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Anticipating Emerging Mosquito-borne Flaviviruses in the USA: What Comes after Zika?

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New mosquito-borne diseases have emerged on multiple occasions over the last several decades, raising fears that there are yet more poorly understood viruses that may emerge in the USA. Here, we provide a data-driven ‘watch list’ of viruses in the Flaviviridae family with high potential to emerge in the USA, identified using statistical techniques, to enable the public health community to better target surveillance. We suggest that public health authorities further incorporate predictive modeling techniques into disease-prevention strategies.

The start of the 21st century was marked by multiple emerging mosquito-borne diseases. West Nile virus was introduced to the eastern USA in 1999 and has since spread across the continental USA, infecting tens of thousands of people and causing widespread mortality in bird populations [1]. A mutation in a strain of chikungunya virus increased overall infectiousness in the invasive mosquito vector, *Aedes albopictus* (Asian tiger mosquito), increasing the risk of autochthonous disease transmission in temperate zones, with outbreaks occurring in Italy and France [2]. More recently, Zika virus spread from Oceania to South America, and has continued north at a rate exceeding 15 000 km/year [3], causing severe neurological diseases, including Zika

congenital and Guillain-Barré syndromes. In each case, the science and public health communities lacked basic knowledge about these previously geographically limited viruses, and interventions were put in place only after the pathogen had become established. Our question is not *if* another mosquito-borne pathogen will emerge in the USA, but *which* will be next?

The sheer number of potential emerging pathogens underscores the infeasibility of comprehensive surveillance. Of over 530 known arboviruses, viruses transmitted by arthropod vectors such as ticks or mosquitoes (as listed in the International Catalogue of Arboviruses [<https://www.cdc.gov/arbocat/>]) that infect humans or domestic animals, most are poorly studied and knowledge gaps include information as basic as which species of mosquito transmit which pathogens. Without a complete list of possible vectors, health agencies are unable to adequately plan for outbreaks or target virus surveillance. It is also difficult to predict whether an imported case of disease will initiate local transmission without knowing the efficiency at which mosquito species in the area can transmit the virus.

Unfortunately, development of diagnostic tools, and studies to assess vector competence and vectorial capacity (which are very labor intensive) are often undertaken only after disease has become endemic. But, without this information, health agencies are ill-equipped to prevent outbreaks, and are limited to economically costly, reactive strategies to disease emergence.

To narrow the list of potential emerging diseases, we have created a ‘watch list’ of flaviviruses (the family that includes many well-known arboviruses including West Nile, dengue, yellow fever, and Zika viruses) that might emerge in the USA, based on known associations of flaviviruses with mosquito species currently found in the USA (Box 1). We ordered this watch list by the number of predicted vectors of each virus. Transmission dynamics of mosquito-borne diseases are determined by many additional factors (e.g., mosquito abundance, human exposure, biting preference, genetic lineage), and our ranking should therefore not be interpreted as a measure of risk of emergence. Rather, this watch list provides a starting point to guide future empirical and

Box 1. Detailed Methods of the Predictive Model

Drawing on traits of known vector-virus pairs, in recent work, we developed a statistical model of trait combinations associated with the propensity of a virus to be vectored by a mosquito species, referred to as a link [15]. Known links were compiled from the literature on experiments showing which mosquito species can transmit the virus from an infected to a susceptible host. Fifteen traits of mosquitoes and 12 traits of viruses were used to construct a predictive model (Table I). We then applied the resulting model to data on all flaviviruses known to infect humans and the mosquito species found in the USA. Our resulting list prioritizes viruses based on the number of predicted mosquito vectors found in the USA and do not include other factors known to be important to transmission dynamics (e.g., population density, host preference, larval habitat type). We provide an exhaustive list of viruses from which public health professionals can further prioritize candidate viruses based on entomological and epidemiological factors that influence transmission dynamics. For example, Rocio virus, which circulates in wild bird populations in Brazil and caused a human epidemic in Sao Paulo in 1975 [16], may be more highly prioritized due to the mobility of the zoonotic reservoir population and history of epidemic risk.

Table I. Traits Used in the Predictive Model, Listed in Order of Importance

Vector traits:	Subgenus, continental range, number of viruses vectored, geographic area, larval habitat, habitat discrimination, biting time, host breadth, urban preference, anthropophily, endophily, artificial container breeder, permanent habitat, salinity tolerance
Virus traits:	Year isolated, vector breadth, disease severity, host range, genome length, viral group, viral clade, host breadth, symptoms, vectored by other arthropods, mutated envelope

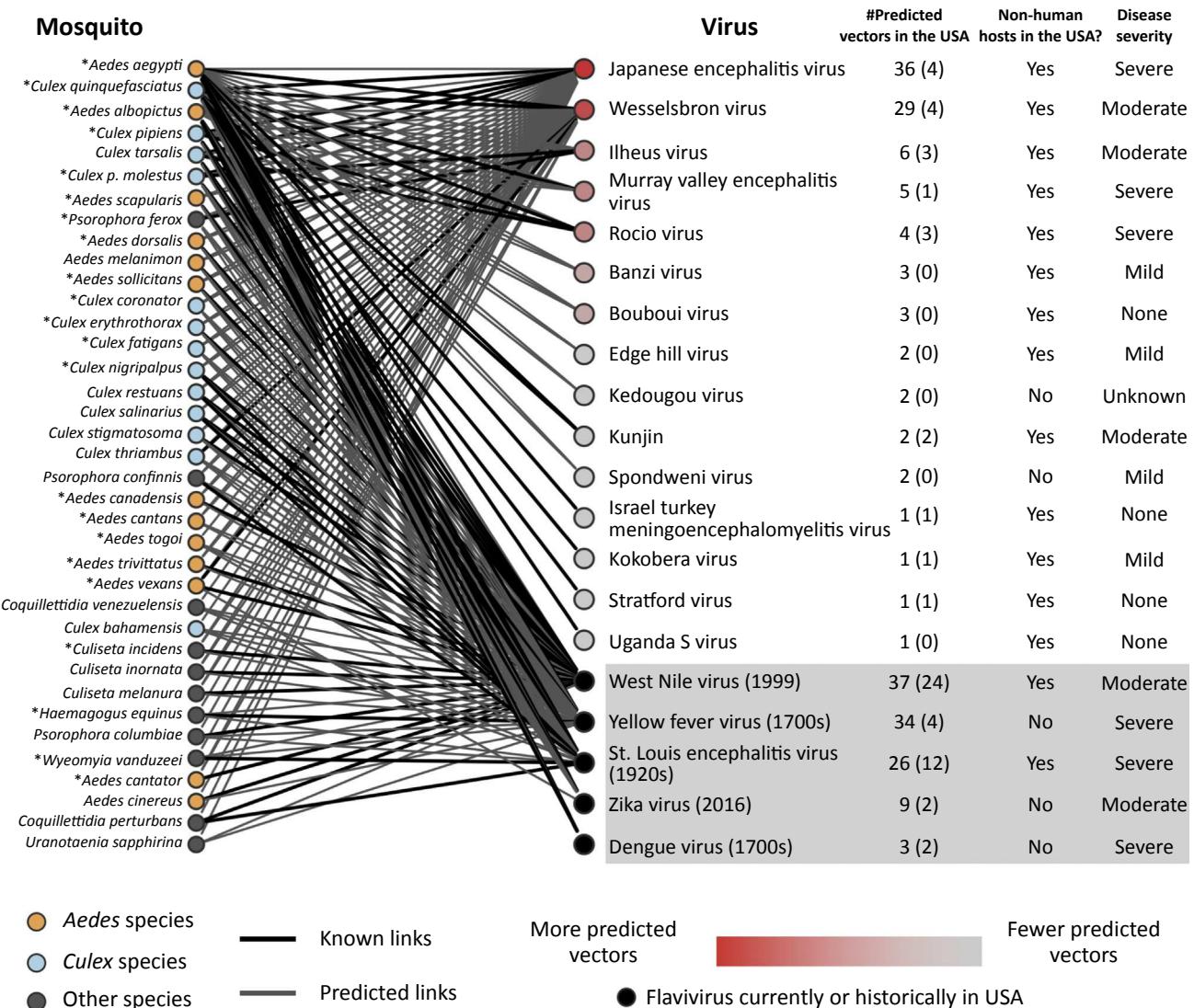


Figure 1. Network of flaviviruses Known (Black) or Predicted (Gray) to be Transmitted by mosquito species Found in the USA. Starred mosquitoes readily bite humans. Mosquitoes and viruses are rank-ordered, from top to bottom, by the predicted associations of flaviviruses with mosquito species (not taking into account other relevant epidemiological characteristics), with the number of known vectors in the USA in parentheses. The presence of a non-human host in the USA, which could potentially serve as a zoonotic reservoir, is noted, as well as disease severity as defined by Mackenzie *et al.* [14]. Viruses that are currently or have been historically found in the USA are shown in the gray box at the bottom of the list, with their approximate year of introduction, or first known case, in parentheses, and are not included in the original ranking.

modeling efforts in the emergence of mosquito-borne pathogens.

The resulting network of potential virus-vector pairs, or predicted links, in the USA (Figure 1) contains 37 mosquito species and 20 viruses, only five of which are

currently or have historically been found in the USA. Two viruses, Japanese encephalitis virus and Wesselsbron virus, have many more predicted vectors than the other viruses (36 and 29, respectively). Closely related to West Nile virus, Japanese encephalitis virus causes over

67 000 reported cases annually, with the majority in Asia [4]. While only 1% of infected people develop Japanese encephalitis, there is a 20–30% mortality rate among cases that progress to that stage [5]. In its native Asian range, Japanese encephalitis virus requires a

non-human host, the domestic pig, to amplify the virus. In North America, there are several bird species that are competent reservoirs for the virus [6]. Much less is known about Wesselsbron virus, which has been historically restricted to the geographic region of sub-Saharan Africa, where it most commonly infects sheep and other livestock [7]. While symptoms of Wesselsbron virus in humans are relatively mild, it causes abortion in goats and cerebellar hypoplasia (a form of microcephaly) in calves [8,9], which is a significant concern for the livestock industry.

The virus with the most predicted links is West Nile virus (37 links). Other USA-endemic viruses have 3–34 predicted mosquito vectors. Yellow fever virus, which caused an outbreak in New Orleans as recently as 1905, is predicted to have 34 mosquito vectors. Since the introduction of the yellow fever vaccine in the mid-20th century, transmission has been mostly restricted to Africa and South America [10]; however, the 2016 epidemic in Angola demonstrates the inadequacy of current immunization regulations in some areas. By contrast, dengue virus, which is locally transmitted in Puerto Rico (and, on rare occasions, states along the Gulf Coast) is only predicted to be vectored by three mosquito species endemic to the USA. Despite the small number of competent vector species, serological surveys along the Texas–Mexico border found evidence of recent infection in 2% of the population, translating to an estimated 100 000 dengue cases in the continental USA annually [11]. The high number of cases highlights the importance of not just the number of predicted vectors, but their identity, in disease transmission, in this case, *Aedes aegypti*, a mosquito species that is well adapted to live with humans and is a highly efficient vector of many human pathogens. Notably, the top-ranked viruses in our watch list are predicted to be vectored by mosquitoes that prefer to feed on humans (e.

g., *Ae. aegypti*, *Ae. albopictus*, *Culex quinquefasciatus*) and are therefore likely to transmit pathogens between humans.

These viruses illustrate, but do not exhaust, the future risk of emergence of viruses circulating elsewhere in the world. With the rise in globalization and availability of air transportation, a mosquito-borne pathogen can travel across the world in less than 24 h, connecting countries with active transmission to countries without disease (e.g., Zika and chikungunya). While several states in the USA, notably Florida, have large mosquito-surveillance programs, most do not [12], and the accompanying virus-surveillance programs screen for a limited number of pathogens. The difficulty in preventing outbreaks of Zika in the USA highlights the need to shift from reactive to proactive surveillance and control strategies for mosquito-borne diseases. Focusing on those viruses with a high potential to emerge could improve the efficiency and reliability of surveillance without overly burdening public health institutions and help to guide future vaccine development, such as the Coalition for Epidemic Preparedness Innovations [13]. Predictive modeling, such as the method highlighted here, is not a single solution, but does provide novel information that, in combination with conventional methods, can improve the preparedness of our public health systems. Finally, the approach we present here can be applied to other disease systems to identify groups of viruses and bacterial pathogens most likely to emerge in the USA or any other country.

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