Review Article

Current and Emerging Pharmacotherapies for Zika Virus: A Comprehensive Review

Queeny Wilcy Noronha[1], Thanshifa Fathima[1], Ramdas Bhat[2], A R Shabaraya[3]

From [1] UG student, Department of Pharmacy Practice, [2] Assistant Professor, Department of Pharmacology, [3] Principal and Head of Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Post Farangipete, Mangalore, Karnataka, India-574143

Corresponding to: Ramdas Bhat, Assistant Professor, Department of Pharmacology, Srinivas college of Pharmacy, Valachil, Mangalore -574143 Karnataka, India. **Email:** ramdas21@gmail.com, **Tel.:** +91 7795772463

ABSTRACT

Zika virus is a single-stranded RNA virus that belongs to the Flaviviridae family and was first identified in the Zika Forest of Uganda in 1947. Since 2007, there have been several outbreaks of Zika virus in various countries, with the most significant outbreak occurring in Brazil in 2015. The virus is primarily transmitted by infected Aedes mosquitoes, but it can also be sexually transmitted, transmitted through blood transfusions, and from mother to child during pregnancy. While most people who become infected with Zika virus experience mild or no symptoms, there is a potential for severe outcomes, including neurological complications like Guillain-Barre syndrome and congenital birth defects like microcephaly. This article provides an overview of Zika virus, its transmission, symptoms, and potential impacts on public health. Despite no specific antiviral treatment available for Zika virus, there are ongoing efforts to develop vaccines and treatments. The potential for sexual transmission of Zika virus has also led to recommendations for safe sexual practices, particularly for pregnant women or women who may become pregnant. Continued research is needed to better understand the virus and its potential impacts on public health, including long-term effects and the potential for the virus to be transmitted through other routes. The emergence of Zika virus as a significant public health concern highlights the need for continued vigilance and research to mitigate the potential impacts of this and other emerging infectious diseases. Given the threat of Zika virus and its ability to spread across international borders, global collaboration and coordinated responses are essential to address emerging infectious disease threats. It is essential to continue investing in research and development to reduce the impact of emerging infectious diseases on public health.

Key words: Zika virus (ZIKV), Mosquito, RNA, World Health Organization (WHO), Infection

An RNA flavivirus known as the Zika virus (ZIKV) was first discovered in Uganda, Africa, in 1947. For many years, the virus was not seen as a serious threat to public health; nevertheless, in 2007, an epidemic was discovered in the Yap Islands in the Pacific [1]. Further breakouts occurred in French Polynesia in 2015 after which they expanded to other Pacific Islands and, starting in 2016, migrated quickly into Americas [2]. The World Health Organization (WHO) declared a public health emergency in 2016 due to possibility ZIKV infection during pregnancy might have catastrophic consequences for the infant, such as microcephaly and neurological impairment [3].

Despite a decline in transmission since 2017, the virus is still present and outbreaks are still a possibility [4]. The emergence of ZIKV in South America has been the subject of extensive research, with previous reviews covering this topic [5]. Nonetheless, the emphasis of this review is on recent discoveries from 2019 to 2020, including updates on epidemiology, transmission, immunogenicity and host variables, clinical characteristics, and potential therapies [6]. As our understanding of the virus grows, ongoing research is assisting in the discovery of new strategies for ZIKV prevention and treatment. Nonetheless, the risk of outbreaks and the terrible side effects caused by ZIKV infection highlight the ongoing need for research into this virus and the development of effective treatments [7].

Epidemology

Human infection incidents were few and uncommon before 2007. Serological testing and viral isolation were the main sources of human infection reporting, which suggested extensive dispersion in Africa and Southeast Asia but no significant outbreaks [8-10]. In the island of Yap, there was an event in 2007, which resulted in 49 confirmed cases and 59 probable cases over the course of a four-month period [11-13]. With 294 confirmed cases over a 10-week period, French Polynesia had another significant outbreak in 2013 [14]. The virus entered the Americas in 2014. Cases of locally acquired infection were found on Easter Island, while instances in northeastern Brazil were discovered in 2015 [15-16].

The 2013 chikungunya virus epidemic was similar to the rising frequency of the Zika virus in the Americas [17]. Because most infected persons do not seek medical attention, it is challenging to assess the number of Zika cases [18].

While Colombia has reported more than 25,000 suspected cases, Brazilian officials believe that there have been close to 1.5 million infections since the outbreak started [19-22].

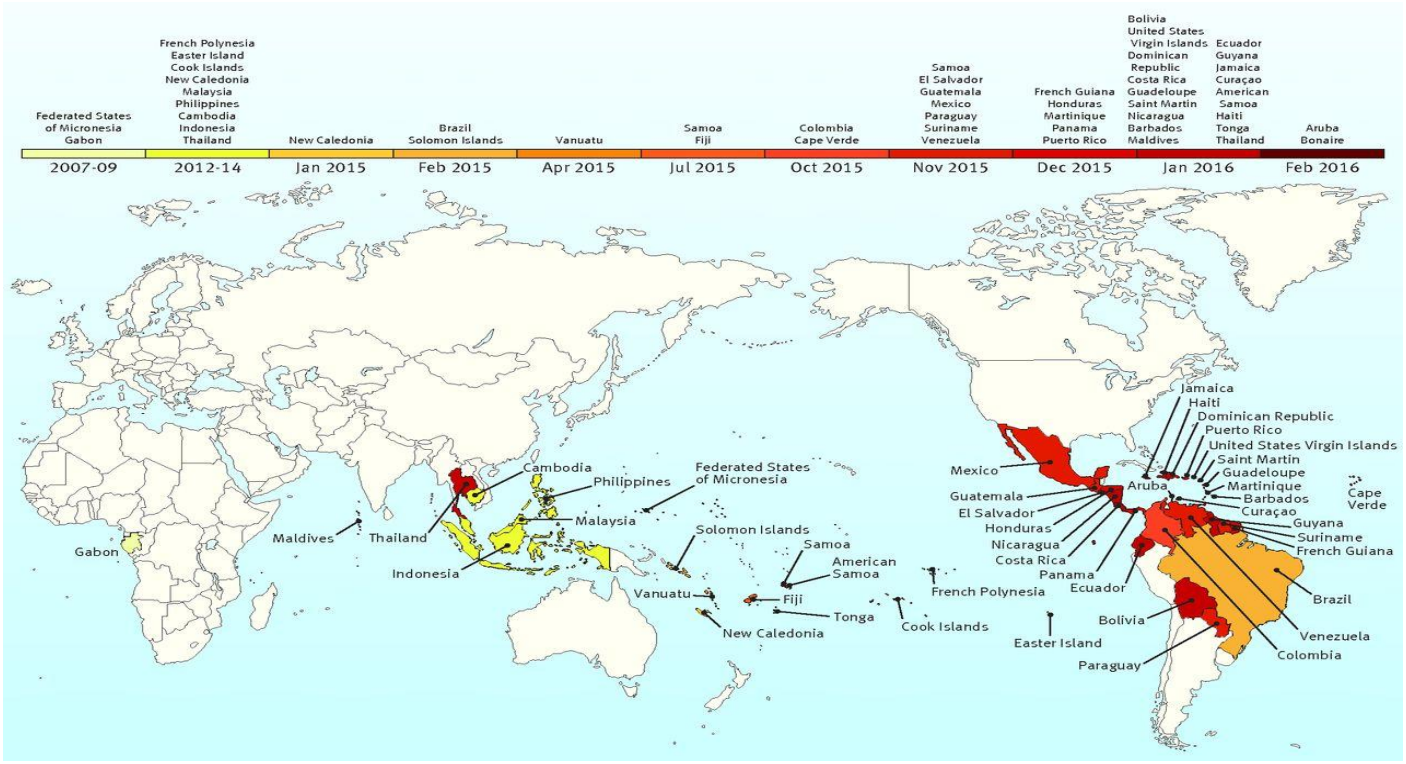

Figure 1: Areas of locally acquired Zika virus infection, June to February, 2016, Adapted from World Health Organization situation report,19 February 2016 [7]

Clinical Manifestations

The majority of Zika virus patients don't exhibit any symptoms. If so, symptoms are often mild (rash, fever, conjunctivitis, muscle and joint pain, malaise, and headache), start 3–14 days after infection, and last 2–7 days. Although other arboviral and non-arboviral conditions might also present with same symptoms, a laboratory confirmation of Zika virus infection is necessary [23].

Complications

Zika virus infection during pregnancy causes microcephaly and other congenital deformities in the foetus, such as limb contractures, high muscle tone, eye abnormalities, and hearing loss. Congenital Zika syndrome is the umbrella term for these clinical features. The risk of congenital deformities following Zika virus infection during pregnancy is unknown; it is estimated that 5-15% of babies born to mothers who contracted the virus while pregnant show signs of Zika-related problems. Congenital defects can develop after an infection, whether it is symptomatic or not. Preterm birth, stillbirth, and foetal death are other complications of zika infection during pregnancy [24].

Treatment

The current gold standard of therapy for Zika virus (ZIKV) infection is symptomatic treatment as there is no particular antiviral vaccine or medication available. It is important to take analgesics and antipyretics carefully to avoid side effects such hepatopathy, allergies, and nephropathy. As clinical diagnosis and serological analysis can be imprecise, aspirin administration should be avoided to prevent bleeding issues in individuals who have been incorrectly diagnosed with ZIKV infection [25]. A typical symptom of rashes is severe pruritus, which may be controlled by avoiding hot showers and overusing soap as well as using enough skin moisturisers. If these efforts are unsuccessful, calamine or menthol-based cooling creams can be utilised, and older antihistamine medications may offer comfort owing to their calming effects.

As it is uncertain how well corticosteroids would treat this ailment, they should be avoided [26]. The diagnosis of Guillain-Barré syndrome (GBS) should be made when the patient exhibits areflexia, clinical progression, and progressive weakening affecting two or more limbs over the course of up to four weeks. Because there is a possibility of respiratory muscle paralysis, patients with suspected GBS should be closely watched in intensive care units. Plasmapheresis and hyperimmune intravenous immunoglobulin (IVIG) are two treatment options for GBS that, although being pricey

treatments, shorten the time it takes for a patient to recover [27].

Virology and Pathogenesis

The Flaviviridae family, which also contains other medically relevant mosquito-borne viruses including DENV, WNV, and yellow fever virus, is home to the positive-sense, single-stranded RNA virus known as the Zika virus [28]. A polyprotein that is broken down into 10 proteins, including the capsid, envelope, and seven nonstructural proteins, is encoded by its 10,794-nucleotide genome. It also includes two noncoding sections at its 5' and 3' ends. Both the African and Asian subspecies of the virus originated in East Africa in the late 19th or early 20th century, and both have since migrated to numerous regions, including the Pacific Islands and the Americas [29].

Many genomic regions were shown to be under strong negative selection pressure in recent research on the molecular evolution of the Zika virus, which might have resulted in recombination events and the elimination of deleterious polymorphisms [30]. To ascertain the effect of this discovery on the virus's transmission, zoonotic maintenance, and epidemiology, more research is required. The AXL receptor tyrosine kinase and other entry and adhesion factors let the virus invade host cells through cellular receptors and infect keratinocytes, immature dendritic cells, and fibroblasts [31]. Zika virus antigens were exclusively found in the nucleus of infected cells, unlike other flaviviruses, suggesting a unique replication location that needs more research. Cellular autophagy boosts Zika virus replication in skin fibroblasts [32].

Diagnosis

The overlap with other arboviruses makes it difficult to reliably diagnose Zika virus infection based only on clinical signs. Because of this, a precise diagnosis requires laboratory testing. Patients with an acute fever, rash, myalgia, or arthralgia who have recently gone to places where the Zika virus is still being transmitted need to get tested for the virus as well as for CHIKV, DENV, and Zika virus. A PCR-based diagnostic and a serologic assay, both of which are commercially accessible and authorized for use in emergency situations, are both available.

Based on the clinical data supplied by the healthcare practitioner, the laboratory chooses the proper test.Serologic testing is not advised during the acute period of sickness; instead, molecular amplification tests, such as RT-PCR, are the method of choice. Nonetheless, if samples test negative for the Zika virus by RT-PCR, serologic testing can be taken into consideration. Due to cross-reactivity with other flaviviruses, such as DENV, serologic testing has limits in terms of specificity. Thus, employing a different testing method, positive serologic test results should be verified. The kind of sample used can also alter the likelihood of detection, and additional specimen types, such urine and saliva, are being examined for their potential diagnostic value [33].

Viruria may last longer than viremia, and saliva and urine may be acceptable substitutes, particularly when drawing blood is difficult. According to one study, Zika virus RNA can be found in urine up to 20 days after viremia has been eliminated. As a result, when the Zika virus is clinically suspected, RT-PCR urine testing should be considered. Similarly, salivary RT-PCR testing has been shown to improve the rate of infection diagnosis during the acute phase, but blood remains the preferred sample. Large reference laboratories typically conduct Zika virus testing, and it is best to contact local public health organisations before testing to organise sample collection [33].

Prevention and Control of Zikv

Mosquitoes pose the most risk for ZIKV infection, hence it is important to manage and limit their breeding grounds in order to stop the virus from spreading [34]. Mosquito nets, insect repellents, and closing cracks and gaps can all help with this. Larvicides should be used with insecticides that are suggested by the WHO Pesticide Evaluation System. Insect repellents should not be used to infants less than two months; however, mosquito nets can shield them from bites [35].

The Centers for Disease Control and Prevention advises using mosquito repellents with active chemicals such picaridin, DEET, eucalyptus oil, IR3535, oil of lemon, and para-menthane-diol, which are safe for use by expectant and lactating moms. Nevertheless, children under three years old should not use repellents that include para-menthane-diol, lemon oil, or eucalyptus oil. Flying insect foggers with Tetramethrin and Cypermethrin and indoor mosquito-killing sprays with Imidacloprid and -Cyfluthrin can both kill mosquitoes [36].

Before receiving blood transfusions, it is advisable to get tested for ZIKV infection to stop blood-borne illness. Pregnancy should be avoided in high-risk locations until the virus has been completely eradicated, or increased caution should be used because ZIKV infection has been associated to microcephaly [37]. The spread of ZIKV can also be stopped by using a variety of vector control techniques. A technique that works well is giving mosquitoes a bacterium that regulates their number. To manage mosquito populations, Wolbachia, an intracellular bacterium, can be used as a biopesticide [38]. Toxorhynchites splendens mosquito larvae can be used since the adults consume honeydew, fruit, and nectar while the larvae do not feed on blood but rather the

larvae of other mosquito species [39]. Using sterile males to cause infertility in wild, fertile Aedes species mosquito females is another successful tactic [40].

CONCLUSION

The Zika virus is a newly emerging disease that, while less dangerous to adults than SARS and MERS, can cause foetal defects if contracted during pregnancy. It is one of the TORCH illnesses, which can result in congenital abnormalities. To manage potential Zika-related problems in different countries, medical community knowledge must be increased, vector control strategies improved, and disease surveillance systems expanded.

REFERENCES

1. Dick GW, Kitchen SF, Haddow AJ. Zika virus (I). Isolations and serological specificity. Transactions of the royal society of tropical medicine and hygiene. 1952 Sep 1;46(5):509-20.
2. Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, federated states of Micronesia. New England Journal of Medicine. 2009 Jun 11;360(24):2536-43.
3. Musso D, Nilles EJ, Cao-Lormeau VM. Rapid spread of emerging Zika virus in the Pacific area. Clinical Microbiology and Infection. 2014 Oct 1;20(10): O595-6.
4. Krow-Lucal ER, de Andrade MR, Cananéa JN, et al. Association and birth prevalence of microcephaly attributable to Zika virus infection among infants in Paraíba, Brazil, in 2015–16: a case-control study. The Lancet Child & Adolescent Health. 2018 Mar 1;2(3):205-13.
5. Gulland A. Zika virus is a global public health emergency, declares WHO. BMJ. 2016 Feb 2; i657.
6. Musso D, Ko AI, Baud D. Zika virus infection—after the pandemic. New England Journal of Medicine. 2019 Oct 10;381(15):1444-57.
7. Baud D, Gubler DJ, Schaub B, et al. An update on Zika virus infection. The Lancet. 2017 Nov 4;390(10107):2099-109.
8. Gorry C. Cuba confronts Zika: all hands-on deck. MEDICC review. 2016; 18:6-10.
9. MRet D. al. 2009 Zika virus outbreak on Yap Island, Federated States of Micronesia. N. Engl. J. Med.; 360:2536-43.
10. Haddow AD, Schuh AJ, Yasuda CY, et al. Genetic characterization of Zika virus strains: geographic expansion of the Asian lineage. PLoS neglected tropical diseases. 2012 Feb 28;6(2): e1477.
11. Dick GW, Cocina SF, Haddow AJ. Zika aislamientos de virus y especificidadserológica. Transactions of The Royal Society of Tropical Medicine and Hygiene. 1952; 46:509-20.
12. Campos GS, Bandeira AC, Sardi SI. Surto de vírus Zika, Bahia, Brasil. Emerg Infect Dis. 2015; 21:1885-6.
13. Simpson DI. Zika virus infection in man. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1964;58(4):335-8.
14. Macnamara FN. Zika virus: a report on three cases of human infection during an epidemic of jaundice in Nigeria. Transactions of the royal society of tropical medicine and hygiene. 1954 Mar 1;48(2):139-45.
15. Fagbami AH. Zika virus infections in Nigeria: virological and seroepidemiological investigations in Oyo State. Epidemiology & Infection. 1979 Oct;83(2):213-9.
16. Smithburn KC. Neutralizing antibodies against arthropod-borne viruses in the sera of long-time residents of Malaya and Borneo. American J Hygiene. 1954;59(2):157-63.
17. Darwish MA, Hoogstraal H, Roberts TJ, et al. A sero-epidemiological survey for certain arboviruses (Togaviridae) in Pakistan. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1983 Jan 1;77(4):442-5.
18. Olson JG, Ksiazek TG. Zika virus, a cause of fever in Central Java, Indonesia. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1981 Jan 1;75(3):389-93.
19. Basarab M, Bowman C, Aarons EJ, Cropley I. Zika virus. BMJ. 2016 Feb 26; i1049.
20. Cao-Lormeau VM, Roche C, Teissier A, et al. Zika virus, French polynesia, South pacific, 2013. Emerging infectious diseases. 2014 Jun;20(6):1085.
21. Tognarelli J, Ulloa S, Villagra E, et al. A report on the outbreak of Zika virus on Easter Island, South Pacific, 2014. Archives of virology. 2016 Mar;161(3):665-8.
22. Nelwan EJ, Pohan HT. Dengue convalescent rash in adult indonesian patients. Acta Med Indones. 2014 Oct 1;46(4):339-40.
23. Musso D, Ko AI, Baud D. Zika Virus Infection — After the Pandemic. Longo DL, editor. New England Journal of Medicine. 2019 Oct 10;381(15):1444–57.
24. Plourde AR, Bloch EM. A literature review of Zika virus. Emerging infectious diseases. 2016 Jul;22(7):1185.
25. Simmons CP, Farrar JJ, van Vinh Chau N, Wills B. Dengue. New England Journal of Medicine. 2012 Apr 12;366(15):1423-32.
26. Ansar V, Valadi N. Guillain-Barré syndrome. Primary Care: Clinics in Office Practice. 2015 Jun 1;42(2):189-93.
27. Lanciotti RS, Kosoy OL, Laven JJ, et al. Propriedadesgenéticas e sorológicas do vírus Zika associado a umaepidemia, estado da Micronesia, 2007. Emerg Infect Dis. 2008;14(8):1232-9.
28. Kreil TR, Berting A, Kistner O, et al. West Nile virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data. Transfusion. 2003 Aug;43(8):1023-8.
29. Gatherer D, Kohl A. Zika virus: a previously slow pandemic spreads rapidly through the Americas. Journal of General Virology. 2016 Feb 1;97(2):269-73.
30. Faye O, Freire CC, Iamarino A, et al. Molecular evolution of Zika virus during its emergence in the 20th century. PLoS neglected tropical diseases. 2014 Jan 9; 8(1): e2636.
31. Hamel R, Dejarnac O, Wichit S, et al. Biology of Zika virus infection in human skin cells. Journal of virology. 2015 Sep 1; 89(17):8880-96.
32. Buckley A, Gould EA. Detection of virus-specific antigen in the nuclei or nucleoli of cells infected with Zika or Langat virus. Journal of general virology. 1988 Aug; 69(8):1913-20.
33. Musso D, Ko AI, Baud D. Zika virus infection—after the pandemic. New England Journal of Medicine. 2019 Oct 10;381(15):1444-57.
34. Fu KW, Liang H, Saroha N, et al. How people react to Zika virus outbreaks on Twitter? A computational content analysis. American journal of infection control. 2016 Dec 1;44(12):1700-2.
35. Labib BA, Chigbu DI. Pathogenesis and manifestations of zika virus-associated ocular diseases. Tropical Medicine and Infectious Disease. 2022 Jun 15;7(6):106.

36. Kazmi SS, Ali W, Bibi N, Nouroz F. A review on Zika virus outbreak, epidemiology, transmission and infection dynamics. Journal of Biological Research-Thessaloniki. 2020 Mar 4;27(1).
37. Vraga EK, Bode L. Using expert sources to correct health misinformation in social media. Science communication. 2017 Oct;39(5):621-45.
38. Burd I, Griffin D. The chasm between public health and reproductive research: what history tells us about Zika virus. Journal of Assisted Reproduction and Genetics. 2016 Apr; 33:439-40.
39. Benelli G, Jeffries CL, Walker T. Biological control of mosquito vectors: past, present, and future. Insects. 2016 Oct 3;7(4):52.
40. Singh RK, Dhama K, Malik YS, et al. Zika virus–emergence, evolution, pathology, diagnosis, and control: current global scenario and future perspectives–a comprehensive review. Veterinary Quarterly. 2016 Jul 2;36(3):150-75.

How to cite this article: Ramdas Bhat, Queeny Wilcy Noronha, Thanshifa Fathima, A R Shabaraya. Current and Emerging Pharmacotherapies for Zika Virus: A Comprehensive Review. Indian J Pharm Drug Studies. 2022;1(3) 97-101.

Funding: None *Conflict of Interest: None Stated*