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ZIKA VIRUS: AN OVERVIEW OF CURRENT UNDERSTANDING

Abdullah Al Hasan*[1], Sayema Khanum[1] and A.T.M. Zafrul Azam[2]

[1]Department of Pharmacy, Southeast University, Banani, Dhaka-1213, Bangladesh.
[2]Department of Pharmaceutical Chemistry, University of Dhaka, Dhaka-1000, Bangladesh.

*** Corresponding Author: Abdullah Al Hasan**
Department of Pharmacy, Southeast University, Banani, Dhaka-1213, Bangladesh.

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ABSTRACT
Zika virus (ZIKV), a flavivirus closely related to dengue (DENV), West Nile (WNV), Japanese encephalitis (JEV) and yellow fever (YFV) viruses, has appeared since 2007 to cause a series of epidemics in many parts of the world including Micronesia, the South Pacific, and the Americas. After its assumed evolution in sub-Saharan Africa, Zika virus spread in the distant past to Asia and has probably appeared on multiple occasions into urban areas involving *Aedes* (*Stegomyia*) spp. mosquitoes and human hosts. There is a high potential for ZIKV emergence in urban areas in the tropics that are infested with competent mosquito vectors i.e. *Aedes aegypti* and *Aedes albopictus*. This review describes the current understanding of the epidemiology, transmission, clinical characteristics and diagnosis of Zika virus infection, potential strategies to control the ongoing outbreak through vector-centric approaches, the prospects for the development of vaccines and therapeutics as well as the future outlook with regard to this disease.

KEYWORDS: Zika virus, Microcephaly, Flavivirus, Envelope protein, Pregnancy, Vaccine.

INTRODUCTION
Zika virus is an **ar**thropod-**bo**rn **virus** (arbovirus) belonging to the genus *Flavivirus* and the family *Flaviviridae*.[1,2] The virus is named after the Zika Forest in Uganda (zika means "overgrown" in Lugandan), where the virus was first recovered from a sentinel rhesus monkey that was being used in a yellow fever research project; the agent was eventually described as Zika virus in 1952.[3] The genus *Flavivirus* comprises many viral species, including the dengue, yellow fever and West Nile viruses.[1,2]

ZIKV infection in humans was first described in Nigeria in 1954.[4] For half a century, fewer than 20 human infections were documented.[5] The first reported outbreak of Zika fever occurred in 2007 on the Western Pacific island of Yap in the Federated States of Micronesia[6] followed by a larger epidemic in French Polynesia in the South Pacific in 2013 and 2014,[7] with an estimated 30,000 symptomatic infections.[8,9] These epidemics were followed by smaller Pacific outbreaks in 2014[10–12] and in 2015.[13–16] In 2015, ZIKV emerged in the Americas (Brazil) and as of the end of January 2016, autochthonous circulation of this virus has been reported in more than 20 countries or territories in South, Central and North America and the Caribbean.[14,17–22] The emergence of Zika virus was associated with the description of neurological complications: Guillain-Barré syndrome (GBS) in adults in French Polynesia and microcephaly in neonates in Brazil.[21,23–27] ZIKV is following the path of dengue and chikungunya (CHIKV) virus, spreading to all countries infested with *Aedes aegypti* and *Aedes albopictus* mosquitoes.[28]

EPIDEMIOLOGY
Zika virus was isolated on several occasions from *Aedes africanus* mosquitoes after its discovery in 1947.[29] Serological and entomological studies have suggested that ZIKV is widespread throughout many countries. The virus was detected in Thailand,[30] Malaysia,[31] Uganda,[32] Nigeria,[33] Indonesia,[34] Senegal,[35] and Cote d'Ivoire.[36] Moreover, antibodies against ZIKV were detected in healthy people from India,[37] Egypt,[38] Vietnam,[30] Kenya,[39] Sierra Leone,[40] and Pakistan.[41]

The 2007 outbreak in the State of Yap, Federated States of Micronesia, resulted in an estimated 5000 infections among the total population of 6700.[6] Subsequent outbreaks occurred on many Pacific islands, including French Polynesia (in 2013 and 2014),[7,23,42,43] New Caledonia (in 2014),[44] Easter Island (2014),[45] Cook Islands (2014),[46] Samoa (2015) and American Samoa (2016).[47] In contrast to these outbreaks, in the past 6 years, only occasional cases of ZIKV infection have been reported in Thailand,[48,49] East Malaysia,[50] Cambodia,[51] the Philippines,[52] and Indonesia.[53,54]

Zika virus was first identified in the Americas in March 2015,[55] and by April 2016, the virus had spread to at least 33 countries and territories in the Americas.[22,55] By September 2015, investigators in Brazil noted an increase in the number of infants born with microcephaly (MC), in the same areas in which Zika virus was first reported,[27] and by February 2016, more than 4300 cases of microcephaly had been reported.[56] French Polynesian investigators also identified an increased number of microcephaly after the Zika virus outbreak in that country.[57,58] On 1st February 2016, the World Health Organization (WHO) declared a global public health emergency due to the ZIKV threat.[59]

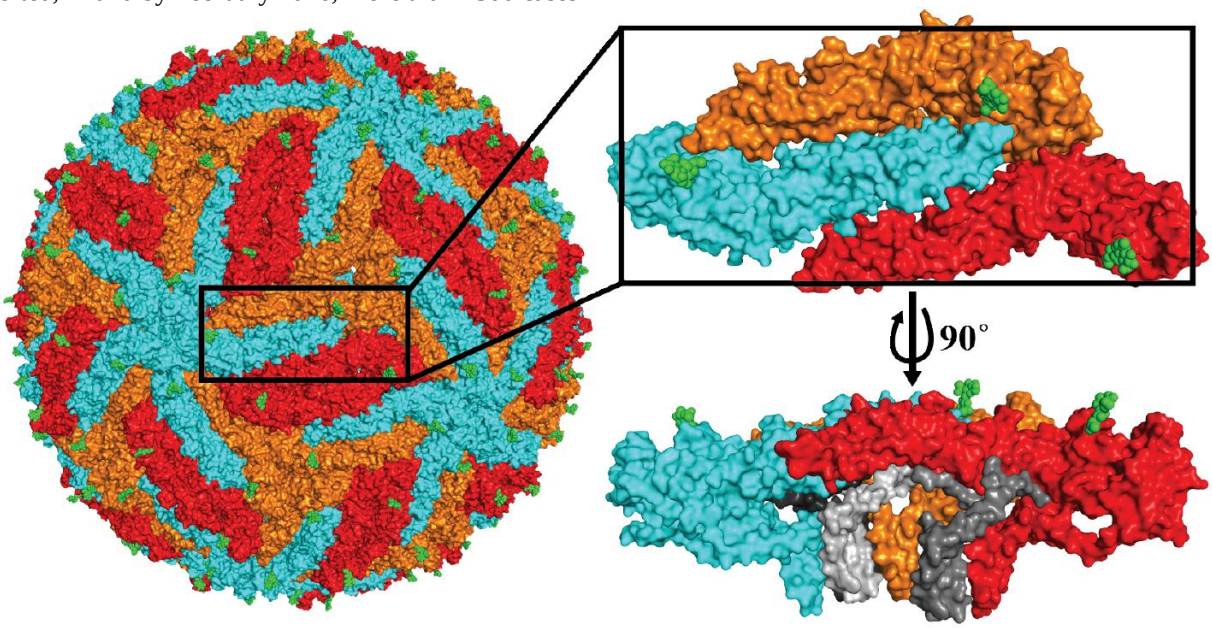

Figure 1: The cryo-EM structure of ZIKV at 3.8Å (PDBID: 5IRE).[63] E proteins (red, cyan and orange); M proteins (three shades of gray); Glycan (green). ZIKV has a single glycosylation site in E protein (Asn154). Glycosylation at Asn154 in E of West Nile virus has been linked to neurotropism.[64] Figures created using PyMOL (The PyMOL Molecular Graphics System, Version 1.7.5.0 Schrödinger, LLC).

MOLECULAR VIROLOGY

Zika virions are small, spherical particles (**Figure 1**) that contain a single-stranded, non-segmented RNA of positive-sense and approximately 11 kb in length. The genomic RNA has one open reading frame (ORF) that is flanked by 5′ and 3′ non-coding regions (NCR). The genome is translated into a single polyprotein (**Table 1**) that is subsequently cleaved by both viral and host cell proteases, resulting in three structural proteins that form the virion (capsid (C), pre-membrane/membrane (prM/M) and envelope (E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5).[60]

Table 1: Genome structures of ZIKV strains

	Length	
Gene or genomic region	**African MR 766 prototype strain[a]**	**French Polynesia H/PF/2013[b]**
5′ NCR	106 nt[c]	107 nt
Capsid	122 aa[d]	105 aa
PrM	178 aa	187 aa
Envelope	500 aa	505 aa
NS1	342 aa	352 aa
NS2A	226 aa	217 aa
NS2B	130 aa	139 aa
NS3	617 aa	619 aa
NS4A	127 aa	127 aa
NS4B	252 aa	255 aa
NS5	902 aa	904 aa
3′ NCR	428 nt	428 nt
Complete genome	10,794 nt	10,617 nt

[a] Data are from reference [61].
[b] Data are from reference [62].
[c] nt, nucleotides.
[d] aa, amino acids.

The non-structural proteins NS2B/NS3 includes a serine protease that along with host proteases co-translationally and post-translationally cleaves the polyprotein into its components.[65] C binds to the viral RNA to form a nucleocapsid, prM prevents premature fusion with host membranes, and E (primary flavivirus antigenic site) mediates cellular attachment, entry and fusion.[66] The viral nonstructural proteins regulate viral transcription and replication and also attenuate host antiviral responses.[60,67,68] For example, NS5, the most highly conserved of the flavivirus NS proteins functions as a RNA-dependent RNA polymerase.[69] Generally, flavivirus virions exist in three major states, namely immature, mature and fusogenic, which are

noninfectious, infectious and host membrane binding states, respectively.[63]

PHYLOGENY

A growing number of ZIKV genome sequences and their phylogenetic relationship with other members of the *Flavivirus* genus are being determined.[70,71] ZIKV is placed in the clade X mosquito-borne *Flavivirus* cluster, along with Spondweni virus (SPOV).[72] These results, based on partial sequencing of the gene for NS5, were confirmed by sequencing the complete coding region of the NS5-encoding gene.[73] Phylogenetic analyses of ZIKV revealed the existence of two main virus lineages (African and Asian). A different ZIKV subtype of the West African circulated in the *Aedes* species in Central Africa.[74] Studies showed that ZIKV that emerged in the Pacific islands and in South America belongs to the Asian lineage.[7,18,19,52,75]

TRANSMISSION

Zika virus is generally maintained in a sylvatic environment, in a zoonotic cycle between mosquitoes (*Aedes* spp. and other species) and non-human primates.[76] This virus has been isolated from several different mosquito species in nature: *Ae. africanus*, *Aedes furcifer*, *Aedes metalicus*, *Aedes taylori*, *Aedes aegypti*, etc. in Africa. *Ae. aegypti* was suspected to have an important role in the urban transmission (mosquito-human-mosquito) of Zika virus in Nigeria.[33] In Asia, authentic evidence incriminated *Ae. aegypti* as the urban vector after Zika virus was identified in a mosquito pool collected in Malaysia.[31] The virus is transmitted from infected female mosquitoes to humans during a blood meal.[77] Brazil displays high infestation rates of both the widely distributed *Ae. aegypti* and *Ae. albopictus*. The former species is the principal vector for dengue virus,[78] and the latter has been found to be competent to transmit chikungunya virus;[79] both of these viruses co-circulate simultaneously with Zika virus within Brazil.[78,80,81]

Mosquito-borne transmission

Several mosquito species, primarily belonging to the stegomyia and diceromyia subgenera of aedes, including *A. africanus*, *A. luteocephalus*, *A. furcifer*, and *A. taylori*, are likely enzootic vectors in Africa and Asia.[31,77] In urban and suburban environments, ZIKV is transmitted in a human–mosquito–human transmission cycle. Two species in the stegomyia subgenus of aedes (*A. aegypti* and *A. albopictus)* [82] have been linked with most of the known ZIKV outbreaks.

Nonmosquito transmission

Considerable evidence indicates that ZIKV can be transmitted from the mother to the fetus during pregnancy. ZIKV RNA has been identified in the amniotic fluid of mothers whose fetuses had cerebral abnormalities,[47,57,71,83] and viral antigen and RNA have been identified in the brain tissue and placentas of children who were born with microcephaly,[84] as well as in tissues from miscarriages.[47,84] Cases of peripartum transmission of Zika virus have been reported among mother–infant pairs.[85] Transmission of Zika virus through a blood transfusion is likely to occur.[86] Sexual transmission to partners of returning travelers who acquired Zika virus infection abroad has been reported.[87–89] Replicative viral particles, as well as viral RNA have been identified in sperm and viral RNA has been detected up to 62 days after the onset of symptoms.[90–92] Zika virus RNA and/or protein has also been detected in saliva,[93] urine,[94] amniotic fluid[83] and placental tissues,[84] highlighting the possibility of other modes of transmission.

CLINICAL MANIFESTATIONS

The incubation period for ZIKV is expected to be generally less than 1 week. Serosurvey results from Yap indicated that only 19% of persons who were infected had symptoms that were attributable to ZIKV. Common symptoms were macular or papular rash (90% of patients), fever (65%), arthritis or arthralgia (65%), non-purulent conjunctivitis (55%), myalgia (48%), headache (45%), retro-orbital pain (39%), edema (19%) and vomiting (10%).[6] The rash is generally maculopapular and pruritic and fever is generally short-term and low-grade.[95] Other symptoms that have been observed along with acute ZIKV infection include hematospermia,[87,90] transient dull and metallic hearing,[50] swelling of the hands and ankles,[50,96] and subcutaneous bleeding.[97]

Neurologic complications

A temporal and geographic relationship has been observed between GBS and ZIKV outbreaks in the Pacific and the Americas.[23,42,98–100] A study in French Polynesia revealed a strong association between GBS and previous ZIKV infection; the findings from electrophysiological studies were compatible with the acute motor axonal neuropathy (AMAN) subtype of GBS.[43] Meningoencephalitis[101] and acute myelitis[102] also have been reported.

Adverse fetal outcomes

Microcephaly can occur as a result of fetal brain disruption sequence, a process in which, after relatively normal brain development in early pregnancy, collapse of the fetal skull follows the destruction of fetal brain tissue.[103,104] This damage can occur late during the second trimester or even early in the third trimester.[105–107] The findings of ZIKV RNA in the amniotic fluid of fetuses with microcephaly[47,57,71] and in the brain tissue of fetuses and infants with microcephaly,[84,106,107] as well as the high rates of microcephaly among infants born to mothers with prior ZIKV infection,[95] provide strong evidence linking microcephaly to maternal ZIKV infection. However, much remains to be revealed regarding the association of ZIKV with microcephaly and other fetal malformations. The greatest risk of microcephaly is in the first trimester.[58,108,109] In case reports of microcephaly, documented maternal ZIKV infection most often occurred between 7 and 13 weeks of gestation.[47,57,71,95,106]

PATHOGENESIS

The symptoms of Zika virus infection usually appear three to eleven days after the mosquito bite occurs.[87,110] The viremic period is expected to be shorter than that of other flaviviruses. Viral RNA has been detected in serum samples from days 0-11 after the onset of symptoms.[73,111]

Experimental study demonstrated an enlargement of astroglial cells and the destruction of the pyriform cells of Ammon's horn in the brains of mice that had been infected intracerebrally. The virus appears to be formed within the endoplasmic reticulum network, in close association with host cell membranes.[112,113] Intracerebral-inoculated mice exhibited encephalitis with neuronal degeneration, cellular infiltration and areas of softening.[29]

Zika virus induced an antiviral state in the infected fibroblast skin cells, with enhancement of IFN-α and IFN-β gene expression and upregulation of the expression of IFN-stimulated genes (ISGs). Moreover, Zika virus induced an upregulation in the expression of Toll-like receptor 3 (TLR-3), retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated gene-5 (MDA-5). Eventual autophagosomes and autophagy were associated with the enhancement of viral replication in skin fibroblast cells.[113]

DIAGNOSIS

The diagnosis of infection by ZIKV is based on clinical, epidemiological and laboratorial criteria. As the symptoms of ZIKV disease can easily be confused with those of other arbovirus-induced diseases, ZIKV infection can be misdiagnosed; thus, the differential laboratory diagnosis is important.

The mainstays of the routine diagnosis of ZIKV infection are the detection of viral nucleic acid by RT-PCR and the detection of anti-ZIKV IgM antibodies by IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA). In most instances viremia is transient and diagnosis by RT-PCR has been most successful within 1 week after the onset of clinical illness.[73,110] In contrast, ZIKV RNA was detected in serum approximately 10 weeks after infection in a pregnant woman whose fetus had evidence of congenital ZIKV infection.[107] Experience with related flaviviruses suggests that anti-ZIKV IgM will appear as viremia wanes within the first week after symptom onset and will persist for several months.[114] RNA loads have been detected up to approximately 7.3×10^6 copies/ml in serum,[73,85,96,115] 2.2×10^8 copies/ml in urine,[85,90,94] 2.9×10^7 copies/ml in semen,[90] and 2.0×10^6 copies/ml in breast milk samples.[85]

RT-PCR testing of serum samples obtained within the first week of clinical illness and MAC-ELISA testing of samples that are not tested by RT-PCR or that are not found to be positive by RT-PCR are likely to have the highest diagnostic yield.[116] Recent ZIKV infection may also evoke a positive MAC-ELISA result for dengue. The plaque reduction neutralization test (PRNT), used to differentiate antibodies of closely related viruses, can be used to help verify MAC-ELISA results.[117] However, this test is labor-intensive, costly and is not widely performed. RT-PCR and immunohistochemical testing have been useful in establishing ZIKV infection in tissues of fetal losses and full-term infants who died shortly after birth.[84,106]

Microcephaly and other fetal abnormalities may be detected as early as 18 to 20 weeks of gestation.[47,57,95,118] Although ultrasonography is not a highly sensitive means of detecting fetal abnormalities,[119] findings associated with ZIKV infection that have been noted on ultrasound have included, in addition to microcephaly, an absent corpus callosum, cerebral calcifications, ventricular dilatation, abnormal gyration, hydrops fetalis, anhydramnios, and intrauterine growth retardation.[57,95,106,120]

PREVENTION, TREATMENT AND CONTROL

There is currently no approved Zika virus vaccine. Subunit vaccines representing ZIKV proteins, DNA vaccines expressing viral proteins and other viral vectors expressing viral antigens could be explored for ZIKV vaccine development.

No clinically approved therapy is currently available for treatment of any flavivirus infections. Treatment for uncomplicated Zika virus infection focuses on symptoms. The use of fluids and acetaminophen (paracetamol) or dipyrone is recommended to control fever and provide pain management. In the case of an itchy rash, antihistamines may be considered. However, aspirin and other anti-inflammatory drugs are not recommended due to the increased risk of bleeding complications.[121]

Due to the similarity between ZIKV and DENV, it is reasonable to speculate that inhibitors active against both ZIKV and DENV could be found. However, cautions should be taken when extrapolating DENV experience to ZIKV drug discovery. This is because the biology of the two viruses could be very different. To prevent microcephaly in a ZIKV-infected pregnant woman, an inhibitor would need to possess a property of brain penetration. An ideal drug needs to pharmacologically inhibit ZIKV in both brain and systemic sites. However, a non-brain penetrating compound with good systemic exposure may restrict viremia and prevent fetus infection.

Prevention and control measures center on avoiding mosquito bites, reducing sexual transmission, and controlling the mosquito vector. Effective methods of prevention of ZIKV among pregnant women include but not limited to avoiding unnecessary travel to areas of ongoing ZIKV transmission, avoiding unprotected sexual contact with partners who are at risk for ZIKV

infection,[116] and using mosquito repellent, permethrin treatment for clothing,[122] bed nets,[123] window screens,[124,125] and air conditioning.[126,127] *A. aegypti* vector control relies on elimination of *A. aegypti* mosquito breeding sites, application of larvicides, and application of insecticides to kill adult mosquitoes. However, each of these approaches has substantial limitations.

An integrated prevention and vector-control approach in combination with timely detection of illness, communication of up-to-date and correct information, and development of a rapid response that involves the community are recommended to tackle Zika virus.

CONCLUSION

The causative connection between Zika virus infection and microcephaly as well as Guillain-Barré syndrome needs to be revealed by well-designed case-control and prospective cohort studies to ensure that another etiology or co-factor is not overlooked. Beyond the immediate future, past work on flavivirus vaccines and therapeutics should provide platforms and approaches that can accelerate product development for Zika virus. Better surveillance facilitated by inexpensive, simple point-of-care diagnostics will be needed to identify sites with sufficient disease incidence to conduct clinical trials on future products against flaviviruses.

With Zika virus spreading rapidly throughout the tropical and subtropical regions, critical gaps remain in our knowledge of this virus. Rapid responses to contain the outbreak must be implemented urgently. Recent global increases in the incidence and spread of DENV, CHIKV and now ZIKV, all with *A. aegypti* as the primary vector, suggest common reasons for their emergence, such as globalization and urbanization.[28,128] Other possible explanations include viral introduction to previously unexposed populations and viral mutations affecting transmission or virulence.

There is a clear need to rapidly address identified research gaps.[129] These include a complete understanding of the frequency and full spectrum of clinical outcomes resulting from fetal ZIKV infection and of the environmental factors that influence emergence, as well as the development of discriminating diagnostic tools for flaviviruses, new vector control strategies, effective therapeutics and vaccines.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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