

The Evolution and Challenge of the *Zika virus* and its Uncharted Territory in the Neurological Realm

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Commentary

The *Zika virus*, an *Aedes* mosquito-borne flavivirus, was first identified in 1947 in *Rhesus Monkeys* in a vegetative region of Africa known as Zika. It is closely related to other flaviviruses such as dengue, yellow fever, West Nile and *Japanese encephalitis viruses* and shares a similar symptomology, namely malaise, headache, flushing, nausea and vomiting. Zika's distinguishing feature is a macropapular rash covering the body with accompanying arthralgia. While relatives of Zika, namely Yellow Fever and Dengue, require infection of humans and monkeys to maintain themselves in mosquito populations, Zika relies solely on mosquitoes as its reservoir, with humans as occasional hosts. The true extent of its vectors and subsequent vector-host interactions still remains unknown. The known vector, the female *Aedes* mosquito, transmits infection by taking a blood meal from host, and is usually present below vegetation, below buildings, and in areas with standing water [1].

Initial studies on the virus showed that it was able to cross the blood brain barrier and had a greater affinity to the nervous system when studied in mice [2], a clear divergence from typical flavivirus behavior. Despite this, the virus receded from the curiosity of researchers and tabloids of the public due to its mild symptomology. It has resurfaced with a vengeance, however, having been proclaimed a public health emergency this past February, and a possible microcephaly epidemic [3].

While a mild febrile illness was the main sequelae thought to be caused by the virus, the recent outbreaks have shown a notable increase in neurological sequelae. The neurological commitment of the virus goes far beyond what was previously thought with its potential link to autoimmune central nervous system (CNS) diseases, neurodegenerative disorders, and microcephaly/subsequent development of mental retardation when infected in the fetus [4]. The two sequelae that are taking the limelight of the manifestations are Guillain-Barré syndrome (GBS), leading to life-threatening paralysis, and fetal birth defects/malformations, when infected during pregnancy [5,6].

This complex gamut of neuropathological responses has taken to the forefront of research studies on the virus, though the amount of evidence linking the virus and neurological disorders is largely anecdotal thus far. Only a handful of studies have been published till date, and of these the data is somewhat inconsistent due to weaker study designs based on observation and hypothesized associations instead of conclusive, testable cause and effect [7]. More scientific evidence is needed to confirm these associations, and the uncertainty

makes the virus all the more frightening. The case evidence is compelling, however, with numbers reaching the thousands in number of babies born with severe birth defects and people developing GBS symptoms, both groups showing serology of Zika on hematological analysis [3,5,6]. To establish a definitive causative link, research needs to take a comprehensive approach and shift back to basic science.

The initial neurotropism shown by the virus and pathogenesis of its associated microcephaly is still unknown. Emerging hypotheses speak to its possible infiltration of the neuronal cortical layers causing degeneration; others speak to it causing hypertrophy of astrocytes, leading to enlargement and extension of cellular processes as the virus proliferates [2,8]. Disruption of glial cells, such as astrocytes, alters CNS homeostasis and, in development, can lead to the sequelae of mental retardation, deafness, and vision loss in the fetus. Still other hypotheses point to the virus causing an aberrant immunological response in the body, leading to attack of normal tissues, giving rise to subsequent immune mediated and inflammatory neurologic diseases after infection with the virus [9].

The challenge of the virus and the quest for definitive, concrete answers are complicated by the paucity of literature on *Zika virus*, with a paltry 25 articles published between 1952 and 2009 [4]. 2016 has seen a surge of studies on the virus, resulting in over 200 publications in the past few months alone based on a recent Pubmed search. With the strides medicine has taken in the past 50-60 years in terms of the increasing precision of study design, the bigger than ever data sets on large populations, and the novel statistical methods that will allow for the discovery of relevant, reproducible patterns and relationships from these data sets, the investigations underway regarding *Zika virus* are far more sophisticated than before. And should yield characterizations and relationships that can decisively guide the evolution of public health interventions to protect spread and progression of complications of the virus at a quicker pace than in the past.

Even with more sophisticated research methodology, however, there are wide gaps that need to be addressed. While analysis of previous outbreaks has produced several data points, is the current *Zika virus* identical to that in the past or has it evolved perpetuating its challenge? After lying in relative obscurity for the past 60+ years, why has it suddenly resurfaced and with a completely different set of manifestations? With the environmental changes and vast globalization the world has undergone, the different interactions with medications, nutrients, and the microbiome target populations have evolved within—leading to a multitude of characteristics, from a molecular level to a genomic level—would it be accurate to extrapolate past data on

predicting current implications of the virus, especially with the recent development of the neurological dimension?

These research gaps and questions need to be addressed systematically. The rapid and sudden resurgence of the virus—across South America, the Southeastern parts of the US and different parts of Asia—and its possible severe implications neurologically, especially in the context of the development of the fetus and an immunological response leading to paralysis, demands conclusive and decisive action.

Observational and case study/cohort analyses can help develop a better comprehensive understanding of the clinical spectrum of the virus in terms of diagnostics and possible counter measures such as vector control and vaccines, but in the context of neurological sequelae, new studies should be approached with more rigor especially on a molecular, developmental and pathological scale. Anecdotal and epidemiological data can help in tracking the progress and spread of the virus, but shifting back to controlled animal studies and focusing on “why” is necessary to establish definitive causation and correlations: are the increases in neurological outcomes due to the increase in incidence of the virus or due to a change in the virulence of the virus itself?

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