

Transmission of Four Serotypes of Dengue Virus in Several Asian Countries Literature Review

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ABSTRACT

Background: The serotype of the virus that causes infection in a person can influence the severity of the dengue disease experienced so it is necessary to monitor and understand the dengue virus serotypes circulating in an area. **Method:** We searched for studies through two electronic databases (Pubmed and Science direct). In the first stage, database search, 74 studies were obtained. The criteria for including studies were four human dengue virus serotypes published in 2013 – 2023. In the final search there were 10 studies included. **Results:** Serotypes DENV-1, DENV-2, DENV-3 and DENV-4 have been reported in Singapore but DENV1 and DENV-2 are the main causes of dengue cases in this country. Serotypes DENV-1, DENV-2, DENV-3 and DENV-4 have been reported in Indonesia but the prevalence of certain serotypes can vary from year to year and between regions in the country. Serotypes DENV-1, DENV-2, DENV-3 have been reported in Nepal but DENV-2 is found in high altitude and cold weather areas. Serotypes DENV-1, DENV-2, DENV-3 and DENV-4 have been reported in Pakistan but serotype DENV-1 is the main cause of dengue cases in this country. Serotypes DENV-1, DENV-2, DENV-3 and DENV-4 have been reported in India, however serotype DENV-4 was found to be the main cause of dengue cases both alone and in combination with dengue causes in this country. Serotypes DENV-1, DENV-2, DENV-3 and DENV-4 have been reported in Thailand but serotype DENV-2 is the main cause of dengue cases in this country. Serotypes DENV-1, DENV-2, DENV-3 and DENV-4 have been reported in Sri Lanka but serotype DENV-2 is the main cause of dengue cases in this country. Serotypes DENV-1, DENV-2, DENV-3 and DENV-4 have been reported in China but serotype DENV-2 is the main cause of dengue cases in this country.

Conclusion: Countries in Asia remain endemic for all four DENV serotypes, although some genotype-related evolution has been found in certain strains.

Key words: Asian Countries, Dengue Virus, Serotypes, DENV-1, DENV-2, DENV-3, DENV-4.

INTRODUCTION

Dengue is an infectious disease caused by infection with the dengue virus (DENV) which is transmitted by mosquitoes *aedes aegypti* and *Aedes albopictus* who are infected¹⁻⁴. About half of the world's population is now at risk of dengue fever with an estimated 100–400 million infections occurring each year⁵. Dengue is found in tropical and sub-tropical climates, mostly found in urban and semi-urban areas⁶⁻⁸ and they breed in places with stagnant water, such as bathtubs, flower vases, or water reservoirs that are not properly sealed⁹⁻¹¹ as well as the large number of non-degradable single-use containers that function as breeding grounds in the household environment for the main vector¹². Dengue infection can occur through a human-to-mosquito-to-human cycle¹³. Mosquitoes that bite people infected with the Dengue virus will become carriers of the virus and can transfer the virus to other people when they bite them¹⁴. Apart from that, the spread of the Dengue virus also occurs through international travel. If a person is infected with Dengue in one area and goes to another area with a vector mosquito population, they can spread the virus to a new area if they are bitten by a mosquito and the mosquito becomes infected.^{15,16}.

Vector control remains the most effective method to reduce the risk of spreading the dengue virus¹⁷ and will likely remain a major component in

suppressing dengue fever cases even if the vaccine is widely accepted¹⁸. The success of vector control in each region must be adjusted to the local transmission dynamics of each region¹⁹. The spread of the Dengue virus is often related to the rainy season²⁰. *Aedes* mosquitoes tend to breed in places with stagnant water caused by high rainfall¹. The rainy season and warm climate support the growth and reproduction of mosquitoes, thereby increasing the risk of spreading the Dengue virus²¹. Environmental factors such as overcrowding, poor sanitation, lack of access to clean water, and accumulation of water reservoirs that are not properly sealed can increase the risk of spreading the Dengue virus.^{22,23}. Apart from that, human behavior such as not keeping the environment clean, throwing rubbish carelessly, and people's habits are not routine, draining water reservoirs, and drinking places for livestock which become breeding places for mosquitoes.²⁴, not using protection against mosquito bites, such as the use of anti-mosquito nets or the use of repellants often affects the spread of the Dengue virus^{25,26}.

Climatic factors such as temperature, humidity, wind speed and mobility correlate with the incidence of dengue fever in an area²⁷. Dengue (DHF) virulence can vary in each region depending on factors that influence the spread and severity of the disease. These factors include the density of the vector mosquito population and variations in virus strains²⁸. The variations in Dengue virus (DEN) strains consist of

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Table 1. Review of research related to the spread of dengue virus serotypes in several countries in Asia published in 2018-2020.

Author	Sample	Findings
Taslim, et.al, 2018 ⁴⁰	Serum from dengue fever patients	The predominant serotypes are DENV-2 and DENV-4 and not serotypes DENV-1 and DENV-3. Makassar City has DENV-2 and DENV-4 serotypes, infections are dominated by DENV-2, the Maros region also has DENV-2 and DENV-4, but DENV-4 is the dominant serotype while Gowa City only has DENV-2 serotype infections (Indonesia)
Rajarethinam, et al., 2018 ⁴¹	DHF Patient Serum	The predominant serotypes associated with epidemics in the last decade in Singapore are DENV-1 and DENV-2, while the proportion of cases due to DENV-3 and DENV-4 remains low
Kusmintarsih, et al., 2018 ⁴²	DHF Patient Serum	In Purwekarto, the largest population was found to be DENV-3 (55%), DENV-1 (23%), and DENV-2 and DENV-4 each at 11% (Indonesia)
Rahayu, et.al, 2019 ⁴³	<i>Aedes Aegypti</i> positive DENV	In total, 22.20% of dengue mosquitoes were positive for DENV-1, 25% for DENV-2, 17% for DENV-3, but none were positive for DENV-4 (Indonesia).
Khan, et.al, 2020 ⁴⁴	DHF Patient Serum	In Pakistan DENV-2 is the most common serotype followed by DENV-1 then DENV-3, then DENV-4
Prajapati, et.al., 2020 ⁴⁵	DHF Patient Serum	Three serotypes DENV-1, 2 and 3 were detected and no DENV-4. The spread of DENV-2 in non-endemic areas such as the hilly areas of Nepal which are considered free of dengue fever due to the high altitude and cold weather.

Table 2. Review of research related to the spread of dengue virus serotypes in several countries in Asia, published in 2021-2022.

Author	Sample	Findings
Rai, et.al., 2021 ⁴⁶	DHF Patient Serum	In India, DENV-4 (97.87%) was found to be the most dominant DENV serotype either alone or as co-infection, followed by DENV-2 (8.51%) and DENV-3 (4.25%). In 47 positive cases, coinfection with more than one serotype detected in 4 cases (8.51%). Analysis of dengue cases in 2017, DENV-4 dominates the serotype (33.97%), followed by the emergence of DENV-2 (32.05%), DENV-3 (25.64%), and DENV-1 (25.00%) .
Poltep, et.al., 2021 ⁴⁷	DHF Patient Serum	The four DENV serotypes are the dominant strains in Thailand. In 2019 DENV-2 was found in 51% of deaths followed by DENV-1 (35%), while the percentage of DENV-4 and DENV-3 was low. In 2020, DENV-2 continued to dominate in terms of percentage of deaths (65.7%), followed by DENV-1 and DENV-4, but there were no deaths associated with DENV-3
Wijesinghe, et al., 2021 ⁴⁸	DHF Patient Serum	DENV-2 is the most dominant type in Sri Lanka. Four cases of DENV coinfection were recorded during the study period in patients. Interestingly, all four DENV serotypes were detected in larvae <i>Aedes albopictus</i> , which is the prominent immature vector form identified during the study period in the area, showed 9.8% VT (Vertical Transmission) of DENV. Except DENV-4, three other DENV serotypes were identified in larvae <i>Temples of the Egyptians</i> with VT 8.1%
Zhu, et.al., 2022 ⁴⁹	DHF Patient Serum	Phylogenetic analysis showed that DENV-2 was the dominant epidemic serotype, and the dengue epidemic in China was closely related to imported viruses from Southeast Asian countries

four serotypes of Dengue virus (DENV) which can cause infection in humans²⁹. This DENV is single-stranded RNA virus with a genome size of 10.7 kb and belongs to *Flavivirus*. The DENV genome encodes three structural proteins, namely capsid (C), membrane (M), and envelope (E) proteins, and seven nonstructural proteins, including NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5^{30,31}. There are four DENV serotypes, namely DENV-1, DENV-2, DENV-3, and DENV-4, which are genetically related but antigenically different³². Variations in virus strains can influence the severity of the disease. Some strains of Dengue virus can have higher virulence than others³³.

Dengue virus serotypes are related to the incidence of Dengue Hemorrhagic Fever (DHF) because the virus serotype that causes infection in a person can influence the severity of the dengue disease experienced³⁴. Basically, there are four known dengue virus serotypes (serotypes 1, 2, 3, and 4). When a person is infected with one of the serotypes, they will develop lifelong immunity to that serotype. However, acquired immunity only protects against the same serotype, and does not provide protection against other serotypes. When someone who already has immunity to one serotype is exposed to another serotype, there is a risk of increasing the severity of dengue fever. This is because the body's immune reaction to a different serotype can produce a stronger response and potentially cause more severe dengue symptoms, including an increased risk of bleeding³⁵. Therefore, within a region or population, the prevalence of different dengue virus serotypes can influence the severity and frequency of dengue incidence. If the dominant serotype in an area has a tendency to cause more severe

disease, then the likelihood of severe dengue fever in that area is also higher³⁶.

Monitoring and understanding the dengue virus serotypes circulating in an area is important to inform measures to prevent, control and manage dengue³⁷. This helps health authorities in planning prevention efforts, vector control, treatment, and educating the public about the dangers of dengue fever and appropriate preventive measures. It is known that prevention efforts and careful planning can help reduce the incidence of dengue fever. Collaboration between health institutions and the government can help integrate efforts to prevent and control dengue fever³⁸. Data from around the world shows that Asia ranks first in the number of dengue fever sufferers every year³⁹. So it is very important to conduct a literature study regarding the epidemiology of dengue virus serotypes in Asia. "This study wants to review research related to the transmission of 4 DENV serotypes in several countries in several Asian countries."

MATERIALS AND METHOD

Resources

We searched for studies through two electronic databases (Pubmed and Scinedirect). In the first stage, database search, 74 studies were obtained. The criteria for including research were four human dengue virus serotypes published in 2013 – 2023. As for review articles, unpublished works and research protocols were not eligible for inclusion. In the final search there were 10 studies included.

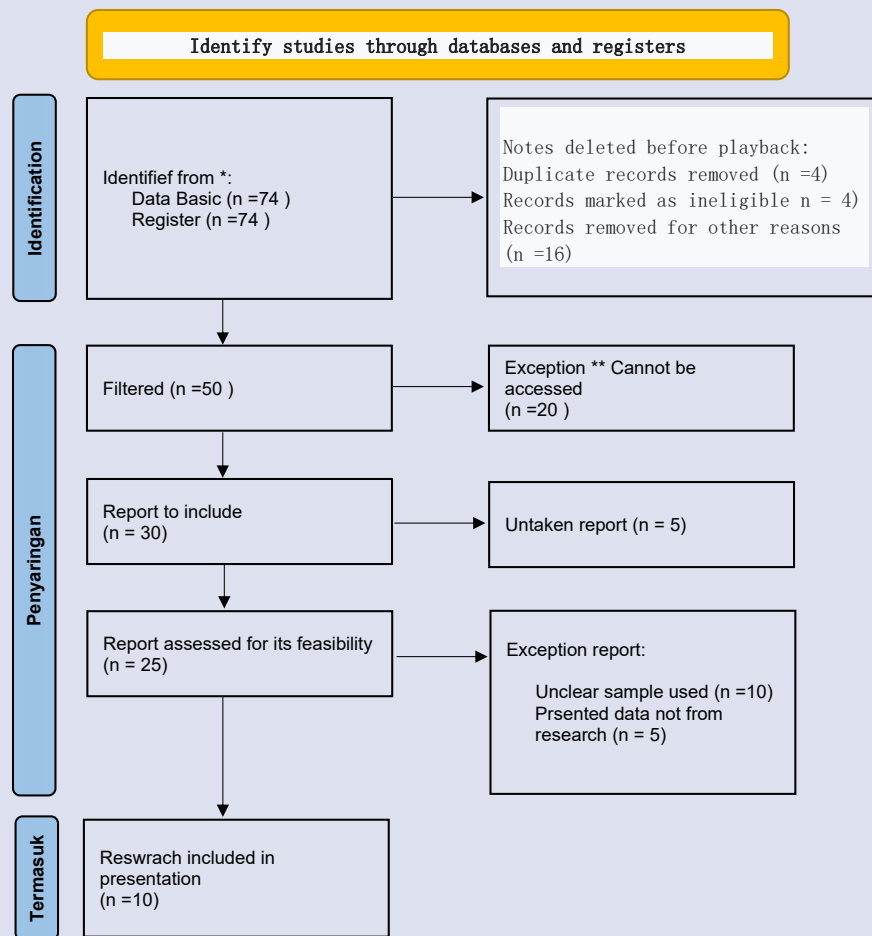


Figure 1. Study Selection Flowchart.

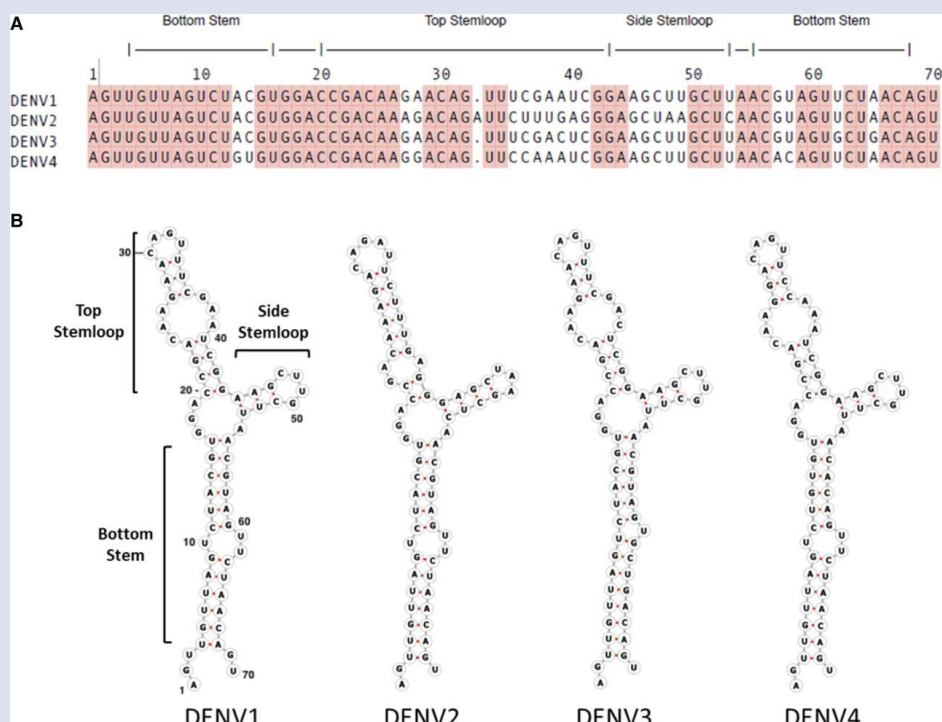


Figure 2. Dengue Virus RNA promoter structure.

Search terms

The keywords used in the search have two main domains, namely Asia, dengue virus, four serotypes or: DENV-1, DENV-2, DENV-3, DENV-4.

RESULTS

Based on a literature study conducted, data was obtained that Asia remains endemic for the four DENV serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). However, there are new threats related to the evolution of this dengue virus serotype where cases have been found in 1 individual has more than 1 serotype.

DISCUSSION

The immune response developed against one DENV serotype failed to provide long-term immunity against the remaining three serotypes. Secondary infection with a different DENV serotype is also associated with more severe disease, a phenomenon known as antibody-dependent enhancement phenomenon⁵⁰. To find dengue virus (DENV) serotypes from dengue patient serum, it is usually done using a laboratory method called *Reverse Transcription-Polymerase Chain Reaction* (RT-PCR)^{44 46}. The differences in the structure of the Dengue Virus RNA promoter in the four DENV serotypes can be seen in the following image

Description : The sequence and secondary structure of the SLA promoter element that recruits the NS5 protein to initiate minus-strand RNA synthesis is highly conserved among the four dengue virus serotypes (DENV1-4) 2022⁵¹. (A) Sequence alignment of the first 70 nt of DENV1, DENV2, DENV3, and DENV4. Regions corresponding to the predicted secondary structure elements (bottom helix, top and side stem-loops) are shown at the top. Conserved nucleotides are shaded. (B) Predicted SLA RNA secondary structures for the four DENV serotypes, as confirmed by SHAPE⁵².

Although dengue fever has been recognized as a public health threat, understanding of its molecular epidemiology is still limited. Where information regarding DENV serotypes for each region has not yet been obtained as an optimal reference. This literature review examines several dengue serotype findings in several countries in Asia. The epidemiology of dengue fever in Singapore over the past decade shows several interesting trends. Although all four DENV serotypes have been endemic in Singapore since they were monitored in the 1980s,⁵⁷The predominant serotypes associated with epidemics in the last decade have oscillated between DENV-1 and DENV-2, while the proportion of cases due to DENV-3 and DENV-4 remains low. The low incidence of infections associated with DENV-3 and DENV-4 in Singapore contrasts with their more frequent involvement in outbreaks in the Southeast Asian region in the past 20 years. Thailand and the Philippines, where these two serotypes were first recorded, have regularly reported epidemic transmission of DENV-3 and DENV-4. Singapore experienced oscillating DENV-1 and DENV-2 epidemics over a 13-year period from 2004 to 2016. Older adults appeared to be more affected by DENV-2 than DENV-1. Although there are no major changes in the type of primary dengue vector breeding habitat, *Ae. of Egypt*, its spread spread throughout the island. Singapore continues to be under threat of a dengue fever epidemic⁴¹

Meanwhile in Indonesia, several serotype variations in each region were found, Makassar City has DENV-2 and DENV-4 serotypes, infections are dominated by DENV-2, the Maros region also has DENV-2 and DENV-4, but DENV-4 is the dominant serotype while Gowa City only has DENV-2 serotype infections⁴⁰. In Purwokerto, the largest population was found to be DENV-3 (55%), DENV-1 (23%), and DENV-2 and DENV-4 each at 11%. DENV-1 Purwokerto is more diverse than other cities in Indonesia, GENV-2 was identified as the Cosmopolitan genotype which is similar to strains from Indonesian cities in general,

and from Southeast Asia and China, India, Africa and Australia. The GENV-3 isolate is classified as genotype 1 which is commonly found in the Southeast Asia region. Almost the same as DENV-2, DENV-3 also shows considerable genetic diversity and has undergone evolution so that its characteristics are generally different from other countries. The DENV-4 obtained was found to be similar to the Southeast Asian and American strains as well as Taiwan⁴². Meanwhile, in Yogyakarta, in total, 22.20% of dengue mosquitoes were positive for DENV-1, 25% for DENV-2, 17% for DENV-3, but none were positive for DENV-4.⁴³. On dengue endemic areas in South Sulawesi (Makassar, Maros, Gowa) the dominant serotypes are DENV-2 and DENV-4 and not serotypes DENV-1 and DENV-3. Makassar City has DENV-2 and DENV-4 serotypes, infections are dominated by DENV-2, the Maros region also has DENV-2 and DENV-4, but DENV-4 is the dominant serotype while Gowa City only has DENV-2 serotype infections⁴⁰. Between the two studies, there are differences in epidemiological data on DENV serotypes, this is because the research was conducted in different places. This is of course the basis that in a country there are differences in dominant serotypes if there are differences in environment and regional characteristics.

If we go to Nepal, three serotypes DENV-1, 2 and 3 are detected and there is no DENV-4. DENV-1 isolates (n=2) from Nepalese individuals were closely related to the Indian genotype V, while DENV-2 isolates (n=3) came from the Cosmopolitan Iva genotype which was closely related to the Indonesian isolates. Historical DENV isolates obtained between 2004 and 2013 were grouped with Cosmopolitan IVb, Cosmopolitan IVa, and Asian II genotypes. All Nepalese isolates belonged to different lines with different ancestries. Molecular analysis revealed that the dengue epidemic consists of different serotypes 1 and 2 genotypes raising concerns about the potential role of different genotypes in causing dengue hemorrhagic fever. Additionally, our results show the spread of DENV-2 in non-endemic areas such as the hilly areas of Nepal which are considered dengue-free due to the high altitude and cold weather.⁴⁵

In Pakistan DENV-2 is the most common serotype followed by DENV-1 then DENV-3, then DENV-4. Data show that DENV1 patients are more likely to have abnormal liver function tests; DENV2-infected patients are more likely to show arthralgia and neurological symptoms; DENV3 patients were more likely to complain of burning during urination and had elevated lymphocyte counts and low hematocrit; and DENV4 patients were more likely to report headaches and rashes. Notably, there was no dengue hemorrhagic fever or other manifestations of severe dengue fever in patients with primary or secondary infections⁴⁴.

In Sri Lanka DENV-2 is the most dominant type. Four cases of DENV coinfection were recorded during the study period in patients. Interestingly, all four DENV serotypes were detected in larvae *Aedes albopictus*, which is the prominent immature vector form identified during the study period in the area, showed 9.8% VT (Vertical Transmission) of DENV. Except DENV-4, three other DENV serotypes were identified in larvae *Temples of the Egyptians* with VT 8.1%⁴⁸

It's different with India. The geographic area affected by dengue fever in Mysuru in South India is expected to expand further due to rising temperatures and urbanization. DENV has four antigenically distinct serotypes (DENV-1-4), within which there is considerable genetic variation resulting in phylogenetically distinct evolution. In 2016, DENV-4 (97.87%) was found to be the most dominant DENV serotype either alone or as co-infection, followed by DENV-2 (8.51%) and DENV-3 (4.25%). In 47 positive cases, coinfection with more than one serotype detected in 4 cases (8.51%). Analysis of dengue cases in 2017, DENV-4 dominates the serotype (33.97%), followed by the emergence of DENV-2 (32.05%), DENV-3 (25.64%), and DENV-1 (25.00%)⁴⁶

Thailand is a hyper-endemic country for dengue fever with cocirculation of four serotypes and tens of thousands of infected cases every year. The genetic diversity of the dominant genotypes of each serotype tended to increase slightly over time with fluctuating changes, followed by a stationary phase after 2000. This indicates that the four DENV clades became the dominant strains in Thailand. In 2019 DENV-2 was found in 51% of deaths followed by DENV-1 (35%), while the percentage of DENV-4 and DENV-3 was low. In 2020, DENV-2 continued to dominate in terms of percentage of deaths (65.7%), followed by DENV-1 and DENV-4, but there were no deaths associated with DENV-3⁴⁷. Meanwhile in China Phylogenetic analysis in China shows that DENV-2 is the dominant epidemic serotype, and the dengue epidemic in China is closely related to imported viruses from Southeast Asian countries^{49,50}.

When grouped, the results show that DENV-1 is dominant in Singapore and Pakistan. DENV-2 is dominant in Singapore, Thailand, Sri Lanka and China, DENV-4 is dominant in Nepal and India, while in Indonesia no particular serotype has been found that is dominant in causing dengue fever. This is because several regions in Indonesia have different characteristics and their territories are spread over several islands. Apart from that, there has been no research on the vertical transmission of dengue virus serotypes that covers all regions in Indonesia⁵¹⁻⁵⁵.

CONCLUSION

Several countries in Asia were found to be endemic to these four DENV serotypes, however, DENV has undergone evolution regarding several genotypes in certain strains.

RECOMMENDATION

Research related to monitoring and understanding dengue virus (DENV) serotypes that are prevalent in each region, it is important to take preventative control and management steps in each region to provide information on steps to prevent, control and manage dengue fever in the region.

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