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Editorial

Prioritizing the 'Dormant' Flaviviruses

Probably the most disturbing fact of the ongoing Zika epidemic is that this virus is not new. Zika is not new to science, as SARS coronavirus was when it first emerged in 2003, nor did it experience dramatic evolutionary change like influenza does through reassortment. Instead, Zika has been lurking in the shadows for almost 70 years. It was hidden in developing countries with poor disease surveillance, isolated island populations in the Pacific, and poorly studied animal hosts. We knew about Zika in 1947 when it was discovered in a jungle in Uganda. We knew the epidemic potential when Zika barraged through Micronesia in 2007. In retrospect, we should have also been aware of its link to microcephaly in the Pacific island outbreaks. We knew the possibility of sexual transmission when an American mysteriously infected his wife after returning from a field trip in Senegal in 2008. Yet, we were still unprepared.

In the past two years, the scientific community has rallied to combat the Zika outbreak and fill the long-standing deficit of Zika knowledge. More than 30 candidate vaccines are in development, and scientific papers on the virus are more than ten times as abundant as Zika publications before 2014. Important aspects about the virus' biology and transmission, like its tissue tropism, interaction with Dengue, persistence in body fluids, and its structure have been elucidated. However, this wealth of knowledge only came after Zika was declared a public health emergency, opening up research dollars and scientific opportunity.

Zika virus is one of 53 viruses in the genus flavivirus currently recognized by the International Committee on Taxonomy of Viruses. Five of these are big hitters, causing epidemics and widespread morbidity and mortality: West Nile virus, Yellow Fever virus, Japanese Encephalitis virus, Dengue virus, and now Zika virus. Twenty-one other flaviviruses are known to cause infections in humans. Perhaps more than any other viral genus, it seems the flaviviruses are especially primed for human infection: RNA viruses with high mutation rates, vector-borne, and found in a wide range of vertebrate and invertebrate hosts. Unsurprisingly, the flaviviruses that only rarely infect humans, or have yet to do so, are vastly understudied with research output for most viruses in this group having plateaued in the years immediately following their discovery. With the exception of a big push by the Rockefeller Foundation and US Government to characterize arboviruses in the 1940s and 1950s that led to the discovery of many of these viruses, there has been a paucity of studies investigating these 'dormant flaviviruses' over the last 40 years.

Our global approach to emerging infectious disease research has been reactive for too long, with an increase in scientific investigations and funding (e.g., for surveillance, experimental studies, or countermeasures) only coming after international spread. González-Salazar et al.'s manuscript in this issue (2017) uses an ecological niche modeling approach to identify potential, currently unrecognized, vertebrate hosts for Zika virus in Mexico. This is an interesting approach to help target zoonotic disease surveillance in the animals that may serve as most likely natural reservoirs, and a good start. We need more analytical tools like this. We know virtually nothing about the sylvatic cycle, the vectors, the non-human reservoirs, or the general ecology of Zika. International efforts to map the potential distribution of Zika are focused on *Aedes aegypti* and *A. albopictus*, but we lack knowledge on the 17 other mosquito species that have been tested positive over the years, nor what other viruses these vectors may carry.

We need more predictive tools to forecast the risk that viruses pose before they become epidemics or pandemics. We need creative approaches, and multi-disciplinary col-

laborations to develop these sets of tools. Mathematical modelers need to work with field scientists, clinicians, bioinformaticians, virologists, and veterinarians, and we all need to collaborate more with laboratory scientists who can design experiments to validate our models. If phylogenetic and structural models predict an increase in host range for a virus, how can we design in vitro or in vivo experiments to test this? How can we make the most of the scattered information available on host range, vector range, and viral biology from the last 70+ years of disjunct studies to better prioritize the 53 known flaviviruses for future research? Yaounde virus, Kedougou virus, and Sepik virus are hardly household names, but they are the closest known relatives to viruses we know well—West Nile, Zika, Yellow Fever. How many more flaviviruses will we discover in ecosystems around the world if we make a concerted effort to find them? How can we then include these novel viruses into our prioritization schemes?

Just as weather forecasting seemed like an impossibility before the advent of satellites, computer algorithms, and telecommunication equipment, to some naysayers the era of pandemic forecasting may seem impossible, or a very a long way off. It is not. We are in this era now, but these are still early days. A growing and diverse community of scientists are working hard each day to build and experiment with tools to forecast and prevent emerging viruses. Many of these analytics can be applied directly, right now, to improve public health. For example, they can identify geographic regions, host species, host traits, vectors, and viral traits that rank their likelihood of disease emergence. This allows agencies to target how they prioritize field surveillance or prioritize which viruses we should research more *before* they infect humans on a wide scale. They can also start to estimate how many other unique flaviviruses are out there on the planet so that we can begin to catalog and characterize them all. These messages should not be lost in our rush to focus on the current public health emergency. Part of our public health response should be to set research priorities for those quiescent viruses we already know about before they become the next Zika.

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