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REVIEW

# Zika virus in Vietnam, Laos, and Cambodia: are there health risks for travelers?

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## Abstract

Vietnam, Laos, and Cambodia have reported first cases of Zika virus (ZIKV) infection since 2010 (Cambodia) and 2016 (Vietnam and Laos). One case of ZIKV-related microcephaly was recognized among a hundred infected cases in these areas, raising a great concern about the health risk related to this virus infection. At least 5 cases of ZIKV infection among travelers to Vietnam, Laos, and Cambodia were recorded. It is noticeable that ZIKV in these areas can cause birth defects. This work aims to discuss the current epidemics of ZIKV in Vietnam, Laos, and Cambodia and update the infection risk of ZIKV for travelers to these areas.

**Keywords** Zika virus infection · Travelers · Zika virus–infected travelers · Vietnam · Laos · Cambodia

## Introduction

Zika virus (ZIKV) is a mosquito-transmitted flavivirus, and ZIKV infection is considered as an acute infectious disease [1]. ZIKV is spread mostly by an *Aedes* species vector known to be *Ae. aegypti* or *Ae. Albopictus*, which are also the most mode of transmission of chikungunya and dengue. During blood meal, the mosquitoes are infected by ZIKV circulating in the blood of viremic humans. After the extrinsic incubation period, the presence of ZIKV in mosquito saliva can be transmitted to other humans via a bite [1]. ZIKV non-vector transmission has been reported by mother-to-child transmission during pregnancy, sexual transmission, transfusion of blood and blood products, and organ transplantation [2]. The key measure for ZIKV infection prevention is to protect yourself from being bitten by mosquitoes during the day and early evening as guided by the World Health Organization (WHO) [1]. The most common clinical manifestations of ZIKV infection are fever, rash, headache, myalgia, conjunctivitis, and arthralgia [3]. The current situation of ZIKV presence and circulation is complex, and most previous publications have given uncertain explanations for herb immunity. The most

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interesting hypothesis is natural or acquired immunity to multiple flaviviruses which plays a crucial role in the protection against indigenous ZIKV strains [4–6].

The widespread and long-term presence of ZIKV throughout many countries of Southeast Asia between 6 years (based on virological evidence) and 60 years (based on immunological evidence) has been documented [7–11]. Researchers found that ZIKV could be more transmissible in the Southeast Asian population due to the adaptation of mosquitoes and an increase in levels of viremia in human [6]. We lack knowledge of immune response of ZIKV in Asian areas [6] and currently, there are no specific estimates of the pre-existing immunity to ZIKV throughout Southeast Asia [6]. There are some challenges in researching of ZIKV immunity. Firstly, the duration of protective immunity to ZIKV has not been clearly established, although the previous studies indicated that the infection of ZIKV contributes to lifelong protection [12]. Secondly, the Dengue virus antibodies have been given to be cross-reactive with ZIKV [13–15]; this may reduce the intensifying effects and protective possibility of the Dengue virus antibodies among confirmed individuals with ZIKV infection [15]. Thirdly, cross-reactive Dengue virus antibodies create a challenge to define the serological assays for the previous infection of ZIKV. Therefore, it is difficult to assess the level of pre-existing immunity of infected people in the tropical countries and territories such as Southeast Asia where there is frequent circulation of Dengue virus annually.

In comparison with other areas in the world such as in America, the number of confirmed cases with ZIKV disease in Southeast Asia was lower [16, 17]. An explanation could be the widespread background immunity in the population [18]. In 2016, there were 8 out of 11 countries in Southeast Asia that reported the presence of ZIKV. At present, Myanmar, Lao People's Democratic Republic, and Timor Leste lack of published information about ZIKV [16]. Overall, in Southeast Asia, ZIKV in the non-island countries has been reported more frequently than in the island countries [16]. In Thailand, they saw the prevalence of ZIKV in 30 over 76 provinces from four regions—the central, north, east, and west of Thailand with a total of 115 pregnant women who have confirmed of ZIKV infection [4]. Not only the local ZIKV infection cases have been confirmed but also several cases have been reported in travelers[1] returning from Southeast Asian countries, particularly 3 cases in Thailand and 2 cases in Indonesia [16, 19]. Moreover, ZIKV has many similar symptoms (fever, headache, myalgia, arthralgia, and maculopapular rash) with other arboviral infections, such as dengue or chikungunya fever [20]. Interestingly, the ZIKV incubation period in *Aedes* mosquitoes was also similar to that of dengue virus or other arboviruses. While the estimated incubation period of Zika among infected patients ranges from 3 to 14 days [21], the figures are from 1 to 12 days for chikungunya [22] and from 3 to 14 days for dengue [23]. Therefore, it is not easy to diagnose exactly ZIKV infection in the rural areas where specific diagnostic tests are lacking [24, 25] which are the recommended tests for each specific case like RNA nucleic acid test (NAT) testing, Zika virus IgM testing, and reverse-transcription polymerase chain reaction (RT-PCR) [26].

[1] Traveler is someone who visits a foreign country for pleasure and interest or work.

## Zika virus infection in Vietnam, Laos, and Cambodia

### Vietnam

In early 2016, Vietnam reported the first case of ZIKV infection in humans, and at least 232 other cases were detected in this country ever since [27]. Recent data have indicated that the current ZIKV epidemic in Vietnam mostly spreads across the south and the central Highlands, whereas no cases have been recorded in the north [28]. The explanation may be partly considered that, in the south of Vietnam, there is a hot and humid climate all year round, chartered with the rainy season and the dry season; hence, it is a convenient condition for the development and reproduction of mosquito vectors of ZIKV, particularly *Aedes m*osquito species known popular in the country with tropical wet climate. In contrast, *Aedes* mosquitoes have not survived the winter in the north. There exist the spread risks for local people inside this country due to the high mobile traveling population from the south to the north and around the country, especially during holiday seasons [28]. There is, so far, no evidence identifying the local ZIKV strain which is present only in Vietnam, but a hypothesis may exist that ZIKV circulation strain in this country is highly related to other Asian countries' strains belonging to the Asian lineage [28]. Recent studies documented that the Asian strains seem to be less virulent than the African strains. ZIKV infections in infected humans caused by both African and Asian strains present the common clinical manifestations including fever, rash, headache, myalgia, conjunctivitis, and arthralgia [29–31]. Nevertheless, several in vitro and in vivo experiments have indicated that ZIKV infections with African strains are characterized by more severe neurological symptoms, while neurological symptoms caused by the Asia strains are more protracted [29]. In June 2016, Vietnam reported the first case of microcephaly in a newborn girl whose mother was likely to be exposed to ZIKV during the second trimester [28, 32]. A new study has shown that ZIKV in Vietnam can cause the infection in fetus, which raises more awareness about health risks among travelers, especially pregnant women visiting this country [33]. The genetic analyses have indicated that the ZIKV strains in Vietnam belong to Asian [27, 33–35] or American lineage [36].

### Laos

Lao People's Democratic Republic reported the first event of ZIKV in 2016 [37, 38]. This was an autochthonous case of virus infection [38], but the information on ZIKV in this country is limited. No information on travelers infected with ZIKV in this country has been recorded.

### Cambodia

Several cases of ZIKV infection in Cambodia have been detected since the first case was reported in August 2010 [6, 37, 39–41]. The ZIKV strains isolated from patients in this country are genetically close to the strains circulating in America and the Pacific [37, 40, 42]. However, a new study has shown that viruses isolated from a traveler having visited Cambodia belong to Asian lineage [43].

As in Vietnam, ZIKV in Cambodia has had low prevalence and low-level impact on public health [40]. In animal models of Zika virus infection, the Cambodia ZIKV strain (CAM/2010) caused less severe microcephaly than the virus isolated from Venezuela (VEN/2016) [44]. Furthermore, the CAM/2010 was also reported to be less infectious in mosquito *Aedes aegypti* than the strain circulating in America [45].

## Infection risks of Zika virus for travelers to Vietnam, Laos, and Cambodia

Since the presence of ZIKV was first detected in Vietnam, Laos, and Cambodia, hundreds of local cases were reported in these areas in 2016; however, there have been only 5 reported cases of this virus infection among travelers who have been to Vietnam and Cambodia since January 2016 (Table 1). There were no reported cases of travelers who were infected with ZIKV from Laos (Table 1).

One of the first travelers who suffered from ZIKV infection in these three countries was a 61-year-old Israeli man who visited Hoi An, Hue, and Ho Chi Minh City in Vietnam in December 2015 [34, 35]. After traveling to Hong Kong for 2 other days, he returned to Israel and experienced symptoms of virus infection (headache, fever, and malaise) [34]. The presence of ZIKV was then detected on his blood by both RT-PCR and serologic tests [34].

Two first other travelers who were exposed to ZIKV in Vietnam were a German woman staying in Ho Chi Minh City from August 2015 to August 2016 and a Japanese man visiting Ho Chi Minh City in November 2016 [27, 36]. After that, when one of them traveled to Japan in September 2016 and another in November 2016, they revealed symptoms of back pain, conjunctivitis, and rash (German patient) or only conjunctivitis and rash (Japanese patient) [27, 36]. Doctors diagnosed ZIKV infection in these patients, and ZIKV was detected and isolated from the urine (German patient case) or urine specimen (Japanese patient case) [27, 36]. Another case of ZIKV infection in travelers visiting Vietnam was one from South Korea; however, the information on this case is still limited [41].

ZIKV infection was also diagnosed in one healthy Chinese traveler who had a business trip to Cambodia for 7 days in October 2016. He was found ill with the ZIKV symptoms (high fever, muscle pain, and chill) when returning to China in November 2016 [43]. The laboratory tests detected ZIKV on his blood serum [43]. This was the first ZIKV infection case reported with the typical Zika symptoms accompanied by severe liver injury as well as coagulation disorders [43].

Since the ZIKV infection cases reported in Vietnam, Lao, and Cambodia, overall, for follow-up health care and treatment for these cases, the health authorities in these countries adequately provided infected individuals with the information about potential risks of ZIKV infection and assessed individuals' clinical signs and symptoms with individualized risks, as well as implemented measures for monitoring pregnant women's health status and timely detect possible fetal complications of ZIKV infection. ZIKV diagnostic tests remain unavailable to most clinical settings in these countries, only prior to several prestigious health settings with modern laboratory

**Table 1** The reported cases of Zika virus infection in travelers to Vietnam, Laos, and Cambodia

| No | Cases of travelers | Citizen | Visited country, time | Diagnosed in the country, time | Reference |
|---|---|---|---|---|---|
| Vietnam | | | | | |
| 1 | 61-year-old man | Israel | Vietnam, December 2015 | Israel, December 2016 | [34] |
| 2 | Korean traveler | Korean | Vietnam, 2016 | Korean, 2016 | [41] |
| 3 | 40-year-old man | Japanese | Vietnam, November 2016 | Japan, November 2016 | [27] |
| 4 | 49-year-old woman | Germany | Vietnam, 2015–2016 | Japan, September 2016 | [36] |
| Laos | | | | | |
| 0 | No case in traveler was reported | | | | |
| Cambodia | | | | | |
| 1 | 29-year-old man | Chinese | Cambodia, October 2016 | China, November 2016 | [43] |

and experienced laboratory personnel [37, 46, 47]. Hence, it seems challenging to estimate the current ZIKV epidemic in Vietnam, Laos, and Cambodia for all real Zika virus–infected individuals (the local cases and the cases among travelers returning from these countries), although there have been numerous historical and scattered reports of cases of ZIKV from the continents in the world [48]. In a recent review of significant epidemics of ZIKV in Thailand [4], there is currently no clear evidence of the level of immunity against ZIKV in populations in Southeast Asia. Besides the hypothesis of existing background immunity, we need further studies for the health risks of ZIKV infection in Southeast Asia. The Isaac I. Bogoch report showed that Southeast Asian countries have a higher level of travel-associated transmission of ZIKV based on the number of travelers coming from America which had a high prevalence of ZIKV [49]. In addition, according to the reports on the tourism, a high number of the travelers arriving in Vietnam, Lao, and Cambodia in this year (2016) are estimated at 10 million [50], 4 million [51], and 5 million [52], respectively. The number of cases of ZIKV-infected travelers who were in Vietnam, Laos, and Cambodia in the current epidemic period indicates the potential health risks for travelers visiting these areas, although the number of confirmed cases in travelers from these three countries in this review is remarkably lower compared with the data from other endemic regions. Previous studies demonstrated that 93 cases returning from America and 10 cases from the Pacific were infected with ZIKV [35, 53], in comparison with 3 cases of ZIKV infection returning from Thailand [16, 19]. About travelers from Africa, the data from a GeoSentinel analysis (2012–2016) showed only one case of traveler returning from Africa [35]. The high number of ZIKV infection cases in America with more virulent strain is due to a combination of factors, including favorable climatic conditions for the mosquitoes' development, ZIKV non-vector transmission like sexual transmission or transfusion of blood and blood products, and a population with high mobility [54]. Notably, ZIKV in Vietnam was found to have the capability of infecting the fetus during pregnancy [33]. However, the infection rates among travelers in Vietnam, Laos, and Cambodia are very low and the virulent strain circulating in these areas is less than that in America.

Available information for Zika in some countries may not be updated in national reporting and monitoring systems [55]. From perspectives in Vietnam, Laos, and Cambodia, we want to note that travelers should learn and heed about the emerging issues of ZIKV disease in the place they plan to visit, no matter how many times they have visited the country. We also suggest that further studies should be considered to explore knowledge gaps of the socioeconomic factors leading to ZIKV outbreak: the correlations among other flavivirus infection and the ZIKV infection severity level, the ZIKV immune formation duration, and the level of immunity in the community required to prevent ZIKV re-circulation.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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**Informed consent** Not necessary; this is a review.

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