The Rise of Zika in the 2010's

What is Known About this 'New' Flavivirus

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Abstract

Over the past decade, Zika has caused global unrest, affecting peoples mainly across the Pacific, and the Americas. In recent years, the main vector has been mosquitoes, allowing for the proliferation of this disease. Before 2007, this virus went broadly unstudied due to its asymptomatic nature. Once it caused outbreaks in Brazil, and French Cambodia, high rates of microcephaly have also been recorded. Symptoms in adults present mildly, while symptoms in neonatal development are more severe. There are no confirmed or commercial treatments for ZIKV, although this area is under heavy investigation.

Introduction

In 2015, the Zika virus (ZIKV) has been classified as a modern pandemic, and the World Health Organization declared a public health emergency following several outbreaks *(Plourde, 2016).* ZIKV is a member of the faviviridae family, causing exanthemata *(Paixao, 2016).* It is further classified as a positive sense RNA flavivirus, with its closest relative being the Spondweni virus which originates from Africa. ZIKV traces its lineage back to Asia, and originally Africa as well *(Plourde, 2016).*

History

The first isolated strand of ZIKV was found in a Rhesus monkey (with fever) in the Zika forest of Uganda, in 1947 *(Mlakar, 2016)*. The first human infected cases (3) were found in Nigeria, in 1954 *(Plourde, 2016)*. By the early 1970's, 38% of ZIKV patients expressed neutralizing antibodies in their blood serum. Due to its asymptomatic nature, it was considered a 'silent' disease until 2007 *(Paixao, 2016)*.

In 2007, ZIKV had its first major endemic on Yap Island, Micronesia. The main targets were women, averaging at about 36 years of age with an infection rate of over 73%. Only fifth of the total affected individuals expressed symptoms *(Paixao, 2016)*. ZIKV hadn't gained attention until this point due to a history of few sporadic cases. When ZIKV spiked, so did the incidence of Guillain-Barre Syndrome *(Zupanc, 2016)*.

From 2008 to 2013, ZIKV went silent again with less than a dozen reported cases. Of these cases, more modes of transmission were observed. In 2013-2014 there was a Pacific endemic amongst various countries, focused in French Cambodia with over 28,000 reported cases. Non-autochthonous cases were reported simultaneously in various countries across the globe. In 2014, Easter Island, Chile reported over 51 cases, also mostly women. *(Paixao, 2016)*

2015 saw ZIKV's largest endemic in Brazil. Over 18 of the 27 Brazilian states were affected *(Enfissi, 2016)*. This presented the first mosquito transmitted cases. In this year alone, there were over

440,000 – 1.3 million reported cases in Brazil. There was also an increased reporting of atrophic neonatal CNS development at this time *(Meaney-Delman, 2016)*. This massive outbreak led the World Health Organization to call a public health emergency on Feb 1, 2016 *(Zupanc, 2016)*.

The ZIKV Relationship with *Aedes* Mosquitoes and Microcephaly

The main global vector for ZIKV is the *Aedes* clade of mosquitoes. The foremost of the 6 species being *Aedes aegypti* which is the most common. The *Aedes* mosquitoes are highly associated with yellow fever, dengue fever, and chikungunya *(Meaney-Delman, 2016)*. The ZIKV related activity of these mosquitoes (under study) have shown to peak in the morning and afternoon, with moderate activity throughout the day. The activity diminished around night time *(Zupanc, 2016)*. These mosquitoes reproduce quickly and their eggs are hardy in structure, able to survive through long period of drought (despite thriving in moist environments). Between countries, *Aedes* mosquitoes are able to incorporate viruses such as ZIKV into local transmission cycles by blood feeding on viremic travelers. *(Paixao, 2016)* Since mosquitoes blood feed, they do not only infect humans, but animals as well – leading to multiple (suggested) animal reservoirs of ZIKV. The average incubation time of ZIKV in mosquitoes is ~10 days. *(Plourde, 2016)*

When blood feeding, ZIKV is shown to be received similarly to other flaviviridae through skin cell receptors. The skin cell types include: fibroblasts, keratinocytes, and dendritic cells, with fibroblasts being the most easily infected type. Through these cells, ZIKV is able to enter lymph nodes and the blood stream. Fibroblasts are easily overtaken by the ZIKV replication cycle, however many cell nuclei have shown to contain antigenic properties. ZIKV has over 10.8 thousand nucleotides that code for over 3.4 thousand amino acids. There are two noncoding regions, one 5' and the other 3', that flank the characteristically large open reading frame commonly found in flaviviruses. The RNA is kept inside of the capsid for the arthropod ZIKV *(Plourde, 2016)*. The noncoding regions are made of structural proteins on the 5' end, and nonstructural proteins on the 3' end. The full genome (extracted and synthesized by the Ion Torrent platform) can be found on the GenBank databse *(Cunha, 2016)*.

After isolating strains from Africa (found between 1954-2007), there is evidence to suggest that ZIKV is able to purge deleterious polymorphisms via recombination. ZIKV replicates by taking over existing autophages, causing a lack of centrosomes for brain development (i.e. attenuating the growth of hNPCells) *(Xu, 2016)*. This is a plausible link to the highly associated neonatal condition, microcephaly. *(Plourde, 2016)*

The link with microcephaly has been heavily traced through pregnant women. Pregnant women are not more susceptible than other groups, and potential risk factors that may increase susceptibility have not been identified or confirmed. Microcephaly is the reduction of head size (atrophic). What further

complicates this relationship is that there is no universal scientific definition for microcephaly, and symptoms are also highly associated with other serious conditions. It can be detected at 18-20 weeks of gestation, but not without complication. *(Meaney-Delman, 2016)*

Background Screening & Symptoms

In grown adults, there are a variety of ZIKV related symptoms, including: fever, headache, rashes, myalgia, and arthralgia (Mlakar, 2016). The symptoms of ZIKV are usually mild and nonspecific when compared to other arboviruses. Over 55% of the reported cases from 1954 – 2016 were travelers. ZIKV has a high co-infection rate with chikungunya and dengue fever, but the probability of recovery is also high. Sexual and blood transmission have been reported, mostly in 2013 and 2014. There was a high reporting of blood transmission from asymptomatic blood donors in French Cambodia (Paixao, 2016). Only 1 in 5 infected adults show symptoms of illness, which will only last roughly 3-12 days; death is rare (Meaney-Delman, 2016).

There have been multiple cases, with evidence of perinatal transmission of ZIKV. In neonatal development, there is a vastly different expression of (vertically transmitted) symptoms. These include: microcephaly, ventriculomegaly, and calcification of the fetus and placenta. The ZIKV virus targets the central nervous system (CNS) in fetuses. Electron Microscopy of tissues show evidence of the flaviviridae family, and also tests positive in reverse transcription polymerase chain reactions (RT-PCR) (Mlakar, 2016). In 2015, there were over 3,500 reported cases of microcephaly in ZIKV affected areas, with 46 neurological related deaths (Paixao, 2016). Many neonatal ZIKV cases have shown high ZIKV RNA in amniotic fluid. Due to the high CNS association, ocular defects such as cataracts are reported as well (Meaney-Delman, 2016).

While all of these numbers may be alarming, this information may be overestimated due to a severe lack of baseline rates for microcephaly in Brazil. The same goes for ZIKV, which before 2007, was not a point of interest and lacks statistical evidence or baseline rates to effectively draw any conclusions on this virus. A plausible link to CNS damage and microcephaly has been formed, but cannot be confirmed just yet (Plourde, 2016).

Treatments

To begin this section, it should be stated that there are no confirmed treatment or vaccination options for ZIKV. The technology to develop vaccines is available, but the necessary information about ZIKV is not (Zupanc, 2016). RT-PCR has repeatedly shown to be the main method of detection, but has to be done within a week of symptomatic onset, or risk testing negative. Neonatal detection is usually only done post-mortem when tissues can be studied in detail (via RT-PCR or immunohistochemical staining). The CDC

and governments can only offered suggestions such as avoiding travel to countries with ZIKV, or preventative measures against mosquito bites (Meaney-Delman, 2016).

Nature Medicine has published the study for over repurposing 6,000 existing drugs. Of these drugs, the most promising are Emricasan, Nicosamide, and PHA-690509. Emricasan has shown to prevent caspase activity (i.e. cell death causing microcephaly) without affecting hNPC growth. The latter two drugs have shown to inhibit the replication of ZIKV strains, with PHA-960509 being compatibily used with Emricasan. These are all still undergoing clinical trials, and may not produce results for a long time (Xu, 2016). Many promising drugs have to be tested for non-harmful clinical application, and toxicity (Mumtaz, 2016).

Discussion & Conclusion

When studying the movement of ZIKV, there is evidence that the Brazilian endemic can be traced to Asian strands of the virus, and evidence to suggest that ZIKV has undergone environmental adaptation while spanning continents (Mlakar, 2016). While being perpetuated by the Aeda mosquitoes, it is difficult to identify an Aedes based attack rate due to the variability between the 6 species. The tracking of ZIKV is also complicated by analogous diseases (previously mentioned). While it appears that women are more affected, this could be due to women reporting more so than men (Paixao, 2016).

ZIKV has a high association with neurological atrophy and microcephaly, but this relationship is not universally accepted. There is still high potential for misdiagnosis (Paixao, 2016). The last flavivirus-birth defect relationship was confirmed over 50 years ago, by the rubella virus. Collectively, this information heeds caution for scientists to confirm the connection. In exploring this validity of this relationship, some scientists have explored Shepard's Criteria for identifying a teratogen and Bradford Hill's criteria for causal relationships. Both sets of criteria have been met, but more study is needed to further validate (Rasmussen, 2016).

ZIKV is a 'new' and rising disease, with slim amounts of useable case studies. Global Warming has the potential to factor into this rise in incidence (and of other arboviruses), with the high association of the *Aedes* mosquitoes. The surveillance studies that have been conducted have the potential to be under representative *(Paixao, 2016)*. There are many questions for this virus, and all of its factors. Most of the information regarding ZIKV is still under heavy investigation. The statistical reliability of any findings is no available at the moment *(Plourde, 2016)*. Clinical testing for the safety of patients, and efficiency of potential vaccines will take a long time, but these findings will prove vital to the study of the Zika Virus.

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