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Ecology of Dengue Virus

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ABSTRACT

Dengue virus and its interactions with *Aedes* mosquito vectors and human hosts have garnered significant scientific interest over the past decade. Despite extensive research, many aspects of these interactions remain poorly understood, highlighting the need for further investigation to develop effective therapeutic and preventive strategies to reduce the spread of dengue virus and the prevalence of the disease. The key challenges underpinning the relevance of dengue virus studies include the insufficient current preventive measures, the limited efficacy of approved vaccines, the absence of antiviral therapies with proven clinical efficacy, the risk of complications, and other factors. The review provides a characterization of dengue virus virions, highlighting the four virus serotypes, mutation rates and genome evolution. Genotypic and serotypic variations, which are regularly identified through the study of regional viral circulation, have the potential to give rise to new dengue strains, which can cause subsequent epidemics. The review details the stages of the viral life cycle in vertebrate and invertebrate hosts. Viral replication, transcription, and translation within cells of vertebrate and invertebrate hosts are examined, along with both typical and atypical routes of infection transmission. The ecology of *A. aegypti* and *A. albopictus* vectors, vector competence and the factors that reduce vector competence under natural conditions are discussed. Strategies for targeted intervention in the interactions between the pathogen, vector, and vertebrate host are examined. The most probable driver for the global expansion of the virus is the active migration of infected individuals. Research focused on identifying critical points in the protein interactions of the pathogen, vertebrate and invertebrate hosts, and exploring mechanisms to inhibit these interactions, appears promising for reducing the risk of dengue infection. The detection of imported cases of dengue fever in Russia underscores the need to implement measures for increasing public awareness regarding transmissible diseases and to minimize contact with potentially infected individuals when visiting tropical and subtropical regions.

Keywords: DENV; dengue fever; transmissible diseases; phylogeny of viruses; gene evolution.

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Экология вируса денге

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АННОТАЦИЯ

Возбудитель лихорадки денге, его взаимодействие с комарами *Aedes* и организмом человека вызывают пристальное внимание исследователей на протяжении последнего десятилетия. Несмотря на значительное количество научных публикаций в этой области, знания о механизмах такого взаимодействия содержат множество пробелов, заполнение которых создаст перспективы для разработки набора лечебных и профилактических мероприятий по борьбе с заболеваемостью и распространением вируса лихорадки денге. Ключевые проблемы, обусловливающие актуальность изучения вируса лихорадки денге, включают недостаточную полноту профилактических мер, малую эффективность одобренных вакцин против этого вируса, отсутствие противовирусной терапии с доказанной клинической эффективностью, существование риска развития осложнений при инфицировании и некоторые другие. В обзоре приводится характеристика вирионов вируса лихорадки денге, освещается информация о четырех серотипах вируса, скорости мутационного процесса и эволюции его генома. Генотипические и серотипические изменения, регулярно выявляемые при исследовании циркуляции вируса на ограниченной территории, способны привести к появлению новых штаммов вируса лихорадки денге, которые в дальнейшем могут стать причиной возникновения последующих эпидемий. Также в обзоре приводятся сведения об этапах жизненного цикла вируса в позвоночном и беспозвоночном хозяев. Рассматриваются процессы репликации, транскрипции и трансляции вируса в клетках позвоночного и беспозвоночного хозяев, а также типичные и атипичные пути передачи инфекции. Обсуждаются экология переносчиков *A. aegypti* и *A. albopictus*, вопрос векторной компетентности переносчиков и факторы, понижающие векторную компетентность в естественных условиях. Рассматриваются стратегии целевого вмешательства во взаимодействие патогена, переносчика и позвоночного хозяина. Наиболее вероятная причина экспансии вируса в мире — активная миграция людей, инфицированных вирусом лихорадки денге. Перспективными кажутся исследования, направленные на определение критических точек в белковом взаимодействии патогена, позвоночного и беспозвоночного хозяев, поиске механизмов ингибирования этого взаимодействия для снижения вероятности инфицирования вирусом лихорадки денге. Выявление завозных случаев заболевания лихорадкой денге на территории Российской Федерации говорит о необходимости введения мер по информированию населения о трансмиссивных болезнях и необходимости минимизации контактов с предположительно инфицированным переносчиком при посещении тропических и субтропических регионов.

Ключевые слова: DENV; лихорадка денге; трансмиссивные заболевания; филогения вирусов; эволюция генов.

Как цитировать

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BACKGROUND

Dengue fever is an acute transmissible viral disease classified as a "neglected tropical disease." It is caused by dengue arboviruses belonging to the family *Flaviviridae*, genus *Flavivirus* (arboviruses of antigenic group B) [1]. The ineffectiveness of infection control measures, occurrence of epidemics, and severity of the disease determine the relevance of this topic and sustain global scientific interest. A search of the *PubMed* biomedical research database as of April 4, 2025, using the query *DENV* for the period from 2015 to 2025 yielded 5253 scientific publications[1] and *Dengue virus* yielded 13,257 scientific publications[2]. Each year, 50 to 528 million people become infected with, and approximately 10,000–20,000 people die from the disease. Currently, dengue fever is found predominantly in south and southeast Asia, Africa, Oceania, and the Caribbean. Countries with documented local dengue transmission are listed in Table.

In the Russian Federation (RF), only imported cases of dengue fever have been detected to date [2]. There have been reports of dengue fever cases of varying severity in nonendemic regions—Russia [2, 3] and Hungary [4]—and epidemic outbreaks of viral disease in endemic regions—China [5–7], Colombia [8], Brazil [9], Bhutan [10], and Vietnam [11].

Previous studies documented the ecological features of dengue virus, its interactions with the environment, susceptible hosts, vectors, and its role in the formation of stable parasitic systems.

VIROLOGY AND INTERACTIONS WITH THE ENVIRONMENT

The causative agent of dengue fever is the dengue virus (DENV), a single-stranded RNA virus belonging to the genus *Flavivirus*, family *Flaviviridae*. DENV exhibits high phenotypic dispersion [12]. The virus has four antigenically related but genetically distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4 [13]. Each dengue serotype exhibits moderate antigenic heterogeneity [14]. The DENV genome consists of 10,200 nucleotides encoding three structural proteins capsid (C), envelope (E), and membrane (M), as well as seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [15].

Epidemiological studies of dengue fever have led to the hypothesis of infection parity. These observations indicate that shock and hemorrhagic dengue regularly occur in regions where two or more DENV serotypes circulate simultaneously or sequentially [16]. For example, DENV-1 and DENV-2 were detected during an epidemic outbreak in Brazil [17], and DENV-1, DENV-2, and DENV-3 were detected in Bhutan [10]. Severe forms of dengue fever occur in two immunological groups: individuals aged one year and older who are infected with two or more different dengue viruses with a temporal interval ranging from one year to more than 20 years; and children under one year of age with passively acquired antibodies who are infected with DENV for the first time in hyperendemic regions [18]. Scientific reports indicate that infection with a single DENV serotype provides long-term protection against the same serotype (homotypic immunity) and short-term protection against other serotypes (heterotypic immunity) [16]. This underscores the role of intraspecies DENV diversity, including "competing" viral serotypes that can cause severe disease when their distribution ranges overlap.

RNA viruses, such as DENV, are characterized by a high mutation rate. Inefficient repair processes undertaken by their RNA polymerases result in a mutation rate approximately six orders of magnitude higher than that observed in eukaryotes [12]. This explains why only a few DENV serotypes have been detected and described [18]. A fifth serotype has been reported, but has not yet been

Table 1. Countries With Reported Cases of Local Dengue Transmission

WHO Region	Countries
Africa	Benin, Burkina Faso, Cabo Verde, Chad, Côte d'Ivoire, Ethiopia, Ghana, Guinea, Mali, Mauritius, Niger, Nigeria, São Tomé and Príncipe, Senegal, Togo
Americas	Brazil, Colombia, Costa Rica, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela, Peru, Bolivia
Eastern Mediterranean	Afghanistan, Djibouti, Egypt, Oman, Pakistan, Saudi Arabia, Somalia, Sudan, Yemen, Israel
Europe	Croatia, France, Italy, Portugal, Spain, Germany, United Kingdom
South-East Asia	India, Indonesia, Myanmar, Sri Lanka, Thailand, Nepal, Bangladesh
Western Pacific	Australia, Cambodia, China, Lao PDR, Malaysia, Philippines, Singapore, Vietnam

[1] https://pubmed.ncbi.nlm.nih.gov/?term=DENV&filter=datesearch.y_10
[2] https://pubmed.ncbi.nlm.nih.gov/?term=virus+dengue&filter=datesearch.y_10

confirmed, and there is limited information on it [12]. Phylogenetic and phylogeographic investigations of DENV indicate the presence of numerous missense mutations within viral genomes, complicating the determination of their origin and migration pathways. The phylogeography of the three main DENV-3 genotypes has been revised based on the sequence of the envelope protein E in 200 strains occurring in 31 countries over 50 years (1956–2006) [19]; the phylogeny of DENV-2 based on the NS3 nonstructural protein gene in Thailand, Singapore, Japan, the Philippines, the USA, Vietnam, Taiwan, Sri Lanka, and China [20]; and the evolutionary dynamics of DENV-1, DENV-3, and DENV-4 [21]. Despite their limitations, these investigations provide information on the prevalence of specific genotypes within each DENV serotype, mutation rates, and patterns of viral circulation in endemic areas. Genotypic and serotypic changes resulting from mutation may give rise to new viral strains that can trigger epidemics when they spread to new territories. Therefore, knowing the genotypic composition of each circulating DENV serotype is useful for assessing future risks posed by emerging dengue virus strains [21]. Due to the high mutation rate, some DENV genotypes and subtypes may cause more severe disease. *In vitro* investigations have shown that certain strains exhibit high virulence in cells of both vertebrate and invertebrate hosts [22]. The number of genotypes identified for each DENV serotype has led to the development of a new nomenclature, which involves specifying the particular genotype when defining a DENV serotype [23]. However, despite modern technological capabilities, there are challenges in implementing this nomenclature in clinical practice. These challenges are related to virus identification; for example, DENV infection may be asymptomatic, and cases of dengue fever are not always recognized in healthcare settings, as infected individuals may not seek medical attention. These limitations suggest that the current scientific data on DENV genotypes and serotypes are incomplete. There are various hypotheses regarding the timeline of DENV emergence. One of the hypothesis is that DENV is a relatively recent virus, first recorded 120–215 years ago [13]. Another hypothesis, based on the earliest documentation of dengue fever dating back to 265–420 BCE in China during the Qing dynasty, is that the virus has existed for more than 1500 years [24]. Thus, information on the temporal existence of DENV requires further investigation.

INFECTIOUS DISEASES AND THEIR INTERACTIONS WITH THE SUSCEPTIBLE HOST

The development of DENV infection in humans begins with the bite of an infected mosquito. Atypical routes of infection include cutaneous–mucosal contact, blood exposure through wounds, vertical transmission from mother to fetus, aerosol, and sexual transmission [24].

DENV can replicate in the cells of the liver, spleen, lymph nodes, kidneys, and other organs [25]. Information on histopathological changes in tissues and organs infected with human and animal DENV is limited. *In vitro*, DENV-infected *Vero* cells form syncytia by fusing regions of the cytoplasm [26]., Focal necrosis, hemorrhages, and inflammatory infiltrates were observed in liver tissues in mice infected with DENV1 (BR/Alfenas/2012) obtained from a patient with hemorrhagic dengue fever in Brazil [9]. Additionally, the DENV capsid may interfere with nucleosome assembly in human hepatocytes, suggesting nuclear abnormalities [27]. These histopathological changes are consistent with scientific reports on the DENV life cycle, demonstrating the ability of the virus to alter cellular membranes. Cell surface receptors of host organisms that interact with DENV have not yet been characterized [15]. However, Electron microscopy has shown that dengue virions are spherical, with a relatively smooth surface, diameter of approximately 50 nm, an external protein layer on the lipid bilayer, and an internal nucleocapsid core [16].

DENV replication begins with attachment of the virus to a host cell membrane receptor. The virus enters the cell via clathrin-mediated endocytosis. Acidification within the endosome triggers conformational changes in the envelope protein E, releasing the viral genome into the host cell cytoplasm. After the genome is released, it is transported to the endoplasmic reticulum (ER), where transcription and translation of structural and nonstructural DENV genes occur. Negative-sense RNA is copied, before positive-sense RNA, catalyzed by RNA-dependent RNA polymerase. Newly synthesized proteins and genomes are assembled into new viral particles [15]. Newly formed virions exit the infected cell via endocytosis and cell lysis [15]. Virions are assembled on the ER membrane, and immature virions with a spiked surface pass through the Golgi apparatus (GA) where they mature and undergo modifications. The DENV switches between the infectious and noninfectious states of mature and immature virion depending on conformational changes in membrane protein M and envelope protein E at different environmental pH levels [16]. Transition to the mature smooth-surfaced virion is driven by conformational changes in the envelope protein E [16]. Thus, the DENV life cycle occurs within single-membrane organelles—the ER, GA, and clathrin-coated vesicles [28].

Viremia in an infected human develops 4–5 days after the infected-mosquito bite and persists for up to 12 days post-infection. During this period, the infected individual serves as a source of infection for the invertebrate host [15].

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EPIDEMIOLOGY AND INTERACTIONS WITH THE VECTOR ORGANISM

Invertebrate vectors of DENV are mosquitoes of the species *Aedes aegypti* and *Aedes albopictus* [28]. Research on the interaction of the virus with its vector primarily focuses on identifying critical points in this interaction and determining effective strategies to limit spread of the virus [28]. *A. aegypti* are endophilic mosquitoes, primarily found indoors. Their development and reproduction occur in water-filled containers, and they feed during the daytime, predominantly on human blood. *A. aegypti* occurs in all continents, with populations in tropical and subtropical zones [16]. *A. albopictus* are exophilic, developing in near-ground water bodies, and are considered more aggressive than *A. aegypti*. They feed outdoors during daytime, also predominantly on human blood. Nonhuman primates can serve as reservoir hosts for DENV transmission by *A. albopictus* [1, 16].

Effective transmission of DENV requires initial replication in epithelial cells of the midgut of the invertebrate host. After initial replication, the virus spreads to the hemolymph, muscles, and salivary glands, and is released in mosquito saliva during the next feeding episode [29]. This process occurs relatively rapidly. Thus, the mosquito midgut is the foci of DENV infection [29].

DENV utilizes plasmin to enhance its entry into midgut cells and promote infection in the mosquito. Plasmin, a broad-spectrum serine protease, induces fibrinolysis by degrading fibrin clots in humans. Uncontrolled increases in plasmin levels in human serum can cause generalized hemorrhagic conditions within minutes [29]. DENV exploits human plasmin to degrade the glycocalyx of mosquito midgut epithelial cells [29]. AaTI, a Kazal-type plasmin inhibitor in mosquitoes, binds plasmin, counteracting its proviral effect and inhibiting its proteolytic activity in the midgut lumen. DENV strains that can induce fibrinolytic activity in humans may enhance viral adaptation to the invertebrate host and are maintained through natural selection, directing viral evolution toward higher virulence. Many sites in the DENV phylogeny have undergone multiple mutations and are examples of parallelism, reversion, and homoplasy [14]. Although DENV genotypes capable of inducing human plasmin activity have not been identified, they are presumed to occur among all viral serotypes. The plasmin-inhibitor AaTI is a promising candidate for strategies aimed at blocking viral transmission, potentially exerting stronger effects in patients with hemorrhagic manifestations [29].

The innate immunity of the invertebrate vector plays a key role against DENV infection, which is regulated by numerous factors, including apoptotic and proteolytic processes [30]. High parasitic load is believed to cause vector death. However, DENV does not appear to suppress the mosquito while residing in the epithelial cells of its midgut, but viral presence has been reported to disrupt the function of single-membrane organelles (ER and GA). Only minor changes in lifespan and development were reported in mosquitoes infected with all DENV serotypes [31]. No reduction in the population of *A. aegypti* and *A. albopictus* has been reported, in line with the theoretical suggestion that the vector host resists both infection penetration and progression of the viral life cycle within its body. The interaction between *A. aegypti* and DENV seems to be a dynamic coevolutionary process in which the vector attempts to protect itself from infection, whereas the virus undergoes adaptive selection favoring its survival without causing significant harm to the host [30]. Characterization of a protective phenotype in mosquitoes is only partially described in the reports, but it is hypothesized that the vector host may evolve toward pathogen inhibition [31]. For example, some mosquito species can halt the development of malarial ookinetes and oocysts via melanotic encapsulation — melanin deposition on the surface of the invading pathogen — or by lysing ookinetes during their migration through the mosquito midgut. Mosquitoes may limit parasite development and dissemination by destroying sporozoites during migration to the salivary glands via the hemolymph. However, pathogen development in incompetent vectors may result in high insect mortality [32].

Regarding the dissemination of agents of transmissible diseases, it has been hypothesized that reducing vector populations may increase the intensity of parasite transmission. Reduced competition among vectors for access to vertebrate hosts is a driving factor in the evolution of increased pathogen virulence [33, 34]. Pathogens are subjected to selective evolutionary pressure depending on their transmission and dissemination strategies. Pathogens, such as DENV, may evolve toward phenotypes with higher virulence for vertebrate hosts than related pathogens whose life cycle involves only a single host [32].

Several natural factors influence the dissemination of DENV and direct its evolution toward higher virulence. For example, ambient temperature influences dengue outbreaks by altering *Aedes* vector competence [35]. Moderate ambient temperatures ranging from 25 °C to 30 °C are conducive for the life cycle of the mosquito, whereas exposure to temperatures above 40 °C results in death of eggs, larvae, pupae, and adults, and temperatures below 10 °C arrest development of subsequent life cycle stages of the mosquito and virus. Thus, the vector competence of *A. aegypti* is determined by environmental conditions [35]. In addition, obligatory intracellular arthropod symbionts, Gram-negative pleomorphic bacteria of the family *Ehrlichiaceae*, genus *Wolbachia*, reduce mosquito vector competence by limiting DENV dissemination [28].

CONTROL STRATEGIES

Research on dengue fever is relevant to cover gaps on the development of treatment and prevention strategies for combating DENV. Key problems highlighted in the reports include the limited efficacy of approved vaccines, the lack of clinically effective antiviral therapy, and the high risk of severe disease [3]. The spread of DENV is most likely driven by human factors. For many years, public health authorities have focused on controlling DENV transmission by infected mosquitoes, implementing mosquito control programs at international airports by spraying insecticides in the passenger cabins of arriving aircraft. However, there is no convincing evidence to support the effectiveness of these efforts to prevent the introduction of DENV-infected mosquitoes into new areas. The most likely global source of DENV is infected humans [18]. The scales of passenger and cargo traffic, mass migration, and tourism drive DENV epidemic emergence.

Efforts to control the spread of DENV should involve a comprehensive program to reduce the incidence of dengue fever. Measures targeting case detection and treatment, prevention of infection in humans, mosquitoes, and reservoir hosts, as well as interventions directed at the pathogen—including the development of viral inhibition strategies at critical points in its life cycle in both vertebrate and invertebrate hosts—may all form part of this integrated approach. Investigations of protein interactions within the DENV–human–invertebrate host triad are ongoing to identify effective targets for controlling viral transmission and appear promising [27, 36, 37]. There are DENV-associated proteins closely linked to processes of replication, transcription, translation, immunity, transport, and metabolism in DENV, vertebrate, and invertebrate hosts. These findings suggest common host requirements for completion of the DENV life cycle [37]. To date, the key protein interactions between the virus and its hosts remain undefined.

New high-technology approaches, including transgenic methods, are also under consideration. Genetic modification of invertebrate vectors to reduce or eliminate their capacity to transmit infectious diseases has been proposed, but doubts remain about the technical feasibility of such projects [37]. Buchman et al. (2020) proposed an insect sterilization method involving transfecting mosquito embryos during the cleavage stage with a plasmid encoding a single-chain fragment of a human antibody against DENV-1C19 scFv. The resulting genetically modified mosquitoes were resistant to infection with all DENV serotypes and were indistinguishable from nonmodified mosquitoes in fitness parameters, fecundity, male and female fertility, male mating success, and lifespan [31]. Thus, reducing vector competence in invertebrate carriers is a promising avenue for the development of effective genetic control strategies for DENV.

There were no reports suggesting the possibility of concurrent infection with multiple serotypes or genotypes of DENV within human or invertebrate hosts. However, some reports described the long-term transmission of defective DENV genomes in nature. For example, a DENV-1 lineage with a stop codon mutation in the envelope gene was detected in both humans and mosquitoes in Myanmar [38]. Defective genomes lacking large regions of nucleotide sequence have a replication advantage over full-length parental genomes, but replicate only through complementation in the presence of coinfecting functional viruses. Although such defective interfering particles compete with functional viruses, they may also facilitate the persistence of infection [38].

CONCLUSION

The high mutation rate of DENV, driven by the imperfections of its RNA-dependent RNA polymerases, supplies evolutionary material in the form of multiple missense mutations and, under selective pressure, directs viral evolution toward greater virulence in both vertebrate and invertebrate hosts. The source of viral dissemination worldwide is infected humans. Increasing volumes of passenger and cargo traffic trigger epidemics when a particular DENV serotype is introduced into regions where a different serotype previously circulated. Research should prioritize measures aimed at identifying and treating infected individuals, and implementing preventive strategies to control infections in both humans and invertebrate hosts. Thus, research into interdependent protein interactions and the proteomics of DENV, *Aedes* mosquitoes, and humans appears to be the most promising. Disrupting these interdependent protein interactions at various stages of the DENV life cycle in vertebrate or invertebrate hosts may interfere with viral cell entry, and the transcription and translation of its genome.

Efforts to control infections spread by reducing vector populations have had little impact on the epidemiological situation of dengue fever. Eliminating breeding sites and interrupting vector life cycles may serve as a driving factor for expanding the species diversity of invertebrate DENV vectors through viral adaptation to changing environmental conditions. Therefore, further research should focus on identifying and elucidating critical points in the infection of both mosquitoes and humans by DENV. The increasing number of imported cases in the RF highlights the need for public education regarding transmissible diseases common in tropical and subtropical regions, and for minimizing contact with potentially infected vectors.

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