Study maps potential route to effective dengue vaccines

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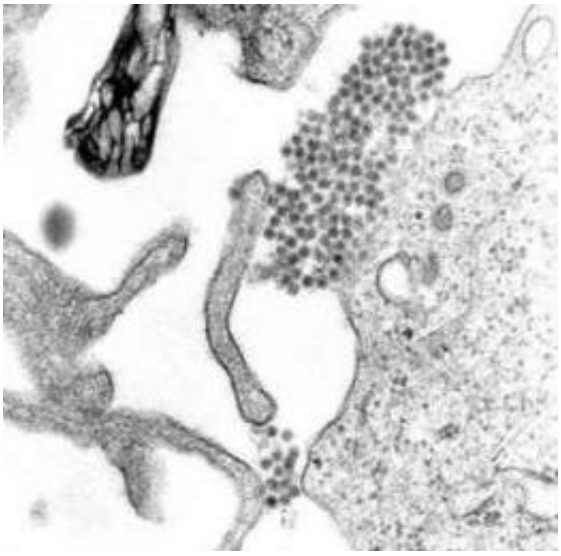

A TEM micrograph showing Dengue virus virions (the cluster of dark dots near the center). Image: CDC

(Medical Xpress)—The mosquito-borne dengue virus infects up to 390 million people a year. Symptoms of dengue fever include a measles-like rash, fever, body aches and joint pain. In a small subset of cases, the disease develops into life-threatening dengue hemorrhagic fever, resulting in bleeding and low platelet count; this can progress to dengue shock syndrome, which manifests as dangerously low blood pressure.

There are four dengue virus serotypes, DENV1-4. The risk factors for

developing disease include exposure to a heterologous DENV serotype, the specific infecting strains, the interval of time between infections, age, ethnicity, genetics, and others. Neutralizing antibodies (NAbs) are believed to provide long-term protection against infection and the development of severe forms of dengue.

The goal of researchers is to produce dengue vaccines that provide protection against all DENV serotypes, but vaccine development is inhibited by a lack of knowledge about the association of homotypic and heterotypic NAb titers. A group of researchers from Nicaragua, the U.S. and the U.K. have collaborated on a study into the correlation between antibody titers and protection from symptomatic infection. They have published their results in the *Proceedings of the National Academy of Sciences*.

The researchers analyzed data from the Nicaraguan Pediatric Dengue Cohort Study (2004 to present), described as a community-based study featuring passive surveillance with an active cohort of ~3500 children aged two to 14. Data was culled from healthy annual blood samples; symptomatic dengue infections were confirmed in children who presented to the health center with suspected dengue.

Using the data to reconstruct the immunological histories for each child, the authors analyzed the results and concluded that higher preinfection neutralizing antibody titers correlate with a lower probability of symptomatic infections in children. They also determined that levels 0f cross-reactive neutralizing antibodies are maintained in healthy children over a long period of time, possibly due to re-exposure.

The authors write, "We observed that a higher median preinfection NAb titer or NAb titer to the 2° infecting serotype, but not the NAb titer to the 1° serotype, was significantly associated with reduced probability of 2° symptomatic DENV infection, indicating that cross-reactive NAbs

determine protection, as others have proposed."

The researchers also found by tightening or loosening their own criteria for inapparent infections that the protective effect of preinfection NAbs remained. In addition to determining that higher levels of cross-reactive preinfection NAbs likely confer reduced probability of developing symptomatic dengue, they also believe that in endemic settings, NAb titers do not become increasingly type-specific.

The study also suggests that the major independent predictor of symptomatic infection is epidemic force, and that age and the time between 1° and 2° infections were lesser predictors. While this contrasts with the results of previous studies, the authors note that those studies used age and the years between infections as indirect measures of NAb titers, while the current study directly observes the effect of NAb titers on infection outcomes.

They write, "Our findings have potential implications for vaccine development and implementation. Vaccines that generate higher levels of NAb titers will potentially reduce the probability of symptomatic infection, but the level of NAbs required for protection against symptomatic disease may differ from year to year in endemic settings."

More information: Neutralizing antibody titers against dengue virus correlate with protection from symptomatic infection in a longitudinal cohort. *PNAS* 2016 ; published ahead of print January 4, 2016, DOI: 10.1073/pnas.1522136113

Abstract
The four dengue virus serotypes (DENV1–4) are mosquito-borne flaviviruses that infect ~390 million people annually; up to 100 million infections are symptomatic, and 500,000 cases progress to severe disease. Exposure to a heterologous DENV serotype, the specific

infecting DENV strains, and the interval of time between infections, as well as age, ethnicity, genetic polymorphisms, and comorbidities of the host, are all risk factors for severe dengue. In contrast, neutralizing antibodies (NAbs) are thought to provide long-lived protection against symptomatic infection and severe dengue. The objective of dengue vaccines is to provide balanced protection against all DENV serotypes simultaneously. However, the association between homotypic and heterotypic NAb titers and protection against symptomatic infection remains poorly understood. Here, we demonstrate that the titer of preinfection cross-reactive NAbs correlates with reduced likelihood of symptomatic secondary infection in a longitudinal pediatric dengue cohort in Nicaragua. The protective effect of NAb titers on infection outcome remained significant when controlled for age, number of years between infections, and epidemic force, as well as with relaxed or more stringent criteria for defining inapparent DENV infections. Further, individuals with higher NAb titers immediately after primary infection had delayed symptomatic infections compared with those with lower titers. However, overall NAb titers increased modestly in magnitude and remained serotype cross-reactive in the years between infections, possibly due to reexposure. These findings establish that anti-DENV NAb titers correlate with reduced probability of symptomatic DENV infection and provide insights into longitudinal characteristics of antibody-mediated immunity to DENV in an endemic setting.