a few, to more serious conditions like GBS and microcephaly (7, 8). These disorders can be further distributed between adults and infants, with the virus manifesting into specific diseases in each age group. So far, most of the published research concerning ZIKV has involved experimental studies that have provided valuable insight into the innerworkings of this virus and how it causes infection in humans (4–25). However, to grasp the severity and real-life implications of the ZVI on different age groups, observational studies are necessary.

Most of the data collected from the observational studies involve the effects of ZIKV on neonates (32–41, 43–48), whereas only a limited number of studies have highlighted its effect on adults (49–55). Furthermore, most

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of these observational studies regarding ZIKV have emerged from South America, particularly Brazil (32–41). Since the 2015 ZIKV outbreak, Brazil has reported a vast number of ZVI cases with most of them involving neonates. CZI in neonates causes neurological disorders and diseases like microcephaly. Moreover, it was reported that the infected infants had undergone in-utero exposure to ZIKV during pregnancy, resulting in CZS. Whereas in adults, observational studies have shown ZVI to cause multiple conditions like GBS, Acute Anterior Uveitis and cross-reactivity of ZIKV antibodies with DENV. However, a gap in literature exists concerning all these areas. Especially, the association between GBS and ZIKV, the sexual transmission of ZIKV, and the effects of cross-reactivity between ZIKV and anti-DENV antibodies require further investigation.

Conclusion

In this review, we attempted to enlighten the reader about the threats that ZIKV poses to the human population. ZIKV was presented in the light of observational studies rather than experimental studies to stress its damaging capabilities in real-life settings. In that, we highlight the damage it is capable of in infants and adults alike, worldwide, with Brazil being one of the countries reporting the most ZIKV cases and ZIKV-related observational studies. The reviewed research covers multiple disorders and diseases caused by ZIKV, including microcephaly, developmental disorders in children, GBS, cross-reactivity of DENV and anti-ZIKV antibodies, and Acute Anterior Uveitis. It is concluded that neurological disorders/ diseases are most prevalent in neonates with CZI, while the clinical manifestations of ZIKV in adults involve different organs. We also highlight gaps in the literature regarding ZIKV-related-complications that future experimental studies need to address. These include in-utero transmission or Guillain-Barre syndrome or its persistence in the male reproductive tract, cross-reactivity, and sexual transmission.

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Conflict of interest statement

The authors declare there is no conflict of interests.

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