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Review Article

Review on Zika Virus Infection: An Overview

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ABSTRACT

Globally, one of the recent causes of public health concern is the one caused by the arthropod-borne flavivirus transmitted by mosquitoes, called Zika virus. In all over the world, approximately, 1.5 million people have infected with this ZIKV disease. This disease is isolated in 1947 from the serum of Rhesus macaques in the forests of Africa, the virus has been quickly emerging on the landscapes of western hemisphere over the past few years (Africa, Asia and Oceania), as a health threat to the masses. From 1969 to 1983 the geographical distribution of Zika virus expanded to equatorial Asia – including Pakistan, Malaysia, India and Indonesia. The Zika virus is phylogenetically related to other medically important mosquito-borne flaviviruses of global public health significance, such as Japanese encephalitis, West Nile, dengue, and yellow fever viruses .The Zika virus infection causes Zika fever that is responsible for several neurological complications like Guillain-Barre Syndrome and congenital malformations like microcephaly in infants born to infected mothers. The primary mode of transmission of ZIKV between humans is through the bite of an infected female mosquito of the Aedes species, which are widely spread in tropical areas. Common diagnostic approaches used for the detection of the virus include molecular amplification (RT-PCR) on serum samples and serological testing for detection of ZIKV IgM antibodies. No Zika virus vaccine exists. There are no licensed antiviral drugs to prevent or treat ZIKV infection or disease. In vitro and in vivo evaluation of therapeutic efficacy of several different types of vaccines, drugs as wells as compounds with anti-ZIKV activity is being carried out that offers hope for human protection against this catastrophic epidemic. The other various alternatives are being evaluated for optimized surveillance, patient management, and public health intervention in the current Zika virus epidemic.

1. INTRODUCTION

Zika virus (ZIKV) is an Aedes mosquito borne flavivirus that is the recent cause of a pandemic and public health concern. It was first isolated in April 1947 from the serum of Pyrexial rhesus monkey found in the greens of Zika forests in Uganda, Africa. In 1948, ZIKV was isolated from Aedes africanus mosquitoes indicating that the virus might be mosquito-borne. Virus has been so called as Zika virus after the locality from where it was first isolated. Zika virus has been quickly emerging in the western hemisphere over the past few months [1].

Sero-surveillience studies in humans, suggest that Zika virus is widespread throughout Africa, Asia and Oceania [2]. It was first detected in humans in Brazil, in the northeast and was subsequently recognized in other states and several South American countries including Colombia, Ecuador, Suriname, Venezuela, French Guiana and Paraguay. Transmission has been known in Central America (Panama, El Salvador, Honduras and Guatemala), the Caribbean (Martinique, Puerto Rico, Dominican Republic and Haiti) and Mexico. Transmission also occurred in travelers returning from the infected regions to non-endemic countries including United States, Canada, Japan and Western Europe. However, these studies may overestimate the virus's true prevalence, given serologic overlap between Zika virus and related flaviviruses, such as dengue virus (DENV) and West Nile virus (WNV) [2].

In early 2015, an outbreak of ZIKV occurred in the state of Rio Grande do Norte, Brazil. Results of analysis revealed a high likeness of the sequences with Asian lineage. One theory regarding the introduction of ZIKV in Brazil is the arrival of the new emergent virus in 2014, during FIFA World Cup. In March 2015, another outbreak of ZIKV was occurred in the state of Bahia. The results of investigation on this outbreak showed that the obtained ZIKV sequences belonged to the Asian lineage with 99% identity with a sequence from a ZIKV isolate from French Polynesia and extend to other Pacific Islands. Since January 2016, a sum of 20 countries in the Americas has reported ZIKV infections [1]. Given the immense information available on Zika virus, this literature review focuses on the Zika virus epidemic globally especially India and the ways to combat this virus successfully.

2. HISTORY AND DISCOVERY

Zika virus was first isolated from the serum of a Rhesus macaque in the Zika forest, while studying yellow fever. One year later, the virus was also found in the mosquito Aedes africanus which was caught on a tree platform in the same forest. The virus as a transmissible agent was first isolated and described by a group of researchers at the East African Virus Research Institute in Entebbe, Uganda in 1952. In 1952 the first human cases were noted by detecting neutralizing antibodies to Zika virus in the sera of individuals from Uganda and also from the United Republic of Tanzania [3].

The discovery of ZIKV and many other arboviruses was a result of the research programs on yellow fever sponsored by the Rockefeller Foundation from 1914 to 1970. ZIKV was discovered in the course of a study of the vector responsible for the cycle of sylvan Yellow fever virus in Uganda[4] .Over a 10-year period from1937 to 1947, 10 different viruses were isolated at the Yellow Fever Research Institute, Entebbe, Uganda, including 7 new viruses: (1) WNV (1937), (2) Bwamba virus (1937), (3) Semliki Forest virus (1942), (4) Bunyamwera virus (1943) (5) Ntaya virus (1943) (6) Uganda S virus (1947) (7) ZIKV (1947) . Four of these viruses were related, belonging to the genus Flavivirus (WNV, Ntaya virus, Uganda S virus, and ZIKV) [5]. It was subsequently isolated from a human in Nigeria in 1954. From its discovery until 2007, confirmed cases of Zika virus infection from Africa and Southeast Asia were rare. The first outbreak of the disease outside of Africa and Asia was in April 2007, on the island of Yap in the Federated States of Micronesia. The condition was characterized by rash, conjunctivitis, and arthralgia, and was initially thought to be dengue. The Chikungunya and Ross River viruses were also suspected. However, serum samples from patients in the acute phase of illness contained RNA of Zika virus [6].

In 2007, however, a major epidemic occurred in Yap Island, Micronesia. More recently, epidemics have occurred in Polynesia, Easter Island, the Cook Islands and New Caledonia [7, 8].

From 1969 to 1983 the geographical distribution of Zika virus expanded to equatorial Asia – including Pakistan, Malaysia, India and Indonesia. For example, in 1983, 13% of human volunteers based in Lombok, Indonesia, had neutralizing antibodies to Zika virus [9].

3. CLASSIFICATION AND NOMENCLATURE

Zika virus (ZIKV) belongs to the genus Flavivirus in the family Flaviviridae. Currently, the genus comprises 53 virus species, which are transmitted by the bite of mosquitoes (27 species), ticks (12 species), or no known arthropod vector (14 species). Within the Flavivirus genus, ZIKV is a mosquito-borne virus that is phylogenetically closely related to other medically important mosquito-borne flaviviruses of global public health significance, such as Japanese encephalitis virus (JEV), West Nile virus (WNV), dengue virus (DENV), and yellow fever virus (YFV). These mosquito-borne flaviviruses can be divided into two major classes based on their clinical presentation in humans: encephalitic flaviviruses (represented by JEV and WNV), which cause invasive neurological diseases, with birds serving as their natural vertebrate hosts and Culex species mosquitoes as their principal vectors ; and non-encephalitic or viscerotropic flaviviruses (exemplified by DENV and YFV), which cause lethal hemorrhagic fever, with non-human primates acting as their vertebrate hosts and Aedes species mosquitoes as their primary vectors [10].

4. VIROLOGY AND PATHOGENESIS

ZIKV is an approximately 11 kb positive-sense RNA virus that belongs to the genus Flavivirus in

the family Flaviviridae, which includes several other mosquito borne viruses of clinical importance. Its closest relative is Spondweni virus, the only other member of its clade. Virions of ZIKV are 40–60 nm in diameter, spherical in shape and have a lipid envelope [7].

The Zika virus genome contains 10,794 nt encoding 3,419 amino acids. Like other flaviviruses, Zika virus is composed of 2 non-coding regions (5′ and 3′) that flank an open reading frame, which encodes a polyprotein cleaved into the capsid, precursor of membrane, envelope, and 7 nonstructural proteins. The genomic RNA has a single long open reading frame flanked by 5′- and 3′-terminal non-coding regions that shape specific secondary structures necessary for genome replication and translation .A key component on the surface of the virus is E protein that plays a role in the receptor binding and membrane fusion. The domain III of E protein includes a group of epitopes which are targets in neutralizing antibodies, serological tests and vaccines. Mosquito vectors adaptation and easy transmission of virus may be related to loss of N154 glycosylation site in the E protein. In addition, NS1 codon usage modification to human housekeeping genes that could make viral replication easier and increase viral titers may be related to the new spread of the Asian lineage of ZIKV to the Americas and Oceania [4, 6].

A study of Zika virus's molecular evolution, based on viral strains collected from 4 countries in West Africa during 1947–2007, identified several sites within the Zika viral genome that were under strong negative selection pressure. This finding suggests frequent purging of deleterious polymorphisms in functionally important genes and the possibility of recombination, which occurs rarely among flaviviruses [11].

Pathogenesis of ZIKV is almost unknown; however, it is found that mosquito-borne flaviviruses initially replicate in dendritic cells close to the inoculation site and then spread to lymph nodes and the blood. Moreover, infectious ZIKV has been detected in human blood before the beginning of symptoms .After mosquito inoculation of a human host; the virus enters skin cells through cellular receptors, enabling migration to the lymph nodes and bloodstream. Few studies have investigated the pathogenesis of Zika virus infection. One study showed that human skin fibroblasts, keratinocytes, and immature dendritic cells allow entry of Zika virus. Several entry and adhesion factors (e.g., AXL receptor tyrosine kinase) facilitate infection, and cellular autophagy, needed for flaviviral replication, enhancing Zika virus replication in skin fibroblasts [2].

After cellular entry, flaviviruses typically replicate within endoplasmic reticulum-derived vesicles. Although flaviviral replication is found to occur in cellular cytoplasm, studies suggest that ZIKV antigens can be found in nucleus of the infected cells. This finding suggests a location for replication that differs from that of other flaviviruses and merits further investigation. After the replication, ZIKV may distribute from the lymphatics and blood stream to infect other organs of the body such as myocardium, central nervous system, skeletal muscles and to the fetus [6].

5. GENETIC DIVERSITY

ZIKV is one of the two viruses in the Spondweni virus clade and is very much similar to the Spondweni virus, which was first identified in South Africa [2, 7, 11, 12].

Genetically, it was postulated that the virus originated in East Africa and then spread to West Africa (West African or Nigerian cluster) and Asia (Asian genotype) approximately some 50-100 years ago. Phylogenetic analysis shows that Zika virus can be classified into distinct African and Asian lineages; both emerged from East Africa during the late 1800s or early 1900s [13].The Asian lineage originated during the virus's migration from Africa to Southeast Asia, where it was first detected in Malaysia. From there, Zika virus spread to the Pacific Islands, separately to Yap and French Polynesia, and then to New Caledonia, Cook Islands, Easter Island, and the Americas. Phylogenetic data based on the nucleotide sequence of all 29 complete or near-complete ZIKV genomes retrieved from GenBank (as of May 2016) have confirmed that all the eighteen 2015–2016 American epidemic strains are derived from a common ancestor of the Asian lineage, the same strain which has been circulating since the 2013 outbreak in French Polynesia [10]. Despite its considerable degree of genetic variation, little is known about the impact of viral genetic variation on the pathogenicity of ZIKV of the African and Asian lineages, as well as among different strains

within the Asian lineage. Thus, more research is needed to extend our understanding of the evolution and diversity of ZIKV and to explore the biological effects of viral genetic variation on the outcome of ZIKV infection.

6. ZIKA VIRUS FEVER

Though Zika fever is a mild self-limiting disease, it has gained importance due to the increasing incidence of neurological complications following Zika fever like Guillain-Barre Syndrome and congenital malformations like microcephaly in infants born to infected mothers [1, 2, 10].

7. TRANSMISSION

The primary mode of transmission of ZIKV between humans is through the bite of an infected female mosquito of the Aedes species (including Aedes aegypti, Aedes albopictus, Aedes africanus and yellow head aedes mosquitoes), which are widely spread in tropical, sub-tropical (Aedes aegypti) and temperate (Aedes albopictus) areas [1, 2, 4, 14].

8. MODES OF TRANSMISSION

8.1. VECTORS

A vector may be defined as an arthropod that transmits the virus from one vertebrate to another by bite. The most common mode of biological transmission is infection during a viremic blood meal and injection of infectious saliva during blood feeding (horizontal transmission). The virus 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.

The Aedes aegypti mosquito appears to be the major vector in Asia and was the suspected primary vector for the French Polynesia outbreak .Aedes mosquitoes are widely distributed globally, and native habitats of most species are warm tropical and subtropical regions [15].

ZIKV is transmitted by Aedes mosquitoes, which are daytime active and aggressive biters. The virus has been isolated in species in the genus Aedes, such as Aedes aegypti, Aedes albopictus, and in arboreal mosquitoes such as Aedes furcifer, Australopithecus africanus, Aedes luteocephalus, Aedes apicoargenteus, Aedes vitattus, and Aedes hensilli. A 10 days' incubation period has also been identified with these vectors [6, 9 2, 1].

The mosquito acquires the virus during a blood meal, following which the virus replicates and is transmitted to a host at the next meal. Isolation studies of the virus and the antibodies against the virus from various non human primates and other wild animals suggest multiple reservoirs for the virus. Most of the arboviruses cause zoonoses that usually depend on nonhuman animal species for maintenance in nature. Many animal species are host reservoirs of arboviruses ; humans, with few exceptions (DENV, CHIKV, or YFV) are dead-end or accidental hosts (hosts from which infectious agents are not transmitted to other susceptible hosts) [4].

8.2. NON VECTORS

8.2.1. 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. This report was further supported in 2015 by Musso et al., who found a high viral RNA load and replicative virus in the semen and urine of the hematospermic patient, which had developed 2 weeks after clinical cure and clearance of virus from his blood, suggesting that sexual transmission of the virus can occur after recovery from the infection also [16]. The prolonged presence of the virus has been detected in the semen up to 62 days after onset of febrile illness. Another case of sexually transmitted ZIKV infection was reported in February 2016, at the Dallas County Health and Human Services department [16].

8.2.2. PERINATAL TRANSMISSION

Substantial evidence now indicates that Zika virus can be transmitted from the mother to the fetus during pregnancy. The detection of RNA of ZIKV in fetal amniotic fluid has been reported, indicating that the virus had crossed the placenta and possibly caused mother to child infection. Such fetuses had cerebral abnormalities that were detected by ultrasonography, and viral antigen and RNA have been identified in the brain tissue and placentas of children who were born with microcephaly and died soon after birth, as well as in tissues from

miscarriages. The frequency of and risk factors for transmission are unknown. These reports suggest that ZIKV may have the potential to infect the fetus and potentially cause neuro-developmental dysfunction, especially microcephaly [17].

Two cases of peripartum transmission of Zika virus have been reported among mother–infant pairs. Zika virus RNA was detected in both infants; one infant had a mild rash illness and thrombocytopenia, whereas the other was asymptomatic. Intrauterine transmission of the virus has been discovered when the Zika virus RNA was found by reverse transcription PCR (RT-PCR) in amniotic fluid of 2 mothers with symptoms of Zika virus infection during pregnancy, delivered babies with microcephaly. Probable intrapartum transmission has also been described wherein 2 newborns were found to be viremic with Zika virus <4 days after being born to infected mothers. The likely routes of perinatal transmission are transplacental during delivery, breastfeeding and by close contact between the mother and her baby through saliva and other body fluids exchange. Transmission through breast milk has not been documented, although the breast milk of a woman who became symptomatic with Zika virus infection on the day of delivery contained infective Zika viral particles in high titer. Although it is possible that ZIKV could be passed from mother to fetus during any trimester of pregnancy, limited data from one study has indicated that ZIKV maternal infection in the first trimester might carry a greater risk of fetal microcephaly [18].

8.2.3. BLOOD TRANSFUSION

Although the transmission of Zika virus through a blood transfusion has yet to be reported, it is likely to occur, given the transmission of other, related flaviviruses through this route [19].When an outbreak of ZIKV was reported in French Polynesia between 2013 and 2014, 3% of blood donations tested positive for zika virus by reverse transcriptase PCR [14]. Given that the majority of persons with ZIKV infection are asymptomatic and among them are blood donors, to prevent blood transfusion related ZIKV infection, blood donations must also be screened for ZIKV In February 2016, the Brazilian health officials reported the infection of ZIKV from blood transfusion from an infected donor. Then it became essential to screen the blood samples for ZIKV before transfusion in reported areas of ZIKV outbreaks [6]

8.2.4. OTHERS

ZIKV infections have also been documented through laboratory exposure [20].Occupational transmission of the virus can occur in the laboratory, suggesting that precautionary measures be taken by the researchers and health workers when handling suspected ZIKV and other related infected samples.

Other supposed routes of transmission are mucocutaneous contact to the virus in infected blood, hemodialysis or transplantation [18].

ZIKV has also been detected in the saliva of 19.2% of infected individuals and was found in patients' urine , but the epidemiological significance of these kinds of body fluid have not yet been determined. It is unidentified whether ZIKV can be spread by respiratory droplets. 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. These findings indicate that ZIKV may interact with other known viral infections, which call for rapid assessment [16].

Further studies are required to delineate the importance of these modes of transmission.

8.2.5. ANIMAL BITES

ZIKV is most likely maintained in a sylvatic cycle that includes non-human primates and mosquitoes with cyclic epizootics among monkeys in Uganda. Another emerging facet of the zoonosis has been the probable transmission through bites of monkeys and other non-human primates. In the sylvatic transmission cycle, humans possibly serve as incidental hosts; however, in areas without non-human primates, humans probably serve as primary intensification hosts. One case of Zika virus transmission occurred after a monkey bite in Indonesia. Two infections in laboratories have been reported. A volunteer became infected after subcutaneous injection of infected mouse brain suspension.

9. SYMPTOMS FOR ZIKA VIRUS INFECTION

ZIKV infection in humans starts following a bite from an infected mosquito with, the incubation period for Zika virus being about 3-12 days after the mosquito bite. Symptoms may last about 4-7 days. Approximately 60%-80% of infections do not produce any symptoms or signs [2].

Reports have shown that ZIKA fever has non specific clinical symptoms. According to the CDC, infection with Zika in most cases causes only mild flu-like symptoms with Fever, Skin rash, Red eyes, Joint pain, Fatigue, , Myalgia (muscle pain), Conjunctivitis, Asthenia, Headache, being the most common symptoms [1].Other indications include lymphadenopathy, edema, retro‑orbital pain, and diarrhea [1,9]. 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. What makes it harder to detect is that only 1 in 5 people even develop symptoms, which could be one of the reasons why it spreads so fast. There is no specific date of clinical onset, and the beginning of the illness is usually subjective [1].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).

Moreover, links between Zika outbreaks and Guillian-Barre Syndrome (GBS), an illness in which the body's own immune system attacks the nerves, have been reported in the past for several countries in the Americas and French Polynesia. In severe cases of GBS, the individual can be completely paralyzed. Further evidence is needed to establish a causal link between Zika virus infection and these neurological/neuro developmental impairments or auto-immune conditions [2, 10].

Besides, there is a potential for Zika to cause birth defects, specifically microcephaly. Congenital central nervous system malformations such as microcephaly in fetuses and newborns from mothers possibly exposed to Zika virus during pregnancy were also notified during recent Zika disease outbreaks.

10. DIAGNOSIS AND TREATMENT

Evaluation of clinical manifestations of Zika virus infection alone is unreliable for diagnosis of Zika virus infection. This is mainly because of clinical overlap with other arboviruses. Evaluation for Zika virus, CHIKV, and DENV should be undertaken concurrently for all patients who have acute fever, rash, myalgia, or arthralgia after recent (previous 2 weeks) travel to an area of ongoing Zika virus transmission. Commercial assays have been developed, including a PCR-based assay that has been approved by the Comminutes European (RealStar Zika Virus RT-PCR Kit 1.0, altona Diagnostics, Hamburg, Germany) and a serologic assay that has been approved by the US Food and Drug Administration for restricted use in emergency situations.

10.1. LABORATORY DIAGNOSIS

Molecular amplification (e.g., RT-PCR) on serum samples remains the most specific diagnostic approach and is the preferred testing method for Zika virus during the acute phase of illness (<7 days from symptom onset) . The viremic period is believed to be small, as the virus can be detected in the blood from day 0 to 4 after the onset of symptoms. The time required for the recognition of viral RNA in blood may also depend on the viral load during the acute phase of the disease, because viremia decreases over time. A negative PCR result in blood collected 5–7 days after the onset of symptoms does not exclude the flavivirus infection. Therefore, serologic testing should be considered [1, 6, 2, 21].

Serologic testing (i.e., enzyme-linked immunosorbent assay or immunofluorescence assays) is used for the detection of ZIKV IgM antibodies from day 4 to 5 after the onset of symptoms. In general, the time duration for which the specific IgM antibodies for flaviviruses remain detectable is 2–3 months, but sometimes for a longer period of time, while the specific IgG antibodies remain detectable for several months. Other arboviruses , specially those linked with chikungunya and dengue may also interfere with the serologic testing and cause false-positive results for ZIKV infection limiting its specicficty.

Besides, serologic testing is not recommended during the acute phase, when Zika virus IgM may be undetectable. Therefore, positive serologic test results should be confirmed with a confirmatory seroneutralization assay such as plaque reduction neutralization test to ascertain the specificity of the observed antibodies [6].

At present, there is no validated commercial assay for ZIKV serological diagnosis. Therefore, serological confirmation should be performed in a laboratory with expertise in discriminating flaviviruses.

Various other specimens, at different time frames, may also be used for the detection of ZIKV RNA particularly when blood collection is difficult. The detection period of ZIKV RNA in saliva (6–8 days after the onset of symptoms) is not considerably longer than the presence of RNA in blood. However, it is advantageous because of being non-invasive, and one study reported even higher sensitivity in testing [6].

Similar to other flaviviruses, urine may also be used to detect ZIKV RNA. In fact, ZIKV may stay in the urine and remain positive for a longer duration than in the serum. Several studies have reported the detection of ZIKV RNA in urine more than 10 days after disease onset. Still at this point, there is no validated data that suggests the replacement of blood with urine as a sample specimen [1, 2, 6].

A study has reported the time of stay of ZIKV in the semen of infected men for more than 3 weeks, while another study has reported ZIKV RNA in the semen for up to 62 days [6, 21].

Although diagnostic testing is performed primarily on serum or cerebrospinal fluid, the diagnostic utility of other specimen types (e.g., urine, saliva, amniotic fluid, placenta and tissue) is being evaluated.

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 post-symptom onset

• Utilization of pan‑Flavivirus technique together with sequencing

• Serological tests such as Elisa which specifically detects an anti‑Zika IgM.

Recently, Moulin et al. developed an algorithm for the detection of Zika infection in travelers who returned with nonspecific febrile illness from areas with concurrent epidemics [22].

10.2. TREATMENT, PREVENTION AND CONTROL

As with the other mosquito-borne flaviviruses , treatment for uncomplicated Zika virus infection focuses on treatment of symptoms .ZIKV illness is generally mild in nature, requiring no specific treatment. No Zika virus vaccine exists; thus, prevention and control measures focus on avoiding mosquito bites, reducing sexual transmission, and controlling the mosquito vector. There are no licensed antiviral drugs to prevent or treat ZIKV infection or disease. Infected patients should increase their fluid intake and rest for longer durations. Fluid loss through vomiting and sweating should be corrected with adequate rehydration [23].

Potentially effective methods that are focused on reducing infections among pregnant women include avoiding unnecessary travel to areas of ongoing Zika virus transmission, avoiding unprotected sexual contact with partners who are at risk for Zika virus infection, and using mosquito repellent, permethrin treatment for clothing, bed nets, window screens, and air conditioning [6].

The most effective A. aegypti vector control relies on an integrated approach that involves elimination of A. aegypti mosquito breeding sites, application of larvicides, and application of insecticides to kill adult mosquitoes. However, each of these approaches has substantial limitations Community-level strategies target mosquito breeding through elimination of potential egg-laying sites (e.g., potted plant saucers, water storage units, and used tires) by drying wet environments or using insecticide treatment.

Men who reside in or have traveled to an area of active Zika virus transmission and who have a pregnant partner should abstain from sexual activity or use condoms during sex; similar guidelines apply for men with a non-pregnant female sex

partner who is concerned about sexual transmission of Zika virus.

Once infection has occurred, diligent clinical monitoring and supportive care are the mainstays of treatment. Caring for patients with severe ZIKV disease manifestations, especially patients who were exposed in utero, are challenging for all involved and require a substantial allocation of health care resources that are often limited in their availability. Because of these challenges, the WHO has called for development of a ZIKV vaccine, with an initial focus on protecting women of childbearing age.

Two recent reports describing the successful testing of experimental ZIKV vaccines in animal models one by Pardi et al. and another by Richner et al. are welcome news. Both groups engineered messenger RNAs (mRNAs) with sequences encoding the ZIKV precursor membrane (prM) glycoprotein and envelope (E) glycoprotein. The E protein is critical to viral attachment, entry, and replication in the infected host [24].

In the case of ZIKV vaccines, most of the available data have been generated with the use of animals that have had no previous exposure to flaviviruses; these animals are not representative of most human populations, which will probably be immunized once a vaccine is available. Past successes with other flavivirus vaccines, together with more recently obtained ZIKV data, suggest that perhaps neutralizing antibodies will be required and are sufficient to confer protection against ZIKV. Despite the challenges, the pace of ZIKV vaccine research and development has been impressive. The recently published data from Pardi et al. and Richner et al. represent an important step toward the goal of protecting people from ZIKV through active immunization [24].

11. ZIKA VIRUS IN INDIA

On 15 May 2017, India notified first confirmed cases of Zika Virus Disease to the World Health Organization. Although Zika is no longer a Public Health Emergency of International Concern, WHO maintains that vigilance to Zika needs to remain high. Ever since the suspected causal association between Zika virus and microcephaly and GBS was declared as a Public Health Emergency of International Concern in February 2016, WHO has been supporting the Ministry of Health and Family Welfare for enhancing Zika virus surveillance and scaling-up vector control measures among other activities.

Cases of Zika in India are not unexpected, as all countries with Aedes mosquitoes are potentially at risk for local mosquito-borne Zika virus transmission. It is strongly suspected to cause birth defects and neurological problems in newborns and as birth rate is high in the country special care needs to be taken. Since India provides fertile climate for the aedes aegypti mosquito to grow and multiply, there is the potential of an outbreak situation in the country. Till such time as India remains unaffected, there is a window of opportunity to prepare. It also gives an opportunity to test the plans.

12. RESEARCH AND FUTURE OUTLOOK

The ZIKV disease is believed to have infected 1.5 million people around the world since its outbreak in Brazil and dramatic spread globally. Scientists are warning people living in tropical climates, and especially pregnant women, about this new and alarming virus that once only affected subtropical forests in Africa as an emerging public health threat.

The neuroteratogenic nature of ZIKV infection is posing serious threats to unborn lives therefore, it is necessary to develop an ideal ZIKV prophylactic or therapeutic agent urgently. Researchers are having tough time finding a treatment for ZIKV partly because of serious consequences of vaccines and drugs to unborn lives and pregnant women. However, in vitro and in vivo evaluation of therapeutic efficacy of DNA vaccine, recombinant subunit vaccine, and ZIKV purified inactivated vaccine offers hope for human protection. Large number of food and drug administration (FDA) approved drugs as wells as compounds with anti-ZIKV activity offer valuable opportunity to control the massive bio-burden of this catastrophic epidemic [25].

Based on the previously acquired experience with other flaviviruses, different ZIKV vaccine platforms have been developed and proved to be highly efficacious in preclinical studies in mice and nonhuman primates. ZIKV vaccine technologies

included purified inactivated viral (PIV) particles, purified virus-like particles (VLPs) and viral subunit proteins, live-attenuated vaccines, chimeric vaccines, and viral and nonviral vectors encoding ZIKV structural proteins. PIV vaccines are safe because the inactivation process eliminates virus replication while maintaining the antigenicity of the structural proteins. Their immunogenicity is lower than that of live-attenuated viral vaccines, thus requiring booster doses. VLPs and viral subunit proteins have the same safety and immunogenic features of PIV vaccines. Due to their good safety profile, their use is advisable in immunocompromised individuals and in pregnant women. Experimental studies in mice and in Rhesus macaques demonstrated that an alum-adjuvanted formalin-inactivated PIV vaccine derived from the Puerto Rico ZIKV strain induced envelope (E)-specific antibody and cell-mediated immune response, neutralizing antibodies, and complete protection against challenge with homologous or heterologous strains of ZIKV. Phase I clinical studies are currently investigating safety and immunogenicity of this PIV vaccine in healthy male and nonpregnant female adult subjects who are naive to flaviviruses or with previous immunity against flaviviruses [26].

Vector-based vaccines are designed to deliver viral antigens that are targeted by protective immune responses.

Research activities for the production of ZIKV vaccines during the last year have been intense and extraordinary, leading to the development of several candidate vaccine platforms, which have been demonstrated to be highly immunogenic and protective in relevant animal models, including studies in nonhuman primates. Some of these vaccines have already passed on to experimentation in humans in phase I and phase II clinical trials, and results are expected to be available soon.

Finally, live-attenuated and replication-competent vaccines are expected to provide long-term immunity and to be highly effective. However, these vaccines should be avoided in immunocompromised individuals and in pregnant women because of the risk of reversion of pathogenicity, induction of vaccine-associated disease, and infection of the fetus [25, 26].

Besides, two novel approaches that have shown considerable promise in recent years are the genetic control of A .aegypti mosquitoes and the development of mosquitoes that are resistant to arbovirus infection [27].

The first field-trialed genetic control strategy is known as RIDL (the Release of Insects carrying Dominant Lethal genes) and involves the mass rearing of A. aegypti that have been genetically modified to express a repressible lethal gene. During their rearing in insectaries, the mosquitoes are provided with a dietary supplement not present in nature (eg, tetracycline), and this supplement represses the lethal gene activation. Only male mosquitoes are released and these compete with wild males to mate with wild females. Offsprings do not survive to the adult stage because they do not receive the dietary additive in the wild. Lines of RIDL males have been shown to have minimal fitness costs (ie, they are competitive with wild males) and the recent field release in Bahia, Brazil, reportedly achieved a 95% reduction in local mosquito populations.

An alternative approach is the use of endosymbiotic bacteria to prevent arboviruses replicating within the mosquito. The Wolbachiabacteria from Drosophila fruit flies can prevent DENV transmission in A. aegypti mosquitoes without significant fitness costs.Wolbachia has also been shown to inhibit the replication of additional arboviruses such as chikungunya virus and yellow fever virus, strongly suggesting potential inhibitory effects against ZIKV.Whereas RIDL is a self-limiting approach (the genetic modification is not perpetuated in wild populations), Wolbachia-based control strategies rely on this endosymbiont successfully invading wild mosquito populations.
An important benefit of these environmentally friendly, species-specific approaches is the reduced dependence they pose for insecticides—an increasingly important feature of future disease vector control. Moreover, suppressing the mosquito population, or rendering it arbovirus-resistant, holds great potential in the simultaneous control of ZIKV, DENV, chikungunya, and yellow fever viruses. 150 countries presently have A. aegypti and are vulnerable to future outbreaks with all of these viruses. Implementing these novel technologies across the globe must be considered because of the multifaceted benefits they possess in controlling several emerging infectious diseases.

These strategies provide baseline data and roadmap to prosecute further research for the development of novel therapeutic strategy to curb the explosive rise in ZIKV, which is useful to help the large vulnerable sections of the society.

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