# Scientists discover how dengue vaccine fails to protect against disease

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Developing a viable vaccine against dengue virus has proved difficult because the pathogen is actually four different virus types, or serotypes. Unless a vaccine protects against all four, a vaccine can wind up doing

more harm than good.

To help vaccine developers overcome this hurdle, the UNC School of Medicine lab of Aravinda de Silva, Ph.D., professor in the UNC Department of Microbiology and Immunology, investigated samples from children enrolled in a dengue vaccine trial to identify the specific kinds of antibody responses that correlate with protection against dengue virus disease. In doing so, the researchers discovered that a small subpopulation of antibodies binding to unique sites on each serotype are linked to protection. The research, published in the *Journal of Clinical Investigation*, provides important information for vaccine developers to consider when creating a dengue vaccine, which has long eluded scientists.

The four dengue virus serotypes are mosquito-borne flaviviruses that infect hundreds of millions of individuals each year in Southeast Asia, western Pacific Islands, Africa, and Latin America. Nearly 100 million individuals report flu-like symptoms. Though rarely deadly, the virus can cause severe illness, especially when a person who was previously infected with one serotype (and recovers) is then infected by a second serotype. This happens because antibodies from the first infection help the virus replicate during the second infection through a process called antibody dependent enhancement. A dengue vaccine induced antibody response weighted towards a single dengue virus serotype can mimic this phenomenon.

Several vaccines have been in clinical development for years, and most show that they induce neutralizing antibodies against all four serotypes. Yet, research has also shown that the creation of neutralizing antibodies alone does not correlate to protection against clinical disease. The de Silva lab conducted experiments to compare the properties of antibodies against wild-type Dengue viruses and the properties of antibodies produced by a leading vaccine candidate—Dengvaxia—which the

pharmaceutical company Sanofi Pasteur created using all four dengue virus serotypes in one formulation.

Experiments led by Sandra Henein, research associate in the UNC Department of Microbiology and Immunology, and Cameron Adams, a medical and graduate student in the UNC Medical Scientist Training Program (MD/Ph.D.), showed that wild type infections induced neutralizing and protective antibodies that recognized a part of the virus—an epitope—unique to each serotype. The vaccine, though, mainly stimulated neutralizing antibodies that recognized epitopes common among all serotypes. In vaccine trials, these antibodies did not protect children from dengue. In the past, researchers have considered all dengue neutralizing antibodies to be protective in people. This appears to not be the case, according to this UNC-led research.

"Our results suggest that a safe and effective dengue virus vaccine needs to stimulate neutralizing antibodies targeting unique sites on each of the four dengue serotypes," Adams said. "Not merely the neutralizing antibodies against cross-reactive epitopes common to all four dengue types."

**More information:** Sandra Henein et al, Dengue vaccine breakthrough infections reveal properties of neutralizing antibodies linked to protection, *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI147066

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