Research Article

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# Integrative Phylogenomics and Spatial Epidemiology Reveal the Role of Avian Migration in Japanese Encephalitis Virus Evolution

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## Abstract

Japanese Encephalitis Virus (JEV) is a zoonotic flavivirus, which is responsible for outbreaks of vector-borne encephalitis in Asia, affecting presently around four billion people. The genetic variability of JEV, their phylogenetic relationships and the geographical distribution is evaluated to determine the trend of its transmission and evolution. Viral vectors were found to be highly divergent, with birds and mosquitoes being the main vectors in viral transmission. In analyzing avian migratory pathways, GIS showed that the number of accommodations significantly increased in East and Southeast Asia, particularly in China and Japan. In this study, genetic data were used to assess with BIOEDIT, MEGA and QGIS software and spatial data were added to capture the relationship between the migration of birds and the transmission of JEV. The findings highlighted the adaptability and evolutionary nature of the virus and confirmed that the One Health approach is better. The findings of this study will be invaluable in improving the control of Japanese Encephalitis, surveillance, vaccine development and management of vectors.

## 1. Introduction

Japanese Encephalitis is one of the most severe forms of vector-borne viral encephalitis that is mainly present in Eastern Asia, the Pacific and some parts of Australia **(Wang and Liang 2015)**. Japanese encephalitis (JE) is an acute viral encephalitis due to Japanese encephalitis virus (JEV) which belongs to the genus flavivirus, a member of the family Flaviviridae **(Guo *et al.* 2024)**. This disease is zoonotic and spread by mosquito bites. This virus can severely infect children and has caused a large number of epidemics in Asia. Recent research suggests that the endemic areas are at risk of infection and are a major threat to public health **(Wei *et al.* 2025)**. The transmission cycles of JEV are complex and the mosquitoes are the main vectors with pig and birds as amplifiers. Of these avian species, migratory birds are important in the transmission and spread of JEV **(Ricklin *et al.* 2016)**. These migratory birds are natural hosts of the virus and can spread the virus between regions of the country during migrations. Such a dynamic provides room for genetic variation of JEV, giving it the ability to survive in a wide range of environments **(Hameed *et al.* 2021)**. The countries with JEV strains to which the birds migrate, such as China, India, Vietnam and Japan, have been recorded to have a high level of genetic variation **(Gao *et al.* 2013)**. There are innovative developments in the field of integration of geospatial data and biosciences in studying the epidemiological, genomic and phylogenomic features of JEV **(Peng *et al.* 2025)**. These tools can be used for genetic frequency distribution analysis and geographical spread of the virus and can be used to get some insights into the virus behavior **(Trifonov and Rabadan 2010)**. The goal of the study is to combine the genetic and geographical information using tools like multiple sequence alignment, phylogenetic trees, and geospatial analysis **(Janies 2019)**. This study uses BIOEDIT, MEGA and QGIS software and analytical tools based on python to analyze the factors that affect the evolution and spatial distribution of JEV **(Longbottom *et al.* 2017)**. It is of prime importance to understand the modes of JEV transmission for effective control measures including immunization and vector control. In addition, ecological and geographical information can be used to help identify which factors affect the transmission of viruses and to help implement measures to limit the occurrence of them **(Park and Lee 2025)**. In this study, a multidisciplinary approach is used with a focus on the interrelationship of human, animal and environmental health to help mitigate JEV risk **(Adnyana *et al.* 2023)**. This research will contribute greatly to understanding how bird migration, genetic variation, and spatial distribution of the JE virus relate to each other and can impact on the distribution and control of the disease by genomics and spatial analysis **(Larison *et al.* 2021)**.

## 2. Materials and Methods

Interdisciplinary cooperation, including geographical information and computational analysis and construction of phylogenetic trees, was used to conduct a comprehensive and deep evaluation of the epidemiological, genomic and geographical characteristics of JEV **(Yan *et al.* 2026)**. The study workflow involved the following steps: data collection, sequence comparison, phylogenetic testing, geographical representation and combination of the genotype data with geographical information **(Zou *et al.* 2024)**. The first step is to retrieve data, where information is gathered from NCBI data base of JEV, listed with geographic coordinates of each sequence and additional data that was supplemented based on geographical location **(Li *et al.* 2025)**. By employing specific search, based on the region of the target gene and the genotype information, it is possible to use various search methods. Partial sequences, duplicate sequences, ambiguous (annotated) sequences and low-coverage sequences were not supplied for analysis **(Markello and Adams 2013)**.

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To capture broad data, sequences from a variety of geographic origins and different genotypes were added up to the date of 22nd December, 2025. 50 sequences were obtained from the NCBI GenBank database using the pre-established search criteria **(Muhee *et al.* 2026)**. Accession number, sequence length, collection date, host species, geographic origin and genotype classification were collected and curated into metadata for subsequent downstream analysis **(Nyathi *et al.* 2025)**. It is therefore important to ensure the reproducibility and transparency of the data set by providing accession numbers in **Table S1**, and showing the workflow for curating and filtering the data set in the updated **Figure 1**.

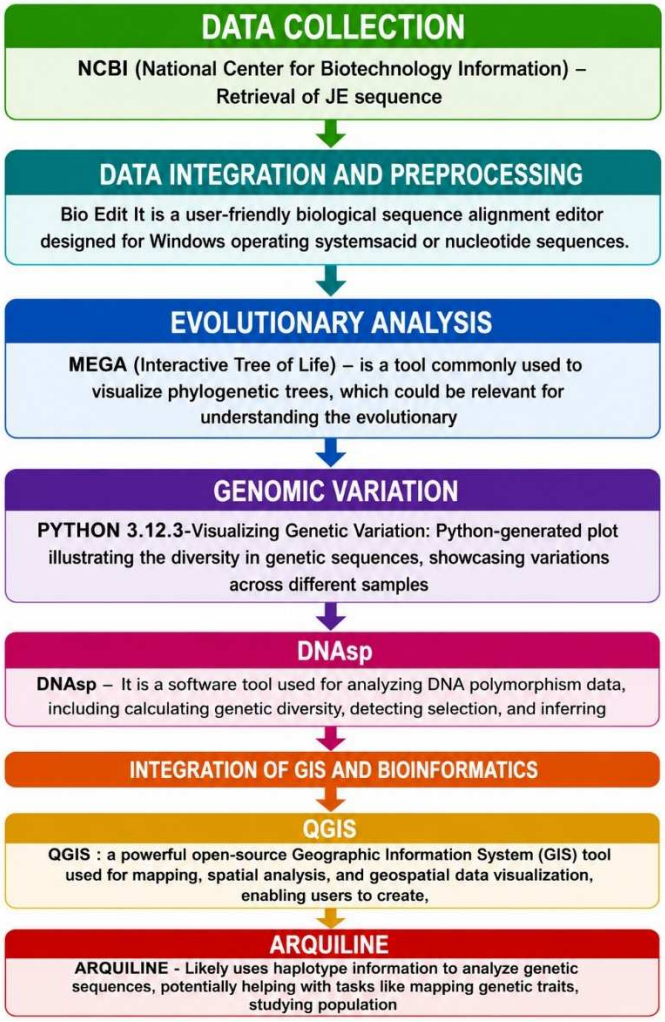


**Figure 1.** The overall methodology adopted in the current study.

The data sets were used as the basis for further analysis. Multiple sequence alignment was done using the acquired genetic sequences with the software BIOEDIT **(Sanchez-Villeda *et al.* 2008)**. To exclude poorly aligned areas and gaps, sequence alignment and sequence trimming was carried out before the phylogenetic analysis. This allowed capturing genetic variation among the JEV strains and enabled phylogenetic analysis **(Paranjpe and Banerjee 1996)**. A phylogenetic analysis was performed using MEGA software to construct evolutionary trees for the purpose of comparison among different JEV strains. This analysis has included some insights into the genetic variation of JEV and evolutionary model **(Han *et al.* 2014)**. The exact percentage of genetic difference between two related organisms can be determined numerically. The average pairwise genetic distance was therefore analyzed using python tools, which showed the variations in the JEV genome for the various regions **(Liao *et al.* 2025)**. Geospatial software called Quantum Geographic Information System (QGIS) was used to combine the genetic and geographical data. The next step in the analysis was to identify the geographical origin of the JEV strain sequences using the metadata information **(Graser *et al.* 2025)**. The aim of the graduated point map is to analyses the spatial structure of genetic variation in order to understand the geographical distribution of the transmission of JEV. The spatial mapping showed that migratory bird routes were involved in the spread of the virus, with genetic variations found in the areas along these routes **(Longbottom *et al.* 2017)**. Further statistical analyses were conducted to make the results easily interpretable. The relationship of geographical regions, bird migration and genetic score indices were explored in this study. The results showed that migratory birds are reservoir hosts for JEV, which affects the genetic diversity and distribution of the virus **(Hameed *et al.* 2021)**. In the present study, the spatial distribution of JEV sampling locations was the main focus of the GIS based analysis but other environmental and ecological factors like climate, vector abundance, land use and patterns of migratory bird movement may also contribute to viral spread and should also be investigated in future studies through integrated spatial-statistical approaches **(Zhao *et al.* 2021)**. Innovative and efficient techniques and approaches were adopted in the study design to obtain epidemiological and genetic profile of JEV. The biological and geographical approach used in this study thus allowed the identification of factors that might affect the geographic distribution and continued circulation of JEV **(Moore 2021)**. It is a comprehensive approach that has been designed to improve understanding of JEV and to facilitate the development of targeted public health prevention and control measures, such as improved surveillance, the development of vaccines and management of JEV vectors **(Sahu *et al.* 2022)**. The methodology is planned to be expanded in the future to include a wider geographic coverage, more strains and to include environmental and climate information to increase the knowledge of the background information of JEV transmission **(Kulkarni *et al.* 2018)**.

## 3. Results

### 3.1. Geographical Characteristics

The compiled dataset covers a wide range of biological sequence knowledge, including genetic, geographic, host, temporal, and geographical variations. Table S1 represents a sequence identified by the series' distinct "Sequence_ID." Additional data necessary for sequence comparison in ecological, epidemiological, and genetic research is also included. The variety of the "Average Pairwise Differences," which calculate the genetic dissimilarity across sequences, is one of the dataset's most notable features. Some of the sequence elements, such as LC687613.1 (151.16) and LC461959.1 (159.54), are genetically quite distant, and these values have been fluctuating from 53.82 to 150. Such a wide range suggests additional selecting factors, which could result from regional variations in pathogenicity, host spectrum, or environmental variables. The overall methodology adopted in the current study is shown in **Figure 1**. Geographically speaking, the information spans a broad spectrum of countries, including Vietnam, the Philippines, China, India, and Japan. Further geographical classification is made possible by some entries' better geographical resolution, such as Kochi in Japan and Zhejiang in China. The fact that Zhejiang, China, accounts for most of the entries suggests that the area is interesting and could be perfect for further local research or epidemic cases. The geographic extent further emphasizes the dataset's value for changes in gene regions concerning geographic locations, which are crucial for ecology, host-pathogen interactions, and disease vector transmission. Accordingly, the diversity of hosts in the provided dataset adds to the study's overall significance. Animals such as pigs, cattle, *Sus scrofa domesticus*, *Bos taurus*, the vector mosquito, *Culex tritaeniorhynchus*, and *Culex pipiens pallens* are among the hosts, in addition to humans. A significant indicator of vector-borne infections, especially those responsible for zoonotic diseases, is the inclusion of mosquito vectors. A single health approach that considers the health of people, animals, and the environment is necessary because some can infect humans and animals. The presence of humans and cattle as

hosts raises the likelihood of zoonotic spillover, which is essential to monitor in regions with a high human-animal interaction. Time-series data from 2004 to 2021 were included in the data set. While some records contained complete collection dates, others provided only the year of sample collection. Understanding genetic sequences' ontogeny and synchronic relevance is greatly aided by this time dimension. In other words, variations in genetic variability throughout time make evaluating adaptation, mutation, and the consequences of environmental change or disease prevention possible. Also, some months and years have relatively many collection dates. For example, the presence in Zhejiang, China, in August 2019 could be due to captive sampling or outbreaks or specific surveying efforts in these regions.

The entries are each followed by the latitude and longitude coordinates to make the data more useful by allowing it to be visualized geospatially. High resolution geographical coordinates are needed for the distribution of genetic variations, for the identification of regions showing high genetic polymorphism, as well as for the obtaining of sequence data related to the geographical distribution of climate, habitat type or population density. In this example, the observed clustering may be either because sampling was targeted or because the region is of special ecological or epistemological value, such as the province of Zhejiang in China, for which dense sequences were observed. In addition, data from Yamaguchi and Kochi, Japan show samples from a variety of hosts including domestic animals and insects. With this information, there's a ton of potential for research in a variety of fields. Genetic variation measurements in evolutionary biology can be used to detect host and regional differentiation and adaptation. It may be useful from an epidemiological standpoint when studying the epidemiology of a disease, outbreak dynamics, and the importance of habitats and geographic areas in the development of the disease-causing organism. A similar function can track the evolution and spread of particular sequences, estimate the likelihood of inter-species spread and clarify the significance of the lineages. In addition, the focus of the data set on vector-borne infections, hosts, and geographical distribution reflects the current global health targets, especially zoonoses.

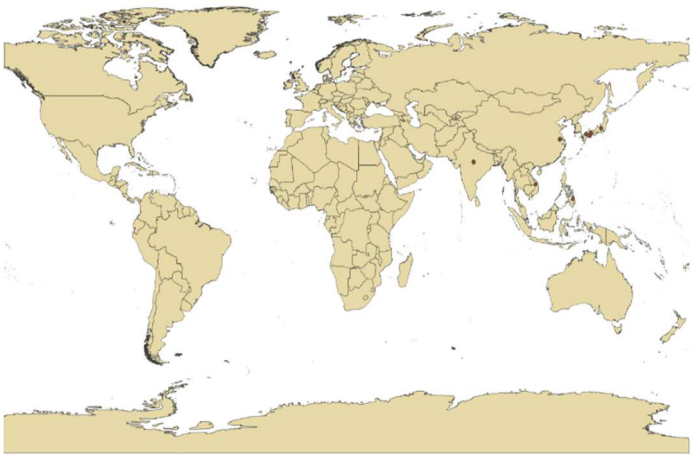

**Figure 2.** The geographical location of sampling points is based on the dataset's entries on the world map. These points are particular geographic areas that contain the obtained samples, and there are several large concentrations: East Asia, for example, China and Japan; South Asia, for example, India; and Southeast Asia, for example, the Philippines. The clustering patterns indicate regions that have been more intensively studied or sampled, perhaps associated with investigations of vectors, zoonoses, or host-pathogen relationships. Areas apart from these highlighted areas have few or no data dots, suggesting low sampling or a different sampling focus in these areas, such as Africa, the Americas, and Europe. That is why the focus of this map is shifted to the area of coverage and the areas of interest for ecological and epidemiological research.

### 3.2. Geographic points of interest

In **Figure 2**, geographic locations of interest around the world are shown, and the data points used to determine are largely those associated with ecological or biological studies. The points are clustered in areas of the world, including East Asia, South Asia, and Southeast Asia, with a notable density in countries such as China, Japan, India, and the Philippines. The significant East Asian clustering, especially in areas like China's Zhejiang Province and Japan's Kochi, identifies areas of considerable sampling or research focus, which may be related to investigations of zoonotic infections, vector-borne diseases, or organism genetic diversity. The inclusion of points in South Asia (including India) and Southeast Asia is based on their high population density and ecological diversity, making them important areas for research into infectious diseases, biodiversity or interactions between host and pathogen.

There are few data points in important areas of the map, such as Africa, South America and parts of Europe, suggesting a deliberate bias towards Asia Pacific or a failure to conduct sampling attempts in other regions. This spatial bias might be due to research objectives about the local ecological dynamics, endemic species or disease outbreaks. The lack of sites in the polar regions and many in the Americas may indicate that much of the data is skewed towards tropical and temperate regions where host-vector-pathogen interactions are more active. The map outlines the geographic distribution and concentration of study's focus areas and acts as a spatial visualization tool. It offers information on ecological relevance, genetic or epidemiological study hotspots, and regional research goals. This visualization is critical for determining gaps in the sampling and planning for future sampling directions, suggesting potential hotspots for biodiversity and/or public health protection.

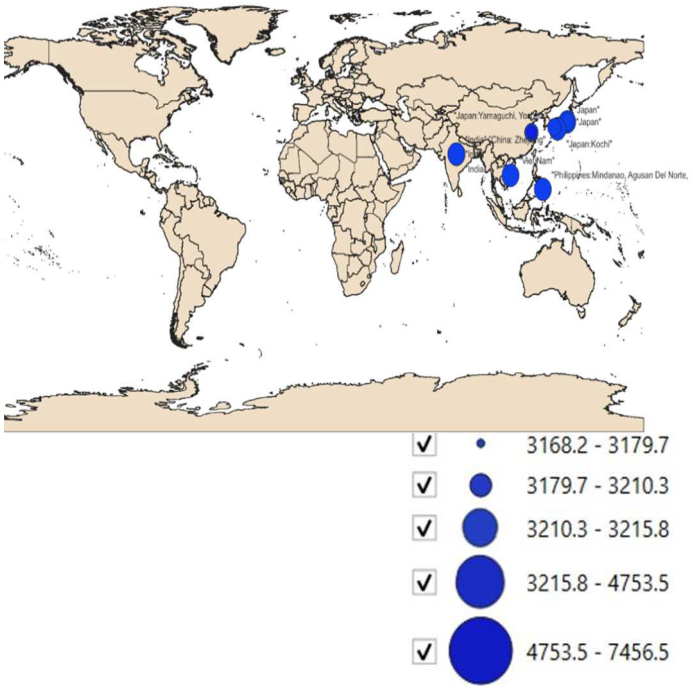


**Figure 3.** A graduated point map of the geographic location of data points is illustrated as blue circles with different areas. Each circle is drawn to scale (with sizes corresponding to numerical values indicated by the scale bar at the bottom), which may represent variation, pathogens, or another relevant statistic, such as genetic variability. The sizes of the circles are proportional to those values; a larger circle indicates a higher value and vice versa. Some major sampling sites are in China, Japan (Kochi, Yamaguchi), the Philippines (Mindanao, Agusan Del Norte), and India. These areas show where researchers concentrated their sampling or research efforts; the East and Southeast Asia region stands out clearly, but other areas of the world have been revealed to have quite different degrees of data coverage.

### 3.3. Graduated Point Map of Geographic Distribution

**Figure 3** displays a heat map with the locations of the data-containing points represented by blue circles of different sizes; the key to figuring out where the points are is the color's intensity. The graduated scale numbers on the left most likely correspond to the location on the map on the left, which shows quantitative data such as the pathogen load, population density, or genetic host variation. Bigger circles indicate greater values, while circles with lesser diameters indicate smaller values, as seen in the preceding pictures. Most of the data points comprise East Asia, South Asia, and South East Asia. Notable locations include China, Japan, Kochi, and Yamaguchi, and the Philippines, Mindanao, and Agusan Del Norte. The size of the circles indicates areas of more biological or ecological interest, and regions with more excellent study or sampling activity are the focus of this spatial depiction. The considerable species variety, high population density, comparatively large proportions of zoonotic diseases or vector-borne pathogens, and the fact that East and Southeast Asia are research focal centers may all contribute to the clustering pattern. Low sample density or a focus on ecological/epidemiological niches may cause the dearth of data points in significant Americas, Africa, and Europe regions. The graduate map's consistency in the application is highly useful for highlighting dataset variances, which may help draw specific conclusions, identify areas for further study, or assess the distribution of phenomena under investigation. In essence, this map efficiently draws attention to the crucial study topics and graphically represents the significant quantitative qualities.

**Figure 4.** Based on the multiple sequence alignment of nucleotide sequences of JEV of various strains, the sequences are numbered consecutively with row labels referring to the actual strains and columns referring to positions in the nucleotides. The conserved regions appear as the vertically aligned bases where all strains are represented with the same nucleotide; the mutations are indicated with the different nucleotides. Adequate contrast facilitates free viewing of sequence homogeny and heterogeneity; the four nucleotide bases are color-coded with adenine, thymine, guanine, and cytosine. Precisely, the regions of strict conservation and variation are pinpointed, and these may correspond to functionally or structurally significant genomic entities, as well as genetic variability among the strains. This analysis is crucial for tracking JEV evolution, defining conserved targets for diagnostic and vaccine, and discovering new genetic variations associated with strain-specific adaptation or pathogenicity.

### 3.4. Phylogenetic analysis

Multiple sequence alignment of nucleotide sequences from different strains of JEV (identified by access number e.g., "AJ577638.1", "MN403081.1") is shown in **Figure 4** as letters and symbols. It shows the continuity of the sequence and the variations between the strains from one another. The rows are sequences and the columns are single nucleotide positions. The conserved regions correspond to the vertical lines of the same nucleotide (A, T, G, C), while polymorphic sites correspond to the vertical lines of different nucleotide at a certain position. As with the previous alignments, the colouring is provided to highlight the four nucleotide bases, A, T, G and C, to allow the identification of constant and variable positions. Conserved blocks are more likely to be indicative of genome regions that are evolutionarily important and contain regions that are of functional importance and/or structural significance, and which are not readily evolved to change. In contrast, variable regions of the genes are polymorphic due to mutations, gene rearrangements or selective pressures from the host or environment. This alignment is important for studying the genetic evolution and phylogenetic analysis of various strains of JEV. The reported modification may include the development of new sublineages, switching to a new host or some other strategies to avoid the host immune system. In addition, preserved sections may be used as the basis for making diagnostic instruments, vaccines and antiviral drugs. This alignment is the basis of a preliminary assessment of the variation and dynamics of JEV in the genome.

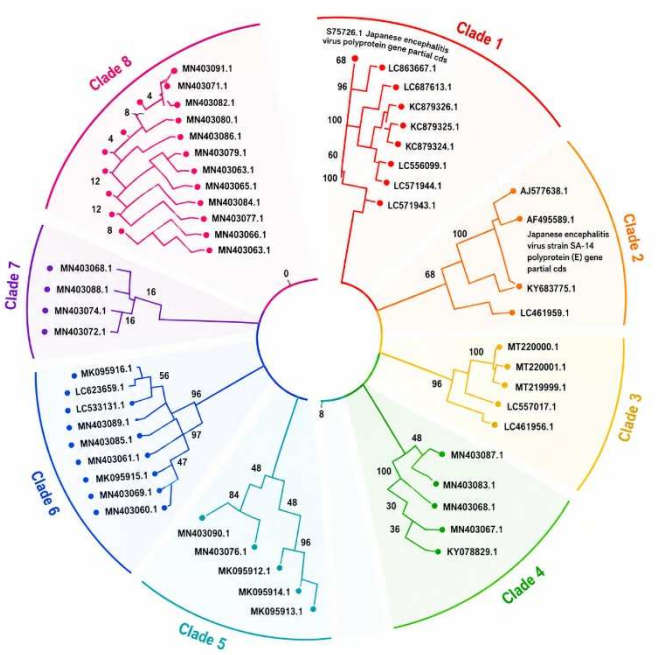


**Figure 5.** The epidemiologic tree of JEV is shown by the branch map of Japanese encephalitis virus strains by partial nucleotide sequences of polyprotein or envelope (E) gene. Phylogenetic analysis was performed using the Maximum Likelihood method implemented in MEGA software. The best-fit nucleotide substitution model was selected using the "Find Best DNA/Protein Models" function in MEGA based on the lowest Bayesian Information Criterion (BIC) value. The GTR+G+I model was identified as the most suitable model and was subsequently used for phylogenetic tree construction with bootstrap analysis of 1000 replicates. The tree was built by the maximum likelihood approach, and the bootstrap values at the branching points of the tree are the level of confidence of the clade. The accession numbers locating the sequences from GenBank are also presented on the branches. The tree also shows that genetically related strains group together into clades; bootstrap values are significant (96-100). Circulating strains like "AF455589.1" (JEV strain SA-14) are also used for reference.

The **Figure 5** shows a tree in the context of phylogenetics, a graphic representation of the relations between objects that are sequences of DNA. Sequences with accession numbers (such as S75726.1, LC638667.1) might represent strains of JEV. A phylogenetic tree is based on nucleotide or protein sequence data, and is built on a branching pattern that represents the evidence of divergence. The circles are used to represent an ancestor and the arrows to show the different ways a strain can be derived from the common ancestor. Genetic relatedness is the basis for the classification of sequences into distinct clades while the isolation of sequences is due to divergence. Not surprisingly, various values of branch support are shown at particular nodes, with values of 96 and 100 being the most commonly

used. The nodes with low bootstrap support values (<70) should be treated with cautiousness because support for them may be less.

There exists a significant genetic diversity among the JEV strains in the tree. For example, sequences such as "S75726.1" group together within a clade, that is a collection of sequences with several distinct variants of a gene, and this grouping is more notable compared to other sequences, which creates a branch off of more divergent sequences. Assessment of circulating strains can be helped by the presence of reference strains e.g. a vaccination strain known as "AF455589.1 Japanese encephalitis virus strain SA-14". Such comparisons are critical to track genetic variation that could indicate changes in previously reported vaccination effectiveness. Sequences with analogous prefixes (e.g., "MN403") in the clusters indicate the number of isolates from the same epidemic and/or geographic location, meaning they are genetically related and have evolved recently.

The topology of the tree indicates that the possibility of backcrossing or sublineages in the JEV population exists. This observation is indicative of the evolution of the virus, and the particularly high mutation rates of RNA viruses. They have several biological implications for such conclusions. Phylogenetic studies provide information on the distribution of JEV and the changes it has undergone in the past, as seen from an epidemiological point of view. Genetic methods can be used to trace the origin of the strains, the geographical spread of diseases and the factors responsible for the genetic variation. A knowledge of the relationship between the circulating strains and reference or vaccine strains is essential for public health and vaccine use. If there is a significant antigenic difference between the two strains and the currently used vaccines in the UK then modification of existing vaccines may be necessary in response to these strains. The branches of the tree show that the virus can evolve, as seen by the genetic diversity among the different variants. The analysis of these genetic variations can highlight changes that could increase pathogenicity, host-parasite specificity or immune evasion.

## 4. Discussion

This study has comprehensively examined the genetic structure, migratory patterns of birds and geographical distribution of JEV to provide important insights into the evolutionary, transmission, and ecological history of JEV. The phylogenetic tree analysis explicitly showed a substantial genetic variation between JEV strains. Further, it explained the high adaptability of the virus to the different hosts and environmental changes. Then, there are indications of clustering that are common in the branching pattern of the phylogenetic tree, along with the development of new clades and sublineages that may result from selective forces such as those of host immunity and environment. The findings highlight the importance of monitoring any changes that occur in the genome as they occur frequently and could influence the virulence of the virus, the vaccine's efficacy, and viral immune evasion. This is made evident by the geospatial analysis conducted in the study to show that migratory birds are involved in transmitting JEV. Bird migration routes were also genetically very diverse, such as in Zhejiang, China, and Kochi, Japan, in east and southeast Asia, respectively. In addition, the virus is found in several different geographic regions, which helps to suggest that migratory birds carry this virus from one geographical region to another. The genetic and geographical analysis data described in this paper were merged with the help of various tools, such as the QGIS software, to map the regions where high genetic polymorphism was found and provide a detailed overview of the role of ecological factors in JEV transmission. This information is crucial in determining which areas are most likely to experience spillover from animals to humans, and hence make these areas a target for surveillance and control vectors.

Host diversification analysis revealed that the virus is amplified and transmitted by pigs, cattle and some mosquito species. The data set covered humans and animals, acknowledging the interlinkages between humans, animals, and the environment in the transmission of JEV in line with the One Health concept. The presence of genetically diverse strains in areas with a high risk of human-animal interaction, especially in endemic areas is disquieting. It means that health interventions need to be based on an integration of the ecological, epidemiological and genetic data. The genetic variability of the study sample was analyzed in time showing cyclic evolution of JEV over time. Certain outbreaks might help to explain periods of greater genetic distance, such as adaptation to changing environmental conditions, or change in the types of vectors. These findings highlight the importance of continuous genomic surveillance to identify new strains and understand the potential impact of these changes in their disease management. The temporal and regional scale of the data is adequate for investigating potential drivers of JEV distribution and evolution, such as climate change and habitat changes.

This study introduces an interdisciplinary research framework that combines genomes, phylogenetic analysis and geostatistical modeling to gain insight into JEV transmission and evolution. Understanding the genetic features and environmental cues of the pathogen is crucial for developing public health interventions such as the development of vaccines, control of vectors, and the use of the appropriate surveillance system. The present study was mainly conducted for alignment and phylogenetic analysis but detailed study of mutation hot spots, conserved sequences and functionally important genomic regions will be carried out in future studies to understand the evolution and functional significance of the genetic variation of JEV. The use of advanced techniques like the Bayesian phylogenetics, time-scaled evolutionary analysis, phylogeographic diffusion modelling, machine learning based spatial prediction, selection pressure analysis and haplotype network analysis would yield more insights into the evolution and epidemiology. Future research could include variables like temperature, humidity, and precipitation, along with a larger geographic area, to better understand the prevalence of JEV and develop strategies to prevent and control outbreaks.

## 5. Conclusion

This work elucidates the interaction between genetic differentiation, migratory birds, and the global spatial distribution of JEV. The phylogenetic tree analysis revealed substantial genomic variety, suggesting that the virus exhibits significant evolutionary activity. Spatial analysis underscored the role of avian migration in viral transmission and identified areas of heightened genetic diversity in East and Southeast Asia. The integration of genetic, ecological, and epidemiological data substantiates the application of the One Health strategy in mitigating JEV transmission. This data is crucial for enhancing surveillance, vaccine research, and vector control to manage this zoonotic virus more effectively.

## 6. Disclosure Statements

### 6.1. Author Contribution

**NN:** Methodology, Investigation, Data curation, Formal analysis, Bioinformatics analysis, Visualization, Writing – original draft. **CP:** Methodology, Investigation, Phylogenomic analysis, Sequence analysis, Data curation, Formal analysis, Visualization, Writing – original draft. **JANA:** Methodology, Computational analysis, Phylogenetic analysis, Investigation, Data curation, Visualization, Writing – original draft. **DJ:** Investigation, Spatial epidemiological analysis, Data curation, Statistical analysis, Visualization, Writing – original draft. **RBSK:** Investigation, Epidemiological data collection, Data curation, Statistical analysis, Interpretation of results, Writing – review & editing. **LR:** Methodology, Molecular and evolutionary analysis, Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **TA:** Investigation, Spatial data analysis, Validation, Interpretation of results, Visualization, Writing – review & editing. **KMS:** Conceptualization, Supervision, Project administration, Methodology, Validation, Interpretation of results,

Funding acquisition, Writing – review & editing, and final approval of the manuscript. KMS served as the corresponding author and was responsible for overall coordination of the study and manuscript.

### 6.2. Declaration of Generative AI

The authors used generative artificial intelligence tools solely for language editing and grammatical correction. The AI tools did not contribute to the study design, data collection, analysis, interpretation, or generation of scientific content. All content has been reviewed and approved by the authors, who take full responsibility for the integrity and accuracy of the work.

### 6.3. Ethics approval (for clinical/animal studies)

This study is entirely computational and does not involve human participants, clinical samples, identifiable personal data, or experimental animals. All analyses were performed using publicly available datasets and in silico methods. Therefore, ethical approval from an institutional review board or ethics committee was not required.

### 6.4. Informed Consent Statement

This study utilized publicly available datasets that do not contain identifiable personal information. Therefore, informed consent was not required.

### 6.5. Data Availability Statement

The computational data used and generated from this study are available from the corresponding author upon reasonable request.

### 6.6. Acknowledgment

Not Applicable

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### 6.8. Conflicts of Interest

The authors declare that they have no known financial, personal, academic, or other relationships that could inappropriately influence, or be perceived to influence, the work reported in this manuscript. All authors confirm that there are no competing interests to declare.

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### 6.10. Supplementary Information

Supplementary material is available for this article at https://jomi.aayvu.com/SuppFile/221919/1/

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## 7. Reference


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