The New Epidemic of Zika Virus Infection in the Americas:

How and Why

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INTRODUCTION

Zika virus has existed on this planet for at least 70 years. What caused it to leave Africa and spread eastward across the globe? What led to the explosive epidemic in South and Central America? Why does Zika virus infection cause congenital abnormalities? What is the risk of sexual transmission? The World Health Organization has termed it a global health emergency; will it reach the United States? How can we stop it? This paper will focus on the known science that may help answer some of the questions surrounding this burgeoning epidemic.

A BRIEF HISTORY OF ZIKA VIRUS

Zika virus is a flavivirus, similar in many respects to the related zoonotic pathogens of Dengue, Chikungunya, West Nile, Yellow Fever, and Japanese encephalitis. It is the latter virus, in fact, to which Zika virus is most closely related virologically, including its neuro-tropic predilection.

Zika virus was first isolated from mosquitoes in the Zika forest of Uganda in 1947.[1] Human disease caused by Zika virus was described in Nigeria just a few years later in 1953, but at that time it was an obscure, mild, self-limited illness. Even through 2006 there were only 13 reported cases of human illness caused by Zika virus, with low sero-prevalence rates reported in inhabitants of African regions where it was endemic.

The geographic leap in 2007 from Africa to the Yap Islands in Micronesia was felt at first to be an anomaly. Clinical manifestations were similar to prior outbreaks in Africa, where the virus produced a mild, febrile rash illness without associated hospitalizations or deaths. In the Yap Island outbreak, however, the virus demonstrated the ability to spread more aggressively through a susceptible population. A post-outbreak serologic survey revealed that a full 73% of the population had been infected.[2]

In 2013 Zika virus reached French Polynesia, and produced a significant outbreak over several years, affecting an estimated 32,000 people, or two-thirds of the inhabitants. It soon spread to other islands of the south Pacific, reaching Easter Island off the coast of Chile in 2014. What followed was one of the most rapidly expansive epidemics in recent viral history.

In 2015 Zika virus was discovered in continental South America, with the initial descriptions of an acute, mild, febrile illness with rash reported from Bahia, Brazil in March 2015. (During the summer of 2014 that region of Brazil was at the center of the complex of stadiums that hosted the World Cup Soccer Tournament, and some argue that this was the original nidus for introduction of the virus.) The illness did not cause alarm initially, as the symptoms seemed just a milder form of other endemic viral syndromes. It soon became apparent, however, that Brazil was experiencing an outbreak of a new viral pathogen. What followed was an explosive tour de force of Zika virus infections that in just a few months, by October of 2015, had spread to 14 Brazilian states, with an estimate by the Brazilian Ministry of Health of 1.3 million cases.[3]

Rapid spread to Colombia and to Central America followed, with Zika virus autochthonous spread (i.e. in country transmission – mosquito to human) occurring in 33 countries and territories in the Americas at the time of this writing, most recently the U.S. territory of Puerto Rico. But it was not simply the appearance of a new viral pathogen in an immunologically naïve population that earned Zika virus its infamy, but rather the simultaneous, seemingly bizarre surge of congenital malformations that shadowed it.

COMPLICATIONS OF ZIKA VIRUS INFECTION

Human infection with Zika virus consists of an acute febrile illness with rash, conjunctivitis, and body aches. It is less severe clinically, but is symptomatically indistinguishable from the other more familiar South American zoonoses of Dengue and Chikungunya, and notably less severe than Yellow Fever. Infection with Zika virus is asymptomatic in 80% of cases, and is mild and self-limited in the remaining 20%. Infection during pregnancy, however, can result in vertical transmission and devastating fetal outcomes.

By September of 2015, the Brazilian Ministry of Health reported an alarming (more than twentyfold) increase in reported cases of microcephaly in just over six months. By January of 2016 over 4,100 microcephalic births had been reported. Brazilian Neonatal ICUs became inundated with cases. The Brazilian Society for Medical Genetics established the Zika Embryopathy Task Force, which investigated a cohort of reported cases and was able to make the initial scientific link to Zika virus, as well as to define the Zika embryopathy syndrome.[4] In addition to severe microcephaly, associated congenital abnormalities included extensive intracranial calcifications and macular atrophy. Lissencephaly (reduction in normal gyri), pachygyria (malformed gyri) and arthrogryposis (congenital musculoskeletal contractures related to peripheral nerve malformation) were also described.

The incidence curve of the microcephaly epidemic in Brazil correlated temporally with the clinical epidemic of the Zika virus illness. Mothers of microcephalic infants demonstrated serologic evidence of acute Zika virus infection. Zika virus RNA was detected in amniotic fluid and cord blood of infected pregnant women, in brain tissue of microcephalic neonates, in tissue and fluids from still-borne infants, and in fetal tissue from miscarriages. The link is all but irrefutable.

Further investigation of the complex epidemiology of this connection will hopefully be able to define the magnitude of the risk, which at this point remains unclear. It seems apparent that symptomatic Zika virus infection in the first trimester seems to portend the greatest risk and severity of Zika embryopathy, but infection during any trimester carries some risk of adverse fetal outcomes. Interestingly, a look-back study of Zika virus in French Polynesia did demonstrate an increased risk of microcephaly,[5] which did not draw attention at that time.

Along with the increase in fetal abnormalities in Zika-endemic regions, there has also been an increase in the incidence of Guillian-Barre Syndrome (GBS). This association has been reported widely from Brazil, Columbia, Central America, and Mexico, and was in fact described in the French Polynesian outbreak. While scientific proof of the causality of Zika virus infection and GBS has not yet been obtained, the association is indeed strong.

BACK (BRIEFLY) TO VIROLOGY

So then, was it a change in the virus itself that produced the Zika virus epidemic? Analysis of genomic

Fig. 1. The *A. aegypti* mosquito is the main vector for Zika virus transmission in the Americas. In the U.S., the Centers for Disease Control and Prevention estimates its distribution along the southern border and as far north as Pennsylvania. Photo from the CDC Public Health Image Library.

RNA has been carried out on what are known to be three main clones of the virus. Genomically, American strains of Zika virus are much more closely related to the Asian genotype than to the African. Detailed genomic analysis, however, reveals that African, Asian and American strains demonstrate very little clonal genetic drift, with 88% overall nucleotide homology.[6] Detailed virologic investigation has concluded that it is unlikely that viral evolution alone, resulting in a fundamental change in viral structure or pathogenesis, can account for the Zika virus epidemic in the Americas.

THE CRITICAL ROLE OF THE MOSQUITO VECTOR

Mosquitoes, by virtue of vector transmission of deadly pathogens, kill more humans than any other animal on earth. There are two critical variables in the transmission of viral pathogens from mosquitoes to humans: 1) the natural behavior of the vector species in relation to human habitats; and 2) its vector competence, or the proficiency with which the infected mosquito is capable of transmitting disease to humans.

In Africa, where the endemicity of Zika virus disease is low, the predominant mosquito vector is *Aedes africanus*. This mosquito prefers quiet, sparsely inhabited jungle habitats, and takes its blood meals from multiple primates, including humans. It is rarely found among human villages or in areas of any disruptive activity.

In Asia and the South Pacific mosquito vectors for the Zika virus include *A. hensilli* and *A. polynesiensis*. These mosquitoes are more apt to co-inhabit the same areas as humans, but after a blood meal they have low levels of infectious virus in their saliva, and thus low

vector competence. This situation was clearly a step up in epidemic potential from Africa, as demonstrated by higher seroprevalence rates, but it was still far from what has been seen in Brazil.

In stark contrast, mosquito vectors for Zika virus infection in the Americas consist of *A. aegypti* and to a lesser extent *A. albopictus*, which exist throughout the Americas, including the United States. *A. aegypti*, the main vector for Zika virus transmission, is, in fact prevalent all along the Gulf Coast and southern border of the United States.

A. aegypti is an aggressive, silent, day-biting mosquito, with an affinity for human habitats. It prefers urban settings, tolerates indoor environments, and it takes multiple blood meals in rapid succession from multiple hosts. In addition, a high concentration of infectious virus is present in its saliva, which gives it high vector competence and accounts for the high likelihood of infection following a bite from *A. aegypti*.[7]

A. aegypti's predilection for an urban habitat, combined with the high population density of eastern cities in Brazil, provided the perfect fuel for a combustive epidemic. This substrate was further complicated by socio-economic and cultural factors, including the well-documented underutilization of prenatal care among Brazilian women. Brazil, as is the case with the majority of Central and South American countries, is a predominately Catholic country, with comparatively low availability and utilization rates for birth control.

It is no coincidence that over the last 10 years the incidence of Dengue and Chikungunya, and now Zika virus, has increased globally. These are all mosquito-borne flaviviruses transmitted by the same *A. aegypti* vector, so it is likely that as the habitat range of this mosquito species continues to expand, so too will the diseases it carries.

THE PROBLEM OF SEXUAL TRANSMISSION OF ZIKA VIRUS

During infection with Zika virus, viral RNA has been detected in blood, CSF, urine, saliva, amniotic fluid, breast milk, and semen. But though the virus is present transiently (for a few days) in most of these fluids, it is much more persistent in semen, where Zika virus RNA can be detected for at least two months after its disappearance from blood. In fact, the viral titers in semen exceed by orders of magnitude those found in blood in the initial stages of infection.[8] The human testes, it seems, represent an immunologic haven where viral persistence is permitted with no risk to the host. Consequently, as is the case with Ebola virus, sexual transmission of Zika virus is a significant risk both in endemic areas and for men returning from them to non-endemic zones. This has led to the current CDC recommendations that women who are pregnant should avoid all unprotected sexual contact, for the duration of pregnancy, with men who either reside in endemic zones, or who have returned home from them. In the absence of a male partner at risk, women returning from Zika endemic countries should postpone pregnancy for eight weeks, to allow for resolution of viremia. Men returning from endemic zones should avoid inducing pregnancy for six months.[9]

DIAGNOSIS AND PREVENTION OF ZIKA VIRUS INFECTION

The immunologic response of humans to flavivirus infection is complex, and antibodies to one member of the group can cross react with assays for other members. This is true not only from the standpoint of primary infection, but also of immunization. Thus, infection with Dengue and or Chikungunya, or vaccination for Yellow Fever, can produce a clustering of similar antibodies that can confound attempts at a serologic diagnosis of Zika virus. An accurate diagnosis depends upon analyses of the relative magnitude of specific antibodies to the different flaviviruses, the relative quantitative amounts of specific IgG and IgM antibodies, and the ability of those antibodies to neutralize Zika virus cell cultures. That is why at the time of this writing the CDC performs all Zika virus testing at the Arboviral Diagnostics Lab in Colorado. While this restricted approach to diagnosis yields the most accurate results, it also leads to a delay in turn-around time (currently four to six weeks).

There is no vaccine or treatment for Zika virus infection. In fact, only in the last six months have mouse models been developed to even begin to study this perplexing virus. While considerable funding for vaccine development has become available, and multiple biopharmaceutical firms have stepped up, it will likely be years before any viable vaccine candidate will surface. There is reason to be optimistic, though, as effective vaccines for Yellow Fever, Japanese Encephalitis, and now Dengue have been successfully produced.

Postponing travel to Zika endemic areas, especially for women who are pregnant or who are trying to become pregnant, is an obvious immediate preventive measure. Restrictions on unsafe sexual activity, as mentioned previously, also apply. For those who must travel to areas where Zika virus is endemic, prevention of mosquito bites with DEET for skin and permethrin

for clothing is recommended. Screened-in living quarters and air conditioning provide a modicum of additional risk reduction.

The effectiveness of larvicides and insecticides has waned after decades of use in mosquito-infested areas of the Americas. In impoverished countries, control of mosquito breeding grounds in standing water is problematic. Novel approaches such as genetically engineered male mosquitoes, which produce larvae incapable of maturation, are being studied, but widespread use of such a clever yet costly intervention is likely to have little overall impact.

Given the wide geographic distribution of *A. aegypti* (recently estimated by the CDC to involve 30 states including the entire southern border of the U.S. and extending along the east coast as far north as Pennsylvania) and of *A. albopictus* (further north to the Great Lakes and into southern New England), there is little doubt that autochthonous transmission of Zika virus will occur in the United States in the summer and fall of 2016. There are, however, many socio-economic, cultural, public health, and other resource differences between the U.S. and our neighbors in the southern hemisphere, and we are fortunate to have had a preview of the Zika virus's capabilities in order to prepare.

Considerable federal money has been diverted by the Obama administration to Zika virus preparedness. On April 1 the CDC hosted the first of its Zika Action Plan Summits focusing on awareness and planning for a Zika epidemic in the U.S., with the aim of leveraging national, state, and local resources. The first priority is education of, and resource allocation to, senior state and local government officials in regions in the southern United States most likely to be affected early.[10]

SUMMARY

The coalescence of factors that has resulted in the explosive epidemic of Zika virus infection and its consequences in South and Central America came about due to the perfect storm of a virus introduced into a non-immune and socio-economically susceptible population by an aggressive, ubiquitous, and frighteningly efficient mosquito vector. The adverse fetal outcomes, the implications of sexual transmission, and the lack of an effective prevention strategy have stunned the medical community and strained the fabric of societies where it is endemic. Fear of spread into the continental United States and beyond has generated nearly unprecedented media attention, and has catapulted Zika virus to the top of the list of most feared contemporary infectious diseases.

While it is certain that the epidemic will reach the United States, the magnitude of the epidemic will depend on the extent to which we can educate, organize, and deploy resources, while the quest for a vaccine is undertaken. While the challenge is great, and the consequences of inadequate preparation severe, I believe we have not entered the game too late.

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