

Review Article

Exploring the Intricacies of Encephalitis in Mosquito-Borne Diseases through Vector-Host-Pathogen Interactions: A Critical Review

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Abstract

Environmental changes, medication resistance and sociodemographic shifts have all contributed to a dramatic increase in vector-borne diseases in the last 40 years, impacting both people and domestic animals. Pandemics like the Dengue fever epidemic that hit Bangladesh in 2023 show how devastating these illnesses may be on a global scale. The authors of this work stress the significance of comprehending vector-host-pathogen pathways via their examination of arboviruses in Asia. The ecology and biology of Culex, Culiseta and Aedes species in connection to Dengue Virus, Japanese Encephalitis (JE), Eastern Equine Encephalitis (EEE) and Western Equine Encephalitis (WEE) are explored in a thorough literature review that utilizes MeSH terminology. Beginning with the Japanese Encephalitis Virus (JEV), this article examines the virus's transmission from insects to vertebrates and, inadvertently, to humans as a disease. We then go on to dengue encephalitis, breaking its intricate pathophysiology into parts. This includes aspects like immune-mediated consequences, systemic problems and direct invasion. The Aedes mosquito is a key player in the human-mosquito-human cycle that transmits Dengue Virus (DENV) and the extrinsic incubation time impacts outbreaks. Continuing to focus on the neuroinvasive effects on horses and people, we have Eastern Equine Encephalopathy (EEE). The interaction between birds and Culiseta melanura mosquitoes highlights the transmission of the enzootic cycle. At last, we look at Western Equine Encephalitis (WEE), which WEEV causes and how it affects both horses and people. Importantly, Culex species, which include mosquitoes and birds, serve as vectors in the enzootic cycle. Factors including climate change and international travel are included in the study's conclusion, which emphasizes the significance of continuing research to monitor and reduce the worldwide effect of these arboviruses.

Keywords: Dengue Virus; Japanese Encephalitis (JEE); Eastern Equine Encephalitis (EEE); Western Equine Encephalitis (WEE); Viral Transmission

Introduction

The last four decades have seen a tremendous increase in the incidence of vector-borne illnesses that may infect both people and domestic animals. Typically, the primary causes are alterations in the natural environment (such as deforestation, new dams and irrigation systems, etc.), medicine resistance and sociodemographic changes (such as urbanization, increased population density, substandard housing, etc.). However, sudden and unexpected emergencies like the Dengue fever pandemic in Bangladesh in 2023 are not unheard of. A rise in international commerce and travel has made these catastrophes more probable. Although such emergencies are still very difficult to foresee, compiling a list of prospective arbovirus vectors in Asia can help with risk prediction. Previously geographically isolated illnesses have expanded throughout the globe, leading to an increase in the prevalence of diseases transmitted by mosquitoes [1]. When it comes to the transmission and dissemination of arboviruses, such as dengue, West Nile Virus (WNV), Eastern Equine Encephalitis (EEE) and Western Equine Encephalitis (WEE), vector-host-pathogen interactions play a crucial stage in the process. Vectors are necessary to transfer these viruses from one host to another. In the case of dengue and West Nile virus, mosquitoes are the most common vectors, whereas *Culicoides* midges are responsible for EEE and WEE. Several molecular and ecological interactions occur during the delicate dance between the vector, the host and the pathogen. While feeding on an infected host, often a person or a bird, mosquitoes may get infected. After that, the virus passes through a complicated chain of internal processes inside the mosquito, finally reaching the salivary glands. When the infected mosquito bites a new host, it injects the virus into the bloodstream, the first step in the infection process. Several elements influence whether or not viral transmission is successful. These include the host's immunological response, the vector's competence and environmental conditions [2]. To create successful measures to prevent the spread of these arboviruses and reduce the impact of related illnesses on human and animal populations, it is essential to have a thorough understanding of the intricacies of these interactions.

Methodology

We performed a comprehensive literature review. By using MeSH terms like "Dengue Virus", "Japanese Encephalitis (JEE)," "Eastern Equine Encephalitis (EEE)," "Western Equine Encephalitis (WEE)," and "Viral Transmission," we searched credible resources like PubMed database. The goal of this work package is to compile the most up-to-date research on the ecology and biology of the *Culex*, *Culiseta* and *Aedes* species as they relate to the transmission of Dengue Virus, Japanese Encephalitis (JEE), Eastern Equine Encephalitis (EEE), Western Equine Encephalitis (WEE).

Vector-Host-Pathogen Mechanism

Japanese Encephalitis Virus (JEV)

A major public health issue, Japanese Encephalitis (JE), is caused by the flavivirus known as JEV, which is mostly spread by mosquitoes. An underappreciated tropical illness, the virus claims a disproportionately high number of lives annually in East Asia [5]. Flaviviruses, such as JEV, may spread rapidly due to the nature of their insect vectors, the prevalence of metropolitan areas and the ease of international travel [7]. According to Pujhari, et al., the virus has formed a complicated web with the help of insects, vertebrates as reservoirs and unintentional hosts like humans [8]. Also, some areas, like Cambodia, have mosquitoes that might spread JEV and other arboviruses [4]. In addition to affecting humans, the virus multiplies in vulnerable hosts such as pigs, ducks and chickens, meaning its effects go beyond only human health [3]. As a top cause of viral encephalitis in Asia, it is essential to understand the ecology and evolution of JEV [6]. Sanborn, et al., noted that the dynamics of the virus's transmission and possible control methods may be better understood via the continuing investigation of the virus's virome diversity in mosquitoes. JEV transmission is complex and involves vectors, hosts and environmental variables thus, it's important to avoid and manage it using comprehensive tactics [9].

Species	Presence	Vector Status	Reference
<i>Culex Pipiens</i>		Proven vector of WN virus	[58, 59]
		Potential vector of RVF virus (virus isolation, vector competence studies)	[60]
		Potential vector of JE virus (vector competent studies)	[61]

<i>Culex Modestus</i>	Palaearctic distribution	Proven vector of WN virus	[62, 63]
<i>Culex Theileri</i>	Presence in some parts of Europe	Proven vector of WN virus in South Africa	[64]
		Potential vector of RVF virus (isolation and laboratory studies)	[65]
<i>Aedes Albopictus</i>	Presence in some parts of Europe	Proven vector of dengue virus	[66]
		Suspected vector of VEE viruses (vector competence studies)	[67]
		Potential vector of EEE virus (isolation and laboratory studies)	[68]
		Potential vector of WN virus (isolation and laboratory studies)	[69]
		Suspected vector of JE virus (natural infection)	[70]
<i>Aedes Vittatus</i>	Western Mediterranean distribution	Potential vector of Dengue virus (Experimental transmission, natural infection)	[71]
<i>Aedes Dorsalis</i>	European boreal distribution	Potential vector of WEE virus (experimental transmission, natural infection)	[72]
<i>Aedes Vexans</i>	Whole Europe	Suspected vector of RVF virus (natural infection)	[73]
<i>Aedes Caspius</i>	Whole Europe	Potential vector of RVF virus (experimental transmission)	[74]

Table 1: Suspected vector species for some arboviroses in European countries.

Transmission of Japanese Encephalitis Virus (JEV): A flavivirus, Japanese encephalitis (JE) has a strong kinship with St. Louis and West Nile encephalitis viruses. Bite vectors of the *Culex* mosquito family, especially *Culex tritaeniorhynchus*, transmit the JE virus to humans. It is widely believed that *Culex* and maybe some *Aedes* mosquitoes are responsible for transmitting JEV from wild reservoir hosts, such as Ardeid birds, or amplifying hosts, such as farmed pigs, to people. But JEV can still circulate in places where Ardeid birds and domestic pigs aren't very common, like Singapore, where sentinel poultry is monitored for the virus long after pig production has ended. Different regions may thus have different JE epidemiology [11,12]. Several Asian regions have demonstrated that domestic ducks and poultry are susceptible to JEV [13-16]. A serosurvey in the Cambodian province of Kandal revealed that the infectious force of JEV, or the probability of infection at any given moment, was similar to that experienced by pigs [14]. In addition to developing considerable viremia after being bitten by infected mosquitoes, young ducklings and chicks may be able to infect mosquitoes that feed on them [17-22]. This suggests that young fowl may be competent hosts to transmit JEV to vectors [23]. But no one has looked at chickens as potential natural hosts for JEV in any detail just yet.

Dengue Encephalitis

According to Baheti, et al., dengue encephalitis is an uncommon but serious side effect of dengue virus infection that results from the virus directly invading the central nervous system [20]. Dengue encephalitis has a complicated pathophysiology that incorporates several different mechanisms. According to research, there are three main pathogenic mechanisms for the neurological consequences of dengue infection: the virus's direct invasion of the central nervous system, which results in neurotropic effects like meningitis and encephalitis; systemic complications that lead to encephalopathy and stroke; and post-infectious immune-mediated complications that include acute disseminated encephalomyelitis and Guillain-Barre syndrome [23,24,27]. Furthermore, several individuals with neurological symptoms discovered the virus in their cerebrospinal fluid, suggesting that it directly affects the central nervous system [21,22,25,26]. Emphasize the significance of comprehending vector-host-pathogen interactions in dengue encephalitis and the function that mosquito vectors play in transmitting dengue virus and other flaviviruses. These results demonstrate the complex pathophysiology of dengue encephalitis, which includes host defense mechanisms, viral virulence factors and the function of mosquito vectors in virus transmission.

Transmission of Dengue Virus (DENV): Infected female mosquitoes of the genus *Aedes*, particularly *Aedes aegypti* and *Aedes albopictus*, are the most common vectors for the transmission of dengue fever [28]. But in other parts of the globe, the other two vectors, such as *Aedes polynesiensis* and *Aedes niveus*, are the ones that serve as secondary vectors [29]. It is believed that DENV transmission occurs in a human-mosquito-human cycle. In this case, mosquitoes get the infection by feeding on an infected

person's blood. DENV replicates in the mosquito's midgut for three to five days before moving on to the salivary gland, which may take up to fourteen days. The adult virus may then infect people who are vulnerable to it by biting an infected mosquito. The anticipated duration between when a mosquito becomes sick and when it may spread the disease, known as the Extrinsic Incubation Period (EIP) is about 5 to 14 days. A crucial factor in determining the severity of dengue epidemics is that the EIP affects the percentage of infected mosquitoes that survive to spread the disease [30-32]. Despite the wide variation in parameter estimates for the EIP, this trait makes it suitable for modeling dengue transmission patterns [33].

After a mosquito bite, the virus travels through the blood and starts to multiply in cells that the virus has identified as potential hosts, such as monocytes and dendritic cells in the skin. Endothelial cells, hepatocytes and other cells are all subject to the virus's effects, which include immunological abnormalities, cytokine overproduction and cell death [36]. According to Martins, et al., this causes signaling pathways to start the apoptotic process, which adds to the severity of the illness [35-39]. In addition, the virus hinders routes for thymidine production, which impacts the replication of the virus [34]. Functioning autophagy components also make it easier for viruses to replicate their RNA and produce infectious viruses [40,41]. After infecting certain immune cells, the virus travels to lymph nodes to replicate. Variegated cytopathies manifest in different degrees of severity after viral infection of various liver cells [37]. The first stage of dengue infection is a fever and the second stage is severe dengue, sometimes called Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS), which may be fatal. Different serotypes of the virus may cause secondary infections, which can increase the severity of the illness via antibody-dependent enhancement [35,37,38]. All of these results point to the complex ways in which the Dengue virus causes illness by infecting and controlling host cells (Fig. 1).

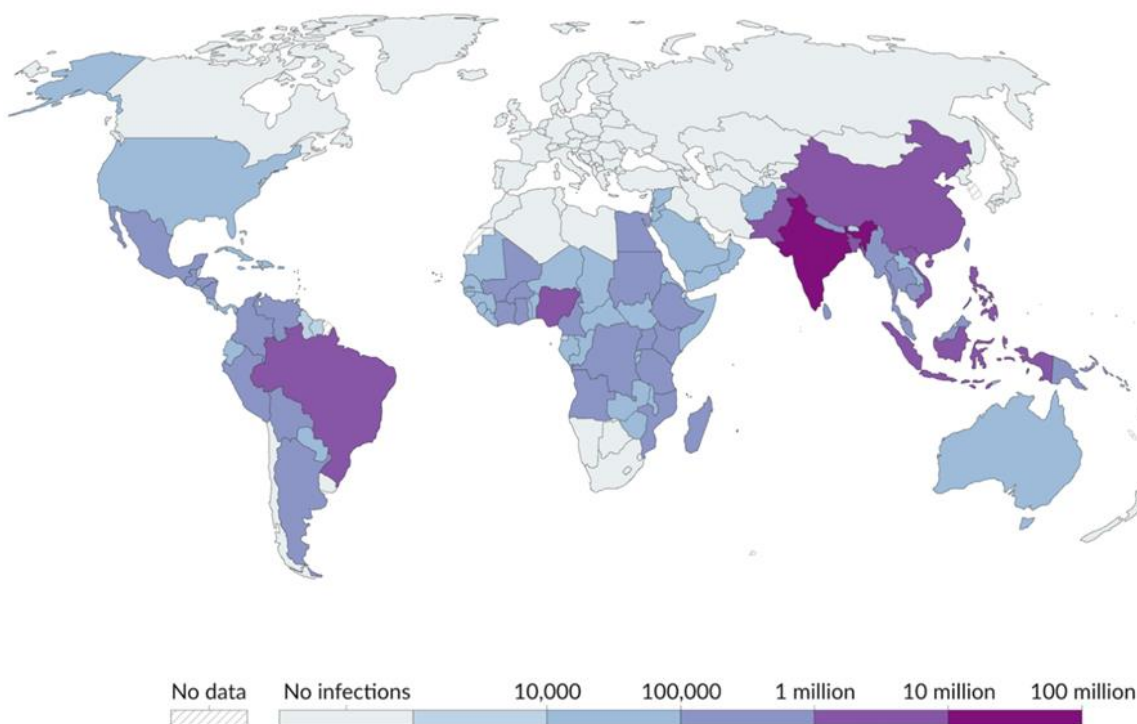


Figure 1: Recent distribution of dengue virus in the whole world.

Eastern Equine Encephalitis

The virus known as Eastern Equine Encephalitis (EEE) causes a destructive form of arboviral neuroinvasive illness in horses. Survivors of this disease often have severe neurological sequelae and a high death rate [39,40]. Among neuroinvasive arboviral infections in the US, EEEV has the greatest case-fatality rate. Animals and people alike are susceptible to the virus's devastating encephalitis, which may lead to fatalities or lasting neurological consequences [47,53]. During the transmission season, outdoor activities near forested wetlands have been linked to the illness marked by localized radiography symptoms. There is strong evidence that EEEV is highly pathogenic to horses and people and it has been suggested that outbreaks in the northeastern United States may originate in Florida [44]. Multiple U.S. states have seen infections due to the virus. The epidemiology of the

virus has been investigated by using the persistence of antibodies to EEEV in birds [42]. Using GIS and spatial statistics, researchers in Florida have examined the geographical epidemiology of EEE [44]. According to Sah et al., our results highlight the importance of EEE as a public health problem and the need for ongoing monitoring and mitigating methods to combat this fatal zoonotic virus transmitted by mosquitoes.

Transmission of Eastern equine encephalitis Virus (JEV): Birds and *Culiseta melanura* mosquitoes, which lay their eggs in freshwater hardwood swamps, are the main vectors in the enzootic cycle that transmits Eastern equine encephalitis (EEE) [46]. This cycle is crucial for the virus's maintenance and mosquitoes, especially *Aedes sollicitans*, are a major vector for EEE transmission to horses and birds [50]. The virus is very contagious and may spread by airborne particles [45]. The increase in EEE occurs at the same time as the virus's vectors and the main hosts, which are birds [41,42]. Also, the virus may make people sick with encephalitis, which can lead to death or permanent brain damage in those who have it [47]. Savage, et al., state that the American Robin and Common Grackle are the most significant reservoir hosts for the virus according to the EEEV transmission model [48]. In addition, the virus has the ability to infect macrophages and dendritic cells, which affects its pathogenesis [43]. Elevated mortality rates among equine and human cases of EEE highlight the seriousness of the disease [44]. In general, a web of relationships exists between birds, mammals and mosquitoes that allows the EEE virus to spread and infect hosts, ultimately leading to severe cases of encephalitis [46].

Bangladesh	2022	2021	2020	2019	2018
Japanese Encephalitis	82	82	32	86	96
Dengue	62,382	28,249	1,193	1,01,354	10,148
India					
Japanese Encephalitis	1271	489	718	2496	1707
Dengue	-	1,64,103	44,585	2,05,243	1,24,493
United State					
Dengue	1,247	205	354	1,474	483
Eastern Equine Encephalitis	-	112	142	184	107
West Nile Virus	1,126	2,911	731	971	2,647
La Crosse Encephalitis	22	40	88	55	86
Saint Louis Encephalitis	33	17	16	17	8

Table 2: Statistical report of JEV, DENV, EEV, WEEV of last five year (2018-2022) [75].

Western Equine Encephalitis (WEE)

Western Equine Encephalitis (WEE) is a serious neurological disease caused by the Western Equine Encephalitis Virus (WEEV), a member of the Alphavirus genus. WEEV is transmitted to humans and horses by mosquitoes and is known to cause lethal encephalitis in both species [50]. The virus is primarily found in North and South America. It is closely related to other New World alphaviruses, such as the Eastern Equine Encephalitis Virus (EEEV) and the Venezuelan Equine Encephalitis Virus (VEEV) [51]. WEEV, EEEV and VEEV are considered naturally emerging pathogens and potential biological weapons, posing a significant public health threat. The virus is known to persist in the environment, with strains remaining genetically unchanged for long periods, indicating local persistence. The enzootic cycle of WEEV involves birds and mosquito vectors, with birds serving as primary hosts for the virus [46]. The virus has been the cause of multistate outbreaks in the United States, highlighting its potential for widespread impact. Surveillance and research on WEEV have been conducted using various animal models, including house finches and cotton rats, to understand its transmission dynamics and pathogenesis [56]. Additionally, studies have explored the potential for antiviral treatments against WEEV, indicating the ongoing efforts to develop therapeutic interventions for this disease.

Transmission of Western Equine Encephalitis Virus (JEV): According to Baxter and Heise (2018), the virus that causes Western Horse Encephalitis (WEE) is the Western Equine Encephalitis Virus (WEEV), an alphavirus that is common throughout the Americas

[50, 51]. Mosquitoes and birds keep WEEV in an enzootic cycle; humans and horses are considered dead-end hosts [54]. Animals and people alike are susceptible to the virus's devastating encephalitis, which may lead to neurological complications or even death [46]. There are several viruses in the Venezuelan equine encephalitis complex. However, the principal enzootic vectors of WEEV are species of the subgenus *Culex* (Melanoconion) Theobald [57]. The virus has a tight relationship with two other potentially lethal equine encephalitis viruses—the Eastern Equine Encephalitis Virus (EEEV) and the Venezuelan equine encephalitis virus (VEEV) [53]. Most West African enzootic viral transmission occurs in an enzootic cycle involving mosquitoes and birds, with birds acting as the virus's principal amplifying hosts [52]. Multiple bird species and mosquitoes are involved in the virus's role in epizootic transmission cycles [56]. When controlling and monitoring WEEV and similar arboviruses, knowing how the virus spreads and which hosts and vectors are involved is vital (Fig. 2).

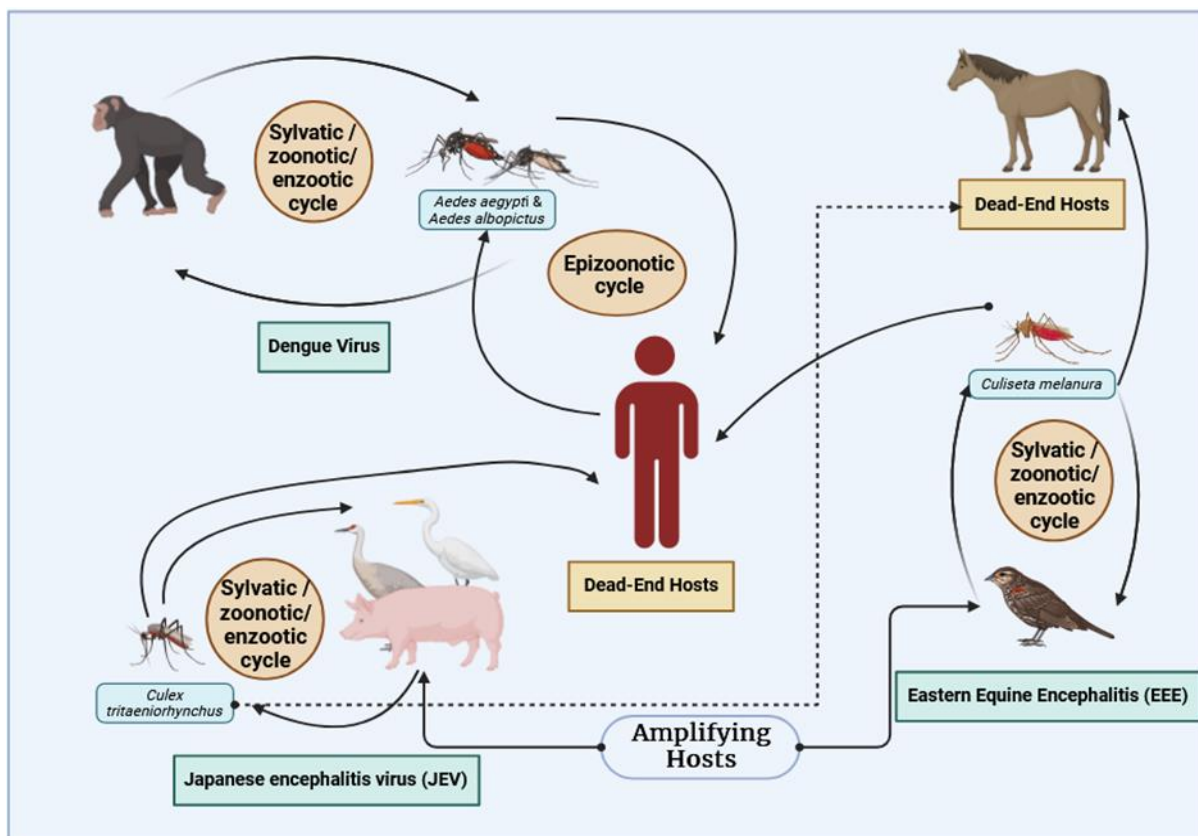


Figure 2: A visual representation of various kind of mosquito borne diseases from animal to human [46-56].

Conclusion

In conclusion, the emergence and spread of vector-borne diseases, such as those caused by arboviruses like the Japanese encephalitis virus (JEV), the Dengue virus (DENV), the Eastern Equine Encephalitis Virus (EEEV) and the Western Equine Encephalitis Virus (WEEV), present significant challenges to the public health of the entire world. Regarding the transmission cycles of these viruses, the delicate dance between vectors, hosts and pathogens highlights the need to grasp the processes under the surface fully. To contribute to this knowledge, this extensive literature review aimed to investigate the vector-host-pathogen relationships for JEV, DENV, EEEV and WEEV. Some ecological, molecular and environmental variables play a role in the transmission dynamics of these viruses. These dynamics entail the complicated connections between mosquitoes, birds, animals and humans. To develop effective preventative and control measures, it is essential first to identify the primary vectors, hosts and transmission patterns. Based on these results, it is clear that continued study is necessary to monitor and reduce the influence of arboviruses on human and animal populations. A proactive and multidisciplinary strategy is necessary to handle the complex difficulties presented by vector-borne illnesses and minimize the possible catastrophic implications of these diseases. This is because global variables such as climate change, urbanization and international travel are continuing to develop.

Conflict of Interest

The authors have no conflict of interest to declare.

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