Late this August, researchers from the US Centers for Disease Control and Prevention (CDC) reported that almost every US state experienced cases of West Nile virus disease in 2021. Of the nearly 3000 cases logged that year, 69% were neuroinvasive. More than 2000 people were hospitalized and more than 200 died.

None of this alone was unprecedented. More than 3 times as many cases had been reported in 2003. And the virus was already the most common cause of mosquito-borne disease in the continental US by 2021. What was unusual about that year was that more than half of the cases came from just 3 counties in Arizona. With nearly 1500 known infections, more than 1000 hospitalizations, and 101 deaths, the state’s Maricopa County had the largest-ever single outbreak of West Nile virus in a US county.

Nationwide, fewer than 1000 infections that were not neuroinvasive were reported to the CDC in 2021, the most recent year for which final data are available. But CDC researchers estimate that roughly 60,000 to 140,000 of these less severe cases flew under the radar.

West Nile virus is mainly transmitted to humans by *Culex* species mosquitoes. In Maricopa County, greater than normal rainfall, among other factors, likely contributed to the large number of cases.

“Over time, we can expect to see these dramatic surges in cases of West Nile virus,” Kristy Murray, DVM, PhD, assistant dean and co-founder of the National School of Tropical Medicine at Baylor College of Medicine and Texas Children’s Hospital in Houston, said in an interview with *JAMA*. “As temperatures in the US warm, the environment is more conducive to mosquito breeding, propagation, and an expansion of their range.” Shorter winters and longer summers also give mosquitoes more time to be active and transmit disease.

But the number of West Nile virus cases will vary greatly from year to year. “The effect of climate on vector-borne diseases is very complicated,” said Scott Weaver, PhD, director of the Institute for Human Infections and Immunity at the University of Texas Medical Branch. Warmer temperatures are extending the geographic distribution of mosquitoes and ticks in the US. But rates of human disease also depend on the habitats and migratory patterns of animal hosts that harbor the pathogens that infect mosquitoes and ticks. “These are all being affected by climate change,” Weaver said.

The level of exposure people have to West Nile virus depends on the amount of transmission occurring between birds—the pathogen’s animal hosts—and mosquitoes. But mosquito populations are not well predicted by weather patterns or climate. That means “[t]here really is no good way to predict where we will see the most cases of West Nile virus year to year,” Weaver noted.

West Nile virus outbreaks will likely occur in areas of the US where the disease has been relatively uncommon, and not only because of the insects’ expanding range. “These viruses replicate faster and spread more quickly to the mosquito salivary glands in warmer temperatures,” Weaver said, resulting in higher rates of transmission to humans. However, he noted, very high temperatures can reduce mosquito survival. And whereas large amounts of rainfall in the western US tends to create more mosquito habitats, too much rain washes those habitats out in the East.

**Not on the Radar**

From 1999, when the first US cases of West Nile virus were identified in New York, to 2022, nearly 57,000 cases—about half of them neuroinvasive—and almost 2800 deaths have been reported to the CDC. Millions more cases, most of them mild or asymptomatic, have likely gone unreported. Murray and colleagues have estimated that nearly 7 million cases occurred in the US between 1999 and 2016. Even that number is likely an underestimate, she says.

According to the CDC, about 20% of people who are infected with West Nile virus develop a fever and flu-like symptoms, with fatigue and weakness sometimes persisting for weeks or months. Less than 1% of people with West Nile infections develop neuroinvasive disease, usually meningitis, encephalitis, or acute flaccid paralysis. Older adults and people who have certain comorbidities or are immunocompromised are most at risk for severe disease.

Children can also become seriously ill. But clinicians haven’t necessarily looked for...
West Nile virus in children, even in those hospitalized with encephalitis and meningitis. A few years ago, Murray found that West Nile virus was the most common infectious cause of pediatric encephalitis at Texas Children's Hospital between 2010 and 2017, but that clinicians were more likely to test for herpes simplex virus or enterovirus.

Adults haven’t been tested enough for West Nile virus either. In an earlier study from Murray’s team, clinicians at 9 Houston, Texas, hospitals ordered tests for only 37% of adults and children admitted with encephalitis or meningitis during the West Nile virus seasons of 2005 to 2010. “We were really amazed at how few tests were ordered for West Nile virus for these patients during the times that we would expect transmission,” Murray said.

There’s no specific therapy for West Nile virus disease beyond supportive care. Some clinicians may wonder why they should order a test for a disease that has no treatment. Murray’s response: “It is really important for us to be able to identify and accurately report these cases to understand the disease burden in the population.” If the amount of disease is consistently underestimated, there is little incentive to develop a vaccine or treatment options, she said.

The current attention on post–COVID-19 condition, or long COVID, may help to bring awareness about how serious West Nile virus infection can be. “We’re learning more about these neuroinvasive viruses and how, even when the virus clears, the inflammatory response wreaks havoc in the brain, causing these longer-term issues,” Murray said.

Need for a Vaccine

There’s also a growing worry that mosquitoes are becoming resistant to commonly used insecticides. Currently, there aren’t any good strategies for combatting mosquito insecticide resistance, according to Weaver. “Rotating insecticides to slow the development of resistance and using higher doses of insecticides are not good solutions because that will kill other insects and arthropods that are beneficial,” he said. “The ability to control mosquitoes through traditional insecticide methods is certainly going away pretty quickly, which eliminates a big tool to prevent human disease.”

In an email, Roxanne Connelly, PhD, a medical entomologist at the CDC, said that although insecticide resistance is a concern for the agency, it’s “not so widespread that we are seeing increased mosquito populations around the country.” Mosquitoes may thrive in pockets of the country where insecticide resistance is a problem. But because several factors, such as local weather patterns and ecology, contribute to the number of mosquitoes in an area, Connelly said it’s difficult to say that insecticide resistance is the sole culprit.

The consistently high numbers of disease and death each year from West Nile virus has led researchers to call for an all-out push to develop a vaccine. “We’re not making headway with other prevention strategies in reducing the burden of disease and the number of deaths,” said Carolyn V. Gould, MD, a medical epidemiologist at the CDC’s Arboviral Diseases Branch, adding that vector control strategies and personal protective measures are challenging to implement. In addition, patients receiving the monoclonal antibody rituximab can develop severe neuroinvasive complications from West Nile virus infection, tick-borne encephalitis, and other arboviral diseases.

Several human vaccines against the virus have been tested, but none have advanced past phase 2 clinical trials. Gould and other researchers from the CDC’s Division of Vector-Borne Diseases recently proposed several approaches to overcome the hurdles. One major reason for the stalled trials is that West Nile virus outbreaks are unpredictable and sporadic, making it difficult to enroll enough participants susceptible to severe disease into a phase 3 trial. And it would be hard to assess whether a vaccine candidate prevents infection because the presence of viruses in the blood is short-lived. A strategy then may be to use immune protection in animal models of disease as a surrogate end point. This approach is already being used to test chikungunya virus vaccines.

“There are good models of West Nile disease in mice,” Gould said. “One alternative pathway to vaccine licensure would be to use the animal models to determine whether the human immune response to West Nile virus would protect the animals from disease.” Postmarketing studies would be required to verify the clinical benefit and safety in people.

In the meantime, the CDC recommends several ways that people can avoid mosquito bites, such as using insect repellent, wearing clothing that covers the arms and legs, treating clothing and gear with 0.5% permethrin, using screens on windows and doors, and emptying standing water in yards.

As for treatments, the CDC maintains an up-to-date literature review of possible therapeutic agents for West Nile virus disease, including intravenous immunoglobulin, monoclonal antibodies, and corticosteroids.

“The upshot is that the data are inconclusive about the efficacy of any of these agents;” Gould said. The literature mostly consists of case series and case reports, while the few randomized clinical trials have been small and with considerable variability in dosing and timing of drug administration. Currently some clinicians use intravenous immunoglobulin to treat patients who have very severe disease or are immunocompromised. “There are no safety concerns with doing that,” Gould explained, “but there’s also no clear benefit at this point.”

She advises physicians to have a high clinical suspicion of West Nile virus if a patient has a fever and neurological symptoms during the peak arboviral season, which runs from July through September but could be prolonged in the future. For most people, the diagnosis will be based on antibody testing. But in patients who are immunocompromised, particularly patients receiving rituximab, a molecular test is required that is unlikely to be available through commercial laboratories. Clinicians should contact their state or local health department to find out where to send the sample for molecular testing. Cases should be managed with supportive care and reported to public health authorities.

“I worry about cases of West Nile virus increasing over time without having anything to combat them,” Murray said. “We are spending an incredible amount to control mosquitoes, for the constant surveillance of infected mosquitoes, and the clinical costs associated with West Nile virus cases. This virus isn’t going to go away.”

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Conflict of Interest Disclosures: Dr Murray reported being on the scientific advisory board for Valneva, which is developing a chikungunya virus vaccine candidate. Dr Weaver reported having intellectual property on vaccine development for chikungunya virus vaccine (no active commercialization). No other disclosures were reported.

Note: Source references are available through embedded hyperlinks in the article text online.