A Zika vaccine – late to the party that we must attend

LONDON, UK-----22nd February 2016-----ExpertREACT. The latest Zika virus outbreak is serious. It brings the nasty, unexpected cocktail of potential long-term sequelae, expanding geographical range coupled with local (autochthonous) and sexual transmission. We are still developing an Ebola vaccine; we cannot ignore a Zika vaccine.

Once again, an infectious pathogen catches us by surprise. On 1st February 2016 the World Health Organisation (WHO) declared the Zika-linked condition (caused by the Zika virus, ZIKV) a global health emergency (1). There has been a strong call for women in affected countries to avoid unprotected sex and in some countries, delay pregnancy. These are “extraordinary” circumstances probably not seen since the HIV-AIDS epidemic decades ago.

ZIKV is a member of the Flaviviridae family that includes several mosquito-borne viruses of major clinical importance such as yellow fever virus, Japanese encephalitis virus and dengue virus. Similar to Ebola, which recently caused its largest outbreak (starting in Guinea in 2013), we have known about the Zika virus (ZIKV) for as long ago as 1947 (Uganda). To date, ZIKV transmission has been documented in 46 countries and territories since 2007 (2). 34 countries/territories reported local ZIKV transmission between 2015 and 2016, six have indications of ZIKV circulation (mainly in Asia) and in five ZIKV outbreaks have ended (all in the Western pacific).

ZIKV typically causes a mild, acute, self-limiting illness characterized by rash, high fever, and joint pain. Normally, only 20% of people infected are symptomatic with clinical signs typically subsiding within a week. Unlike other the major Flaviviridae, the case fatality rate (CFR) of ZIKV infection appears to be extremely low. Only three ZIKV-associated deaths have been confirmed in Brazil up to November 2015 despite ~1.5m cases recorded since the outbreak began in 2015 (3).

Up until this latest 2015/16 outbreak, it was thought that a ZIKV infection was not associated with long-term sequelae. However, this is now being called into question by the extraordinary observation that 4,783 cases of congenital microcephaly and/or CNS malformation cases have been reported in Brazil (mostly North Eastern) over a period of ~4 months (as of 30 January 2016) (3).

Microcephaly is a condition where a child’s head circumference is smaller than that of other children of the same age, race, and sex. The condition may cause intellectual impairment, epilepsy and ophthalmological disorders. Similarly, in French Polynesia a review of birth data by authorities found an increase in the number of microcephaly cases that followed the ZIKV outbreak in 2013-2014. In children born between March 2014 and May 2015, 9 microcephaly cases occurred (the historical average is 0 to 2 microcephaly cases per year) (4). Studies are investigating the association of ZIKV infection and microcephaly, including the role of other contributory factors (e.g. prior or concurrent infection with other organisms, nutrition, and environment) (X). These studies should confirm or disprove a causal relationship between microcephaly and ZIKV infection. In all, six countries (Brazil, French Polynesia, El Salvador, Venezuela, Colombia and Suriname) have reported an increase in Zika-linked microcephaly.

ZIKV has also been associated with an increase in Guillain-Barré syndrome (GBS) in the same set of countries, Brazil, French Polynesia, El Salvador, Venezuela, Colombia and Suriname. GBS is a rare, sometimes fatal, immunological disorder of the peripheral nervous system. Mortality rates vary from 2% in the US to 5.3% in Brazil and 10% in Mexico. The association of GBS with pathogen infection is not an unusual finding. Historically, GBS is recognised as a rare complication of dengue virus, chikungunya virus and Campylobacter jejuni infections where in the latter it can implicated in 25% of cases (5).

During the ZIKV outbreak in French Polynesia (2013-2014), 42 GBS cases occurred (6). This equated to a 20-fold increase in GBS incidence, compared to a four- to nine-fold increase during a Chikungunya virus outbreak that followed in 2014-2015. As in the case of the observed increase in microcephaly, studies are ongoing to confirm or disprove a causal link between ZIKV infections and GBS.

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It is also a possibility that co-circulating viruses in the Americas such as dengue and Chikungunya may be, at least in part, contributing to the observed increase in GBS. ZIKV-associated GBS might be due to a more pathogenic ZIKV genotype or sequential infection with dengue virus followed by ZIKV (6).

ZIKV is of particular concern to global health because of its risks of wider geographical spread and the possibility of sexual transmission. For the former, importation can occur to non-endemic countries as travellers return from endemic countries. 52 known travel-associated ZIKV cases have been confirmed in the continental US (7), where the condition has been made nationally notifiable. In addition, local (autochthonous) transmission is also predicted to occur where the Aedes aegypti and/or Aedes albopictus mosquitoes are present. Such regions include southern Europe, US (gulf coast, Florida), Australia, China, South Korea and Japan. At present authorities do not expect any difficult to control outbreaks but the added component of sexual transmission brings a new level of uncertainty.

What can the global health community do about this new pandemic virus? Aside from preventative recommendations and mosquito vector-based control programs, we have no specific antiviral or vaccine for this unwelcome visitor. It is reported that a ZIKV vaccine developed by the US National Institute of Allergy and Infectious Diseases (NIAID) may enter clinical development in late 2016 (8). In addition, Sanofi, GSK, Inovio Pharmaceuticals, NewLink Genetics, Hawaii Biotech, Protein Sciences, GeoVax Labs, and PaxVax are all reportedly working on ZIKV vaccines (as well as The Butantan Institute of Brazil, meaning Brazil might become self-sufficient in ZIKV vaccine production). However, based on our calculations (9) using the clinical development times for other flavivirus vaccines, a ZIKV vaccine may be not be approved until around 2024. Just as in the case of Ebola, this latest outbreak will most likely have decreased substantially due to increasing natural (herd) immunity and vector control. Can global stakeholders afford to take the risk of not developing a Zika vaccine? Our recent analysis (9) suggests a vaccine could be a low-to-moderate commercial opportunity (higher than Ebola) based on the epidemic so far i.e. mostly PAHO countries and limited SE Asia. The number of countries could increase driving up commercial potential.

In summary, a Zika vaccine could be late to the party but, in our view, this is a party we have no choice but to attend.

References and Notes:


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