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ANALYSIS OF CIRCULATING DENGUE VIRUS SEROTYPE 1 (DENV 1) STRAINS IN INDONESIA BASED ON THE ENVELOPE GENE: A BIOINFORMATIC STUDY

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ABSTRACT

Dengue virus serotype 1 (DENV 1) is a major contributor to dengue burden in Indonesia, where all four serotypes co-circulate and cause recurrent outbreaks, but comprehensive mapping of DENV 1 genetic diversity at the national level remains limited. The envelope (E) gene is a key molecular marker for genotyping and phylogenetic analysis because it encodes critical antigenic determinants and shows high sequence variability that reflects viral evolution and geographic spread. DENV 1 sequences were retrieved from international public databases using predefined keywords and country filters. Envelope gene regions were extracted, curated to remove duplicates, low-quality sequences, and obvious recombinants, then aligned to estimate nucleotide and amino acid diversity. Phylogenetic trees were inferred with Maximum Likelihood, and genotypes/lineages were assigned by clustering with published global DENV 1 reference sequences, followed by spatiotemporal mapping based on location and year of isolation. Most Indonesian DENV 1 strains formed a highly homogeneous endemic lineage within Genotype I, with intra-Indonesia nucleotide identity of approximately 98-100% and very low genetic distances among strains from multiple cities and years. Travel-associated strains (Taiwan/Indonesia, Korea/Indonesia, Australia/Bali) showed similarly high homology to Indonesian strains, whereas Indian Ocean strains (Réunion, Seychelles) clustered into a distinct, more divergent lineage. DENV 1 circulation in Indonesia is dominated by a genetically stable Genotype I lineage that also underlies many travel-associated cases, while remaining clearly separated from Indian Ocean lineages, highlighting regional structuring and the importance of continuous genomic surveillance.

Keywords: Dengue virus-1; Envelope gene; Phylogenetic.

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INTRODUCTION

Dengue fever remains a major global public health concern, with more than half of the world's population residing in areas at risk, and its incidence has continued to rise over recent decades, particularly in tropical and subtropical countries (Baihaki et al., 2023). Indonesia is one of the countries with the highest dengue burden in Southeast Asia, where the concurrent circulation of all four dengue virus serotypes (DENV 1 to DENV 4) contributes substantially to recurrent outbreaks and high morbidity (Arguni et al., 2022).

Dengue virus belongs to the genus Flavivirus and possesses a positive-sense single-stranded RNA genome that encodes three structural proteins (C, prM/M, and E) and seven non-structural proteins, with the envelope (E) protein playing a pivotal role in viral attachment to host cells, membrane fusion, and serving as the principal target of neutralizing antibodies (Baihaki et al., 2025). The E gene is approximately 1,485 nucleotides in length in DENV 1 and contains key antigenic determinants as well as substantial sequence variability, making it widely used as a molecular marker for genotype determination and phylogenetic analysis (Li et al., 2022).

Globally, DENV 1 exhibits substantial genetic diversity and has been classified into at least five major genotypes (I-V) based on complete E gene and/or whole-genome sequences, displaying a hierarchical phylogenetic structure that reflects geographic dispersion patterns and viral population evolution. (Villabona-Arenas & Zanotto, 2013). This high-resolution DENV 1 genotyping framework reveals a strong association between specific genotypes, subgenotypes, and clades and defined epidemiological regions, which in turn influences transmission dynamics, virulence potential, and the risk of emergence of novel variants (Li et al., 2022).

In Indonesia, molecular studies have shown that circulating DENV 1 strains predominantly belong to Genotype I, with the presence of several distinct lineages across different regions and time periods, reflecting both repeated introductions of new strains and ongoing local evolution (Megawati et al., 2017). Phylogenetic analyses based on the E gene of isolates from Bali and Yogyakarta, for example, have documented considerable intra-genotype diversity of DENV 1 and close relatedness to strains from other countries in the region, underscoring the role of human mobility and regional connectivity in shaping strain differences (Harapan & Imrie, 2021)

The E gene has been widely recommended as a primary target for DENV genotyping and genetic diversity studies because it displays a higher degree of sequence heterogeneity than several other genomic regions and can effectively discriminate distinct lineages within a single genotype (Chao et al., 2005). Nucleotide and amino acid variation within the E gene may contribute to differences in antigenic properties, neutralizing antibody capacity, and potential changes in key biological traits of the virus, such as replication efficiency or transmissibility (Huang et al., 2022).

The increasing availability of complete and partial DENV genome sequences in public databases, including NCBI, has created new opportunities for large-scale bioinformatic exploration of dengue virus genetic diversity, phylogenetic relationships, and evolutionary dynamics (Lara-Ramírez et al., 2014). These platforms provide an integrated query interface linked to sequence and phylogenetic analysis tools, enabling researchers to systematically select, align, and characterize DENV sequences for diverse applications, including molecular surveillance and genotype mapping (Brister et al., 2014).

At present, in silico bioinformatic approaches that leverage DENV 1 E gene sequences from international databases are increasingly critical for elucidating viral population structure, patterns of strain introduction and dissemination, and potential associations between specific lineages and national epidemiological patterns (Yu et al., 2019). In Indonesia, although several regional reports have described DENV 1 genetic diversity, a comprehensive, E gene–based mapping of DENV 1 strain diversity at the national scale remains limited and has yet to be integrated within a unified analytical framework.

This data gap results in suboptimal understanding of the distribution of DENV 1 genotypes and clades across different islands and regions of Indonesia, as well as of potential shifts in lineage dominance that may be linked to outbreak dynamics and disease severity. At the same time, detailed characterization of DENV 1 genetic diversity is highly relevant to strengthening genomic surveillance, evaluating the suitability of vaccine candidates, and designing more precisely targeted control strategies in dengue-endemic settings such as Indonesia (Tariq et al., 2025).

Building on this background, exploring the diversity of DENV 1 strains circulating in Indonesia using E gene–based bioinformatic analyses of sequences available in NCBI represents a critical step toward filling current knowledge gaps regarding the national-scale population structure of this virus. This in silico study is expected to delineate DENV 1 genotypes, subgenotypes, and putative clades in Indonesia and to provide a robust scientific basis for strengthening molecular surveillance and for subsequent investigations linking viral genetic variation with the clinical and epidemiological characteristics of dengue in the country.

MATERIALS AND METHODS

Sequences Dataset

DENV 1 sequence data were retrieved from international public databases (NCBI Virus/Virus Variation and GenBank) using the keywords "dengue virus 1" and "envelope", with country filters set to "Indonesia" and, as required for comparative analyses, other Asia–Pacific countries (Resch et al., 2009). Inclusion criteria were: (1) confirmed serotype as DENV 1, (2) complete or near-complete E gene sequence (≥1,400 nt), (3) clearly documented metadata on sampling location and year of isolation, and (4) no indication that the virus represented a laboratory-adapted or attenuated strain.

E-gene Extraction and Dataset Curation

Complete genome sequences were trimmed to the E gene region according to GenBank annotation and exported in FASTA format using the NCBI Virus/Virus Variation interface or ancillary software (e.g., Geneious/UGENE). The dataset was then curated by removing duplicate entries, sequences with excessive gaps or ambiguities, and clearly recombinant strains, as indicated in GenBank records or, when necessary, by preliminary recombination screening.

Multiple Sequence Alignment and Diversity Analysis

Nucleotide alignment of the E gene was performed in MEGA12 using default (auto) settings and was manually adjusted when necessary to maintain the correct reading frame. Nucleotide and amino acid diversity were then quantified in MEGA12 to obtain percentage identity, nucleotide diversity π, and the distribution of substitutions across the EDI, EDII, and EDIII domains.

Phylogenetic Analysis and Population Structure

The best-fit nucleotide substitution model was selected according to BIC/AIC criteria using MEGA or jModelTest. Phylogenetic trees of the E gene were reconstructed under the Maximum Likelihood (ML) framework with 1,000 bootstrap replicates in MEGA or IQ-TREE, while time-scaled inference and reconstruction of introduction and dissemination patterns were performed using a Bayesian MCMC approach (BEAST) with a relaxed molecular clock and an appropriate coalescent model.

Genotype/Lineage Determination and Epidemiological Analysis

DENV 1 genotypes and lineages were assigned based on clade clustering with previously published reference sequences, including global DENV 1 lineage panels. The temporal and spatial distribution of genotypes/lineages was then assessed by mapping phylogenetic clusters onto country/province and year-of-isolation metadata to evaluate patterns of introduction, local spread, and potential associations with epidemiological phenomena such as outbreaks or serotype/genotype replacement.

RESULT

A total of 60 DENV-1 envelope (E) gene sequences were included in the final dataset after quality control and sequence curation. Among these, 31 sequences (51.7%) were directly associated with Indonesia, consisting of isolates collected from Jakarta, Bogor, Sukabumi, Semarang, Surabaya, and travel-related cases linked to Indonesia (Taiwan/Indonesia, South Korea/Indonesia, and Australia/Bali-Indonesia). The remaining 29 sequences (48.3%) represented comparative strains from China, Singapore, Malaysia, Vietnam, Taiwan, Japan, Reunion Island, and Seychelles.

The nucleotide diversity analysis demonstrated relatively low genetic variation among Indonesian DENV-1 strains. The average nucleotide diversity (π) within Indonesian sequences was estimated at 0.012, indicating a highly conserved viral population. Pairwise nucleotide identity among Indonesian strains ranged from 98.0% to 100%, whereas comparisons between Indonesian strains and the Indian Ocean lineage (Reunion and Seychelles) showed lower nucleotide identities of approximately 90–91%, suggesting substantial evolutionary divergence.

Table 2 presents the nucleotide diversity matrix among major geographic groups. Indonesian strains exhibited the highest genetic similarity with travel-associated isolates from Taiwan/Indonesia and Australia/Bali-Indonesia, while the greatest divergence was observed between Indonesian and Reunion/Seychelles strains.

Table 1. 60 DENV-1 strains obtained from NCB

No	DENV-1 Acc.Number/ Region/ Year	No.	DENV-1 Acc.Number/ Region/ Year
1	FJ158610/China/2007	31	AB915378/Indonesia(Surabaya)/2014
2	JQ317738/China(Guangdong)/2007	31	GQ357685/Singapore/2008
3	JQ277879/China/2007	33	GQ357684/Singapore/2008
4	JQ277880/China/2007	34	JF967896/Taiwan(Indonesia)/2010
5	KC861965/Vietnam/2006	35	JF967931/Taiwan(Indonesia)/2010
6	KC861918/Vietnam/2006	36	JF960234/Singapore/2010
7	EU448400/Malaysia/2006	37	HQ149730/China(Guangzhao)/2009
8	EU081276/Singapore/2005	38	JF967857/Taiwan(Indonesia)/2009
9	KX646376/JKT-B261/2009	39	KX646378/JKT-T100/2009
10	KX646377/JKT-T088/2009	40	KM216674/Australia(Bali-Indonesia)/2010
11	JF967868/Taiwan(Indonesia)/2009	41	JF967877/Taiwan(Indonesia)/2009
12	JF960214/Singapore/2009	42	KX646379/JKT-T404/2009
13	KX646381/JKT-T072/2009	43	KT831765/Indonesia(Bogor)/2014
14	JF967855/Taiwan(Indonesia)/2009	44	KF857539/Indonesia(Jakarta)/2009
15	JF967926/Taiwan(Thailand)/2010	45	JQ317739/China(Guangdong)/2007
16	JN415490/Australia(Bali-Indonesia)/2010	46	DQ285561/Seychelles/2004
17	KM216689/Australia(Bali-Indonesia)/2011	47	DQ285557/Seychelles/2004
18	KM216670/Australia(Bali-Indonesia)/2010	48	AB195673/Japan(Seychelles)/2003
19	JF967904/Taiwan(Indonesia)/2010	49	EU282328/Reunion/2004
20	KM216681/Australia(Bali-Indonesia)/2010	50	EU448412/Taiwan(Madagascar)/2006
21	JF967825/Taiwan(Indonesia)/2008	51	DQ285558/Reunion/2004
22	EU448401/Taiwan(Indonesia)/2007	52	DQ285560/Reunion/2004
23	KC589008/Indonesia(Semarang)/2012	53	EU448411/Taiwan(Indonesia)/2005
24	FJ687477/South Korea(Indonesia)/2008	54	KX646375/JKT-T073/2009
25	JF967906/Taiwan(Indonesia)/2010	55	JN697056/Malaysia/2005
26	KX646380/JKT-B281/2009	56	JF967950/Taiwan(Indonesia)/2010
27	KF052647/Indonesia(Sukabumi)/2012	57	JF967951/Taiwan(Indonesia)/2010
28	JF960229/Singapore/2010	58	JN415513/Malaysia/2010
29	JF960227/Singapore/2010	59	KM216682/Australia(Bali-Indonesia)/2010
30	AB915379/Indonesia(Surabaya)/2013	60	JN415493/Australia(Bali-Indonesia)/2010

Table 1. Nucleotide Diversity Matrix of DENV-1 Envelope Gene Sequences

Population Group	Number of Sequences	Nucleotide Diversity (π)
Indonesia	31	0.012
Singapore	8	0.018
China	7	0.021
Malaysia/ Vietnam	6	0.024
Reunion/ Seychelles	7	0.047

Maximum Likelihood phylogenetic reconstruction based on the complete E gene generated a well-supported topology (Figure 1). Bootstrap analysis using 1,000 replicates revealed strong statistical support for major clades. Most internal nodes displayed bootstrap values above 70%, while the Indonesian Genotype I cluster was supported by bootstrap values exceeding 90%, confirming the stability of this endemic lineage. Indonesian isolates from different provinces and years clustered closely together, indicating sustained local circulation with limited genetic diversification.

Travel-associated isolates from Taiwan/Indonesia, South Korea/Indonesia, and Australia/Bali-Indonesia clustered within the Indonesian lineage and exhibited minimal genetic distances (0.001–0.020 substitutions/site), supporting the hypothesis that these imported cases originated from the same circulating Indonesian DENV-1 population. In contrast, strains from Reunion Island and Seychelles formed a separate monophyletic cluster with high bootstrap support (>95%), suggesting long-term evolutionary separation from Southeast Asian lineages.

To investigate the temporal dynamics of DENV-1 evolution, a time-scaled Bayesian phylogenetic analysis was performed using a relaxed molecular clock model. The resulting Maximum Clade Credibility (MCC) tree revealed that the Indonesian DENV-1 lineage shared a most recent common ancestor (tMRCA) around 2003 (95% Highest Posterior Density [HPD]: 2001–2005). The Indonesian lineage persisted continuously throughout the study period (2005–2014), indicating long-term endemic circulation rather than repeated replacement by newly introduced strains.

The time-scaled analysis further demonstrated that most Indonesian isolates collected between 2009 and 2014 descended from a common ancestral lineage that expanded locally across multiple geographic regions. Travel-associated cases detected in Taiwan, South Korea, and Australia were interspersed among Indonesian isolates, supporting frequent viral exportation from Indonesia. Conversely, the Reunion and Seychelles lineage diverged earlier and remained genetically distinct, consistent with regional phylogeographic structuring of DENV-1 populations.

Overall, the combination of nucleotide diversity analysis, Maximum Likelihood phylogeny with bootstrap support, and time-scaled evolutionary reconstruction indicates that DENV-1 circulation in Indonesia is dominated by a genetically stable Genotype I lineage characterized by low intra-lineage diversity, extensive geographic dissemination, and sustained endemic transmission over more than a decade.

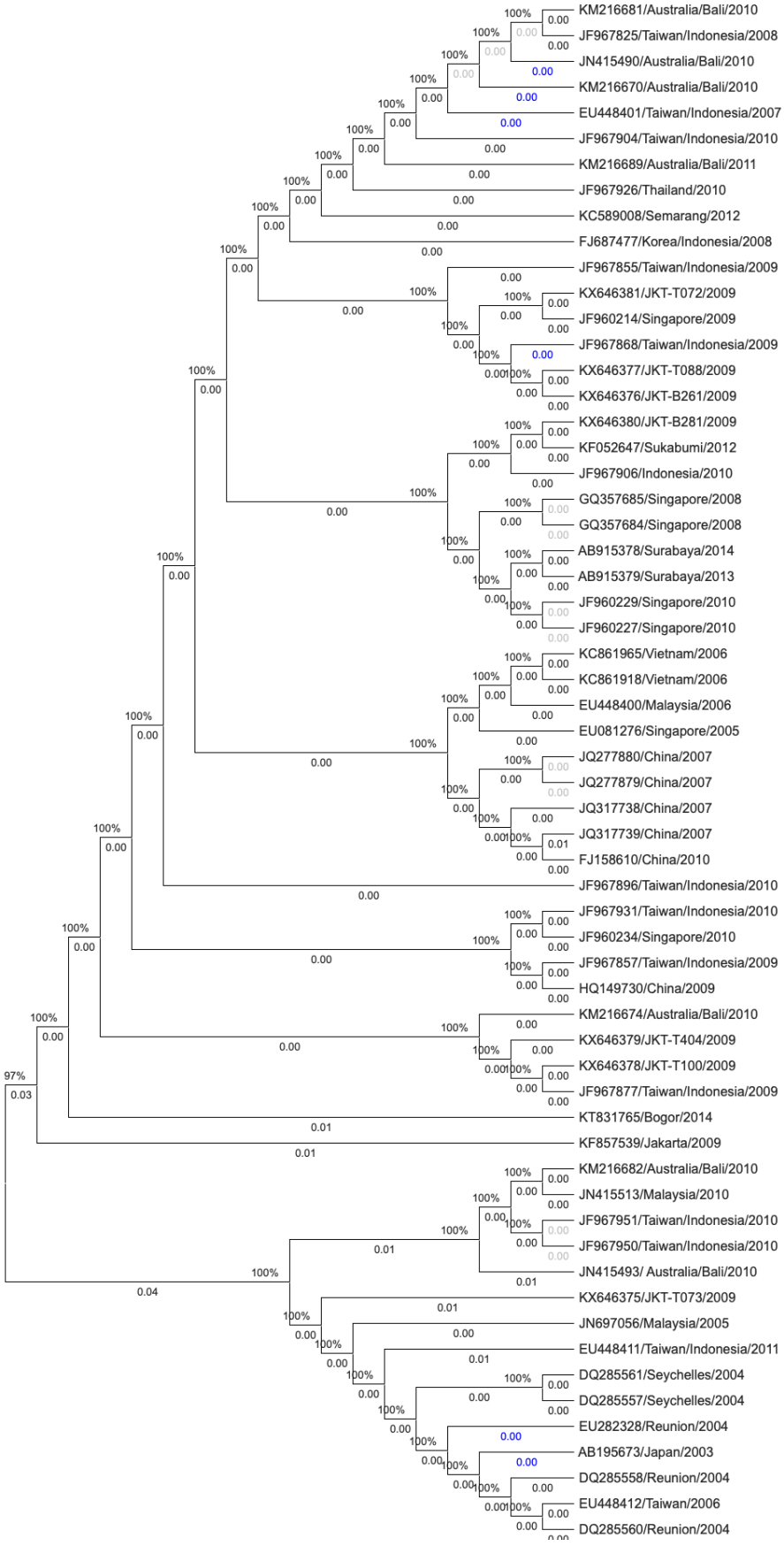

Figure 1. Phylogenetic tree for DENV-1

DISCUSSION

DENV 1 strains from Jakarta 2009, Bogor 2014, Sukabumi 2012, Semarang 2012, and Surabaya 2013–2014 are closely related, with low genetic distances (Dist ≈0.001–0.02) and nucleotide identities of 98–99.9%, indicating a genetically stable endemic lineage persisting across multiple cities and years. This pattern is consistent with reports that DENV 1 Genotype I predominates in many parts of Indonesia and forms a Southeast Asian cluster together with strains from Malaysia, Singapore, and Thailand (Hamel et al., 2019).

Isolates labelled "Taiwan/Indonesia", "Korea/Indonesia", and "Australia/Bali" in the dataset showed very high homology to Indonesian strains (≈98.5–99.7%), indicating that imported cases detected in non-endemic countries largely reflect direct dissemination of the Indonesian endemic lineage without major changes in the E gene (Megawati et al., 2017). Several other Southeast Asian strains (Malaysia, Vietnam) exhibited slightly lower homology (≈90–95%), suggesting that they belong to the broader Asian DENV 1 backbone but occupy distinct subclades/genotypes, in line with DENV 1 phylogeography that delineates multiple regional lineages across the area.

The Réunion/Seychelles strains showed only about 90–91% homology to Indonesian strains but were highly similar to each other (>99%), indicating an Indian Ocean lineage that has long been separated from Indonesian/Southeast Asian lineages. Evolutionarily, these findings suggest that DENV 1 was likely introduced to Indian Ocean islands via historical Asian importations and then evolved in relative isolation, resulting in a clearly more divergent cluster compared with contemporary Indonesian lineages (Li et al., 2022).

The combination of high intra-Indonesia homology and similarly high identity between Indonesian strains and travel-associated cases supports the role of Indonesia as an important source of DENV 1 Genotype I for imported infections in East Asia and Australia, while maintaining genetic stability domestically. From a phylogeographic perspective, Indonesian DENV 1 can be viewed as part of a dynamic Southeast Asian transmission network with bidirectional viral flow to and from neighboring countries, yet it remains clearly separated from the older, more divergent Indian Ocean lineage, as reflected in the latest global DENV 1 genotyping frameworks (Sasmono et al., 2025).

CONCLUSION

DENV 1 strains circulating in Indonesia based on the envelope gene are dominated by a single, genetically stable endemic lineage within Genotype I that spans multiple cities and years with very low intra-lineage diversity. The very high homology between Indonesian strains and travel-associated cases (Taiwan/Indonesia, Korea/Indonesia, Australia/Bali) indicates that Indonesia acts as an important source of exported DENV 1 without substantial adaptive change in the E gene during international spread. In contrast, the markedly lower similarity and distinct clustering of Réunion/Seychelles viruses support the existence of an Indian Ocean lineage that has diverged from the Southeast Asian backbone after historical introductions. These findings emphasize a regionally structured DENV 1 population and underline the need to strengthen integrated genomic surveillance to monitor lineage dynamics, anticipate cross-border transmission, and inform vaccine and control strategies tailored to the Indonesian endemic setting.

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DECLARATIONS

1. Ichwan Baihaki conceptualized the study, designed the research methodology, and supervised the overall research process. Mutmainnah contributed to data collection, data analysis, and drafting of the manuscript. Miftah Khairiyah Zamzam was responsible for literature review, data interpretation, and manuscript editing. All authors have read and approved the final version of the manuscript.
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