Pre-existing Immunity Case Study: Zika Virus

**Background:** Zika virus (ZIKV) is a member of the Flaviviridae family. It is closely related to the dengue viruses. Following the explosive outbreak of ZIKV in the Americas in 2015-2016, many theories arose as to how ZIKV spread so quickly. Antibody dependent enhancement (ADE) of infection whereby non-neutralizing antibody can bind to a virus and then allow the virus-antibody complex to enter cells via the Fc receptor is thought to play an important role in the severity of dengue infection. Dengue antibody has been demonstrated to enhance ZIKV infection of Fc receptor bearing cells in vitro and in immunodeficient mice, but epidemiologic studies have not illustrated ADE of ZIKV in these dengue-endemic areas.

**Challenges:** It is well documented that any flavivirus antibody can enhance the infection of another flavivirus in vitro. It has been difficult to demonstrate ADE of infection in vivo for flaviviruses other than dengue. Teasing out the protective vs pathologic effects of pre-existing flavivirus antibody on ZIKV is complicated.

**Proposed Approach:** Review of the epidemiologic data during and following the ZIKV outbreak has not found evidence that pre-existing DENV antibody is responsible for the neurological complications of ZIKV or for the rapid spread of ZIKV through the Americas. In addition, some studies have shown that recent DENV infection may protect against ZIKV infection.

**Conclusions:** The role of pre-existing flavivirus antibody in ZIKV infection is not well understood. Controlled human infection models may help better characterize the protective and pathologic effects of pre-existing DENV antibody on ZIKV and vice versa.