Modeling Dengue: Determining the Most Effective Vaccine Strategy

January 21, 2013

G Brennan

Dengue virus is the most common mosquito-borne viral infection in the world, with more than 500,000 cases of symptomatic dengue infection reported annually. Children are more susceptible to severe forms of the disease, including dengue hemorrhagic fever/dengue shock syndrome, and therefore they are more likely to require hospitalization. For these reasons, considerable effort has been directed towards the development of a vaccine, and several candidates have entered clinical trials. However, with nearly 3 billion people at risk of infection, even if a vaccine were approved today, we would not be able to adequately vaccinate everyone at risk. Therefore, Drs. Dennis Chao and M. Elizabeth Halloran (Vaccine and Infectious Disease Division), in collaboration with investigators from the Dengue Vaccine Initiative and the University of Florida, developed a computational model of infection and vaccination to determine how to most effectively deliver a limited supply of Dengue virus vaccine.

The team developed a model designed to simulate seasonal dengue virus transmission in a semi-rural region of Thailand with exposure to all four dengue virus serotypes. The model simulates a population of 207,591 individuals that spend time at home and at work or school. Each of these individuals is classified as susceptible, exposed, infectious, or recovered. Symptomatic individuals may remain home until they recover, while recovered individuals are immune to infection with all Dengue virus serotypes for the first 120 days after infection, and then only to the specific serotype they had been infected with. Similarly, the model simulates two populations of mosquitos. Uninfected mosquitos remain in a given building until they bite an infected human. After an incubation period, these infected mosquitos can transmit dengue virus to susceptible humans, and will occasionally migrate to nearby buildings.

During the simulation, the authors seeded the epidemic by randomly exposing two people to each serotype daily to simulate the influx of dengue virus infected mosquitos from neighboring regions. The simulated season peaked in the July-August period, and resulted in a 5% infection attack rate, which measures the number of infected people relative to the number of exposed people. These infected people went on to infect an additional 1.9 to 2.3 people, a value known as the reproductive number, R. These values correspond closely with the observed values for dengue virus infection in

Thailand. Using these data, the authors determined that approximately 80% of the total population would need to be vaccinated to control dengue infection, a number unlikely to be met during the first years of vaccine availability.

The authors simulated several 10 year vaccine roll-out strategies. In one simulation, only children 2-14 years old were vaccinated, reaching 70% vaccination of this population after three years, and then continuing to vaccinate only 2-year-olds. Under these conditions, dengue virus incidence dropped by approximately 60% over the first three years. After the first three years, however, when only 2-year-olds are being vaccinated, the incidence declined much more slowly. Therefore, the team asked what would happen if a "catch up" vaccination program was initiated for adults after the initial three year vaccination program for children. Including adults in the later vaccine program resulted in a faster decrease in incidence after the first three years, relative to vaccinating only children.

This simulation suggests that targeted vaccination of children would be the most efficient use of limited dengue virus vaccine stocks, particularly in reducing hospital visits and the most severe disease. Unfortunately, vaccination of children alone, according to this model, will be insufficient to stop dengue transmission. Therefore, once children are protected, a catch-up vaccination strategy to inoculate adults would continue the rapid decline in dengue virus infection. It is important to note that these results apply to a hyperendemic area and a vaccine effective against all four serotypes of the virus. Some vaccines currently in clinical trials do not protect against all four serotypes, and may require different vaccination strategies to most efficiently protect the population.

Chao DL, Halstead SB, Halloran ME, Longini IM Jr. 2012. Controlling dengue with vaccines in Thailand. *PLoS Neglected Tropical Diseases*. Epub ahead of print, doi: 10.1371/journal.pntd.0001876.

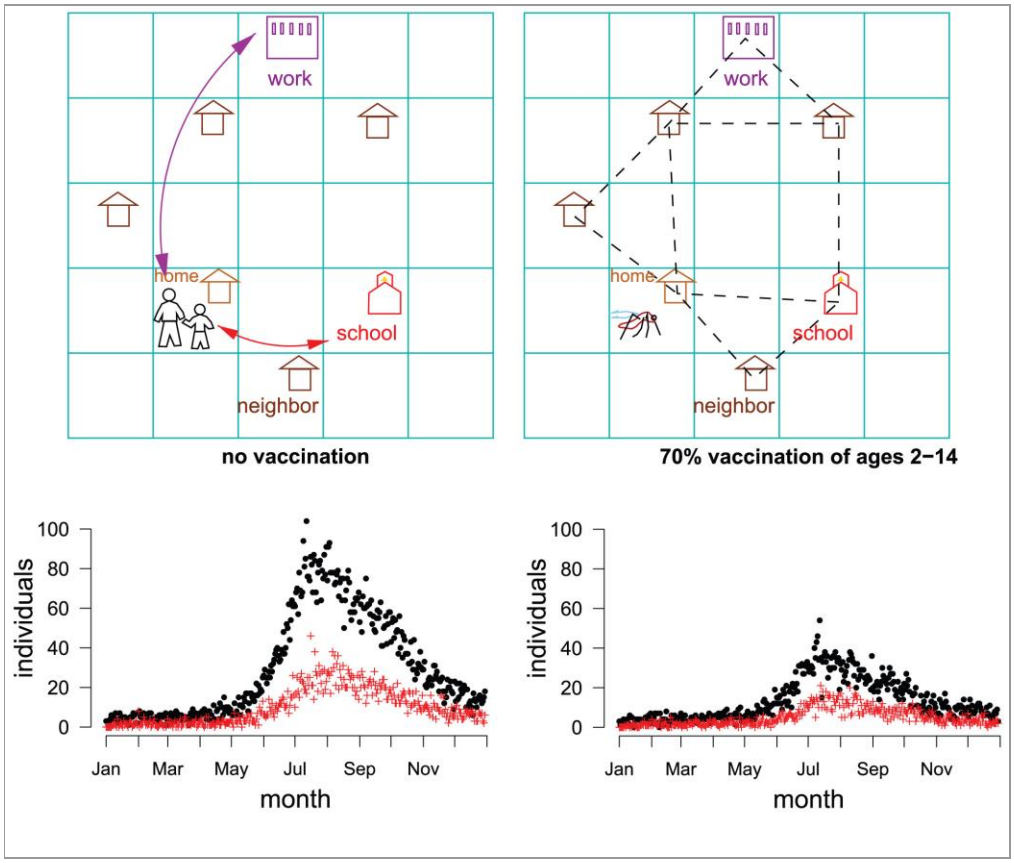

Image modified from Chao, et al., PLOS NTDS, 2012.

Schematic diagram of the dengue transmission model, diagramming how human movement (top left), or mosquito movement (top right) is simulated. Bottom images display the incidence of newly infected (black) and symptomatic (red) patients in the case of no vaccine (bottom left), or after vaccinating 70% of children (bottom right).