

# Zika Virus: An Update and Its Implication for Vaccine Development



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## Abstract

The rapid spread of Zika virus (ZIKV) worldwide has been considered as an emerging global public health problem. ZIKV congenital infection causes microcephaly in newborns and its infection is related to Guillain-Barre syndrome in adults. ZIKV infects and replicates in neural stem cells and causes their apoptosis that leads to the reduction of cortical layer thickness in the developing brain of a fetus. Presently, there is no effective vaccine or drug for the prevention or treatment of ZIKV infection. Development of a safe and effective ZIKV vaccine is imperative to prevent congenital complications of ZIKV infection in pregnant women. Like other flaviviruses, ZIKV is also encompassed by envelope and M proteins, which contain several epitopes for neutralizing antibodies and have the potential for vaccine development. This review focuses on the recent advancements in the field of the ZIKA vaccine development.

**Keywords:** Guillain-Barre syndrome; Microcephaly; Vaccine; Zika virus

**Abbreviations:** Env: Envelope; DENV: Dengue Virus; RNA: Ribonucleic Acid; WHO: World Health Organization; ZIKV: Zika Virus

## Introduction

Recent emergence and the spread of Zika virus (ZIKV) in several countries around the globe have been considered as an emerging global public health problem. ZIKV is an arbovirus that belongs to the flavivirus genus. ZIKV is an enveloped, spherical virus containing a single-stranded positive RNA with a genome consisting of 10,794 nucleotides. The RNA of ZIKV is translated into a polyprotein that is co & post-translationally cleaved into 11-mature proteins. ZIKV was first identified in the Zika forest of Uganda in 1947 [1]. ZIKV is primarily transmitted by the infected *Aedes* mosquito's bites [2] and resides in the salivary glands of infected mosquitoes. ZIKV is also sexually transmitted, and the ZIKV RNA has been observed in sperm and urine after 62 days post infection [3,4]. In America, the increasing number of cases of congenital microcephaly and Guillain-Barre syndrome cases are related to ZIKV infection [5-7]. On February 1st, 2016, World Health Organization (WHO) declared the ZIKV infection as an international health emergency [8]. It is found that the ZIKV infects and replicates in the neural stem cells of the developing brain and causing their apoptosis. The ZIKV infection causes reduction of the cortical layer thickness in the developing brain. ZIKV is able to cross the placenta, detectable in amniotic fluid and causes intrauterine growth restriction of the developing

fetus in pregnant women [9-11]. Using a mouse model, Fernanda et al. proved that the ZIKV can target the cortical progenitor cells leading to microcephaly and impaired neurodevelopment in newborns [9].

The ZIKV congenital infection, intrauterine growth restriction and other devastating clinical manifestations urgently required the development of a safe and effective ZIKV vaccine. At present, there is no effective vaccine or drugs for the prevention or treatment of ZIKV infection. Envelope (E) and M protein are expressed on the surface of the virion and contain neutralizing epitopes, which can elicit neutralizing antibodies that block the infection of ZIKV. Multiple strategies and platforms have been used to develop an effective ZIKV vaccine. A recent study found that the lipid nanoparticle encapsulating modified mRNA vaccine encoding nonstructural genes elicit high titers of neutralizing antibodies and provide sterile protection in mice [12]. Authors have chemically synthesized the mRNA with type 1 cap as well as 5' and 3' untranslated regions to increase translation efficiency and intracellular stability. The chemically synthesized mRNA also contains signal sequence from human IgE for gene expression. This vaccine consists of modified prM-E RNA containing mutations that demolish the conserved fusion-

loop epitopes in the E-protein, and this strategy could minimize the generation of cross-reactive antibodies that may enhance the infection of dengue virus. An RNA nanoparticle technology has been used to produce a candidate ZIKV vaccine and identifies CD8+ T cell epitopes in E-protein [13].

ZIKV infection induces robust antibodies response that cross-react with other flaviviruses like Dengue virus (DENV) [14]. The ZIKV specific neutralizing and monoclonal antibodies have also been reported previously [15]. A neutralizing antibody, ZIKV-117 has proven to be protective against ZIKV infection in mice and limits the fetal pathology in pregnant mice [16]. This antibody is directed against the quaternary epitope on ZIKV envelope (Env) protein dimer-dimer interface. Elegant studies have developed the DNA vaccine expressing pre-membrane (Prm) and Env proteins. This DNA vaccine showed protection against ZIKV challenge in mice and rhesus monkeys [15,17]. This study also shows that passive protection against ZIKV infection in mice and monkeys can be achieved through the adoptive transfer of purified IgG from vaccinated animals [15,17]. It indicates that antibodies can provide passive immunity against ZIKA infection. Reduction in the number of CD4+ and CD8+ T lymphocytes in vaccinating animal did not affect the protective efficacy [17].

Plasmid DNA vaccine (VRC-ZKADNA085-00-VP; VRC5288) developed by Vaccine research center (VRC), National Institute of Allergy and Infectious Disease (NIAID) has entered into a Phase I clinical trial. The plasmid DNA vaccine expresses full-length prM-Env proteins consisting of Japanese encephalitis virus (JEV) stem and the transmembrane region has also been reported. Insertion of JEV stem and transmembrane region enhance the secretion of viral particles, reduced the protective efficacy and immunogenicity compared to the unchanged prM-Env [18]. Another Phase I clinical trial has initiated by the In-vivo Pharmaceuticals. In this study, plasmid DNA vaccine expressing prM-Env (GLS-5700) has been used. This plasmid DNA vaccine proved the efficacy in immuno compromised mice and plasma IgG mediate the protection. Three more Phase I clinical studies have been initiated by the U.S. Army, NIAID, and Beth Israel Deaconess Medical Center (BIDMC) to check the efficacy and immunogenicity of ZIKV PIV (ZPIV) vaccine developed by WRAIR. The PIV represents the purified formalin inactivated virus adjuvanted with alum. The other ZIKV vaccines are in progress include recombinant vector-based vaccines [17], RNA-based vaccines [19] and subunit vaccines. Since many ZIKV vaccines are at different stages of development and it will be very difficult to choose a safe and effective vaccine candidate. It would be achieved through the careful examination of preclinical and early clinical data and other considerations.

## Challenges

An effective ZIKV vaccine should prevent ZIKV infection and protect from viral infection particularly in pregnant women.

ZIKV vaccination of women during pregnancy has several issues to be addressed. First, in order to protect a developing fetus, the ZIKV vaccination protective immunity in pregnant women must be achieved at the time of first and early second trimester. However, many pregnant women do not know about their pregnancy until their first trimester. The replicating live virus vaccine may provide protective immunity at single dose is not generally considered as a good candidate vaccine for pregnant women. Inactivated virus, recombinant and other nonreplicating vaccines are good for pregnant women; need to be administered at multiple doses to achieve the protective immunity and hence extending the time window for pregnant women. Second, for the long-term goal, the ZIKV vaccination should be provided in the pediatric population to generate protective immunity in women at the childbearing age before their pregnancy and to prevent sexual transmission of ZIKV. It can be achieved if the ZIKV vaccine is safe, durable and provide robust immunogenicity.

## Conclusion

Effects of ZIKV infection during pregnancy and developing fetus should be minimized or eliminated by the administration of a safe and effective ZIKV vaccine in women. Therefore, the global public health goal is to prevent the ZIKV epidemics in future. Neutralizing antibodies against ZIKV found to control and prevent the ZIKV infection. Development of an effective ZIKV vaccine using different platform, such as recombinant vector based vaccine, purified inactivated virus vaccine, nucleic acid vaccine and is achievable in rodent and primate models. Studies have shown that the protection is mediated through the vaccine-elicited antibodies. Multiple Phase I clinical trials have been initiated for the ZIKV vaccines. Protective efficacy in human, cross-reactive antibodies to other flaviviruses and protection against congenital ZIKV syndrome are the main issues for an effective ZIKV vaccine.

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