Zika: From Lush Forest to Pandemic

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Before the Zika fever had hit the headlines, Zika was known amongst the scientific community and bird-watchers as an overgrown tropical forest of Uganda, a protected area of about 25 hectares for research under the Uganda Virus Research Institute.

The Zika virus (ZIKV), causative organism of the Zika fever, is a member of the family *Flaviviridae*, genus *Flavivirus*. Genome of the Zika virus is a single stranded, non-segmented, positive sense 10794 bases long RNA[1] that encodes a 3419 amino acid long polyprotein. The polyprotein is subsequently cleaved into smaller proteins: the capsid (C), the precursor membrane (prM), the envelope (E), and the non-structural proteins (NS). The C proteins form the 25-30 nm diameter icosahedral capsid which is surrounded by a host-membrane derived lipid bilayer containing the envelop proteins E and M. The virion has a diameter of 40 nm and has surface projections of 5-10 nm.

The virion enters the host cell by receptor-mediated endocytosis (involving clathrin-coated vesicles) initiated by the binding of the E protein to a receptor protein on the host cell. The virus' envelop fuses with the endosomal membrane and the viral RNA is released into the host cytoplasm where it is translated by the host cell machinery to form the viral polyprotein. Replication of the viral RNA by the non-structural proteins released from the polyprotein occurs in cytoplasmic viral factories in the endoplasmic reticulum of the host cell and forms a double-stranded RNA genome. The negative-sense RNA copy of the viral genome is used as a template for transcription to form ssRNA genomes that are assembled into new virions in the endoplasmic reticulum, transported to the Golgi apparatus, and exocytosed outside the cell. Host cells initially infected by mosquito-vector bite are the epidermal keratinocytes, dermal fibroblasts, and immature dendritic cells. Subsequently the infection spreads to the lymph nodes and an immune reaction is mediated.[2] ZIKV antigens have been detected in the nuclei of infected cells.[3]

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An incubation period of 3-12 days has been suggested.[4] Extrinsic incubation period in mosquitoes is of about 10 days. About one in five infected persons develops symptoms that include fever, joint pain, maculopapular rash that spreads to palms and soles, and conjunctivitis. Other manifestations that may appear are anorexia, diarrhoea or constipation, abdominal pain, and dizziness. Myalgia, headache, retroorbital pain, edema, and vomiting have been reported less frequently.[5] Recovery occurs within a week and hospitalization is usually not required. Presence of ZIKV in blood can be detected by the presence of virus-specific Ig M antibodies.[5] However, they may cross-react with dengue virus and yellow fever virus. The presence of viral RNA in blood and urine can be confirmed by Real Time-Polymerase Chain Reaction (RT-PCR).[6,7]

The ZIKV was first isolated from a caged *Rhesus* monkey at Zika in 1947.[8] It was later found to be present in a mosquito collection from Zika, suggesting an enzootic mosquito-monkey cycle. It is now known to be an arbovirus like the chikungunya, dengue, West Nile, and yellow fever viruses, transmitted by the *Aedes* mosquito species (*A aegypti*, *A africanus*, *A albopictus*, *A apicoargenteus*, *A furcifer*, *A hensilli*, *A luteocephalus*, *A vittatus*, etc.). However, medical importance of Zika virus lost significance for the next four decades, during which human encroachment of the Zika forest continued. Occasional transmission to humans was encountered during this period. Since the infection is often asymptomatic or is associated with mild symptoms with no harsh outcomes requiring hospitalization, it did not generate much interest amongst the patients, physicians, research scientists, or governments, until 2007, when an outbreak was reported from Yap Island,

Micronesia.[5] Over 73% Yap residents above 3 years of age were estimated to be infected with Zika virus. However, no deaths, hospitalizations, or neurologic complications were reported. Since there was no evidence of mutation in the viral genome, the change in epidemic behaviour could be due to lack of immunity in inhabitants of Yap Island. Zika fever symptoms are mild and resemble dengue and chikungunya infections, therefore under-reporting may also be responsible for missing any previous outbreaks of the disease.

The ZIKV spread to countries of Africa, Asia, Pacific Islands and the Americas including Nigeria, Kenya, Ethiopia, Egypt, Cambodia, French Polynesia, Easter Island, Cook Islands, Senegal, Malaysia, Thailand, Haiti, El Salvador, Colombia, Honduras, Venezuela, Mexico and Puerto Rico. Three geographically distinct lineages of the virus were identified: two African and one Asian.[9] Sexual and perinatal transmission of the ZIKV has been reported,[10-12] and a potential risk of transfusion-transmitted ZIKV infection has been demonstrated recently.[13]

Recently, the Zika fever has been linked to the Guillain-Barre syndrome,[14] an autoimmune disease involving rapid-onset muscular weakness that may be triggered by a prior infection including infection by *C. jejuni* bacteria and viruses such as cytomegalovirus, Epstein-Barr virus, varicella zoster virus, and even the influenza virus. Trans-placental transfer of the Zika virus was indicated when its presence was detected in the amniotic fluid samples obtained from two pregnant women, whose foetuses had been diagnosed with microcephaly.[15] Microcephaly may result from congenital infection (e.g. toxoplasmosis (caused by a parasite found in undercooked meat), rubella, herpes, syphilis, cytomegalovirus and HIV), chromosomal abnormalities like Down syndrome, exposure to drugs, alcohol, and environmental toxins like arsenic or mercury, exposure to radiation, certain metabolic disorders, severe malnutrition during foetal life, and premature fusion of skull bones. The association between microcephaly and intra-uterine infection of Zika was strongly supported by the autopsy of the foetal brain of a late-pregnancy termination carried out on a European woman who had developed Zika fever in the thirteenth week of her pregnancy. A large amount of viral genomic RNA was detected in the brain, but not in any other organs of the foetus. There was no evidence of any genetic abnormality in the foetus, and no other pathogens were found.[16]

Brazil reported almost 4000 suspected cases of microcephaly by the end of January 2016, many of these were associated with neurological syndrome and congenital anomalies.[17] Since many congenital infections are associated with various forms of brain damage (e.g. rubella), a task force and registry was established by the Brazil Ministry of Health to investigate the ZIKV-related cases of microcephaly.[18] From a cohort of 35 infants with microcephaly born during a 3 month period from August-October 2015, 71% infants had severe microcephaly (head circumference ≤ 3SD below mean), almost 50% had one neurologic abnormality, and amongst the 27 infants who had neuroimaging studies, all were abnormal. The long term consequences of abnormal brain development in microcephaly can range from mild developmental delays to severe deficits in motor functions and/or intelligence.[18] The exact mechanism leading to microcephaly has not yet been elucidated, however, in a recent report published in the New England Journal of Medicine, Rasmussen et al have acknowledged the causative link between Zika virus and microcephaly.[19] Foetal growth retardation or even death, placental insufficiency, and injury to the foetal central nervous system have also been found to be associated with Zika infection during pregnancy.[20]

No specific antiviral treatment drugs or vaccines are currently available for ZIKV. Rest and symptomatic treatment are recommended. To prevent further spread of infection, persons suffering from Zika fever should avoid being bitten by mosquitoes by the use of nets and insect repellents, and should also avoid unprotected sex. Since Zika virus was detected in semen 17 days after acute infection, and the Zika virus RNA was detected in semen 62 days after the onset of symptoms,[21] infected males should avoid unprotected sex with female partners who may conceive or are already pregnant. Screening of blood samples for ZIKV RNA prior to transfusion has been suggested,[22] especially in case of transfusions to pregnant women; and suspected cases of Zika virus transmission by blood transfusion have been reported in Brazil.[23] Zika virus transmission through breast feeding or organ transplant has not been mentioned in medical literature.

Spread of infection can be checked by vector control: reducing breeding places for mosquitoes, insecticide spraying in mosquito habitats, release of genetically modified sterile male mosquitoes, avoiding mosquito exposure by using screens, bed nets, appropriate clothes, and insect repellent creams.

The Pan American Health Organization (PAHO) issued epidemiological updates and alerts urging enhanced surveillance of the disease, guidelines for international reporting, case management, and personal preventive measures.[17] The Centres for Disease Control and Prevention (CDC) issued a level 2 alert on 15th January, advising pregnant women to postpone their visits to countries with Zika infection.[20] On January 18, 2016, the World Health Organization announced its support to countries to control Zika.[24]

Many pharmaceutical companies are engaged in designing tests and vaccines for the ZIKV. However, their appearance in the market shall take some time. Besides, vaccinating entire populations may be prohibitively expensive. A better course of action is to implement public health strategies targeted at containing the infection. Development of broad spectrum anti-viral drugs that can be safely used in pregnancy is urgently required. Some countries have advised their women against planning a pregnancy until the epidemic has abated. The Zika fever is the first vector borne disease reported to infect the foetus and cause abnormal birth outcomes. The Zika virus is also the first vector borne disease that can readily spread by sexual means, and also has the potential to spread via blood transfusions.

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