Dengue is the most important arthropod-borne viral disease of humans, posing a risk to approximately half of the world's population. It is found in tropical and sub-tropical climates worldwide (Fig 1). Dengue is transmitted to humans by two mosquito species: the yellow fever mosquito *Aedes aegypti* and the Asian tiger mosquito *Aedes albopictus*.

An adult female mosquito requires a blood meal to produce her eggs. If the mosquito feeds from a human with dengue virus, it becomes infected, with the virus first infecting its midgut. It takes approximately 7-14 days for the virus to infect the salivary glands, which enables the mosquito to transmit the virus to another human during its next blood meal.

There are four serotypes (distinct variations) of dengue virus: DENV-1, 2, 3, and 4. Infection with a serotype results in a flulike illness. Being infected with more than one serotype increases the risk of developing the life-threatening dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).
Prior to the 1950s, each serotype occurred in isolation and human infection with two or more serotypes was rare. However, with increased global connectedness and climate change, all four dengue virus serotypes now co-occur in endemic areas throughout the world and dengue epidemics and severe disease have become fairly common.

At present, however, the interactions of the four dengue virus serotypes within their natural vectors (mosquitoes) are poorly understood, as are the potential implications for the development of dengue epidemiology. A mosquito may acquire multiple dengue serotypes from a single blood meal (coinfection) or from separate blood meals (superinfection). The virus can also be passed between mosquitoes through sexual transmission or from the female mosquito to her eggs (vertical transmission).

In general, the outcome of virus-virus interactions may be neutral, where the viruses have no effect on each other; synergistic, one (or both) virus facilitates replication or transmission of the other virus; or antagonistic, where one virus benefits at the expense of the other.

The most commonly reported outcome of virus-virus interactions is superinfection interference in which the primary infection prevents infection by a second virus. This has been demonstrated mostly in laboratory cultures but not in the natural vector.

We investigated how infection of the yellow fever mosquito Ae. aegypti with one DENV serotype affects its susceptibility to a second DENV serotype. We infected four- to seven-day-old adult females of Ae. aegypti with either DENV-2 or DENV-4. After seven days, we provided a secondary blood meal containing the other serotype. A control group was fed a noninfectious blood meal (NI). Mosquitoes infected with DENV-4 were significantly less susceptible to the secondary infection of DENV-2 (Fig. 2). Although not statistically significant, mosquitoes infected with DENV-2 were less susceptible to a secondary infection of DENV-4.

The midgut and population dissemination rates for DENV-2 were at least four times higher than those of DENV-4 when each virus was administered seven days after consuming either a noninfectious blood meal or a blood meal containing the other serotype.

Collectively, these findings demonstrate that superinfection interference occurs among DENV serotypes within the mosquito, but whether it leads to competitive displacement depends on the biological characteristics of interacting strains. These results may explain the commonly reported displacement of DENV serotypes in some regions but not in others. Further studies are needed to explore the potential outcome of interactions among all four serotypes of the dengue virus.

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