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\* Corresponding Author: Marwa M. Hussein  
Email: [marwa.m@uodiyala.edu.iq](mailto:marwa.m@uodiyala.edu.iq)

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## Advancements in Understanding the Pathogenesis, Diagnosis, and Treatment of Zika Virus: A narrative review

Marwa M. Hussein <sup>1\*</sup> , Noor A. Hasan <sup>2</sup> ,  
Mariam S. Abdulazeez <sup>3</sup>, Manar I. Hasan <sup>4</sup>

<sup>1</sup> University of Diyala, College of Dentistry, Diyala ,Iraq.  
ORCID  : <https://orcid.org/0009-0007-3618-4533>  
<sup>2</sup> University of Diyala, College of Dentistry, Diyala ,Iraq.  
ORCID  : <https://orcid.org/0009-0006-7000-3305>  
<sup>3,4</sup> University of Diyala, College of Medicine, Diyala ,Iraq.

### Abstract

*Zika virus (ZIKV) has emerged as a serious global health threat, with expanding geographic transmission and association with neurological complications. As ZIKA virus spreads rapidly and more knowledge of its long-term effects are needed to guide clinical management and public health policy. This in-depth review gives an analysis of the historical background, epidemiology, pathogenesis and clinical manifestations associated with Zika virus. This review intends to focus on the many-sided nature of this virus, which affects pregnant women and children; presents problems in regard to developing a treatment regimen or vaccine, and provides testimony to how important vector control measures are. Screening, monitoring and possible interventions of the fetus in controlling Zika virus during pregnancy are all subjects for further study. Moreover, there is also a look at the advances and problems in Zika virus vaccine development. In conclusion, this review revealed the need of the interdisciplinary and combined effort to take on new public health challenges and control spreading of Zika virus.*

**Keywords:** Zika virus, virus pathogenesis, Zika infection, Zika syndrome, Diagnosis .

## Introduction

Zika is a mosquito-borne virus that has become the focus of large amounts media attention because it affects public health around the world. For the world's medical systems, one of their greatest challenges after Zika virus emerged in the early 21st century has been dealing with Zika-virus infected patients. Knowing the pathogenic, diagnosis and treatment of Zika virus is necessary for fighting this infectious disease (1). The Zika virus wasn't until an outbreak of disease broke on Java and Micronesia that we first became aware. Later, outbreaks took place in several regions such as the Americas, Southeast Asia and Pacific Islands. Rapid spread for Zika virus, and its associations with

very serious health problems (especially in pregnant women and their newborn babies), is worrying. The review will look at the present state of therapy for Zika virus infections including antivirals, immunotherapy and supportive care (2). Osteoarthritis can be explained as swelling pain in the joints, while arthralgia means joint pain without swelling. Yet these terms are often highly imprecise in many studies. Human viral arthritis is associated with parvoviruses, alphaviruses (like chikungunya and Ross river virus), hepatitis B virus, hepatitis C virus, Epstein-Barr virus (EBV) and Zika. But to date, no one has any idea about the exact rate of incidence or prevalence for ZIKV arthritis and joint pain. However, unlike the operational case definitions for chikungunya, and Zika virus infections which only include arthralgia as a primary symptom of human infection, many people are more familiar with having incapacitating polyarthralgia or true arthritis. Moreover, this is central to both what characterizes people's disease immediately after being infected (the acute phase (3, 4). Various immune cell including cytokines, and inflammatory processes that contribute to renal injury are showed in the discussion of the function of immune system dysregulation in kidneys failure. Infection with ZIKV triggers pro-inflammatory cytokines that suppress virus replication and glomerular damage. Virus spread is governed by the glomerular micro-environmental response of IFN. Human mechanisms could avoid replicating ZIKV in the kidneys. Antibodies or host factors already present could neutralize viral infectivity and prevent clinical disease (5, 6). This comprehensive review aims to present an in-depth analysis of advancement in understanding the pathogenesis, diagnosis and treatment associated with Zika virus infection. The clinical manifestations of Zika viruses, the mechanisms by which they function to interfere with host immune systems and how high-tech diagnostics can be suited for accurate detection are among key topics in this study.

#### Historical Background and Global Impact of Zika Virus

The Zika virus (ZIKV), which was discovered in 1947 at Uganda's Zika Forest, has an interesting history. This was when it was still only a little-known virus, which caused mild illness in humans from time to time. In 2007, however, a large outbreak on the island of Yap in Micronesia completely shifted Zika's place under the sun (7), followed by a major epidemic in French Polynesia from 2013-2014. This outbreak raised initial concerns due to an apparent connection to Guillain-Barré syndrome in adults. During this outbreak, the virus was found to cause microcephaly and other severe fetal brain defects by crossing the placenta, revealing Zika's previously unrecognized potential as a teratogen. On a molecular level, Zika is an enveloped, positive-sense RNA virus in the Flaviviridae family. It utilizes host cell machinery to replicate its genome and structural proteins like envelope (E) and membrane (M) that aid entry into host cells and evasion of the immune response. Factors like E protein glycosylation may contribute to Zika's neurovirulence. Continued circulation in countries like Brazil, combined with the virus' ability to persist asymptotically in semen, pose ongoing risks of congenital infections(7,8)

It was the link with pregnancy that produced Zika's most worrying consequence. In 2015, a wave of cases of microcephaly or measles-like birth defects was reported in Brazil. Later investigations established a clear connection between Zika virus infection of the mother during pregnancy and microcephaly in newborns, defining it as an international public health emergency by WHO one year later (9).

The wider spread of Zika virus in the Americas and elsewhere further increased its global impact. The primary vector for transmission is an *Aedes* mosquito species, which inhabits tropical and subtropical areas. Travel-related cases also played an important role in bringing the virus to new areas (10).

The profound adverse effects of the Zika virus infection on public health have triggered numerous research efforts to elucidate its epidemiology, transmission dynamics, clinical manifestations and long-term sequelae. A lot of progress has been made by scientists who have worked on cracking the genetic code of Zika, classifying different strains and looking at how viruses interact with their hosts to get insights into mechanisms that cause illness (11).

There has also been worldwide cooperative work to develop diagnostic methods that can accurately identify Zika virus infections. Many serological tests and molecular techniques have been developed and improved upon, which allow medical professionals to rapidly determine if a case of Zika virus infection has occurred (12).

### **Pathogenesis of Zika Virus Infection: Insights into Viral Replication and Host Interactions**

The pathogenesis of ZIKV infection is complex. Both the virus and host immune system take part in it. Elucidating the molecular mechanisms governing viral replication and host interaction is an important precondition for developing effective strategies to combat this contagious disease (13).

The Zika virus enters the human body through a bite delivered by an infected *Aedes* mosquito. After entering the bloodstream, it principally targets skin cells and dendritic and immune-system type B cells. Early in the infection, unique viral envelope proteins allow attachment and penetration of host cells. Zika virus primarily uses heparan sulfate, a glycosaminoglycan found on many cell surfaces, as an attachment receptor through binding of its envelope protein E, while cell membrane molecules like DC-SIGN, AXL, and TIM/TAM receptors may act as co-receptors to facilitate viral and membrane fusion necessary for cell entry (14).

Inside the host cell, Zika virus starts to replicate. It uses the machinery common in all animal cells to produce viral proteins and then go on creating samples of its own genetic material again and again (spreading like wildfire). The replication process produces new infectious viral particles. Interestingly, the Zika virus has been found to be neurotropic (preferentially infecting neural progenitor cells, neurons and glial cells of the central nervous system) (15).

Zika virus-host immune system interaction is one of the most important factors determining disease outcome. After infection, the host immune response is turned on to limit viral spread. Natural immune cells such as macrophages and, natural killer cells sense the presence of the virus, produce cytokines and chemokines to attract other types of immunocytes to site (16).

Yet Zika virus has acquired many tricks to avoid and control the host immune response. It inhibits the synthesis of interferons, which are important antiviral molecules capable of restricting viral replication. Furthermore, it appears that Zika virus can control host immune signaling pathways and interfere with normal immune functions; this leaves these cells unable to produce an anti-viral response in adequate numbers (17).

It has been hypothesized that this dysregulation of the immune response during a Zika virus infection may be responsible for creating severe complications, such as neurological disorders and fetal abnormalities. These complications are still not fully understood and research is ongoing (18).

Viral proteins and host factors which mediate pathogenesis have been most studied in research efforts. Non-structural protein 1 (NS1) and Non-structural protein 5 (NS5) are among the key viral proteins implicated in immune evasion, as well neuro-virulence. Also, host factors related to viral entry and replication as well as immune response are

being investigated for potential targets of therapeutic intervention. NS1 and NS5 interfere with the host immune response through mechanisms such as preventing activation of antiviral cytokines and innate immune sensors, allowing the virus to evade detection and control by the body's innate and adaptive immune defenses. Investigation of cellular factors involved in immune signaling pathways could reveal new therapeutic strategies to enhance immune-mediated clearance of Zika virus (19).

### Clinical Manifestations of Zika Virus Infection: From Mild Symptoms to Severe Complications.

The table below illustrates the clinical symptoms caused by Zika virus infection. Initially, symptoms are mild, such as fever, rash, muscle aches, headache, and conjunctivitis, which may go undiagnosed. However, the infection can progress to severe complications, most notably Guillain-Barré syndrome, which leads to muscle weakness and potentially paralysis. Infection during pregnancy is particularly dangerous due to its association with congenital Zika syndrome and the associated serious neurological malformations and developmental delays.

**Table.1:** Clinical Manifestations and Complications of Zika Virus Infection

Clinical Manifestations	Description
Mild Symptoms	- Fever
	- Rash
	- Headache
	- Muscle and joint pain
	- Conjunctivitis
Severe Complications	- Guillain-Barré syndrome (muscle weakness, paralysis)
	- Congenital Zika syndrome (microcephaly, brain abnormalities, ocular abnormalities, hearing loss, joint contractures)
	- Neurodevelopmental delays in infants exposed during pregnancy
	- Possible links to cognitive impairment and neurodegenerative diseases in adults

### Diagnostic Methods for Zika Virus Detection: Current Approaches and Emerging Technologies

There is an urgent need for accurate and timely tests that can be used to detect a ZIKV infection. Various techniques have been developed for detecting Zika virus in patient specimens. This section covers the existing methods and new technologies for detecting Zika virus As shown in Table 2 (8).

**Table. 2:** Zika Virus Diagnostic Methods: Current Approaches and Emerging Technologies with Sensitivity and Specificity (7, 13, 15)

Serological Tests	Molecular Methods	Emerging Technologies
- Enzyme-linked immunosorbent assay (ELISA): Detects Zika virus-specific antibodies (IgM and IgG) produced by the immune system in response to infection. Sensitivity: Varies.	- Reverse transcription-polymerase chain reaction (RT-PCR): Amplifies and detects Zika virus genetic material (RNA) in patient samples, such as blood ,	- Isothermal amplification methods: Techniques like Loop-mediated isothermal amplification (LAMP) and Recombinase polymerase amplification (RPA) offer rapid

Specificity: Varies. (7)	urine, and cerebrospinal fluid. Sensitivity: High. Specificity: High.	and sensitive detection for Zika virus RNA without the need for extensive equipment. Sensitivity: Varies. Specificity: Varies.
- Plaque reduction neutralization test (PRNT): Confirms Zika virus infection by measuring the level of neutralizing antibodies in the blood. Sensitivity: Varies. Specificity: Varies.(13)	- Real-time RT-PCR (qRT-PCR): A more sensitive and specific variant of RT-PCR that allows real-time monitoring of amplification, providing quantitative results. Sensitivity: High. Specificity: High.	- Next-generation sequencing (NGS): Enables comprehensive genomic analysis of Zika virus, facilitating strain identification, surveillance, and tracking of viral evolution. Sensitivity: High. Specificity: High.
- Rapid diagnostic tests (RDTs ): Immunochromatographic assays that provide quicker results (within minutes) and can be performed at the point of care. These tests detect Zika virus-specific antigens or antibodies. Sensitivity: Varies. Specificity: Varies.(7)		- Point-of-care nucleic acid tests: Portable devices that integrate sample preparation, amplification, and detection, allowing on-site testing in resource-limited settings. Sensitivity: Varies. Specificity: Varies.

These diagnostic methods have different degrees of sensitivity and specificity, turnaround time, equipment requirements and cost-effectiveness. Different factors, such as stage of infection and available resources in particular determine the choice between diagnostic approaches. Still others are used primarily for individual diagnosis rather than surveillance or research (20, 21).

In addition, given the development of new technologies for testing Zika virus, diagnostic tests continue to change. Work in progress is aimed at improving the sensitivity, specificity and availability of diagnostic assays to aid early detection efforts (22).

In general, a variety of diagnostic techniques are available to detect Zika virus infection. Besides serology, methods such as RT-PCR to test for viral genetic matter have also been used. One area in which emerging technologies portend great advances is rapid, portable detection. (12, 23, 24).

### Imaging and Laboratory Findings in Zika Virus Infection: Key Indicators for Diagnosis

Zika virus infection Diagnosis and management require appropriate imaging studies as well as laboratory findings. Table.3 describes the most important indicators used in imaging studies and laboratory tests for diagnosing Zika virus infection.

**Table. 3: Zika Virus: Imaging and Laboratory Findings for Diagnosis and Management (12, 23)**

Imaging Studies	Laboratory Findings
- Neuroimaging: When Zika virus infections are complicated with neurological involvement, special characteristics can be detected by checks of magnetic resonance imaging (MRI) and , computed tomography (CT), such as microcephaly, brain calcifications, ventriculomegaly or cortical malformations.(12)	- Hematological Abnormalities: Typical blood test abnormalities include leukopenia, thrombocytopenia and atypical lymphocytosis in the peripheral blood.

- Ocular Imaging: Doctors rely on check-ups and imaging techniques (including funduscopy, optical coherence tomography) to diagnose the ocular manifestations of Zika virus infection.(23)	- Viral Detection: For example, molecular diagnostic tests (that is to say RT-PCR) find Zika virus genetic material in clinical samples of blood, urine and cerebrospinal fluid.
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These imaging and laboratory findings are important markers in the diagnosis for Zika virus infection. Put them in the light of clinical manifestation, travel history and exposure to Zika virus. Moreover, correct diagnosis of Zika virus infection also requires comprehensive evaluation and inter-disciplinary cooperation (12, 21, 24-26).

### **Treatment Strategies for Zika Virus Infection: Antiviral Agents, Immunotherapy and Supportive Care**

With no specific antiviral agents targeted at Zika virus yet, management of the infection mainly involves supportive care and relief from symptoms. There are also immunotherapy techniques being looked at to combat Zika virus infection. The most common treatment modules for Zika virus infection including antiviral agents, immunotherapy and supportive care are as follows: treatment methods for Zika virus infection including antiviral agents, immunotherapy and supportive care (24,25).

#### **Antiviral Agents**

Zika virus is an area of active anti-viral research. In the preclinical and clinical settings, various compounds with possible antiviral activity against Zika virus are under investigation. Examples are direct-acting antivirals that inhibit viral replication or entry, as well as host-targeted antivirals which alter host factors critical for the virus infection (27). Zika virus treatment Small-molecule inhibitors, nucleoside analogs and other drug candidates are being tested for their effectiveness and safety. (27, 28).

#### **Immunotherapy**

The immunotherapy approach uses the immune system to fight against Zika virus infection. As a possible form of treatment, passive immunization with convalescent plasma obtained from persons who have recovered from the Zika virus is being considered. Infected individuals receive plasma that contains Zika virus-specific antibodies to induce temporary immunity and help empty the body of infected cells (29).

#### **Supportive Care**

Since there is no specific antiviral treatment, supportive care plays an important role in the management of Zika virus infection. Therefore, this is also how one treats symptoms like fever and pain with analgesics as well as antipyretics or anti-inflammatories. In the case of Zika virus, pregnant women require special attention to prevent complications in both mother and unborn child. (17, 27, 30).

### **Management of Zika Virus Infection during Pregnancy: Screening, Monitoring, and Fetal Intervention**

#### **Screening**

Pregnant women, including those in Zika-affected or traveling to areas where the virus is circulating should receive routine testing for Zika infection. In brief, screening means examining the woman's history of travel to areas with active Zika virus circulation and testing maternal blood or other clinical specimens in laboratory for viral RNA or specific antibodies (IgM and IgG).

Further screening by ultrasound can be used to determine the stage of fetal development and whether or not congenital Zika syndrome is present (31).

### **Monitoring**

Women with definitive or suspected Zika virus infection require close monitoring in order to establish the course of disease and possible effect on fetus. It involves regular prenatal check-ups, serial ultrasounds and special fetal imaging studies to assess rate of growth, development or anomaly (30, 31)

These serial ultrasound examinations are especially important for the detection of signs of fetal abnormality. These include microcephaly (small head), intracranial calcifications, ventriculomegaly and other structural anomalies associated with congenital Zika syndrome such as clenched fists or cleft lip/palate (32).

### **Fetal Intervention**

If prenatal imaging or screening tests detect fetal abnormalities, specialized interventions may perhaps be undertaken to provide relevant care and support for the affected fetus. This includes consulting with maternal-fetal medicine specialists, pediatric neurologists and other healthcare professionals to devise a whole treatment plan (33).

Some fetal interventions involved genetic counseling, prenatal imaging studies (e.g., MRI of the unborn child), multidisciplinary team discussion to support decision making giving rise and undertaking continuing monitoring through non-invasive checks on mother's condition so as to evaluate whether or not abnormalities have progressed (34).

Besides the concrete measures described above, pregnant women who have contracted Zika virus should also receive intensive counseling and assistance on how to avoid mosquito bites or further exposure to Zika. Entails the use of insect repellents, wearing protective clothing and reducing outdoor activities in areas with Zika virus (35).

Management of Zika virus infection in pregnancy, however, requires an interdisciplinary team which includes obstetricians and gynecologists specializing in maternal-fetal medicine; infectious disease specialists; neonatologists appearing on the scene when necessary. The cooperative effort intends to offer care for the pregnant woman and her developing fetus with early detection of complications, so that if intervention is necessary, it can be performed in time (31, 36).

### **Vector Control Measures to Prevent Zika Virus Transmission: Mosquito Control and Environmental Interventions**

As shown in Table 4. The focus in controlling the spread of Zika virus (ZIKV) is on effective mosquito control measures and environmental interventions to raise down Aedes-mosquitos, which serve as vectors for all stages of zikavirus infection. The following section describes important vector control and environmental interventions to prevent Zika virus spread (37)

**Table. 4:** Effective Strategies for Zika Virus Prevention: Mosquito Control and Environmental Interventions (35, 36, 37)

Mosquito Control	Environmental Interventions
<p>- Source Reduction: Specialised attempts to remove likely mosquito breeding sites, including standing water in discarded cups, tyres or gutters and other vessels containing rainwater This means community involvement and education directed at getting rid of stagnant water, adopting reasonable waste disposal measures(35)</p>	<p>- Urban Planning and Infrastructure Improvement: Planning and maintaining urban landscapes to prevent the spread of mosquito breeding areas. Such measures include a drainage system and the regular maintenance of water storage facilities, along with urban development techniques designed to minimize mosquito-friendly environments.</p>
<p>- Larval Control: Treatment of water sources where Aedes mosquito larvae breed, including artificial containers and water storage facilities. Larvicides kill mosquitoes at the larval stage, preventing adult emergence(36)</p>	<p>- Community Engagement and Education: Informing communities about the need for vector control, use of personal protection measures and community-based campaigns to get mosquito breeding sites under control is also important. Local stakeholders and community leaders playing an active role in mosquito control will increase the effectiveness of environmental interventions.</p>
<p>- Adult Mosquito Control: Spraying with or fogging of insecticides to reduce the number of adult mosquitoes in areas where transmission is high, or use in response to outbreaks. The interventions are frequently carried out in collaboration with the public health authorities and vector control agencies(37)</p>	<p>- Integrated Vector Management (IVM): Taking an integrated strategy of multiple vector control methods, including environmental modification, larval and adult mosquito elimination, surveillance and community involvement. Sustainable control outcomes IVM stresses evidence-based practice adjusted to local conditions.</p>

### Vaccine Development against Zika Virus: Progress, Challenges, and Future Perspectives

As important as ever is the development of safe and effective vaccines against Zika virus (ZIKV). This section describes the progress, problems and outlook for vaccine development against Zika virus.

#### 1. Progress in Vaccine Development:

- A number of candidate vaccines against Zika virus are now in preclinical and clinical development. The inactivated vaccines, live attenuated vaccines and DNA-based ZIKV vaccine approaches all aim to induce protective immune responses against the virus.
- Many of these vaccine candidates have shown favorable results in preclinical studies, stimulating a strong immune response and protective effect against Zika virus infection. Such advances have made possible clinical trials to evaluate vaccine safety, immunogenicity and efficacy in human populations (38).

#### 2. Challenges in Vaccine Development:

- Immunological Considerations: Antibody-dependent enhancement ( ADE) of ZIKV infection is one obstacle in vaccine design, because it makes necessary the careful assessment of a vaccine's effect on immune responses; an excessively strong response may result in enhanced susceptibility when exposed to subsequent infectious stimuli.

- **Cross-Reactivity with Other Flaviviruses:** As there is a risk that Zika virus vaccines could provoke immune responses in individuals with prior exposure to dengue, the development of such vaccines needs therefore to consider potential cross-reactivity between flaviviruses.
- **Clinical Trial Design and Implementation:** Conducting clinical trials for Zika virus vaccines presents logistical and ethical considerations, particularly in populations at risk of Zika virus exposure. Ensuring sufficient sample sizes, appropriate endpoints, and long-term follow-up are critical for assessing vaccine safety and efficacy (38).

## **Conclusion**

Zika virus infection has shown that this global health issue is multifaceted. Knowledge of the historical origin and worldwide spread of the virus, as well as its pathogenesis, clinical presentation and diagnostic tools has continuously advanced. This combined focus on the management of infection and disease throughout pregnancy, treatment options; as well as the centrality of vector control measures to Zika prevention efforts highlights how much importance needs to be attached both individually and collectively toward conquering this public health menace. With the field of research and public health care developing constantly, coordination between prevention measures, early identification strategies, and treatment methods for infected individuals themselves will be crucial to reducing harm from Zika.

## **Declarations**

### **Acknowledgment**

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### **Ethics statement**

This study was conducted in accordance with the ethical standards and guidelines outlined in the journal's "Ethics Approval" section.

### **Availability of Data and Materials**

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

### **Competing Interests**

The authors declare that they have no competing interests.

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## Authors' Contributions

**MMH:** designed the study, performed the statistical analysis, and drafted the manuscript; **NAH:** contributed to the design of the study and critically revised the manuscript; **MSA:** contributed to assembling the statistical dataset and performed the analyses; **MIH:** contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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