Why are there no human West Nile virus outbreaks in South America?

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More than two decades have passed since the West Nile virus (WNV) arrived in the Americas. After its first detection in New York City in 1999, it spread rapidly across North America, causing multiple outbreaks in human and bird populations in the US.[1] WNV is one of the most important zoonotic viruses, accounting for approximately seven million human infections in the US between 1999 and 2016.[1] In 2019, a major WNV epidemic occurred in Arizona, the largest reported in North America to date.[2] WNV spread to Central America and the Caribbean between 2001 and 2004.[1] In South America, WNV was reported in horses in Argentina in 2006,[3] and flamingos in Colombia in 2012.[4] There is subsequent evidence of ongoing WNV transmission throughout South America, including in Brazil and Venezuela.[1,5]

An intriguing question is why large human WNV outbreaks have not yet been reported in South American countries. In tropical and subtropical areas, warm temperatures, a high avian species diversity, and the presence of *Culex* mosquitoes provide suitable conditions for the development and maintenance of WNV transmission,[5] and some studies have already demonstrated the competence of South American *Culex quinquefasciatus* to transmit WNV efficiently.[6] Moreover, Saint Louis encephalitis virus (SLEV), a related flavivirus transmitted by *Culex* vectors and bird hosts, is endemic throughout the Americas.[1] Since the ancient WNV genotype has been detected in Brazil[7] and the presence of WNV in resident South American birds has been confirmed,[8] WNV appears to be endemic in the South American region.

Given this assumed endemic circulation of WNV within the mosquito–bird cycle, four main hypotheses have been proposed to explain the lack of reported human WNV outbreaks in South America. First, and most obviously, there is under-reporting. Most WNV infections in humans are asymptomatic, and symptomatic cases of human WNV infection may be masked by other mosquito-borne arboviruses that cause similar clinical symptoms. Infection may be misdiagnosed as chikungunya, Zika, Mayaro, dengue, or malaria. Other factors that may contribute to the apparently silent circulation of WNV in South America are the lack of outbreak investigations, and delays in diagnostic screening of animals and humans during the infectious phase, undermining virus detection and confirmation of infection.[9] It is also worth mentioning that some outbreaks of WNV in human populations in remote regions, such as Amazonian tribes and forest-dwelling communities, may not be reported to the public health system.

Second, the co-circulation of other species of flaviviruses may provide cross-protection. For example, other phylogenetically similar flaviviruses, such as Rocio virus and SLEV, are endemic in Brazil. These other flaviviruses also infect birds and are maintained by culicid mosquitoes. In South American countries, imported arboviruses such as dengue, Zika, and chikungunya viruses, which are all disseminated by *Aedes aegypti* mosquitoes, have caused large epidemics in the past decade.[10] Consequently, infections by other flaviviruses may provide cross-protection against infection or symptomatic disease caused by the WNV, and may limit the number of deaths and outbreaks due to WNV.[10] Additionally, the absence of severe cases suggests that antibody-dependent enhancement (ADE), which occurs when cross-reactive antibodies from a previous flaviviral infection increase the pathogenicity of a related virus, is absent in South America.

Third, genomic mutations may decrease the level of virulence of WNV. Distinct genetic variants of WNV show different levels of pathogenicity among bird and mammal species. Beasley[11] isolated an attenuated WNV strain from a bird in Mexico in 2003, and López et al.,[12] identified a new strain in Colombia that was closely related to attenuated strains detected in Texas in 2002. Genomic mutation of WNV may explain the lack of human cases of WNV encephalitis or severe disease in Colombia and other South American countries. Fourth, competition between SLEV and WNV may have limited the spread of WNV in South American countries,[1] as has been reported in the US.[13]

Given these uncertainties, WNV epidemiology in South America remains a puzzle. There is an urgent need to obtain a better understanding of its clinical characteristics and distribution to prevent it from becoming

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a major public health problem. The emergence of WNV in the Americas has modified ecosystems in the region, influencing human, veterinary, and wildlife health, and affecting the spread of other viruses. Notably, there are no human vaccines or antiviral drugs for the treatment of WNV infection. In addition, viral mutation or the establishment of a more virulent strain in the South American region could lead to future epidemics of WNV.[10] Each country should maintain surveillance of neuroinvasive arboviral disease, implement notification of human and animal cases, develop clinical management guidelines, and conduct sentinel surveillance of WNV infection in established sentinel hospitals.

Contributors

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Declaration of interests

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