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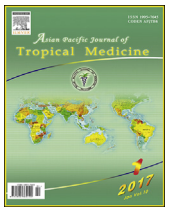

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Zika virus from a Southeast Asian perspective

Nitwara Wikan[1], Duncan R. Smith[1,2]✉

[1]Institute of Molecular Biosciences, Mahidol University, Thailand

[2]Center for Emerging and Neglected Infectious Diseases, Mahidol University, Thailand

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ABSTRACT

Phylogenic evidence suggests that the strain of Zika virus causing an unprecedented outbreak of disease in the Americas had its origin in Southeast Asia, where reports of isolated cases of Zika virus infection have occurred since 2010. Why there has been no large outbreak of Zika infection in Southeast Asia remains unclear and whether such an outbreak will occur in the future is a question of significant concern. This review looks at Zika virus from a Southeast Asian perspective and highlights some of the possible scenarios with regards to Zika virus in this part of the world as well as highlighting some of the research questions that need to be urgently addressed.

1. Introduction

The history of Zika virus, from the first isolation from a sentinel monkey exposed in the Zika Forest near Entebbe, Uganda in 1947 to its current status as a public health emergency of international concern has been comprehensively reviewed elsewhere [1]. Despite the origins of the current outbreak in South, Central and North America which trace its roots to a Zika virus from Southeast Asia, little attention has been paid to Zika virus in this part of the world, and in particular the current and future impact of transmission of Zika virus in a region home to more than a half a billion people remains largely unexplored.

Serological studies published in the late 1950s and 1960s, often describing samples collected several years before publication, showed a wide geographic footprint for Zika virus in Southeast Asia, ranging from Pakistan [2] to the Philippines [3]. Despite this however, there was only one reported small cluster of disease associated with Zika virus in Southeast Asia which occurred in Indonesia in 1977/1978 [4]. However, in the last six years, the presence of Zika virus in Southeast Asia (Table 1) has been established directly in Cambodia [5], the Philippines [6], Thailand [7] and Indonesia [8] as well as indirectly in Malaysia through a visitor to Malaysia who was diagnosed with Zika virus infection on their return to their home country [9]. The presence of Zika virus in both Thailand and Indonesia was similarly first indicated by indirect evidence based on tourists to those countries [10–13], and tourists to Southeast Asia continue to be diagnosed with Zika infection upon their return to their home country [14]. Overall however, the evidence clearly establishes the widespread and long term (at least 6 years based on virological evidence and as much as 60 years based on immunological evidence [3,15,16]) presence of Zika virus in Southeast Asia, and yet circulation of this virus has not been associated with a significant disease outbreak.

The significant question is therefore why Zika virus has been circulating in much of Southeast Asia for many years, and yet has not been associated with an outbreak on the scale of that occurring in the Americas. In addition there has been no

First author: Nitwara Wikan, Institute of Molecular Biosciences, Mahidol University, Salaya Campus, 25/25 Phuttamonthon Sai 4, Salaya, Nakhon Pathom 73170, Thailand.
Tel: +66 (0) 2441 9003 to 7
Fax: +66 (0) 2441 1013.
✉Corresponding author: Duncan R. Smith, Molecular Pathology Laboratory, Institute of Molecular Biosciences, Mahidol University, Salaya Campus, 25/25 Phuttamonthon Sai 4, Salaya, Nakhon Pathom 73170, Thailand.
Tel: +66 (0) 2441 9003 to 7
Fax: +66 (0) 2441 1013
E-mails: duncan_r_smith@hotmail.com, duncan.smi@mahidol.ac.th
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Table 1
Summary of recent (2010–present) cases of Zika virus infection in Southeast Asia.

Country	Case year	Diagnosis method	Cases	Resident/tourist	References
Cambodia	2010	RT-PCR, sequencing	1	Resident	[5]
Indonesia	2013[a]	RT-PCR, sequencing	1	Tourist	[11]
	2015[a]	RT-PCR, sequencing	1	Tourist	[12]
	2014/2015	Virus culture/RT-PCR sequencing	1	Resident	[8]
Malaysia	2014	Serology	1	Tourist	[9]
Philippines	2012	RT-PCR, virus recovery and sequencing	1	Resident	[6]
Thailand	2013	RT-PCR, sequencing	1	Tourist	[10]
	2013	Serology	1	Tourist	[13]
	2012–2014	RT-PCR, serology	7	Residents	[7]
	2014	RT-PCR, serology	1	Tourist	[14]

[a] No year of presentation of patient given explicitly in publication.

apparent reported increase of cases of Guillain–Barre syndrome in adults or microcephaly in newborns in the region as seen with the outbreaks in French Polynesia and Central and South America (reviewed in Ref. [1]). The evidence would suggest that two (not necessarily completely exclusive) possible mechanisms exist that account for the vastly different nature of the virus in the two populations (Southeast Asian and South, Central and North American), with the population impact being predominantly mediated by either virological or immunological consideration.

2. Zika virus in Southeast Asia: transmission

Zika virus is a mosquito transmitted flavivirus [1] and these flaviviruses are normally maintained in nature by transmission between mosquitoes and non-human primates, rodents or birds, although for Zika virus specifically neither birds nor rodents have been implicated in maintenance of the virus. For some flaviviruses, such as Japanese encephalitis virus, infections of humans occurs as a result of spill over from this transmission cycle and human infection is a dead end for transmission, as the levels of human viremia are too low to support subsequent transmission to a mosquito [17]. In other cases, such as infection with dengue virus, human infection can result in considerable viremia allowing the establishment of urban transmission cycles [18] in the presence of a suitable mosquito vector. While enzootic transmission cycles are normally maintained by forest dwelling mosquitoes, urban transmission cycles are generally maintained by anthropophilic mosquito species such as *Aedes aegypti* and *Aedes albopictus* (*Ae. albopictus*).

To date, no natural reservoir of Zika virus has been identified in Southeast Asia. Non-human primates have been implicated as potential reservoirs in Africa (reviewed in Refs. [1,19]), and it is likely these play a role in maintaining the virus in Southeast Asia. Interestingly, Zika virus was originally identified [20] in a Rhesus macaque (*Macaca mulatta*), a species not native to Africa. In Southeast Asia, Rhesus macaques are only indigenous in Burma, northern Thailand and Vietnam, and their range does not extend to other countries with known transmission in Southeast Asia including Cambodia, Indonesia and the Philippines [21]. Thus, Rhesus macaques are unlikely to be a significant reservoir in Southeast Asia. Other macaque species such as the long-tailed macaque (*Macaca fascicularis*) are indigenous in all countries where Zika virus has been identified in Southeast Asia [22] and thus perhaps warrant specific surveillance for Zika virus. It is noteworthy that one reported case of transmission of Zika virus in Indonesia is reported to have occurred after a monkey bite in Ubud Monkey Forest [12] where the monkey species present is *Macaca fascicularis*, although transmission by mosquito bite cannot be formally excluded. While transmission of flaviviruses through animal bites is a poorly documented occurrence, the presence of Zika virus in saliva (reviewed in Ref. [1]) would indicate this is a viable transmission route.

Surveys have suggested that Southeast Asia (Burma, Thailand, Malaysia, Singapore, Indonesia, Philippines, Borneo, Brunei, Vietnam, Laos and Cambodia) is home to some 871 mosquito species and 18 subspecies in 21 genera [23]. These species include mosquitoes implicated in Zika virus transmission (reviewed in Refs. [1,19]) such as *Aedes vittatus* (originally described as *Culex vittatus*), *Ochlerotatus vigilax* (previously known as *Aedes vigilax*), *Aedes aegypti* and *Ae. albopictus* all which are distributed widely in Southeast Asia [23]. While it is known that mosquito populations can show marked differences in their ability to transmit flaviviruses, Southeast Asian *Ae. albopictus* have been shown to be competent transmission vectors for Zika virus [24], and the range of potential vector species present would suggest this is not a limiting factor in Zika virus transmission in the region. However, a change in the mosquito transmissibility of Zika virus occurring between Southeast Asia and French Polynesia cannot be excluded. In particular the lesson from the outbreak of Chikungunya virus in and around the Indian Ocean from 2004 to 2009 was that a relatively small change in viral genotype could have profound effects on viral transmissibility and epidemic potential [25].

The scattered cases of Zika virus in Southeast Asia have occurred in a population of over half a billion people, spread over an area of more than 4.5 million km^2. The rare occurrence of the observed cases despite the widespread presence of suitable transmission vectors would argue strongly against Zika virus being maintained in an urban transmission cycle in this region, and would suggest that the cases seen to date are spill over from the sylvatic maintenance of this virus in nature.

The cases reported recently for both indigenous infection in Southeast Asia [5–8] and infection of tourists to Southeast Asia [9–13] have generally been characterized by relatively mild disease, with fever, muscle and joint pain and sometimes rash and headache as the main symptoms reported, although some possible neurological deficit in one tourist has been reported [9]. While it is possible that additional cases of infection have occurred in these countries in which infected people did not seek treatment as a consequence of mild symptoms, or that cases have been misdiagnosed as infections with the highly

similar dengue virus which is endemic in the region [26] as even with detailed serological investigations Zika virus infections can give positive results in dengue virus immunological assays [27], the evidence does not support large scale infections with Zika virus ongoing in this region.

As noted previously, the level of viremia during infection is a key factor in facilitating urban transmission. Given the scattered and isolated nature of the cases occurring in Southeast Asia, there is no solid data on levels of viremia seen during infection. The nearest parallel to the situation in Southeast Asia would be the outbreak seen in Yap State in 2007 where there were 49 confirmed cases of Zika infection, and the level of viremia observed there was reported as low, and indeed it did not prove possible to isolate the virus from blood of infected patients [28]. Thus it would seem likely that the virus circulating in Southeast Asia produces a low level of viremia, precluding the establishment of an urban transmission cycle. While the Yap State strain of Zika virus clearly had a Southeast Asian origin, it most likely represents a separate strain of the virus from the strain that caused the French Polynesia and South and Central America outbreaks. However, a low level of viremia in the cases of Zika virus infection seen in Southeast Asia would support the notion that the cases seen represent enzootic cycle spill over.

3. Zika virus in Southeast Asia: virological considerations

There is some supporting evidence of a gradient of Zika virus pathogenicity, with reported indigenous Southeast Asian and Yap State cases being relatively mild, with increased cases of severe disease being reported from the French Polynesia outbreak, in particular with regards to the number of cases of Guillain–Barre syndrome [29]. While the first reports of microcephaly in fetuses and newborn infants came from Brazil [30,31], a recent study documented the existence of fetal brain anomalies including microcephaly as a consequence of the outbreak in French Polynesia [32]. In support of the association between Zika virus and microcephaly, the virus has been recovered from the brain of fetuses aborted for reasons of microcephaly [33]. A recent study that showed high susceptibility of human neuronal progenitor cells to Zika virus [34] used a strain of the virus reported to be closely similar to the original Zika virus isolate [20], and thus of an African lineage. However, more recent studies have shown signs of microcephaly in mice, and infection of human cortical progenitor cells leading to cell death with a Brazilian isolate [35] and infection of primary human fetal neural progenitors and subsequent cell death with an isolate from Puerto Rico [36]. Interestingly, the early reports of Zika virus highlighted the strong neurotropism of this virus seen in mice [37]. Several studies have now determined the sequence of recent isolates associated with the outbreak in South, Central and North America, with a particular focus on isolates associated with microcephaly and while a number of amino acid substitutions have been observed in these isolates, detailed analysis has shown that isolates from microcephaly cases do not have common substitutions [38], suggesting that neurotropism is an inherent rather than a recently acquired attribute of Zika virus.

Critically however, to date there has been no study investigating neurotropism of the indigenous Southeast Asian Zika virus, and as such it is difficult to establish whether the indigenous Southeast Asian strain is a risk to the childbearing population in this region, and whether there has indeed been an increase in neuropathogenicity of Zika virus as it has spread around the globe.

4. Zika virus in Southeast Asia: immunological considerations

Dengue is endemic in all Southeast Asian countries and studies in Thailand have suggested that more than 95% of adults in Thailand have neutralizing antibodies to at least one of the four dengue virus serotypes [39]. In addition, many countries in Southeast Asia, including Thailand have active vaccination campaigns for protection against Japanese encephalitis virus, with high levels of coverage [40]. It is possible that natural or acquired immunity to multiple flaviviruses has a protective effect against indigenous strains of Zika virus, resulting in either immunity or dramatically reducing disease severity. However, countering this argument is the widespread circulation of dengue in Brazil, and in addition, it is clear that vaccination against yellow fever virus, a related flavivirus does not offer protection against Zika virus infection [41]. Cross-reactive immunological protection for the peoples in Southeast Asia against indigenously circulating Zika virus is an attractive proposition as this suggests that Zika virus does not, and will not present a significant and long term threat. However, on balance it seems unlikely that this is supported based on the evidence. A recent serosurvey in Thailand [42] showed evidence of antibodies that detected Zika virus E protein in a high proportion of samples. While it is likely that in many cases the antibodies represent cross-reacting antibodies to dengue virus (through natural infection) or to Japanese encephalitis virus (through vaccination), in some cases antibodies to only Zika virus E protein were detected (and not Japanese encephalitis virus or dengue E proteins). As such there is a small possibility that Zika virus is circulating in Thailand and elsewhere in Southeast Asia at a much higher level that is currently supposed with little or no clinical symptoms associated with infection. In this scenario, the population of Southeast Asia could be already largely protected against Zika virus. However, given the intensive screening for flaviviral infections in humans and mosquitoes over much of Southeast Asia, this scenario again seems unlikely. Of particular concern are recent studies that have shown that antibodies directed against Zika virus envelope protein domain I/II can enhance DENV infection [43], and conversely antibodies against DENV can enhance Zika virus replication [44]. In countries such as those in Southeast Asia with high seropositivity to DENV, and apparent low transmission of Zika, this could indicate a future large scale outbreak.

5. Conclusions

Zika virus has been present and circulating throughout much of Southeast Asia for between 6 [5–13] and 60 years [3,15,16] and the current pattern of cases observed to date is consistent with spillover from sylvatic transmission cycles. The major concern for the population of Southeast Asia is that the virus has undergone a marked change that has made the virus more transmissible through either a mosquito adaptation, or through an increase in levels of human viremia. In this case the virus could ‘return’ to Southeast Asia, and in a devastating form. This could be potentiated by the widespread DENV

seropositivity, and the enhancement of Zika virus replication by pre-existing anti-DENV antibodies [44]. Urgent questions that need to be addressed are the true levels of circulation of Zika virus in Southeast Asia, a more comprehensive understanding of the immunological status of peoples in Southeast Asia, as well as increased knowledge of the relative pathogenicity of the indigenous strain of Zika virus, particularly with regards to its neurotropic potential. In addition, active and ongoing surveillance for cases of Zika virus, together with enhanced mosquito control programs are urgently required.

Conflict of interest statement

The author declares no conflict of interest.

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