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Zika virus: a new threat from mosquitoes

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In the winter of 2015, the first dengue vaccine (Dengvaxia) was approved for clinical use. Dengue virus is the most prevalent mosquito-transmitted viral pathogen in humans (Qin and Shi, 2014). Even though the approved Dengvaxia has its weaknesses (e.g., low protection against serotype-2 virus), it has been recently licensed to Mexico, Philippines, and Brazil. While the world is celebrating the first dengue vaccine, another mosquito-borne virus, Zika virus (ZIKV), emerged to cause global threat, causing thousands of infants with brain defects and adults with neurological diseases (Fauci and Mores, 2016). In December 2015, the World Health Organization (WHO) added ZIKV to the second tier of three diseases ranked as serious, and issued travel warnings to ZIKV epidemic areas (with more than twenty-three countries). The ongoing pandemic is explosive. More than four million ZIKV infections are expected in America by the end of 2016.

HISTORY AND CURRENT STATUS OF ZIKV

ZIKV was first isolated from a Rhesus monkey in the Zika forest in Uganda in 1947. The virus was subsequently isolated from a human in Nigeria in 1954. Until 2007, ZIKV activity had been restricted in African continent and a few Asian countries; only 14 sporadic human cases had been documented. Since 2007, ZIKV has expanded outside of Asia and Africa, causing an outbreak on Yap island in Micronesia with 49 confirmed and 59 probable cases of ZIKV infections (Duffy et al., 2009). Subsequently, a major ZIKV epidemic occurred in French Polynesia in 2013, followed by rapid spread to countries in Oceania. Meanwhile, imported cases were also reported in Norway, Germany, Australia, France, Canada, Japan, and Italy (Cao-Lormeau and Musso, 2014).

In 2015, the largest ZIKV outbreak took place in Brazil, resulting in an estimated 440,000–1,300,000 cases (Bogoch et al., 2016). Subsequently, ZIKV began to rapidly spread northwards across South and Central America, reaching Mexico by late November 2015. According to WHO and Pan American Health Organization (PAHO), between November 2015 and January 2016, local transmission of the virus was detected in 14 new countries and territories in America. The first case of ZIKV in the United States was reported in January 2016 in a traveler who recently returned from Latin America to Texas (McCarthy, 2016).

BIOLOGY AND TRANSMISSION OF ZIKV

ZIKV is a single-stranded, positive-sense, RNA virus. The virus belongs to the Spondweni serocomplex within the genus *Flavivirus*, family *Flaviviridae*. Other mosquito-borne flaviviruses of public health importance include dengue, West Nile, Japanese encephalitis, and yellow fever viruses. Currently, only 18 full-length genome sequences were deposited in the GenBank. Phylogenetic analyses have classified the ZIKV strains into the African and Asian lineages (Haddow et al., 2012). The current epidemic ZIKV

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strains in the Americas belong to the Asian lineages (Enfissi et al., 2016).

The genome of ZIKV, approximately 11,000 nucleotides in length, contains a single open reading frame (ORF) flanked by 5' and 3'noncoding regions (NCR). The ORF encodes a polyprotein with three structural proteins (capsid, premembrane or membrane, and envelope) and seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5). The structural proteins form virion, and are responsible for virus attachment to cells, membrane fusion, and virion assembly. The nonstructural proteins are required for viral replication and evasion of host immunity, as demonstrated in other flaviviruses.

ZIKV is transmitted to humans mainly by *Aedes* mosquito species, the same vector for dengue and yellow fever viruses. Multiple *Aedes* species, including *Aedes albopictus*, *aegypti*, and *polynesiensis*, have been evidenced to carry and transmit ZIKV efficiently. Other potential transmission routes of ZIKV in humans include perinatal, sexual, vertical, and transfusion transmission. Such non-mosquito transmission routes have also been confirmed for other mosquito-borne viruses. Since eighty percent of ZIKV infections (see below) are asymptomatic, the transmission route of blood transfusion raises the need for testing ZIKV contamination in blood bank. Without vaccine and therapeutics, mosquito control and avoiding mosquito bites are the most effective means to prevent ZIKV infection.

CLINICAL MANIFESTATIONS

Like many other arboviral infections, a substantial proportion of ZIKV infections are subclinical and asymptomatic. The disease caused by ZIKV infection is usually mild and requires no special medical treatment or hostiptalization. The most common clinical manifestations include fever, myalgia, rash as well as eye pain and prostration. Infected individuals usually recover in a week. Guillain-Barré syndrome and other neurologic conditions (including meningitis, meningoencephalitis, and myelitis) are also observed in recent outbreaks in the Pacific area. The clinical manifestations are very similar to dengue and many other arboviral infections.

Prior to the recent epidemics, ZIKV infection was not reported to cause severe diseases (such as hemorrhagic fever) or death. However, the ongoing epidemic of ZIKV infection in Brazil is correlated to a 20-fold increase in incidence of microcephaly, a rare neurological condition at birth in which the newborn's head is much smaller than normal. Children with microcephaly usually have developmental issues and need life-time support. As of January 2016, Brazil's Health Ministry has reported a total of 3,530 case of microcephaly, including 46 deaths. Importantly, ZIKV was isolated from the amniotic fluid of the mothers; in addition, ZIKV was detected from a Brazilian infant with microcephaly who died shortly after birth (Vogel, 2016). Macular neuroretinal atrophy was also seen in infants with microcephaly (Ventura et al., 2016). Despite lack of direct evidence, Brazilian authorities have claimed great risk of microcephaly appeared to be associated with ZIKV infection during the first trimester of pregnancy. The public health officers even suggest postpone pregnancy to minimize the risk of babies with microcephaly. On 17 January 2016, WHO issued an epidemiological alert about the association of ZIKV infection with congenital malformations and neurological syndromes (PAHO, 2016).

CHALLENGE AND PROSPECT

ZIKV is expanding rapidly throughout the world with unique characters that have never been seen in other flaviviruses. Although ZIKV has been identified for nearly 70 years, there is a large knowledge gap about this virus and its diseases. First, it is critical to study the ecologic, entomologic, viral, and host determinants that account for its rapid transmission and disease association. Viral genome analysis combined with reverse genetic studies will help identify potential viral determinants (Zhao et al., 2014). Second, flavivirus infection has never before been linked to birth defect. Clinical investigation, animal models (that can recapitulate human diseases), and laboratory studies are needed to explain this unexpected result. At the current time, mosquito control remains to be the most effective way to reduce ZIKV infection. Vaccine development is urgently needed to stop ZIKV infection. Based on the success of vaccines against other flaviviruses (Japanese encephalitis, yellow fever, tick-borne encephalitis, and dengue), both live attenuated and inactivated ZIKV vaccines can be envisioned in the future. The timeline for ZIKV vaccines could be years away due to the development process.

Currently, no case of ZIKV infection has been reported in mainland China. However, in parallel to the recent experience with dengue and Chikungunya, we expect that imported and autochthonous cases of ZIKV infections will appear in China in the coming years. China annually has 84,332 travelers from ZIKV epidemic areas (Bogoch et al., 2016); the introductions of similar mosquito-borne viruses by tourists have already been documented for dengue and chikungunya. Due to the wide distribution of Aedes mosquitoes in China, autochthonous outbreak will be inevitable following the imported cases. To reduce imported ZIKV infections, we recommend that travels to ZIKV-epidemic regions be minimized, especially for women who are pregnant or about to become pregnant. When visiting ZIKV-epidemic regions, travelers should take appropriate measurements to minimize mosquito bites. Since majority of ZIKV-infected individuals are asymptomatic, molecular diagnostics is needed to monitor the prevalence of ZIKV infection in population. Rapid diagnostic assays (including detection of virus and serology method) are critically needed to monitor the spread of ZIKV and patient care. The

government, public health system, hospitals, and science community need work together to prepare, prevent, and control this emerging flaviviral pathogen.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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