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# ADVANCES IN ZIKA VIRUS: AN OVERVIEW OF RESEARCH AND CLINICAL TRIALS

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**ABSTRACT :**

Zika virus (ZIKV), an emerging mosquito-borne flavivirus, remains a major public health concern due to its strong association with congenital abnormalities, severe fetal neurodevelopmental defects, and neurological complications such as Guillain–Barré syndrome. First identified in Uganda in 1947, ZIKV is transmitted mainly by Aedes mosquitoes, with sexual, vertical, and blood-borne transmission also well-documented [1–4]. The 2015–2016 global epidemic established the critical role of ZIKV as a primary cause of congenital Zika syndrome, including severe microcephaly [4,8]. India continues to experience sporadic outbreaks, with the World Health Organization reporting 151 confirmed cases during 2024 across Maharashtra, Karnataka, and Gujarat [7]. Despite significant advances in understanding viral pathogenesis, structural biology, and diagnostic modalities, no vaccine or specific antiviral therapy is licensed for routine clinical use [5,6]. This comprehensive narrative review summarizes major developments in ZIKV research, focusing on candidate vaccine platforms (purified inactivated, DNA, mRNA, viral-vector, and virus-like-particle vaccines), clinical trial pipelines, diagnostic innovations, candidate antiviral molecules, and key public health priorities [6,9,10–18]. Literature was retrieved through PubMed, Scopus, Google Scholar, and official public health databases. Candidate platforms demonstrate high immunogenicity in early-phase clinical studies, yet challenges remain regarding durability of immunity, flavivirus antibody cross-reactivity, and trial recruitment due to unpredictable outbreak epidemiology [6,9,15]. Sustained research, vector control, and global collaboration remain essential.

**Keywords:** *Zika virus, vaccine development, clinical trials, immunogenicity, antiviral therapy*

## 1. INTRODUCTION

Zika virus (ZIKV) is an enveloped, positive-sense, single-stranded RNA virus belonging to the genus Orthoflavivirus within the family Flaviviridae [1]. First isolated in 1947 from a rhesus macaque in the Zika Forest of Uganda, human infections were subsequently documented across tropical Africa and Asia during the 1950s [1,2]. For nearly six decades, ZIKV was regarded as a neglected pathogen causing sporadic, mild, and self-limiting febrile illness [2,3]. However, its global health trajectory shifted dramatically following major urban epidemics in Yap Island (2007), French Polynesia (2013–2014), and particularly the explosive 2015–2016 pandemic across the Americas [2,4,19]. The 2015–2016 outbreak in Brazil uniquely linked maternal ZIKV infection to severe birth defects, prompting the World Health Organization (WHO) to declare a Public Health Emergency of International Concern (PHEIC) in February 2016 [4,20].

ZIKV is primarily transmitted to humans through the bite of infected female Aedes mosquitoes, predominantly Aedes aegypti and Aedes albopictus [2,21]. Non-vector modes of transmission—including sexual transmission, intra-uterine vertical transmission, intrapartum exposure, and blood transfusion—have been thoroughly characterized, complicating control efforts [2,22,23]. While approximately 80% of ZIKV infections are asymptomatic or present as mild clinical disease, infection during pregnancy poses severe risks, including congenital Zika syndrome (CZS), fetal loss, and severe neurodevelopmental deficits [3,4,24]. In adults, ZIKV is strongly linked to Guillain–Barré syndrome (GBS) and acute disseminated encephalomyelitis [4,25]. To date, no specific antiviral treatment or preventive vaccine is approved for clinical use, reinforcing the urgency of continued research, surveillance, and vaccine development [5,6,15].

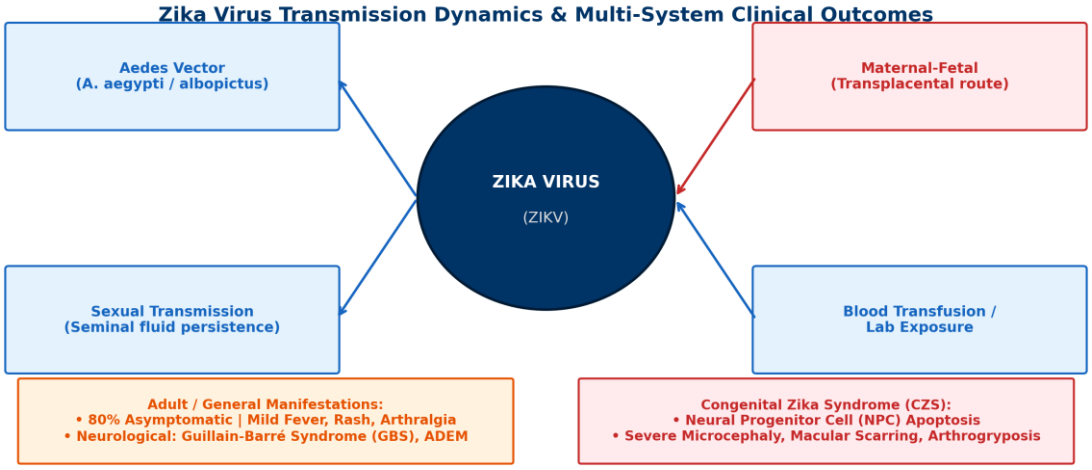



**Figure 1. Zika virus transmission modalities, systemic dissemination, and clinical outcomes across populations.**

## 2. EPIDEMIOLOGY AND GLOBAL BURDEN

Since its re-emergence in the Pacific Ocean and the Americas, ZIKV has expanded its geographical footprint to over 86 countries and territories across Latin America, the Caribbean, Southeast Asia, Africa, and the Western Pacific [2,5]. Although reported human incidence declined substantially after 2017 due to widespread population immunity in epidemic centers, low-level endemic transmission, sporadic focal outbreaks, and silent circulation persist globally [5,20]. Modeling studies indicate that millions of individuals remain at risk of ZIKV exposure in tropical and subtropical regions where Aedes mosquito vectors are established [21].

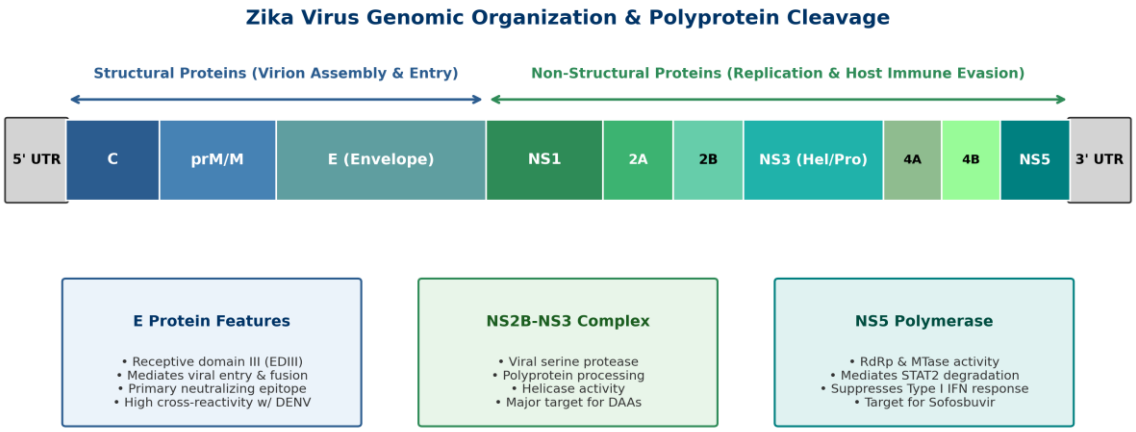
### *2.1 Zika Virus Epidemiology in India*

In India, ZIKV surveillance was intensified following the global PHEIC declaration. The first laboratory-confirmed human infections were documented in Gujarat in late 2016, followed by major outbreaks in Rajasthan (2018), Madhya Pradesh (2018), Kerala (2021), and Uttar Pradesh (2021) [7,26]. According to the WHO Disease Outbreak News report published in January 2025, India reported 151 laboratory-confirmed ZIKV cases during 2024 across three states: 140 in Maharashtra, 10 in Karnataka, and 1 in Gujarat [7]. The report noted that no ZIKV-associated microcephaly or GBS cases were observed during this specific period [7]. The co-circulation of all four dengue virus serotypes and chikungunya virus in these Indian regions poses significant diagnostic challenges and highlights the critical requirement for robust integrated vector control and clinical surveillance [7,26,27].

## 3. VIRAL STRUCTURE, GENOMICS, AND PATHOGENESIS

The ZIKV genome comprises a single-stranded positive-sense RNA molecule of approximately 10.7 kilobases, flanked by 5' and 3' non-coding regions [1,8]. The genome encodes a single long polyprotein that is co- and post-translationally cleaved by viral and host proteases into three structural proteins—capsid (C), precursor membrane/membrane (prM/M), and envelope (E)—and seven non-structural (NS) proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 [1,8,28]. High-resolution cryo-electron microscopy structures revealed that the E protein mediates host cell receptor binding and membrane fusion, making it the primary target for neutralizing antibodies [8,29]. The non-structural proteins orchestrate viral RNA replication, polyprotein processing, and host innate immune evasion; for example, NS5 suppresses type I interferon signaling by mediating STAT2 degradation [28,30].

**Figure 2. Genomic organization of Zika virus encoding structural and non-structural polyproteins, with functional roles in pathogenesis.**



Following cutaneous inoculation by an infected mosquito vector, ZIKV infects skin fibroblasts, epidermal keratinocytes, and immature dendritic cells [2,31]. The virus disseminates through lymphatic channels into systemic circulation. During pregnancy, ZIKV exhibits strong tropism for placental syncytiotrophoblasts, cytotrophoblasts, and Hofbauer cells, crossing the placental barrier to invade the fetal compartment [3,32]. In the fetal brain, ZIKV preferentially infects neural progenitor cells (NPCs), leading to cell cycle arrest, apoptosis, dysregulated differentiation, and premature depletion of NPC pools [3,4,33]. This targeted neuro-disruption accounts for the severe brain malformations, cortical thinning, and intracranial calcifications characteristic of CZS [4,33].

## 4. CLINICAL MANIFESTATIONS AND COMPLICATIONS

The incubation period of ZIKV disease ranges between 3 and 14 days. Symptomatic disease, occurring in roughly 20% of infected individuals, is generally characterized by mild, self-limiting acute febrile illness lasting 2 to 7 days [2,5]. Classic manifestations include low-grade fever, maculopapular rash (often descending and pruritic), non-purulent conjunctivitis, arthralgia (mainly affecting small joints of hands and feet), myalgia, and retro-orbital headache [2,5,34]. Because these clinical features heavily overlap with dengue fever and chikungunya, accurate differential laboratory diagnosis is mandatory [2,27].

### *4.1 Congenital Zika Syndrome (CZS)*

Maternal ZIKV infection during any trimester—though highest risk occurs during the first trimester—can cause severe congenital anomalies collectively termed Congenital Zika Syndrome (CZS) [3,4,24]. Clinical features include severe microcephaly with partially collapsed skull, thin cerebral cortex, intracranial subcortical calcifications, macular scarring and pigmentary retinal mottling, congenital contractures (arthrogryposis), sensorineural hearing loss, and hypertonia [3,4,35]. Long-term follow-up demonstrates profound motor, cognitive, and visual impairments requiring multidisciplinary care [24,35].

### *4.2 Neurological Manifestations in Adults*

In adult and pediatric populations, ZIKV infection is causally associated with Guillain–Barré syndrome (GBS), an autoimmune peripheral neuropathy characterized by progressive muscle weakness and ascending paralysis [4,25]. In rare instances, direct neuroinvasion or post-infectious neuroinflammation can lead to acute disseminated encephalomyelitis (ADEM), transverse myelitis, encephalitis, sensory neuropathies, and cranial nerve palsies [1,4,36].

## 5. ADVANCES IN DIAGNOSTIC APPROACHES

Reliable diagnosis of ZIKV infection requires integrating clinical presentation, travel/exposure history, and laboratory testing [2,5]. Molecular testing using Reverse Transcription Polymerase Chain Reaction (RT-PCR) is the gold standard during the acute phase (up to 7–14 days post-symptom onset) for detecting viral RNA in serum, whole blood, urine, and saliva [2,37]. Urine specimens often maintain detectable viral RNA for longer durations than serum [37]. In pregnancy, RT-PCR testing of amniotic fluid can confirm fetal infection [3,37].

Beyond the acute molecular window, serological assays evaluating ZIKV-specific IgM antibodies via enzyme-linked immunosorbent assay (ELISA) are utilized [2,5]. However, serology is severely complicated by extensive structural homology and antigenic cross-reactivity between ZIKV and other flaviviruses, particularly dengue virus (DENV) [2,38]. Plaque Reduction Neutralization Testing (PRNT) provides higher specificity by assessing neutralizing antibody titers, but PRNT interpretation remains ambiguous in individuals with prior flavivirus exposure or vaccination (e.g., yellow fever, Japanese encephalitis) [2,38]. Recent diagnostic innovations focus on NS1-based recombinant antigen assays, multiplex RT-PCR platforms, point-of-care microfluidic devices, and monoclonal antibody-based rapid tests to differentiate ZIKV from DENV in endemic zones [37,39].

## 6. ADVANCES IN ZIKA VIRUS VACCINE DEVELOPMENT

Vaccine development remains the foremost strategy to prevent ZIKV outbreak resurgence and protect high-risk populations, particularly pregnant women [6,9,15]. An ideal ZIKV vaccine must elicit robust, durable neutralizing antibody titers and T-cell responses without inducing harmful cross-reactive antibodies that could mediate antibody-dependent enhancement (ADE) of dengue virus infection [6,9,40]. Multiple technological platforms have entered clinical development [6,10–18].

### *6.1 Purified Inactivated Zika Vaccines (ZPIV)*

Purified inactivated virus (ZPIV) vaccines utilize whole, chemically inactivated virions to present full native structural antigens without the ability to replicate [10]. In Phase 1 human clinical trials (e.g., NCT02963909, NCT02937233), alum-adjuvanted ZPIV demonstrated high tolerability and robust immunogenicity, achieving over 92% seroconversion by day 57 across multiple dosing cohorts [10]. Passive transfer of serum from ZPIV-vaccinated human subjects conferred full protection against ZIKV challenge in immunocompromised mouse models [10,41].

### *6.2 DNA Vaccines*

DNA vaccine candidates incorporate plasmid DNA encoding ZIKV structural proteins (prM-E) driven by eukaryotic promoters [11,12]. GLS-5700, a synthetic plasmid DNA vaccine administered via electroporation, elicited positive binding antibody responses in 100% of Phase 1 trial participants and conferred protective neutralizing activity [11]. Similarly, the National Institute of Allergy and Infectious Diseases (NIAID) developed VRC5283 and VRC5288 [12]. In Phase 1 studies, VRC5283 (encoding ZIKV prM-E) demonstrated superior immunogenicity, inducing robust neutralizing antibody and CD4+/CD8+ T-cell responses, leading to its advancement into Phase 2 clinical evaluation [12,15].

### *6.3 Messenger RNA (mRNA) Vaccines*

mRNA platforms offer rapid, scalable manufacturing and strong immunogenicity by encoding ZIKV prM-E proteins encapsulated in lipid nanoparticles (LNPs) [14,42]. Early clinical candidates mRNA-1325 and mRNA-1893 were evaluated in Phase 1 dose-escalation trials [14]. While mRNA-1325 demonstrated modest immunogenicity, mRNA-1893 (incorporating optimized signal sequences and structural modifications) induced potent, dose-dependent neutralizing antibody titers in both flavivirus-naive and baseline flavivirus-seropositive adults [14,42]. mRNA-1893 received FDA Fast Track designation and progressed to Phase 2 testing [14,15].

### *6.4 Virus-Like Particle (VLP) and Recombinant Protein Vaccines*

Virus-like particles (VLPs) assemble structural envelope proteins into non-infectious retrovirus- or baculovirus-derived shells that mimic native viral architecture without carrying viral genetic material [13]. Preclinical evaluations of ZIKV VLPs demonstrated high neutralizing antibody titers, balanced Th1/Th2 cellular responses, and protection against lethal viral challenge in animal models [13,43]. Recombinant subunit vaccines targeting Domain III of the E protein (EDIII) are also in development to minimize cross-reactive ADE-inducing epitopes while focusing the immune response on ZIKV-specific neutralizing sites [40,44].

### *6.5 Viral-Vector and Live-Attenuated Vaccines*

Recombinant viral-vector platforms—including adenovirus (Ad26.ZIKV.S, ChAdOx1 Zika) and rVSV vectors—express ZIKV antigens in host cells, evoking potent humoral and cytotoxic T-cell responses following a single dose [6,9,45]. Live-attenuated vaccine candidates, such as mutants lacking the NS1 glycosylation site or 3' UTR deletions, offer long-lasting immunity but require rigorous safety verification to rule out viral persistence or transplacental transmission in pregnancy [6,9,46].

## 7. OVERVIEW OF CLINICAL TRIALS

To date, over 20 ZIKV candidate vaccines have entered Phase 1 and Phase 2 human clinical trials [6,15]. Table 1 summarizes the clinical development status, platform characteristics, and key immunological observations of major representative ZIKV vaccine candidates.

| Candidate | Platform | Clinical Phase | Key Immunological / Clinical Findings | References |
|---|---|---|---|---|
| ZPIV | Purified Inactivated | Phase 1 | 92% seroconversion by day 57; well-tolerated with mild local reactions. | [10,41] |
| GLS-5700 | DNA Plasmid | Phase 1 | 100% binding antibody response after 3 doses; persistent neutralizing activity. | [11] |
| VRC5283 | DNA Plasmid | Phase 1 / 2 | Robust neutralizing antibody & T-cell responses; advanced to Phase 2 trial. | [12,15] |
| VRC5288 | DNA Plasmid | Phase 1 | Safe and immunogenic; VRC5283 selected for phase advancement. | [12] |
| mRNA-1893 | LNP-mRNA | Phase 1 / 2 | High neutralizing antibody response in seronegative and seropositive adults. | [14,42] |

| | | | | |
|---|---|---|---|---|
| mRNA-1325 | LNP-mRNA | Phase 1 | Demonstrated basic safety but lower immunogenicity relative to mRNA-1893. | [14] |
| Ad26.ZIKV.S | Viral Vector (Ad26) | Phase 1 | Elicited durable neutralizing antibodies and cellular immunity post single dose. | [45] |
| ChAdOx1 Zika | Viral Vector (ChAd) | Phase 1 | High seroconversion and anti-E protein T-cell stimulation; good safety profile. | [6,9] |
| ZIKV VLP | Virus-Like Particle | Preclinical / Phase 1 | Elicited high neutralizing titers; protected animal models against challenge. | [13,43] |

## 8. ANTIVIRAL DRUG DEVELOPMENT AND REPURPOSING

Currently, no specific antiviral therapeutic is approved for ZIKV treatment [2,6]. Clinical management remains entirely supportive, focusing on fluid resuscitation, antipyretics, and analgesics [2,5]. Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) must be strictly avoided until dengue fever is definitively excluded due to increased risk of hemorrhagic manifestations [2,5].

Antiviral research efforts encompass direct-acting antivirals (DAAs) and host-targeting agents (HTAs) [6,47]. Direct targets include the NS2B-NS3 protease (essential for viral polyprotein processing) and the NS5 RNA-dependent RNA polymerase (RdRp) [28,47]. Nucleoside analogs such as sofosbuvir (originally approved for Hepatitis C virus) and remdesivir have demonstrated potent inhibition of ZIKV replication in cell cultures and animal models [47,48]. Drug repurposing screens have identified candidates like chloroquine, nitazoxanide, and broad-spectrum entry inhibitors that reduce viral load in vitro [48,49]. Furthermore, human monoclonal antibodies (mAbs) targeting non-overlapping epitopes on the ZIKV E protein (e.g., ZIKV-117) have shown high protective efficacy in pregnant animal models by reducing placental viral burden and preventing fetal damage [6,50]. Clinical translation requires rigorous evaluation of safety, transplacental transfer kinetics, and pharmacokinetic profiles during pregnancy [6,50].

## 9. CHALLENGES IN VACCINE DEVELOPMENT AND CLINICAL EVALUATION

Despite rapid technological progress, several formidable scientific, regulatory, and epidemiological hurdles impede the licensure of a ZIKV vaccine [6,9,15].

### *9.1 Antibody-Dependent Enhancement (ADE) and Flavivirus Cross-Reactivity*

A primary immunological concern is antibody-dependent enhancement (ADE) [6,40]. Sub-neutralizing levels of cross-reactive antibodies generated by prior ZIKV vaccination or infection can facilitate viral entry into Fc-gamma receptor-bearing cells during subsequent dengue virus (DENV) infection, potentially exacerbating dengue severity [40,51]. Conversely, pre-existing anti-dengue antibodies can influence ZIKV vaccine immunogenicity [38,40]. Designing vaccines that elicit highly specific neutralizing responses while minimizing cross-reactive ADE-inducing epitopes remains a critical priority [40].

### *9.2 Waning Incidence and Phase 3 Efficacy Trial Feasibility*

The sharp decline in natural ZIKV transmission following the 2015–2016 epidemic has created an extreme epidemiological challenge for Phase 3 efficacy trials [6,9,15]. Unpredictable transmission dynamics, low case attack rates, and geographical dispersion make traditional field efficacy trials statistically underpowered and prohibitively expensive [6,15]. Consequently, regulatory pathways may need to rely on validated immunological correlates of protection or controlled human infection models (CHIM), subject to stringent ethical oversight [6,15,52].

### *9.3 Reproductive Safety and Inclusion of Pregnant Women*

Because pregnant women and their fetuses represent the primary target population for ZIKV prevention, demonstrating reproductive and developmental toxicity (DART) safety is paramount [3,6]. However, ethical concerns traditionally exclude pregnant individuals from early-phase clinical trials, creating a regulatory dilemma regarding how to safely generate safety and efficacy data in this vulnerable cohort [6,53].

## 10. FUTURE PERSPECTIVES AND PUBLIC HEALTH PRIORITIES

Addressing the lingering threat of ZIKV requires a multi-pronged approach integrating biomedical innovation with robust public health infrastructure [2,5,6]. Future biomedical priorities must focus on advancing multi-valent flavivirus vaccines (combining DENV and ZIKV targets) to eliminate ADE risks, defining standardized serological correlates of protection, and completing Phase 2/3 trials for leading mRNA and DNA candidates [6,9,14,15]. Monoclonal antibody therapies hold immense promise as passive immunoprophylaxis for pregnant women exposed to ZIKV during outbreaks [6,50].
From a public health standpoint, strengthening vector surveillance (monitoring mosquito density and insecticide resistance), implementing innovative vector control strategies (such as Wolbachia-infected Aedes mosquitoes), expanding molecular laboratory diagnostic capacity, and offering targeted preconception counseling in endemic zones remain imperative [2,5,21,54]. International cooperation through global outbreak networks is vital to ensure rapid response capabilities when future epidemics arise [5,6].

## 11. CONCLUSION

Zika virus remains a critical re-emerging global health threat due to its devastating neurotropic effects during fetal development and its capacity for rapid epidemic expansion. Over the past decade, extraordinary progress has been made in characterizing viral structural biology, defining pathogenic mechanisms of CZS, and advancing novel vaccine platforms including purified inactivated, DNA, mRNA, viral-vector, and VLP vaccines into human clinical trials. Early-phase trials demonstrate favorable safety and high immunogenicity; however, the absence of licensed vaccines or specific antivirals underlines persistent challenges related to ADE risks, unpredictable outbreak epidemiology, and complex trial logistics in pregnancy. Sustained research investment, global surveillance, and collaborative public health frameworks are vital to translate these promising biomedical candidates into approved, accessible interventions for high-risk populations worldwide.

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