Researchers warn of 'fever from the forest'

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More than a thousand years ago, somewhere in Southeast Asia, a fateful meeting occurred between a mosquito-borne virus that infected mainly monkeys and a large, susceptible group of humans. The result: the world's first outbreak of dengue fever.

Today, dengue virus — which can produce high fever, excruciating joint pain and even death — has spread throughout tropical Asia, Africa and South America, and in 2008 it re-appeared in the Florida Keys. It could be even more widespread along the U.S. Gulf Coast but there is no surveillance in place to detect it.

Annually dengue strikes about 100 million people and causes an estimated 50,000 deaths, thriving in the urban environments infested by Aedes aegypti, the mosquito species primarily responsible for human dengue transmission.

Meanwhile, the virus' forest-dwelling counterpart – known as "sylvatic dengue" — continues to flourish in Southeast Asia and West Africa, cycling between non-human primates and the mosquitoes that feed on them. Since the 1970s, sylvatic dengue has received very little scientific attention — a situation that badly needs to be remedied, according to the authors of "Fever from the forest: Prospects for the continued emergence of sylvatic dengue virus and its impact on public health," an article published online June 13 in *Nature Reviews Microbiology.*

"This virus continues to circulate in the forests, and now economic and ecological pressures are driving more and more people into the forests in

Africa and Southeast Asia," said University of Texas Medical Branch at Galveston assistant professor Nikos Vasilakis, lead author of the paper. "In the last 10 years we've seen a number of outbreaks of disease with real public health impact caused by what we call zoonotic viruses, viruses that start out in wild animals but can also be transmitted to humans — look at SARS, Nipah and Hendra, for example. Sylvatic dengue could be capable of a similar emergence — or rather, re-emergence, since we know previous dengue spillovers into urban and near-urban settings have occurred."

Dengue virus may also be capable of movement from the widespread urban cycles into primates and forest mosquitoes of Latin America, which would establish a new reservoir for human infections in the New World.

In the paper, Vasilakis and his collaborators identify two factors that make a dengue re-emergence a "clear and present danger": rapid human population growth near and in tropical forests, and the fact that little or no genetic change would be needed for sylvatic dengue to adapt to human hosts and urban mosquitoes.

"Experiments show that there is little or no adaptive barrier to the emergence of sylvatic dengue into human populations," Vasilakis said. "In other words, the virus can emerge from its current environment at any time, without further adaptation."

The article also presents additional reasons for boosting research into sylvatic dengue, among them the possibility that its behavior in nonhuman primate animal models might offer critical new perspectives on the pathology of human dengue. (Most monkeys tested so far show no clinical signs of the disease, limiting their usefulness as experimental models.) Another significant issue is the possibility that vaccines against human dengue, which could be licensed in as little as five years, might

push the virus to the brink of eradication in the urban, human transmission cycle, leaving an ecological opening that could be filled by sylvatic dengue.

"We see a precedent for this with yellow fever, where we have a very good vaccine — urban yellow fever has been nearly eliminated in some regions — but we don't have good vector control programs, and especially in South America we now have outbreaks fueled by sylvatic yellow fever," Vasilakis said. "If we eradicate human dengue and then stop vaccinating, as we often do after the disease disappears, we could see a re-emergence of dengue from a sylvatic source."

With the exception of a research program in Malaysia that ended in 1975, fieldwork on sylvatic dengue has been minimal, according to Vasilakis. In the article, he and his fellow authors call for new surveillance programs to monitor mosquitoes, non-human primates and humans in areas where sylvatic dengue is endemic, as well as the development of new diagnostic tools that will enable researchers to more easily accomplish those studies. (One such surveillance effort is now underway in Senegal, funded by the National Institutes of Health and led by UTMB professor Scott Weaver, the paper's senior author.)

"Of all the viruses with the potential to shift from animals into humans, the most likely to do so are those that, like sylvatic dengue, are carried by the non-human primates and/or bats," Vasilakis said. "For our own good, we need to know as much as we can about this virus."

Provided by University of Texas Medical Branch at Galveston