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Dengue virus: Urgency in our warming world

Why is this important? In the summer of 2023, Mexico and countries in Central America and the Caribbean were in the news because of extensive outbreaks of the mosquito-borne dengue virus (DENV) (1). These outbreaks were at least partially weather-related: Warmer temperatures exacerbated by El Niño and global warming are linked to heavier-than-normal precipitation in the region, which has facilitated increased reproduction of *Aedes aegypti* and *Aedes albopictus* mosquitoes that spread DENV. Outbreaks have been particularly deadly in Peru, Brazil, and Bolivia, but other areas are experiencing major outbreaks, including Bangladesh (2),Chad, which reported its first outbreak (3), and Europe. The city of Paris, France fumigated to kill the spread of these mosquito vectors in 2023 (4).

Why is DENV different? DENV infections are pernicious for several reasons. For one, a person's first infection is typically not serious and may even be asymptomatic. Those with symptoms, which are often non-specific and flu-like, may be suspected as having a different viral infection or even malaria. More severe DENV infections occur when a previously infected person is reinfected with a different serotype of the virus. These serotypes are akin to distinct fingerprints, necessitating the immune system to tackle each one separately to elicit responses to subsequent infection that are more nuanced. Only reinfection with the same serotype is durably protected by immunity; reinfection with a different serotype may cause more severe disease, termed "dengue shock syndrome" or "dengue hemorrhagic fever," depending upon signs in the patient. In total, DENV encompasses four distinguishable serotypes that are based upon their antigenic properties. Variation within serotypes can be substantial (5), and so, while rare, same-serotype reinfections may also be serious.

How exactly is a patient with a second infection of DENV at *higher risk of serious disease*? After an initial infection, a person's immune system targets the viral envelope protein with neutralizing antibodies, just as with other enveloped viruses. The initial high concentration (or *titers*) of these IgG antibodies can be effective against the same DENV serotype – though may offer limited cross-protection against other serotypes. But effectiveness wanes over time as titers fall, particularly in cross-protection against a different serotype. The neutralizing antibodies are still effective against the initial infection serotype, binding and blocking it. They can also protect against viruses within the same serotype, i.e., a *homologous serotype*. These antibodies can also still bind to the DENV envelope proteins of other serotypes (*heterologous serotype*), but they cannot block viral entry due to a lack of neutralizing activity. So the lack of neutralizing activity confers an ability to DENV to infect some cells even more efficiently, as cells bear receptors to the antibodies (Fc-gamma receptors [FcγRs]), increasing entry of virus into cells and overall viral loads and thus, the severity disease.

This expansion of the DENV cellular host range and infectious burden is called antibody-dependent enhancement (ADE) or immune enhancement. Interestingly, IgA antibodies induced by infection have been reported to oppose ADE by IgG-enhancing antibodies and can contribute to virus neutralization (6). T-cell responses during secondary infections may also contribute to immune enhancement.

What other viruses are related to DENV? DENV are classified as flaviviruses, a genus that includes yellow fever, Japanese encephalitis, West Nile, and Zika viruses (all spread by mosquitoes), as well as tick-borne viruses like Kyasanur Forest disease, Alkhurma disease, and Omsk hemorrhagic fever (7). DENV has a single positive-stranded RNA genome of about 11,000 nucleotides that encodes both structural and non-structural proteins. Among the non-structural proteins are several that inhibit the type 1 interferon response, the innate immune system's first line of defense.

Treatments and Vaccines. Currently, there are no available antiviral drugs to treat DENV. In recent years, two vaccines, Qdenga® and Dengavaxia®, have been marketed.

Qdenga is a live-attenuated tetravalent vaccine reported to be >80% effective against hospitalization and 60% effective against disease. However, it is only approved in Europe, the United Kingdom, Brazil, Argentina, Indonesia, and Thailand. Its manufacturer, Takeda, is not pursuing approval in the U.S. (8).

Dengvaxia®, produced by Sanofi-Pasteur, is a recombinant vaccine with the backbone of a live-attenuated yellow fever virus containing envelope genes from all four dengue serotypes. While efficacy is relatively high in the first 2 years after vaccination, at later times an elevated incidence of hospitalization and severe disease was noted in some persons who were non-DENV-immune upon vaccination (9). The FDA has approved its use only for individuals aged 6-16 living in endemic areas.

New DENV vaccines developed at the U.S. National Institutes of Health and elsewhere have highly promising immunogenicity characteristics, and several are now in clinical trials (9-12). The NIH-developed vaccine induces impressive cross-reacting protection in animals and in Phase 1 human studies, so safety and efficacy from current human Phase 2/3 trials are awaited with great anticipation. The ultimate goal, of course, is a safe, effective, and affordable vaccine for universal use for reducing DENV disease severity (13). However, vaccine development is slowed by the possibility of ADE, so animal studies are especially extensive and human studies are done with extreme care. Any vaccine for DENV must be able to elicit production of broadly neutralizing antibodies against all four viral subtypes, to avoid risking ADE and more severe disease among vaccinees.

Environmental control. Because DENV infection is difficult to prevent and treat, preventive strategies beyond vaccines are essential in the short-term. Mosquito control efforts depend upon insecticides, mosquito netting, and drainage of small containers and reservoirs of standing water, preferred larval habitats of *Aedes* mosquitoes. There are innovative strategies such as the introduction of mosquito fish (*Gambusia* sp.) that prey on mosquito larvae. These approaches are only successful with a high degree of community mobilization since they depend on widespread cooperation of the citizenry. In some ecological niches, introduction of mosquito fish has been unsuccessful because they have fed on other mosquito predators.

Other innovative approaches include the use of biologically modified mosquitos, and infecting mosquito populations with intracellular bacteria, the *w*Mel strain of *Wolbachia pipientis* (14,15). This bacterium reduces the vectorial capacity of the mosquito such that one study reports 86% effectiveness (16) at reducing hospitalization from DENV infections. Large-population effectiveness is not yet clear, but there are

no known environmental risks (17). Several other research teams have shown promising results with genetically modified mosquitoes (18), but concerns are substantial as to potential complications of releasing genetically modified organisms into the wild.

The future. The 2024 global situation suggests dengue to still be a growing and serious health menace, exacerbated by mosquito proliferation in temperate regions as the climate warms. Dengue outbreaks are becoming more serious due to climate change and different viral strains are emerging, emphasizing the importance of vaccines and environmental control efforts. Better prevention/mitigation and treatment approaches are needed in nations with warming climates that were not previously dengue endemic. The southern United States and southern Europe are two of many examples. Dengue is a "neglected tropical disease," not receiving as much attention or investment because it disproportionately affects the world's poor. Developments of vaccines, antivirals, and biological vector control will make a difference only if accompanied by global investment and advocacy. Vaccine hesitancy (19) will require multidisciplinary research, action, and community engagement.

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