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Molecular evolution of dengue virus: Bayesian approach considering 1,581 whole genome sequences from January 1944 to July 2022

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Abstract

Dengue is a viral disease transmitted by mosquitoes that in recent years has spread rapidly across all continents. The dengue virus is transmitted by female mosquitoes *Aedes aegypti* species and, to a lesser extent, of the *Aedes albopictus* species. There are four distinct but closely related serotypes of the virus that causes dengue (DENV

INTRODUCTION

Dengue fever (DF) is a tropical disease caused by the dengue virus (DENV) belonging to the Flaviviridae family [1]. Considered a zoonotic arbovirus, it is mainly transmitted by the female mosquitoes of the *Aedes aegypti* species, and to a lesser extent by other species such as *Aedes albopictus, Aedes polynesiensis, Aedes scutellaris* [1]. Humans are the main reservoir and host causing global spread and therefore it has been a major public health concern, with an incidence increase of 30-fold in the last five decades [2]. It was estimated from de 2013 Global Burden of Diseases (GBD) that, in that year, there were 58·40 million dengue cases in 141 countries, with a 18% hospital admission rate and over 13,000 deaths. The annual global cost with the disease was 8,9 billion dollars [3].

DF is a systemic and dynamic infection with a broad clinical spectrum of manifestations that may range from asymptomatic disease to serious and life-threatening hemorrhagic syndromes, known as dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). Both these phases are considered complications, and uncomplicated cases are characterized by self-limited fever, lasting usually for 5–7 days. Dengue can be debilitating during the acute illness stage and classical clinical features in adults include high fever (usually biphasic), severe headache, retroorbital pain, myalgia, arthralgia, nausea, vomiting, and petechiae. Leukopenia and thrombocytopenia are frequent findings[2]. No effective therapy is currently available and treatment is purely symptomatic, requiring a high level of patient care. Patients can be hospitalized to facilitate fluid replacement and blood transfusions, when indicated. Severe cases occur in approximately 500,000 people/year and present a mortality rate of up to 10% for hospitalized patients and 30% for non-hospitalized patients[4].

A single-stranded RNA virus, DENV has a positive-sense genome, containing approximately 10,700 bases. This genome contains a single open reading frame (ORF) which, when cleaved, gives rise to three structural proteins, capsid [C], pre-membrane [prM], and envelope [E], and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5) [5–7]. The various genotypes of DENV arise due to the action of an RNA polymerase that lacks proofreading activity, resulting in at least one new mutation being produced with each replication of its genome [7,8].

About 1,000 years ago, it is estimated that an infectious cycle between non-human primates and mosquitoes gave rise to the four serotypes of dengue virus as they are known today and they share approximately 65% amino acid sequence similarity. The first time the virus was isolated, in 1943 in Japan, was named DENV1 (with 5 genotypes) and this same serotype was reported in the Americas in 1977 and in Africa in 1984[8,9].

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Approximately 400–600 years ago, DENV2 (with 5 genotypes) diverged from the sylvatic ancestor and was first isolated in Hawaii in 1945, in 1964 in Africa and 1953 in the Americas[9,10]. In 1956, DENV3 (with 4 genotypes) and DENV4 (with 4 genotypes) were first reported in Asia (Philippines and Thailand). DENV3 arrived in 1962 in Asia, in 1963 in the Americas and in 1984 in Africa. DENV4 had its report not as faithful as it happened with the other serotypes so, it was not reported until 1981 in Americas[9,11,12].

These four serotypes are genetically similar and share approximately 65% of their genomes but each dengue virus serotype shows antigenic differences which often have spatial and temporal disjunct distributions. One genotype of one serotype can persist for many years in a given geographic region and then die out and even be replaced by a new genotype or lineage but still cause very similar disease[13,14] in humans lineage replacement events had several explanations: a) the stochastic nature of DENV transmission; b)variations in conditioning within a population; c) increased viremia in the human host are cited as reasons for these antigenic differences; d) Co-circulation of multiple dengue serotypes, however, epidemiological studies have shown that immune enhancement is also a strong line of evidence [12,15,16].

The dengue fever is a serious public health problem in many countries around the world, and the lack of specific treatments and effective vaccines makes disease control more difficult. In addition, the lack of basic infrastructure in growing population areas, such as sanitation, garbage collection, water treatment, and sewage treatment, creates an environment conducive to the proliferation of the dengue mosquito. Although awareness campaigns, environmental cleanup and sanitation, and case monitoring can help reduce the incidence of the disease, ongoing research is essential to better understand the pathogenesis of the disease, the factors that affect the transmission of the virus, and how environmental factors can influence mosquito control. This research is crucial to develop more effective strategies for the prevention, diagnosis, and treatment of dengue [7,17,18].

The present study evaluated and reviewed the temporal spreading and evolution of dengue virus serotypes worldwide by Bayesian method evaluating 1,581 whole genome sequences (WGS) of dengue virus obtained between January 1944 to July 2022.

METHODS

Dengue virus serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) WGS with available country and year of sampling were downloaded from GenBank and nextstrain [19] (Supplementary material). All dengue virus WGS were aligned by the MAFFT v7 and visually inspected with AliView v1.26. The best-fitting nucleotide substitution (GTR) model was selected using a hierarchical likelihood ratio, Akaike information criterion, and Bayesian information criterion tests with Model Finder in IQ-TRE web server (http://iqtree.cibiv.univie.ac.at/). Dengue virus maximum likelihood phylogenetic tree was inferred according to the best-fitting model using IQ-TRE web server (http://iqtree.cibiv.univie.ac.at/). We used this tree to obtain root-to-tip regressions in TempEst v1.5.

Time-scaled phylogenetic trees, evolutionary rates, and demographic histories of dengue virus WGS were evaluated using the Bayesian coalescent framework implemented in BEAST v2.6.2, which uses a Markov Chain Monte Carlo (MCMC) sampling method to obtain posterior distributions of tree topologies and parameter estimates[20]. Bifurcating nodes with posterior probability greater than 0.95 were considered statistically well supported. For each run of 900 million of MCMC, the marginal likelihood was estimated via path sampling (PS) and stepping stone (SS) methods and the resulting Bayes Factors (BF) (ratio of marginal likelihoods) was used to select the best-fitting clock/demographic model. The models can be compared to evaluate the strength of evidence against the null hypothesis (H0) defined in the following way: $2\ln BF < 2$ indicates no evidence against H0; 2-6, weak evidence; 6-10: strong evidence, and >10 very strong evidence. Both SS and PS estimators indicated the uncorrelated lognormal (UCLN) relaxed molecular clock (Bayes Factor = 30.3) as the best-fitted model to the dataset under analysis. Besides, we have used the GTR substitution model.

MCMC were run for 900 million generations to ensure stationary and adequate effective sample size (ESS) for all statistical parameters. Tracer v.1.6 software was used to diagnose MCMC, adjust initial burn-in. Bayesian coalescent analyses were performed to estimate the viral dynamics and the time to the Most Recent Common

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Ancestor (tMRCA). The time-scale calibration was based on the isolation date of samples. Uncertainty in parameter estimates was evaluated in the 95% highest posterior density (HPD 95%) interval. TreeAnnotator v1.8.2 was used to summarize the maximum clade credibility (MCC) tree from the posterior distribution of trees.

Dengue virus phylogeographic analysis, incorporating both spatial and temporal information, was performed with BEAST v2.6.2 using a discrete trait, symmetric substitution model with Bayesian stochastic search variable selection (BSSVS). The reversible discrete Bayesian phylogeographic model with a continuous-time Markov chain rate reference prior was performed. The number of viral migrations between locations was estimated using 'Markov Jump' counts of location-state transitions along with the posterior tree distribution. Migratory events across time were summarized using the SPREAD v.1.0.7. BFs>3 were considered as well supported diffusion rates constituting the migration graph.

RESULTS

In the present study, 1,581 WGS of dengue virus collected between January 1944 to July 2022 were evaluated. The distribution of the WGS were: Southeast Asia (n=361; 22.8%), North America (n=313; 19.8%), South America (n=288; 18.2%), China (n=168; 10.6%), South Asia (n=153; 9.7%), Oceania (n=148; 9.4%), Africa (n=89; 5.6%), West Asia (n=28; 1.8%), Japan/Korea (n=19; 1.2%), and Europe (n=14; 0.9%).**Table 1** shows the distribution of WGS by country, the most frequent were: Thailand (n=198), Brazil (n=151), USA (n=136), China (n=129), India (n=92), Nicaragua (n=85), Venezuela (n=64), New Caledonia (n=59), Singapore (n=46), Taiwan (n=39), and Mexico (n=38). The correlation between the nucleotide divergence and the years of sequence collection was positive ($R^2 = 0.91$; $p<0.01$) (**Figure 1**). Dengue virus substitution rates was 5.34E10-4 (HPD 95%: 4.53E10-4 to 6.85E10-6) nucleotides per site per year (s/s/y).

Figure 2 shows the phylogenetic tree of dengue virus WGS in the world by serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). The tMRCA of DENV-1 was 1884-11-15 (HPD95%: 1882-01-28; 1890-08-27) in Southeast Asia, DENV-2 was 1723-01-29 (HPD95%: 1714-05-22; 1728-10-09) in Europe, DENV-3 was 1921-04-12 (HPD95%: 1918-05-25; 1924-03-13) in Southeast Asia, and DENV-4 was 1876-03-28 (HPD95%: 1865-08-02; 1899-08-27) in Southeast Asia.

Phylogeographic data demonstrate the origin of dengue virus serotypes that circulated in the world (**Figure 3**). The molecular origin of the dengue virus was in Spain in 1682 (BF=38), later it was disseminated in Asia (Indonesia in 1838; BF=15) and Oceania (Papua New Guinea in 1844, BF=13). After this period, the virus spread to Asia (Malaysia, BF=13; India, BF=28; and China BF=30 in 1890) and in North America (USA; BF=35 in 1895).

In South America, it was first disseminated to Ecuador in 1897 (BF=15) and then to Brazil in 1910 (BF=38). During this same period there were disseminations to American countries such as the USA (BF=35) in 1915, Mexico (BF=20) in 1916, Puerto Rico (BF=18) in 1920, Cuba (BF=15) in 1922, Haiti (BF=10) in 1925, Nicaragua (BF=11) in 1925, El Salvador (BF=15) in 1928, Costa Rica (BF=18) in 1930, Panama (BF=17) in 1930, Jamaica (BF=7) in 1931, Trinidad and Tobago (BF=9) in 1932, Venezuela (BF=19) in 1932, French Guiana (BF=6) in 1934, Colombia (BF=15) in 1936, Peru (BF=13) in 1936, Paraguay (BF=11) in 1937, and Argentina (BF=7) in 1937 (**Figure 3**).

Dengue virus was initially disseminated in the African continent in 1917-04-07 (HPD95%: 1910-03-21; 1925-05-09), first in Senegal (BF=14) and after in Mauritania (BF=8) in 1919, Guinea-Bissau (BF=7) in 1920, Ivory Coast (BF=10) in 1922, Burkina Faso (BF=8) in 1925, Benin (BF=6), Cameroon (BF=5) in 1925, Gabon (BF=9) in 1926, Kenya (BF=14) in 1929, Djibouti (BF=7) in 1930, Somalia (BF=10) in 1930, Angola (BF=11) in 1932, Tanzania (BF=12) in 1934, and Mozambique (BF=6) in 1935. In Europe low dissemination occurred and this process initially was in Spain (BF=12) in 1682, France (BF=7) in 1938, Italy (BF=8) in 1955, Germany (BF=7) in 1957, and Portugal (BF=11) in 1965. Dissemination in Middle Eastern countries has been detected in countries such as Saudi Arabia (BF=18) in 1945 and Pakistan (BF=11) in 1947. In Asia, dengue virus was detected in Indonesia (BF=15) in 1838, India (BF=28) in 1842, Sri Lanka (BF=6) in 1845, Nepal (BF=7) in 1845, Bangladesh (BF=9) in 1846, Myanmar (BF=10) in 1848, Laos (BF=9) in

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1850, Thailand (BF=25) in 1854, Vietnam (BF=9) in 1858, Malaysia (BF=13) in 1860, Taiwan (BF=10) in 1861, Philippines (BF=12) in 1864, Singapore (BF=18) in 1865, China (BF=30) in 1867, South Korea (BF=13) in 1867, and Japan (BF=14) in 1869. In Oceania was detected in Papua New Guinea (BF=13) in 1838, Australia (BF=17) in 1850, New Caledonia (BF=8) in 1855, Fiji (BF=8) in 1857, Tonga (BF=6) in 1860, Samoa (BF=6) in 1862, Cook Island (BF=7) in 1865, and French Polynesian (BF=6) in 1870 (**Figure 3**)

DISCUSSION

Differing information regarding the origin of the DENV virus maintains the constant search for data that can provide a better understanding of this disease, which is one of the most important and also neglected in the world. Phylogeographic studies can help to understand the dispersion and evolution of a virus, as well as understand the dynamics of transmission and thus help to improve strategies for control and prevention of the dengue virus [21,22]. The present study reviewed the molecular evolution of dengue virus serotypes worldwide with 1,581 WGSs with sampling dates from Jan/1944 to Jul/2022. The results demonstrated that the tMRCA of DENV-1 was 1884 in Southeast Asia, DENV-2 was 1723 in Europe, DENV-3 was 1921 in Southeast Asia, and DENV-4 was 1876-03-28 in Southeast Asia.

DENV infections represent a major health and economic problem worldwide, and although most cases are asymptomatic or induce a mild degree of illness, the WHO estimates that around 500.000 people per year who develop severe dengue syndrome, need hospitalization[23,24]. With slave trade vessels and trade routes, the world's main urban vector of the dengue virus, *A aegypti* , originated in West Africa and arrived in Europe at the end of the 17th century [9]. Although there is a strong line of assertion that dengue originated in Asia, between the 19th and 20th centuries, our data point to the appearance of dengue in Spain in 1682 and later in 1838 in Indonesia. Break-bone fever or "Quebranta huesos" was a popular name do describe the disease and was used by a doctor from Puerto Rico when he described a febrile illness in 1771, and in 1801 the Queen of Spain, Maria Luisa de Parma, mentioned in a letter that she was suffering from a disease that caused bone and joint pain, presence of jaundice, hemorrhage, and fever. These symptoms are clinically consistent with those of dengue and this statement reinforces that the onset of dengue originated in Spain [23,24].

Stica et al., (2021)[27], used Bayesian evolutionary analyses and estimated the emergence of DENV1 in 1660s, and the time of divergence of the other DENV1 genotypes from the Malaysian wild isolate in 1886s [27]. Regarding the origin of DENV2, there are studies that suggest the common ancestor of DENV2 may have emerged even earlier than previously thought, possibly in Asia or Africa. A phylogeographic analysis conducted by Wei and Li (2017)[28] indicated that the most recent common ancestor dated back to 1917 [28]. However, Walimbe (2014)[29] showed that DENV-2 diverged from the sylvatic genotype around 1860, while Costa et al. (2012) dated the time to the most recent common ancestor to 338 years ago (1674)[29,30]. An analysis by Stica et al. (2022)[27] estimated that the epidemic genotypes of DENV2 diverged from wild isolates in the year 1733, suggesting an earlier origin of the virus and in this sense, our study corroborates the authors' findings and the date indicated for the emergence of DENV2 was 1723 in Europe [27]. Costa et al. (2012)[30] found the time to the most recent common ancestor of DENV3 to be in 1904, while in our analyses, we found an approximate date of April 12, 1921 (HPD95%: May 25, 1918; March 13, 1924). In relation to DENV-4, according to our analysis, the molecular origin is estimated to have emerged between the years of 1865 and 1899, even before serotypes 1 and 3. Costa et al (2012)[30]determined the time to the most recent common ancestor to be 203 years ago (1809). Our analyses are consistent with the findings of Costa et al. (2012)[30] regarding the oldest DENV serotype, although the authors found the TMRCA of DENV-2 dating back to 1674 while in our study, it was estimated to be 1723 [30].

DENV1 has 5 distinct genotypes, and Villabona-Arenase et al. (2013)[31], demonstrated that genotypes I, IV and V are the main genotypes worldwide [8,31]. In 2016, Bruycker-Nogueira [32] performed a phylogeographic analysis of the dengue virus in the Americas from 1962 to 2014. DENV-1 genotype V seems to be the most prevalent in the last 40 years and, among the 5 genotypes until now classified and, in the Americas it represents 99% of prevalence, in Africa it accounts for 43% and in India/Nepal/Bangladesh, 100%. The

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authors also showed that the current diversity of DENV-1 in the Americas was due to the introduction of genotype V from India in the early 1970s and again in the early 1980s[32]. DENV1 was first reported in 1943 in French Polynesia and Japan, followed by reports in Hawaii in 1944 and 1945, with increasing reports in the Asian region from the late 1950s. The first introduction of DENV1 in Africa was estimated to be in 1946, following its introduction from South Asia to West Africa[33] but the first report of DENV1 occurred in 1984 in Sudan [9]. In Colombia, DENV-1 was introduced around the 1970s and was related to the virus circulating in the Lesser Antilles[34]. In the 1980s and 1990s, Brazil, Mexico, and Puerto Rico began to present continuous reports of DENV-1 [9].

Dengue virus serotype 2 (DENV2) is known to have five main genotypes, labeled I-V and, the most recent data suggest that serotypes 1 and 2 are the most prevalent in the world [8,35,36]. Our analyses revealed that the dengue virus serotype 3 (DENV3) arrived in Southeast Asia in 1921 but Araujo et al., 2009 [37] estimated that it arrived around 1890, and Twiddy et al. (2003) [38]estimated it to be in 1900. This difference could be justified due to our dataset covering a longer period of analysis (January 1944 to July 2022), with more data available, in addition, to the difference between the methodologies used by the authors (partial genomes analysis and maximum likelihood tree method) and ours (complete genomes analysis and maximum clade credibility tree method).

DENV-3 was first reported in the Philippines and Thailand in 1953 and it presents 5 previously described genotypes. Genotypes I and II consist of strains isolated from the Asian region, while those of genotype III are distributed in Asia, the Caribbean, the Americas, and Europe[35]. In Africa, the oldest known sequence of DENV-3 comes from Mozambique in 1985, but its occurrence has been sporadic. In the Americas, the first reports emerged in 1963 in Puerto Rico, but most other countries did not have occurrences until the end of the 1980s. Since 1990, there have been records of DENV-3 occurrence in China, Vietnam, Cambodia, and Singapore [9].

DENV-4 has 4 main genotypes (I, II, III, and sylvatic) and exhibits greater conservation in its genome compared to the other DENV serotypes[35,39,40]. The first strain, DENV4-1, was detected in 1956 in the Philippines and was the exclusive strain of transmission for 20 years, where it evolved and spread to Thailand, Cambodia, Australia, and China before diverging into other genotypes [40]. Alfsnes et al. (2021)[33] showed that DENV-4 emerged in West Africa in the early 1950s, then this would be the earliest reported occurrence of the DENV-4 serotype[33].

The circulating DENV rapidly changes its genome through random mutations that accumulate over time, especially due to the co-circulation of multiple serotypes. These mutations can lead to the emergence of new serotypes, as was the case with DENV5, the fifth serotype recently discovered [41]. In 2007, in Malaysia, a dengue outbreak hit the state of Sarawak and samples from a severe case, which had been classified as dengue 4, did not respond to diagnostic tests for confirmation of the four know serotypes. In 2013, it was announced that, after genotyping, it was discovered that this case belonged to a new serotype, DENV5[42,43]. This serotype only circulates in the forests of Sarawak, among non-human primates and follows the sylvatic cycle, and is genetically similar to the other 4, suggesting that the ancestral origin is shared and has so far been associated with only one outbreak, indicating a low transmission rate [14].

In recent years, the global incidence of dengue fever has been increasing, and the notification of the different types of dengue virus (DENV) may be inaccurate due to various types of biases, especially in areas with limited resources for virological diagnosis. Therefore, the reported numbers of cases of the disease may not reflect the true extent of its occurrence [9] OPAS. Through computational modeling, it is estimated that over 390 million dengue infections occur annually, of which 96 million manifest the severe form of the disease[44]. Phylogeographic analysis is a valuable tool to understand the relationship between the phylogenetic and geographic relationships of dengue virus (DENV) serotypes, which can provide important information about the genetic diversity of the disease over time and space. Additionally, phylogeographic analysis can help understand the transmission dynamics of the virus both within a particular region and between different regions, allowing healthcare professionals to take more effective preventative and control measures. This information can also be used to identify when a new strain of DENV emerged and how it circulates within

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and outside the region even before surveillance systems can detect its presence, enabling a faster and more effective response to dengue epidemics [27,45,46].

While waiting for the development of a vaccine, prevention and control measures should be adopted, such as vector control, healthcare services with a good team and adequate infrastructure, which includes raising awareness among healthcare professionals and effective measures in dengue diagnosis [47]. The reduction of breeding sites, with targeted elimination of vector populations using insecticides and larvicides through spraying in the sources, around houses with positive cases of the disease, and also mass outdoor spraying in neighborhoods or cities, serves as a measure of prevention and control of the disease[48]. Basic sanitation management and proper management of water storage containers and waste disposal are essential in vector control, which is closely linked to the concepts of environmental hygiene. These integrated actions for vector control can interfere not only in the transmission of the dengue virus but also in other diseases that depend on this environmental control, such as diarrhea and malaria. However, in the context of social vulnerability, in environments affected by ongoing humanitarian crises, in the process of recovery or regions that host refugee populations, these environmental approaches are hardly applied due to rapid population expansion, leading to a lack of sanitation infrastructure in these places, which results in an increase in the incidence of diseases in susceptible individuals[49].

Some studies have suggested vector control at the molecular level. Lopez et al. (2021)[50] observed that dengue virus particles interact with proteins in the *Aedes aegypti* vector (AeSNAP and ATPase), suggesting that these influence DENV viral dissemination and that further studies are necessary to clarify these findings so that anti-vector measures can target specific mosquito molecules, representing a promising alternative measure compared to current methods[50].

Urgent actions are necessary to control dengue, which is expanding, where it is possible to generate innovative and effective tools in vector control in urban populations, mainly protecting high-risk areas.

The natural evolution of DENV occurred through purifying selection, meaning that most changes in amino acids were deleterious and quickly purified, leading to an evolution of viral proteins that caused an increase in fitness for infection between mosquitoes and primates[35]. The selection pressure, such as from the immune system of both the human host and the mosquito host, as well as the interaction between different serotypes, leads to new variants of the virus [27].

The rate of variability of DENV is heterogeneous, meaning that a different genotype within the same serotype may have a higher or lower rate of variation. As a result, we can understand that phenomena such as population dynamics and viral epidemiology are directly linked to this heterogeneity [51]. Li et al. (2022)[52] pointed to the existence of variation in the predominant selective force among different serotypes of the dengue virus, evidenced by the identification of positive selection in several proteins, including structural (capsid, membrane and envelope) and nonstructural NS2A, NS3A, NS2B, NS4A, and NS4B. In addition, the authors observed that these selective forces vary between continents in some of the analyzed genes, providing valuable information about the evolution of dengue virus serotypes [52].

Dengue cases have been reported in African countries since the 19th century. The four serotypes have already been isolated on the African continent, with DENV2 and DENV3 causing most of the epidemics[48].

One of the causes of underreporting has been the identification of febrile illnesses and their treatment as malaria instead of dengue, as presumed at the time of medical care [53]. Isolated dengue outbreaks are frequently recorded in Africa, occurring mainly in the eastern region. However, due to the precarious surveillance infrastructure and under-recognition of the disease, cases are not properly characterized. These available data make it difficult to determine whether African populations are truly vulnerable to dengue in the same proportions as populations in Asia and Latin America[53].

Therefore, some studies report possible hypotheses for the low dengue incidence in Africa, suggesting that the African population may be less vulnerable to dengue infection than other ethnic groups. Race, as suggested in some studies, may be a factor influencing resistance to infection, where black patients showed

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greater resistance to the disease. In epidemics reported in Cuba (1981) and Los Angeles (1998), white ethnic groups showed greater susceptibility to the disease, particularly in the development of severe forms and even death. Genetic polymorphisms in cytokines and coagulation proteins have been proposed as mechanisms of resistance in black individuals, but further studies are needed to determine this fact [53,54].

The main vector of dengue transmission, the *Aedes aegypti*mosquito, originated in Africa and spread to other continents. Other species also contribute to the transmission of the disease, such as*Aedes albopictus* , *Aedes african* us, and *Aedes luteocephalus* [53]. Another hypothesis for the underreporting of dengue in the African region is that the transmission vectors *A. aegypti* and *A. albopictus* have shown lower susceptibility to all 4 DENV serotypes in controlled laboratory environments. This reduced efficiency of the vector for disease transmission may explain the lower disease prevalence rates in the African region than expected, although further studies are needed to explain this phenomenon [53,55].

Dengue transmission is highly dependent on climatic factors, and attention has been focused on predicted climate changes that may influence the spread of the disease to currently unaffected areas. Dengue is rare in Europe, but cases have been reported in Croatia and France, raising concerns about the potential emergence of dengue in Europe, especially with the predicted climate changes. The concern is that the main dengue vectors are already present in Europe, such as*A. albopictus* , a secondary vector of the disease found in many European countries including the Netherlands, Switzerland, Russia, Slovenia, France, Spain, and Greece. However, the presence of the vector does not necessarily mean that the region has the disease, as a combination of factors including the presence of the virus in the population, hosts, vectors, and appropriate climatic conditions (temperature, humidity, precipitation) are required for transmission. Nevertheless, the presence of the vector in the region increases the risk of dissemination if the combination of factors becomes favorable, as indicated by the indicators [47,56].

In conclusion, the dengue disease has had a significant impact on global health worldwide and the present study provides an overview of the molecular evolution of dengue virus serotypes, showed the origins of serotypes DENV-1 - DENV4 (DENV-1 in 1884 in the Southeast Asia, DENV-2 in 1723 in Europe, DENV-3 in 1921 in Southeast Asia, and DENV-4 was 1876 in Southeast Asia). The molecular origin of the dengue virus was in Spain in 1682, later it was disseminated in Asia (Indonesia in 1838) and Oceania (Papua New Guinea in 1844). After this period, the virus spread to Asia (Malaysia; India, and China in 1890) and in North America (USA in 1895). In South America, it was first disseminated to Ecuador in 1897 and then to Brazil in 1910. During this same period there were disseminations to American countries such as the USA, Mexico, Puerto Rico, Cuba, Haiti, Nicaragua, El Salvador, Costa Rica, Panama, Jamaica, Trinidad and Tobago, Venezuela, French Guiana, Colombia, Peru, Paraguay, and Argentina. In the African continent this virus was disseminated in Senegal, Mauritania, Guinea-Bissau, Ivory Coast, Burkina Faso, Benin, Cameroon, Gabon, Kenya, Djibouti, Somalia, Angola, Tanzania, and Mozambique. In Europe low dissemination occurred and this process was in Spain, France, Italy, Germany, and Portugal. Dissemination in Middle Eastern countries has been detected in countries such as Saudi Arabia and Pakistan. In Asia, dengue virus was detected in Indonesia, India, Sri Lanka, Nepal, Bangladesh, Myanmar, Laos, Thailand, Vietnam, Malaysia, Taiwan, Philippines, Singapore, China, South Korea, and Japan. In Oceania was detected in Papua New Guinea, Australia, New Caledonia, Fiji, Tonga, Samoa, Cook Island, and French Polynesian.

Authorship

Jonas Wolf, Ana P. Souza, Raine F. de Schardosim designed the study. Jonas M. Wolf performed the bioinformatic analyses. Jonas M. Wolf, Ana P. Souza, Raine F. de Schardosim, Arthur Pille, Jucara G. Maccari, and Luiz A. Nasi wrote the first draft of the manuscript and contributed to the literature review and discussion of the results. All authors contributed to and have approved the final manuscript.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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