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ZIKA VIRUS: A GLOBAL HEALTH CHALLENGE FOR POLICY MAKERS

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ABSTRACT

Zika virus (ZIKV), a flavivirus first identified in Uganda in 1947, has emerged as a significant global health concern. Although generally presenting with mild symptoms, its association with severe neurological conditions such as microcephaly and Guillain-Barré syndrome (GBS) has raised alarms worldwide. In 2016, the World Health Organization (WHO) declared ZIKV a Public Health Emergency of International Concern (PHEIC), underscoring the urgency of coordinated action. This paper outlines the virology, epidemiological history, clinical features, transmission mechanisms, diagnostic methods, complications, vaccine development efforts, and policy-level implications. A multifaceted public health strategy focused on vector control, robust diagnostics, vaccine development, and risk communication is crucial to mitigating the ongoing and future threats posed by ZIKV.

KEYWORDS: ZIKV, microcephaly, Guillain-Barré syndrome, flavivirus.

INTRODUCTION

The past two decades have seen a rise in vector-borne viral infections, with diseases such as dengue, chikungunya, and Japanese encephalitis posing serious threats globally. Among these, ZIKV has gained attention due to its rapid geographic expansion and unusual complications. Though initially confined to Africa and Asia, ZIKV outbreaks in the Pacific Islands and the Americas marked a turning point in its global epidemiology. The WHO's declaration of ZIKV as a PHEIC highlighted the pressing need for global awareness and preparedness. Despite typically mild clinical presentations, the virus's potential to cause congenital anomalies and neurological disorders has added to its public health importance.

ZIKV, an arthropod borne virus(arbovirus) is a negative sense RNA containing Flavivirus, which is now being considered as an emerging threat to the world, especially in the tropical countries. Recently, first autocanthous transmission of ZIKV has been reported in Brazil but the first evidence of human infection was noted in 1952.[1] Sporadic cases and serological evidences of ZIKV were reportedshowing that ZIKV was active in several Asian and African countries before emerging in pacific region and America. There was not a single publication on this virus from 1983 to 2006 until the Yap island outbreak.[2] This paper entails a complete overview of the ZIKV, its epidemiological characteristics, situational analysis, clinical presentations, complications and way forward.

ZIKV Confined within African and Asian limits

The history dates back to sixty years from now, when ZIKV was first isolated from a rhesus monkey, RH766, who was part of Rockefeller Foundation's program for research on jungle yellow fever. The monkey had been placed in a cage on a tree platform in the Zika forest (*zika* meaning "overgrown" in the Luganda language), near the East African Virus Research Institute in Entebbe, Uganda. After the episode of febrile illness in monkey, a transmissible agent was isolated by intracerebral inoculation of serum into the mice. This agentcame to be known as ZIKA virus, which was named after the ZIKA forest.[3,4] After that the ZIKV was also isolated from *Aedes africanus* mosquitoes trapped in the same forest. In laboratories, transmission of ZIKV from Aedes aegypti to different animals was reported in 1956. The virus was then isolated from humans in Nigeria during studies conducted in 1968 and during 1971–1975. In one of thosestudies, 40% of the persons tested had neutralizing antibody to ZIKV.[5] In next 30 years(1951-1981) serological evidence of ZIKV was found in many African and Asian countries such as Uganda, Tanzania, Egypt, Central African Republic,

Sierra Leone, Gabon, India, Malaysia, the Philippines, Thailand, Vietnam, and Indonesia.[6] At the same time, the virus was isolated from Aedes aegypti mosquitoes in Malaysia and Côte d'Ivoire and humans in Senegal. In 1981 serologic evidence of ZIKV illness in Indonesia was found by Olson et al.[7] The spatial and temporal milestones of ZIKV has been briefly illustrated in Table 1.

ZIKV hits Pacific

Before 2007, no transmission of ZIKV was reported outside of Asia and Africa. The first documented ZIKV outbreak was reported from Yap island which is the westernmost of the four states of The Federated States of Micronesia. Yap state comprises of four closely grouped islands and several outer islands with a population of 7391 persons (2000 census data). The outbreak was noted by physicians on this island and was characterized by rash, conjunctivitis, subjective fever, arthralgia, and arthritis. In the initial investigation three patients tested positive with a commercially available dengue IgM kit, but due to slight differences in clinical manifestations, the confirmation was sought from Centre for Disease Control and Prevention (CDC). They isolated ZIKV RNA from14% of the serum sample by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay in Arbovirus Diagnostic and Reference Laboratory at Colorado. Later in the prospective surveillance, 49(26%) of 185 cases were confirmed to be suffering from ZIKV infection. The estimate of infected patients was 73% (CI 95%, 68-77) of the population; hospitalization and fatal cases were not reported.[8]

No further Zika cases were detected in the Pacific until October 2013, when an explosive outbreak occurred in French Polynesia. The French Polynesian outbreak confirmed 383 ZIKV cases which lasted for six months (October 2013 to March 2014) and is estimated to have infected more than 32,000 cases or 86% (95% CI: 75-93%) of the population. Considering the close geographic and cultural ties, the subsequent outbreaks in Easter Island (January to May 2014; 89 suspected cases of which 51 were confirmed), in New Caledonia (January to July 2014; more than 1,385 confirmed cases and January to May 2015; 82 confirmed cases; and in the Cook Islands (February to May 2014; 932 suspected cases of which 54 were confirmed)can be attributed to the outbreak in French Polynesia. The travel pathways between these pacific islands also support the strong suspicion.[9,10]

American Continent Comes in contact with New Flavivirus

ZIKV strikes American continent in February 2014 when the first case of indigenous transmission of ZIKV was confirmed by Chilean public health authorities on Easter Island (Chile), and since then cases were reported until June 2014.In early 2015, ZIKV infection was reported in Brazil during ongoing outbreak of an illness characterized by macula-papular rash, fever, myalgias/arthralgia, and conjunctivitis caused by DENV and CHIKV.[8,11] The Brazilian Ministry of Health(MOH)in May 2015 confirmed autochthonous transmission of ZIKV in the north-eastern part of the country which was the first documented outbreak in Brazil and in the Americas. It was also estimated that between 497 593 and 1 482 7013 cases of Zika virus infection have occurred since the outbreak began.[12] In October 2015, the Ministry of Health of Colombia reported the first autochthonous case of ZIKV infection in the Department of Bolivar and ZIKV was laboratory confirmed in 9 of 98 samples from Bolivar in October 2016 itself.[13] The presence of ZIKV vector in different regions underlines the potential of virus to spread further in American continent and beyond as seen in recent outbreaks in different parts of world. Till date around 84 countries have showed the signs of transmission of ZIKV(Table 2). The risk potential is accentuated with urbanization and globalization in urban settings where Aedes mosquito is present which has been the case with Chikungunya and Dengue disease spreading worldwide. From October 2015 onwards there has been accelerated rate of ZIKV spread in South and Central America.

Virology

ZIKV is a member of family flaviviridae which consist of single stranded positive sense RNA having10,794 nucleotides encoding 3,419 amino acids. The closest relative of ZIKV is Spondweni virus which is the only other member of the clad within the mosquito-borne cluster of flaviviruses. Ilheus, Rocio, and St. Louis encephalitis viruses are the next related members. The other members of the family are yellow fever virus, dengue, Japanese encephalitis, and West Nile viruses. [14]There have been two ZIKV lineages African and Asian, in which African lineage is further split in East and West African clusters some authors described three different lineages (West African, East African and Asian).[10,15] The Asian lineage is expanding,which is evidenced by its emergence during the recent outbreaks in Pacific and South America. [16]

The pathogenesis of ZIKV is not known due to scarce information but as it is a mosquito-borne flaviviruses, theseare believed to replicate initially in dendritic cells near the site of inoculation, which then spread to lymph nodes and the bloodstream.[17] It is a well-known fact that flaviviral replication occurs in cellular cytoplasm but ZIKV virus antigen could be found in infected cell nuclei also.[18] Infectious ZIKV has been detected in human blood as from the date of onset of illness to 11 days after onset of illness and in animal studies the virus was isolated from the serum of a monkey 9 days after inoculation.[15,19] ZIKV is known to be killed at temperatures over 60°C and chemicals such as potassium permanganate /ether.[20]

Transmission

The transmission dynamics of ZIKV closely resembles the other emerging arboviruses like Dengue and

Chikungunya. The resemblance is not only limited to vector similarity but also the trend in spread across continents and following same path.[21]

The vector responsible for ZIKV transmission are Aedes mosquitoes and is known to be transmitted by the bite of infected females. Initially ZIKV was adapted to an enzootic cycle, involving arboreal mosquitoes in Africa, but with recent outbreaks is a cause of great concern for public health officials all over the world due to its adaption to an urban and peri-urban cycle involving human as reservoirs and urban mosquitoes as vector. The involvement of Aedes aegypti and other mosquitoes of Stegomyia subgenus such as A. africanus, A. apicoargenteus, A. luteocephalus, A. aegypti, A. vitattus, and A. furcifer is a potential threat to more than half of world population living in urban and peri-urban areas.[10, 20]

The perinatal transmission and sexual transmission has been reported and virus has also been isolated from semen and urine sample in one of the cases. Although the most common mode of transmission is vector borne but perinatal and sexual transmission has been reported. Also the virus has been isolated from urine and semen samples.[21-23] During French Polynesian outbreakan unexpectedly high number of asymptomatic blood donors (42/1,505; 3%) were found to be having ZIKV infection and it represents the potential risk to transfusion safety.[24] Although significance of this mode of transmission is currently unknown but the possibility cannot be ruled out and several questions remain unclear related to the possible impact of ZIKV in blood transfusion.[25]

Laboratory Diagnosis

ZIKV can be tested in a Biosafety level (BSL)-2 facility.[26] Tests for ZIKV should be done in view of signs and symptoms corresponding to the infection. Since the samples required to be tested have not been well established, therefore all the possible samples of serum, EDTAplasma, saliva, urine and semen should be collected as per CDC guidelines.

- Acute phase(3-5 days): Detection of viral genome by RT-PCR in maternal serum and amniotic fluid.
- In Convalescent phase (≥5 days): − Serology by testing IgM antibodies in blood. Plaque Reduction Neutralization Test (PRNT): this is a confirmatory diagnosis.

Other serological tests applied in the diagnosis are complement fixation test, hemagglutination inhibition, Immunoglobulin M antibody capture enzyme-linked immunosorbent assay(MAC-ELISA) and capture ELISA for IgG and ELISA (double antigen sandwich) kits.[27]

Clinical Symptoms

Historically the majority of the cases caused by ZIKV infection were considered self-limiting and clinical picture of its syndrome varies from no signs and symptoms to an influenza-like viral illnesses seen in other epidemic arbovirus infections including DENV and CHIKV. The clinically apparent febrile illness is observed in approximately 20 % of the infected individuals although hospitalization is rarely required. The most frequent reported symptoms during the yap island outbreak included maculopapular rash (90%) followed by fever (65%), arthralgia/ arthritis (65%), non-purulent conjunctivitis (55%), Myalgia (48%), headache (45%). Other constitutional symptoms were retro orbital pain, edema and vomiting.[9] Along-with the abovementioned symptoms malaise, dizziness, anorexia, photophobia, gastro intestinal disorders, sore throat, cough, aphthous ulcers, back pain, sweating and lymphadenopathies are some of the other reported symptoms in different outbreaks.[28,29] These symptoms are non-specific and Zika fever can be easily confused with other bacterial and viral infections, especially with other arboviruses in endemic areas.

According to WHO epidemiological update on Zika, the case definition of

1. Suspected case includes Patients with rash or elevated body temperature (> 37.2 °C) with one or more of the following symptoms (not explained by other medical conditions): a) Arthralgia or myalgia b) Non-purulent conjunctivitis or conjunctival hyperemiac) Headache or malaise
2. A suspected case with laboratory positive result for the specific detection of Zika virus.[30]

Microcephaly and ZIKA: Strong Plausible association.

The increased incidences of microcephaly in recent times amongst new born in some parts of the world have been linked to ZIKV suggesting a causative association between microcephaly in newborns and ZIKV infection during pregnancy. Although not proven, researchers are studying the possible linkage between this surge in microcephaly cases in neonates and ZIKV infection and still strong evidences are needed to confirm or refute it.[31]

Microcephaly is a congenital condition associated with abnormal brain development. The long-term sequel of incomplete brain developmentdepends on underlying brain anomalies and can range from mild developmental delays to severe motor and intellectual deficits like cerebral palsy. Apart from congenital infections, microcephaly can result from chromosomal abnormalities; exposure to drugs, alcohol, or other environmental toxins; premature fusion of the bones of the skull (craniosynostosis); and certain metabolic disorders. This entity became a matter of research in September 2015, when Brazilian health authorities began to receive reports of an increase in the number of infants born with microcephaly from physicians of northeast Brazil region where an outbreak of Zika virus infection was recognized in early 2015. In October 2015, the Brazil Ministry of Health (MoH)confirmed an upsurge in

birth prevalence of microcephaly in this region compared with previous estimates (approximately 0.5/10,000 live births) based on review of birth certificates and reports of major congenital anomalies.[32,33] The Brazil Ministry of Health taking different theories into consideration behind the microcephaly outbreak established a task force to investigate the possible association of microcephaly with Zika virus infection during pregnancy and a registry in November 2015 for incident microcephaly cases (head circumference ≥2 standard deviations (SD) below the mean for sex and gestational age at birth) and pregnancy outcomes among women suspected to have had Zika virus infection during pregnancy.[29,33]

In registry, among a cohort of 35 infants with microcephaly, born during August–October 2015 in eight of Brazil's 26 states, the mothers of all 35 had lived in or visited Zika virus-affected areas during pregnancy. The major findings include 25 (71%) infants had severe microcephaly (head circumference >3 SD below the mean), 17 (49%) had at least one abnormality during neurological examination and among 27 infants who underwent neuroimaging studies, all had abnormalities, with calcification being most common. Tests for other congenital infections were negative. All infants had a lumbar puncture as part of the evaluation and cerebrospinal fluid (CSF) samples were sent to a reference laboratory in Brazil for Zika virus testing; results are not yet available.[33,34]

In December 2015, PAHO reported the identification of Zika virus RNA in amniotic fluid samples from two pregnant women by reverse transcription polymerase chain reaction (RT-PCR). The fetuses in these two women were found to have microcephaly by prenatal ultrasonography and Zika virus RNA from multiple body tissues including brain was isolated from an infant with microcephaly who died in the immediate neonatal period. These events prompted new alerts from different authorities including variousMoH, the European Centre for Disease Prevention and Control and CDC concerning the possible association of microcephaly with the recent outbreak of Zika virus infection.[34,35]

In recently published preliminary report from Cohort Study carried out in Rio de Janeiro it was seen that out of 42 pregnant women with PCR positive ZIKV infection 12 had some abnormality in ultrasonography or Doppler, including intrauterine growth restriction, CNS findings, and fetal death. And it is important to be kept in mind that all these mothers were without any other known risk factors for adverse pregnancy outcomes as they were screened for various congenital infection after enrollment in study.[32]

There are at least 2 ecological Studies, 1 cohort study and 11 case reports/ series from brazil only and 2 case reports / series from other countries which have been published till date. All these studies have shown biological evidences/ temporal association of microcephaly with ZIKV outbreak.[36]

It is interesting to know that the virus which was present for last 60 years and as associated with mild illness in endemic areas has suddenly gained the world attention due to microcephaly. Till recently no fetal cases of ZIKV infection was reported even in the endemic areas. But this may be due to possible early acquisition of immunity in endemic areas underreporting of cases, or due to the rarity of the disease until now. The recent upsurge of microcephaly in ZIKV infected mothers can be topic of immunological research and may be attributed to genomic changes in the viruswhich have been reported recently.[37,38]

ZIKA and Guillain barre Syndrome: Lesson from French Polynesia Outbreak

Guillain-Barre syndrome (GBS) is an acute polyradiculoneuropathy caused by the body's immunesystem typically occurring after minor viral and bacterial infections. Motor function is usually affected, beginning distally and progressing proximally over up to a 4-week period. Patients have generalized weakness, areflexia, and a varying degree of sensory disturbances and involvement of cranial nerves.[39,40,41] The pathophysiology is incompletely understood, but is known to mostly occur 2–8 weeks after an infection. Guillain-Barre syndrome is the leading cause of non-traumatic paralysis, with a global incidence of 1–4 per 100 000 persons-years. The range of infections reported to have preceded Guillain-Barre syndrome include upper respiratory infections, notably influenza and pseudo-influenza, digestive tract infections, notably Campylobacter jejuni, as well as Cytomegalovirus and Epstein Barr virus.[42]

During the French Polynesian outbreak there was 20-fold increase in the incidence of GBS in the island country. In recently published case control study it was seen that 42 patients who developed a Guillain-Barre syndrome during the Zika virus outbreak had experienced Zika virus infection. The antibodies IgG or IgM were present in 98 percent of GBS group and was significantly associated with it (p value <0.0001). This study by Cao-Lormeau VM et al provides the first strong evidence for association between GBS and ZIKV infection.[40] Similarly in case of El Salvador outbreak 136 GBS cases have been reported 3 months(5 December 2015 to 5 March 2016) which is substantially more for a quarter year compared to the annual average number of GBS cases.[43]

In 2015 in the Brazilian state of Bahia, 42 GBS cases were reported, among which 26(62%) had a history of symptoms consistent with Zika virus infection. A total of 1708cases of GBS were registered nationwide, representing a 19% increase from the previousyear (1439 cases of GBS in 2014), though not all states reported an increase in incidence (35,43). A total of 12 ZIKV

affected countries have reported increased GBS incidence and/or laboratory confirmation of ZIKV infection among GBS cases.[44]

As with microcephaly, Zika virus association with GBS is under evaluation although case control study has demonstrated association between two but there are still many unanswered questions. Especially the variability in disease in different regions. An outbreak of Zika virus infection in Cape Verde during2015–2016 involving thousands of cases and possibly caused by an African strain of the virus has not been linked to any neurologic disorders. Further investigations are needed to identify the potential role of other factors (including infections) known to be associated, or potentially associated, with GBS.[36] GBS being one of the differential diagnosis of acute flaccid paralysis(AFP) so the surveillance of AFP may be utilized for searching of GBS cases due to ZIKV.

ZIKV vaccine: A Promise for future

The production of ZIKV vaccine is in pipeline and may be available by the end of this year. The race of production of vaccine is on and very soon it will be reality as the vaccine is easy to produce. The Phase I clinical trial will be started by mid or late summer once the volunteers are enrolled but this would be only after the approval of regulators such as United States Food and Drug Administration / Health Canada according to a Canada based vaccine developer. But other groups are less confident about the early prospects for a vaccine considering the longtime usually associated with vaccine development. Recently dengue vaccine launched by Sanofi's Pasteur was only approved last month which took 20 years in the making. Although some of them feels that it would take 3-5 years for full production but the possible candidate was based on an existing vaccine against dengue and other on a vaccine against West Nile which makes the schedule of vaccines convincingly fast.[45] The possible association of ZIKV with adverse pregnancy outcomes makes pregnancy a vulnerable group and should be considered a priority group for developing as well as evaluating vaccines. [46]But the issue remains that of safety evaluation which is the cornerstone of any vaccine development. The robust mechanism has to be devised during its clinical trials as it's a pregnancy related vaccine but safety assessment is a real challenge. Although there is an increased attention on the evaluation of safety of immunization in pregnancy but barriers remain such as lack of standard definitions of outcomes and measurement of these outcomes. [47]Although there are several barriers in developing vaccines for pregnant women but these barriers are surmountable with collaborative efforts and strong stewardship. So these vaccines may not be useful for these outbreaks but certainly it will be of great help in any future epidemics.

Public health implications

Even with limited evidence linking Zika virus to neurologic disorders, the severe potential risks demand immediate firm action to protect public health. Now the concern of policy makers worldwide should be on the various preventive and rehabilitative measures against infection and its complication since the treatment modalities are still in nascent stage. The vaccine is one of the corner stone in prevention and remains a viable option but the battle must focus on the mosquitoes. The adaptation of ZIKV to an urban or peri-urban cycle, involving Aedes aegypti and other mosquitoes of the Stegomyia subgenus as vectors and humans as amplification hosts, should be of prime concern to public health officials. With more than half of the world's human population living in areas infested with these mosquitoes, the potential for major urban epidemics of ZIKV, DENV, CHIKV, yellow fever, epidemic polyarthritis, and other as yet unknown mosquito-borne viruses that might emerge, is irresistible, and underscores the desperate need to develop more effective mosquito control.[20] The approaches to involve the release of genetically modified male mosquitoes to interrupt reproduction are being examined. The complication of ZIKV in pregnant women is of great concern and should be dealt delicately. The affected pregnant women should be provided with appropriate choices considering the social and medical implications. The prohibition on abortion should be exempted in cases of microcephaly with strict vigilance. This kind of exemption already exists for anencephaly in countries like Brazil but yet to be done in cases of microcephaly. Many countries have issued travel advisory for travelers visiting ZIKV infected regions to wear condoms for a month while having sex with man(oral, vaginal or anal). This has been done with the possibility of its sexual transmission and virus being isolated from sperm though it may not be major mode of transmission.[48]

The WHO recommends applications of key interventions such as integrated vector control; personal protection against mosquito bites; provision of appropriate management for all patients with Guillain– Barre syndrome and for women before, during, and after pregnancy; and prevention of Zika virus transmission through sexual contact or blood transfusion. Most of these may not be newinterventions, but they do need strengthening. Populations at risk must be informed of the potential current and future risks of neurologicdisorders through different channels, wherever the virus is being or could be locally transmitted. As the putative link between Zika virus and neurologic disorders is reinforced, refined, or even refuted, public health measures will be adjusted accordingly.[49]

Conflict of Interest: None.

Author's contribution: VH designed and planned the work. DK conceptualized the content of paper and reviewed the paper and gave major inputs in every section. NK made critical decisions on sequence alignment and did editing and proof reading. KS performed the major literature search and helped in

drafting the paper. AKM coordinated with the team and edited and reviewed the paper. MK carried out the editing, proof reading and reference management.

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Table 1: Historical milestones of ZIKV.

S. No.	Year	Milestones
1.	1947	First identified in Rhesus monkey in Uganda
2.	1948	Isolated from Aedesafricanus
3.	1952	Demonstration of antibodies in humans
4.	1954	First isolation of virus in man during Jaundice outbreak
5.	1956	Artificial transmission of virus to monkey and by Aedes ageypti
6.	1961	First isolation in Southeast Asia , from Aedes ageypti mosquito of Malaysia
7.	1968	ZIKV isolated from humans in Nigeria
8.	1971-75	Neutralizing antibodies to ZIKV in humans
9.	1951-81	Serological evidence of human ZIKV infection in some African and Asian countries
10.	2007	Outbreak in Yap island (outside Asia and Africa)
11	2013-14	Largest outbreak in French Polynesia
12	2014	ZIKV spread in other parts of pacific: New Caledonia, Cook Islands, Vanuatu, Solomon, Fiji. In total 11 countries showed transmission.
13.	2014	First indigenous transmission in Easter Islands, Chile (American continent)
14.	2015	Emergence of ZIKV in north Brazil
15.	February 2016	Documented ZIKV transmission in 48 countries.
16	August 2016	More than 69 countries have confirmed ZIKV transmission
17	March 2017	Till date 84 countries have been reported transmission (Last situation report on ZIKA virus by WHO
18	May 2017	India lately reported three cases of ZIKV to WHO(from Nov. 2016- Feb 2017) which was otherwise category 4 according to ZLKV classification.
19	2018	India reported 261 ZIKV cases, including significant outbreaks in Rajasthan (154 cases) and Madhya Pradesh (130 cases)
20	2021	India reported 234 ZIKV cases
21	2022	India reported 2 ZIKV cases
22	2023	India reported 23 ZIKV cases
23	2024	India reported 151 ZIKV cases, with Maharashtra accounting for 140 cases, Karnataka 10, and Gujarat 1

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