

Zika

An emerging teratogenic virus

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Zika virus was first discovered 69 years ago from studies on the vector of Yellow Fever in Uganda. The virus was isolated from a Rhesus Monkey and a year later was isolated from the vector, *Aedes africanus* mosquito. Although Zika virus was first described that long in Africa, it was rarely reported to cause disease in humans with a total of 14 reported cases before 2007.¹ This low number of reports is likely to be an underestimation of the burden of disease due to underdiagnosis. The Zika virus is from the family of *Flaviviridae* with several of these viruses such as Dengue, Chikungunya, Yellow Fever viruses transmitted through arthropod vectors of types of mosquitoes from the genus *Aedes* of multiple species, most commonly *Aedes aegypti*, which is widely distributed in several continents. The first indication of possible epidemic nature of Zika virus was recognized in 2007 in the state of Yap of the federation of Micronesia, an island (6 km wide by 15 km long with a population of approximately 7400 persons) located northeast of Papua New Guinea in the Pacific Ocean, where an estimated 73% of the population had recent infection with Zika virus.² The infection was diagnosed either by reverse transcription polymerase chain reaction (RT-PCR) or by immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) and confirmed by plaque-reduction neutralization test carried out at the Centers for Disease Control in the United States. The infection was mild characterized by rash, fever, arthralgia and conjunctivitis. As this report came from isolated areas in the Pacific and associated with mild disease and no mortality, it did not provoke enough interest from world leading public health organizations. The second sign of the epidemic potential came in 2013-2014 when an outbreak had hit the French Polynesia islands in the Pacific Ocean. As a vector-borne disease linked to types of *Aedes* mosquitoes that are

wide-spread in the world, it was a matter of time when it would show up in other regions. This has manifested in mid-2015 in South America especially in parts of northern Brazil and neighboring countries. It is not clear if mass gathering of Fédération Internationale de Football Association (FIFA) World Cup in the summer of 2014 and/or International Canoe Racing event have contributed to the Zika virus spread to Brazil. However, recent transmission to the Americas seems to have originated in the Pacific Islands as phylogenetic analysis of the sequences of Brazilian strains show a 99% identity with a sequence from a Zika virus isolate from French Polynesia.³ Emergence and spreading of Zika virus indicated by phylogenetic studies have suggested that the date of the emergence of Zika virus in east Africa was approximately 1920 and to Asia approximately 1945. The virus was first detected in 1966 in Malaysia and subsequently across south-east Asia. Recent studies have shown that the Zika virus strains from Micronesia and French Polynesia are related to the Asian lineages.⁴

Globalization and urbanization has broken the barriers that limit epidemics to isolated areas. This is believed to have contributed to the widespread of other vector-borne flaviviruses such as Dengue and Chikungunya that share the same transmission dynamics and may have been the driving force behind the spread of Zika virus with the concern that it will become as widespread. As of 8 June 2016, 60 countries and territories report continuing mosquito-borne transmission of Zika virus. Most are in Latin America, Southeast Asia and islands in the Pacific Ocean. The risk of spread of the current epidemic of Yellow fever virus in Angola and Democratic Republic of Congo and Ebola in West Africa are examples of how the world is connected and response to epidemics needs to be international. Sexual transmission has been confirmed

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in few cases of viremic individuals.⁵ Blood transfusion is a potential source of transmission of the virus with few cases identified in Brazil and French Polynesia.⁶ The importance of the Zika virus infection was undermined by the nature of the disease in the host characterized by mild illness with extremely rare mortality. Most infected individuals have minimal symptoms of fever, rash and arthralgia and the majority are asymptomatic. The symptoms are short with rapid disappearance of the rash in one week. There is a suggestive evidence that Zika virus may be more adaptable to humans. N-linked glycosylation signal of the E protein of Zika virus was found in strains isolated from the outbreak in the Pacific islands and not other strains.³

Birth defects and neurological disorders. The main concern of Zika virus infection is the probable teratogenicity. Zika is the only new virus to be associated with congenital anomalies for over 30 years. In May 2015 was the first reported cases of Zika virus infection from Brazil.

Later in the year, the Brazilian Ministry of Health reported increased incidence of microcephaly. The rate was 20-fold more than previous years. It was noticed that this increase in the incidence of microcephaly was associated with recent Zika virus infection. Subsequent reports indicated the virus ability to cross the placenta and was recovered from newborn to Zika virus infected mothers.⁷ A report from the French Polynesia outbreak found increase in fetal central nervous system malformations. The WHO made a statement on the early 2016 that a causal relationship between Zika virus infection birth defects and neurological disease is strongly suspected. It declared a Public Health Emergency of International Concern.⁸

Infection in early pregnancy poses the highest risk for microcephaly and possibly other birth defects. Early fetal loss or death have been noted in association with maternal infection that occurred in early weeks of gestation. Recent experimental infection in a pregnant mouse model showed fetal birth defects which further supports the teratogenicity of the Zika virus infection.⁹ In South America, Brazil in particular, the estimated absolute risk of an affected baby is 4 per 1000 pregnancies with evidence of recent Zika virus infection. In a recent report from Brazil, ultrasonography detected fetal abnormalities in 29% of pregnant women with Zika virus infection.¹⁰ Ocular anomalies have been reported in up to 35% among infants with microcephaly in Brazil. These included optic-nerve and pigment abnormalities, chorio-retinal and neuro-retinal atrophy, macular atrophy, lens subluxation, and iris coloboma.¹

Old studies conducted in mice in the 1950s and 1970s indicated that Zika virus is neurotropic, and

more recent studies have shown the capability to cause neural-cell death.¹¹ Placental infection has been shown, but the mechanism by which the virus crosses the placenta to the fetus and how frequent is not clear. The differential susceptibility of pregnant women to the teratogenic effects of Zika virus is not well understood. Local cellular immune responses are important in the protection of the fetus from various infectious agents including viruses.

Guillain-Barré like syndrome had a temporal and geographic relationship and Zika virus outbreaks in the Pacific and the Americas. The association between Zika virus infection and Guillain-Barre syndrome was demonstrated in a case-control study during the French Polynesia outbreak. Also, meningoencephalitis and acute myelitis were reported as a complication of acute Zika virus infection.

Prevention and control of Zika virus. There is no specific therapy for Zika virus infection and treatment is supportive with focus on symptoms. The disease is mostly self-limited and short lived. No vaccine exists yet for the prevention of Zika virus infection but active research is ongoing. Variety of vaccine candidates are under development, including inactivated virus, virus-like particles, DNA, live vectored vaccines, subunit vaccines, and live recombinant virus. All are in preclinical development and few are expected to enter clinical studies in early 2017. Classical preventive measures of vector control and avoidance of mosquito bites are essential, but also limiting travel of fertile women to areas with high viral transmission. Other preventive measures include using mosquito repellent, bed nets, window screens, and air conditioning. *A. aegypti* is difficult to control as it has cryptic breeding sites indoor and outdoor. The bite is commonly painless and happens at daytime. Therefore, it is important to have integrated approach with mobilization of the community through awareness campaigns. The approach relies on elimination of *A. aegypti* breeding sites, larvicides, and insecticides to kill adult mosquitoes. Indoor residual spraying and the use of larvicides have been effective in vector control of Dengue in some settings.

Current and future challenges. Timely diagnosis of Zika virus infection is important which is one of the main challenges. Reverse transcription polymerase chain reaction is sensitive and specific, but correlates with viremia which is short lived and may be without symptoms. Serology cross reactivity with other flaviviruses, such as Dengue and Chikungunya, and the possibility of other unknown serotypes complicates the diagnosis of Zika virus infection. Serological confirmation requires neutralization antibody test that is

labor intensive and requires a live virus. Animal models for developmental defects due to viral infection have been developed and likely to aid in the understanding of the infection and spectrum of complications. A new vector control products and strategies such as genetic modification of the vector and effective vaccines are needed.

Risk to the Kingdom of Saudi Arabia. Few thousands of cases of Dengue virus disease are diagnosed every year in the Kingdom of Saudi Arabia (KSA). Almost all cases are centered on the red sea coast especially in Jeddah/Makkah region and Jazan. *Aedes aegypti* is the vector of transmission of Dengue and it is spread at the west coast. During Hajj season an estimated more than 8000 pilgrims come from South America and more for Islamic Holy sites visits which happen throughout the year. Travel from KSA to South America is common and likely to increase during the coming Summer Olympics in 2016. Kingdom of Saudi Arabia also attract a large expatriate workforce from areas endemic for flaviviruses. For these reasons and as Zika virus infection is commonly asymptomatic it is plausible to predict introduction of Zika virus to KSA. This requires urgent preparedness and response measures. Active surveillance is critical to measure the risk and gauge the response to such a threat. Serological cross reactivity of the ELISA test with Dengue and Chikungunya complicates surveillance and requires the establishment of appropriate biosafety level 3 laboratory for more specific neutralizing antibody test. Surveillance goes beyond diagnosis of Zika cases to congenital anomalies and Guillain-Barré syndrome. Serosurvey studies are needed to assess possible introduction of Zika virus to KSA and the burden of disease. Awareness of physicians of the potential diagnosis of Zika virus infection is important and especially relevant in pregnancy. Entomological studies of the vector are important to aid transmission control. Preventive measures as outlined above are critical to limit infections transmitted through *Aedes aegypti* such as Dengue and Zika viruses.

This calls for a comprehensive public health plan that is multisector and well-coordinated.

References

1. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika Virus. *N Engl J Med* 2016; 374: 1552-1563.
2. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009; 360: 2536-2543.
3. Baronti C, Piorkowski G, Charrel RN, Boubis L, Leparco-Goffart I, de Lamballerie X. Complete coding sequence of zika virus from a French Polynesia outbreak in 2013. *Genome Announc* 2014; 2: e500-e514.
4. Gatherer D, Kohl A. Zika virus: a previously slow pandemic spreads rapidly through the Americas. *J Gen Virol* 2016; 97: 269-273.
5. D'Ortenzio E, Matheron S, Yazdanpanah Y, de Lamballerie X, Hubert B, et al. Evidence of sexual transmission of Zika virus. *N Engl J Med* 2016; 374: 2195-2198.
6. Musso D, Nhan T, Robin E, Roche C, Bierlaire D, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. *Euro Surveill* 2014; 19. pii: 20761.
7. Driggers RW, Ho CY, Korhonen EM, Kuivanen S, Jääskeläinen AJ, et al. Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities. *N Engl J Med* 2016; 374: 2142-2151.
8. World Health Organization. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations February 1st, 2016. <http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/>
9. Cugola FR, Fernandes IR, Russo FB, Freitas RC, Dias JLM, Guimarães KP, et al. The Brazilian Zika virus strain causes birth defects in experimental models. *Nature* 2016; 534: 267-271.
10. Brasil P, Pereira JP Jr, Raja Gabaglia C, Damasceno L, Wakimoto M, Ribeiro Nogueira RM, et al. Zika Virus Infection in Pregnant Women in Rio de Janeiro - Preliminary Report. *N Engl J Med* 2016; Mar 4. [Epub ahead of print].
11. Bell TM, Field EJ, Narang HK. Zika virus infection of the central nervous system of mice. *Arch Gesamte Virusforsch* 1971; 35: 183-193.
12. Cao-Lormeau VM, Blake A, Mons S, Lastère S, Roche C, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet* 2016; 387: 1531-5339.