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Research paves the way for the development of vaccines for emerging viruses

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The search for vaccines, treatments and preventive methods against infection by emerging viruses is one of the major challenges of global epidemiology. New pathological agents continue to emerge, such as the arbovirus transmitted by insects (in this case, mosquitoes) that causes West Nile fever, named after its identification in Egypt in the 1950s.

The disease affects thousands of people each year and is asymptomatic in 80 percent of cases. Roughly one in five infected people develops fever and other symptoms. In fewer than 1 percent of cases, especially among older people and children, the disease has significant neurological consequences, affecting the central nervous system, causing meningitis, encephalitis, and in extreme cases, an acute paralysis that leads to death. As yet, there are no vaccines against the virus.

First isolated in the West Nile District of Uganda in 1937, the disease did not have much epidemiological relevance until the 1990s. Carried by mosquito-infected migratory birds from Africa, the virus was spread through Europe from France to Russia. It reached North America in 1999 and has caused outbreaks in Canada (1999-2007), the United States (1999-2012) and Mexico (2003). Since then, more than 20,000 cases have been reported in North America, with almost 1,800 deaths.

"West Nile virus hasn't reached Brazil, but it's only a matter of time before it does," said virologist Paolo Zanotto of the University of São Paulo's Biomedical Science Institute (ICB-USP) in Brazil. "How long will it take for migratory birds that spend the summer in North America

to bring the virus to their winter refuges in Central America? West Nile virus is coming."

Hence the importance of a new study Zanotto co-authored. By confirming that one of the acknowledged lineages of the virus—lineage eight—is not very virulent, the work points to the development of a vaccine within a few years. The relatively mild lineage 8 strains could theoretically "teach" the immune system to defend the organism against all lineages, especially the more widespread lineages 1 and 2, as well as 7, the most virulent. This immune defense strategy is similar to that used by flu vaccines, which combine the most recent strains of the influenza virus to combat the emerging strain to which humans have not developed immunity.

The article is published in *PLoS Neglected Tropical Diseases*. It describes the study of the biological and phylogenetic characteristics of West African lineages of West Nile virus.

In this study, three novel genes isolated from samples of the virus collected in West Africa by Di Paola and Fall were sequenced. The genes in question were representative of the most globally widespread lineage (1), the most virulent (7), and the least virulent (8). Once sequenced, the genes were compared with the 862 West Nile virus gene sequences available from GenBank. Of these, 770 were lineage 1a from the Americas.

To reduce computer processing requirements, all lineage 1a sequences were removed, except for a single representative sequence. The researchers ended up with 95 sequences for phylogenetic analysis. The results included the discovery of two important traits of lineages 7 and 8. In the case of lineage 8 (the least virulent), they detected substitution of the gene P122S, which induces mutations that may be linked to the lineage's low replication rate, and could, therefore, explain its low

virulence.

"This is why lineage 8 would be ideal for a vaccine," Zanotto said, adding that the development of a vaccine based on a virus with very low virulence would be capable of conferring immunity against the more dangerous lineages 1, 2 and 7 without the risk of producing symptoms of the disease.

In the case of lineage 7, the Brazilian and Senegalese virologists were able to identify a mutation in gene S653F NS5 that is associated with an increased resistance to interferons, proteins made and released by the immune system's white blood cells in response to the presence of viruses and other pathogens to interfere with their replication. This mutation could help explain the high virulence of lineage 7.

"With the exception of a single possible accidental infestation, which occurred in vitro in Africa, lineage 7 has never been isolated in humans," Zanotto said. "But it was devastatingly lethal to mice in laboratory tests."

The low virulence of lineage 8 and high virulence of lineage 7 were tested, confirmed and measured both in vitro using infected cells, and in vivo, by inoculating mice in the Dakar laboratory. In the case of lineage 8, the virus displayed low capacity to replicate in vitro and almost no virulence in mice.

More information: Gamou Fall et al, Biological and phylogenetic characteristics of West African lineages of West Nile virus, *PLOS Neglected Tropical Diseases* (2017). DOI: 10.1371/journal.pntd.0006078

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