zoonotic diseases

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Review

Dengue Virus in the 21st Century: Transmission, Pathogenesis, and Climate-Driven Challenges

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Simple Summary

Dengue fever is a rapidly growing public health threat driven by climate change, urban growth, and expanding mosquito populations. This review aims to bring together current scientific evidence on dengue transmission, immune responses, diagnostic tools, vaccines, and the impact of weather patterns on disease outbreaks. By combining knowledge from epidemiology, genetics, and climate science, this study provides a clear synthesis to help researchers and public health experts better understand disease dynamics. Ultimately, these insights can support the development of stronger early warning tools, improved outbreak prediction, and more effective disease prevention strategies to protect vulnerable communities worldwide.

Abstract

Dengue virus (DENV) remains a major global public health challenge, driven by the expanding distribution of *Aedes* vectors, rapid urbanization, and increasing climate variability. This review aimed to synthesize current evidence on dengue transmission dynamics, immunopathogenesis, molecular epidemiology, diagnostic and therapeutic advances, vaccine development, and the influence of climatic factors on disease patterns. A comprehensive search of major electronic databases was conducted to identify relevant literature, followed by a qualitative synthesis of the evidence. The evidence highlights complex transmission cycles involving *Aedes aegypti* and *Aedes albopictus*, with transmission strongly influenced by temperature, humidity, rainfall, and extreme climate events. Advances in immunopathogenesis research have improved understanding of mechanisms associated with severe disease, including antibody-dependent enhancement and dysregulated inflammatory responses. Diagnostic innovations, such as reverse transcription polymerase chain reaction (RT-PCR), NS1 antigen detection, and point-of-care technologies, have enhanced case identification, while prevention strategies increasingly incorporate integrated vector management, digital surveillance systems, and emerging vaccines. Integrating epidemiological, molecular, and

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climatic information may strengthen early warning systems, improve outbreak prediction, and support more effective dengue prevention and control strategies.

Keywords: dengue virus; transmission dynamics; immunopathogenesis; molecular epidemiology; climate change; arboviral diseases

1. Introduction

Dengue fever, caused by the dengue virus (DENV) and transmitted primarily by *Aedes aegypti* and *Aedes albopictus* mosquitoes, remains one of the most rapidly spreading vector-borne diseases worldwide [1–4]. Over the past five decades, its global incidence has increased approximately 30-fold, with expanding geographic reach into new countries and, within affected regions, from urban to rural settings. The World Health Organization (WHO) currently estimates 390 million dengue infections per year, of which roughly 96 million manifest clinically with any level of disease severity [5].

Dengue virus comprises four antigenically distinct serotypes, and secondary heterologous infections may increase disease severity through antibody-dependent enhancement (ADE). These virological characteristics are central to understanding dengue epidemiology, disease severity, vaccine development, and future transmission dynamics.

Approximately half of the world's population now lives in dengue-endemic areas across more than 130 countries in tropical and subtropical regions. Although dengue has historically been concentrated in Southeast Asia and the Western Pacific, the Americas have experienced the greatest increase in reported cases over recent decades. Between 2019 and 2023, more than 14 million suspected cases were reported in the Region of the Americas, including marked increases in countries previously considered lower-burden settings, such as Peru, Bolivia, and several Caribbean islands. These trends reflect the combined influence of rapid urbanization, increasing human mobility, and climatic changes on dengue expansion [6–19].

The public health burden of dengue is multifaceted. Severe dengue (formerly known as dengue hemorrhagic fever or dengue shock syndrome) carries a case-fatality rate that can exceed 20% when clinically unmanaged, yet drops below 1% with timely diagnosis and appropriate supportive clinical management. Beyond mortality, the disease imposes substantial economic costs through direct medical expenses, lost productivity, and large-scale vector control programs. Annual global cost estimates range from US$8–40 billion when disability-adjusted life years (DALYs) and indirect costs are included [6–19].

The co-circulation of multiple DENV serotypes in hyperendemic regions creates complex epidemiological dynamics and contributes to the persistence of transmission and the occurrence of severe disease, particularly during secondary heterologous infections through antibody-dependent enhancement (ADE) [3,6,15–19].

Recent years have witnessed unprecedented outbreaks even in temperate regions with established *Aedes* populations. Autochthonous transmission has been documented in southern Europe (France, Italy, Spain), the southern United States, and Japan, fueled by rising temperatures and imported cases. These events underscore that dengue is no longer exclusively a tropical disease but an emerging threat in a warming world [20–23].

Climate change is considered an important driver of dengue epidemiology and may contribute to the expansion of the geographic range and seasonal suitability of its principal vectors, *Aedes aegypti* and *Aedes albopictus*. However, these effects interact with other factors, such as urbanization, human mobility, vector control, and socioeconomic conditions. Rising mean temperatures accelerate larval development, shorten the extrinsic incubation period

of the virus within the mosquito tissues, and increase biting rates, thereby enhancing vectorial capacity in both endemic and previously non-endemic areas. Concurrently, alterations in precipitation patterns—more intense rainfall events interspersed with prolonged dry periods—create abundant peri-domestic breeding sites while simultaneously stressing municipal water storage practices that favor artificial containers as larval habitats [20,22]. Sea-level rise and coastal flooding further exacerbate transmission risk in densely populated low-lying urban centers by promoting saline-tolerant *Aedes* populations and displacing communities into higher-density settings with inadequate sanitation. Empirical models project that, under moderate to high emission scenarios (Representative Concentration Pathways [RCP] 4.5–8.5), an additional one to two billion people could be newly exposed to dengue transmission by 2080, with the most dramatic range expansions expected in temperate regions of Europe, North America, East Asia, and high-altitude areas of East Africa and the Andean region. These climate-driven shifts not only amplify outbreak magnitude and frequency but also complicate predictive surveillance and timely deployment of limited public health resources [21–23].

Understanding transmission mechanisms remains critical for effective control. Beyond the classic urban *Aedes aegypti* cycle, growing evidence points to the role of peri-domestic breeding sites, vertical transmission within mosquito populations, and sylvatic cycles involving non-human primates in parts of Southeast Asia and West Africa. Each of these pathways presents distinct opportunities and challenges for surveillance and intervention [14–16,18,19,22].

Advances in dengue research have accelerated over the past decade. The licensure of Dengvaxia® (Sanofi Pasteur) in 2015, followed by Qdenga® (Takeda) in 2022, marked important milestones, although their differing indications and performance highlight persistent immunological challenges. At the same time, progress in antiviral therapies, monoclonal antibodies, and next-generation vaccine candidates offers promising prospects for dengue prevention and treatment [3,6,7,17,18,22].

Despite these advances, fundamental gaps persist. The precise determinants of severe disease progression, the long-term impact of repeated heterotypic infections, and the durability of vaccine-induced protection in naïve populations remain incompletely understood. Moreover, predictive models that integrate climate, entomological, immunological, and human movement data are still in their infancy, limiting proactive outbreak response [3,6–10,17,18,24].

This study therefore seeks to address these persisting challenges by synthesizing current knowledge on dengue transmission dynamics, immune responses, and innovative control strategies, with particular emphasis on recent field trials and epidemiological shifts observed between 2020 and 2025. To provide historical context for these recent developments, the review also summarizes key milestones in the evolution of dengue epidemiology and arboviral emergence. By critically appraising the strengths and limitations of contemporary approaches, we aim to identify priority research areas and inform evidence-based policies for sustainable dengue prevention in an era of rapid environmental and demographic change. Ultimately, the present work aims to contribute to the global effort to reduce the burden of dengue through enhanced understanding of its evolving epidemiology and the translation of scientific advances into effective public health action.

2. Methods

This study was designed as a narrative review aimed at synthesizing contemporary evidence on dengue virus transmission, pathogenic mechanisms, molecular epidemiology, diagnostic innovations, preventive strategies, vaccine development, and the influence of climatic factors on epidemiological patterns. Although not following the stringent

protocol of a systematic review, this narrative approach employed rigorous, transparent, and replicable search and selection procedures.

2.1. Databases and Search Strategy

A comprehensive search was conducted in the following electronic databases: PubMed, Scopus, Web of Science, and Google Scholar. The search included articles published up to May 2026. Search terms were combined using Boolean operators and included: "dengue virus" OR "DENV" AND "transmission dynamics" OR "vector ecology" OR "Aedes aegypti" OR "Aedes albopictus" AND "pathogenesis" OR "immunopathogenesis" OR "ADE" AND "diagnosis" OR "NS1" OR "RT-PCR" OR "point-of-care tests" AND "prevention" OR "vector control" OR "vaccination" AND "molecular epidemiology" OR "genomic surveillance" AND "climate change" OR "temperature" OR "rainfall" OR "epidemiological modeling".

Additional hand-searching of reference lists and relevant review articles was performed to ensure comprehensive coverage.

2.2. Inclusion and Exclusion Criteria

Studies were included if they:

1. were published in English;
2. focused on virological, epidemiological, clinical, immunological, entomological, climatic, or public health dimensions of dengue;
3. presented original data, systematic/narrative reviews, meta-analyses, modeling studies, or surveillance reports;
4. provided sufficient methodological detail to support interpretation.

Exclusion criteria comprised:

1. articles unrelated to dengue virus or lacking scientific relevance;
2. studies without accessible full text; (excluded only after exhaustive retrieval attempts failed, as lack of primary data prevented reliable quality assessment)
3. publications with unclear methodology or insufficient data;
4. opinion pieces lacking empirical or structured scientific analysis.

2.3. Data Extraction and Evidence Synthesis

The study selection process was structured and documented. The electronic database search initially retrieved 685 records. After removing duplicates, 450 unique studies were screened based on title and abstract. Of these, 118 full-text articles were assessed for eligibility against the pre-established inclusion and exclusion criteria, resulting in the final inclusion of 81 publications.

Data were extracted manually and synthesized qualitatively. Themes were organized into major domains: transmission dynamics, pathogenic mechanisms, diagnostic technologies, prevention and vaccine strategies, molecular epidemiology, and climate-associated epidemiological trends. Findings were compared across studies to identify convergences, divergences, methodological strengths, and knowledge gaps. No statistical pooling or meta-analysis was performed, given the heterogeneous study designs and review objectives.

3. Literature Review

3.1. Dengue Virus Transmission Dynamics

The dengue transmission cycle is fundamentally of the human–mosquito–human type and depends on interactions between the virus (DENV), the vector, and the vertebrate host. Female *Aedes aegypti* and *Aedes albopictus* acquire the virus by feeding on the blood of viremic individuals. After ingestion, DENV infects the mosquito midgut epithelium,

crosses the intestinal barrier, replicates, and reaches the salivary glands; only then does the mosquito become capable of transmitting the virus through salivary inoculation during subsequent bites [25]. The period between ingesting infected blood and the ability to transmit (the extrinsic incubation period) depends primarily on ambient temperature and viral genotype and represents a critical determinant of transmission dynamics [26].

From an ecological and behavioral perspective, *A. aegypti* is a highly anthropophilic and domiciliated vector, showing strong preference for domestic environments and diurnal biting behavior with frequent human contact. These characteristics make it the primary vector of dengue in urban settings. In contrast, *A. albopictus* exhibits more eclectic habitat use, occupying peri-urban and rural environments with greater association with vegetation, and is less strictly anthropophilic. Historically, it has played a secondary role in urban transmission; however, under specific circumstances—such as high vector densities, the presence of susceptible human populations, and favorable climatic conditions—it may act as a secondary vector or even as the primary vector in localized outbreaks [27,28].

Differences in vector competence between mosquito species—defined as the intrinsic capacity to acquire, support replication, and transmit the virus—result from a combination of immunological and anatomical barriers, including the midgut and salivary gland barriers, as well as virus–mosquito interactions (viral genotype × mosquito population), vector-associated microbiota, and abiotic factors such as temperature [25,26]. In practical epidemiological terms, *A. aegypti* generally exhibits higher DENV transmission rates in both laboratory and field studies, although outcomes vary according to mosquito population and viral lineage [26]. Furthermore, it has been indicated that the proportion of *A. aegypti* mosquitoes that develop abdominal infection and subsequently become capable of releasing infectious saliva is directly dependent on the level of viremia in the human host on which they feed. Although biologically expected, this relationship was robustly quantified, demonstrating that variations in human infectivity, modulated by viremia magnitude, decisively influence the probability of successful viral introduction and establishment of transmission events [29].

In addition to the classical horizontal transmission cycle, alternative and less frequent mechanisms may contribute to viral persistence under specific ecological conditions. Vertical transmission, characterized by transovarial passage of DENV from infected females to their progeny, has been documented in both *A. aegypti* and *A. albopictus* under laboratory and field conditions [30]. Although the efficiency of this mechanism is generally low and insufficient to sustain epidemics independently, vertical transmission may contribute to viral maintenance during inter-epidemic periods, particularly when environmental conditions are unfavorable for continuous horizontal transmission [30]. Other mechanisms, such as mechanical transmission and venereal transmission between mosquitoes, have been experimentally suggested but are considered epidemiologically marginal and likely restricted to rare or localized events [31]. Consequently, while horizontal human–mosquito–human transmission remains the dominant and epidemiologically relevant pathway, these alternative routes may function as auxiliary processes that facilitate viral persistence and re-emergence in specific ecological contexts [32].

Beyond transmission routes, the maintenance and emergence of dengue outbreaks are strongly shaped by ecological, environmental, and demographic factors. Seasonality plays a central role: in tropical and subtropical regions, the convergence of elevated temperatures, increased precipitation, and higher relative humidity enhances mosquito survival, reduces the extrinsic incubation period, and expands *A. aegypti* and *A. albopictus* population densities, thereby creating temporal windows of heightened epidemiological risk [27,33].

This process is spatially heterogeneous and favors the formation of urban hotspots, areas characterized by persistently high vector densities sustained by inadequate infrastructure, water storage practices, exposed solid waste, and microclimatic conditions that maximize breeding site availability. Within these hotspots, transmission may persist even during inter-seasonal periods, functioning as focal points of viral maintenance [34]. Population mobility, including daily intra-urban commuting as well as regional and international movement, constitutes another critical axis, as viremic individuals introduce the virus into new areas where susceptible mosquito populations can initiate autochthonous transmission cycles [35]. Finally, climate change has become an increasingly important driver of dengue transmission by expanding the geographic suitability for Aedes vectors and prolonging transmission seasons. However, its effects interact closely with urbanization, human mobility, and local environmental conditions, collectively increasing the probability of DENV introduction, establishment, and long-term persistence in contemporary urban environments. The influence of climatic factors on dengue epidemiology is discussed in greater detail in Section 3.4 [34,36].

In summary, effective dengue control depends on integrated strategies that combine vector management, personal protection, and continuous entomological and virological surveillance. These interventions should be adapted to local vector ecology and regional differences in vector competence, which substantially influence transmission intensity and epidemiological risk.

3.2. Dengue Virus Pathogenic Mechanisms

3.2.1. Dengue Immune Response

The dengue virus is responsible for causing a broad spectrum of reactions in the human immune system, varying in severity depending on both host characteristics and pathogen-related factors [17,37–40]. Overall, there are four viral serotypes (DENV-1 to DENV-4), and infection with one serotype does not confer cross-protection; instead, it predisposes individuals to more intense clinical manifestations, primarily due to the magnitude and nature of the host immune response [37–39,41].

The innate immune response constitutes the first line of defense and is initiated by infection of dendritic cells, monocytes, and macrophages, with viral recognition through pattern recognition receptors, followed by the production of type I interferons and pro-inflammatory cytokines. In mild cases, this response is efficient and properly regulated, promoting early viral control [17,37,39,42]. In contrast, excessive activation of innate immunity, with exaggerated release of cytokines such as RANTES, CXCL10, CXCL11, TNF-α, and IL-6, among others, is associated with endothelial dysfunction, increased vascular permeability, and a higher risk of plasma leakage [37,38,41].

The adaptive immune response involves the production of neutralizing antibodies and the activation of virus-specific T lymphocytes. Although essential for protection, this response may contribute to disease severity during secondary heterologous infections through the phenomenon of antibody-dependent enhancement (ADE), in which subneutralizing antibodies facilitate infection of Fc gamma receptor–positive cells, amplifying viral replication and inflammation [17,37,39,40,42,43]. Additionally, excessive T-cell activation and regulatory T-cell dysfunction favor progression to dengue hemorrhagic fever and shock [17,37,40].

In children, the immune response to dengue virus infection presents specific characteristics that decisively influence the clinical expression of the disease. The relative immaturity of the immune system, particularly regulatory mechanisms, is associated with a proportionally more intense innate response, characterized by elevated production of pro-inflammatory cytokines and increased susceptibility to endothelial dysfunction. Fur-

thermore, children have a higher risk of progression to severe forms during secondary infections, partly due to the ADE phenomenon, potentiated by the presence of maternal antibodies or incompletely neutralizing humoral responses [17,44]. Recent evidence also associates obesity and overweight in children with a significantly higher risk of developing severe dengue manifestations when compared with normal-weight peers [41].

3.2.2. Entry, Replication, and Dissemination

DENV encodes 10 proteins, cleaved from a polyprotein synthesized from a single RNA molecule. Of these 10 proteins, three are responsible for infection and release, while seven have more diverse functions, acting in replication and immune evasion. Functionally, they are divided into structural proteins (E—envelope, C—capsid, and M—membrane) and nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [1,45,46].

The structure of DENV is susceptible to conformational changes depending on temperature and pH, capable of managing the accessibility of its epitopes [47]. While DENV remains within the mosquito organism, the envelope structure stays compact due to the strong interaction between E protein dimers [48]. When the virus enters the human bloodstream, the physiological temperature and pH relax this outer layer, allowing the virus to infect its target cells (macrophages, lymphocytes, and monocytes) through receptor-mediated endocytosis [49–51].

After endocytosis, the virion is transported by clathrin-coated vesicles (CCVs) to the endosome. The more acidic pH environment is responsible for catalyzing structural changes in the E protein, enabling membrane fusion and the passage of the uncoated nucleocapsid into the cytoplasm, followed by genome release [1,45,49].

Subsequently, the RNA is transported to the endoplasmic reticulum, where it functions as messenger RNA (mRNA) via a cap-dependent mechanism for polyprotein production. During and after the translation process, the polyprotein is cleaved into individual proteins and polypeptides [52]. The C-prM-E polyprotein contains the C, E, and prM proteins, anchored to the endoplasmic reticulum membrane through lipophilic junctions, with the C portion facing the cytoplasm on the outer side of the membrane, while the prM and E portions are located in the lumen of the organelle [1,45]. Concurrently, the NS5 protein transcribes the +RNA into -RNA, which is used for the synthesis of numerous additional +RNA copies that serve as templates for genomic RNA production [1,45].

The process of viral particle docking and assembly is mediated by NS2A through the electrostatic interaction between RNA and capsid particles. This nonstructural protein is responsible for binding to codons at the 3′ untranslated region (UTR) end of newly synthesized RNA and to the NS3 protein in a process that can occur sequentially, alternately, or even involve multiple copies of NS2A. When NS2A recruits and binds to NS3B, the NS2B–NS3 protease complex is formed. The polyprotein anchors are cleaved (likely by the NS3B portion of the protease), releasing the C protein for nucleocapsid formation around the RNA–NS2B–NS3 complex, while the prM and E proteins remain attached to the membrane of the endoplasmic reticulum lumen [53–55].

The E, prM, and NS1 proteins, which are essential for viral particle formation, are associated with the endoplasmic reticulum membrane. Therefore, the nucleocapsid must be enveloped by the endoplasmic reticulum—through the budding process—surrounded by the lipid envelope containing the E and prM proteins in an immature state [55].

The importance of the pr segment lies in its ability to prevent the virus from fusing with the cellular membrane, and the main difference between a mature and an immature virion is primarily the presence of this segment [46]. The process is completed in the extracellular space, under a more basic pH of 7.0, marked by the release of the pr segment from the E proteins, preparing the virus for infection [1,3,55].

3.2.3. Current Vaccine Landscape and Emerging Immunization Platforms

The second approved vaccine, Qdenga® (TAK-003), uses a live-attenuated virus derived from DENV-2 as the backbone, associated with the expression of structural components from the other serotypes. Unlike Dengvaxia®, it can be administered regardless of prior serostatus, representing a considerable advance for immunization programs [56]. Phase III trials indicated an overall efficacy of approximately 80% against virologically confirmed dengue, with higher performance against DENV-2 and moderate efficacy against DENV-1 and DENV-3 [56,57]. However, efficacy against DENV-4 remains less robust, reflecting both intrinsic differences in immunogenicity and limited circulation of this serotype in the studied cohorts, which reduces statistical power for precise estimates. In terms of safety, TAK-003 showed a favorable profile, with no increased risk of hospitalization or severe disease in seronegative individuals, highlighting its promise for expanding vaccination coverage in endemic regions [56,57].

Despite these advances, important challenges remain for the implementation of dengue vaccination programs. The heterogeneous circulation of DENV serotypes, regional differences in baseline population immunity, and the need for continuous post-marketing surveillance complicate the development of universal vaccination strategies. Furthermore, the evaluation of long-term vaccine effectiveness is influenced by the cyclical epidemiology of dengue and temporal fluctuations in serotype circulation, particularly the limited occurrence of DENV-4 during clinical follow-up, highlighting the importance of continued longitudinal studies and real-world effectiveness assessments [56–58].

In addition to approved vaccines, several emerging platforms have been evaluated. mRNA-based vaccines, inspired by the success of this technology in other arboviruses, have shown strong induction of neutralizing antibodies and cellular responses in preclinical models, with advantages such as rapid production and adaptability to new serotypes or variants [58,59]. Protein subunit vaccines, especially those targeting the envelope protein domain III (EDIII), have demonstrated consistent immunogenicity and low ADE risk, although potent adjuvants are required to achieve a robust response [59,60].

Virus-like particles (VLPs) represent another promising strategy as they mimic viral structure without genetic material, inducing a strong humoral response with an excellent safety profile [61]. Next-generation live-attenuated vaccines are also under development, including multivalent versions capable of limited replication, providing a solid immune response with reduced risk of adverse events [58,61,62]. These platforms are at various clinical and preclinical stages but are progressing rapidly in response to the global need for effective alternatives.

The integration of these vaccines into public health strategies will depend on their population-level efficacy, cost-effectiveness, and community acceptance. Vaccination, when combined with traditional measures such as vector control, epidemiological monitoring, and climate-based early warning systems, could substantially reduce the global disease burden. However, factors such as inequalities in access, structural limitations of healthcare systems, and social behaviors may influence the real impact of interventions [56,59,63,64]. Thus, while vaccine development represents a crucial tool in dengue control, its full effectiveness will only be achieved through a multifactorial, evidence-based, and continuous approach.

3.3. Dengue Virus Molecular Epidemiology

DENV comprises four antigenically distinct serotypes (DENV-1 to DENV-4), sharing approximately 65–70% nucleotide identity across the genome. Within each serotype, multiple phylogenetically distinct genotypes have been recognized based on sequence divergence in the envelope (E) gene. Currently, five genotypes are recognized for DENV-1,

six for DENV-2, five for DENV-3, and four for DENV-4, with additional sylvatic lineages described for DENV-2 and DENV-4 [6–19,24,65,66].

Genetic variation within serotypes arises primarily through the error-prone nature of the viral RNA-dependent RNA polymerase, which lacks proofreading activity, generating a mutation rate of approximately 10^{-4} to 10^{-5} substitutions per site per year. Although flaviviruses were long considered recombination-reluctant, intra-serotypic recombination events have now been convincingly documented in DENV-1, DENV-2, and DENV-4, while inter-serotypic recombination remains exceedingly rare, likely due to superinfection exclusion mechanisms [6–13,24,65,66]. These low-frequency recombination events can nevertheless generate novel genetic constellations with potential epidemiological consequences [3,14–18,66].

Global dispersal patterns of DENV genotypes reflect complex interactions between human mobility, vector distribution, and stochastic founder effects. For instance, the Asian-American genotype of DENV-2 displaced the indigenous American genotype throughout the Americas after its introduction in the early 1980s, correlating with the re-emergence of dengue hemorrhagic fever in the region. Similarly, genotype shifts within DENV-1 and DENV-3 have repeatedly been associated with increased epidemic activity in Southeast Asia and Latin America [3,8–16,19,24,65,66].

Phylogenetic analyses based on complete E-gene or whole-genome sequences have become the cornerstone of molecular surveillance. Time-scaled Bayesian phylogenies, often employing relaxed molecular clock models, allow estimation of the time to most recent common ancestor (MRCA), substitution rates, and historical migration routes. Such approaches estimated that modern epidemic DENV-1 lineages emerged from sylvatic ancestors in Southeast Asia around the 1940s, followed by multiple independent exportations to the Pacific, Americas, and Africa [3,10–19,24,66].

Genomic data also contribute critically to understanding virulence determinants. Specific amino acid substitutions in the E protein (e.g., E390, E203) and nonstructural proteins NS1, NS2A, and NS5 have been associated with altered epidemic potential and disease severity across multiple studies. Clade replacement events within DENV-2 Cosmopolitan genotype in Sri Lanka (2017) and DENV-3 genotype III in Brazil (2000s) were both accompanied by increased reporting of severe cases, supporting the hypothesis of genotype-specific fitness advantages [7–16,19,24,66].

Emerging evidence suggests that intra-host viral diversity and minority variants may influence transmission success and clinical outcome. Deep sequencing of acute-phase samples from Nicaragua revealed that bottleneck size during mosquito transmission is smaller than previously estimated, allowing minority variants to become fixed in new hosts and potentially contributing to rapid adaptive evolution [6–9,16–19,65,66].

The integration of genomic data with traditional epidemiological indicators has given rise to "genomic epidemiology" frameworks for dengue. Phylodynamic models that jointly estimate transmission trees and population dynamics have successfully reconstructed unobserved transmission chains during the 2013–2014 French Polynesia outbreak and quantified the impact of travel restrictions during the COVID-19 pandemic on DENV importation rates [3,6,7,17–19,66].

The genomic dataset available on the Nextstrain platform for dengue virus (DENV), accessible at the path dengue/all/genome, provides a comprehensive overview of global DENV diversity based on whole-genome sequences. As of the most recent update, the dataset comprises 3940 whole-genome sequences from contemporary and historical surveillance samples, encompassing all four DENV serotypes (DENV-1 to DENV-4). Earlier dates displayed in the phylogeny represent molecular clock estimates of ancestral divergence rather than actual sampling dates. Nextstrain curates these sequences from public reposito-

ries, aligns them, and processes them using standardized phylogenetic pipelines, producing interactive visualizations that enable high-resolution evolutionary and epidemiological interpretation [67].

The phylogenetic tree generated from the dataset illustrates the deep divergence among serotypes and the extensive branching within each, consistent with global circulation, repeated introductions, and region-specific evolution (Figures 1–5). Metadata integrated into the visualization—especially sampling date and geographic location—enable phylodynamic analyses that track temporal trends and geographic movement of viral lineages. The dataset highlights both historical samples from the early 20th century and dense sampling from recent years, allowing researchers to contextualize contemporary outbreaks against the backdrop of long-term evolutionary history [67].

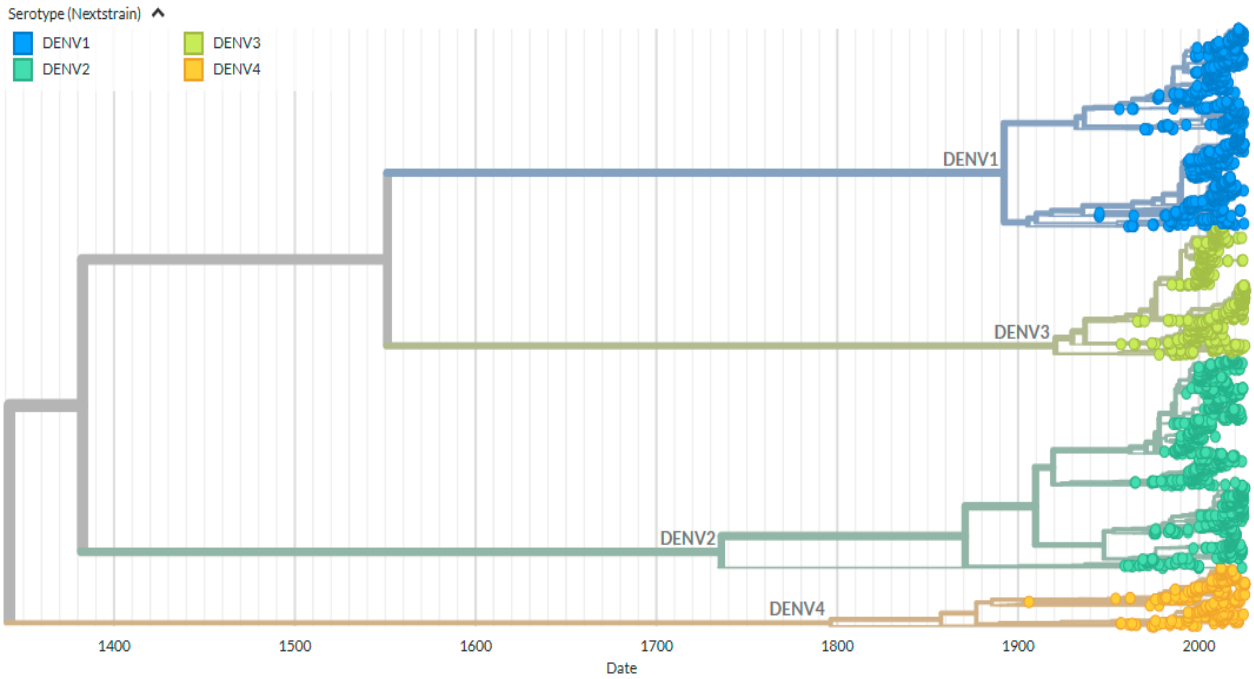

Figure 1. Time-scaled phylogenetic visualization of dengue virus (DENV) genomic diversity based on publicly available whole-genome sequences displayed through the Nextstrain dengue genomic surveillance platform. The visualization includes genomes representing all four DENV serotypes and illustrates their temporal and evolutionary relationships. Dates preceding the earliest available sampling records may represent model-based molecular clock estimates of ancestral divergence rather than actual sampling dates. The figure is presented for illustrative purposes, and no independent phylogenetic reconstruction was performed by the authors.

The time-scaled phylogeny (Figure 1) revealed clear separation of the four DENV serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) and provided estimates of their most recent common ancestors. DENV-1 was inferred to have originated around 15 November 1884 (highest posterior density [HPD] 95%: 28 January 1882 to 27 August 1890) in Southeast Asia. According to the evolutionary estimates presented in the platform, the estimated MRCA of DENV-2 was dated to 29 January 1723 (HPD95%: 22 May 1714 to 9 October 1728) in Europe. DENV-3 was estimated to have emerged on 12 April 1921 (HPD95%: 25 May 1918 to 13 March 1924) in Southeast Asia, while DENV-4 was traced back to 28 March 1876 (HPD95%: 2 August 1865 to 27 August 1899), also in Southeast Asia [67]. Additionally, the estimated overall substitution rate for DENV was 5.57×10^{-4} substitutions per site per year (95% highest posterior density [HPD]: 4.58×10^{-4} to 6.81×10^{-6}) (Figure 2) [67].

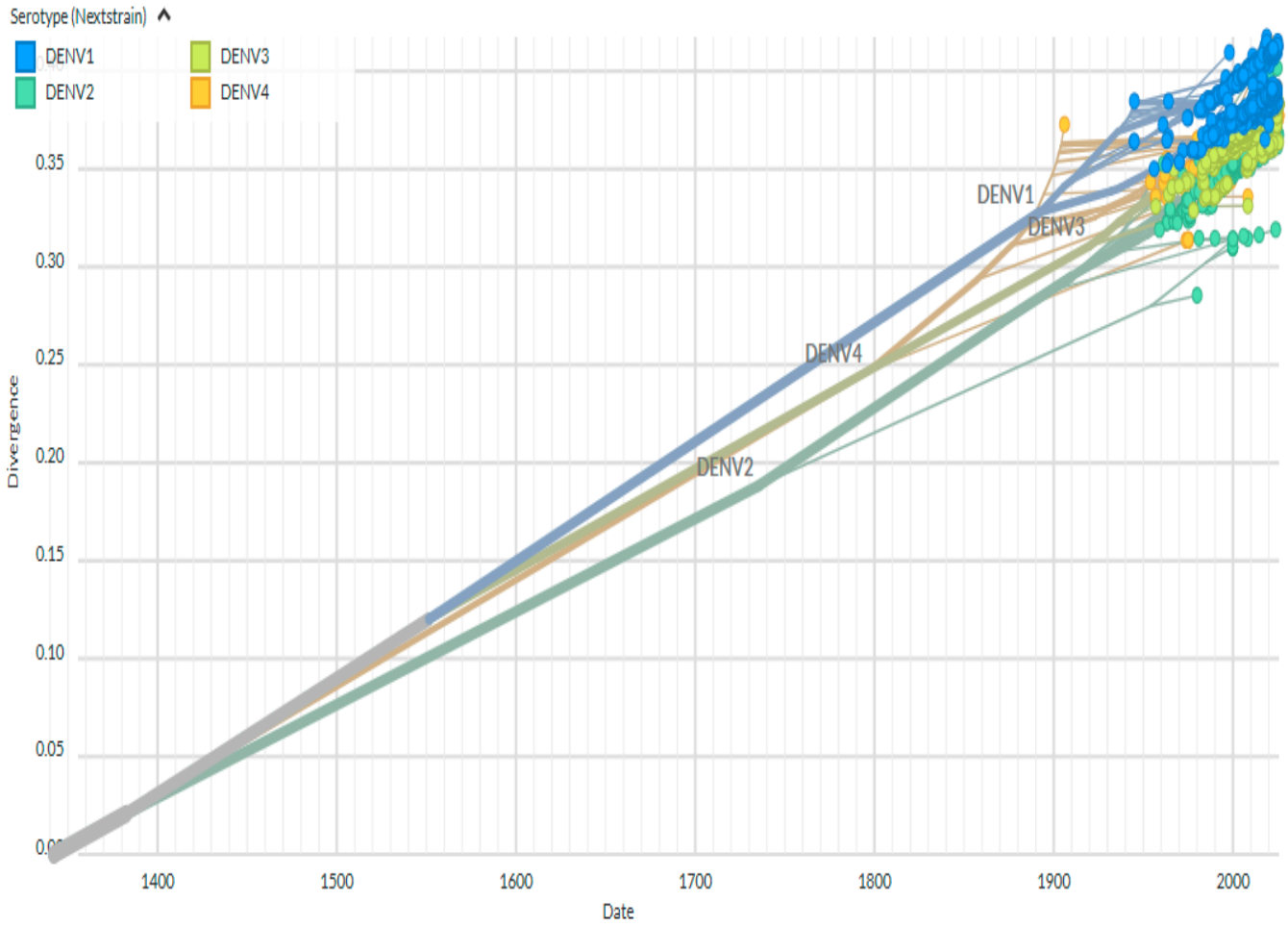

Figure 2. Root-to-tip visualization of publicly available complete dengue virus (DENV) genome sequences included in the Nextstrain dengue genomic surveillance dataset. The visualization illustrates the relationship between genetic divergence and sampling time within the dataset and is presented to provide an overview of the temporal structure of DENV genomic diversity. The figure is based on publicly available data and analyses displayed through the Nextstrain platform and does not represent an independent analysis performed by the authors.

The time-resolved visualization available through the Nextstrain dengue genomic surveillance platform provides a geographic overview of DENV genomic sequences over time. The interactive visualization includes a temporal component that allows changes in the geographic distribution of sampled viral lineages to be followed over time; however, Figure 3 presents a static snapshot of this visualization. Model-based evolutionary estimates displayed through the platform suggest a probable ancestral geographic origin compatible with Spain around 1682. These estimates represent model-based evolutionary inferences rather than definitive historical events. According to the evolutionary patterns displayed in the visualization, DENV subsequently spread across Asia, Oceania, Africa, the Middle East, Europe, and the Americas [67]. The detailed historical chronology and model-based estimates of viral dissemination are described in the accompanying text.

The earliest inferred spread occurred in Oceania and Asia, with introductions into Papua New Guinea and Indonesia around 1838, followed by rapid dissemination throughout South, Southeast, and East Asia, as well as across Pacific islands, between 1842 and 1870. In South America, the earliest inferred introduction occurred in Ecuador in 1897, followed by Brazil around 1910. Between 1915 and 1937, the virus expanded throughout the Americas, reaching North America, Central America, the Caribbean, and additional

South American countries. In Africa, the earliest estimated introduction occurred in Senegal around 1917 (95% HPD: 21 March 1910 to 9 May 1925), followed by gradual dissemination across West, Central, East, and Southern Africa during the following decades. Limited spread was also inferred in Europe after the ancestral origin in Spain, with introductions into France, Italy, Germany, and Portugal between 1938 and 1965, while the Middle East was reached through Saudi Arabia in 1945 and Pakistan in 1947 [67].

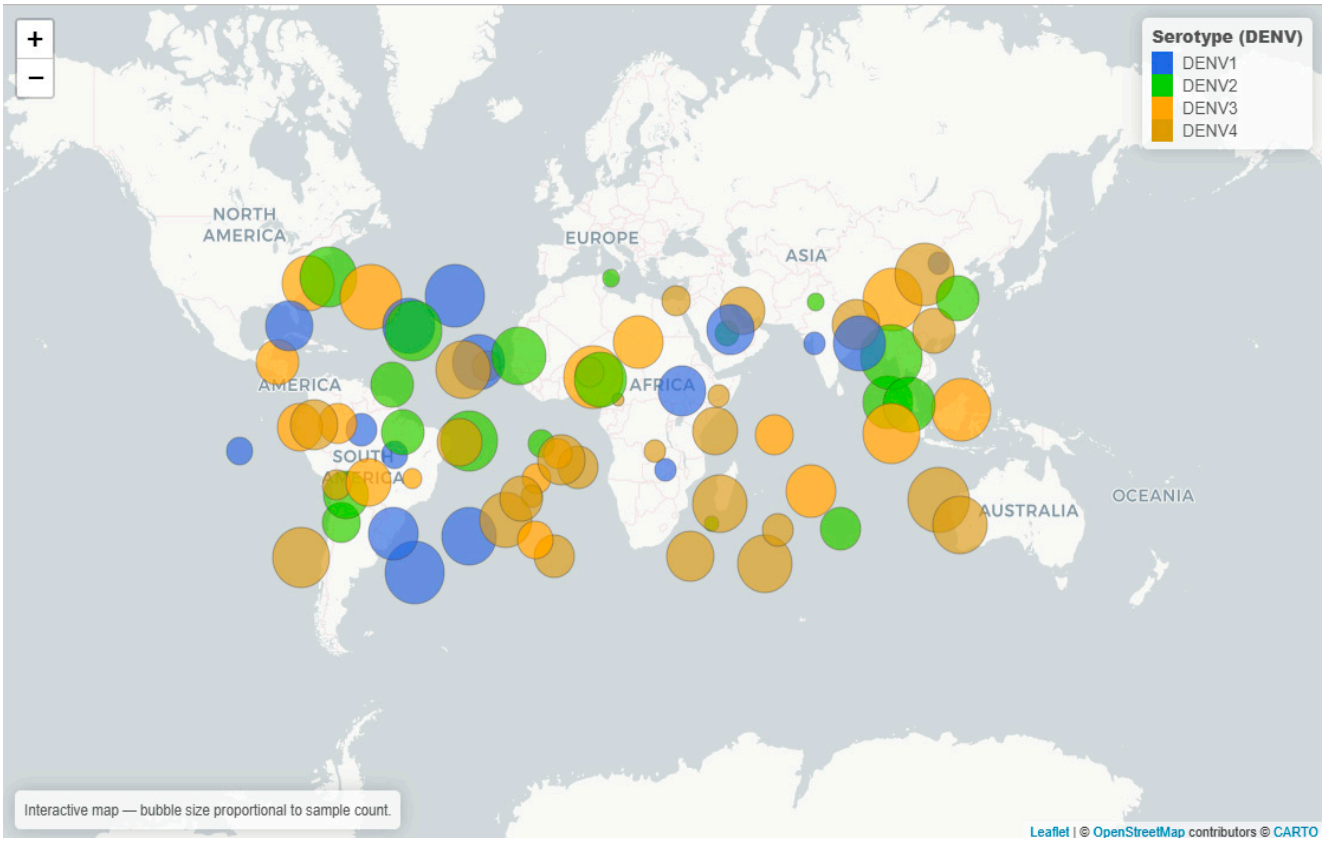

Figure 3. Worldwide geographic distribution of dengue virus (DENV) serotypes based on publicly available genomic data displayed through the Nextstrain dengue genomic surveillance platform. The visualization illustrates the geographic distribution of sampled DENV genomes and the representation of the four DENV serotypes across different regions. Geographic patterns shown in the figure reflect the available genomic sampling and should not be interpreted as a direct measure of the true prevalence or incidence of each serotype.

Figure 6 presents a historical timeline highlighting key milestones in arboviral epidemiology, providing a comparative backdrop for the emergence of dengue and other Aedes-borne pathogens, such as Zika virus, from the late 18th century to 2019. The chronological sequence underscores that while the earliest dengue-like cases in Europe date back to 1784 in Spain, followed by the virus's first isolation in 1943, contemporary times have seen a significant resurgence. This is evidenced by the detection of autochthonous dengue cases in Croatia and France (2010), a major outbreak in Madeira Island, Portugal (2012), and recurring local transmission events in France and Spain between 2013 and 2019. The timeline contextualizes these events alongside the introduction and spread of the Zika virus in Europe during 2013–2019, emphasizing a broader structural shift where European territories are becoming increasingly susceptible to multiple invasive arboviral threats [68].

Beyond reconstructing viral evolution, genomic surveillance has become an essential tool for outbreak investigation [65,67]. Whole-genome sequencing enables the rapid characterization of circulating viral lineages, distinguishes local transmission from independent

introduction events, and supports the monitoring of viral dissemination [65]. These data help identify transmission chains during outbreaks and support timely implementation of public health control measures [65–67]. Continuous genomic surveillance also enables the early identification of newly introduced viral lineages before they become widely established [65,67]. Detecting these introduction events helps distinguish imported cases from sustained local transmission and supports the monitoring of serotype and genotype replacement, contributing to a better understanding of epidemic dynamics [65–67]. When integrated with epidemiological surveillance, genomic data also support public health decision-making by informing surveillance and vector control strategies [65–67].

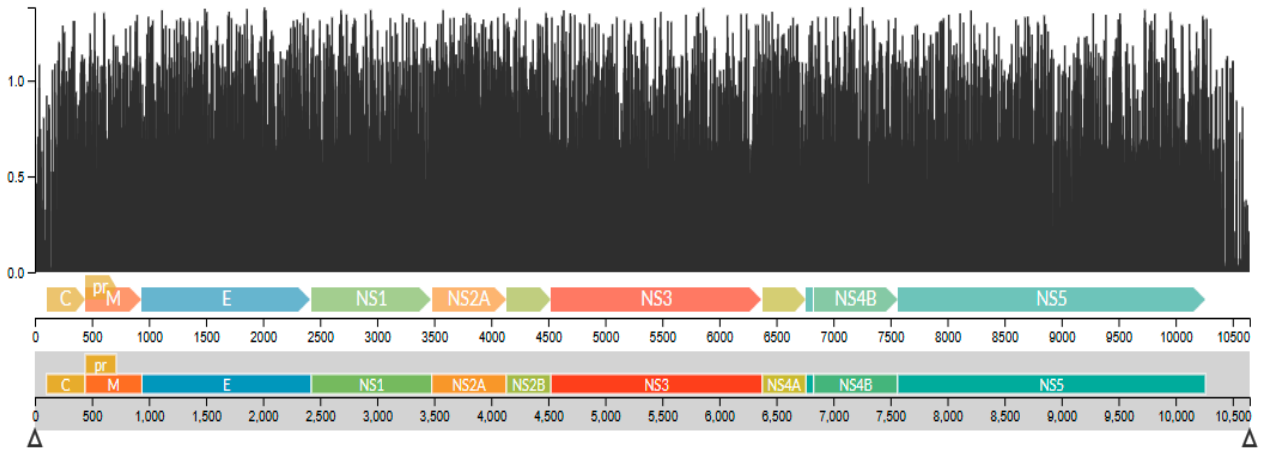

Figure 4. Nucleotide diversity of publicly available dengue virus (DENV) genomic sequences displayed through the Nextstrain dengue genomic surveillance platform. The visualization illustrates patterns of genetic diversity among DENV genomes and provides an overview of the genomic variation represented in the available dataset. The figure is presented for illustrative purposes and does not represent an independent nucleotide diversity analysis performed by the authors.

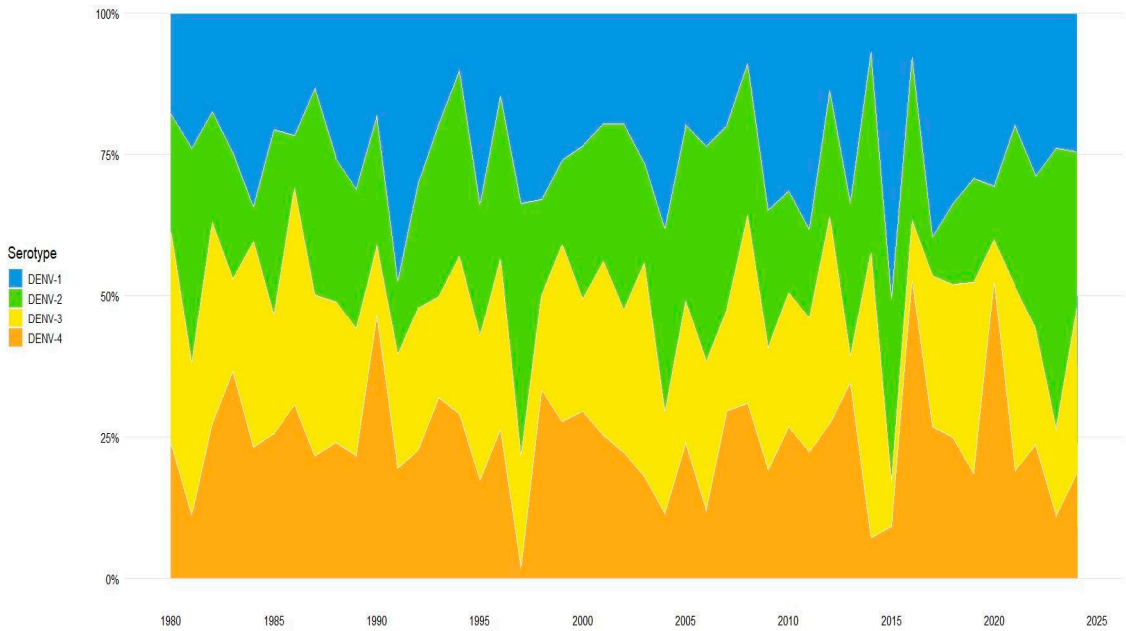

Figure 5. Relative frequency of dengue virus (DENV) serotypes represented in the publicly available genomic dataset displayed through the Nextstrain dengue genomic surveillance platform. The visualization illustrates the relative representation of DENV-1, DENV-2, DENV-3, and DENV-4 among the available genomic sequences. These frequencies reflect the composition of the available genomic dataset and should not be interpreted as estimates of the actual epidemiological prevalence of each serotype.

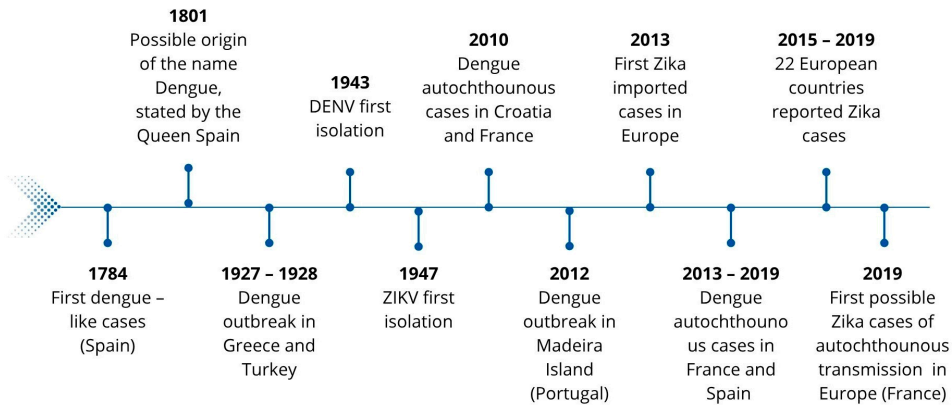

Figure 6. Historical timeline of dengue virus emergence and epidemiological milestones in Europe, contextualized alongside other major invasive arboviruses (Adapted from Silva et al., 2020 [68]).

In summary, molecular epidemiology has evolved from a descriptive tool into an operational pillar of dengue control programs [66]. Continuous refinement of sequencing technologies, coupled with open data-sharing initiatives such as the Viral Hemorrhagic Fever Genomics Initiative and GenBank, ensures that genomic surveillance will remain central to anticipating and responding to the next phase of dengue's global expansion [6–10,18,19,24].

3.4. Dengue Virus Epidemiology and Climatic Conditions

Dengue has become one of the fastest-expanding arboviral diseases worldwide, with transmission currently established in more than 130 countries. Its geographic distribution has expanded considerably over recent decades, driven by the interaction between climatic changes, rapid urbanization, human mobility, and local health system capacity. These interconnected factors have increased the frequency and magnitude of outbreaks while promoting the co-circulation of multiple serotypes across endemic regions [5,34,69].

3.4.1. Relationship Between Climatic Conditions and Viral Transmission

Climatic conditions play a central role in the dynamics of dengue transmission by influencing the life cycle, population density, and vector competence of *Aedes aegypti* and *Aedes albopictus*. Ambient temperature affects larval development, blood-feeding rates, and the extrinsic incubation period of the virus in mosquitoes: average temperatures around 25–30 °C are considered optimal for vector development and survival and may shorten viral incubation, resulting in higher transmission potential [70,71].

Variables such as precipitation and relative humidity are strongly associated with dengue incidence; rainfall creates favorable environments for the formation of aquatic breeding sites, while high humidity increases adult mosquito survival [72].

However, these climatic drivers do not act in isolation. The translation of favorable weather into actual transmission depends heavily on the coverage and efficacy of local vector control programs, which can suppress mosquito populations even under optimal climatic conditions [73]. Global climate change, characterized by rising mean temperatures, altered precipitation patterns, and extreme weather events (such as floods and droughts)—can modify vector distribution and density, prolong transmission seasonality, and extend risk zones to previously unaffected areas [73]. These changes are particularly relevant in Europe, where the expansion of *Aedes albopictus*, the recent establishment of *Aedes aegypti* in Cyprus, and increasing reports of autochthonous dengue transmission in countries such as France, Italy, and Spain indicate the increasing potential for dengue transmission in Europe. Climate projections further suggest that the Mediterranean region may become increasingly suitable for dengue transmission, reinforcing the need for integrated surveillance and vector control strategies [3,33,35,74]. Events such as El Niño have

been associated with temperature and precipitation anomalies that precede major dengue outbreaks in various regions [75,76].

3.4.2. Epidemiological Modeling and Forecasting

Epidemiological models have been widely used to predict dengue outbreaks based on climatic variables. Modeling approaches that use historical data and climate projections demonstrate that dengue transmission is sensitive to variations in temperature, rainfall, and humidity, and that climate change scenarios may expand climatic suitability for vectors into new geographic regions [77–79].

However, models relying solely on meteorological parameters risk overestimating risk zones, as they may overlook critical non-climatic factors such as herd immunity, local vector control efficiency, and human movement patterns. Beyond classical models, research integrating time series, meteorological data, and machine learning methods has explored the prediction of incidence patterns based on remote sensing and the analysis of large datasets, enabling risk forecasting and supporting early warning systems [80–82].

Climate-informed early warning systems have increasingly integrated meteorological forecasts with entomological, epidemiological, and environmental surveillance data to identify periods and locations at increased risk of dengue transmission. These climate-sensitive surveillance approaches support timely vector control interventions, optimize resource allocation, and strengthen public health preparedness, particularly in areas experiencing recent expansion of Aedes vectors [80–82].

Despite their growing utility, predictive models remain subject to important sources of uncertainty. Their performance depends on the quality, completeness, and spatial resolution of climatic, epidemiological, and entomological data, while factors such as population immunity, socioeconomic conditions, human mobility, and the effectiveness of local vector control programs may substantially influence transmission dynamics. Therefore, climate-based forecasts should be interpreted as decision-support tools that complement, rather than replace, conventional epidemiological surveillance [80–82].

3.4.3. Social and Environmental Inequalities

Dengue epidemiology is deeply associated with social and environmental inequalities. Poor urban conditions, lack of adequate sanitation, deficient solid waste collection, and unplanned land occupation significantly increase transmission risk. Vulnerable populations living in urban peripheries are often the most exposed to the vector and face limitations in access to healthcare services and preventive measures [64,70,71]. These socioenvironmental and economic determinants do not merely run parallel to climate variables; rather, they interact synergistically with them. For instance, deficient water supply infrastructure forces residents to store water in open containers, which, combined with rising temperatures, amplifies vector breeding potential.

Therefore, a balanced epidemiological interpretation must view climate as a catalyst whose impact is either amplified by socioeconomic vulnerability and fragmented healthcare infrastructure, or mitigated by robust vector control and public health resilience. The integration of epidemiological, climatic, and socioenvironmental data is essential to strengthen health surveillance and develop effective public policies. Systems that combine meteorological information with vector monitoring and human case data enable the identification of higher-risk areas and guide vector control interventions, strategic planning, and mitigation actions. Understanding the relationship between climate and dengue epidemiology is crucial to mitigating the impacts of the disease in the context of global climate change, underscoring the need for intersectoral and sustainable approaches to dengue control and prevention [64,70].

4. Conclusions

Dengue virus continues to pose a substantial global public health challenge, particularly in regions undergoing rapid urbanization and environmental change. The expansion of *Aedes* mosquito vectors, combined with increased human mobility and population density, has facilitated sustained transmission and recurrent outbreaks. This review underscores the multifactorial nature of dengue epidemiology and highlights the need for integrated and adaptive control strategies. The transmission dynamics of dengue are strongly shaped by climatic variables such as temperature, rainfall, and humidity. These factors directly influence mosquito survival, breeding patterns, viral replication, and human exposure risk. Climate variability and extreme weather events further complicate prediction efforts, reinforcing the importance of incorporating climate data into surveillance and early warning systems.

Advances in understanding dengue immunopathogenesis have provided important insights into disease severity and clinical heterogeneity. Mechanisms such as antibody-dependent enhancement and dysregulated inflammatory responses play a central role in the progression to severe dengue. These findings not only improve clinical risk stratification but also inform vaccine development and therapeutic research. Significant progress has been made in dengue diagnostics, with molecular and antigen-based assays improving early detection and case confirmation. The expansion of point-of-care technologies offers promising opportunities for timely diagnosis in resource-limited settings. However, challenges related to access, cost, and implementation persist and must be addressed to ensure equitable diagnostic capacity.

Prevention strategies have evolved beyond traditional vector control approaches. Innovative interventions, including digital surveillance platforms and community-based strategies, demonstrate the potential for sustainable impact when integrated into public health systems. Vaccine development, particularly with next-generation candidates such as TAK 003, represents a critical component of long-term dengue control, although continued evaluation of safety, efficacy, and population-level impact remains essential. Molecular epidemiology has emerged as a powerful tool for understanding dengue virus diversity, transmission pathways, and outbreak dynamics. Genomic surveillance enables the identification of circulating serotypes and genotypes, supports outbreak investigation, and enhances predictive modeling. Integrating molecular data with epidemiological and climatic information strengthens preparedness and response strategies.

In conclusion, effective dengue control requires a comprehensive and interdisciplinary approach that integrates epidemiology, immunology, molecular science, diagnostics, and climate research. Continued investment in research, surveillance infrastructure, and climate-resilient public health policies is essential to reduce disease burden, improve outbreak prediction, and protect vulnerable populations in an increasingly interconnected and climate-sensitive world.

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