Review Article

A Review on the Incidence, Interaction, and Future Perspective on Zika Virus

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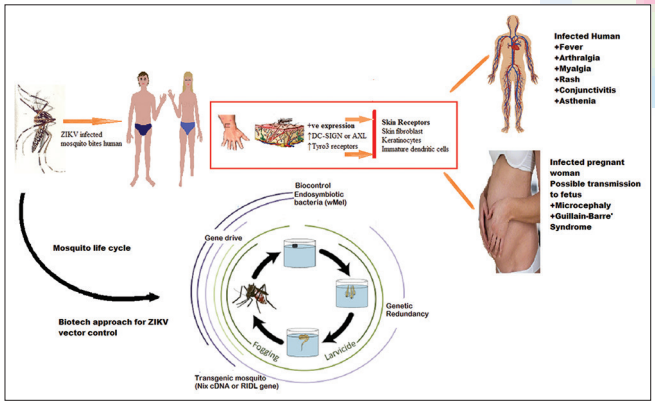
ABSTRACT

Zika virus (ZIKV) belongs to the family *Flaviviridae* and genus Flavivirus. It is a single-stranded positive-sense ribonucleic acid (RNA) virus, has its origin traced to Zika forest in Uganda. Its infection leads to ZIKV fever, characterized by arthralgia, myalgia, rash, conjunctivitis, and asthenia. Clinical presentation of the infection is nonspecific and may often be confused with symptoms of other flaviviral diseases (dengue, West Nile [WN], and chikungunya). Recently, ZIKV has been associated with congenital malformations and neurological complications such as microcephaly and Guillain–Barre' syndrome. The viral tropism revealed an infection of the skin fibroblasts, keratinocytes, and immature dendritic cells through enhanced expression of dendritic cell-specific intracellular adhesion molecule 3-grabbing nonintegrin or anexelecto (Greekword: 'uncontrolled') and tyrosine protein kinase receptor 3 systems. Silencing of T-cell immunoglobulin (Ig) and mucin domain 1 (TIM-1) and AXL RNAs has shown blockage of viral entry through their anti-TIM-1 and anti-AXL antibodies, hence serving as a potential target for ZIKV drug development. Biotechnological approaches targeted toward ZIKV vector control include the development of transgenic mosquitoes to disrupt the genome pool of wild strains and use of an endosymbiotic bacterium to prevent replication of arboviruses within its vector. Other approaches include the use of gene drive and exploration of the genetic redundancy to disrupt the receptors used by the virus to gain entry into its host. It is also imperative to explore the modality through which neutralizing antibodies block this viral infection as this may prove as a potential target to arrest the viral life cycle.

KEY WORDS: Flavivirus, microcephaly and Guillain–Barre' syndrome, mosquito, receptors, Zika virus



Graphic Abstract

INTRODUCTION

Zika and other Flaviviruses are considered a global threat with the recent multiple outbreaks in many countries. We reviewed the incidence, interaction, and future perspective of Zika virus (ZIKV). Efforts were made to describe the virus-host cellular tropism with specific highlights of potential target sites on human receptors that can be exploited to stop ZIKV entry into human cells. Finally, we discussed the possible genetic approaches that can be used to control ZIKV vector (mosquito), hence limiting its spread.

METHODS OF LITERATURE SEARCH

We conducted an extensive online search on articles available on the PubMed, Elsevier, Centers for Disease

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Prevention and Control (CDC), and WHO websites as well as other official online health databases of some countries using the following keywords: Zika virus, Flaviviruses, Guillain–Barre syndrome, Vector Borne diseases, Viral tropism, and Effective vector (mosquito) control. We initially obtained over 125 articles published between 1952 and 2016, of which 98 articles were finally used for this review.

HISTORICAL BACKGROUND OF ZIKA VIRUS

The first reported case of ZIKV was in rhesus monkeys in 1947 in Uganda, and the same year witnessed the first human isolation case in Uganda and Tanzania.[1-3] Since then, only narrow outbreaks in the world were recorded in the 1950s. However, sporadic human outbreaks were reported from the 1960s in Africa and Asia.[4] In 2007, there was a report of ZIKV outbreak in Yap Island (Federated States of Micronesia, Pacific), the first reported case outside of Africa and Asia,[5] while the French Polynesia, Pacific, recorded the largest outbreak from October 2013 to March 2014.[6,7]

GEOGRAPHICAL SPREAD OF THE VIRUS

The geographical spread of this virus can only be ascertained from information accumulated through seroprevalence survey, virological studies, epidemics, and diagnosis of periodically reported cases. The recent outbreak in Brazil is a good example of how important it is for surveillance and concerted efforts toward tracking of dangerous diseases.[8] A detailed list of countries with viral outbreak since its first reported case till the recent outbreaks in early 2016 is shown in Table 1 (Modified and updated from Ioos *et al*.,[8] Kindhauser[31]).

DESCRIPTION OF VIRAL MATERIAL

ZIKV is an arthropod-borne virus (arbovirus) which was first reported in rhesus monkeys in 1947 and 1952. It has its origin traced to Zika forest, a tropical forest near Entebbe in Uganda. The first human isolation of the virus was also in Uganda and Republic of Tanzania.[1,9]

ZIKV belongs to the *Flaviviridae* family of Flavivirus genus. It is a single-stranded positive-sense ribonucleic acid (RNA) virus and it is close to the Spondweni, Kedougou, and Bagaza viruses.[8,10] It has about 11,000 nucleotides with a 5′- and 3′-untranslated regions on either side of one open-reading frame [Figure 1][12] which encode a polyprotein[8,10] that is processed into three structural proteins (Capsid C, precursor membrane prM, and Envelop

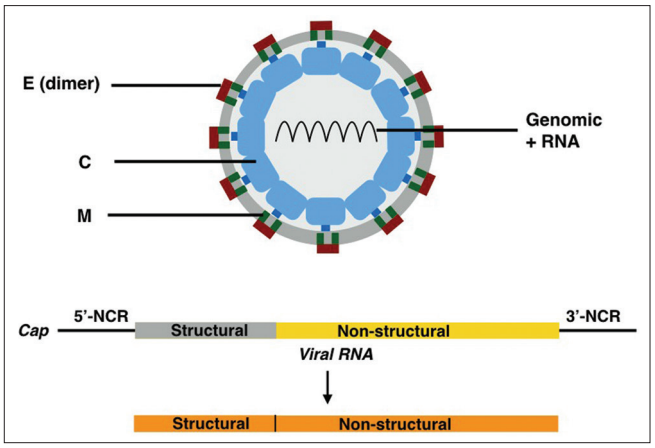

Figure 1: Structure of Zika viral protein

E) and seven nonstructural proteins (NS1–5)[11] [Figure 2]. Buckley and Gould carried out an extensive research to detect virus-specific antigen in the nucleoli of Zika or Langat virus-infected cells and to decipher the role of the nucleus in Flavivirus replication cycle.[13] Their study revealed that monoclonal antibody 541 (MAb 541) was specific for Flavivirus envelope proteins (ENV) and MAb 109 specific for Flavivirus NS1 glycoproteins, and the association of these viral proteins with the nucleus/nucleolus of infected cells is indicative of their transient transport back and forth from the cytoplasm to the nucleus. Buckley and Gould also suggested that ZIKV has altered viral properties different from other classes of flavi-arboviruses (yellow fever [YF] virus (YFV), WN virus [WNV], Ntaya virus, and Bussuquara viruses).[13]. The structural and non-structural protein of ZIKV is shown in [Figure 2].[12]

Reported strains of Zika virus

Comparative genomic studies have revealed the presence of subclades indicating two major lineages: the Asian ZIKVs (six strains) and the African ZIKVs (four strains) [Figure 3].[14]

POTENTIAL RESERVOIRS OF THE VIRUS

There is no definite pointer to the reservoirs of this virus; however, some studies have suggested a primate reservoir. Shapshak *et al*. discussed the roles played by mosquitoes as vectors and spread of the ZIKV.[10]

Transovarial transmission (TOT) was established in mosquitoes including *Aedes aegypti* and *Aedes furcifer-taylori* and revealed a developing zone for virus survival in the dry season. McCrae and Kirya earlier proposed TOT as a contributory route for ZIKV and other arboviruses spread in Uganda, hence the call for serious attention to halt the TOT with strategies to overcome seasonal survival of the arbovirus.[15] TOT acts as a branch that adds to

Table 1: Reported Zika virus cases by seroprevalence survey, virological studies, epidemics, and diagnosis of periodic outbreaks

Countries and territories	Sporadic cases/epidemics		Comments	References
	Number of cases (*n*)	Year		
Uganda	1	1952	First human case	[9]
		1964	Serology study	[1]
Tanzania	1	1952		[9]
Nigeria	2	1954	Isolated in a young girl	[83]
		1975	Serologic isolation in mosquitoes Sporadic human cases	[19]
Cambodia	1	1999	Sporadic human cases	[8]
Ivory coast	1	1999	Sporadic human cases isolation in mosquitoes	
Micronesia (Yap)	185 reported with 108 confirmed and probable cases	2007	49 cases of ZIKV were established (using PCR or a specific neutralizing antibody response to ZIKV in the serum) and 59 were categorized as probable (patients with anti-ZIKV IgM antibody who possibly had a cross-reactive neutralizing-antibody response). A substantial percentage of Yap residents above 3 years of age were infested with ZIKV	[5,54,30]
Australia	1	2013	Imported cases (ex-Thailand)	[8]
Philippines	1	2012		
Indonesia	1	1977-1978	Exported cases in Australia in 2013 Serologic study	[84]
	17	2013		
Malaysia	1		Serologic study isolation in mosquitoes	[85]
Thailand	7	2012-2014	Molecular or serological testing was used to confirm the presence of ZIKV among Thai residents	[86]
New Caledonia	114	2013-2014	Autochthonous cases (Dumbea) Imported cases (e.g., FP)	
	32			
FP	383	2013-2015	From October 2013 to April 2015, there were more than 8750 reported cases of ZIKV infection, with 383 cases established using PCR and an estimated 32,000 clinical consultations made with no death recorded	[6] [8,51,87,88]
Brazil	138	2015-2016	Between November 2013 and February 2014, 42 patients presented at hospital with GBS 138 clinical cases of neurological syndrome reviewed. 58 (42%) present neurological syndrome with a preceding history of viral infection. Of the 58, 32 (55%) present symptoms consistent with Zika or dengue infection November 2015, report of 3 deaths among two adults and a newborn with ZIKV infection 2975 suspected cases of microcephaly were also reported 3893 suspected cases of microcephaly, with 49 deaths. Of these, 3381 currently being investigated. ZIKV detected in samples from newborns or stillbirths in six cases 88 confirmed cases associated with ZIKV infection	[31,89]
The United States	3358	2015 2016	Both travel and locally acquired. 28 sexually transmitted. 8 GBS cases	[90]
The US territories	1977	2015 2016	Both travel and locally acquired. 37 cases of GBS	[90]
Cabo Verde	7081 suspected cases are reported	2015-2016	Some of the suspected cases were later confirmed positive by PCR	[31]
Colombia	239	2016	201 GBS cases with a history of suspected ZIKV infection reported before February 14, 2016. None of these cases have been laboratory confirmed for ZIKV infection or other possible causes	[91]
Suriname		2015 2016	10 GBS cases reported in 2015, 2 cases laboratory confirmed by RT-PCR to have a ZIKV infection. Three GBS cases were reported during the first 3 weeks of 2016	[91]
El Salvador		2015 2106	Recorded 118 GBS cases from December 1, 2015, to January 8, 2016, including five deaths. None of those reported GBS cases have been laboratory confirmed for ZIKV infection or other causes	[91]
Mexico	3	2015	The third case history of been to Colombia	[31]
Guatemala	1	2015		[31]
Paraguay	6	2015		
Panama	4	2015	95 additional cases had symptoms that were compatible with ZIKV	[31]
Honduras	2	2015		
French Guiana	2	2015		
The Bolivarian Republic of Venezuela		2016	252 cases of GBS suspected to be related to ZIKV were reported. The largest number of cases (66) was reported from six municipalities of Zulia state. ZIKV was confirmed in three reported GBS cases by RT-PCR	[91]
Puerto Rico	1	2016	1 GBS case with laboratory-confirmed ZIKV infection reported	[91]
Finland	1	2016	This is a case of importation of the virus from Maldives by a Finish national who had earlier worked in Maldives only to report ill and tested positive to ZIKV upon his arrival to Finland	[31]
Guyana	1	2016		[31]
Ecuador	8	2016	Out of this 8 reported cases, 3 were imported from Columbia, and one from the Bolivarian Republic of Venezuela	[31]
Barbados	3	2016		[31]
Plurinational State of Bolivia	1	2016		[31]
Haiti	5	2016		[31]
France	3	2016	One of the reported cases tested positive to GB only, one to GB and ZIKV while one also tested positive for ZIKV only	[31]
Dominican Republic	10	2016	Two of the ten reported cases were imported from El Salvador	
Nicaragua	2	2016		
Curacao	1	2016		[31]

Contd...

Table 1: Contd...

Countries and territories	Sporadic cases/epidemics		Comments	References
	Number of cases (*n*)	Year		
Jamaica	1	2016		[31]
Cape Verde		2015, 2016	7081 suspected cases of Zika reported between late September 2015 and January 17, 2016	[31]
Chile	3	2016	All reported and confirmed cases were imported from travelers from Colombia, the Bolivarian Republic of Venezuela, and Brazil	
South Africa	1	2016	Diagnosed in a Colombian business person	[92]
Ecuador	8	2016		[31]
Central African Republic		1979		[31]
Singapore	381	2016		[93]
Virginia	18	2016		
Martinique			Two GBS case with laboratory-confirmed ZIKV infection reported	[91]
Hawaii and Slovenia		2016	One case of microcephaly potentially associated with Zika infection each	[94]

FP=French Polynesia, RT-PCR=Real-time polymerase chain reaction, GBS=Guillain–Barre syndrome, GB=Guillain–Barre, ZIKV=Zika virus

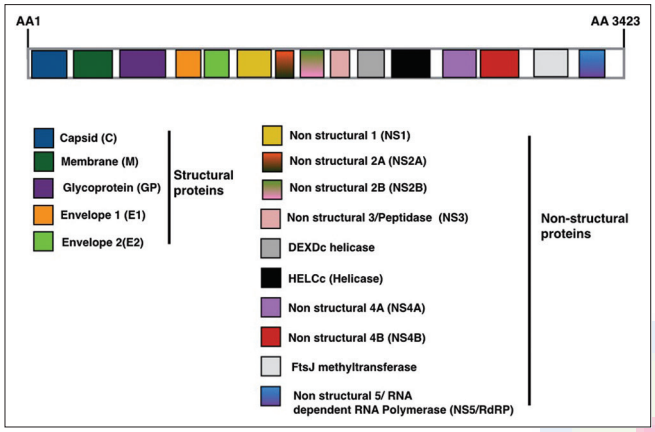

Figure 2: Structural and nonstructural protein of ZIKV

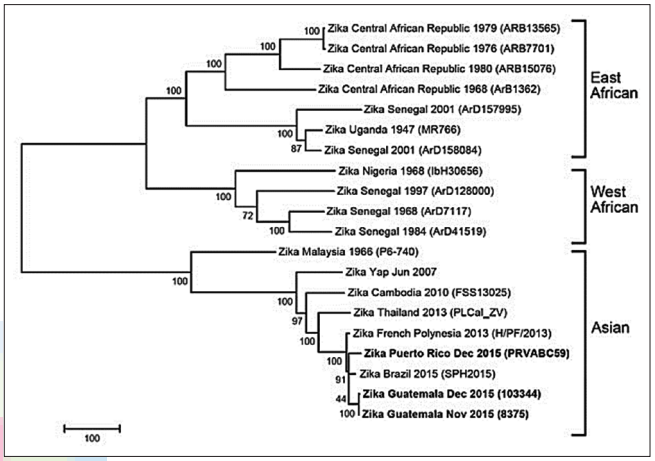

Figure 3: Phylogenetic tree of Zika virus isolates identified from Guatemala and Puerto Rico in December 2015 (indicated in boldface) compared with reference isolates obtained from GenBank. The isolates from Guatemala and Puerto Rico grouped with other Asian genotype viruses. The tree was derived by neighbor-joining methods (bootstrapped 1000 times) using complete genome sequences. Location, year identified, and GenBank strain identification for the viruses used in tree construction are shown. Scale bar indicates a number of nucleotide substitutions per site. GenBank accession numbers.: KU321639 (Brazil 2015 SPH 2015), KJ776791 (French Polynesia H/PF/2013), KF383115 (Central African Republic ARB1362), KF383116 (Senegal 1968 ArD7117), KF383117 (Senegal 1997 ArD128000), KF383118 (Senegal 2001 ArD157995), KF383119 (Senegal 2001 ArD158084), KF268948 (Central African Republic 1979 ARB13565), KF268949 (Central African Republic 1980 ARB15076), KF268950 (Central African Republic 1976 ARB7701), EU545988 (Yap 2007), KF993678 (Thailand 2013 PLCal_ZV), JN860885 (Cambodia 2010 FSS13025), HQ234499 (Malaysia 1966 P6-740), HQ234501 (Senegal 1984 ArD41519), HQ234500 (Nigeria 1968 IbH 30656), LC002520 (Uganda 1947 MR766), KU501215 (Puerto Rico PRVABC59), KU501216 (Guatemala 8375), and KU501217 (Guatemala 103344)

the vertebrate–mosquito cycle of arboviruses.[16] The population and size of monkeys have also influenced the rate of virus propagation while egg and adult ticks have also been established as sources of YF. All these act as a potential reservoir enhancing the vertebrate–mosquito life cycle ensuring the survival of arboviruses.[16]

Another major reservoir of ZIKV is monkeys. It can be recalled that the first ZIKV was isolated from a febrile sentinel monkey in Uganda during the 1947 YF outbreak.[1] The YF outbreak as described by Dick *et al*. in Uganda has revealed the two roles played by monkeys as host for arboviruses. First is that they act as an enzootic state and second as epizootics in both Zika forest in Western Uganda (Bwamba County) and Central Uganda zone of forest savannas.[1] Morens and Fauci described the enzootic state involved in the so-called enzootic mosquito–monkey–mosquito cycle.[17]

There are reports that anti-Zika antibodies have been observed in rodents in Pakistan and animals such as ourang-outang, zebras, and elephants, indicating the possibility of being reservoirs.[18,19] The 1972 Zika forest YF epizootic in Uganda showed that several closely related arbovirus antibodies were present in monkeys. These include chikungunya (CHIK), Wesselsbron (WESS), O'nyong-nyong, WN, YF, and ZIKV. These viruses had cross-reactivity; although the YFV was lethal to human, it was shown to be mild in monkeys in their sylvan natural habitat.[20,21]

The search is still ongoing for other potential ZIKV reservoirs. However, quick areas to look at are the reservoirs of Flavivirus as potential for ZIKV [Table 2].[95]

Table 2: Reservoirs of Flaviviruses as potential sources of Zika virus

Dengue virus	Japanese encephalitis virus	St. Louis encephalitis virus	Yellow fever virus	West Nile virus
Bats, guinea pigs, horse, mice, chipmunk, pig, rabbit, and Yucatan miniature pig	Monkeys, birds, pigs, cow, horse, and rodents	Armadillo, anteater, birds, opossum, raccoon, rodents, and squirrel	Bat, hedgehog, mongoose, monkey, opossum, rodents, kinkajou, wild dog, wild birds, and squirrel	Cat, horse, birds, alligator, rabbit, raccoon, deer, primates, rodents, reptiles, opossum, birds, and dog

There is also an indication that snakes are reservoirs for Eastern equine encephalitis virus in North America and this broadens the list of potential ZIKV reservoirs and other related viruses. This trend will lead to the understanding of additional reservoirs for Flaviviruses.[22]

MODES OF TRANSMISSION

ZIKV has been established as a human virus transmittable through mosquito–human–mosquito cycle, like other arboviruses such as dengue (DENV) and YFVs. The vector is acquired by hematophagous arthropods through their blood meal. The arthropod serves as a breeding host where the virus thrives for life and is only transferred to other hosts during subsequent blood meals.[8]

Active transmission to human has been tipped to be from daytime active-infected mosquito bites which are potential reservoirs. The virus has been isolated in species in the genus *Aedes*, such as *A. aegypti*, *Aedes albopictus,* and in arboreal mosquitoes such as *A. furcifer*, *Australopithecus africanus*, *Aedes luteocephalus*, *Aedes apicoargenteus*, *Aedes vitattus*, and *Aedes hensilli*. A 10 days' incubation period has also been identified with these vectors.[4]

Sexual transmission

There have been reports that ZIKV could be sexually transmitted among humans. In 2011, it was reported that a biologist might have sexually transferred the virus to his wife upon his arrival from mosquitoes' study in Senegal. Laboratory tests found Zika antibodies in both his and his wife's blood.[23,24] This report was further supported in a 2015 report by Musso *et al*., who found a high viral RNA load and replicative virus in the sperm and urine of the hematospermic patient, 2 weeks after clinical cure and clearance from his blood.[25] Another case of sexually transmitted ZIKV infection was reported in February 2016, at the Dallas County Health and Human Services department.[26]

Mother-to-child (prenatal) transmission

Vogel[27] and Calvet *et al*.[28] independently reported the detection of RNA of ZIKV in fetal amniotic fluid, an indication that it had crossed the placenta and possibly cause mother-to-child infection. Tetro also reported on the ZIKV outbreak in Brazil, in which the viral RNA was detected both in the mothers' and amniotic fluid samples from the fetuses. These reports suggest that ZIKV may have the potential to infect the fetus and potentially cause neurodevelopmental dysfunction, especially microcephaly.[29]

Calvet *et al*. also reported the first confirmed autochthonous instance of ZIKV infection in a human immunovirus (HIV)-infected patient in Rio de Janeiro, Brazil. The patient was observed to have developed minor signs followed by an episode of recovery without showing major laboratory abnormalities.[28] These findings indicate that ZIKV may interact with other known viral infections, which call for rapid assessment.

Occupational transmission

There has been a reported case of occupational transmission in the laboratory,[30] warning researchers and health workers to obey and take precautionary measures when handling suspected ZIKV and other related infected samples. Additional measure includes vaccinating laboratory staffs in health facilities.

Transmission by blood transfusion

In February 2016, the Brazilian health officials reported the infection of ZIKV from blood transfusion from an infected donor.[31] It will then be essential to screen blood samples for ZIKV before transfusion in reported areas of ZIKV outbreaks.

VIRAL INTERACTION AND CELLULAR TROPISM

To provide information on the receptors used to gain entry in addition to the cellular targets of the recent ZIKV isolate (similar to isolates of previous outbreaks) and to provide general insights into the interaction between ZIKV and its human host, Hamel *et al*. undertook an exploratory research. In their findings, ZIKV was shown to attack and infect skin fibroblasts, immature dendritic cells, epidermal keratinocytes, and this has been shown to be enhanced by the expression of dendritic cell-specific intracellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN) or a Greek word anexelekto, which means "uncontrolled" (AXL) and tyrosine protein kinase receptor 3 receptors. In contrast, the expression of T-cell Ig and mucin domain 1 (TIM-1) or TIM-4 proteins (members of the phosphatidylserine

receptors) had only minimal or negligible role on the entry of ZIKV.[32]

Viral ENV is the first line of action on entry into a host cell where it interacts with various receptors and attachment factors on the cell surface which determine the viral cellular tropism. Factors including laminin receptor, scavenger receptor class B, integrin αvβ3, prohibitin, claudin-1, heat shock proteins, and natural killer cell receptor have been shown to interact with the viral cells in mammals or mosquitoes with an obscure role and physiological significance.[33] Another nonspecific attachment factor for Flaviviruses is heparan sulfate which aggregates viral particles and aids viral entry into host cell by interacting with primary receptors including lectin C-type receptors (such as DC-SIGN, also called CD209), mannose receptor, and C-type lectin domain family 5 member A) as indicated by their roles in binding and infection of myeloid cells by Flaviviruses.[34-36]

The possibility of ZIKV to elicit specific innate immune response in infected cells (primary human fibroblasts) was determined by analyzing the antiviral gene expression profile at various time points post-ZIKV infection. The results revealed that ZIKV infection leads to the induction of pattern recognition receptors (PRRs) which can identify pathogen-associated molecular patterns (PAMPS). This is illustrated by the increased expression of toll-like receptor 3 (TLR3) messenger RNA and transcription of dead (Asp-Glu-Ala-Asp) box polypeptide 58 (retinoic acid-inducible gene 1) and melanoma differentiation-associated protein 5 genes supposedly used in the recognition of other members of the Flavivirus family.[37,38] Recognition of this viral PAMPS by TLR3 and other PRRs also initiates a cascade of signaling pathways resulting in an enhanced transcription of factors known to assemble antiviral machinery. This cascade includes improved expression of interferon-α (IFN-α) and IFN-β gene, upregulated expression of various IFN-stimulated genes (ISGs) such as oligoadenylate synthetase 2, interferon-induced GTP-binding protein, and ISG15, as well as the expression of chemokine (C-X-C motif) ligand 10, a ligand for chemokine receptor CXCR3, and inducement of inflammatory antiviral chemokine CCL5. Skin fibroblast infection with ZIKV was also found to initiate a number of inflammasome components as proved by an increased expression of absent in melanoma 2 and interleukin-1 β transcripts.

It was also observed that a combination of anti-TIM-1 and anti-AXL antibodies totally repealed ZIKV infection. This is further confirmed by the results obtained when both TIM-1 and AXL RNAs were silenced leading to the downregulation of expression of both receptors. Furthermore, the presence of AXL small interfering RNA completely inhibited AXL expression and thus repealing the viral infection. It was later reported that TIM-1 serves as an attachment factor which aggregates viral particles on cell surface while AXL could participate in internalizing the aggregated viral particles. In contrast, inhibition of TLR3 expression resulted in an upsurge in the viral RNA copy number 48 h after infecting the cells with the virus, indicating the significance of TLR3 in inducing an antiviral response against the ZIKV virus. It was also shown that types I and II IFNs inhibited ZIKV replication in a dose-dependent manner as shown by reduced discharge of viral particles when measured by plaque assay. This shows that the virus is very sensitive to the antiviral effect of these IFNs.

ZIKV replication was also shown to increase as a result of autophagosome formed in infected skin fibroblast cells. This is corroborated by the observation of several double-membrane intracytoplasmic vacuoles typical of autophagosomes. Furthermore, ZIKV infection resulted in the formation of an autophagosome-specific marker, cytosolic microtubule-associated light chain 3 colocalized with that of the viral ENV. Finally, there are speculations that ZIKV induces apoptotic cell death which diverts antiviral immune response through enhancing the release of immunity cells from the dying cells as observed in other Flaviviruses such as DENV virus (DNV) and WESS virus.[38,39]

Pathological properties of Zika include viral tropism to the brain and an increased viral titer over many days in intraperitoneally infected mice as shown by Dick *et al*., a finding suggesting that ZIKV can cross the blood–brain barrier.[1] To corroborate this finding, Bell *et al*. reported the viral infection of the neurons and glia-producing intracytoplasmic inclusions referred to as virus factories, which originated from endoplasmic reticulum alongside mitochondria and nucleus of infected mice brain.[40] These intracytoplasmic inclusions are meant to ensure the elimination of unwanted cellular material from the brain. However, depending on viral regulatory mechanisms, its efficacy varies.[41] This mechanism is what makes Flaviviruses escape autophagy, thus ensuring viral replication and amplification.[42]

Signs of infection/clinical presentation

ZIKV infection in humans starts following a bite from an infected mosquito with an incubation period of about 3–12 days. Reports have shown that ZIKA fever has nonspecific clinical symptoms. However, the most common presenting signs include fever, arthralgia, myalgia, rash, conjunctivitis, and asthenia.[8] Other indications include lymphadenopathy, edema, retro-orbital pain, and diarrhea. The virus manifestation could also mimic influenza infection leading to its underreporting. Furthermore, these symptoms are often confused with DENV fever which further

complicates its diagnosis. Some researchers revealed that there are reports of asymptomatic cases of infection.[7,10] There is no specific date of clinical onset, and the beginning of the illness is usually subjective.[43]

Table 3 (Modified from Yap state Department of Health Services presentation, Micronesia.[96]) shows the clinical presentation of ZIKV and its similarity to those of other arboviruses including DENV and CHIK, thereby making precise diagnosis difficult.[8]

There are limited reports on the specific human laboratory alterations; however, the observed alterations include thrombocytopenia and leukopenia. In addition, there are elevated levels of gamma-glutamyl transferase, serum lactate dehydrogenase, and inflammatory parameters (C-reactive protein fibrinogen and ferritin).[44,45]

CONGENITAL MALFORMATIONS AND OTHER NEUROLOGICAL COMPLICATIONS ASSOCIATED WITH ZIKV

In late 2015, the Brazil International Health Regulations National Focal Point reported an estimated 20-fold increase in the occurrence of congenital microcephaly mainly from the Zika-endemic Northeastern region.[46] Similar reports were received from the French Polynesian Health authorities who observed a simultaneous rise in congenital central nervous system deformities with ZIKV infection.[47] Furthermore, Oliveira Melo *et al*. observed ZIKV RNA in the amniotic fluid of two pregnant mothers of microcephalic children.[48] This may be pointing to the fact that ZIKV can possibly infect fetuses which can result in neurodevelopmental dysfunction such as microcephaly.[29]

The previous reports and results of epidemiological studies have linked the occurrence of neurological and autoimmune complications such as congenital microcephaly and GBS with ZIKV infection.[47] GBS, a weakness or paralysis due to an immune attack on the peripheral nervous system, has been associated with ZIKV infection just as it has been linked to other infections. On the other hand, microcephaly which has not been previously associated with flaviviral infection has now been thought to be linked to ZIKV infection, possibly due to the teratogenic effect of the virus rather than immune response. However, a firm link between the two has not been established[27,47,49] and currently, the US CDC is working together with public health officers to ascertain whether a link exists between the viral infection and the rare neurological disorder.[50] Furthermore, ventriculomegaly, abnormalities in cell migration, and congenital contractures arising from the involvement of central or peripheral nervous system have also been reported in brains of fetuses of ZIKV-infected mothers.[48,51,52]

Table 3: Clinical presentation of Zika virus and related Flaviviruses

Symptoms	Dengue	Chikungunya	Zika
Fever	4	3	3
Myalgia/arthralgia	3	4	2
Edema of extremities	0	0	2
Maculopapular rash	4	2	3
Retro-orbital pain	2	1	2
Conjunctivitis	0	1	3
Lymphadenopathies	2	3	1
Hepatomegaly	0	3	0
Leukopenia/thrombopenia	3	3	0
Hemorrhage	1	0	0

Sources: *Numbers indicates severity of symptoms (Scale: 1-10)

On February 01, 2016, owing to the rapid spread of ZIKV with the associated cases of microcephaly, GBS, and other neurological disorders (acute disseminated encephalomyelitis), the disease was declared as a Public Health Emergency of International Concern. This declaration is the 4th of such infectious disease declaration by the WHO since 2007.[53]

AVAILABLE DIAGNOSIS OF THE ZIKV INFECTION IN ALL BIOLOGICAL SAMPLES

The routine laboratory diagnosis of Zika fever is somewhat complicated. In addition, cross-reactivity of antibodies exists between Flaviviruses leading to the wrong diagnosis for another arbovirus.[54]

To properly diagnose ZIKV infection, the differential diagnosis has to be employed including other arboviral diseases including malaria and with clinical presentations as fever, arthralgia, headache, rash, hemorrhagic fevers, encephalitis, and meningitis.[10] The cross-reactivity of antibodies between Flaviviruses and the low rate of release of IgM and IgG during the early phase of infection may hinder the use of serology for prompt diagnosis.[4] Thus, a confirmatory seroneutralization assay such as plaque reduction neutralization test should be carried out to ascertain the specificity of the observed antibodies.[4]

Sequentially, the techniques of diagnosing the virus should include the following:

- Real-time polymerase chain reaction (RT-PCR) and viral RNA isolation in blood samples <5 days postsymptom onset
- Utilization of pan-Flavivirus technique together with sequencing[4,11,44]

- RT-PCR detection of viral RNA in urine if it is no longer detected in the serum[4,11,55]
- Serological tests such as Elisa developed in 2007 by the CDC in Atlanta, which specifically detects an anti-Zika IgM.[56]

Recently, Moulin *et al*.[3] developed an algorithm for the detection of Zika infection in travelers who returned with nonspecific febrile illness from areas with concurrent epidemics of DENV, CHIK, and ZIKV infections as shown in Figure 4.[3]

Aside from using blood samples for diagnosis, detection of ZIKV has also been reported in saliva,[25] urine,[43] and semen.[57]

CHALLENGES FACED BY HEALTH WORKERS IN WORKING WITH THE VIRUS

Health workers and doctors are faced with a huge challenge because the specific diagnosis of the ZIKV is difficult due to the presence of related viruses (Flaviviruses and arboviruses), with different pathogenicity. Olson *et al*. reported the presence of other arboviruses in the outbreak of ZIKV in Indonesia.[58] A similar trend of the presence of additional arboviruses (WN, YF, and WESS) in conjunction with ZIKV was also reported by Fagbami[19] in a study conducted in Nigeria. Furthermore, other viruses that have been found in conjunction with ZIKV include CHIK, Koutango, Bunyamwera, Sindbis, DENV types 1 and 2 which were isolated from Gabon and Senegal[59,60] in.[10]

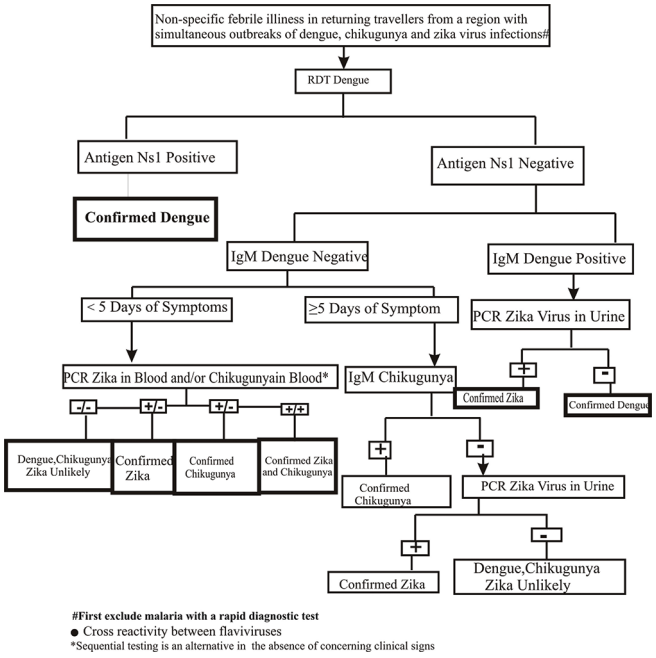

Figure 4: A diagnostic algorithm for travelers with nonspecific febrile illness returning from regions experiencing simultaneous outbreaks of dengue, chikungunya, and Zika virus infections. RDT: rapid diagnostic test

Prompt and proper diagnosis of this ZIKV poses a serious challenge in the health sector, particularly in poor nations with little or no experienced personnel as well as advanced diagnostic equipment. The watch is on, and everyone is expected to be proactive.

MANAGEMENT/PREVENTIVE APPROACHES

There is currently no specific vaccine or treatment for ZIKV. The only solution at present is strict adherence to all preventive measures, most especially preventing bites from a mosquito. Other approaches include fumigation, use of mosquito nets, use of appropriate and approved insecticides, and staying in screened or air-conditioned rooms. In summary, management of the Zika fever involves treatment of symptoms. This could be combined with the administration of acetaminophen and antihistaminic drugs.[8] Wahab *et al*. suggested that the best way to keep out mosquito-borne infection is to eradicate their larvae since the larvae are relatively restricted and concentrated in their habitat and can easily be killed using safe natural larvicidal agents isolated from botanicals.[61] Choffnes *et al*. also suggested the use of a genetically modified sterile strain of insects.[62] Another novel approach was described by Darbro *et al*., involving the use of *Beauveria bassiana*, a fungus capable of reducing the longevity and fecundity of *A. aegypti*.[63]

On the other hand, dwellers of areas where ZIKV has been shown to be endemic often show some immunity against the virus. For example, Fagbami suggested cross-resistance in ZIKV in Nigeria as well as the suppression of the prevalence of other Flaviviruses.[19] Finally, it is advisable for people to observe prevention of sexually transmitted diseases (of which ZIKV has been included) through sex education, abstinence, and safe sex practice, for example, use of a condom, proper disposal of sharp objects and sterilization of indisposable medical equipment, and strict adherence to standard hygiene and contact precautions.

CURRENT AND PROPOSED GENETIC STRATEGIES FOR ZIKA VECTOR CONTROL

Scientists need to develop a new approach to fight the scourge of evolving deadly viruses including ZIKV. Such approaches should be strategic and fast with a long-lasting result if the fight against ZIKV and other related viruses is to be won. Some of such approaches could include the following:

i. The release of insects carrying dominant lethal genes which involve rearing of genetically altered mosquitoes

that express the repressible lethal gene.[64] This is done by feeding the insects an unnatural dietary supplement such as tetracycline which represses lethal gene activation. Upon release, these genetically modified mosquitoes compete with the wild type, mate with the females, and the resulting offspring die before adult stage as they did not receive the supplement in the wild. This has been proved successful in Brazil[65,66]

ii. Walker *et al*. reported the discovery of an endosymbiotic bacterial strain wMel of *Wolbachia* genus that infects insects and prevents replication of arboviruses within the vector, thereby blocking DNV transmission,[67] which has since been introduced into natural populations of the mosquito vectors with success.[68,69] Similar models should also be tested for ZIKV as is currently done in DENV

iii. Use of the gene drive, a genetic manipulation approach that involves transferring DNA that is genetically modified to offspring as diploid unlike the haploid of natural reproduction. This method can ensure the alteration of the mosquito genome and thus render them ZIKV resistant[66]

iv. Manipulation of mosquito genome: In many insects, M factor located on the Y-chromosome determines their sex.[70] In mosquitoes, only adult females feed on blood and transmit pathogens that cause DENV, YF, and possibly other fevers.[71,72] Therefore, mosquitoes' M factor can be manipulated in converting females into males which are harmless, thus achieving a good vector control.[72] Hall *et al*. in 2015 developed a method that led to the identification and naming of a gene *Nix*, which they hypothesized to function as M factor in *A. aegypti*.[73] The *Nix* cDNA is a 985 bp encoding a polypeptide of 288 amino acids with two RNA recognition motifs (GenBank KF7328822). They proved that *Nix* gene is required and sufficient for the initiation of male development as it encodes a splicing factor whose absence shifts alternative splicing of dsx and fru toward female isoforms. Thus, introducing this *Nix* gene into female mosquitoes can produce biased females[73]

v. Another area worth exploring is the potential of genetic redundancy, which entails modifying the genetic composition of the receptors used by the virus to gain entry into its host. This prevents the virus from gaining entry, and the functions of the modified gene are partly or fully compensated by one or more genes as explained by Uba *et al*., 2015, for HIV CCR5 gene[74]

vi. Finally, as Zika closely resembles DENV and WNVs whose vaccine development are already underway, the possibility of altering their scope to cover the recent ZIKV should be exploited.[66] Furthermore, for the development of therapeutics, it is imperative to explore the modality through which neutralizing antibodies have blocked the viral infection as this provides an Achilles heel and a potential target in the viral life cycle.

ECONOMIC LOSSES BY ZIKA VIRUS OUTBREAK

The precise economic losses of the recent ZIKV outbreak are somewhat difficult to calculate owing to the precarious state of the health systems of severely hit poor nations. However, an estimate of the global economic loss was compared to the 2013 DENV fever outbreak, in which a total of $8.9 billion dollars was estimated.[75] In addition, the WHO also estimated that the recent ZIKV outbreak poses an economic burden of about $3.5 billion dollars (or 0.06% of the GDP) on Latin America and the Caribbean alone. These figures were estimated as of February 2016, and the estimated values are expected to be higher should other medical conditions be linked to ZIKV infection as well as a high change in public perception of ZIKV risk.[76]

Funding committed to the fight against Zika virus outbreak

There is a need for swift mobilization of resources to fight the current ZIKV spread. It is interesting to know that huge sums of money have been announced by different agencies to curtail and fight ZIKV infection. Details of funding are shown in Table 4 (Blumenthal,[79] CDC,[97] and World Bank Group.[98] WHO = World Health).

SUGGESTED PREPAREDNESS OF COUNTRIES AGAINST ANY DEADLY DISEASE OUTBREAKS SUCH AS ZIKA AND EBOLA

ZIKV infection poses ethical challenges such as its association with the development of congenital malformations in children of infected mothers which, despite emerging knowledge and discoveries, is faced with uncertainties and diagnostic challenges.[77] Other persistent problems include lack of catalyzing research during emergencies, dearth of prominent research activities such as simple protocols for obtaining consent for research during outbreaks, prompt data collection and sharing, and lack of efficient communications during emergencies.[77] This calls for countries to be prepared and fashion out ways to address these challenges even before such outbreaks. This can be achieved by reinvigorating their (countries) commitment to incorporate ethics in health care and strengthen their preparedness response for epidemics.[78]

Furthermore, Zika pandemic calls for drastic approaches toward prevention and communal health preparedness in alleviating the spread of disease and promoting global

Table 4: Funds pledged by different agencies in the fight against Zika virus outbreak

Organization	Fund pledged/comment
The WHO	$56 million dollars was announced to help fund the "Global Strategic Response Framework and Joint Operations Plan." Only $6.4 million dollars of this fund was allocated for research
The World bank	$150 million dollars was pledged toward the international response to ZIKV which include identifying at-risk individual (pregnant women and women of reproductive age), provision of improved medical care to pregnant women including postnatal care for neurological complication, creation of improved program for public awareness, vector surveillance and control, promotion of access to family planning, self-protection measures, creation of highly coordinated activities for multi-sectorial response to ZIKV spread
The CDC	$60 million dollars was awarded to states, cities, and territories to battle ZIKV. Funding is expected to support activities that would protect the health of pregnant women, improved mosquito control and monitoring, epidemiologic surveillance and investigation, as well as strengthening laboratory capacity toward ZIKV eradication
The Canadian government	The Canadian government announced a $5 million dollars to fight ZIKV. It is expected that $3 million dollars will be invested in research, development of improved diagnostic test, study of ZIKV transmission and prevention, as well as effective mosquito control $950,000 will be channeled to the public health agency and to the PAHO while the final $1 million dollars will be given to international organizations (WHO, PAHO, UNICEF, International Federation of Red Cross, and Red Crescent)
The US government	An initial $1.86 billion dollars was requested by the US government to fight ZIKV epidemic. The government also redirected $589 million from the unspent fund meant to fight the recent Ebola virus toward the fight of ZIKV. About $47 million dollars is expected to go to the NIAID for ZIKV research

Organization, CDC=Centers for Disease Control and Prevention, PAHO=Pan American Health Organization, UNICEF=United Nations Children's Emergency Fund, ZIKV=Zika virus, NIAID=National Institute of Allergy and Infectious Diseases

health. It is high time countries commit the necessary resources to ensure preparedness against any pandemic as advances and discoveries from such research investments hold promise to effective treatments and possible vaccines for various infectious diseases such as Zika and Ebola now and in future. Meanwhile coordination, collaboration, and effective communication across societies and countries are the basis of effective preparedness to prevent disease spread. Some recommended pandemic preparedness for countries include the following:

- Coordination of a resilient global health system infrastructure, personnel, and resources:
  This should include the commitment of funds, the appointment of coordinators as well as the development of an emergency response infrastructure (including emergency response teams of medical care providers, lab technicians, and public health personnel) to effectively ensure prevention, detection, and rapid response to any possible outbreak even before it become pandemics. Local experts, civil society groups, and affected populace should be involved in planning and implementation of the masterpiece to be adopted during any outbreak (Susan *et al*., 2016)
  It is ideal to adopt formerly America's way of curving Ebola outbreaks and now Brazil's strategy against ZIKV outbreaks which include deployment of military personnel and public officials to organize and mobilize supplies, coordinate surveillance activities, construct infirmaries, supervise communal efforts, and establish emergency response operations centers
- Invest more in research: Without adequate knowledge in disease–host interaction, the prevention and eradication of disease outbreak will be difficult. There is a need for more research in pathogenesis, postinfection immunoresponse, disease–host interaction, and other complications associated with disease infection. The current ZIKV outbreak requires an additional knowledge in areas such as its effect on fetal brain development and neurological complications in children and adults. In addition, it is of high priority to understand the rate of perinatal transmission and its effect in the three trimesters of pregnancy during fetal development. Therefore, investments should be made toward such infectious diseases and discovery of vaccines and antiviral treatments to avert economic losses to be incurred while caring for microcephaly, GBS, and other congenital abnormalities associated with Zika and other possible future outbreaks.

Furthermore, information obtained from such research should be shared across the globe as they will help in the development of more accurate and faster diagnosis, vaccine, and antiviral drug development.

Other measures to be considered as recommended by Blumenthal[79] include the following:

- Fast clinical response which should include the proper management of disease symptoms since the ZIKV or other new infections usually do not have a cure as at the time of their outbreak
- Early disease detection and increased surveillance through widespread public awareness and use of early diagnostic detection techniques
- Application of social media and innovative information and communication technology platforms for preparedness against pandemics. Innovative mobile phone technology, website, mobile app, and social media could serve as a great information hub for epidemic preparedness. Instantaneous sharing of information which aids in disease surveillance, prevention, and treatment approaches to any current epidemic disease could be shared across countries with the ability to translate into different languages
- Effective vector control and eradication with recent biotechnological techniques, for example, gene drive technology
- Building and empowering a resilient health-care system

- Fast tracking of vaccine and antiviral development through targeting the viral vulnerabilities
- Proper risk communication across the board.

Sustainable development goal (3) for emergency preparedness

In the year 2000, representatives from 189 United Nations member states created 8 Millennium Development Goals to be realized by 2015 and declared their collective commitment to poverty reduction and improved quality of life. The realization of the Sustainable Development Goals (SDGs) is an important tool for emergency preparedness. Since 1976, emergent infectious disease outbreaks ranging from HIV/AIDS, SARS, H1N1, Ebola, MERS, and WN encephalitis have occurred accounting for a significant percentage of global human deaths yearly.[80] Apart from causing health implications and even death, infectious disease outbreaks also create significant socioeconomic impacts that largely affects education, business, and travel.[81] Thus, SDGs can be achieved through implementation of family planning strategies which among other things lead to poverty alleviation, enhanced nutritional status, saving lives, and prevention of transmission of deadly diseases such as HIV/AIDS and ZIKV.[82]

The disturbing cases of GBS, microcephaly, and other congenital defects in infants reiterate the urgency to fight the Zika outbreak with appropriate resources now. It is thus imperative for the SDG to strengthen its commitment to the implementation of health-care objectives (goal 3) of the fund and the fight against climate change (goal 13) and to ensure the inclusion of a dedicated reserve for an emergency response against infectious disease outbreaks.

CONCLUSION AND FUTURE PROSPECTS

We need to be reminded as humans that the most important race in life is the human race; therefore, all our efforts and expertise must be collectively harnessed and utilized if we need to overcome the scourge of viral outbreaks. It is important to know that this is not the time to play politics with lives for personal gains. Collaborative efforts from advanced countries in tackling this disease will set the pace. Training and personnel assistance to less advanced countries (mostly in Africa) in dealing with such outbreak should be speedily sponsored. In addition, the government of countries hosting religious or sports events in conjunction with health ministries must be proactive to curtail any imported case or spread of this virus before during or after hosting any event.

ZIKV has been known since 1947, its recent sporadic outbreaks in 2007 in Micronesia, and 2013–2014 in Brazil which could be that the less virulent strain has undergone mutation and we could be toying with a monster that may be difficult to tame. If we can eradicate polio, measles, and other (once upon a time life threatening) viral infections, we can do more to stop ZIKV and related arbo/Flaviviruses.

On a final note, ZIKV outbreak should awaken us that with hope, we will surely curtail and control the spread and threat of this virus. Not long ago was the deadly Ebola virus, but when we work as a global nation with concerted efforts and a single goal (to save the human race), we always get the chance to save our own kind. It is important to establish a coordinated rapid response for the surveillance of ZIKV and other related viral outbreaks. Only until then do we see the light of hope.

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Conflicts of interest

There are no conflicts of interest.

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