

An Update on Zika Virus in Asia

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Zika virus (ZIKV) was first isolated in Asia from mosquitoes from Malaysia in 1966. However, the incidence of Zika and Zika-related neurological complications in Asia is not well known. The few studies of Zika in Asia have been inconsistent in pointing to likely transmission levels, with some studies suggesting substantial transmission and others not. Interpretation of existing epidemiological and public health data from Asia is constrained by the non-specific symptomatology of Zika, the high proportion of subclinical ZIKV infections, relatively low viremia, and the lack of accurate serological assays. Here, we update the status of Zika cases from countries in Asia, and highlight some key knowledge gaps. In particular, accurate determinations of the incidence of Zika-related congenital Zika syndrome should be a priority for Zika research in Asia. Additional information will be critical to make informed strategies for the prevention and control of this global public health threat.

Key Words: Zika; Asia; Congenital Zika syndrome; Guillain-Barré syndrome

Introduction

Zika virus (ZIKV) is a single-stranded RNA arbovirus within the *Flavivirus* genus [1]. Zika has been reported in many tropical and sub-tropical regions, where other *Aedes* mosquito-transmitted viruses also circulate including Dengue, Chikungunya and yellow fever viruses [2]. ZIKV was first isolated in 1947 from a sentinel rhesus monkey in Uganda. The first reported human case occurred in a 10-year-old female from Nigeria in 1952 [3, 4]. Only sporadic cases of Zika were subsequently reported in Asia and Africa until 2007 when the first large outbreak of Zika occurred on Yap Island, Federated States of Micronesia [5, 6]. During the Yap outbreak, 74% of residents aged ≥ 3 years developed IgM antibodies against

ZIKV, with 18% having clinical illness [7]. In 2013-2014, a large outbreak occurred in French Polynesia in which approximately 11% of the population sought medical care for possible Zika [8]. Seventy cases of neurological complications such as Guillain-Barré syndrome (GBS) and encephalitis were reported [8, 9]. The Asian lineage strains from French Polynesia were similar to those from Yap Island 2007 and Cambodia 2010 [10].

In 2015-2016, an explosive Zika epidemic occurred in the Americas. Retrospective testing of blood samples from Haiti indicated the presence of ZIKV in the Americas since at least 2014; Reverse transcriptase polymerase chain reaction (RT-PCR) and viral isolation performed on acute fever samples revealed three ZIKV infections from December 2014 caused by Asian lineage strains closely related to viruses from Easter Is-

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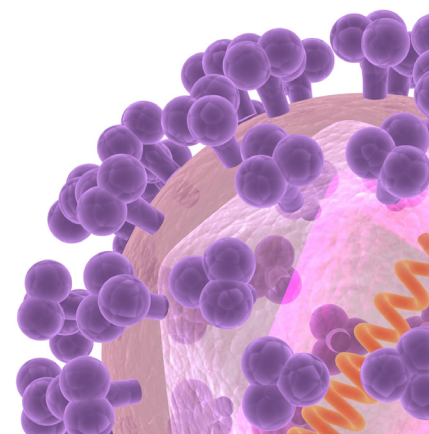
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land 2014 and French Polynesia 2013 [11]. The first Zika case reported in “real time” in the Americas occurred in Bahia state, Brazil in February 2015. By January 2016, about 4,000 suspected cases of microcephaly and 49 deaths had been reported in Brazil. Moreover, 1,708 cases of GBS were reported between January and November 2015 [12, 13]. In February 2016, the World Health Organization (WHO) declared a public health emergency of international concern (PHEIC) due to the explosive epidemic in the Americas and the association of ZIKV infection with microcephaly. The WHO has estimated that about 3-4 million cases of Zika have occurred globally, with 84 countries or territories reporting mosquito-borne transmission. ZIKV-related microcephaly and other central nervous system malformations have been reported in 31 countries or territories; and 23 countries or territories have reported ZIKV-related GBS [14, 15]. As of April 2017, a total of 559,721 Zika cases, with 209,628 laboratory confirmed infections and 3,122 confirmed congenital syndromes, have been documented in the Americas [16].

Although the explosive Zika epidemic that occurred in the Americas has not been observed in Asia, the potential risk of such an epidemic has been the subject of great concern given the widespread distribution of competent mosquito vectors and other supportive conditions in Asia [17]. Mathematical modelling utilizing data from transportation networks, mosquito surveillance, and vector competence studies has suggested that Asian countries are at high risk for large Zika outbreaks; in particular, India with 67,422 travelers arriving per year from Zika-affected areas of the Americas, and 1.2 billion people living in potential transmission regions of the country; China with 238,415 arriving travelers and 242 million at-risk residents; Indonesia with 13,865 travelers and 197 million at-risk residents, the Philippines with 35,635 travelers and 70 million at-risk residents; and Thailand with 29,241 travelers and 59 million at-risk residents [18]. In this review, we update the status of ZIKV infections reported from countries in Asia, and highlight some key knowledge gaps that require further study.

Zika status in countries in Asia

1. Bangladesh

In March 2016, the Bangladesh Ministry of Health (MoH) reported the results from retrospective Zika testing of 101 surveillance blood samples. One of these samples was found to be Zika positive from a 67-year-old man with no history of travel outside of the country [19].

2. Cambodia

ZIKV was first detected in Cambodia in August 2010 by RT-PCR, serological assay, and virus isolation on a blood sample collected during fever surveillance by the United States Naval Medical Research Unit No. 2 (NAMRU-2). The sample came from a 3-year-old boy in Kampong Speu province, with the infecting strain belonging to the Asian lineage [20, 21]. In 2016, Institut Pasteur du Cambodge performed retrospective testing on 2,400 acute serum samples collected from suspected dengue patients between 2007 and 2016. Only 5/2,400 (0.2%) were found to be positive by RT-PCR; one each from 2007, 2008 and 2015, and two from 2009 [22]. In November 2016, Zika was reported in a man from Kampong Cham province [23].

3. China

All reported Zika cases have been imported infections in travelers returning from Zika-endemic countries. The first case was identified in February 2016 by RT-PCR on a blood sample from a 34-year-old man returning from Venezuela [24]. Subsequently, 22 imported Zika cases have been reported, with 15 from Guangdong province (12 travelers returning from Venezuela; three from Samoa) [25, 26]. In Hong Kong, ZIKV infection was reported in August 2016 in a 38-year-old female traveler returning from the Caribbean; another imported case occurred in November 2016 in a 56-year-old man returning from Central America [27, 28].

4. India

Three laboratory-confirmed autochthonous Zika cases were reported to WHO in May 2017 after retrospective testing was performed on blood samples from Ahmedabad district, Gujarat state. One case occurred in a 34-year-old woman who had developed low grade fever shortly after delivering a baby in November 2016. Another case was identified after retrospective testing of 111 antenatal blood samples, with the positive sample coming from a 22-year-old woman in her 37th week of gestation. The third case was from a 64-year-old man detected by retrospective testing of 93 blood samples collected from acute fever surveillance in February 2017 [29]. Previously, a serological study in 1952 found 33/192 (17.2%) serum samples from Sangamner, Bombay state were Zika positive by cross-neutralization test, although flavivirus cross-reactivity may have confounded the results [30].

5. Indonesia

ZIKV infection was first reported from Indonesia in two Australian travelers; one returning from Jakarta in 2012 and the other from Bali in 2015 [31, 32]. Retrospective testing of 103 dengue negative blood samples from a dengue outbreak in Jambi province in December 2014 to April 2015 yielded one ZIKV infection belonging to the Asian lineage [33]. In November 2015, a Zika case in Sulawesi was confirmed by molecular and virological techniques [34]. Previously, serologic evidence of ZIKV infection had been reported from a fever study conducted in Java in 1977-1978, with 7/219 (3.2%) inpatients showing elevated Zika antibodies by hemagglutination inhibition test (HI) [35]. In addition, a study from 1983 demonstrated the presence of Zika antibodies by HI in 9/71 (12.7%) blood samples from Lombok [36]. These serological studies should be interpreted with caution given the potential cross-reactivity of the assays used.

6. Japan

Only imported Zika cases have been detected in Japan. The first three cases were reported in travelers returning from French Polynesia and Thailand in 2013-2014 [37-39]. Eight Zika cases had been reported in Japanese travelers as of September 2016 [40].

7. Korea, Republic of

The Republic of Korea has reported only imported Zika cases. The first case was confirmed by RT-PCR in March 2016 in a 43-year-old male traveler returning from Brazil. As of May 2017, 19 Zika cases had been reported in Korean travelers; eight returning from the Philippines, four from Vietnam, two from Thailand, and one each from Brazil, Dominican Republic, Guatemala, Puerto Rico, and Bolivia [16, 41, 42].

8. Lao People's Democratic Republic (PDR)

The first autochthonous Zika case in Lao PDR was reported to WHO in March 2016 [43]. Subsequently, Institut Pasteur du Laos retrospectively tested 1,353 acute blood samples from patients with suspected dengue in 2012-2013; 18/1,353 (1.3%) were Zika RT-PCR positive with 17 of 18 patients reporting no preceding travel history outside of Lao PDR [44, 45].

9. Malaysia

In September 2014, a German traveler to Malaysia was found to be positive for ZIKV [46]. Subsequently, an autochthonous Zika case was identified in September 2016, followed by another autochthonous case in a 67-year-old man from Petaling Jaya in December 2016 [47]. ZIKV has been present in Malaysia for at least several decades. The first isolation of ZIKV in Asia was from a pool of *Aedes aegypti* mosquitoes collected in Malaysia in 1966 [48]. Previous serological studies had also suggested the presence of Zika in Malaysia before then. Cross-neutralization testing of human sera from Malaysian adults from 1953-1954 showed 75/100 (75%) to have Zika antibodies [49]. Another study from the 1950's using cross-neutralization testing showed 15/79 (19%) human sera from Malaysia and 9/50 (18%) human sera from Borneo had Zika antibodies [50]. A seroprevalence study by plaque reduction neutralization test (PRNT) on sera collected from 71 wild or semi-captive orangutans and 114 humans in 1996-1997 showed Zika antibodies in 8.5% and 44.1%, respectively [51].

10. Maldives

In June 2015, one locally acquired Zika case was detected by RT-PCR in a 37-year-old Finnish man who had been in the Maldives for six months [52, 53].

11. Myanmar

Myanmar reported one locally acquired Zika case in October 2016 in a pregnant expatriate woman living in Yangon [54]. No other Zika cases have been reported by the Myanmar Ministry of Health (MoH).

12. Pakistan

Although ZIKV has not been detected in Pakistan, possibly due to the lack of a national unified arbovirus surveillance system among other potential reasons [55], a serological study from 1983 showed 1 of 43 human sera was positive for Zika by complement fixation test [56].

13. Philippines

Retrospective testing of 267 acute blood samples collected during active fever surveillance of a prospective cohort in Cebu City from 2012-2013 yielded one Zika case by RT-PCR

and virus isolation. The case occurred in 2012 in a 15-year-old boy with mild febrile illness [57]. As of February 2017, the Philippine Department of Health had reported 57 Zika cases including seven cases in pregnant women [58]. Previously, a serological study using cross-neutralization testing showed 19/153 (12.4%) human samples from 1953 had elevated Zika antibodies [59].

14. Singapore

The first reported Zika case in Singapore was an imported infection in a traveler returning from Brazil in May 2016. In August 2016, the first autochthonous case was detected in a 47-year-old female, which was eventually determined to be part of a local Zika outbreak [60]. Between 27 August and 30 November 2016, 455 Zika cases had been confirmed in this outbreak with 15 disease clusters. The estimated reproductive number decreased from 3.62 during the first month of the outbreak to 1.22 during the latter months, coincident with intensive vector control and community engagement measures [61]. Between January and June 2017, an additional 38 Zika cases had been reported by the Singapore MoH [62].

15. Taiwan

All reported Zika cases in Taiwan have been imported from Zika-endemic countries. The first case was detected in January 2016 by airport fever screening in a 24-year-old man returning from Thailand [63]. By May 2017, 14 imported Zika cases had been reported by the Taiwan Ministry of Health and Welfare [64].

16. Thailand

ZIKV infection was first reported from Thailand in early 2013 in a female Canadian traveler returning from southern Thailand [65]. Two additional traveler cases were subsequently identified in a German traveler in November 2013, and a Japanese traveler in July 2014 [39, 66]. Subsequently, retrospective testing was performed on 61 serum samples from 38 individuals in four separate fever clusters from Ratchaburi province in March 2012, Lumphun in May 2013, Sisaket in June 2013, and Phetchabun in July 2014. The four fever clusters were selected for further Zika testing based on the cluster having individuals with two of the following symptoms: rash, conjunctivitis, or arthralgia; and with negative dengue and chikungunya testing. Zika RT-PCR, PRNT and IgM/IgG ELISA revealed 7/38 (18.4%)

febrile individuals had ZIKV infection, with at least one Zika case confirmed in each of the four fever clusters [67]. In another study from Thailand, serological testing of acute blood samples from northeastern Thailand showed evidence of ZIKV infection in 2/21 (9.5%) patients with acute undifferentiated fever [68]. Between January and November 2016, the Thailand Ministry of Public Health (MoPH) had reported 686 Zika cases [69]. In September 2016, the MoPH reported the first two autochthonous cases of Zika-related microcephaly in Asia [70]. The infecting strains are unknown since genetic sequencing was unsuccessful.

17. Vietnam

Zika was first reported from Vietnam in an Israeli traveler in 2015 and a Korean traveler in 2016 [42, 71]. The first two autochthonous Zika cases were reported in April 2016 in a 64-year-old woman from Nha Trang city and a 33-year-old woman from Ho Chi Minh City [72]. In October 2016, the Vietnam MoH reported an autochthonous case of Zika-related microcephaly, with the infecting strain not able to be determined [73, 74]. A total of 219 Zika cases were reported in 2016, and 13 had been reported during the first two months of 2017 [75]. A previous study of samples collected in 1954 showed 2/50 (4%) with evidence of Zika antibodies by cross-neutralization test [49].

Zika epidemiology in Asia

Zika epidemiology and disease burden in Asia is poorly understood. As demonstrated by ZIKV isolation from mosquitoes in Malaysia in 1966, ZIKV has been present in Asia for at least the past several decades [48]. Human serological studies from the 1950's to 1990's have suggested the occurrence of human infections in India [30], Indonesia [35, 36], Malaysia [49-51], Pakistan [56], the Philippines [59], and Vietnam [49]. However, since the serological assays used in these studies may be cross-reactive with other widely circulating Flaviviruses, particularly Dengue and Japanese encephalitis, the results of these studies are not definitive. The first laboratory-confirmed autochthonous ZIKV infection in Asia occurred in Cambodia in 2010 [20]. Retrospective testing of stored blood samples confirmed an earlier human infection from Cambodia in 2007 [22], the same year as the Yap outbreak in the Pacific region. Whether the transmission intensity and geographic range of ZIKV in Asia has changed substantially over the past decade is not

known.

Recent studies have provided mixed indications about the incidence of ZIKV infections in Asia. As documented by the country-specific Zika updates listed earlier, the absolute number of cases reported by health ministries in Asia has been relatively low as compared to, for example, the number of dengue cases. However, these numbers should be assessed in light of the infrequency of routine Zika surveillance systems in Asia, and the low likelihood of Zika being considered as a diagnosis by health care providers. Case detection is also limited by the asymptomatic, mild or afebrile clinical presentation of most ZIKV infections [1]. Some studies have suggested a low incidence of Zika in Asia. A study by Institut Pasteur du Cambodge of 2,400 acute serum samples from suspected dengue patients in Cambodia found only 0.2% to be Zika positive by RT-PCR [22]. However, this result should be interpreted with caution for a couple of reasons. First, since many symptomatic ZIKV infections do not present with fever or dengue-like illness, the choice of samples from suspected dengue patients may have decreased the likelihood of detecting a positive Zika case. Second, ZIKV infections generally result in relatively low viremia, leading to a lower likelihood of detecting ZIKV in acute blood samples by RT-PCR [76]. Nevertheless, five detected Zika cases occurred over an extended period of time from 2007 to 2015, suggesting ongoing ZIKV circulation in Cambodia over that multiyear period. Interestingly, in the neighboring country of Lao PDR, Institut Pasteur du Laos conducted a similar retrospective study of 1,353 acute blood samples collected in 2012-2013. That study found a higher percentage (1.3%) to be Zika RT-PCR positive [45], even though the same caution would apply when interpreting the Lao PDR study as the Cambodia study.

Conversely, some studies hint at more widespread transmission of ZIKV in Asia. The detection of Zika cases in visitors from Zika non-endemic areas to Indonesia [31, 32], Thailand [39, 42, 63, 65, 66], Malaysia [46], Vietnam [42, 71] and Philippines [42] suggests the possibility that substantial transmission had been occurring in these Asia countries. With increased public health testing for ZIKV after the Americas epidemic, many Asian countries began to report Zika cases in 2016. The number of countries in Asia reporting autochthonous cases is notable, indicating a wide geographic range. Some Asian countries have reported a fairly substantial number of cases. For example, Thailand reported 686 cases between January and November 2016, which is probably a gross underestimation, given the limitations mentioned earlier. A study of four fever clusters from Thailand also suggests substantial transmis-

sion [67]. Although the four fever clusters were selected based on specific criteria, these criteria may not necessarily have made Zika detection more likely. And yet, a reasonably high percentage (18.4%) of tested individuals was confirmed to have ZIKV infection. It is also notable that these infections were confirmed in four geographically distant provinces over a three year period, suggesting widespread and multiyear circulation in Thailand. A cohort study undertaken in Cebu also hints at more widespread transmission [57]. This cohort consisted of 1,008 enrolled subjects of whom 854 completed all study activities after 12 months, undergoing 868 person-years of active fever surveillance that was not specifically targeted to detect ZIKV infections [77]. Although only 1/267 (0.4%) acute fever samples was Zika RT-PCR positive, this translates to a point incidence estimate of 0.12 infections per 100 person-years of surveillance in the cohort. However, the use of active fever surveillance to trigger blood collections precluded the detection of any non-febrile symptomatic ZIKV infections, and the use of RT-PCR alone to test acute blood samples would have missed any ZIKV infections otherwise detectable by serological assays. Furthermore, asymptomatic and subclinical infections would have been undetectable by active surveillance. Therefore, the point incidence estimate of 0.12 ZIKV infections per 100 person-years of surveillance may be an underestimation of actual incidence. This, of course, is based on just a single case, and so should be treated with some caution.

The Zika outbreak in Singapore has been the only sizable outbreak documented in Asia. Interestingly, the ZIKV strain responsible for this outbreak was more closely related to circulating ZIKV strains in Asia than to strains responsible for the Americas epidemic [61]. Why, then, did this outbreak occur in 2016 even though repeated introduction of similar ZIKV strains from other Asian countries has likely been occurring before? Could other potentially relevant factors such as pre-existing population immunity to dengue have affected the ability of ZIKV to gain hold in Singapore? A more likely explanation is that Zika outbreaks have indeed occurred in Singapore as well as elsewhere in Asia, but remained undetected. This is made more likely due to the asymptomatic or mild nature of most ZIKV infections.

To more definitively investigate the incidence of ZIKV infection in Asian countries, well designed seroprevalence studies and prospective cohort studies would be extremely informative. Cohorts could undergo active surveillance for febrile and non-febrile illnesses to detect most symptomatic ZIKV infections, and periodic blood collections to assess Zika seroconversion rates. Absolutely critical to these studies would be the

use of accurate serological assays with minimal cross-reactivity with other Flaviviruses. The current lack of such serological assays has been a critical shortcoming in accurate evaluation of ZIKV transmission in Asia.

Zika-related neurological complications in Asia

Zika alone would be of relatively less interest to public health officials if it were not for the association between ZIKV infection in pregnant women and microcephaly in their newborns. Therefore, the question of ZIKV transmission in Asia needs to be linked to the question of whether central nervous system (CNS) complications occur in Asia, and with what frequency. There have been very few reported cases of Zika-associated neurological complications in Asia. Up to now, only two cases of Zika-related microcephaly in Thailand and a single case in Vietnam have been reported. In all three cases, the infecting virus could not be sequenced. Therefore, the relationship of the virus to those strains already circulating in Asia versus strains from the Americas could not be determined. One qualifier to this low number of cases is the low sensitivity of existing reporting systems in Asia to detect such complications, although these systems have been strengthened in some Asian countries [70]. An increase in microcephaly in Bahia state of Brazil was noticed only after an explosive Zika epidemic occurred. It is also noteworthy that an increase in CNS complications during the French Polynesia outbreak was only noted retrospectively following heightened awareness due to the Zika epidemic in Brazil [78]. Similarly, there have been no Zika-related cases of GBS reported to the WHO from Asia [15]. Whether the paucity of reported neurological complications from ZIKV infections in Asia is due to limitations in surveillance systems, host population factors, viral strain differences, or other reasons, determination of the true incidence of Zika-related neurologic complications in Asia is critical. Prospective studies of ZIKV-infected pregnant women and their newborns, and retrospective studies of infants with CNS abnormalities to assess for evidence of maternal ZIKV infection would be highly informative. Prospective and retrospective studies of GBS cases should also be performed to assess for evidence of preceding ZIKV infection.

Infectivity and transmission

If fundamental differences in Zika epidemiology and burden

do exist between Asia and the Americas, viral differences in infectivity between strains from Asia and the Americas could be partly responsible. ZIKVs are divided into two lineages: African and Asian lineage. All recent infecting strains from countries in Asia and the Americas belong to the Asian lineage [21, 79]. Laboratory-based studies assessing possible differences in infectivity and vector competence between African and Asian lineage viruses, and between viruses from Asia and the Americas, have not demonstrated a consistent pattern [80-83]. One important contributing factor to these conflicting findings may be the frequent use of highly passaged viruses with adaptive mutations from cell-culture or mouse passage [84]. Use of low passage viruses or use of *de novo* generated viruses selected from geographically and clinically diverse sources may be necessary [84].

Conclusion

A better understanding of Zika epidemiology and burden in Asia is critical for researchers and public health officials to develop and implement appropriate strategies for prevention and control. Determining the scope of the Zika threat in Asia is likely to have many repercussions, not the least of which is to provide a strong rationale for continued active pursuit of a Zika vaccine. Many questions remain as to whether and why Zika may behave differently in Asia than the Americas. Differences in virus virulence and transmission have been the subject of great interest. Probably the most pressing requirement currently is to determine the actual incidence of Zika-related neurological complications in Asian countries. Challenges in doing so will include the relatively low symptomatic proportion of infections, difficulties in virus detection, and the lack of accurate serologic assays. Nevertheless, conducting appropriate studies in order to clarify these issues will be necessary to effectively counter the Zika threat.

Conflicts of Interest

No conflicts of interest.

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