*Review*

# Progress and Works in Progress: Update on Flavivirus Vaccine Development

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## ABSTRACT

Most areas of the globe are endemic for at least one flavivirus, putting billions at risk for infection. This diverse group of viral pathogens causes a range of manifestations in humans from asymptomatic infection to hemorrhagic fever to encephalitis to birth defects and even death. Many flaviviruses are transmitted by mosquitos and have expanded in geographic distribution in recent years, with dengue virus being the most prevalent, infecting approximately 400 million people each year. The explosive emergence of Zika virus in Latin America in 2014 refocused international attention on this medically important group of viruses. Meanwhile, yellow fever has caused major outbreaks in Africa and South America since 2015 despite a reliable vaccine. There is no vaccine for Zika yet, and the only licensed dengue vaccine performs suboptimally in certain contexts. Further lessons are found when considering the experience with Japanese encephalitis virus, West Nile virus, and tickborne encephalitis virus, all of which now have protective vaccination in human or veterinary populations. Thus, vaccination is a mainstay of public health strategy for combating flavivirus infections; however, numerous challenges exist along the path from development to delivery of a tolerable and effective vaccine. Nevertheless, intensification of investment and effort in this area holds great promise for significantly reducing the global burden of disease attributable to flavivirus infection. (*Clin Ther.* 2017;39:1519–1536)


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## INTRODUCTION

Flaviviruses are important human pathogens that cause widespread infections (Figure).[1] The Zika virus (ZIKV) epidemic recognized in 2015 abruptly aroused international concern for this group of viruses as numbers of infected people expanded rapidly throughout Latin America and confirmed cases of ZIKV-associated microcephaly have now increased to >3000.[2,3] Yellow fever virus (YFV) has continued to cause outbreaks in Africa[4] and South America,[5] leading to tens of thousands of deaths annually. Dengue virus (DENV) has been steadily expanding during the last decades and is now the most common vector-borne virus in the world.[6] West Nile virus (WNV) has become endemic from the East Coast to West Coast in the United States since 1999,[1] revealing that these infections are not confined to tropical nations affected by climatic and sociopolitical challenges. Although vector control could contribute to comprehensive control and prevention programs for flaviviruses,[1] there are substantial limitations to these strategies because of the natural history and transmission ecology of these infections and dependency on sustained public will and infrastructure. Thus, vaccination is the most attractive approach to reduce the burden of human disease caused by flaviviruses.

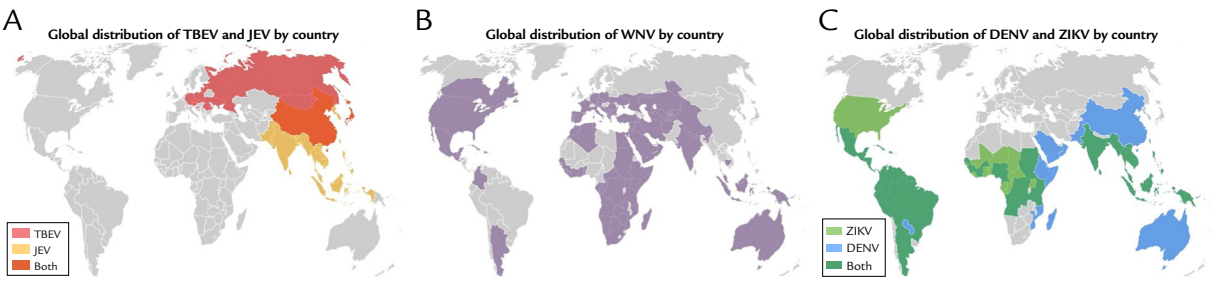


Figure. Distribution of infection and areas of overlap are shown for (A) tickborne encephalitis virus (TBEV) and Japanese encephalitis virus (JEV), (B) West Nile virus (WNV), and (C) dengue virus (DENV) and Zika virus (ZIKV).

Vaccination is widely celebrated as a crowning achievement of modern medicine and a "best buy" in public health.[7] However, there is ample room for improvement. Proper access and implementation of existing vaccines could prevent >3 million childhood deaths each year.[8] Although our ability to immunize against many pathogens has expanded during the last 2 centuries, tools to prevent major global infections, such as tuberculosis, HIV, and malaria, remain elusive.[7] Within the flavivirus family, YFV[9] and Japanese encephalitis virus (JEV)[10] are largely preventable, whereas DENV,[11] and more recently ZIKV,[12] vaccines represent unmet goals. In this review, we survey some success stories in flavivirus vaccinology and take a closer look at vaccine development for ZIKV and DENV as case studies to illustrate both particular aspects of the virology and immunology to these two viruses and general issues that may arise with related flaviviruses and other emerging pathogens for which effective vaccines are not yet available.

## BASIC VIROLOGY AND EPIDEMIOLOGY FOR ZIKV AND DENV

As is true of all flaviviruses (Family: Flaviviridae, genus: *Flavivirus*),[13] ZIKV and DENV are enveloped viruses with positive-sense, single-strand RNA genomes of approximately 11 kb. The flaviviruses, including those discussed in this review, share a common genomic organization, life cycle, and several host-pathogen protein interactions. The subtler genetic and molecular determinants of variation among the members of this group in vector use, host cell tropism, pathogenesis, and immunity are largely still being investigated[14] and are not discussed further here. After fusion and uncoating, a single polypeptide is translated in the cytoplasm of the host cell and cleaved into 3 structural (capsid [C], premembrane [prM], and envelope [E]) and 7 nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5).[3] The virion has icosahedral symmetry and comprises 180 E monomers arranged in antiparallel dimers, which are further arranged into higher-order configurations.[15] In addition to mediating host cell attachment, fusion, and entry, E protein is a major target of antibody (Ab) responses in flavivirus infection.[16]

Most infections by both viruses are mild or asymptomatic,[13] which can be a major barrier to accurate determination of prevalence and surveillance. Clinically, DENV is a common cause of acute febrile illness in the tropics and in returned travelers. Common symptoms include headache, rash, and joint pain. Severe DENV, epidemiologically associated with a second DENV infection by a serotype distinct from the first infection, occurs in a small fraction of infected individuals and may manifest as hemorrhage, shock, end organ damage, or even death.[6,17] The pathogenesis for severe DENV as it relates to vaccine development is discussed further below.

Symptomatic ZIKV infection is difficult to clinically distinguish from DENV or other causes of rash or fever in the tropics because of overlapping symptoms.[18] However, the recent ZIKV epidemic has also been associated with new diseases phenotypes. It is now well established that ZIKV crosses the placenta, infects the fetus, adversely affects neurodevelopment, and causes a range of birth defects collectively termed congenital Zika syndrome.[19–22] Guillain-Barré