The Emergence of Zika Virus as a Global Health Security Threat: A Review and a Consensus Statement of the INDUSEM Joint Working Group (JWG)

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ABSTRACT

The Zika virus (ZIKV), first discovered in 1947, has emerged as a global public health threat over the last decade, with the accelerated geographic spread of the virus noted during the last 5 years. The World Health Organization (WHO) predicts that millions of cases of ZIKV are likely to occur in the Americas during the next 12 months. These projections, in conjunction with suspected Zika-associated increase in newborn microcephaly cases, prompted WHO to declare public health emergency of international concern. ZIKV-associated illness is characterized by an incubation period of 3-12 days. Most patients remain asymptomatic (i.e., ~80%) after contracting the virus. When symptomatic, clinical presentation is usually mild and consists of a self-limiting febrile illness that lasts approximately 2-7 days. Among common clinical manifestations are fever, arthralgia, conjunctivitis, myalgia, headache, and maculopapular rash. Hospitalization and complication rates are low, with fatalities being extremely rare. Newborn microcephaly, the most devastating and insidious complication associated with the ZIKV, has been described in the offspring of women who became infected while pregnant. Much remains to be elucidated about the timing of ZIKV infection in the context of the temporal progression of pregnancy, the corresponding *in utero* fetal development stage(s), and the risk of microcephaly. Without further knowledge of the pathophysiology involved, the true risk of ZIKV to the unborn remains difficult to quantify and remediate. Accurate, portable, and inexpensive point-of-care testing is required to better identify cases and manage the current and future outbreaks of ZIKV, including optimization of preventive approaches and the identification of more effective risk reduction strategies. In addition, much more work needs to be done to produce an effective vaccine. Given the rapid geographic spread of ZIKV in recent years, a coordinated local, regional, and global effort is needed to generate sufficient resources and political traction to effectively halt and contain further expansion of the current outbreak.

Key words: Arbovirus, Flavivirus, Global health security, Public health emergency of international concern, Public health, Viral vector control, Zika virus

INTRODUCTION

The Zika virus (ZIKV) is a mosquito-borne *Flavivirus* that is named after the Ugandan forest where it was first isolated from a rhesus monkey in 1947.[1-3] ZIKV has

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become more of a global threat over the past decade because of its relentless spread, first to the Asia-Pacific region, followed by its rapid entry into the Western hemisphere.[3-9] ZIKV is related to other flaviviruses including dengue, West Nile, and Japanese encephalitis.[8,10] The first major outbreak outside of Africa occurred in 2007 in the Yap Islands of Micronesia,[4] with another large outbreak in 2013 in French Polynesia.[11]

In addition to the concerns over its rapid geographic spread, ZIKV has received much attention from public health officials because of its highly suspected association with maternal-fetal transmission and related newborn microcephaly (as well as other neurological abnormalities).[12-14] The rapid increase in the incidence of microcephaly during the virus' recent geographic expansion has caused the United States Centers for Disease Control and Prevention (CDC) to advise pregnant women to consider postponing travel to any area where ZIKV transmission is ongoing.[12-14] The areas of concern for ZIKV include Barbados, Bolivia, Brazil, Cape Verde, Chile, Colombia, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Haiti, Honduras, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin and Guyana, Venezuela, as well as Samoa in the South Pacific.[3-6,15] In a recent statement, the World Health Organization (WHO) confirms that ZIKV is "spreading explosively" and that the associated level of concern is "extremely high."[16] This was followed by the declaration (February 2, 2016) of public health emergency of international concern (PHEIC) around the current outbreak.[17]

This statement by the Indo-US Joint Working Group (JWG) will review the recent spotlight on ZIKV and its evolution from a relatively geographically isolated virus to a rapidly spreading, dynamically evolving global public health threat. In addition to providing an overview of the fundamental characteristics of ZIKV, we will also focus on areas of immediate need, including more clinical research (especially in the context of ZIKV-associated birth defects), accurate point-of-care testing (POCT), vaccine development, as well as more effective vector management and reduction of viral transmission.

ABBREVIATIONS, DEFINITIONS, AND GLOSSARY OF TERMS

Based on previous reports, the authors of this review wish to maintain consistency within the nomenclature referring to the Zika virus. Consequently, we will utilize the abbreviation "ZIKV" when referring to the virus.[18] With regards to the viral genetic material, we will refer to the ribonucleic acid as "RNA." In cases of emergent infectious diseases, a Public Health Emergency of International Concern (PHEIC) may be declared by the WHO.[19] The Pan American Health Organization (PAHO) helps coordinate public health efforts across all regions of the American continents.[20] When referring to point-of-care testing, the abbreviation "POCT" will be utilized. Finally, the United States Centers for Disease Control and Prevention will be referred to as the "CDC."

HISTORICAL PERSPECTIVE: FROM 1947 TO 2016

Over the years, the ZIKV has evolved from a little-known virus to a global health security threat. It was named after the Zika forest near Entebbe, Uganda[2,21] and was first identified in the late 1940s from the serum of a febrile rhesus macaque (known as "Rhesus 766").[2,18] The serum was subsequently inoculated into mice, followed by successful isolation of a viral agent (ZIKV) from brains of the inoculated animals.[2,18] Shortly after this discovery, ZIKV was isolated from *Aedes africanus* mosquitoes inhabiting the Zika forest.[3,22] Subsequent research indicated that *Aedes aegypti* was also capable of transmitting ZIKV to both monkeys and mice,[23] leading to further suspicion that the virus could potentially infect humans.[1]

Between the early 1950s and the 1980s, an increasing amount of evidence pointed to human illness associated with ZIKV transmission events.[24,25] Human ZIKV infection produces nonspecific signs and symptoms, often leading to a clinical presentation similar to that of dengue fever.[24,25] More severe presentations have also been reported.[11] Although not generally considered "primary hosts" for ZIKV, some consider humans as "occasional hosts" for the virus.[26] The geographic distribution of reported cases and outbreaks has expanded over time,[3-6] with human ZIKV infections reported in Nigeria (1971-1975),[5] Micronesia (2007),[4] Cambodia (2010),[6] Thailand (2012-2014),[9] French Polynesia (2013),[11] and Brazil (2016)[7,8] [Figure 1].

It is now evident that ZIKV has successfully spread outside of Africa and Asia — the two primary regions to which the virus was originally confined.[25] Recent concerns regarding global ZIKV spread are due to its rapid geographic expansion from Brazil (and other South American and Mesoamerican countries)[8,27] to the United States (Texas and Hawaii).[28,29] The discovery of ZIKV cases in Brazil raises concerns about the potential dangers of infestation by *Aedes* (*Stegomyia*) mosquitoes.[8] Moreover, the risk of ZIKV adaptation to life cycles based in densely populated

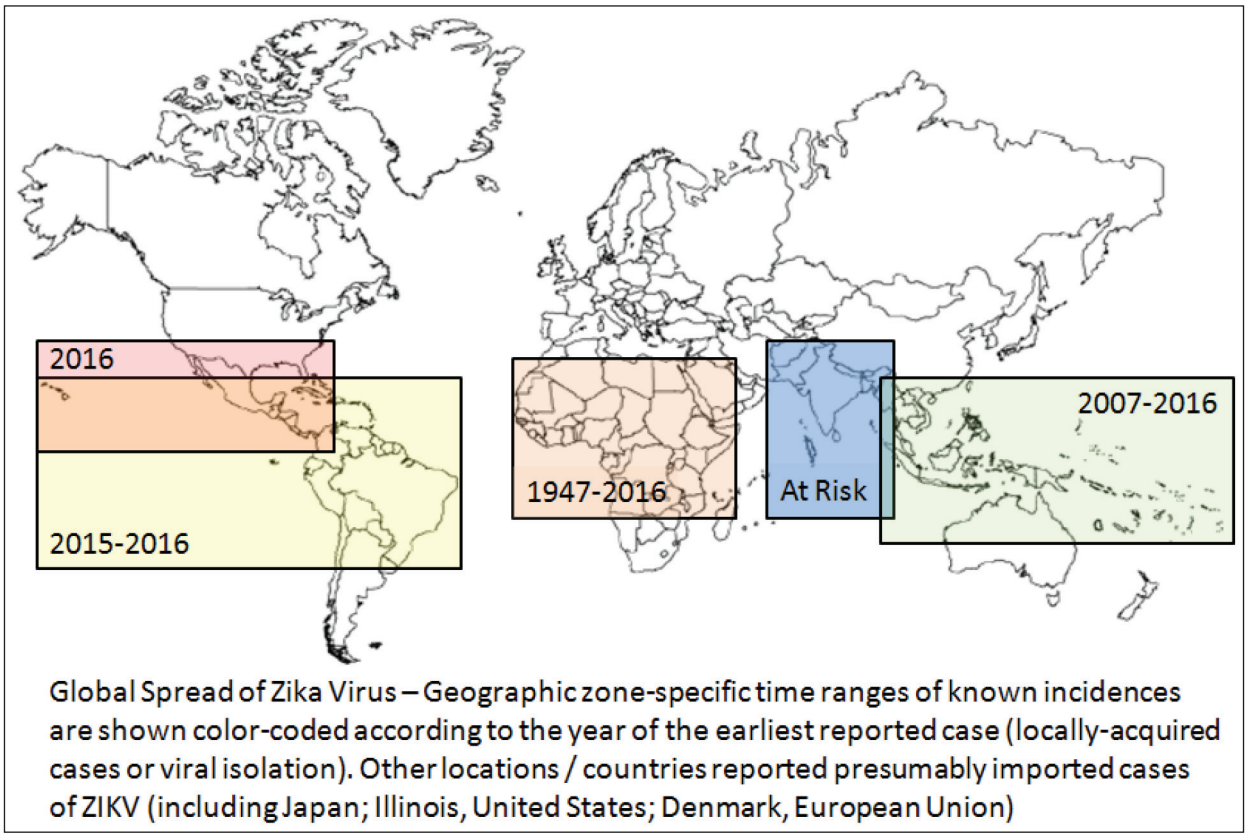

Figure 1: A schematic reconstruction of the geographic spread of the Zika virus. Note the temporal sequence of observed outbreaks, beginning with the initial events outside of Africa (e.g., Asia and Oceania) and ending with the most recent reports (e.g., South America, Mesoamerica and Southern United States)[1-17]

urban environments, coupled with human transmission/amplification via *A. aegypti* and other *Stegomyia* subgenus mosquito vectors, certainly poses a significant (local and global) health security threat.[25,30] Figure 1 depicts the geographic spread of ZIKV over the years.

VIROLOGY

ZIKV belongs to the *Flavivirus* genus;[31,32] one of four genera of the *Flaviviridae* family[33] of viruses, of which there are many and diverse species. Viruses in the *Flavivirus* genus are further subdivided into groups, such as the yellow fever group, the dengue virus group and the Spondweni serocomplex to which ZIKV belongs.[32] Currently, this classification scheme is based on nucleotide sequence analysis of viral genomes. The molecular evolution of ZIKV in the 20th century has been studied using sequence analysis of Zika obtained from mosquitos, humans, and other mammals in Africa.[26] All viruses belonging to the *Flaviviridae*, including the better known yellow fever, West Nile, dengue, and Japanese encephalitis viruses, possess an infectious viral particle (virion) that has an outer lipid membrane in which are embedded the viral envelope protein (E) and membrane protein (M).[31,33-35] The virion contains an icosahedral nucleocapsid of around 50-60 nm.[31,33-35] This is composed of the capsid protein (C), and a genome consisting of a single strand of positive-sense RNA of approximately 11,000-12,000 bases that serves both as a genome and a messenger RNA.[36] The virion attaches via the E protein to a receptor on the cell targeted for infection. The virion is brought into the cell by a process called clathrin-mediated endocytosis, which causes the envelope to be removed, the nucleocapsid to be disrupted, and the genome released into the cytoplasm.[37,38] The genome is translated by the host cell's translational apparatus into a single polyprotein that is proteolytically cleaved into the individual viral proteins: PreM, C and nonstructural proteins NS1 to NS5.[39,40] Some of these proteins form the RNA replication machinery, which causes the production of more genomes by using the negative-sense RNA copy of the viral genome as a template. The genomes are then assembled into nucleocapsids by interaction with capsid protein (C), and the nucleocapsids become enveloped during the budding process that releases them from the cell as infectious virions.[31,33,34,36]

Most viruses belonging to the *Flavivirus* genus are arboviruses or arthropod-borne viruses because they replicate in, and

are transmitted by mosquitoes [Figure 2].[41] Other viruses that are classified in the *Flaviviridae*, such as human hepatitis C virus (member of *Hepacivirus* genus), do not involve the mosquito vector and are transmitted directly from human to human.[42] In this context, the ZIKV E protein inteacts with receptors present on mosquito and on mammalian cells, as well as use their cellular machinery to enter cells, produce viral proteins and RNA, followed by the generation of progeny virions.[35] With ZIKV, as with all arboviruses, an infected blood-feeding female mosquito (e.g., chiefly a species of *Aedes* genus), injects the virions into the skin of a human, followed by infection of cells in the dermis and epidermis (e.g., dermal fibroblasts, epidermal keratinocytes, immature dendritic cells).[35] From there the virus spreads to the lymph nodes where an immune reaction is initiated at the same time the virus is replicating and causing a viremia. The ability of ZIKV, if independently confirmed, to cross the placenta of pregnant women and affect the fetus, would make it very unique from other arboviruses.[43] The highly suspected association between microcephaly and the rapid increase in ZIKV cases during the current outbreak has contributed to the virus' notoriety and is one of the key reasons behind ongoing global containment efforts. Without firm evidence showing cause-and-effect relationship, the association between ZIKV and newborn microcephaly remains to be independently confirmed and verified.[17,44] In some ways, concerns over ZIKV are reminiscent of previous experiences with the rubella virus, which before the advent of rubella vaccination produced severe congenital developmental abnormalities in newborns.[45,46] Another feature of flaviviruses that has to be considered in the current context is the ability of some (e.g., the Modoc virus — an "outlier" virus classified in the *Flavivirus* genus but not believed to be an arbovirus) to cause persistent infection.[47] If ZIKV developed the ability to cause persistent infections and spread human-to-human, the public health community would have to face an entirely new level of situational complexity.

CLINICAL PRESENTATION AND DIAGNOSIS

Symptoms and signs of ZIKV infection usually occur 3-12 days after the mosquito-vector bite and resolve within 2-7 days.[48] Although asymptomatic infection is common, approximately 20% of infected humans with ZIKV become symptomatic with the acute onset of a fever, maculopapular rash, conjunctivitis (and other ophthalmologic manifestations), and arthralgias. The disease is usually mild and lasts up to 1 week. Unlike the Ebola virus, mortality is low and hospitalization is infrequent.[49,50]

The patient's clinical presentation (signs and symptoms are similar to those seen in other mosquito-borne viral infections such as dengue and chikungunya), coupled with the appropriate travel history, should guide the clinician to suspect ZIKV infection. Although ZIKV transmission occurs predominately via mosquito vectors, other modes of transmission have also been proposed, including blood transfusion and sexual intercourse [Figure 2].[17,51]

While the clinical differential diagnosis is not specific, diagnostic testing can be accurate after the 7th day of disease by performing a reversed transcriptase-polymerase chain reaction (RT-PCR) on the serum.[10,52] Furthermore, virus-specific immunoglobulin M (IgM) and neutralizing antibodies are detectable after 7 days of illness, but they are not specific, and there may be cross-reaction with dengue virus and yellow fever virus (YFV).[10,52] In addition, some authors have reported using PCR of the urine to diagnose ZIKV, but this has not been independently confirmed.[53]

Currently, there is no bedside test available for ZIKV. PCR-based tests and neutralization assays (where IgM titer can be tracked) are only available at centralized laboratories such as the CDC. Result reporting may take up to 10 days, depending on the number of specimens being tested, which are highest in the summer months when the arbovirus activity peaks. Cross-reactivity of the tests with other flaviviruses can complicate the diagnostic process.[54] The development and implementation of accurate point-of-care diagnostic testing for ZIKV is urgently needed, especially in the context of multiple emerging viral pathogens, and the need for clinicians to quickly and effectively differentiate between the different possible infections.[55]

CLINICAL MANAGEMENT

The treatment of ZIKV consists chiefly of supportive, symptom-directed care.[10,56] There are no antiviral medications available for ZIKV. Bed rest, antipyretics, maintaining nutrition and hydration, and observing for symptoms of coagulopathy and multi-organ dysfunction/failure are key parameters for care.[52] Antihistamines can be considered for symptomatic management of cutaneous manifestations.[57] Aggressive intravenous hydration, supplemental oxygen administration (as required), and vital sign monitoring are additional (critical) care measures. Although very rare, intensive care admission may be warranted for patients with signs of sepsis or multi-organ failure with the rise in fever, tachycardia, hypotension, renal dysfunction, liver dysfunction, respiratory distress, coagulopathy, rising serum lactate levels, and neurological complications (e.g., Guillain-Barre syndrome [GBS]).[11] Nonsteroidal anti-inflammatory drugs (NSAIDs) and

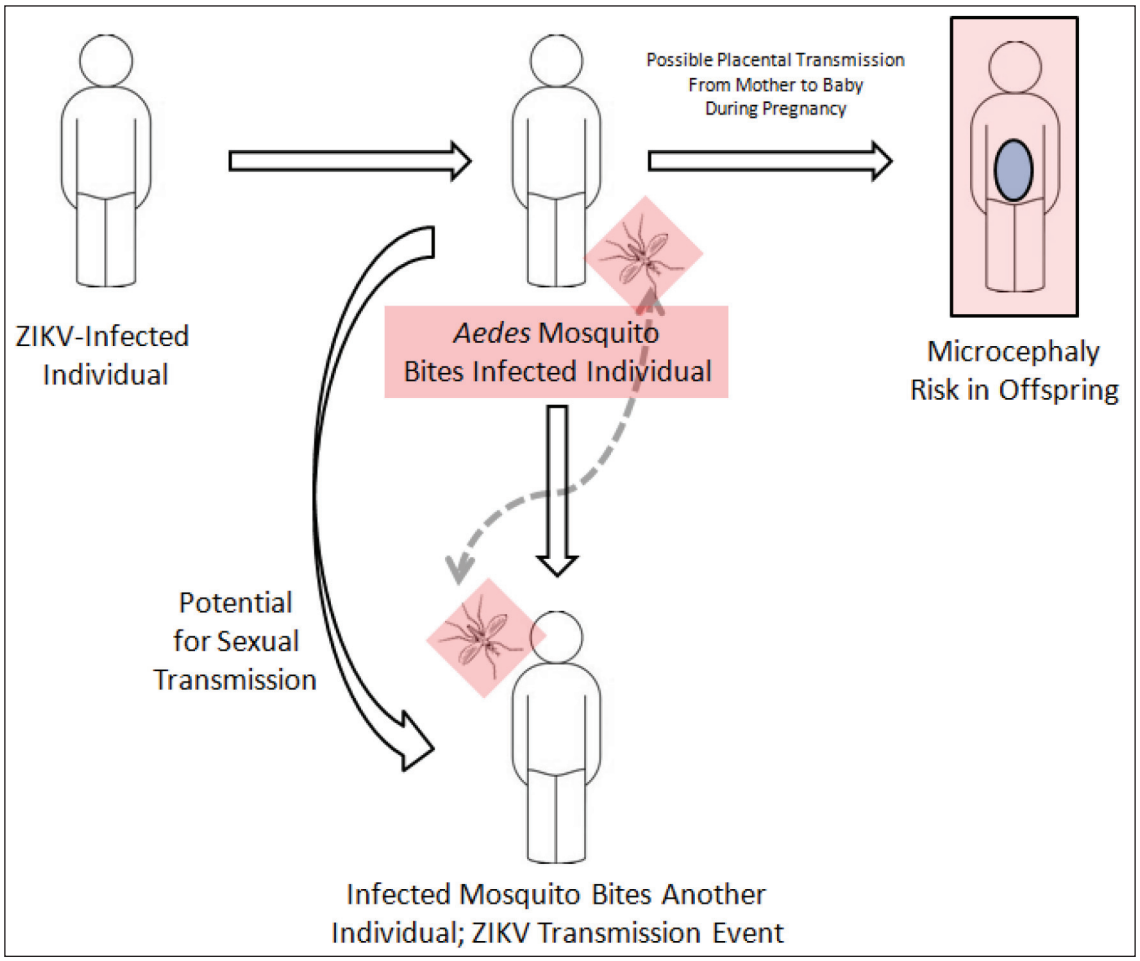

Figure 2: Schematic representation of Zika virus spread, including both the traditional mosquito vector as well as the more recently described transmission via sexual intercourse and blood transfusion. Also shown is the possibility of placental transmission of Zika virus[12-14,20,44,51,64,65,82,83]

aspirin use should be weighed with the risk of hemorrhagic complications in light of ZIKV laboratory tests potentially cross-reacting with dengue hemorrhagic fever. In cases that involve pregnant patients, aspirin and NSAIDs should be avoided.[54,56,58]

If a pregnant woman has a positive laboratory test for ZIKV either in her serum and/or amniotic fluid, then urgent referral to a high risk obstetric/neonatal specialist and infectious disease specialist should be made. Serial sonography to track fetal growth and to monitor for fetal malformations is very important as a part of the high-risk prenatal care, given the potential risk of microcephaly.[59] It is important to acknowledge that although the rate of microcephaly has increased dramatically in ZIKV-affected areas, neither the exact proportion of pregnancies nor the mechanistic details associated with the observed phenomenon are known precisely. In fact, early reports of investigative work performed to elucidate the ZIKV-microcephaly association have produced mixed results.[60] Consequently, much work needs to be carried out in this domain to confirm, quantify, and remediate any risk(s) to the fetus.

SURVEILLANCE

When planning for effective disease control, containment, and prevention of ZIKV, a well-functioning public health surveillance system must be put into place. Best models for such a system come from experiences with dengue and chikungunya fever but are not limited to those viral illnesses.[50,61-63] As per the recommendations of PAHO/WHO,[64,65] the surveillance for ZIKV should be two-pronged:

a. Determining if the virus is autochthonous or has been introduced to an area and
b. monitoring ZIKV cases for clinical progression and any neurological and/or autoimmune sequelae.[61-66]

Considering the widening distribution of *Aedes* mosquito in the Americas, as well as the high mobility of people transiting in and out of the region, further spread of

ZIKV across the Americas represents a clear and present danger. Recommendations for public health authorities in countries without autochthonous transmission of ZIKV include:

a. ZIKV testing of patients who present with fevers and arthralgias with no known etiology where malaria, dengue, and chikungunya are ruled out;
b. Being on high alert for clusters of febrile syndrome of unknown etiology that involves rash, especially where dengue, chikungunya, measles, rubella, and parvovirus B 19 have been ruled out; and
c. Optimizing early detection capabilities to help identify viral strains in circulation and thus enhance the response to the outbreak.[9,64,67]

In countries with autochthonous transmission of ZIKV, the following steps are recommended:

a. Close monitoring of the observed temporal trends and geographical spread of the virus (i.e., tracking any introductions to new areas);
b. Monitoring the impact of viral spread on public health;
c. Providing mechanisms for reliable assessment of clinical severity;
d. Monitoring for potential neurological and autoimmune complications;
e. Identification of pertinent risk factors associated with ZIKV infections; and
f. Whenever possible, identification of specific viral lineages.[9,64,67-70]

Recent high-level regional communications emphasize the need for states and public health authorities to intensify the surveillance of neurological syndromes in all age groups, including the surveillance of congenital anomalies. These concerns are largely due to the highly suspected association between the increase in newborn microcephaly and the rapidly growing number of ZIKV cases.[64,71] Corresponding surveillance systems can be syndrome-, hospital-, or case-based.

ZIKA VIRUS EPIDEMIC RESPONSE

Since there is no specific treatment or vaccine, the response to the current ZIKV outbreak should involve a multipronged, multilateral, coordinated, and comprehensive public health response.[10,17] With ZIKV transmission from French Polynesia to Brazil,[72-74] and the resultant estimated > 1,000,000 cases in Brazil[58] (authors' note — Brazil is the host country of the 2016 Summer Olympics), the anticipated movement of ZIKV into North America,[63] and the first documented case in the USA,[75] a thorough, thoughtful, and level-headed preventive public health approach is imperative.[12-14]

The first public health approach is the incorporation of strategies that acknowledge the recent "urbanization" of zoonotic diseases secondary to population expansion, globalization of trade, and increased ease of travel (new highways, railway links, and air travel). Weaver concisely highlights five strategies or frames of reference where public health authorities can intervene.[76] The first is the interruption of enzootic cycles. In this approach, control of the vector, and host/reservoir infections in the field are needed. However, this can be difficult because of the frequently vast and remote locations that require insecticide application. Also, while vaccination of animals could potentially be applicable here, there is no animal vaccine for ZIKV at this time. Also, introductions of endosymbiotic bacteria (*Wolbachia* spp.) and genetic variants to interrupt the life cycle of arboviruses could be beneficial, but have not been previously attempted with ZIKV (read below under prevention strategies).[76] The second intervention is aimed at preventing enzootic spillover. Here, an attempt would be made to reduce the disease introduction to human population centers by use of bed nets and vaccines. Again, there is currently no ZIKV vaccine available for humans. The third intervention involves limiting urban introductions of disease, or preventing the disease outright, through mosquito control via modulating the *Aedes* "vectorial capacity." The fourth strategy involves active interventions in the urban area. The interruption here would involve vector control, elimination of standing water (e.g., natural or man-made collections of water, pools and containers), and enforcement of adequate garbage management and disposal. Weaver makes it clear that regarding this intervention, socioeconomic factors play an important role.[77] The fifth intervention is the prevention of spillback into the enzootic cycles. Under these conditions, human hosts become a source for reinfection of nonhuman primates.[76]

During an epidemic, "active protections" of the blood supply must be instituted. This is especially true given the increase in global travel, mandating high-quality surveillance whenever reliable diagnostic tests are available.[78] Public health authorities must be ready to intervene if the quality of blood supply is threatened in any way. In the context of the current ZIKV outbreak, this is important for two main reasons:

a. This disease is no longer confined to a single, isolated geographic area; and
b. Blood transfusions may potentially contribute to the spread of the disease.

Although only anecdotally reported, ZIKV transmission through blood transfusion during an active outbreak is

certainly a possibility. For example, it has been reported that approximately 3% of blood donors in French Polynesia were found to be positive for ZIKV using PCR.[72,79] While the residual risk may still exist after the screening, several pathogen inactivation technologies have been applied to blood, including the use of amotosalen and ultraviolet A-type light.[80,81] Given potential risk of newborn microcephaly following ZIKV infection in expectant mothers, concerns over blood supply contamination are well justified,[12-14] especially given the recent reports of human-to-human transmission via sexual intercourse.[51,82]

It has been reported that ZIKV may be prone to become a sexually transmitted disease.[51,82] Musso *et al*.[51] reported that ZIKV particles were identified in semen samples. Same authors reported that no viral particles were detected in urine.[51] If the threat of ZIKV transmission via sexual intercourse were to become substantial, contact tracing similar to that for other sexually transmitted diseases should be considered.[83] Furthermore, public health authorities managing an outbreak must keep in mind that patients can be co-infected with ZIKV and dengue virus at the same time,[84] and that ZIKV virus has been linked to GBS.[11] The precise nature of the relationship between GBS and ZIKV is unknown, but an immunologic origin is suspected, similar to other viral maladies.[85]

PREVENTION STRATEGIES

The prevention and control of ZIKV should be two-pronged:

a. Reduction of vector density, and
b. Personal protection.

These general strategies and corresponding practical approaches will be discussed in the subsequent sections of this report. In addition, the development of ZIKV vaccine should also be mentioned here. Due to the extent of the topic, a more detailed discussion of vaccine efforts was felt to be beyond the scope of the current manuscript. The reader is referred to other sources regarding the most recent updates on ZIKV vaccine research and plans for associated clinical trials.[86] The topic of ZIKV vaccine is both complex and controversial, with time frames for vaccine development being cited anywhere between 1 and 5 years.[87-89]

Reduction of vector density

In terms of effective vector control, WHO promotes Integrated Vector Management (IVM) which aims to improve the efficacy, cost-effectiveness, and overall sustainability of the strategy.[90] Since *A. aegypti* uses a wide range of confined larval habitats, both man-made and natural, it is critical to consistently and continuously apply the three-pronged IVM, incorporating the following considerations.[90-92]

Environmental management

This includes specific environmental modifications and maintenance. Within this subdomain, authorities must ensure reliable water supply management, adequate maintenance and cleaning of water storage systems, sound solid waste management approaches, and changes to human behavior and habitation (e.g., street cleaning or modifications to buildings/structures such as installing and utilizing mosquito screens on windows, and mosquito-proofing of storage containers) [Table 1].

Table 1: Preventive recommendations (References 10, 12, 44, 54, 56, 58, 64, 65, 71)

Strategy	Actions
Reduction of vector and mosquito density	Diligent control and management of environmental factors
	Eliminate or reduce vector breeding sites in common areas (e.g., parks, ponds, schools, waste containers, etc.) to prevent disease propagation
	Conduct mass sanitation campaigns to educate the public about the application and importance of key preventive measures
	Using risk stratification paradigms, identify places such as schools, hospitals, transport terminals, and ensure mosquitoes are removed within a predetermined radius of these critical public locations
	In areas with known viral activity, use proactive mosquito adulticide spraying to interrupt ZIKV transmission
	Ensure proper monitoring and follow-up during integrated actions for vector control (e.g., larval control and adulticide treatment)
Interruption of human-vector contact and personal preventive measures	Individual protection
	Encourage individuals to rest under bed-nets (with or without mosquito repellents)
	Appropriate clothing to cover extremities and exposed areas of skin
	Use repellents containing DEET, IR3535, icaridin. These can be applied to exposed skin or clothing as per product label instructions
	Household/residential protection
	Encourage the installation and use of wire-mesh screens or doors and windows
	Once per week (or more frequently, if feasible): Empty, clean, turn over or dispose containers that can hold water (buckets, flower pots, tires) inside and outside of dwellings to eliminate or significantly reduce any mosquito breeding sites

ZIKV: Zika virus, DEET: N, N-diethyl-3-methylbenzamide, IR3535: 3-(N-butyl-N-acetyl) amino propionic acid ethyl-ester

Introduction of bacteria into, and genetic modification of, the mosquito populations

Up to 60% of all insects carry the bacterial species *Wolbachia*.[93] *Wolbachia* reduces viral spread of dengue fever by *A. Aegypti,* by reducing mosquito-to-human transmission events.[94] This positive epidemiologic effect is facilitated by the spread of *Wolbachia* to offspring through the female's egg. The eggs of females who mate with *Wolbachia*-carrying males will fail to hatch. Infected *Wolbachia* females will have female eggs that hatch and produce offspring in normal numbers that carry the "*Wolbachia* effect."[94,95] This reproductive effect will be minimal initially because few *Wolbachia*-infected mosquitoes will be present in the population, but over time the numbers of males and female mosquitoes infected with *Wolbachia* will expand. This approach has been successful for dengue virus and therefore, may also be effective for ZIKV.[94,95]

Another, relatively new development is the use of genetically modified (GM) mosquitoes whose offspring are not able to survive, especially *A. aegypti* OX513A (noted to have effectiveness against dengue, and thus hopefully ZIKV).[96] This is a genetically engineered strain that owes its effectiveness to the "release of insects carrying a dominant lethal" (RIDL) genetic system.[97,98] OX513A is a bisex RIDL strain.[96] Released males mate with wild females and the offspring of these females will die. Increasing numbers of such males should theoretically reduce mosquito populations below the threshold needed for disease transmission.

Despite the potential benefits of vector modification, there are several facts that public health and government officials and scientists need to know about GM insects used for vector control.[97] First, vectors that are GM are either used to reduce or eliminate vertical transmission, achieve population suppression, or accomplish population replacement. In this way, there will be fewer successful vectors and a resultant decrease in the force of infection, the rate at which individuals acquire disease, or λ,[99] where:

$$\lambda = \frac{\text{number of new infections}}{\text{number of susceptible persons exposed} \times \text{average duration exposure}}$$

Second, key stakeholders must be aware that GM mosquitoes are made through the use of transposons. DNA is placed between transposons and is injected as a plasmid into embryos.[100] The DNA can then reach cell nuclei, but not all of them. There must be the transformation of some (but not all) germ lines for this general strategy to be effective. Third, the above-mentioned RIDL line of mosquitoes is effective, but can be expensive.[96-98] Furthermore, more powerful genetic systems are being produced wherein fewer GM individuals within the population will be needed to be effective. Fourth, the politics of genetic engineering will possibly leave the public at odds with the science because of the GM aspects and the fact that more mosquitoes must be released to be effective. The permanent presence of a mosquito with novel traits is an inherently difficult topic with which to deal, mainly due to the unforeseen future risks. Fifth, GM vectors and wild types need to mate. There may be barriers to mating and genetic drift. Also, adequate rearing methods need to be developed, which can be both costly and time consuming.

Scientists and organizations involved with bacterial modification or GM of mosquitoes will have to be acutely aware of the fact that transgenic technologies carry a number of environmental and safety concerns that will need to be addressed. "Unintended ecological side effects, accidental spread to nontarget species, and horizontal transfer of the transgenes are all unlikely, but possible negative scenarios that can, and must be minimized."[101]

Personal prevention measures

In the setting of a known ZIKV outbreak, infected patients must be reminded to minimize the potential for contact with the vector in order to prevent the spread of the virus. The community members must be well informed and educated about the risk of transmission to others, and should be encouraged to follow key recommendations as summarized in Table 1. Insect repellants like N, N-diethyl-3-methylbenzamide, 3-(N-butyl-N-acetyl) amino propionic acid ethyl-ester or icaridin can be used. For pregnant women, there are no specific restrictions in terms of the use the repellents, as long as the use follows safety instructions provided on product packaging.[18,102,103]

To prevent viral spread, a ZIKV-infected person should avoid being bitten by the *Aedes* mosquitoes during the 1st week of illness. It is advised to stay under the bed-net and the treating health care workers should also be protected from mosquito bites. Pregnant women living or traveling to areas of ZIKV transmission should try to avoid travel to these regions and if necessary, they should avoid the mosquito bites using bed-nets and appropriate clothing. Due to recent reports of ZIKV transmission via sexual intercourse, corresponding patient education must be provided.

Traveler alerts and information

The health authorities should alert the citizens heading to any country with documented spread and circulation of ZIKV and advise them regarding the protective measures as listed in Table 2. Once effective vaccine is developed, consideration should be given to routine immunization of travelers who are visiting ZIKV-affected areas. Additional considerations, including the potential for sexual transmission of ZIKV, must be conveyed to those who plan to travel to areas affected by the outbreak.

ZIKV AS PUBLIC HEALTH EMERGENCY OF INTERNATIONAL CONCERN: GLOBAL ECONOMICS AND HEALTH SECURITY

Currently there are 15 new countries and territories in the Americas where ZIKV has been detected from November 2015 to February 2016. The epidemic has brought significant financial strain to a region that is already experiencing an economic crisis (e.g., Brazil is concurrently facing a significant economic slow-down). Facing nearly 4000 babies born with microcephaly, presumably associated with ZIKV infections, the health system is not able to cope with the increasing demand on medical resources.[17,104] Most of the affected countries depend on tourism and with the ongoing ZIKV outbreak, tourism industry is likely to be impacted negatively. The hotel industry has invested billions of dollars for the upcoming Summer Olympics in August 2016 and the current epidemic situation may have significant financial impact.[105] Similarly in Colombia, which is home to the largest Carnival destination outside Brazil, there have been >20,000 confirmed or suspected cases of ZIKV infection.[106]

In 2014, Ebola was designated a PHEIC.[19] The highly suspected association between ZIKV and newborn microcephaly and the resultant public outcry have certainly been important factors in the recent WHO decision to declare PHEIC.[17] In this context, it will be important to define a PHEIC in scientific, economic, and public health terms. There should be creation of a protocol, agreed to internationally, which can define a point of intervention that facilitates and allows rapid response to a situation of public health/medical significance, especially as it relates to pregnancy-related risks. A regulatory framework should be created for expediting the science and technology required during a PHEIC in regions where there are substantial pharmaceutical centers of research and production in order to fast track the development of point-of-care testing, vaccines and therapeutics.

Finally, ethics and respect for culture are major actors on the international health stage as far as treatment, vaccines, and trials are concerned.[50] This is important for any kind of experimental intervention, regardless of geographic location, socioeconomic factors, or prevailing cultural norms. Therefore, creation of national and/or regional emergency ethics review boards should be aggressively pursued. Such boards need to be given sufficient resources so as to eliminate any undue delays pertaining to the "drug — trial — intervention" evaluation, revision, and approval process. Efforts should be made by the international community to create ethics review committees in every country. If this is not immediately feasible, an effort to create regional ethics review committees encompassing multiple countries should be undertaken.[50]

The full extent of the ZIKV outbreak has yet to be determined. Regional mobilization of economic and medical resources is currently taking place. Previous experiences of the international public health community with SARS and Ebola will hopefully facilitate an appropriate and healthy concern in the medical and

Table 2: Travel recommendations (References 10, 12, 44, 54, 56, 58, 64, 65, 71)

Traveler status	Recommendations
Prior to departure	Travelers heading to a country with known ZIKV transmission events are advised to protect themselves from mosquito bites
	Use mosquito repellents, wear appropriate clothing to minimize skin exposure (e.g., long sleeves, full pants, hats)
	Use insecticides and bed-nets (with or without insecticide)
	Educate travelers about the signs and symptoms of Zika /dengue/chikungunya virus in order to enhance the promptness of symptom identification and reduce the time to required medical attention
While visiting places with known ZIKV transmission	Avoidance of mosquito-infested areas
	Protection from mosquito bites by using repellents and appropriate clothing to reduce skin exposure (see above)
	Avoidance of mosquito bites
	Proactive and proper use of bed-nets and/or insecticide
	Seek professional care in case there are symptoms of Zika/dengue/chikungunya
Upon return	Travelers should contact appropriate health care provider in case ZIKV infection is suspected. Due to some symptomatic overlap, this also applies to dengue and chikungunya viruses

ZIKV: Zika virus

public health communities, which should be sufficient to trigger a heightened awareness and lead to quicker and more effective channeling of resources needed to combat the ZIKV outbreak at all key stakeholder levels (e.g., government, industry, health care institutions, and research).[49,50,107]

MISCELLANEOUS TOPICS

Diagnostic testing for ZIKV remains an area of significant limitation. Currently, the CDC has reported that ZIKV testing is being done at a limited number of facilities (e.g., The Arbovirus Diagnostic Laboratory and several state health departments).[10] The CDC performs a RT-PCR on serum, and can also perform virus-specific IgM and neutralizing antibodies after a week of illness. However, cross-reactivity with other flaviviruses can occur, resulting in reduced specificity.[10] POCT has been regarded as a priority in the areas that are resource limited.[55,108] The WHO has determined that the ideal POCT product should be affordable, sensitive, specific, user friendly, rapid, and robust. Equipment should be either free or readily affordable, and immediately deliverable to end-users.[109]

Currently, there is no POCT for ZIKV. However, the genome has been isolated which offers future promise for a POCT development.[110] This would not be the first time a POCT was developed for an arbovirus. Research teams from across the globe developed a POCT for YFV that was sensitive and specific for identification of the YFV genome with a real-time RT-qualitative PCR and an isothermal method based on helicase-dependent amplication technology (with the same primer probe).[111] Escadafal *et al*. were able to develop YFV rapid molecular assays, a nucleic acid detection method using a recombinant polymerase amplification (RPA) assay with a small portable device, lyophilized reagents, and a real-time RPA that was portable and tested in Senegal.[112] Abd El Wahed, *et al*. have developed a recombinase polymerase amplification assay for rapid diagnosis of dengue, which may also provide a platform for ZIKV diagnostic applications.[113] In view of the rapid geographic expansion of ZIKV across the globe and the concern about microcephaly in newborns, developing a specific and sensitive POCT has been catapulted to a top public health priority.[13,114]

Finally, given the potentially devastating perinatal consequences of ZIKV, it will be imperative to develop a vaccine that is based on a rationale similar to that of rubella vaccine in the past.[45-46] A vaccine that is effective against both the current and potentially mutated ZIKV would be the ultimate, long-term solution to a disease associated with a severe disability affecting large number of newborn children (and their families). As previously outlined, the reader is referred to other sources regarding the most recent updates on ZIKV vaccine research and plans for associated clinical trials.[86-89]

CONCLUSIONS

The full brunt of the ZIKV outbreak has yet to be felt by the global community. Mobilization of economic and medical resources is currently occurring. Following the declaration of PHEIC, the experiences of the international public health community with SARS and Ebola should create an appropriate and healthy tension in both medical and public health communities to trigger a heightened awareness and targeted investment in research infrastructure.[49,50,107] A compelling argument can be made that although the trajectory of global ZIKV spread is difficult to predict,[25] previous experiences with dengue and chikungunya viruses point toward a close link between globalization, urbanization, and the behavior of emerging viruses in the modern era.[25,30,49,50,76] Approaches to such a potential global health security threat should be consistent, proactive, and should involve coordinated, multi-pronged, multilateral collaborative efforts that actively engage local, regional, national, and global agencies and resource pools.[49,50] This position statement by the JWG aims to shed light on the magnitude of the ZIKV outbreak and its impact not only on current but future generations. The ultimate goal of the world public health community should be the containment and the subsequent elimination of ZIKV as a global health security threat.

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Conflicts of interest

There are no conflicts of interest.

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