## EMERGING DISEASE Instant Research from the PREDICT Modeling & Analytics team

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## Identifying the Next Zika: An Analysis of Understudied Flaviviruses

The ongoing Zika virus epidemic was declared a public health emergency of international concern by WHO in February 2016, due to its rapid spread and link to birth defects. Despite discovery in 1947, evidence of human infection, and close relation to high-impact human viruses like Dengue and Yellow Fever, the study of Zika remained limited until the Yap Island, Micronesia outbreak in 2007<sup>1</sup> (Figure 1). The pandemic spread of Zika emphasizes the need to better understand the distribution, host range, and epidemic potential of other understudied flaviviruses<sup>2</sup>.

The PREDICT-2 Modeling & Analytics team compiled a database of all known natural host and vector species for the 53 ICTV-recognized viruses<sup>3</sup> in the genus Flavivirus. In total, 1,768 flavivirus-host associations (including 317 unique mammal species and 743 bird species) and 309 flavivirus-vector associations (149 unique insect vector species) were identified. We then calculated the taxonomic breadth and geographic range of each flavivirus in order to inform both current and potential risks of flavivirus spillover and spread.



**Figure 1:** Publication effort 1900-2016 of each flavivirus (n = 53). Publication counts per virus retrieved from Web of Science on 10/27/16. Virus color based on human impact: nonhuman viruses = green, subclinical viruses (detected only via serology) = blue, rare viruses (<20 pathogenic cases) = purple, epidemic viruses (>20 pathogenic cases) = red. Zika is colored black to emphasize the sharp rise in publications after its human impact changed to epidemic in 2007.

In order to control for the effect of research effort and understand the relative importance of host and vector breadth in the zoonotic potential of Flaviviruses, we developed a generalized linear model of likelihood a virus is zoonotic. We simplify host and vector breadth to the lowest taxonomic group that encompasses all known natural host or vector species. Both non-human host breadth (p = 0.02) and vector breadth (p = 0.03) were significant in determining if a virus is classified as zoonotic, so these variables were used to prioritize viruses for more research (Table 1). Using the IUCN mammalian range and BirdLife spatial files, we created a unique vertebrate host distribution layer for each flavivirus, and combine these to produce a global map of known flavivirus diversity in wild mammals and birds (Figure 2).

Of the 53 flaviviruses, 37 (70%) have been detected in humans, and 25 of these human-



associated flaviviruses have yet to cause significant outbreaks. Using taxonomic breadth of host and vectors, we prioritize 10 of these 25 pre-epidemic flaviviruses for futher research using just two variables (host and vector breadth) that relate to zoonotic and epidemic potential (Table 1).



**Figure 2:** Geographic map of currently known flavivirus diversity in wild mammals and birds (n = 42 viruses). Virus distribution calculated as aggregate range of all mammal and bird hosts for each virus (1 to 294 host per virus, median = 3). Redder regions show higher concentration of unique flaviviruses based on vertebrate host range. Hotspots in the United States and Europe likely due to research bias.

**Table 1:** The top 10 pre-epidemic human flaviviruses prioritized for further research based on large host and vector breadth. Current human infection is classified as subclinical (only detected in humans via serology) or rare (<20 human cases).

Virus	Human Infection	Host Breadth	Vector Breadth	Host Orders	Pub Count
Wesselsbron	rare	Phylum	Phylum	4	113
Usutu	rare	Phylum	Family	11	234
Ilheus	rare	Phylum	Family	4	142
Louping Ill	rare	Phylum	Genus	8	413
Uganda S	subclinical	Phylum	Genus	2	26
Tembusu	subclinical	Class	Family	3	116
Aroa	rare	Class	Family	2	36
Bagaza	rare	Class	Family	2	36
Saboya	subclinical	Class	Species	5	21
Apoi	rare	Order	none	1	15

Zika virus has now been detected in South American mammals<sup>4</sup>, which shows that human transport of a virus can lead to establishment in new animal hosts. Viral adaptability to diverse host and vector species is likely critical for successful formation of new sylvatic cycles. Our analyses highlight the need for ongoing monitoring of host and vector breadth to identify pre-epidemic viruses, potential new viral reservoirs, and geographic areas prone to viral expansion. In particular, we found that Wesselsbron virus and Usutu virus are high priority neglected flaviviruses at risk of becoming epidemic.

## References

- 1. Kindhauser, M. K. *et al.* Zika: the origin and spread of a mosquito-borne virus. Bull World Health Organ 171082 (2016).
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- 4. Favoretto, S. *et al.* First detection of Zika virus in neotropical primates in Brazil: a possible new reservoir. bioRxiv, 049395 (2016).