Q&A: Virologist discusses deadly eastern equine encephalitis virus, a familiar but formidable foe

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Anopheles gambiae mosquito, feeding on blood. Credit: James Gathany, Centers for Disease Control and Prevention

A New Hampshire resident recently died from eastern equine

encephalitis virus (EEE virus), and the virus is spreading across five New England states.

Neither the virus nor the disease, which remains rare, are new. Yet, the pathogen's ability to cause devastating infections in some people and barely any symptoms in others continues to befuddle scientists.

Virologist Jonathan Abraham, associate professor of microbiology in the Blavatnik Institute at Harvard Medical School and an infectious disease specialist at Brigham and Women's Hospital, has studied the virus in detail. In studies published in *Nature* in 2021 and 2024, Abraham and team mapped the structure and behavior of the cell receptors—the entryways on the surfaces of cells—that allow EEE virus and similar viruses to infect their hosts and cause mischief.

Abraham spoke with Harvard Medicine News about the knowns and unknowns of EEE virus and the trajectory of the latest outbreak.

Do we have any sense about what proportion of the people who get bitten by an infected mosquito go on to develop symptoms of the disease?

Not really, because we currently do not screen for exposure to infection. Many people who are infected develop mild symptoms, such as headache, fever, and general malaise, but they are typically not diagnosed because they never seek care.

About two percent of people go on to develop encephalitis, a form of brain infection, which is the most dangerous complication of the disease. Up to one-third of those with encephalitis die from it. And many survivors develop lasting symptoms, including seizures and paralysis, and may require long-term institutional care. So, although it is a relatively

rare complication, the consequences can be devastating.

Are there certain people at higher risk for symptomatic infection and brain inflammation by virtue of age or underlying health conditions?

Yes. Those younger than 15 and those over 50 tend to develop more severe infections. There is no good data on the effect of immune status on the risk for severe illness, but there is some evidence that people with lowered immunity, such as transplant recipients, can have very severe infection.

I should also note that a lot of brain damage we see in this disease is not only caused directly by the virus, but also develops as a side effect of the disseminated inflammation of the brain as it tries to contain the infection.

What is the current treatment for those who do present with symptoms and test positive for the virus?

There is really no specific treatment other than general supportive care. There has been some use of intravenous immunoglobulins, but there's no compelling evidence that they make a meaningful difference in terms of preventing death.

Are there any treatments on the horizon, such as antiviral medicines that can block entry into host cells or halt viral replication?

One of the primary ways the EEE virus causes damage is through two cell receptors, called very low-density lipoprotein receptor, or VLDLR,

and apolipoprotein E receptor 2, or ApoER2. Several labs, including ours, are exploring the use of a decoy molecule that mimics the receptor as a way to lure away the virus, bind to it, and thus prevent it from entering human neurons.

But there is an equally serious challenge that goes along with developing treatments. It is the ability to rapidly identify infected people so they can get the treatment as soon as possible. This is because some people present with fever and quickly progress to coma, but by the time we test, the virus is generally gone from the body. We need rapid diagnostic tests to identify the active viral infection early and treat.

In terms of a vaccine, efforts to develop one have been hampered by the fact that EEE outbreaks are quite sporadic. It's also difficult to predict who would most benefit from vaccination and when. There are, however, some exciting advances in vaccine development for the EEE virus.

The last lethal eastern equine encephalitis outbreak in humans was in 2019. Do we know what drives these ebbs and flows?

We do not. It's most likely related to ecological factors. For example, if we have more rainfall, there are more mosquitoes and therefore more opportunities for transmission. But we are surely missing pieces of the puzzle. One of these pieces is immunity. It likely goes up and down. It could be that in the five years since 2019, human immunity slowly receded, and now we are experiencing the consequences.

The life cycle of the virus is from birds to mosquitoes and back to birds. Humans and horses are dead-end hosts because the virus does not replicate at high enough levels in the blood to provide a good route for

transmission to feeding mosquitos. But the virus can kill these dead-end hosts.

An important question is also what happens with immunity and infection rates in birds over time.

What do you think will be the trajectory of the current outbreak?

The 2019 outbreak occurred in multiple states and involved 38 cases, making it the biggest outbreak in 50 years. Then the weather got cold, it blew away, and then came COVID.

This latest outbreak should be a reminder that this is not our first bout with EEE virus and it won't be our last. It's a reminder that we should have humility and respect for these viruses. As we learned from COVID, viruses are unpredictable.

What comes next is unknowable, but we have to remain vigilant about the possibility that this virus changes. We have to think about what happens if it figures out how to infect people in a way that it can be transmitted from person to person. Obviously, that would be a serious problem even if the virus lost some of its ability to cause severe illness, as many viruses tend to do when they evolve toward better transmissibility.

As an infectious disease clinician and a researcher who studies EEE virus, what precautions do you take?

I try to do anything that decreases the chance of exposure to mosquitoes, such as wearing protective clothing and following recommendations by

local health officials, including curfews. This is because while a severe infection is a low probability on an individual basis, it can have really devastating consequences.

Provided by Harvard Medical School

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