Viral emergence and immune interplay in flavivirus vaccines

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Among arthropod-borne viruses, flaviviruses have had the strongest impact on public health in the past centuries, dating back to large yellow fever outbreaks recorded since the 17th century. Nowadays, dengue virus alone infects hundreds of millions of people worldwide. In the past decade, Zika virus emerged across Latin America, and large outbreaks of yellow fever virus occurred in Angola, Democratic Republic of the Congo, and Brazil.[1,2] Since antiviral treatments are either unavailable or ineffective if administered too late, vaccination is key to combat the growing flavivirus burden. Widely used vaccines exist against human pathogenic flaviviruses including Japanese encephalitis virus in Asia, tick-borne encephalitis virus in Europe and northern Asia, and yellow fever virus in tropical and subtropical regions. By 2019, the tetravalent dengue vaccine CYD-TDV was licensed in 20 countries.[3] Multiple other vaccines against dengue virus,[3] Zika virus, and West Nile virus have also entered clinical trials.[4]

In temperate climates, only a few human pathogenic flaviviruses are endemic and multiple flavivirus infections are usually rare. By contrast, tropical areas harbour a plethora of different flaviviruses. In such settings, pre-existing flavivirus immunity can either be beneficial and provide cross-protection (best case scenario) or dramatically enhance heterologous flavivirus infections (worst case scenario).[5] For most flaviviruses, heterotypic immune interactions are poorly understood. In the 2015 Zika virus outbreak, dengue-mediated immune enhancement was assumed on the basis of strong in-vitro data, yet epidemiological studies showed that dengue immune responses protect individuals from both symptomatic Zika virus infection and the development of congenital Zika syndrome.[6] The clearest case of immune enhancement is observed between dengue virus serotypes. Secondary infection with a heterologous dengue virus serotype is associated with an increased risk of severe disease in humans, through a process called antibody-dependent enhancement (ADE).[3] ADE probably depends on the serotype combination, chronological sequence, and time since previous flavivirus infection.[6] Another factor possibly affecting the outcome of secondary dengue virus infections is the titre of pre-existing anti-dengue virus antibodies. Low titres might favour ADE, whereas high titres might provide cross-protection.[7] Similarly, moderate titres of pre-existing antibodies against Japanese encephalitis virus were shown to prolong and increase viraemia in yellow fever vaccinees.[5] Vaccination of individuals with CYD-TDV who have not been exposed to dengue virus before can increase their risk of severe disease when they are first exposed to dengue virus infection naturally.[8] As a result, the WHO Strategic Advisory Group of Experts on Immunization recommended use of the vaccine only in individuals with pre-existing dengue virus immunity. The usage of CYD-TDV in areas of low dengue endemicity is not recommended.[3]

Beyond dengue, how flavivirus immunity affects current and future flavivirus vaccines is unclear. The complexity of multitypic flavivirus immunity in tropical regions can be best illustrated by the case of Brazil. Brazil is the fifth largest country in the world and home to roughly 210 million people. Brazil is a hotspot of arbovirus circulation with at least 12 endemic flaviviruses pathogenic to humans, including all four dengue virus serotypes, yellow fever virus, Zika virus, West Nile virus, Rocio virus, Saint Luis encephalitis virus, Bussuquara virus, Ilheus virus, and Cacipacore virus (figure). Beyond the genetic diversity of these viruses, the numbers of reported infections are substantial. Up to 1·5 million dengue cases are notified annually in Brazil. During the explosive Zika virus outbreak, more than 8 million Brazilians were infected.[2] In southern Brazil, 500 000 individuals are intended to be vaccinated using CYD-TDV, and a phase 3 clinical trial (registered with ClinicalTrials.gov, NCT02406729) for the tetravalent dengue vaccine TetraVax-DV-TV003 is continuously enrolling participants. In parallel, 23 million Brazilians are being vaccinated against yellow fever virus.[1]

The experiences from CYD-TDV trials and the magnitude of multitypic flavivirus infections in settings such as Brazil, suggest that determination of vaccine efficacy and safety in hyperendemic areas will be increasingly challenging.[8] It seems likely that increasingly large numbers of individuals will have to be enrolled in vaccine trials, and long-term follow-ups will become necessary to identify severe adverse events and potential vaccination-related enhancement of subsequent flavivirus infections. It is also unclear how robust the data are from dengue vaccine trials in South America, after the emergence of Zika and yellow fever mass vaccination campaigns. The global rise of flavivirus infections demands vaccines to protect people living in and travelling to endemic countries. Lack of vaccine safety will dramatically affect the public trust in vaccines for flaviviruses and other diseases, as shown by the recent measles outbreak affecting thousands of unvaccinated children in the Philippines, after the risks of CYD-TDV dengue vaccine became apparent.[11] Vaccines are extremely safe and have saved millions of lives. The problems associated with the dengue vaccine CYD-TDV are therefore an unfortunate event. As a result, new tests are urgently needed to determine flavivirus serological status, ideally suitable for point-of-care testing to allow approaches that pair screening with vaccination.[12] However, the complexity of flaviviral immune interplay might require determination of other flaviviruses besides dengue, and at the very least semi-quantitative techniques including innovative tools for test interpretation that are currently entirely unavailable for point-of-care testing.

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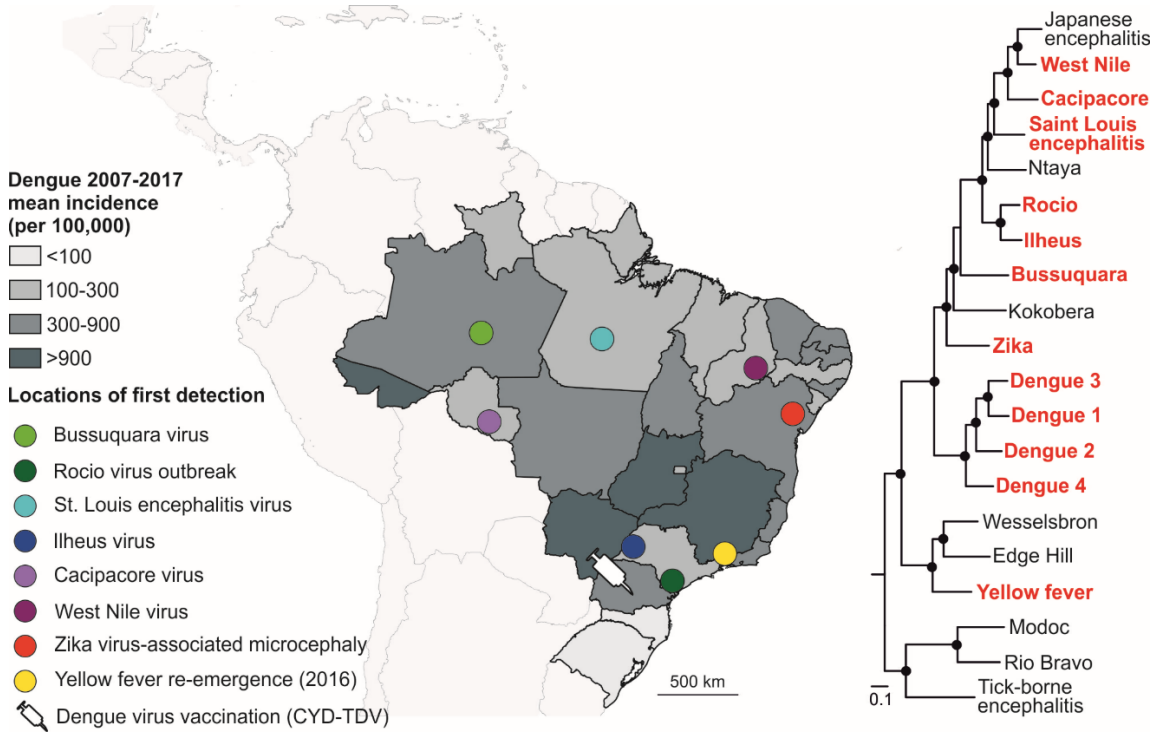

Figure: Circulation and phylogeny of flaviviruses infecting humans in Brazil

Mean dengue virus incidence was calculated using the number of probable annual cases reported by the Brazilian Ministry of Health.[9,10] Larger areas of Zika virus-associated microcephaly and yellow fever re-emergence are represented by single circles for clarity of presentation. Viruses that are endemic in Brazil are shown in red. Phylogeny of major human pathogenic flaviviruses was calculated in MrBayes (v3.2.6; 20 000 trees from 2 000 000 generations using the translated polyprotein gene and a Whelan and Goldman substitution model; black dots indicate posterior probability >0·9; Nienokoue virus was used as an outgroup).

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