

EPIDEMIOLOGY STUDY OF DENGUE VIRUS IN SURABAYA, BOGOR, AND BANGKALAN, INDONESIA 2008-2018

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ABSTRACT

Dengue virus (DENV) is mosquito-borne viral diseases, transmitted by the vector mosquitoes such as Aedes sp. Infection with four serotypes of DENV-1 to 4. Indonesia, dengue haemorrhagic fever (DHF) was first recognized in 1968 in the cities of Jakarta and Surabaya. In 2007, we started DENV surveillance in Surabaya supported by the joined program of the Japan Initiative for Global Research Network on Infectious Disease (J-GRID) established the Indonesia-Kobe University Collaborative Research Center for Emerging and Reemerging Infectious Diseases (CRC-ERID). The results of serotype and genotype, in Surabaya and Bangkalan are similar with previous result in Indonesia, but especially in Bogor similar with Japan 2014. This study showed the importance of continuous virus surveillance in dengue endemic areas, in order to understand the dynamic of dengue infection disease in Indonesia.

Keywords: DENV; Surveillance; Surabaya; Bogor; Bangkalan

ABSTRAK

Virus dengue (DENV) adalah virus yang ditularkan oleh nyamuk, ditularkan oleh nyamuk vektor Aedes sp. Infeksi dengan empat serotipe DENV-1 hingga 4. Indonesia, demam berdarah dengue (DBD) pertama kali ditemukan pada tahun 1968 di kota Jakarta dan Surabaya. Pada tahun 2007, kami memulai pengawasan DENV di Surabaya didukung oleh program the Japan Initiative for Global Research Network on Infectious Disease (J-GRID) mendirikan the Indonesia-Kobe University Collaborative Research Center for Emerging and Reemerging Infectious Diseases (CRC-ERID). Hasil serotipe dan genotipe, di Surabaya dan Bangkalan mirip dengan hasil sebelumnya di Indonesia, tetapi terutama di Bogor mirip dengan Jepang 2014. Penelitian ini menunjukkan pentingnya pengawasan virus secara terus-menerus di daerah endemis demam berdarah, untuk memahami dinamika penyakit infeksi demam berdarah di Indonesia.

Kata kunci: DENV; Pengawasan; Surabaya; Bogor; Bangkalan

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pISSN:2355-8393 • eISSN: 2599-056x • doi: <http://dx.doi.org/10.20473/fmi.v56i4.23415>
 • Fol Med Indones. 2020;56:296-301 • Received 29 Jan 2019 • Accepted 11 Jul 2019
 • Open access under CC-BY-NC-SA license • Available at <https://e-journal.unair.ac.id/FMI/>

INTRODUCTION

Dengue virus (DENV) is mosquito-borne viral diseases that occur in tropical and subtropical regions and transmitted by the vector mosquitoes such as *Aedes aegypti* and *Aedes albopictus* (Halstead 2008). Infection with four serotypes of DENV were designated, DENV-1, DENV-2, DENV-3, and DENV-4 (Gubler 2011). Worldwide, an estimated 2.5 billion people are at risk of infection, estimated that more 50 million infections occur each year, including 500,000 hospitalization, and with the fatality case rate exceeding 5% in some areas (Maria et al 2010).

Indonesia, dengue haemorrhagic fever (DHF) was first recognized in 1968 in the cities of Jakarta and Surabaya (Sumarmo 1987, Ansori et al 2015). More than 100,000 cases of DF/DHF have been annually reported in recent years, phylogenetic analysis revealed that particular types of DENV that spread throughout the region had their origin in Indonesia (Villobona-Arenas & Zanutto 2013, Araújo et al 2009). In 2007, we started DENV surveillance in Surabaya, the second largest city in Indonesia (Kotaki et al 2014). That work was supported by the joined program of the Japan Initiative for Global Research Network on Infectious Disease (J-GRID) established the Indonesia-Kobe University Collaborative Research Center for Emerging and Reemerging Infectious Diseases (CRC-ERID), which is

Indonesian researchers from Institute of Tropical Disease (ITD) Universitas Airlangga and The Center for Infectious Diseases (CID), Kobe University Graduate School of Medicine (Shirakawa et al 2014).

Epidemiology

Virus isolation in Surabaya, East Java, Indonesia

Indonesia has annually experienced approximately 100,000 reported cases of dengue fever (DF) and dengue hemorrhagic fever (DHF) in recent years. However, epidemiological surveys of dengue viruses (DENVs) have been limited in this country. In Surabaya, the second largest city, a single report indicated that dengue virus type 2 (DENV2) was the predominant circulating virus in 2003,–2005. We conducted three surveys in Surabaya during: (i) April 2007, (ii) June 2008 to April 2009, and (iii) September 2009 to December 2010. A total of 231 isolates were obtained from dengue patients and examined by PCR typing. We found that the predominant DENV shifted from type 2 to type 1 between October and November 2008. Another survey using wild-caught mosquitoes in April 2009 confirmed that dengue type 1 virus (DENV1) was the predominant type in Surabaya. Phylogenetic analyses of the nucleotide sequences of the complete envelope gene of DENV-1 indicated that all 22 selected isolates in the second survey belonged to genotype IV and all 17 selected isolates in the third survey belonged to genotype I, indicating a genotype shift between April and September 2009. Furthermore, in December 2010, isolates were grouped into a new clade of DENV1 genotype I, suggesting clade shift between September and December 2010. According to statistics reported by the Surabaya Health Office, the proportion of DHF cases among the total number of dengue cases increased about three times after the type shift in 2008. In addition, the subsequent genotype shift in 2009 was associated with the increased number of total dengue cases. This indicates the need for continuous surveillance of circulating viruses to predict the risk of DHF and DF (Yamanaka et al 2011).

DENV-1 transitions in Surabaya during 2011,–2013 in order to comprehend dengue dynamics during 2008,–2013 in more detail. From January 2011 through December 2011, only GIV strains were isolated, indicating that a genotype shift again took place from GI to GIV. In January 2012, GI and GIV strains started co-circulating, which continued until June 2013. To further investigate this phenomenon, analysis was performed at a clade level. GI and GIV strains isolated in Surabaya formed four and three distinct clades, respectively. Concomitant with co-circulation,

new clade strains appeared in both genotypes. In contrast, some previously circulating clades were not isolated during co-circulation, indicating clade shifts. Among our Surabaya isolates, nucleotide and amino acid differences in the E region were, respectively, 1.0,–2.3% and 0.2,–1.0% for GI isolates and 2.0,–6.3% and 0.0,–1.8% for GIV isolates. Several characteristic amino acid substitutions in the envelope ectodomain were observed in some clades. After July 2013, DENV-1 strains were not isolated and were replaced with DENV-2. This study showed that continuous shifts of more than one genotype resulted in their co-circulation and subsequent disappearance and suggested the relevance of clade replacement to genotype co-circulation and disappearance in Surabaya (Kotaki et al 2014, Soegijanto et al 2013). Fig. 1 shows the monthly data of collected sera and isolated viruses.

We isolated strains of DENV-3 genotype I that potentially cause endemic outbreaks in Surabaya. There is a possibility that DENV-3 is already established in the population and that it will replace the currently circulating strains, leading to an increase in the incidence and rate of severe DHF cases. Continuous epidemiological surveillance is required for monitoring the incursion and spread of this virus. Therefore, the emergence of DENV-3 potentially increases the incidence of secondary heterotypic infection, leading to severe symptoms. Previous studies have shown that the emergence of DENV-3 following the circulation of heterotypic DENV caused outbreaks of DF/DHF (Briseno-Gracia et al 1996, Messer et al 2003). In addition, a cohort study of adult DHF Cuban cases showed that infection with DENV-1 followed by DENV-3, which is also likely to occur in Surabaya, was riskier than DENV-2/DENV-3 infection in terms of the severity of the outbreak (Guzman et al 2008). Furthermore, DENV-3 has significantly higher nucleotide substitution rates than other DENV serotypes, resulting in the emergence of DENV variants with increased transmissibility and/or virulence (Araújo et al 2009).

We previously reported sequential changes in the predominant serotype from DENV type 2 (DENV-2) to DENV type 1 (DENV-1) in November 2008 and from DENV-1 to DENV-2 in July 2013. The predominance of DENV-2 continued in 2014, but not in 2015. We here in phylogenetically investigated DENV-2 transitions in Surabaya between 2008 and 2014 to analyze the divergence and evolution of DENV-2 concomitant with serotype shifts. All DENV-2 isolated in Surabaya were classified into the Cosmopolitan genotype, and further divided into 6 clusters.

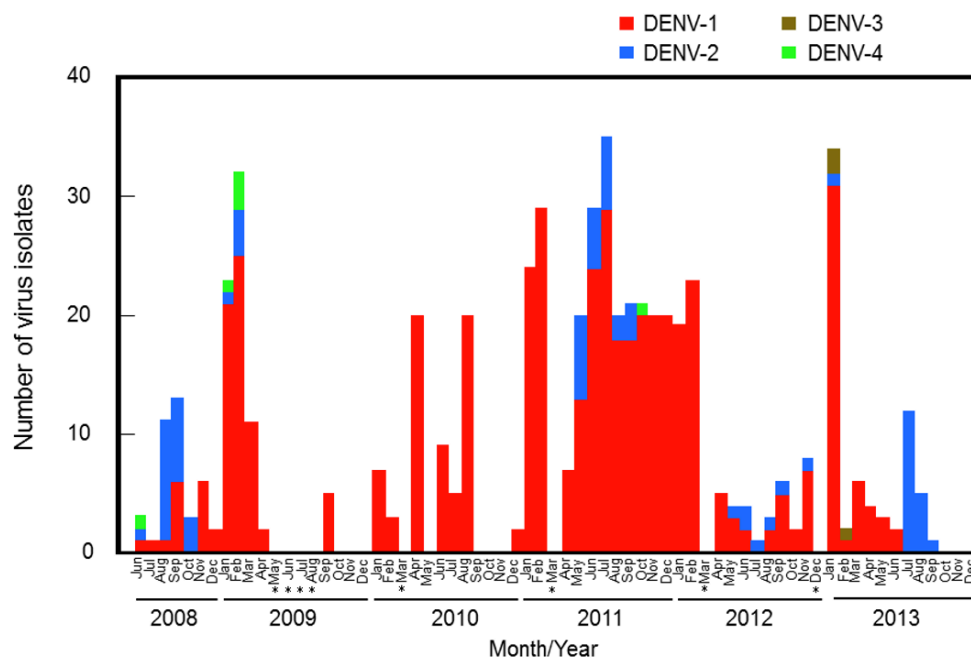


Fig. 1. The monthly number of dengue virus isolates in 2008-2013 (Kotaki et al 2014).

Clusters 1, 3, dominated by Surabaya strains, were defined as the „Surabaya lineage. Clusters 4, 6, dominated by strains from Singapore, Malaysia, and many parts of Indonesia, were the „South East Asian lineage. The most recent common ancestor of these strains existed in 1988, coinciding with the time that an Indonesian dengue outbreak took place. Cluster 1 appeared to be unique because no other DENV-2 isolate was included in this cluster. The predominance of DENV-2 in 2008 and 2013, were caused by cluster 1, whereas clusters 2 and 3 sporadically emerged in 2011 and 2012. The characteristic amino acids of cluster 1, E-170 V and E-282Y, may be responsible for its prevalence in Surabaya. No amino acid difference was observed in the envelope region between strains in 2008 and 2013, suggesting that the re-emergence of DENV-2 in Surabaya was due to the loss or decrease of herd immunity in the 5-year period when DENV-2 subsided. The South East Asian lineage primarily emerged in Surabaya in 2014, probably imported from other parts of Indonesia or foreign countries (Kotaki et al 2016).

Virus isolation in Bogor, West Java, Indonesia

We herein reported the nearly full genome sequence of DENV-1 (figure 2), which is phylogenetically close to the Japanese outbreak strain of 2014. This finding indicates that the Southeast Asian region was the source of the dengue autochthonous outbreak in Japan in 2014. We consider the results of the present study to be useful

for retrospective analyses of dengue outbreaks in Japan (Churrotin et al 2016). In Japan, as of September 17th, 2014, a total of 131 cases have been confirmed. This is a preliminary finding, along with the public health response activity of the first documented autochthonous dengue outbreak in Japan in nearly 70 years (Arima et al 2014).

Virus isolation in Bangkalan, Madura Island, Indonesia

Bangkalan is the biggest city in Madura Island, East Java province, Indonesia. It is located 37.8 km from Surabaya. The number of dengue cases in this city was previously reported to be higher than that in other cities in Madura Island (Department of Health East Java Province 2013). 17 out of 359 blood samples (4.7%) were positive for the isolation of DENV. Serotyping and the phylogenetic analysis revealed the predominance of DENV-1 genotype I (9/17, 52.9%), followed by DENV-2 Cosmopolitan type (7/17, 41.2%) and DENV-3 genotype I (1/17, 5.9%). DENV-4 was not isolated. The viral transition pattern in Bangkalan was similar to that in Surabaya; a serotype shift from DENV-1 to DENV-2 occurred in July 2013 in Surabaya. This shift suggested that viral circulation in Surabaya and Bangkalan was concomitant because workers from Bangkalan commute to and from Surabaya (Sucipto et al 2018). Figure 3 showed phylogenetic trees of DENV-1 isolated in Bangkalan, Indonesia.

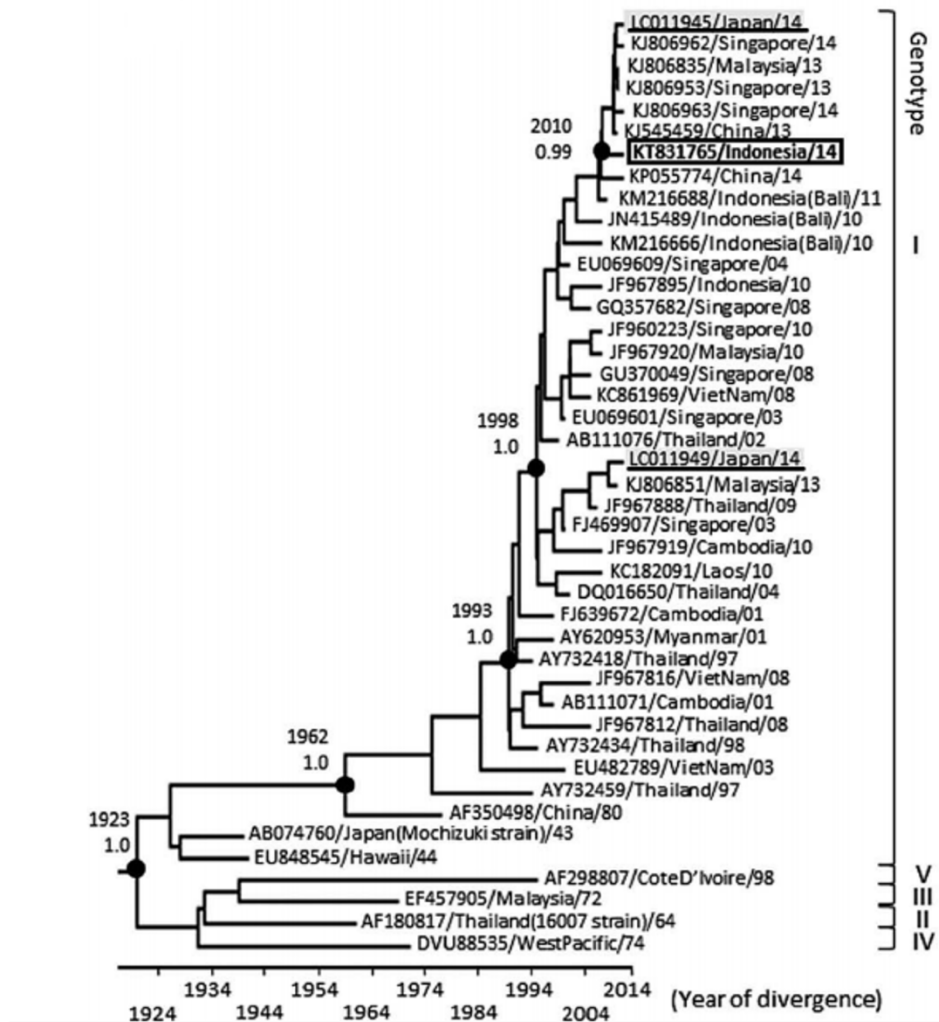


Fig. 2. Markov Chain Monte Carlo (MCMC) trees of DENV-1 isolated in Bogor (Churrotin et al 2016).

Mosquitos vector study

Aedes aegypti and *Aedes albopictus* are the primary and secondary vectors, respectively, of dengue, the most important arboviral disease in the world. The aim of this study was to detect and serotype dengue viruses (DENV) in the vectors *Ae. aegypti* and *Ae. albopictus* in Surabaya, Indonesia. Between 2008 and 2015, 16,605 *Aedes* mosquitoes were collected in 15 sub-districts of Surabaya. *Ae. aegypti* was dominant (90.9%), whereas few *Ae. albopictus* were collected (9.1%). A total of 330 pools of adult *Aedes* mosquitoes were subjected to the serotyping of DENV by RT-PCR. DENV-1 (52.3%) was the most frequently detected serotype, followed by

DENV-2 (40.3%), DENV-4 (4.6%), and DENV-3 (2.8%). The average minimum infection rate for *Ae. aegypti* in various sub-districts of Surabaya was 7.2 per 1,000 mosquitoes, while that for *Ae. albopictus* was 0.7 per 1,000 mosquitoes. The results showed that the predominantly circulating DENV serotype in mosquitoes continuously shifted from DENV-2 (2008) to DENV-1 (2009-2012), to DENV-2 again (2013, 2014), and then back to DENV-1 (2015). The circulating DENV serotypes in mosquitoes were generally consistent with those in humans. Therefore, the surveillance of infected mosquitoes with DENV might provide an early warning sign for the risk of future dengue outbreaks (Mulyatno et al 2018).

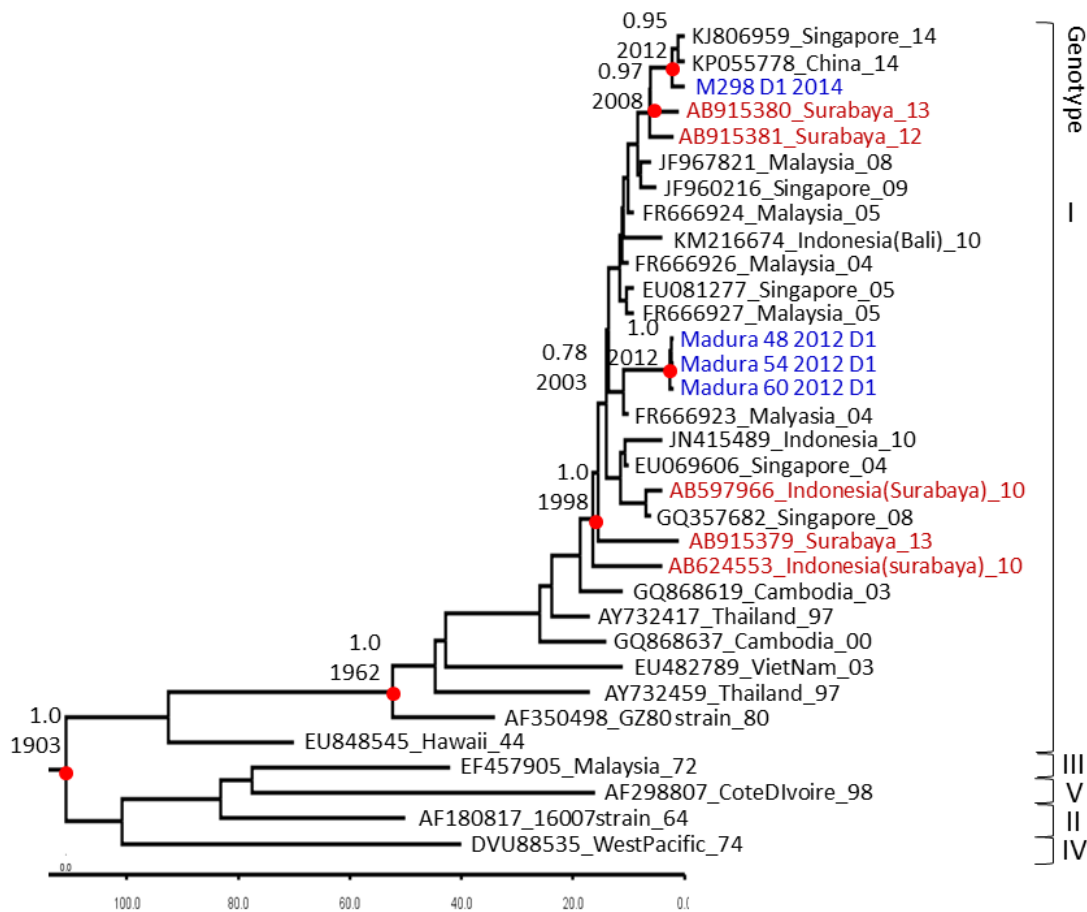


Fig. 3. Phylogenetic trees of DENV-1 isolated in Bangkalan, Indonesia. Phylogenetic trees of DENV-1 was constructed using Bayesian Markov chain Monte Carlo (MCMC) (Sucipto et al 2018).

CONCLUSION

In conclusion, this study presented the molecular data of DENV in Bangkalan, Bogor, and Surabaya, Indonesia. The results of serotype and genotype in are similar with previous result in Indonesia, but especially in Bogor similar with Japan 2014. This study showed the importance of continuous virus surveillance in dengue endemic areas, in order to understand the dynamic of dengue infection disease in Indonesia.

ACKNOWLEDGMENT

This work was supported by the joined program of the Japan Initiative for Global Research Network on Infectious Disease (J-GRID); and Institute of Tropical Disease (ITD) the Center of Excellence (COE) program by the Ministry of Research and Technology (RISTEK) Indonesia.

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