

# Dengue and Zika Virus Infection; Immunopathogenetic Likeness?

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**Mini Review**

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## Abstract

Dengue and Zika viruses are closely related. They have the same mode of transmission, are structurally similar and sequential infections do occur. These observations have led to the hypothesis that these viruses share a common pathogenesis. Both cellular and humoral immunity play a role in Dengue virus infection. Research is being conducted to determine if the same immune mechanisms are responsible for spread and pathogenesis of Zika virus as well.

**Keywords:** Dengue; Zika; Virus; Pathogenesis

## Mini Review

Dengue and Zika virus belong to the “flavivirus” class of viruses and share many similar features. Both are transmitted to people through the bite of an infected mosquito, mainly *Aedes aegypti* in tropical regions. However, in contrast to Dengue virus, Zika virus is also transmitted sexually and through blood transfusions [1,2].

Symptoms of Zika and Dengue viral infection are similar and include fever, skin rashes, conjunctivitis, muscle, joint pain, malaise, and headache. These symptoms are usually mild, lasting for 2-7 days. However, there are certain distinguishing characteristics. Zika virus infection is particularly dangerous during pregnancy as it has been linked to congenital brain abnormalities, including microcephaly [3]. Zika virus is also suggested as a trigger of Guillain-Barré syndrome [4]. In contrast, Dengue virus infection, if severe can result in dengue haemorrhagic fever and dengue shock syndrome.

The two viruses share sequence homology and are structurally very similar. Thus, Zika virus outbreaks are being seen in areas infected with Dengue virus and

sequential infections can also occur. Due to this relationship between the two viruses, it has been established that cross-reactive immune responses exist and that dengue virus immunity may have an effect on the outcome of Zika virus infection.

It has been postulated that dengue virus infection results in a surge of pro-inflammatory mediators such as interferon- $\gamma$  (IFN- $\gamma$ ), tumor necrosis factor (TNF), CXCL10, vascular endothelial growth factor A (VEGFA), as well as the anti-inflammatory cytokine interleukin-10 (IL-10) [5,6]. The proposed mechanism responsible for this inflammatory cytokines surge is antibody-dependent enhancement which enhances viral replication and recruitment of inflammatory cells. Antibodies specific for proteins on the virion surface are generated resulting in opsonization of the virus by Fc receptor bearing cells such as macrophages. Macrophages are a major site of dengue virus replication [7,8]. Cytokine production is stimulated as a result of the interaction between opsonised virus and Fc receptors that further stimulate an array of inflammatory immune cells, contributing to the cytokine storm [9].

Another arm of the immune system that plays a role in disease pathogenesis are virus-specific T cells. During primary infection, both CD4+ and CD8+ T cells are activated and expand rapidly [10]. This results in a generation of large numbers of antigen-specific T cells that are capable of directly neutralizing infected cells and also provide help to B cells in the form of cytokines and other stimulatory factors. Upon subsequent encounter with same viral antigen during secondary Dengue virus infection, virus-specific memory T cells activate and rapidly proliferate and are responsible for extensive burden of the disease process [11]. Since multiple serotypes of Dengue virus exist, it is quite common for dengue virus-specific T cells to cross-react towards different serotypes.

As a result of activation of both arms of the immune system as described above, protecting against dengue virus infection, theories have been proposed regarding the pathogenesis of Zika virus. As mentioned earlier, both viruses are closely related as they share the same vector and there have been reports of sequential infection with both viruses. Studies have shown that Zika virus can more aggressively infect Fc receptor bearing cells that have been previously exposed to Dengue virus-specific antibodies in vitro. Also, Zika virus infection can be neutralized by Dengue virus-specific antibodies in vitro [12-14]. Although, macrophages are the major site of replication of Dengue virus, the cell type serving as a major site of replication for Zika virus is undetermined. There have been very few studies on Zika virus-specific T cells and whether these cross react with dengue virus. Few studies have demonstrated evidence of cross-reactivity of Zika virus-specific T cells to Dengue virus [15]. However, further research is needed to determine if T cells play any role during Zika virus infections and if Dengue virus-cross-reactive T cells can contribute to its pathogenesis. This knowledge is very critical in the development of new therapies for Zika virus infection.

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