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Review Article

# Comparative Genomics, Immunopathogenesis, and Evolutionary Dynamics of Dengue, Zika, Yellow Fever, and Mayaro Viruses

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## Abstract

Arboviral infections remain a major global public health concern, particularly in tropical and subtropical regions. Dengue Virus (DENV), Zika Virus (ZIKV), Yellow Fever Virus (YFV), and Mayaro Virus (MAYV) share similar mosquito-borne transmission cycles but differ significantly in their clinical manifestations and evolutionary patterns. This review provides a comparative analysis of their genomic organization, immune-mediated pathogenesis, mutation dynamics, epidemiology, and clinical outcomes.

All four viruses possess positive-sense single-stranded RNA genomes; however, they differ in replication strategies and protein organization. Immune responses play a critical role in disease progression, particularly in dengue, where antibody-dependent enhancement contributes to severe disease. Mutation analyses highlight substantial genetic diversity in DENV associated with disease severity, while ZIKV evolution is linked to neurovirulence. In contrast, YFV shows relative genetic stability, whereas MAYV demonstrates increasing genetic adaptability with potential for urban emergence.

Recent epidemiological data, including findings from Bangladesh, indicate rising dengue burden and shifting serotype distribution. Clinically, these infections range from mild febrile illness to severe complications such as hemorrhagic fever, neurological disorders, and chronic arthritis. Despite their impact, treatment remains largely supportive, with effective vaccination available only for yellow fever.

This review underscores the need for enhanced genomic surveillance, improved diagnostics, and the development of effective antivirals and vaccines.

## Introduction

Rapid urbanization, climate change, and the spread of mosquito vectors have all contributed to the rise of arboviral infections as a significant global public health concern. Among these, especially in tropical and subtropical areas, the Dengue Virus (DENV), Zika Virus (ZIKV), Yellow Fever Virus (YFV), and Mayaro Virus (MAYV) pose serious and constantly changing risks. These viruses cause a wide range of clinical symptoms, from moderate fever to serious, potentially fatal consequences, and are mostly spread by Aedes and other mosquito species.

The dengue virus, which belongs to the Flaviviridae family, is the most common arboviral illness in the world. An estimated 390 million cases are reported each year, with around 75% of those cases occurring in tropical areas. Dengue's rapid geographic growth and epidemiological relevance are demonstrated by the almost 30-fold increase in its frequency over the past 50 years [1,2]. Clinically, dengue can range from asymptomatic infection to severe forms like Dengue Shock Syndrome (DSS) and Dengue Hemorrhagic Fever (DHF), which are frequently linked to immune-mediated mechanisms such as antibody-dependent enhancement.



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The Zika virus, also a member of the Flaviviridae family, became well-known worldwide during the 2015-2016 outbreak in the Americas. It was connected to neurological issues, including Guillain–Barré syndrome and developmental defects like microcephaly. Since its discovery in Uganda in 1947, ZIKV has expanded throughout Africa, Asia, and the Americas, exhibiting both vector-borne and non-vector transmission pathways, including sexual and vertical transmission [3,4]. The Zika virus, in contrast to dengue, is highly neurotropic and can pass through the placenta, which has detrimental effects on development.

The Yellow fever virus, another flavivirus, is still prevalent in some regions of South America and Africa, where it occasionally causes high-mortality epidemics. Aedes and Haemagogus mosquitoes are involved in both urban and sylvatic cycles that spread the virus. Hepatic tropism, a hallmark of yellow fever, can cause jaundice, bleeding, and in extreme situations, multi-organ failure. Due to vaccination gaps and reemergence in endemic areas, yellow fever remains a hazard even with the availability of an effective live-attenuated vaccine (17D strain) [5].

The Mayaro virus, in contrast to these flaviviruses, is a member of the genus Alphavirus within the Togaviridae family. MAYV, first discovered in Trinidad in 1954, is mainly maintained by a sylvatic transmission cycle involving non-human primates and Haemagogus mosquitoes. Recent data, however, indicates the possibility of urbanization due to adaptation to Aedes vectors. Clinically, Mayaro fever is similar to chikungunya since it causes significant arthritis that can last for a long time. Concerns regarding the virus's potential for future outbreaks are raised by its significant genomic adaptability [6].

Although possessing distinct evolutionary histories and genomic structures, these viruses share many similarities in host immunological interactions, mutation-driven adaptability, and transmission dynamics. To comprehend these arboviruses' pathogenic mechanisms, evolutionary paths, and potential for co-circulation in endemic areas, a comparative study is important. To present a thorough understanding of their rising global threat, this review incorporates current knowledge of their molecular biology, immune-mediated pathophysiology, mutation dynamics, and epidemiological trends.

## Literature review methodology

A structured literature search technique was used for this review to guarantee thorough coverage of relevant studies. Combinations of terms including "Dengue virus," "Zika virus," "Yellow fever virus," "Mayaro virus," "immune pathogenesis," "mutation," and "epidemiology" were used to search databases like PubMed, Scopus, Web of Science, and Google Scholar.

Peer-reviewed English-language publications with an emphasis on the molecular biology, immunopathogenesis, evolution, and epidemiology of the chosen arboviruses meet the inclusion requirements. Priority was given to high-impact evaluations and recent studies, mostly from 2000 to 2025.

Articles not directly related to the comparative scope of this review, research without primary or review data, and non-peer-reviewed sources were among the exclusion criteria. The process of evaluating books is made more transparent and repeatable by this methodical approach.

## Genome organization and molecular biology

Arboviruses such as Dengue Virus (DENV), Zika Virus (ZIKV), Yellow Fever Virus (YFV), and Mayaro Virus (MAYV) share several fundamental structural characteristics despite belonging to distinct viral families. Although all four viruses are enveloped, positive-sense RNA viruses with icosahedral symmetry, their evolutionary diversity is reflected in the differences in virion size, surface structure, and glycoprotein arrangement. Table 1 [1,3,5,6], provides a comparative summary of these physical similarities and differences.

### Comparative genome organization

The family Flaviviridae includes the Dengue Virus (DENV), the Zika Virus (ZIKV), and the Yellow Fever Virus (YFV). These viruses have a single-stranded, positive-sense RNA genome that is roughly 10.8–11 kb in size. These viruses have a single Open Reading Frame (ORF) surrounded by 5′ and 3′ Untranslated Regions (UTRs), which are necessary for translation, genome cyclization, and viral replication [1,3]. While the 3′ UTR lacks a poly(A) tail, which contains conserved secondary structures essential for replication, the 5′ end has a type I cap structure that facilitates host ribosome recognition.

On the other hand, the Mayaro Virus (MAYV), which belongs to the genus *Alphavirus* and the *Togaviridae* family, has a distinct genomic structure. There are two distinct ORFs in its around 11.7 kb positive-sense RNA genome. The second ORF translates structural proteins from a sub-genomic RNA, whereas the first ORF encodes non-structural proteins (nsP1–nsP4) important in viral replication. In contrast to flaviviruses, MAYV has a poly(A) tail at the 3′ end, which reflects variations in evolutionary ancestry and replication strategy [6].

MAYV displays a dual-ORF strategy with sub-genomic RNA synthesis [1,6], revealing basic differences in replication mechanisms, whereas flaviviruses produce a single polyprotein from a single open reading frame (Table 2).

### Comparison of structural proteins

These arboviruses' structural proteins are essential for immune detection, host interaction, and viral entry. Capsid (C), precursor Membrane (prM), and Envelope (E) proteins make up the structural proteins of flaviviruses (DENV, ZIKV, and YFV). Among these, the Envelope (E) glycoprotein is a prominent target for neutralizing antibodies and the main factor that determines viral attachment, membrane fusion, and antigenicity [1,3]. By preventing premature fusion during viral assembly, the prM protein contributes to virion maturation.

The Mayaro virus, on the contrary, has a unique structural protein composition characteristic of alphaviruses, which includes the trans-frame 6K protein and the capsid and



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**Table 1:** Morphological and structural comparison of viruses. The key morphological and structural characteristics of DENV, ZIKV, YFV, and MAYV are presented in this table, which emphasizes the differences in surface features and vector connections as well as the similarities in virion structure.

| Feature | DENV | ZIKV | YFV | MAYV |
|---|---|---|---|---|
| Family | *Flaviviridae* | *Flaviviridae* | *Flaviviridae* | *Togaviridae* |
| Shape | Spherical | Spherical | Spherical | Spherical |
| Envelope | Present | Present | Present | Present |
| Capsid symmetry | Icosahedral | Icosahedral | Icosahedral | Icosahedral |
| Diameter | ~50 nm | ~50 nm | ~50 nm | ~70 nm |
| Surface structure | Smooth (mature virion) | Smooth | Smooth | Spiky (E1–E2 glycoprotein spikes) |
| Genome polarity | Positive-sense RNA | Positive-sense RNA | Positive-sense RNA | Positive-sense RNA |
| Vector | Aedes spp. | Aedes spp. | Aedes/Haemagogus | Haemagogus/Aedes |

**Table 2:** Comparative genome organization and polypeptide processing strategies. This table highlights the essential morphological and structural features of DENV, ZIKV, YFV, and MAYV. It highlights the similarities in virion structure as well as the variations in surface features and vector interactions.

| Virus | Genome Type | Genome Length | ORF Organization | Polypeptide Strategy |
|---|---|---|---|---|
| Dengue virus (DENV) | +ssRNA | ~11 kb | Single ORF | Translated as one polyprotein, cleaved into structural and non-structural proteins |
| Zika virus (ZIKV) | +ssRNA | ~10.8 kb | Single ORF | Single polyprotein processed by viral and host proteases |
| Yellow fever virus (YFV) | +ssRNA | ~11 kb | Single ORF | Single polyprotein, co- and post-translational cleavage |
| Mayaro virus (MAYV) | +ssRNA | ~11.7 kb | Two ORFs | Non-structural proteins are translated first; structural proteins from sub genomic RNA |

envelope glycoproteins E1, E2, and E3. Membrane fusion is mediated by the E1 protein, while receptor binding is managed by the E2 protein. In contrast to the comparatively smooth surface of flaviviruses, MAYV has a distinctive spiky shape due to these glycoproteins forming heterodimers that combine as trimeric spikes on the viral surface [6].

Viral infectivity, host tropism, and immune evasion are all further impacted by variations in glycosylation patterns. Differences in these viruses' pathogenicity have been linked to variations in envelope glycoproteins that impact receptor binding effectiveness and antibody recognition [3,5].

## Immune-mediated pathogenesis

### Host immune response to arboviral infection

Innate and adaptive immune systems interact effectively in the host immunological response to arboviral infections. When a virus enters the body, pattern-recognizing receptors such Toll-Like Receptors (TLRs) identify viral RNA. This triggers antiviral pathways and produces pro-inflammatory cytokines and type I interferons. Although these reactions are necessary for the removal of viruses, dysregulation can increase the severity of the condition by causing excessive inflammation and immune-mediated tissue damage [1, 3].

### Dengue virus: Immune enhancement and cytokine activity

The pathogenesis of the dengue virus is closely linked to immune-mediated mechanisms, especially during secondary infections with a heterologous serotype. Antiviral cytokines, including Interferon-γ (IFN-γ) and Tumor Necrosis Factor-α (TNF-α) are produced by activated naïve T cells during initial infection. However, in secondary infection, cross-reactive memory T cells attach to the new serotype less effectively, which results in increased cytokine production without effective viral clearance.

Antibody-Dependent Enhancement (ADE) is a major mechanism behind severe dengue. Pre-existing non-neutralizing antibodies attach to the virus during this phase, allowing it to enter immune cells like macrophages and monocytes that have Fc receptors. This promotes viral multiplication and sets off a hyperinflammatory reaction indicated by increased levels of chemokines and cytokines. Increased vascular permeability, plasma leakage, and serious clinical symptoms like Dengue Hemorrhagic Fever (DHF) and dengue shock syndrome (DSS) are caused by the ensuing endothelial dysfunction [1].

### Zika virus: Immune adaptation and neurotropism

The Zika virus has unique pathogenic characteristics, namely its capacity to penetrate the placental barrier and infect brain embryonic cells. Microcephaly is one of the severe congenital defects linked to this neurotropism. By altering interferon signaling pathways, especially through non-structural proteins such as NS1 and NS5, ZIKV might evade host immune responses.

Apoptosis and poor neurodevelopment result from the virus's immune-mediated harm to brain tissues. Furthermore, autoimmune disorders, including Guillain-Barré syndrome, have been connected to ZIKV infection, indicating immunological dysregulation that goes beyond direct viral cytotoxicity [3,4].

### Yellow fever virus: Hemorrhagic disease and hepatic tropism

Hepatocytes are the main target of the yellow fever virus, which causes serious liver damage and systemic disease. Hepatocellular apoptosis and necrosis, together with dysregulated cytokine responses, are the outcomes of viral replication in the liver. In extreme cases, jaundice, coagulopathy, and hemorrhagic symptoms are caused by the ensuing hepatic dysfunction.



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Both pathogenic inflammation and defensive antiviral systems are involved in the immune response to YFV infection. The development of the disease is largely influenced by immune-mediated tissue damage and excessive cytokine production, especially in severe and lethal cases [5].

### Mayaro virus: Inflammation causing arthritis

Strong inflammatory reactions, especially in musculoskeletal tissues, are a hallmark of Mayaro virus infection. Like other arthritogenic alpha viruses, MAYV causes pro-inflammatory cytokines to be produced, which aggravate joint pain and inflammation. In certain instances, persistent symptoms could result in chronic arthritis.

Viral entrance into target cells is facilitated, and tissue tropism may be influenced by the interaction between viral glycoproteins and host receptors like Mxra8. It is thought that immune-mediated processes have a major role in the pathophysiology of disease, especially in persistent inflammatory reactions. [6].

### Comparative immunopathogenesis

Although these arboviruses share common features such as induction of innate immune responses and cytokine production, their pathogenic mechanisms differ significantly. The Zika virus exhibits strong neurotropism, whereas the Dengue virus is different in its antibody-dependent enhancing mechanism. While the Mayaro virus is linked to chronic inflammatory reactions in joints, the yellow fever virus mainly targets the liver and causes hemorrhagic illness. Table 3 provides a comparative overview of various immune-mediated pathways.

The existence of cross-reactive immune responses between flaviviruses, especially between DENV and ZIKV, is a significant feature of arboviral immunology. Antibodies produced against one virus may partially recognize another due to structural similarities in the Envelope (E) protein.

Although this kind of cross-reactivity can provide some protection, it can also result in Antibody-Dependent Enhancement (ADE), in which non-neutralizing antibodies make it easier for viruses to enter cells that have Fc receptors. This tendency is well known in dengue and has been suggested as a possible concern in ZIKV and probably YFV consecutive infections.

Cross-reactive immunity's implications underscore difficulties in developing vaccines and give rise to worries about the co-circulation of several flaviviruses in endemic areas.

## Arbovirus evolutionary patterns and mutation dynamics

### Overview of the evolution of arboviruses

The absence of proofreading activity in RNA-dependent RNA polymerases allows RNA viruses to quickly adapt to shifting host and environmental conditions, which is why they have high mutation rates. Dengue Virus (DENV), Zika Virus (ZIKV), Yellow Fever Virus (YFV), and Mayaro Virus (MAYV) are examples of arboviruses that have unique evolutionary paths influenced by vector-host interactions, immunological pressure, and geographic distribution [7,8]. The physical activity, transmissibility, and pathogenicity of viruses are influenced by these evolutionary dynamics.

### Dengue virus: Mutation, fitness, and disease severity

The dengue virus exhibits significant genetic variation among serotypes and genotypes, which influences variations in virulence and tendencies for epidemics [7,8]. A total of 2,667 changes, including 2,040 synonymous and 627 non-synonymous substitutions, were found in DENV-2 isolates from Bangladesh, suggesting active viral evolution under selection pressure [9].

Significantly, compared to moderate infections, severe dengue cases were associated to a higher incidence of mutations, indicating a connection between genetic variation and disease prognosis [9,10]. Several mutations in important viral proteins were shown to be possible virulence factors. For example, mutations in the Envelope (E) protein, such as I322V, were linked to more serious medical conditions, perhaps as a result of changed immune detection and viral entry effectiveness

**Table 3:** Comparative immune pathogenesis of DENV, ZIKV, YFV, and MAYV. This table shows how immune modulation affects the severity of each virus's disease by comparing host immune responses and important pathogenic processes.

| Feature | Dengue Virus (DENV) | Zika Virus (ZIKV) | Yellow Fever Virus (YFV) | Mayaro Virus (MAYV) |
|---|---|---|---|---|
| Primary target cells | Monocytes, macrophages, dendritic cells | Neural progenitor cells, placental cells | Hepatocytes | Fibroblasts, joint-associated cells |
| Important pathogenic mechanism | Antibody-Dependent Enhancement (ADE) | Neurotropism and placental invasion | Hepatic injury and systemic inflammation | Arthritogenic inflammation |
| Innate immune response | Strong IFN response, often dysregulated | IFN evasion via NS proteins | Activation of cytokines and inflammatory pathways | Pro-inflammatory cytokine induction |
| Adaptive immune response | Cross-reactive T cells, suboptimal response in secondary infection | Antibody and T-cell response with immune evasion | Protective immunity but also immunopathology | Sustained immune activation |
| Cytokine involvement | Cytokine storm (TNF-α, IFN-γ, IL-6) | Inflammatory mediators affecting neural tissues | Cytokine dysregulation contributes to liver damage | Persistent inflammatory cytokines (IL-6, TNF-α) |
| Immune evasion | Fc receptor-mediated viral entry | NS1/NS5 inhibit interferon signaling | Limited evasion, more immune-mediated damage | Receptor adaptation (Mxra8-mediated entry) |
| Major clinical outcome | DHF/DSS (vascular leakage, shock) | Microcephaly, Guillain–Barré syndrome | Hemorrhage, jaundice, organ failure | Chronic arthralgia, joint inflammation |
| Severity driver | Secondary infection (heterologous serotype) | Infection during pregnancy | Viral load and liver damage | Persistent inflammation |
| Unique feature | ADE phenomenon | Congenital infection | Effective vaccine available | Potential for chronic disease |



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[9,11]. Similarly, substitutions in the NS5 protein (e.g., G60V) were linked to enhanced viral replication and virulence [12].

Viral variations in severe ($\Delta G$ = -11.5 kcal/mol) and mild ($\Delta G$ = -13.5 kcal/mol) cases have different binding energies, which further implies that mutations may affect viral-host interactions by changing immune evasion mechanisms or receptor binding [9]. Furthermore, the relevance of conserved genomic areas in preserving replication efficiency while permitting evolutionary flexibility is illustrated by silent mutations in NS5 (e.g., G81G, A167A) [7].

## Zika virus: Development and neurovirulence

Although the Zika virus has relatively lower mutation rates than the dengue virus, several changes have had significant effects on the virulence and propagation of the epidemic [3,8]. A major evolutionary change linked to greater human transmission and serious clinical effects was the shift from African to Asian origins.

The development of microcephaly and increased neurovirulence have been closely linked to one of the most prominent mutations in the prM protein, S139N. This mutation contributes to congenital Zika syndrome by making the virus more contagious in neural progenitor cells [13]. A188V in NS1 is another important mutation that has been connected to enhanced immune evasion and higher transmission efficiency [14].

Combined mutations showed synergistic effects that increased viral transmission and toxicity, especially during the 2015 outbreak in Brazil. The relevance of structural changes in viral fitness is highlighted by evolutionary adaptations in the glycosylation patterns of the envelope protein, which further affect host cell entrance and immunological detection [15].

It has been demonstrated that the S139N mutation in the prM protein greatly increases ZIKV infectivity in human neural progenitor cells by stimulating apoptosis and viral multiplication. Mechanistically, this mutation improves neurotropism by promoting more effective viral maturation and release, which raises viral fitness.

Furthermore, ZIKV proteins, including NS4A and NS4B, have been linked to host Akt-mTOR signaling pathway disruption, which results in decreased neurogenesis and elevated autophagy [16]. . Together, these molecular changes lead to developmental problems like as microcephaly and neuronal cell death.

Additionally, by opposing type I interferon signaling and enabling prolonged viral replication within host cells, alterations in the NS1 and NS5 proteins improve immune evasion.

## Yellow fever virus: Episodic evolution and genetic stability

The yellow fever virus has comparatively less genetic variation than the dengue and Zika viruses, which is indicative of long-term adaptability to both urban and sylvatic transmission cycles as well as evolutionary restrictions [5,16]. Periodic outbreaks, however, are linked to the appearance of novel variations with particular amino acid changes, especially in non-structural proteins like NS3, NS4B, and NS5 [5].

Recent outbreak strains show close genetic ties to historical lineages, according to phylogenetic analysis, indicating episodic evolution rather than ongoing diversification [17]. It has been demonstrated that intra-host Single-Nucleotide Variations (iSNVs) occur more frequently than mutations at the population level, suggesting continuous microevolution within infected hosts [17].

It has been demonstrated that mutations in the 3′ Untranslated Region (UTR) change RNA secondary structure, which may have an impact on host adaptability and viral replication efficiency [18]. Furthermore, synonymous and non-synonymous substitutions have been found throughout the genome in comparative analysis of epidemic strains, with a greater intrahost mutation rate than consensus-level evolutionary rates, indicating dynamic viral adaptability during infection [17].

The continued efficacy of immunization programs is explained by the substantial sequence conservation between circulating YFV strains and the attenuated 17D vaccine strain, despite these genetic alterations, as antigenic sites are still mostly intact [5]. YFV's distinct evolutionary strategy, in contrast to other arboviruses, is highlighted by its relative genetic stability and sporadic spurts of diversification.

## Mayaro virus: Genetic adaptability and emerging concern

The Mayaro Virus (MAYV) is able to adapt to a variety of ecological niches because of its remarkable genetic flexibility, which is fueled by mutation and recombination [6,8]. Three main genotypes (D,L, and N) have been found by phylogenetic analysis; genotype D has the largest geographic spread in South America [19]. Circulating strains frequently exhibit strong genetic ties to previously identified regional isolates, suggesting periodic diversification and limited evolution. The ability of the virus to produce new variations and adapt to shifting settings is further demonstrated by recombination events, such as insertions inside the nsP3 protein [6,19].

The E1–E2 glycoprotein complex is essential for both host specificity and viral entry at the molecular level. While E1 promotes membrane fusion, E2 mediates receptor binding. These glycoproteins can have mutations that change their affinity for binding to host receptors like Mxra8, which is a crucial entrance receptor for arthritogenic alpha viruses. These structural modifications may affect tissue tropism, increase viral infectivity, and broaden the host range [20].

Furthermore, higher virulence and tissue targeting in related alphaviruses have been linked to particular N-glycosylation sites, such as N262 in the E2 protein. These changes could lead to increased immunological modulation and toxicity.



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Additionally, these molecular modifications highlight questions regarding the possible transition of MAYV from a sylvatic to an urban transmission cycle, especially in light of growing evidence of vector competence in *Aedes* species. This evolutionary history emphasizes the necessity of ongoing genetic surveillance and the possibility of future outbreaks [6, 21].

### Comparative evolutionary perspectives

Although being RNA-based arboviruses, these four viruses have very different evolutionary histories. Due to immunological pressure and serotype interactions, the dengue virus has a high degree of genetic diversity and has evolved significantly. Key mutations that have important phenotypic effects, especially in neurovirulence, are indicative of the evolution of the Zika virus. While the Mayaro virus exhibits growing genetic flexibility and emerging potential, the yellow fever virus is still comparatively stable, with sporadic evolutionary outbursts associated with outbreaks.

These variations emphasize how important it is to conduct ongoing genomic surveillance in order to identify newly emerging variants that have increased pathogenicity or transmissibility. Table 4 provides a comparative overview of evolutionary traits and mutation processes.

## Regional disease dynamics and epidemiology

### Overview of global epidemiology

The majority of arboviral diseases, including dengue, Zika, yellow fever, and Mayaro virus infections, are found in tropical and subtropical areas where the climate encourages the spread of mosquito vectors. According to Bhatt, et al. [2] and Guzman & Harris [1], the dengue virus continues to be the most common, with an estimated 390 million infections per year and a rapid global growth in recent years. While yellow fever continues to occasionally generate outbreaks in Africa and South America despite the availability of an effective vaccine, the Zika virus has shown epidemic potential with explosive outbreaks, particularly in the Americas [3,5]. Due to its ability to adapt to urban environments, the Mayaro virus—which was previously found only in South American sylvatic regions—is increasingly recognized as a potential new threat [6].

### Dengue epidemiology in Bangladesh (2018–2022)

Dengue incidence has significantly increased in Bangladesh in recent years, with considerable variations in genetic diversity, disease severity, and serotype distribution. 3,759 suspected cases were examined in a hospital-based study at Evercare Hospital Dhaka, between 2018 and 2022; 834 of these cases were found to be dengue-positive based on NS1 antigen examination. A total of 495 samples were successfully serotyped. [1, 9].

Demographic distribution: Males had a higher prevalence (60%) than females (40%), consistent with previous regional observations of dengue epidemiology [2,9]. The age distribution showed that, although it varied by year, both adults and children/adolescents were considerably impacted. In 2018, 2019, and 2022, the age group of 1–10 years old had the highest incidence; however, in 2021, there was a movement toward the 11–20 year age group [9].

Distribution of serotypes and temporal patterns: Throughout the period of the study, a dynamic shift in circulating serotypes was noted. In 2018, DENV-2 was more common, especially among adults, but DENV-3 became more common in later years, especially among children and adolescents. It's interesting to note that there was only one DENV-3 case recorded in 2020; this is probably because there was less transmission during the COVID-19 lockdown [1,9].

Association between serotype and clinical severity: According to Guzman and Harris [1], there was a high association between DENV-3 infection and severe dengue cases, which is in line with earlier findings that linked particular serotypes to more severe disease. Compared to 20.3% in 2018, the percentage of severe cases among hospitalized patients increased in 2019 (50.7%), followed by 2021 (35.3%) and 2022 (33.3%) (9). Fever, nausea, vomiting, abdominal pain, and thrombocytopenia were among the physical symptoms of severe dengue. With a case fatality rate of roughly 3%, complications like hemorrhage, respiratory distress, and pleural effusion were also noted [2,9].

Laboratory findings: Severe cases showed significant biochemical and hematological abnormalities, such as hypoalbuminemia, increased liver enzymes (ALT/AST), and severe thrombocytopenia (<50,000/µl), which indicated systemic involvement and illness severity [1,9].

Genetic diversity and phylogenetic distribution: The circulating dengue serotypes in Bangladesh have different genotype distributions, according to a phylogenetic study. DENV-1 strains were closely related to strains from Southeast Asia and belonged to genotype V. While DENV-3 isolates formed a monophyletic clade under genotype I, DENV-2 strains were categorized under the cosmopolitan genotype, indicating lineage replacement [8,9].

Genetic diversity developed dramatically before 2019, decreased during the COVID-19 pandemic, and then increased once more in 2022, indicating dynamic viral evolution impacted by the amount of transmission [9] (Table 5).

**Table 4:** Comparative mutation and evolutionary features. This table highlights each virus's unique evolutionary dynamics and adaption techniques by outlining mutation rates, evolutionary patterns, and important genomic characteristics.

| Feature | DENV | ZIKV | YFV | MAYV |
|---|---|---|---|---|
| Mutation rate | High | Moderate | Low | Moderate–High |
| Key mutations | E, NS5 | prM (S139N), NS1 | NS3, NS5 | E1–E2 complex |
| Genetic diversity | High | Moderate | Low | Moderate |
| Evolution pattern | Continuous | Adaptive | Episodic | Emerging |
| Unique feature | ADE-linked evolution | Neurovirulence mutation | Vaccine stability | Recombination |



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Disease severity and mutation: According to mutation studies, severe dengue cases had more mutations than mild illnesses. DENV-2 isolates were found to have 2,667 mutations, including both synonymous and non-synonymous changes. Certain structural and non-structural protein mutations have been linked to altered viral fitness and more severe illness [7,9]. Variations in binding energy between moderate and severe cases also point to differences in viral-host interactions that could affect the course of the disease [9].

## Clinical manifestations and therapeutic strategies of arboviruses

### Clinical spectrum overview

Arboviral infections caused through the Dengue Virus (DENV), Zika Virus (ZIKV), Yellow Fever Virus (YFV), and Mayaro Virus (MAYV) can induce a wide range of clinical symptoms, from mild fever or no symptoms to serious and sometimes fatal outcomes. These viruses differ greatly in their pathogenic processes, target organs, and clinical results, even though they have common transmission pathways. [1,3].

### Dengue virus: Clinical severity and management

Dengue infections can range in severity from simple dengue fever to Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). High fever, headache, retro-orbital pain, myalgia, arthralgia, and rash are typical symptoms. Abdominal pain, recurrent vomiting, mucosal bleeding, and fluid accumulation are warning symptoms that may signal the development of a serious condition [1].

Plasma leakage, severe thrombocytopenia, bleeding, and organ damage are the hallmarks of severe dengue. The main focus of medical support is electrolyte balance, careful fluid replacement, and monitoring of hematological parameters. There is currently no antiviral medication that is universally effective. Although the Dengvaxia vaccine has been authorized, its effectiveness varies depending on the serostatus and previous exposure [1,2].

### Zika virus: Mild disease and neurological complications

Low-grade fever, rash, conjunctivitis, and pain in the joints are frequent signs of a Zika virus infection, which is usually mild or asymptomatic. However, serious side effects are becoming more widely acknowledged, especially neurological conditions such as neonatal Zika disease and Guillain-Barré syndrome, which include microcephaly and other developmental abnormalities [3].

Currently, ZIKV has neither a licensed vaccination nor a specific antiviral medication. Rest, hydration, and symptomatic treatment are all part of supportive management. Because of the potential of vertical transmission and fetal problems, prevention is especially important for pregnant women [8].

### Yellow fever virus: Hemorrhagic disease and vaccination

The symptoms of yellow fever are biphasic, with a fever phase at first and, in more severe instances, a toxic phase. Fever, chills, headaches, jaundice, and bleeding are some of the symptoms. Severe instances have a high case fatality rate and can develop into shock, hepatic failure, and renal dysfunction [5].

In contrast to other arboviruses addressed, there is a live-attenuated vaccine (17D strain) that is efficacious and offers durable immunity. According to Monath and Vasconcelos [5], there is no specific antiviral medication; instead, treatment is supportive and involves managing liver impairment and hemorrhagic consequences.

### Mayaro virus: Emerging arthritogenic disease

A Mayaro virus infection usually manifests as a chikungunya-like acute febrile illness with fever, rash, headache, and severe arthritis. Pain in the joints can have a major negative influence on quality of life and last for weeks to months [6].

Currently, no specific antiviral treatment or vaccine is available for MAYV. Pain management and anti-inflammatory medication are the main goals of medical support. MAYV is still underdiagnosed and a growing public health issue because of its potential for urban transmission and clinical resemblance to other arboviruses [6].

### Comparative therapeutic and clinical approaches

Despite the fact that these arboviruses have similar

**Table 5:** Epidemiological characteristics of dengue virus infection in Bangladesh (2018–2022). Using current data, this table highlights the clinical features, demographic distribution, and epidemiological trends of dengue infections in Bangladesh.

| Parameter | Findings |
|---|---|
| Study period | 2018–2022 |
| Total suspected cases | 3,759 |
| Confirmed dengue cases | 834 |
| Serotyped samples | 495 |
| Gender distribution | Male 60%, Female 40% |
| Predominant serotype | DENV-2 (2018), DENV-3 (later years) |
| Most affected age group | 1–10 years (multiple years) |
| Severe dengue prevalence | Highest in 2019 (50.7%) |
| Mortality rate | ~3% |
| Key complications | Pleural effusion, bleeding, thrombocytopenia |
| Key lab findings | Elevated ALT/AST, hypoalbuminemia |



Citation: Antu AD, Bhattacharjee A, Chowdhury A, Dey A, Fiza SA, Akbar GW. Comparative Genomics, Immunopathogenesis, and Evolutionary Dynamics of Dengue, Zika, Yellow Fever, and Mayaro Viruses. Arch Community Med Public Health. 2026;12(2):040-048. Available from: https://dx.doi.org/10.17352/2455-5479.000234

clinical characteristics, there are significant variations in the severity and course of the infection. Yellow fever is linked to hemorrhagic and hepatic involvement, Mayaro is linked to chronic arthritis, Zika is linked to neurological problems and birth abnormalities, and Dengue is linked to immune-mediated severe disease and vascular leakage.

The primary therapeutic approach for all four viruses is medical support, underscoring a crucial need in the development of antiviral medications. The best preventive measure is still vaccination, which is now only accessible for yellow fever and partially for dengue. Table 6 & Table 7 provide a comparative summary of key diagnostic approaches and distinguishing clinical features of these arboviruses.

## Conclusion and future perspectives

Dengue, Zika, yellow fever, and Mayaro viruses are examples of arboviral diseases that pose a complicated and dynamic threat to world health. These viruses differ significantly in terms of genetic evolution, immunological interactions, and clinical outcomes, even though they share ecological habitats and transmission pathways. Due to its enormous genetic diversity and immune-mediated severity, the dengue virus continues to be the most clinically and epidemiologically significant. While the yellow fever virus has a distinct pattern of genetic stability along with substantial mortality in severe cases, the Zika virus reveals how even small genetic changes can have significant neurological effects. Due to its genetic flexibility and growing vector range, the Mayaro virus has rising potential for breakout despite its current restricted distribution.

This review's comparative study highlights how important viral evolution and host immune responses are in determining the dynamics of illness. It also focuses upon important knowledge gaps, especially with regard to arboviruses' cross-reactive immune mechanisms and mutation-driven pathogenicity.

From the perspective of public health, the growing geographic dispersal of vectors triggered by urbanization and climate change is probably going to make it easier for several arboviruses to circulate simultaneously, making diagnosis, surveillance, and control measures more difficult. The critical need for centered medication development is highlighted by the lack of specialized antiviral treatments for the majority of these diseases. Furthermore, safety, cross-protection, and long-term immunity should be given top priority in vaccine research, particularly for dengue and newly developing viruses like Mayaro.

The development of broad-spectrum antivirals, host-virus interaction research, and integrated genomic surveillance should be the main areas of future study. To reduce the burden of arboviral infections, it will be crucial to improve vector management techniques, strengthen healthcare infrastructure, and enhance early diagnostic skills. For future epidemics to be effectively implied, prevented, and managed, a multidisciplinary and internationally coordinated strategy will be essential.

Arboviral research is anticipated to undergo a revolution thanks to emerging technologies including high-throughput sequencing, bioinformatics-driven genomic surveillance, and artificial intelligence-based predictive modeling. These techniques make it possible to watch viral development in real time, identify new variants early, and predict outbreaks more accurately.

Future pandemic preparedness and the development of focused interventions will depend on the integration of these cutting-edge strategies with international surveillance systems.

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### Conflict of interest

The authors declare that they do not have any conflict of interest.

**Table 6:** Comparative clinical characteristics and management approaches. This table highlights variations in disease severity and preventative measures by comparing clinical symptoms, outcomes, and accessible treatment approaches for the four arboviruses.

| Feature | DENV | ZIKV | YFV | MAYV |
|---|---|---|---|---|
| Common symptoms | Fever, headache, myalgia | Mild fever, rash, conjunctivitis | Fever, jaundice | Fever, arthralgia |
| Severe complications | DHF, DSS | Microcephaly, GBS | Hemorrhage, liver failure | Chronic joint pain |
| Mortality risk | Moderate (severe cases) | Low | High (severe cases) | Low |
| Antiviral treatment | None | None | None | None |
| Vaccine availability | Limited (Dengvaxia) | None | Yes (17D) | None |
| Key concern | ADE, severity | Congenital infection | High fatality | Emerging spread |

**Table 7:** Diagnostic Markers and Clinical Features. This table summarizes the main diagnostic techniques and distinguishing clinical characteristics of the main arboviruses.

| Feature | DENV | ZIKV | YFV | MAYV |
|---|---|---|---|---|
| Key diagnostic test | NS1 antigen, RT-PCR | RT-PCR, IgM ELISA | RT-PCR, serology | RT-PCR |
| Detection window | Early (NS1), acute phase | Early infection | Acute phase | Acute phase |
| Serology cross-reactivity | High | High | Moderate | Low |
| Unique biomarker | NS1 antigen | Neurotropism markers | Liver enzymes | Persistent IgM |
| Key clinical sign | Plasma leakage | Microcephaly | Jaundice | Chronic arthralgia |



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## Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author used ChatGPT, Grammarly, and QuillBot for proper grammatical correction and maintaining logical flow. After using all the tools, I reviewed and edited the content as needed and take full responsibility for the content of the published article.


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## Data availability statement

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

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