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Zika Virus Historical Spatiotemporal Distribution and Potential Risk Factors [1900-2018]: Review

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Abstract

This paper is aimed to assess Zika virus (ZIKV) spatiotemporal historical distribution, the potential mechanisms and contributing risk factors for epidemic emerging, the attempt to mitigate, and its future aspect. Available literature from the years 1900 to 2018 were assessed and compiled.

Previous analyses on the partial structural envelope as well as the non-structural proteins gene sequences suggests the occurrence of ZIKV strains ancestor erstwhile in the beginning of 1900s in Uganda. Infection with the virus was also first reported in Uganda since 1947. It gradually distributed to different countries in the world until the present 2018. It was found that ZIKV has multifactorial health challenges from several corners. Its epidemiology has wide reservoirs, susceptible and vector hosts, and different mode of transmission. The potential mechanisms of epidemic occurrences are viral evolution changes in mosquito, presence of human viremia and immunity in endemic exposures, and stochastic introduction to new areas. Moreover, climate change which disrupts health security and sociology-economy favors vector mosquito make ZIKV adaptation and causes global emerging epidemics. Presence of global travel with possibility of human-to-human transmission, urban area preference of the vector mosquito, and climate change adaptation of both the virus and the vector are core current risk for the epidemic. Presence of cross-reactors, absence of both therapeutic drug and vaccine (the only promising future vaccine being ZIKV sub-unit recombinant biotechnology) were exacerbating the risk of Zika infections. The present sole preventive strategy is vector control.

Therefore, defined and prioritized research on the epidemiology, diagnostic techniques, therapeutic drug and preventive vaccine development are recommended. Burst feed transmission should be checked. Capacity building on diagnostic laboratories and risk communication are relevant for developing countries.

Keywords: Aedes mosquito vector; Potential risk; Emerging epidemics; Neurological disorders; Zika virus

Historical Geographic Spreading of Zika Virus [1900-2018]

Zika virus evolution

Zika virus (ZIKV) evolution has been associated with investigation the agent and is identification of the strains from the enzootic cycle in African countries. This disease get more attention due to its rapid expansion in the first two decades of the 21st Century in Asia and Oceania, and more recently by its introduction into the Americas [1]. In this century, ZIKV is the raising infectious viral diseases of greatest concerns for public health globally. Naming of the virus was after Zika Forest in Uganda, where it was first discovered at the Yellow Fever Research Institute in Entebbe, Uganda. It was suggested that virus isolation were made from sentinel monkey, their caged on a tree platform and Aedes africanus mosquitoes captured during feeding on humans [2]. Thus, it was termed as mosquito-borne pathogen. Zika virus determined as a mosquito-transmitted virus spread broadly in tropical regions and caused epidemics [3] which is being favored by vector population. Previous examination of the partial envelope and its non-structural proteins (NS5) by gene sequencing suggested the presence of ancestor of known ZIKV strains in the early 1900's in Uganda [4]. In connection to these, the virus isolated in 1947 from a febrile sentinel rhesus monkey for the first time. After one year, it was again isolated from A. africanusin in Uganda. Five year later, it was identified in humans in Nigeria during 1952 [2]. The first characterization of Zika Virus infection as human disease was from the two cases using sero-conversion and a one case using virus isolation techniques in Nigeria [5]. But, the infection was well-documented in Uganda when Simpson [6] described self-acquired occupational illness. Recently, Weaver et al. [7] and Wang et al. [8] indicated evolutionary relationships of Zika Virus from human, monkey and mosquito [9].

Spatiotemporal Zika virus distribution

Zika virus evolution is powered by the global spread of the anthropophilic vector A. aegypti, the increase of the urban human population size, and expansion of international commerce and travel [10]. Geographical distribution of Zika virus was assessed based on results of sero-prevalence surveys, and viral isolation and characterization from mosquitoes, monkeys and humans. Reports from human travel associated cases [11] were also used to trace the spread of the virus. Cases have been reported in African, European, Oceania and the Americas, particularly in Latin American countries from where it is rapidly spreading to new areas [1,12].

Africa and Asia: Using serological, epidemiological and entomological studies, Robin and Mouchet [13] reported the circulation of Zika virus infection in tropical areas of western African countries including Nigeria, Sierra-Leone Ivory-Coast, Cameroon and Senegal; in central African countries including Gabon, Uganda and Central African Republic; and in Asian countries including Pakistan, Indonesia, Philippines, Malaysia, Cambodia and Thailand. Outside of Africa and Asia continents, first outbreaks of Zika virus infections were also reported from other countries mainly on Yap Island and in Federated States of Micronesia in 2007 [12].

Americana and Pacific Caribbean: Between 2013 and 2015, several significant outbreaks were notified on islands and archipelagos from the Pacific region including a large outbreak in French Polynesia. In 2015, Zika virus emerged in South America with further spread across the Americas [4,14-16]. However, more recently, it has become the main suspected cause of an unusual and completely unexpected micro-cephalic epidemic disease making it an urgent needs for the knowledge about the nature of the disease [17-19].

The current outbreak of microcephaly raised and its occurrence in Brazil in early 2015 speculates a congenital syndrome of the virus transmission [10]. A large increase in the number of newborns with such cases were subsequently identified in Brazil in November 2015. More than 4,500 microcephaly cases have been reported with rapidly spreading right through the Americas [18]. Previously, World Health Organization [17], too reported first infection with the virus from Island of Easter, the Western hemisphere, in 2014 with possible local transmission in the country. As of January 2016, the virus had spread to 19 other nearby countries and territories of the South America, Central America, the Caribbiean, and as far north as Mexico [20]. Several outbreaks are reported with predominantly in those countries with the observation of microcephaly in Brazil in early 2017 as the most affected country [21]. Recently, 14 Zika virus disease cases reported in USA and 15 cases acquired through presumed local mosquito-borne transmission in US Territories had been reported in 2018 [22].

European and Oceania's: Recently, a large increase in zika virus infection were observed due to its worldwide circulation. It has been observed with Dengue viruses [1]. In EU/EEA countries, no locally acquired ZIKA case *via* vector-borne transmission until 24 October 2016. However, 19 countries have documented a total of 1935 travelers associated infections cases where high from France (56%) and followed by 15% from Spain and 8% from the UK. Eight countries also documented a total of 91 cases among pregnant woman since 2015 [23].

WHO, CDC and the European CDC have jointly defined a Zika virus affected country into 4 major categories [24]. The countries were also mapped [25] as indicated in Figure 1.

Category 1: Area with new introduction or re-introduction with active transmission of the disease.

Category 2: Area either with an evidence of Zika Virus transmission before 2015 or area with active transmission that is no longer in the new or re-introduction phase, but where there is no evidence of interruption,

Category 3: Area with interrupted transmission and having a potential for future dissemination/transmission.

Category 4: Area with established vector prevalence and density but with no documented previous or present transmission.

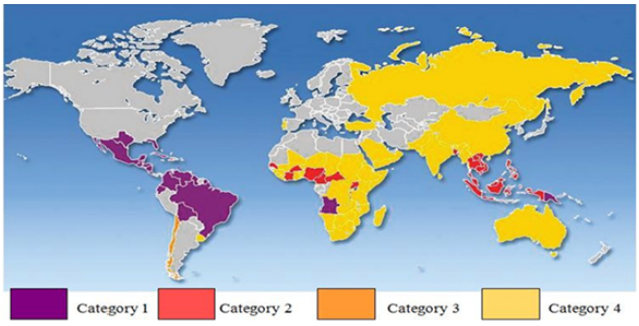

Figure 1: Categories of countries affected by ZIKV [25]

Zika risk areas

For traveler recommendations, countries/territories/subnational areas falling within Zika virus infection were classified under framework in immunologically naïve population. Moreover, CDC [26] showed world map of areas with risk of Zika (Figure 2) where the tropic areas of Asia, The Pacific Islands, The Caribbean, North America, Central America, South America and Africa were found high Zika risk areas [25-27].

Zika virus strain and their geographic distribution

According to Haddow et al. [28] phylogenetic existence of two main Zika virus lineages were identified. These are the African and Asian lineages and the Yap epidemic and the Cambodian lineages (most likely originated in Southeast Asia). Examination of the nucleotide and amino acid sequence alignments revealed the loss of a potential glycosylation site in some of the virus strains, which may correlate with the passage history of the virus.

Most of the African lineage strains were isolated from enzootic vectors [4,29], indicated from continuous investigation outcome from Senegal. The Asian once is identified by the prototype P6-740 strains isolated from Malaysia in 1966 [30] which includes isolates from Cambodia [31], Micronesia [32] and French Polynesia [16], suggesting the origination and spread of the Asian lineage in the Southeast Asia. In connection with Asian cluster, a new ones (American) were emerged with the spread of the virus into this Hemisphere.

Now, this lineage includes the strains from Brazil [33]. Major characteristics of the American ZIKV lineage were its rapid radiation, consistent with a pattern of intense diversification and expansion into new territories with immunologically naïve population [4,29].

Zika Virus Biology and Host Tissue Receptor

Structural and molecular profile of Zika Virus

Zika Virus belongs to genus Flavivirus in family of Flaviviridae. It is closely related to other viruses of public health importance including Dengue, Yellow fever, West Nile and Japanese Encephalitis Viruses within the same family [12,34,35]. Structurally, Zika Virus is an enveloped viruse having icosahedral symmetry. Genetically, it is non segmented, single stranded, positive sense RNA with 10794 kb nucleotides long that encloses for 3419 amino acids [19,32].

Genome encodes a single polyprotein which cleaved post-translationally by host and viral proteases into three structural proteins including the capsid (C), the pre-membrane (prM) and the envelope (E). It has also seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A NS4B and NS5) like other viruses within the family [19,36,37].

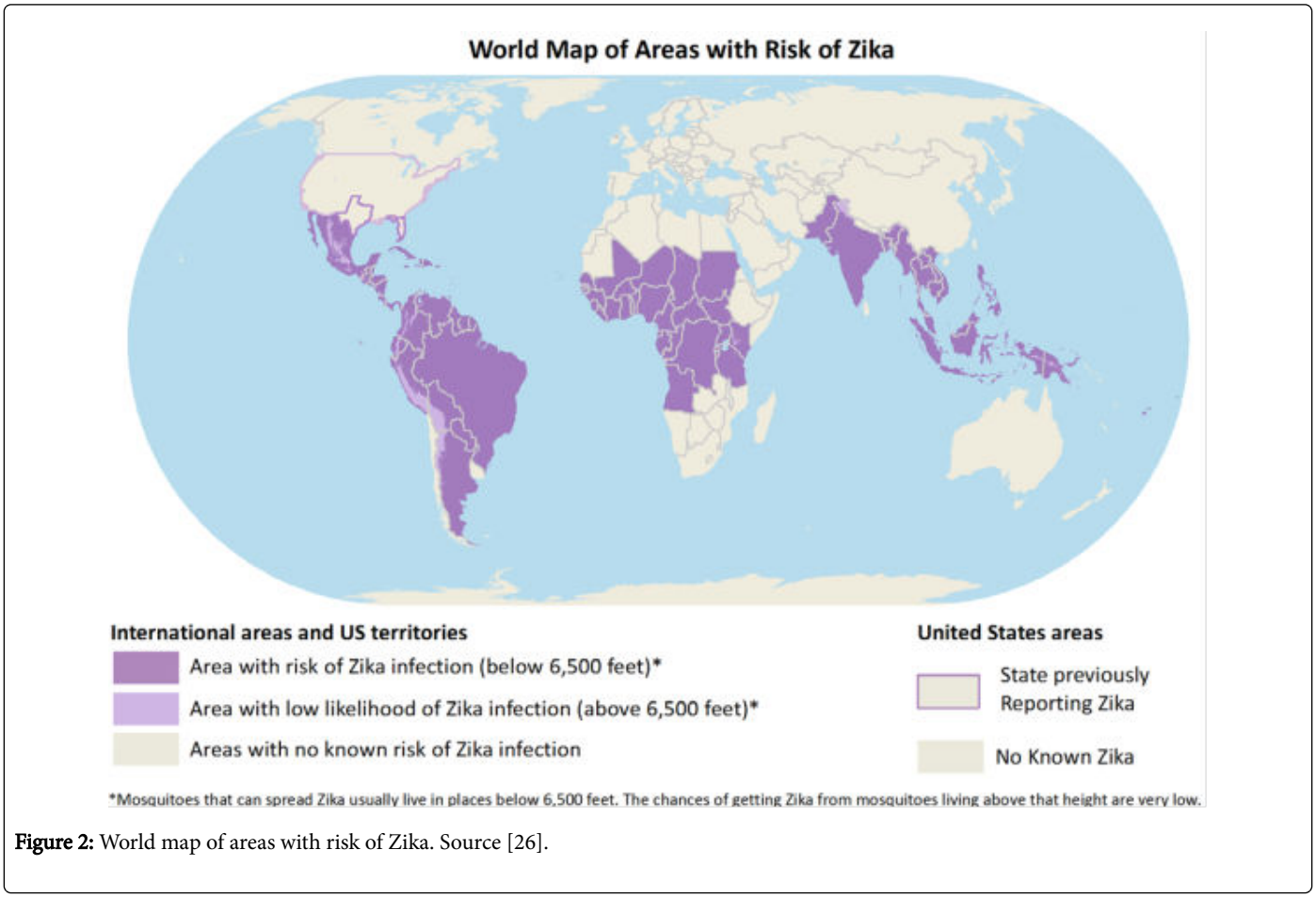

Figure 2: World map of areas with risk of Zika. Source [26].

Zika virus structural function and host receptor interaction

Functionally, the Zika virus is intact and found in such a way that the capsid binds to the viral RNA to form a nucleo-capsid. The viral pre-membrane keep the virus under intact condition not to for fusion with host membranes before being matured. ZIKV envelope mediates functions of cellular attachment of the matured virus to host cell to assist viral entry and fusion with host cell [38].

During infection of both the vector mosquito and/or human, the virus creates new functional genomic association with factors of the respective host [7,8]. These, so called host factors, can be cataloged as pro-viral (dependency factors) or anti-viral (restriction factors). The integrated interaction of host factors viral proteins and its RNAs are the main contributing factors for infection efficacy, pathogenicity, transmission and epidemic potential [4,29,39].

The potential target cells for the virus are likely to be localized to the epidermis and dermis which was determined by susceptibility of skin fibro-blasts. But, 24 hours post infection (hpi), the viral envelope protein will detected in several cells, whereas at 72 hpi, 100% of the infected cells expressed ZIKV [39]. One recent study [39] indicated the infection potential of human multiple skin cell types by the virus, too. Thus, like many Flaviviruses, it was considered to uses multiple 'receptors to mediate attachment and entry into cells followed by replication within the host cell cytoplasm. Dendritic cells are also determined to be permissive to ZIKV and DENV multiplications from which it disseminated to brain tissues [4,39].

Epidemiology

Host and reservoirs of the virus

Although the primary host species has not been well identified, monkeys are presumed to serve as reservoir hosts for ZIKV [40]. Human being are considered as an amplifying host [29]. Thus, both humans and nonhuman primates are appeared to be reservoir for the virus. Using reverse-transcription PCR (RT-PCR), the presence of Zika virus were reported in 10 different species of the genus *Aedes* collected from different environments of Senegal. Similarly it was also detected on *Mansonia uniformis*, *Anopheles coustani* and *Culex perfuscus* [29].

Unlike in primates, serological evidences of ZIKV were not observed in small mammal's vertebrates including squirrels, tree rats, giant pouch rats and civets inhabiting in Ugandan Zika Forest [41]. On the other hand, silent Zika virus circulation was reported by using specific antibody determination in various species of animals including in orangutans, zebra, elephants water buffaloes and rodents found in certain parts of Africa and Asia [16,42]. They could act as sources of infection for susceptible hosts (mosquitos and primates).

Mode of transmission

The frequently suggested mode of transmission of the virus includes, bite by an infected mosquito, maternal-fetal transmission, sexual, blood transfusion, organ transplantation and laboratory exposure [29]. Using molecular diagnostic technic the viral RNA has also been detected in the secretion and excretions of human including in urine, saliva, seminal fluid and breast milk [42-45] which might risk for susceptible population.

Vector mediated transmission

Forest inhabiting species of the genus *Aedes*, especially *Aedes africanus* in Uganda [41], and *A. furcifer*, *A. luteocephalus*, and *A. africanus* in Senegal [29] are responsible for maintenance and sustainable transmission of the virus in African Zika cycle between the vector and the primates. Continuous transmission of the virus within the vector mosquito was maintained by trans-ovary transmission to the offspring from the infected females [29].

Although the virus has been isolated from several *Aedes* species, only a subset of their competent including the *A. aegypti, A. albopictus*, *A. hensilii* and *A. polynesiensis* were considered to be vectors for transmission [29]. Due to its anthropophillic and urban preference natures, *A. aegypti* are accounted a major and a principal spreader of Zika virus in the present outbreaks [46].

As shown in (Figure 3) anthroponotic (human-to-vector-to-human) transmission occurs during the reported outbreaks [9,12,47]. After an infected mosquito bites a human, the first symptoms of ZIKV can develop in 3-12 days which can be shorter or longer incubation periods depending on the resistance and immunity level of infected individuals [47]. Urban cycles of transmission occurs from mosquito to human and vice versa resulting in sustainable disease circulation in the forms of epidemics in the endemic areas [12].

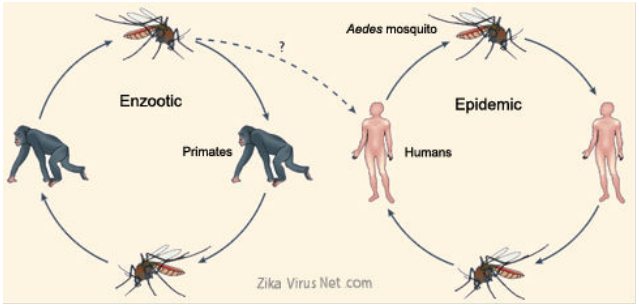

Figure 3: Zika Virus transmission net Source [9]

The potential risks for human infection are associated with the distribution of mosquito species mainly, the *A. aegypti*, associated with global trade related traveling between countries [29,48]. It was suggested that the extrinsic/ non biological multiplication of Zika virus in mosquitoes takes about 10 days [29].

Blood-borne transmission

A ZIKV viremic blood donor could potentially contaminate of healthy individual [49,50] during untested blood transfusions as a hospital based infection. The possible risk were indicated from the suspected cases from Nov 2013 to Feb 2014 where by 2.8% blood donors found virus RNA positive at donation time for in French Polynesia [36]. According to Musso et al. [50] 42 of 1505 (3%) blood donors in this area were identified asymptomatic at blood donation time. But, they were found Zika virus genome positive by PCR which could be a potential risk of transfusion-derived transmission [51]. Hence, Zika virus transmission *via* asymptomatic viremia blood donors can happen in the affected area or from infected travelers [52]. However, blood transfusion derive transmission cases has not yet reported [23,52] due to pre-checking of blood of the donor at health care centers.

Sexual transmission

After detecting the Zika Virus RNA in semen of infected individual [21], sexual transmission of the disease was suggested [53]. In connection to these, sexual mode of transmission was reported in six countries including including Argentina, Chile, France, Italy, New Zealand and USA during the 2015 outbreak of Zika [54].

Maternal transmission

Although breastfeeding transmission was not yet documented, the viral has been detected in the breast milk [45]. On the other hand, this route of transmission were documented for other viruses within families of Flaviviridae [55], indicating the possibilities of transmission of the virus from infected mothers to nursing and breast feeding children. On the other hand, ingestion based oral infection were not assessed. In contrast to breast feeding transmission, trans-placental transmission were confirmed from the documented finding of Zika virus RNA in amniotic fluid of two pregnant women's bearing fetuses that had microcephaly during 2015. These suggested the possibility of the virus being crossing the placenta and causing dame-to-fetal transmission [56]. In connection to trans utrain transmission, symptoms of fever in infected pregnant women has been observed in parallel with fetal growth restriction characterized by anomalous brain development of the fetuses, that finally develop miscarriage. It was also confirmed that Zika virus positive through RT-PCR testing of brain tissue from microcephalic neonate passed within 20hrs of post birth, the placenta and other tissues of 11 and 13 weeks miscarriages in Brazil [57].

Transmission through secretion, excretion, and tissue and organ transplantation

The RNA of Zika virus has been detected in body excretion and secretion of infected individuals [42-44]. The majorities were documented in the blood, urine, saliva, seminal fluid and the breast milk blood, urine, saliva, seminal fluid and breast milk [42,44,50,54]. Compared to blood, ZIKV was more frequently detected in saliva [44]. This was indicated by the fact that out of 182 patients samples collected and tested for ZIKV, 35 (19.2%) were positive in saliva while the blood was negative. But, 16 (8.8%) were positive in the blood while their saliva negative [44]. Yet there are no documented reports of viral transmission through theses secretions and execration as well as *via* cell, tissue and organ donation. However, it was necessary not to exclude these mechanisms of Zika virus transmission [23] as per its family groups, although it is not mandatory.

Potential mechanisms of ZIKV epidemic emergence

The unexpected and climaxed ZIKV emerging into a human-mosquito based cyclic transmission [9] associated with high outbreaks

in 2007 raised a precipitating of infection at the global level [16]. There are several hypotheses explaining this emergence. Some plausible, but not an exhaustive set of examples, are suggested by Musso et al. [16] and Ledermann et al. [58] that are explained below.

Zika virus adaptive evolution *via* vector mosquito

Long ago, ZIKV undertook adaptive developmental evolution from viral genetic drift with subsequent challenging to the population. This evolution is more efficiently transmitted by *A. Aegypti*. Perhaps other closely related mosquito vectors (in the *Aedes =Stegomyia)* subgenus are also incriminated to such evolution. For instance, *Aedes hensilii* is incriminated vector in Yap [58] or *A. polynesiensis* suspected as a vector in French Polynesia [16]. The phylogenetic analyses showed such adaptive evolution of Zika virus in the Southeast Asia and the South Pacific. The evidence was supported by presence of ZIKV and its isolation from *A. aegypti* in the Malaysia since 1966 [30], yet the lack of evidence for major urban epidemics.

Evolutionary adaptation for human viremia

The Asian lineage has been adapted to the highest human viremia [7] which could be characterized by capable of infecting the vector mosquito with higher transmission and spread profiles. Higher viremia could also enhance trans-placental transmission. Informatics studies of ZIKV sequences, suggested an increase in the virus use of human codons, supports this hypothesis [4].

Population immunity from endemic exposure

Enzootic and/or endemic ZIKV circulation in Asia results in relatively stable levels of human herd immunity that limit the potential for recognized outbreaks. This suggests presence of cyclic endemic circulations that maintains population immunity in the range of approximately 20%-50% levels that may reduce the risk of major epidemics [59] but increasing maintenance and circulation of the virus. Under such a condition, theses population can act as sources of infection for travelers.

Stochastic viral introductions

The recent ZIKV emergence resulted from the probability of virus introduction into naïve population, where competent vector involved in aggravation and amplification of the viral transmission and spread risk in previously free areas [60]. Presence of travel from Zika endemic area to the Americas [7], also occupied by a completely ZIKV-inexperienced populations of being with low level/no immunity [60] aggravate infection and outbreaks in non-endemic areas. Increased air travel undoubtedly has increased the risk of such introductions during recent decades [11]. Acquiring infection, human-human transmission (maternal-fetal transmission, sexual, blood transfusion, organ transplantation and laboratory exposure [29] and possibly through saliva and breast milk [44] could make infection complex [11,44,50].

The Potential Risk Factors for Zika Virus Epidemics

Role of climate change

Climate change based vector population dynamics and the vector-borne diseases are attributed to the global diseases burden accounted to the epidemics disrupting of health security with huge socioeconomic impacts in the area [60,61]. The memories of diseases, including Zika virus infection, showed climate change related response [62,63] resulted in challenging for control and prevention. The ongoing in climate change manifested by rising of temperature and other factors were attributed to climate change dependent diseases epidemics [64,65].

Like other viruses spread by mosquitos and ticks [8,66], Zika virus could soon enjoy a greater reach, thanks to climate change [61]. The warmer and humid areas of Africa, Central and South America, Mexico, and the Southeastern United States are suitable for the prominent Zika's vector, *A. aegypti* mosquito [60]. The rough sketch of these mosquitos' life cycles and dietary blood feeding habit, and their reproduction in standing water showed their preference to warmer and relatively stable temperatures. Water filled containers such as buckets, barrels or tires were identified as good egg hatching environment [60,65].

The situation is prevalent in developing Asian and African countries under poor hygiene associated with poverty. These are affected most likely by climate change. It was suggested that the wormer springtime were suitable for the abundance of the vector mosquito in the Southeast and some Arizona Cities of USA attributing to the risk of ZIKV infection [60] in the area.

Contribution of travelers and globalization

Besides the contribution of climate change, the meteorological conditions, travelers from Zika-affected areas have greater role for introduction of the disease in previously free area. Most of those populations were of in poor socioeconomic conditions which facing abundant mosquito population in the area. Mosquito density are expected higher in areas where the living of population below the poverty line [60] especially in developing countries that could be without air conditioning and torn house enable mosquitoes to enter homes more easily. However, *A. aegypti* preferred and flourish in urban dens populated areas, while some of them preferred damp rural area [50,51,60,63].

Zika virus Pathogenesis and Associated Symptoms

Zika virus tissue tropism

Following the infection of vector mosquito from infected person with blood, the virus need to stay long enough, probably a week or more, in mid-gut until suitable ambient temperature for travel to salivary glands achieved. Once the virus in the mosquito saliva, transmission to health individuals happened while biting during feeding [21,60]. Following acquiring of infection, the pathogenesis of Zika virus information was not well documented.

However, the pathogenesis scheme of other vector borne filaviviruses is considered where they initially replicate in local dendritic cells at site of inoculation. Virus spread was happened to the local lymph nodes and the bloodstream [32,58] in the forms of viremia. Experimental study conducted 40 and 60 years ago in mice, indicated brain tissue cell tropism of Zika virus. George Dick and colleagues in 1947 preformed experimental study where Zika virus strain (MR 766) was intracerebral inoculated into 5-6 week old Swiss mouse with serum from infected febrile sentinel Rhesus macaque, and finally isolated the virus from the brain [2] to show brain cell tropism. Although it was thought that replication of filaviviruses was in the cell cytoplasm, certain study suggested the viral antigen can be found in the nuclei of infected cell [14,39]. Zika virus has been detected in

human blood at early infection following illness onset. Viral RNA has also been detected as late as 11 days post onset of the illness [67]. Therefore, in connection with isolation of virus from various tissues, secretion and excretion [42,44,50,54] it can be concluded that Zika virus has multiple tissue tropism in infected human.

Viral pathogenesis

In mice, the pathological lesions of Zika virus was limited to central nervous system (CNS) and manifested neuronal degeneration and cellular infiltration in spinal cord and brain areas in the form of Cowdry type–A inclusion bodies [2]. Beyond the CNS, other tissue including kidney, lung, spleen and liver were supposed to be not infected with the virus. Unlike mice, it was confirmed that other animals including the cotton rats, guinea pigs, rabbits and rhesus monkeys did not developed CNS disease, even after intracerebral inoculation [2,3,40].

Post infection symptoms and differential cases

It was reported in Africa and Southeast Asia, that the virus causes fever, headache, conjunctivitis, myalgia, rash and joint pains in humans [14,68]. Following infection with Zika virus, the symptoms are mild, unrecognized and may last for 2-7 days. It was misdiagnosed as Dengue, Chikungunya, West Nile fever or other viral infections giving similar symptoms as described with flaviviral infections [14]. Only one out of four people infected with Zika virus are believed to develop symptoms [2,16]. About 80% of people who are infected do not become sick. Twenty percent of those become sick shows characteristic Zika virus symptoms characterized by fever, rash, joint pain and conjunctivitis. The illness last several days to weeks in the forms of mild [69]. Although severe clinical manifestations that require hospitalization are uncommon and fatality has not been observed [70], reporting of the Guillain-Barrı Syndrome (GBS) indicates presumed Zika virus infection [16,70]. The symptoms like arthralgia, edema of extremities, mild fever, head-aches, retro-orbital pain, conjunctival hyperemia and maculopapular rashes usually spreading downward from the face to the limbs and frequently pruritic, vertigo, myalgia, and digestive disorder are observed [71].

On the other hand, in a more serious cases, two neurological conditions were reported by Dhurba [72] one with microcephaly characterized small head size with incomplete brain development which may occur when mother gets infected during the first trimester stage of pregnancy. The other second one is with GBS where a person's own immune system damages the nerve cells, causing muscle weakness and sometimes, paralysis in replaces to Zika virus infection reaction [72,73]. The GBS was usually manifested by progressive weakness in response to neuronal damage which initiated from lower limbs and ascends proximally within few weeks. It was accompanied with motor dysfunction and paralysis whereby patients are presenting with reduction or absence of deep tendon reflexes, The syndrome can also extended to cranial nerve disorder [12,72] to the level brain tissue damage. Thus, Zika virus infection was supposed to produce such neurological disorders, too.

Attempt to Control and Prevent Zika virus Infection and Spread

Recently the challenges associated with the development of better diagnostic techniques, and potential therapeutic issue and vaccine for Zika virus was commented by Shan et al. [74].

Diagnosis of Zika virus infection

For the control and prevention action as well as for therapeutic drug development purposes, attempt were made to identify the virus using different diagnostic techniques. Two types of diagnosis for ZIKV were recommended. The direct detection of the virus and/or viral components both from vector mosquito and patient, and the indirect detection of antibodies elicited by ZIKV infection [74,75]. RT-PCR in acutely used to investigate viral RNA. Although there were a challenge in sero-cross reactions with those of other flaviviruses, serologically ZIKV specific IgM detection can also be applied [74]. Thus, the molecular technique (RT-PCR), immunological assay and virus isolations techniques have been recognized for the viral RNA, viral proteins (particularly the NS1 protein) and the live virus detection from various sample from infected cases, respectively [74]. Hence, preferred samples sources were the blood and urine of infected individual [75]. Musso and Gubler [73] have reviewed serological reports of human Zika virus infection from 1954-2014. However, the limitation of serological assays is associated with antibodies cross-reaction derived from different Flavivirus infections [74] mainly from Dengue virus and Chikunguny virus infections [32,74,75].

Therapeutics

Currently, there is no clinically approved therapy for any Flavivirus including for ZIKV [74,75]. According to Shan et al. [74] and Schapiro [75] symptomatic therapy including plenty of rest, fluids rehydration, uses of acetaminophen to reduce fever and pain (but no use of aspirin or non-steroidal anti-inflammatory drugs) were recommended. Although there were no chemotherapy, yet, two strategies were proposed for Zika virus antiviral drug development. The primary suggestion was cost effective one, which consider structural functional manipulation and reformulation of the clinically existing antiviral compound to use as potential for Zika virus treatment [76,77]. The second strategy is to develop legitimate inhibitors of ZIKV infection and replication. Thus, both virus infection and viral enzyme assays could be used to identify the inhibitors from compound libraries. These assays have been extensively employed for Dengue virus drug discovery [8] which need to screen for Zika virus in a logical ways of viral treatment. Considering Zika virus structural, functional and molecular profile, the mechanisms of action of the suggested drugs includes inhibitions of either NS3 (protease and helicase activity), NS5 (RNA-dependent RNA polymerase and methyl-transferase activities) and/or E-protein (fusion activity) [78]. On the other hand, there could be possibility of Zika virus drug resistance development, like that of other Flavivirus, was also suggested and it could be due to swift strains changing the targeted single gene to specific drug. Therefore, it was recommended to use combinations of drugs with multiple targets of action as strategy to overcome the developments of such strain [45,78,79]. On other proposed Zika virus treatment is immunotherapy which involves passive transfer of IgG and the use of human monoclonal antibody for neutralizing [79,80]. In this case, consideration should be made for immune/tissue-compatibility of the donor and recipients.

Vaccination

Currently there is no ZIKV vaccine globally [72]. Shan et al. [74] reported the conceivability of ZIKV vaccines developments in the form of both inactivated and live attenuated virus vaccines. They also suggested biotechnological vaccine [81] approach which contain or express ZIKV structural proteins include subunit, DNA (cDNA-RNA

based) and viral vector vaccine platforms and test the vaccines for their preventive potential. All of them have their own advantages and disadvantages. Given the current urgency, all of the above approaches should be concurrently pursued to expedite the development of an effective vaccine [74].

Vector control and bio-security

The primary focus of transmission prevention is protective measures from mosquito bites throughout the day. According to CDC [21] and DCHH [82] everyone should use the 4-D's defined as DEET (All Day Every Day interaction based use of approved insect repellents); Dress (outdoor wearing of long-loose-light-colored clothing); Drain (Remove all standing water including those in pet dishes, washing pools and birdbaths several times a week around home); and Dusk and Dawn (limiting outdooring activities during active time of the mosquito). Prevention of re-bite by mosquito after onset of illness also help to control secondary infection with other strains of the virus as well as to prevent local transmission and circulation of the virus [9,12,21,47].

Human-Human transmission control

World Health Organization [17] recommended travelers who's with immune disorders or sever chronic illnesses to consult physician before travelling. Men who reside in or have travelled to an area of ongoing Zika virus transmission who have a pregnant partner should abstain from sexual activity or consistently and correctly use condoms during sexual intercourse [53]. Particularly, such activities were useful for control and limiting of human-human transmission, mother-fetus transmission and introduction of virus in new area.

Future aspects of Zika virus

Even though exact spatiotemporal emerging of Zika virus were not known, with only first isolation in Zika Forest-Uganda, the present spread of infection in the world is difficult to scale in connection to climate change and global movement of human beings. The characteristic challenging with Zika virus are associated with its mild symptoms and nonspecific clinical signs, in availability of effective diagnostic laboratory technologies, and sero-cross-reactivity complicates of the virus with other flavivirus within Dengue endemic areas [83]. Nevertheless, given historically high incidence of Dengue virus in the ZIKV infected region and the recent world Chikungunya virus infection experiences, millions of Zika virus infections should be expected in a continues viral spreading [7] in the future. Recently global climate change accounted for the increases vector with the incidence and spread of vector borne diseases including Dengue and Chikungunya. Now Zika virus too. Both the Zika virus and its vector mosquito (*A. aegypti*) will be suggested to be emerging with parallel globalization and rapid urbanization [84] in connection with urban preference of principal vector mosquito. Other possible future challenging for spread of Zika virus include viral mutations affecting transmission or virulence and viral introduction to previously unexposed populations leading to epidemic spread. Further research will be required to determine the associations of adverse birth outcomes and GBS with presence and effects of change in Zika virus virulence [11]. In one way or another, the global risk of Zika virus expansion were mapped under the current situation [27,26] which need updating of the progresses of viral and vector spread in connection with multifactorial epidemiology in the world under a programmed conditions.

Conclusions and Recommendations

Accidental detection of Zika virus in the past associated with doubtful vector-borne disease introduction into a new ecological system get attention for the emerging of the diseases. The present radical spread with significant implications on human health dew frustration at global level. The significant rise in the number newborn babies with characteristic microcephaly and neurological disorders, being with evidence of Zika virus detection in their tissues and that of mother, declared a global emergency [17]. Such explosive spread of ZIKV poses challenges for public health preparedness and surveillance [11]. With regards to its tissue tropism, it can be concluded that Zika virus has multiple tissue tropism in infected individual. ZIKV infection epidemic becoming important due to the most recent unpredicted clinical presentations, difficulty to evaluate the pertaining risks and diseases severity, absence of specific diagnostic reagents, techniques and trained manpower, particularly in developing African and Asians countries. The lake of high-tech molecular virology and pathogenic mechanisms are also on other challenging issue to specify the disease epidemiology. Thus, the future of ZIKV is unpredictable. But, as its transmission is frequently vector mediated (mosquitoes such as *A. aegypti* and *A. albopictus*), Zika virus has the potential of emergence to very large scale. Hence, the vector favoring entire tropical and subtropical world interlinked with recent global climate change are at high risk of ZIKV epidemic in the future.

All areas with suitable environment (water, favour warm and moist climates) for establishment and breeding of *A. aegypti* [60] should enhance surveillance strategies and work on monitoring the *A. aegypti* density and human traveling in connection with the disease emergence. Travelling, especially pregnant women in any trimester, to the affected or endemic areas, should consider the risk for contracting Zika virus [85]. Defined and prioritized research on Zika virus epidemiology, diagnostic techniques, therapeutic drug and preventive vaccine development shall be implemented. Burst feed transmission should also be checked. Strengthen and capacitating of diagnostic laboratories, risk communication technology and trained manpower are found relevant for developing countries.

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