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Infectivity, Disease Transmission and Pathogenesis of Arboviruses in Urban and Sub-Urban Areas of Eastern Uttar Pradesh

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Abstract

This review describes the disease transmission, infectivity, and pathogenesis caused by arboviruses in urban and suburban areas. These viruses cause severe morbidity and disease in the human population, affecting both urban and rural areas in tropical and subtropical climates worldwide. According to WHO surveillance reports, the infectivity and incidence of arboviral diseases are increasing at present, as climatic factors support the growth of vector populations, which have enhanced the frequency, magnitude, and geographical extent of these diseases. This is a challenging task to control the cases of fatal arboviral diseases in rural areas. Arbovirus-generated diseases pose a severe public health concern, as clinical and hospital care are not readily available in many parts of the world. Most of the deaths occur due to the unavailability of clinical care and proper medication. Arboviral diseases affect people all over the world, including in India, in a big way in terms of social, economic, and clinical consequences.

Keywords

Arboviruses, Disease Transmission, Infectivity and Pathogenesis

1. Introduction

Arboviruses (DENV, ZIKV, JEV, and CHIKV) are highly infectious viruses that pose a significant public health threat worldwide. Arboviral diseases are caused by a group of viruses spread by the bite of infected arthropods. Hundreds of viruses, designated as arboviruses, are transmitted by arthropod vectors in complex transmission cycles between the virus, vertebrate host, and the vector. Arboviruses, including dengue, Chikungunya, and Zika viruses, are current public health threats

in tropical and subtropical regions. These viruses cause high infectivity in the human population and expand beyond their geographical ranges [1]. There are two families of viruses, Flavivirusidae and Togaviridae. Flaviviruses belong to the Flavivirus family, and alphaviruses belong to the Togaviridae (**Figure 1**). Consequently, all continents remain on high alert for potential new outbreaks. These viruses are responsible for 17% of total infectious diseases and are estimated to cause approximately millions of deaths worldwide every year [2]. These viruses are found in almost all parts of the world and, until recently, were primarily transmitted between animals, specifically wild animals, but could also infect humans [3].

So far, research has been done on more than 500 arboviruses that have been identified globally, but among them, more than 100 arboviruses can infect humans, and over 40 can infect domestic animals [4] [5]. In India, four serotypes DENV-1, DENV-2, DENV-3, and DENV-4 have been reported and shown their prevalence in North eastern and southern India. Among them, DENV-1 and DENV-2 have been reported to be more harmful as they are geographically found in Eastern Uttar Pradesh. The DENV-3 is often the most prevalent in South Indian states. Studies from UP have shown that DEN-2 has frequently been the most common serotype during outbreaks. For example, one study reported DEN-2 as the dominant serotype in 2020 and 2021. While DEN-2 might be dominant, other serotypes like DEN-3 and even all four serotypes can be found circulating simultaneously. The prevalence of specific serotypes can change from year to year. For example, one study noted that DEN-3 was more prevalent in 2018 and 2019, while DEN-2 became dominant in 2020 and 2021. The co-circulation of DENV1 - 4 serotypes from the E-UP region was also seen. It also shows its incidence and infectivity due to presence of mosquito vectors *Aedes aegypti* and *Aedes albopictus* in different eco-climatic regions.

It is true that geographic range of arthropod vectors differs, which is largely influenced by climate and environmental conditions. Further, human travel and migration are responsible for its spread and introduction in new areas, which potentially alter serotype distribution patterns. Zika and Chikungunya viruses, transmitted by mosquitoes, also have specific geographic distributions. Hence, new biomarkers and diagnostic tools are required to identify strain-specific infectivity, incidence morbidity and mortality in human population. Therefore, adequate knowledge of serotype distribution is essential for developing effective vaccines, as some vaccines may be serotype-specific. Targeting specific mosquito or tick species that transmit prevalent serotypes can improve vector control strategies. Arboviruses cause diseases of great concern. Among these, dengue, Zika, West Nile fever, and yellow fever have the most significant economic and social impact. These viruses have recently re-emerged and continue to pose a public health problem worldwide.

Viruses of dengue, West Nile, Japanese chikungunya, and Zika are transmitted by mosquitoes and by bites from other arthropods. Mosquitoes and other biting

arthropods spread arthropod-borne viruses (arboviruses). Arboviral epidemics have increased in frequency, magnitude and geographical extent over the past decades and are expected to continue rising with climate change and expanding urbanization [6]. There are more than 534 different species of arboviruses, 134 of which can infect humans and wild animals and cause disease, making them a serious threat to public health in tropical areas [7].

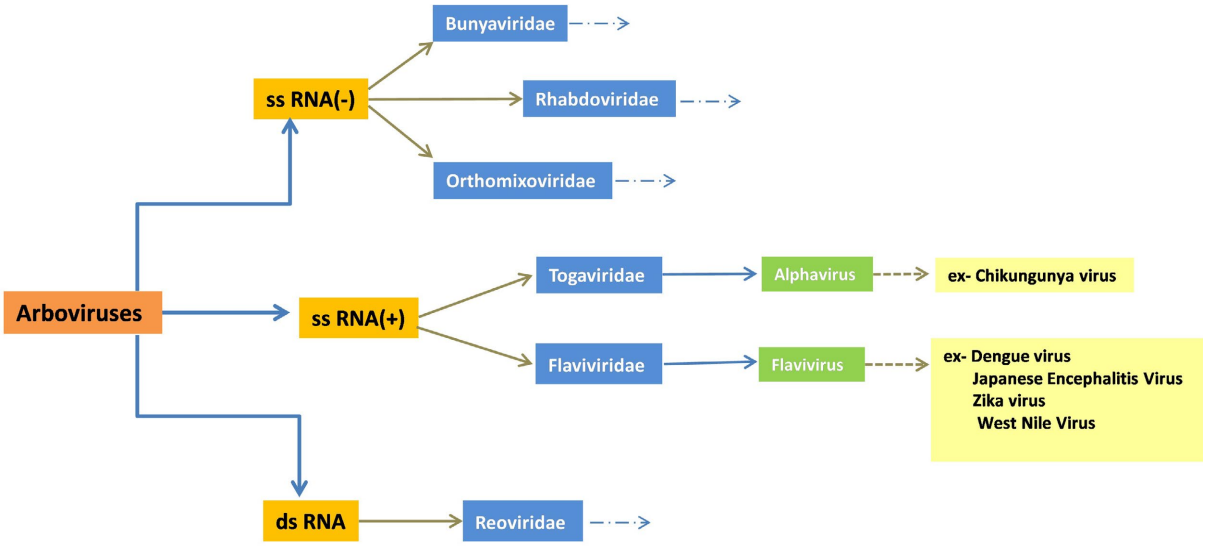

Figure 1. Showing classification of major arboviruses from subtropical regions.

Currently, the world is experiencing a period of intense globalization, which, combined with global warming, directly contributes to the broader dissemination of arbovirus vectors worldwide. Global climate change, rapid urbanization, burgeoning international travel, expansion of mosquito populations, vector competence, and host and viral genetics are responsible for the emergence of arboviral diseases.

This review aims to provide a comprehensive understanding of the pathogenesis of the four main arboviruses today (DENV, ZIKV, YFV, and CHIKV), discussing their viral characteristics, immune responses, and mechanisms of viral evasion, as well as critical clinical aspects for patient management. This includes associated symptoms, laboratory tests, treatments, and existing or developing vaccines, as well as the primary complications, thereby integrating a comprehensive historical, scientific, and clinical approach. This article outlines the pathogenic mechanisms of the four main arboviruses to understand aspects related to viral characteristics, tropism, immune response, and viral evasion, as well as the primary symptoms, pathogenesis, treatment methods, and prevention strategies. It emphasizes the most pertinent points related to clinical management.

2. Source of Data

For writing this comprehensive research review on Emerging Arbovirus diseases,

five medically significant arboviruses—Chikungunya virus (CHIKV), dengue virus (DENV), West Nile virus (WNV), Japanese encephalitis virus (JEV), and Zika virus (ZIKV)—were searched. An extensive search was conducted to explore our research outcomes on Arbovirus diseases from 1999 onwards. The articles were thoroughly read for recent research in this area. For relevant information literature electronic databases were searched, using keywords, and specific terms such as Infectivity, disease transmission and pathogenesismedical subject headings (MeSH) and key text words, such as arboviruses "DENV, ZIKV, YFV, and CHIKV", mosquito vectors, "*Aedes*", "*Culex*", pathogen transmission, epidemic outbreaks, and its control till 2025 were used in MEDLINE. For various database searches, the emphasis was given to collect scientific information "arboviruses and their global impact on human health", mainly related to invasion of human hosts, immune responses, and mechanisms of pathogenesis, symptoms, control measures and precautions.

Most especially for retrieving all articles about emerging arbovirus diseases, electronic bibliographic databases, including PubMed, Scopus, EMBASE, Web of Science, Cochrane Library, SwissProt, and Google Scholar, were thoroughly searched for papers published up to 2025 to compile comprehensive and current information. Backwards citation tracking of a few chosen research articles yielded more pertinent data. Peer-reviewed publications, surveillance reports, outbreak investigations, epidemiological bulletins, and policy documents were among the numerous sources examined. Additionally, information was obtained from regional organizations like the Indian Council of Medical Research (ICMR-NIV), Japan's National Institute of Infectious Diseases (NIID), ASEAN health networks, and the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and European Centre for Disease Prevention and Control (ECDC). Epidemiology, geographic distribution, vector ecology, pathophysiology, clinical manifestation, diagnostics, therapeutic approaches, vaccine development, and public health measures were prioritized in the literature.

Papers were selected on the basis of work done related to arbovirus diseases, and a systematic approach was applied to organize the available information on all facets of biological transmission. From a study point of view, the literature available on genetic basis of vertebrate resistance to viral infection, and phylogenetic evidence of the history of host range shifts in arboviruses. However, glaring gaps in knowledge of many critical subjects, such as the mechanism of viral persistence and the existence of vertebrate reservoirs, were preferentially selected. We have specially tried to find out the cause of reemergence of arbovirus disease, enhancement of pathogen and disease range, host selection and molecular and genetic adaptability among and between the strains in endemic area and outside these sites [8].

3. Epidemiology

For the study of epidemiology, public awareness programs are essential. The Gov-

ernment of India has launched the "Swachh Bharat Mission" to promote village cleanliness. Rural people are aware that Panchayati Raj personnel are responsible for maintaining social structures and public utilities, including the cleanliness of hands, ensuring the safety of drinking water, and controlling insect vectors. A safe drinking water supply is provided to most villages, and shallow pumps have been replaced. Special care is being provided to the patients of AES/JE. Both vaccination and cleanliness drives are operative and have given good results.

Encephalitis Treatment Centres (ETC) and other facilities are equipped with services and supplies to address the demand for fever treatment. In recent years, there has been an average of 15 cases per million people annually. This means that more than 100,000 people are infected with Dengue each year, and 200 to 400 people die. The most recent epidemic occurred in 2017, when there were 188,401 cases and 325 deaths (NVBDCP) [9].

These epidemics have a significant economic impact on the affected countries, including India, as well as public health implications. The incidence of Dengue in India has increased significantly since 2010. There are between 30,000 and 50,000 global cases of Japanese encephalitis each year. Severe disease is estimated to occur in about one in 250 infections. Transmission is seasonal in temperate climates, peaking between May and October, but the risk persists year-round in more tropical climates. The most significant risk for infection is during the rainy season and the pre-harvest period in rice-growing areas, due to increased populations of mosquito vectors. Most mosquito bites occur between dawn and dusk. Twenty-four countries in South-East Asia and the Western Pacific have endemic JEV transmission, placing more than three billion people at risk for infection [10]. Several factors, including ecological, social, cultural, urbanisation, and pollution, contribute to the increase in disease cases. Advanced diagnostic methods, potential vaccination, and clinical interventions are required to save the population, especially children.

Some factors, such as climate change, urbanisation, and uncontrolled population growth, are fuelling their widespread occurrence. Arboviruses encompass a vast collection of genetically diverse viral pathogens, including those responsible for dengue, Zika, and chikungunya. These viruses are peculiar as they are zoonotic and cause serious harm to society, with no particular therapy to neutralise their effect [11].

West Nile Virus (WNV) is primarily maintained in a cycle of transmission between *Culex* species mosquitoes and birds. This is known as the enzootic transmission cycle. The virus can escape this cycle and infect other vertebrates, including humans, which can cause an epidemic or epizootic.

The number of cases of Zika virus disease declined globally after 2017. Still, the virus continues to be transmitted at low levels in some countries in the Americas and other endemic regions. In 2019, the first local mosquito-transmitted Zika virus disease cases were reported in Europe and in 2021, Zika virus outbreak activity was detected in India. To date, a total of 89 countries and territories have reported

evidence of mosquito-transmitted Zika Virus infection, but global surveillance remains limited [12].

Chikungunya virus (CHIKV) causes a disease that results in severe joint pain, which can cause people to stop working [13]. Unlike Dengue, Chikungunya virus disease is characterised by recurrent musculoskeletal disease that primarily affects the peripheral joints and can persist for months to years after acute infection. While Chikungunya Virus Disease (CHIKV) is often self-limiting and has a low fatality rate, the manifestations of CHIKV infection that lead to acute and chronic disability can have significant implications. These include a substantial impact on the quality of life of infected patients, as well as considerable economic and community consequences [14] (**Figure 2**).

4. Impact of Climate Change on the Transmission of Disease Pathogens

During the rainy season, dengue cases increased by approximately 8% for every 1˚C rise in the average temperature in India. This is due to the enlargement of the water surface area and the significantly faster growth of mosquito vectors. The last heavy outbreak of dengue was seen in 2021 to 2023 due to prolonged Aedes aegypti reproduction caused by record-high nighttime temperatures (+3˚C) during the late monsoon/early post-monsoon period of 2024 in Eastern Uttar Pradesh. Water logging brought on by irregular monsoon withdrawal produced a wealth of breeding sites. WNV transmission is more prevalent in areas with higher temperatures and lower precipitation. In general, WNV's geographic distribution and season length are being aided by warming climates. Rainfall is the second major factor that can potentially increase infectivity. Waterlogging and staying up to 4-6 months are highly problematic for the human population. There is a growing chance that Zika, Chikungunya, and WNV may also develop regional transmission cycles. Climate-specific measures are being implemented, including vector management, improved surveillance, early warning systems, and increased community awareness.

Table 1. Age-based susceptibility in eastern UP and India.

Virus	Children	Elderly/Adults
JEV	Highest attack rates (ages 3 - 15), bimodal peaks in 1 - 5 and 12 - 15.	Increased risk in the elderly in non-endemic emerging settings
DENV	Hospitalizations common (~9 yrs mean); paediatric mortality observed (~1.9%)	Neurological complications are possible in adults (0.5% - 21%)
CHIKV	In paediatric AES outbreaks, high fatality (~25%)	No adult-specific regional data
ZIKV	No E-UP data; known high risk to foetuses globally (microcephaly)	Age-based data lacking locally
WNV	Pediatric fatalities documented in early outbreaks	Limited data; adults may experience asymptomatic or mild disease

Children in Eastern UP exhibit a markedly higher susceptibility and severity to JE, Dengue, Chikungunya, and WNV, particularly in encephalitic forms. Elderly populations, while less frequently infected in endemic settings, may face greater mortality, particularly for JE in emerging zones; data on elderly impacts for other arboviruses in the Eastern UP remains scarce. Zika-specific age-related data for the region are lacking (**Table 1**).

5. Vectors

Two mosquito species, *Aedes aegypti* and *Aedes albopictus*, are among the world's most prominent arboviral vectors, which spread arbovirus infection [15]. *Aedes aegypti* is a vector of international concern because it can transmit to humans three important arboviral diseases: yellow fever, dengue, and chikungunya [16]. *Aedes aegypti* are small, dark-colored mosquitoes distinguished by white markings on their legs. Their life cycle consists of four stages: larva, pupa, and adult, which typically takes 8 to 10 days to complete, depending on factors such as temperature, food availability, and larval density [17]. These viruses cause a significant number of asymptomatic infections [15] (**Table 2**).

Table 2. Arboviral diseases and their associated vectors and host diseases.

Arboviral diseases	Pathogen	Primary hosts	Primary non-human reservoir hosts
Dengue	Flavivirus	*Aedes aegypti* and *Aedes albopictus*	Non-human hosts of minor concern
Zika	Flavivirus	*Ae. Aegypti* and Ae. *albopictus*	Non-human hosts of minor concern
Chikungunya	Alpha-virus	*Ae. Aegypti* and *Ae. albopictus*	Non-human hosts of minor concern
Japanese encephalitis	Flavivirus	*Culex*	Pigs, birds
West Nile Virus	Flavivirus	*Culex*	Birds

6. Pathogenesis

Hematophagous arthropods are considered biological vectors, as opposed to mechanical vectors, when they can acquire a specific pathogen while feeding on an infected vertebrate host. Afterwards, the pathogen replicates within the vector and is then transmitted to a new vertebrate host [7]. Arboviruses possess RNA genomes that can be linear or segmented, positive-sense or negative-sense, and single or double-stranded.

Most arboviruses spread among wild animals, and many of them spread to humans and domestic animals that are incidental or dead-end hosts in agriculture. In tropical urban centres, viruses like dengue (DENV) and chikungunya (CHIKV), which no longer require enzootic amplification, are causing widespread epidemics [18] (**Figure 2**).

When injected into the skin, monocyte-lineage cells, such as dendritic cells, Langerhans cells, and macrophages, are among the primary targets [19]. Numerous tissues, including the dermis (skin), blood, bone marrow, lymph nodes, liver, and, less frequently, the brain, have been reported to contain viruses. Endothelial cells, epithelial cells, lymphocytes, hepatocytes, fibroblasts, and keratinocytes are additional potential targets. Heparan sulfate proteoglycans, DC, heat shock protein (HSP) 70, and other receptors are only a few of the receptors that envelope protein (E) interacts with to promote cellular internalisation of DENV and to start receptor-mediated endocytosis, which may or may not be clathrin-dependent. Fc and C1q receptors can also enable entry through an antibody-mediated pathway [20].

Dengue virus (DENV) enters the host through various methods, including diffusion and macropinocytosis. The virus's E protein undergoes irreversible conformational alterations due to the acidic environment of the endosomal membrane, leading to fusion with the endosomal membrane. The viral genome is translated into a single polypeptide, which is processed and cleaved by host and viral proteases, yielding ten viral proteins. These proteins assemble a replication complex through invagination of the endoplasmic reticulum (ER) membrane, enabling RNA replication and shielding viral particles from the host's innate immune response. The virus has evolved various tactics to evade the host's innate response, mainly through its non-structural proteins. DENV can evade the adaptive response by inhibiting the complement response and forming a replication complex that acts as a barrier. It also interacts with antigen-specific immunity, such as priming and activation of T and B cells, antibody production, and neutralisation capabilities [21] [22].

6.1. Viral Entry, Replication, and Release

If successful, the antiviral response will counteract viral replication and infection. However, DENV evades it through its non-structural proteins (NS1 to NS5), which can disrupt receptor signaling, IFN synthesis, and regulation pathways. Additionally, DENV's NS1 protein can inhibit the complement response by interacting with its protein complexes [20]. More passively, DENV evades the immune response by forming the replication complex, which serves as a barrier, and by regulating cellular apoptosis, a standard mechanism used by the immune system to suppress viral replication. Furthermore, DENV's capability of infecting defense cells is itself a means of deregulating the host's antiviral response. Despite its notable role in dengue pathogenesis, the innate response is not typically singled out as a factor in dengue severity. In contrast, the adaptive immune response has been pointed out as the primary contributor, due to impaired immune responses against different serotypes [23].

The adaptive immune response to dengue virus (DENV) involves antigen-presenting cells (APCs) presenting viral antigens to T cells in lymph nodes, leading to the differentiation of T lymphocytes into effector and memory T cells. This provides long-term immunity against the same serotype but short-term immunity against heterotypic infections. DENV interacts with factors such as priming and

activation of T and B cells, antibody production and neutralization properties, and cytokine release, which significantly impact disease pathogenesis (**Figure 2**).

DENV can impair T lymphocyte priming and activation through antigenic variation or apoptosis of APCs, compromising the T cell response. Anti-DENV neutralizing antibodies target specific regions of E and C proteins and can also target NS proteins, especially NS1. Genomic variations within a single serotype can alter these antigens, disrupting the immune response even in homotypic infections. The antibody response to different DENV serotypes is less effective and can enhance viral infection through antibody-dependent enhancement. Autoimmunity may play a role in dengue pathogenesis, with autoantibodies directed against endothelial cells (ECs) and platelets linked to elevated vascular permeability in secondary infections.

6.2. Cytokine Storm and Vascular Permeability

Although cytokine release is a regular physiological event in the immune system [24], one of the primary events in severe dengue cases is the exacerbated release of cytokines. It is primarily observed in secondary infections [25] and is associated with impaired immune responses. Although many in vitro and in vivo experiments using animal models, as well as observational studies, have been conducted to better understand the role of various cytokines, the molecular mechanisms by which the cytokine storm relates to dengue severity remain poorly understood. In addition to viral infection of leukocytes and ECs [26], the NS1 protein's interaction with receptors like TLR-4 [27] [28] can also cause cytokine storm events. The severity of the disease has been primarily linked to high levels of cytokines, including interleukin 1 (IL-1), IL-4, IL-8, IL-10, IL-13, and IL-17, as well as C-X-C motif chemokine ligand 10 (CXCL10), tumor necrosis factor-alpha (TNF-α), vascular endothelium growth factor A (VEGFA), macrophage migration inhibiting factor (MIF), IFN-β, and IFN-γ [26] [28]. In vitro studies have suggested more specific roles for various cytokines, such as MIF's role in EC glycocalyx degradation [29] [30] and the roles of CXCL10, VEGFA, and TNF-α in increased permeability and EC apoptosis [28] [30]. These cytokines are closely linked to the increase in vascular permeability and subsequent plasma leakage, as well as to the disruption of tight junctions [31] and the induction of autophagy [32].

The functions of MIF in EC glycocalyx breakdown and CXCL10, VEGFA, and TNF in enhanced permeability and EC death are among the more specific roles that in vitro investigations propose for several cytokines. For example, a recent longitudinal study suggests that measuring cytokine levels in patients may help predict the severity of dengue. It is interesting to note that anti-inflammatory cytokines, such as IL-4 and IL-10, have been demonstrated to paradoxically increase inflammation by suppressing the immune system and preventing the removal of viruses, thereby increasing the spread of the virus [33]. Furthermore, because DENV has a preference for leukocytes, cytokines such as IL-8, IFN-γ, MIF, TNF-α, and CXCL10, which draw more leukocytes to the site of inflammation, may increase infection and viral replication [34]. A mechanism of positive feedback, in

which the recruitment of leukocytes and the production of cytokines lead to further inflammation, intensifies the cytokine storm during DENV infection. Ultimately, this results in vascular leakage events, which are sustained and exacerbated by thrombocytopenia and coagulopathy induced by DENV [35].

6.3. Coagulopathy and Thrombocytopenia

DENV employs various methods to interfere with coagulation, aiming to control plasma leakage while also inducing vascular leakage through endothelial damage and a cytokine storm. These occurrences can be triggered by the activation and dysregulation of coagulation pathways, as well as by affecting various steps in the coagulation process [36]. Numerous mechanisms have been demonstrated in both *in vitro* and *in vivo* investigations to explain how DENV causes coagulopathy and thrombocytopenia. Through direct infection and interaction with E protein or indirect interaction with cytokines, the virus has been demonstrated to inhibit its activity and disrupt megakaryocyte maturation in bone marrow. In addition to impacting megakaryopoiesis, early activation via DENV NS1 binding to platelet TLR-4 may lead to apoptosis, macrophage platelet phagocytosis, and dysregulated clot formation, resulting in platelet "waste" and thrombocytopenia. Additionally, DENV infection can increase the production of cross-reactive antibodies that target coagulation factors, such as thrombin and plasminogen, as well as platelets, which can lead to fibrinolysis and unbalanced coagulation, ultimately increasing vascular permeability [37]. A simplified schematic representation of the discussed immunological aspects of dengue pathogenesis can be seen in the correlation between Dengue's clinical manifestations and major complications, which are attributed to the dynamic and synergistic actions of all the highlighted factors, ultimately leading to increased vascular leakage and haemorrhage risk [38].

6.4. Genetic Variations

Table 3. Showing various genotypes of arboviruses and their symptoms.

S.N.	Virus	Genome	Identification marker	Serotype or genotype	Symptoms	Mortality
1.	Dengue virus	Positive-sense ssRNA	Non-structural protein 1 (NS1) antigen, and IgM and IgG antibodies	DENV-1, DENV-2, DENV-3, and DENV-4 serotypes	Fever, hemorrhagic fever.	10% - 20%
2.	Japanese encephalitis virus	Positive sense ssRNA	JEV-specific IgM antibodies	single serotype genotypes (I, II, III, IV, and V)	Fever, headache, seizures, encephalitis	20% - 30%
3.	Chikungunya Virus	Positive-sense ssRNA	CHIKV-specific IgM and IgG antibodies	Asian, East/Central/South African (ECSA), and West African genotypes	sudden fever, severe joint pain, headache, and muscle pain	0.13% to 0.35%
4.	Zika virus	Positive-sense ssRNA	ZIKV-specific IgM antibodies,	single serotype	Fever, arthralgia, and myalgia. Neurological manifestations.	8.3%
5.	West Nile Virus	Positive-sense ssRNA	Viral-specific IgM antibody	Asian, East/Central/South African (ECSA), and West African genotypes	Fever, muscle weakness, encephalitis, and meningitis.	10%

Arboviruses possess Positive sense ssRNA, Dengue virus is having 4 serotypes DENV-1, DENV-2, DENV-3, and DENV-4 serotypes, Japanese encephalitis virus, also display 4 genotypes (I, II, III, IV, and V), Chikungunya, single serotype from West African countries, Virus Zika virus Positive sense ssRNA a single serotype, West Nile Virus is Positive sense ssRNA, found in Asia and African countries (**Table 3**).

6.5. Zika Virus

The majority of our knowledge about ZIKV's life cycle comes from researching other closely related Flaviviruses. When female *Aedes* mosquitoes bite people in urban settings, ZIKV is disseminated. The virus enters the mosquito's body by consumption, multiplies within it, and eventually makes its way to the salivary gland. The virus is injected into the skin of a new host by the mosquito during feeding [39]. The site of injection is where viruses are initially replicated in human skin. It has been shown that human primary dermal fibroblasts, epidermal keratinocytes, and immune cells (dendritic cells) allow the infection and replication [40].

To cause viraemia and hematogenous dispersion to peripheral tissues and visceral organs, the virus travels from the skin to the draining lymph node, where it is amplified. ZIKV RNA is typically detected in human blood within the first 10 days (approximately 1.5 weeks) following infection, or within the first 3 - 5 days after the onset of symptoms. The viral load peaks at the onset of symptoms. During the first week after infection, the virus is eliminated at a comparatively high load in saliva, urine, and other bodily fluids, which are typical of a systemic disease. An immune response mediated by cells and antibodies is triggered after infection. While IgG antibodies often stay detectable for months or years and likely provide lifetime protection, IgM antibodies against flaviviruses and ZIKV are typically detectable for two to three months. Still, they can potentially last for more than a year [39].

6.6. West Nile Virus

When the West Nile Virus (WNV) is introduced through mosquito bites, it is thought that specific skin cells—keratinocytes, freshly recruited neutrophils, and skin dendritic cells are where the virus first replicates. More precisely, Langerhans cells (LCs) are where replication takes place [41]. Following infection, Langerhans cells quickly mature and develop into fully functional antigen-presenting cells that produce costimulatory molecules, such as CD54 and CD85, as well as Major Histocompatibility Complex Class II (MHC) [42]. After travelling to nearby lymph nodes, infected neutrophils and LCs enter the bloodstream via efferent lymphatic arteries. Peripheral tissues, such as the spleen, liver, and kidneys, become infected as a result of post-infection or primary infection, which also facilitates the early dissemination of the virus [43].

Early innate immune response, particularly antiviral interferon (IFN) type I re-

sponse, limits the virus's ability to infect and disseminate inside peripheral tissues. The type I IFN response is known to be neutralized by several WNV nonstructural proteins, including NS2A, NS4B, and NS5, via a variety of effector pathways. WNV infection and brain penetration are driven by IFNβ transcription and expression. Matrix metalloproteinases (like MMP9) and pro-inflammatory cytokines (like TNFα) are produced when viral sensors like TLR3 detect WNV. It has been noted that these elements raise BBB permeability, which permits WNV to spread throughout the brain. Pro-inflammatory mediators, such as TNF-α, iNOS, COX-2, IL-6, and IL-1β, are released by infected microglia in response to infection, and these mediators contribute to the death of neurons [44]. Nonstructural protein 1 (NS1) viral antigen, DENV genome variation, sub-genomic RNA, and ADE are among the viral and host factors that are believed to contribute to the development of Dengue disease [45].

6.7. Dengue Fever

Once within the body, the dengue virus infiltrates and grows within the local macrophages. After that, infected local cells move from the infection site to lymph nodes, where they attract monocytes and macrophages, which turn into infection targets. As a result, the virus spreads through the lymphatic system, and the illness intensifies. Numerous symptoms, including flu-like disease and pain, are caused by signaling proteins that virus-infected macrophages create, including interferons, cytokines, chemokines, TNF, and other mediators [45] [46]. These mediators impact the body's hemostatic system. Vital organs like the brain receive insufficient blood and oxygen when blood pressure drops. Additionally, dengue attacks bone marrow, preventing it from producing enough platelets. Dengue infection leads to blood clotting abnormalities, increasing the risk of bleeding, as platelets are essential for blood clotting. A dengue infection raises the risk of bleeding and results in abnormalities in blood coagulation [47]. Severe clinical symptoms, such as Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS), can result from secondary dengue infection, which occurs when a person contracts a different serotype of the virus after having already contracted another serotype.

6.8. Japanese Encephalitis

The severity of JEV pathogenesis is determined by a number of factors. Higher chances of the illness becoming lethal are associated with the host's inability to generate antibodies against the virus. A neurotropic virus's capacity to penetrate the blood–brain barrier is a key determinant of the infection's severity and clinical result. The virus enters the central nervous system (CNS) through white blood cells, most likely T lymphocytes, after a mosquito bite. The virus subsequently attaches itself to the CNS's endothelial cells and enters the cells through a process known as endocytosis [48]. Anterograde axonal transport is the method by which the West Nile virus enters the central nervous system (CNS) by moving along nerve fibers, or axons [49].

Despite the lack of conclusive evidence, the fact that JEV and WNV are members of the same viral family suggests that macrophages may be important in the pathophysiology of JEV [50]. Japanese encephalitis virus (JEV), a mosquito-borne flavivirus, initiates infection following a bite from an infected *Culex mosquito*. The virus first replicates in skin-resident cells and regional lymph nodes, leading to viremia. Primary target cells include monocytes, macrophages, and dendritic cells (DCs). JEV impairs DC maturation, facilitating immune evasion and systemic dissemination. To enter the central nervous system (CNS), JEV crosses the blood–brain barrier (BBB) via multiple mechanisms: direct infection of endothelial cells, the "Trojan horse" strategy using infected immune cells, and disruption of tight junction proteins [51]. These processes increase blood-brain barrier (BBB) permeability, allowing viral access to the brain. In the central nervous system (CNS), JEV exhibits strong neurotropism, infecting neurons in regions such as the thalamus, hippocampus, and brainstem.

The virus induces neuronal death through endoplasmic reticulum stress and activation of the unfolded protein response. It also impairs the function of neural progenitor cells, potentially leading to long-term neurological deficits. The host immune response further contributes to pathology. Activation of microglia and astrocytes leads to the release of pro-inflammatory cytokines (e.g., IL-1β, TNF-α), resulting in neuroinflammation and bystander neuronal injury. While these responses aim to limit viral spread, excessive inflammation exacerbates CNS damage. Clinically, JEV infection ranges from mild febrile illness to severe encephalitis with high mortality. Survivors often experience permanent neurological sequelae. Understanding these pathogenic mechanisms is crucial for developing effective therapeutics and vaccines [52].

6.9. Chikungunya Virus

It has been demonstrated that CHIKV interacts with Langerhans cells and other dendritic cells (DCs). These DCs then facilitate the virus's transmission to the body's various organs, including the brain, heart, liver, kidneys, and muscles. In both people and animals, these cells represent the predominant cell type that infects the target tissues (skin, muscles, and joints). The Chikungunya virus is also known to infect monocytes and macrophages. Both in CHIKF patients and in animal models, these cells have a role in the pathophysiology of CHIKV infection. One of the most prevalent ocular signs of CHIKV infection is uveitis. It has been demonstrated that CHIKV infects fibroblasts in the cornea, sclera, ciliary body, iris, and ocular motor muscles in both human and mouse models [53]. Patients with CHIKF often have joint pain that is remarkably similar to the symptoms of other alphaviruses that can cause arthritis. It is characterized by excruciating joint pain associated with tissue damage and inflammation, as well as the release of inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Protective adaptive immunity may emerge as a result of Chikungunya fever. This suggests that the body produces immune cells and protective factors that can help ward off infections due to surfaces [54].

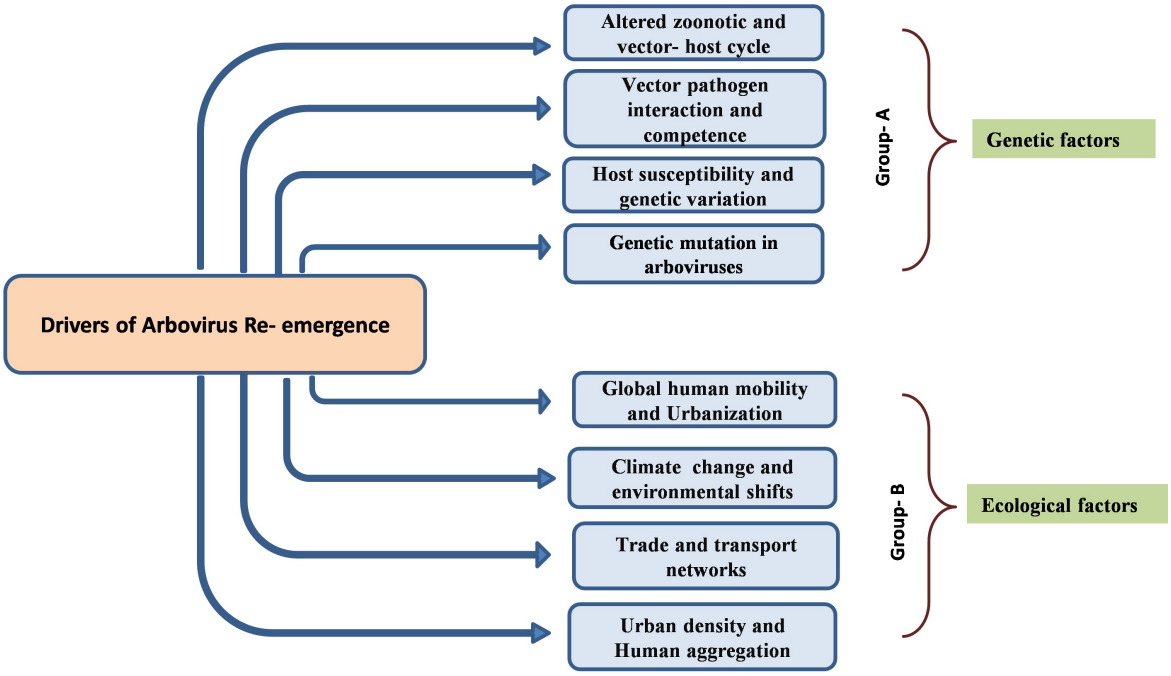

Figure 2. Showing ecological and genetic factors that play a role in the re-emergence of arboviral diseases.

7. Diagnosis

Enzyme-linked immunosorbent assays (ELISA) are used to diagnose arboviruses in biological samples. Both direct and indirect ELISA methods are employed for quick and accurate detection. Field kits based on IgM capture assay detect early antibodies produced during infection [55]. Confirmatory assays, such as PRNT, are used to determine cross-reactivity with closely related viruses. Strain-specific genomic identification is performed using RT-PCR, which offers the advantages of enhanced sensitivity and specificity compared to serological and NGS techniques [56].

8. Vaccines

Vaccines have significantly reduced the burden of infectious and non-infectious diseases, improving public health and extending life expectancy. As emphasized by the World Health Organization (WHO), immunization played a pivotal role in eradicating smallpox, eliminating poliomyelitis from most regions, and reducing measles incidence by 83% in the past two decades [57]. Insect-specific viruses (ISVs) represent a novel and promising platform for advancing recombinant vaccine development against various arboviral pathogens, including dengue, Zika, and chikungunya, due to their distinctive attributes.

Additionally, licensed vaccines are available for animals against WNV, JEV, and Getah virus. The first vaccine that protected from an arbovirus infection was the live-attenuated YFV strain 17D. YFV 17D originates from the Asibi isolate, isolated from an infected individual. Whole virus inactivated vaccines, such as the licensed JEV vaccine IXIARO, are considered safer than LAV approaches [58]. In

collaboration with Moderna, Richner *et al.* characterized a 1-methyl pseudouridine mRNA vaccine coding for prM and ENV proteins with the mRNA encapsulated in a lipid nanoparticle. This vaccine elicited a robust immune response in wild-type and immunocompromised mice using a prime-boost strategy with doses as low as 2 μg [59]. Licensed vaccines against the yellow fever virus (YFV), Japanese encephalitis virus (JEV), dengue virus (DENV), and Venezuelan equine encephalitis virus (VEEV) are available for humans.

Dengue vaccine development is challenging due to the phenomenon of antibody-dependent enhancement. Several vaccine types are in development, but only live-attenuated vaccines have progressed to Phase III trials. DengVaxia, the first dengue vaccine, was licensed in 1998 and has shown higher effectiveness against DENV-3 and DENV-4 than other viral serotypes. It is currently restricted to children aged 9 - 16 who have been previously infected. QDenga, based on a DENV-2 strain, has shown effectiveness against all four DENV serotypes in previously infected patients, but only against DENV-1 and DENV-2 in dengue-naive patients [60]. However, there is no evidence of a higher risk of severe illness in QDenga vaccines compared to DengVaxia vaccines. This could be because QDenga vaccines can induce anti-DENV antibodies against E and prM proteins, which are involved in antibody-dependent enhancement [61].

9. Antiviral Compounds

Table 4. Showing antivirus compounds for the control of arboviruses.

Compound	DENV	JEV	WNV	ZIKV	CHIKV
Baicalein	✓	✓			✓
Curcumin	✓	✓		✓	✓
Delphinidin	✓		✓	✓	
EGCG	✓		✓	✓	✓
Honokiol	✓				
Naringenin	✓				
Quercetin	✓				
Quinine	✓				
ST081006	✓				
Kaempferol		✓			
Isoquercitrin				✓	
Pinocembrin				✓	
Resveratrol				✓	
Fisetin					
Harringtonine					✓
Quercetagetin					✓

Drugs targeting the virus typically provide symptom relief by suppressing and

controlling the infection. However, it is limited by the short window of effectiveness, ineffectiveness against latent viruses, the development of drug-resistant mutants, and toxic side effects [62] (**Table 3**). Specific antiviral medications against arboviral diseases are still in the development phase. Several small molecules, compounds and natural products have shown promising inhibitory effects against replication and transmission. These include dozens of chemical compounds, such as rivabirin, Sofosbuvir, Suramin, and Niclosamide, which are used in drug form to control arboviral infections. A few natural plant products, such as EGCG (epigallocatechin gallate, a flavonoid inhibit replication in arboviruses. Similar effects are shown by Pinocembrin, quinine, polyphenols, curcumin, resveratrol, quercetin, narigenin, and others. Similarly, sirtuin inhibitors like Tenovin-1 have demonstrated broad-spectrum antiviral activity against flaviviruses and alphaviruses—similarly, small molecules like chlorpromazine, monodansylcadaverine and dynesore (**Table 4**). Natural products, such as honey, green tea, wine, apples, onions, tomatoes, grapes, peanuts, fruits, and vegetables, also possess anti-arboviral bioorganic components.

10. Control Measures

In the context of One Health, there is presently an effort to integrate surveillance of human, animal, entomological, and environmental sectors [63]. Surveillance of the incidence and prevalence of infections would enable medical doctors to improve the diagnostic accuracy in patients with typical symptoms. If possible, arboviral diagnostic tests should be incorporated into routine healthcare systems. Healthcare providers should be informed about the prevalent arboviral diseases to identify potential cases [64]. The most effective control method was the integrated approach, which considered the influence of eco-bio-social determinants in the virus-vector-man epidemiological chain, as well as community involvement, starting with community empowerment as an active agent of vector control (**Table 4**).

Suppression strategies include the sterile insect technique, the incompatible insect technique, and transgene-based technologies. In population modification strategies, pathogen-resistant mosquitoes are designed to be released into wild populations, where they can spread their heritable modifications to prevent pathogen transmission. Wolbachia, a heritable insect endosymbiont, when introduced into the mosquito, can crash a mosquito population by cytoplasmic incompatibility or reduce the likelihood of pathogen transmission by infected mosquitoes through competitive interaction with viruses such as dengue, Zika, and other arboviruses [65].

The World Mosquito Program has initiated trials involving the release of Wolbachia-infected mosquitoes in various countries. Remarkably, the city-wide deployment of these modified mosquitoes in Colombia resulted in a substantial reduction in dengue incidence, ranging from 94% to 97% in areas where the insects were well established. Several other countries, including Australia, Malaysia,

Indonesia, Vietnam, and Brazil, have also released Wolbachia-infected mosquitoes to curb the transmission of local mosquito-borne disease [66]. During the early mosquito breeding season, California releases Wolbachia-infected male mosquitoes to suppress the Aedes mosquito population. The UK-based company Oxitec (Oxford, UK) involves the release of antibiotic-dependent OX5034 male mosquitoes in the UK and Florida, USA. These genetically modified mosquitoes have self-limiting genes preventing female mosquito offspring from reaching adulthood. These multifaceted interventions showcase the evolving landscape of vector control methodologies in the pursuit of mitigating arboviral diseases. Despite the success of traditional strategies and the promise of recent developments, the persistence of vector control failures in several countries emphasizes the continued significance of vaccination as the most effective means of preventing arboviral pathogens [67].

A promising strategy to attenuate flavivirus and alphavirus entry is targeted mutations in the envelope (E) proteins that enhance glycosaminoglycan (GAG) affinity. In animal models, multiple flaviviruses and alphaviruses with increased GAG affinity were found to be sequestered in the extracellular matrix and GAG-rich organs. This resulted in reduced neuroinvasiveness and increased the rate of viral clearance from the blood, which subsequently led to improved survival rates. Furthermore, pre-exposure to an attenuated CHIKV GAG-mutant protected mice upon a subsequent challenge with wild-type virus. Moreover, increased GAG affinity is also considered to be the mode of action for one of the mutations associated with the attenuation of the life-attenuated JEV SA14-14-2 vaccine [68].

11. Awareness about Arboviruses

Viruses undergo rapid evolution and develop mutations that enhance their strength, making unsuspecting populations more susceptible. To effectively address emerging arboviral diseases, it is essential to have preparedness and strategic monitoring in place for the early identification of the pathogen and the containment and alleviation of potential outbreaks. Arboviruses, primarily transmitted by arthropod vectors such as mosquitoes, pose a significant public health challenge worldwide. Among these, Zika virus, Japanese encephalitis virus (JEV), dengue virus, West Nile virus (WNV), and chikungunya virus (CHIKV) stand out for their broad impact. Despite their clinical significance, public awareness of these arboviruses varies across different regions and communities. Dengue, being one of the most widespread diseases, often attracts more attention due to its frequent outbreaks and serious complications, such as dengue hemorrhagic fever [69] (**Table 5**).

Public health initiatives in endemic areas have raised awareness, but comprehension of transmission and preventive measures remains variable. The Zika virus gained international attention during the 2015-2016 outbreaks because of its association with congenital defects, particularly in urban Latin America. However, awareness has since diminished. Japanese encephalitis is still vastly unrecognized

outside of Asia, despite its high fatality rate [70]. Public understanding of vaccination and vector control is limited, especially in rural and suburban farming areas where the virus is more common. The West Nile virus, affecting regions of North America and Europe, often goes unnoticed, even in suburban neighborhoods where stagnant water and bird populations facilitate mosquito reproduction [71].

Table 5. Presents various methods used for controlling arboviruses.

Cultural control							
Environmental cleanliness	Adequate drainage	Avoiding contact with vectors	Chemical mixture to kill vectors	Larval breeding control	Community awareness	Covering of water tanks, buckets, and overhead tanks	Routine vaccination
Vectors control							
Genetic control of mosquitoes	Genetic control of paratransgenesis	Biological agents such as larvivorous fish, copepods, *Bacillus thuringiensis*		Sterile insect techniques	*Wolbachia*-based control	Fogging	Use of bio-organic pesticides

Chikungunya, known for inducing severe joint pain, has received moderate attention following outbreaks, particularly in urban and peri-urban locales. Urban and suburban areas, characterised by dense populations and inadequate water management, create ideal conditions for mosquito breeding. Unfortunately, these regions frequently lack sufficient vector control and community involvement. There is an urgent need for ongoing, localised public health education and infrastructure enhancements to reduce arbovirus transmission and increase awareness in both urban and suburban environments [72].

In rural areas, the incidence of arbovirus infection is higher compared to urban areas. This is due to waterlogging caused by heavy rains and the breeding of mosquitoes in rice paddies. In eastern UP, climatic factors, mainly temperature, rain, and humidity, largely support the vectors as well as the pathogen. During the rainy season, agricultural fields, wetlands, rivers, canals, and ponds become ideal breeding habitats for *Culex tritaeniorhynchus*, which causes Japanese Encephalitis, as well as dengue and Chikungunya, in rural children. Zika and West Nile virus have no documented cases, so no targeted rural interventions in Eastern UP.

Urban residence shows significantly higher odds of dengue and chikungunya. Urban areas benefit from vaccination drives for JE targeting children under the age of 15. Urban strategies including repellent distribution, LLIN bed nets, source elimination, and sentinel surveillance, all supported by integrated vector management (IVM) and community education campaigns. Significantly less infectivity of arboviruses is noted in urban areas than in rural areas.

12. Conclusions

The increasing incidence of arboviral infections, particularly those caused by Japanese encephalitis virus, dengue virus, Zika virus (ZIKV), chikungunya virus (CHIKV), and West Nile virus, poses a significant public health concern in the

urban and suburban regions of Eastern Uttar Pradesh. These arboviruses exhibit overlapping clinical manifestations but differ in their vectors, host reservoirs, transmission dynamics, and pathological outcomes. The incidence of diseases is increasing due to the convergence of multiple risk factors, including rapid urbanisation, inadequate vector control, climate variability, and increased human mobility, which have contributed to the sustained transmission and occasional outbreaks in this region.

Therefore, for the control of arbovirus diseases, earlier and appropriate diagnosis is highly essential. Because the window period and incubation period of these viruses are very short, patients must protect themselves during this brief period; hence, the antibody and vaccine therapy seem to be the best options. As the virus invades the host body, it initiates the establishment of an association with the genome of host body cells. It attempts to hijack normal cells, thereby evading the immune system's surveillance. Understanding the pathogenesis of these viruses in both human and vector populations is critical for designing effective surveillance, prevention, and control strategies. Current data indicate a need for integrated vector management, enhanced diagnostic capabilities, public health education, and robust vaccination campaigns where applicable. Additionally, interdisciplinary research combining epidemiology, virology, entomology, and environmental science is crucial to unravel the complex interactions that influence arboviral disease ecology. The ultimate answer to arboviral disease control is the control of the vector population, which will significantly reduce the disease spectrum. A vaccination drive before the rainy season will provide a protective shield for both rural and urban populations.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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