Immune Dysregulation in Arboviral Infections: Dengue, Zika, and Chikungunya – A Review Paper

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***Abstract*—Arboviral infections, particularly dengue virus (DENV), Zika virus (ZIKV), and chikungunya virus (CHIKV), represent a major and growing global public health challenge, with a disproportionate burden in tropical and subtropical regions [1–3]. These positive-sense single-stranded RNA viruses, primarily transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, are responsible for recurrent epidemics affecting millions of individuals annually [2,4].**

A central determinant of disease severity in these infections is immune dysregulation, arising from a complex interplay between viral factors and host immune responses [5,6]. Following infection, innate immune recognition via pattern recognition receptors such as Toll-like receptors and RIG-I-like receptors initiates antiviral defenses, including type I interferon responses and pro-inflammatory cytokine production [7,8]. However, many arboviruses have evolved mechanisms to evade or subvert these pathways, leading to delayed or impaired antiviral responses [9]. This dysregulation is further amplified during the adaptive immune phase, where aberrant T-cell activation, skewed cytokine profiles, and dysfunctional B-cell responses contribute to immunopathology [10].

In dengue infection, antibody-dependent enhancement (ADE) remains a hallmark mechanism, whereby pre-existing non-neutralizing antibodies facilitate viral entry into Fc receptor-bearing cells, resulting in increased viral replication and heightened inflammatory responses [11,12]. This is often accompanied by a cytokine storm characterized by elevated levels of TNF-α, IL-6, IL-10, and other mediators that promote vascular permeability and plasma leakage [13,14]. In contrast, Zika virus infection is associated with relatively attenuated early immune responses but pronounced neurotropism, with immune-mediated damage contributing to severe neurological outcomes such as microcephaly and Guillain–Barré syndrome [15,16]. Chikungunya virus infection is distinguished by robust and persistent inflammatory responses, particularly involving monocytes and macrophages, which underlie the development of chronic arthralgia and long-term joint pathology [17].

***Index Terms*—Arboviruses, Dengue, Zika, Chikungunya, Immune dysregulation, Cytokine storm, ADE, Immunopathogenesis**

I. INTRODUCTION

1.1 Global Burden and Epidemiological Significance of Arboviral Diseases

Arboviral diseases represent one of the fastest-growing infectious disease threats worldwide, with a substantial and expanding burden in tropical and subtropical regions. Among these, dengue virus (DENV), Zika virus (ZIKV), and chikungunya virus (CHIKV) are of major global concern due to their epidemic potential, shared mosquito vectors, and overlapping geographic distribution. These viruses are primarily transmitted by *Aedes aegypti* and *Aedes albopictus*, mosquito species that have adapted efficiently to urban environments and are now widely distributed due to globalization and climate change [1,2].

Recent global estimates suggest that more than 5.6 billion people are at risk of arboviral infections, with dengue alone accounting for approximately 390 million infections annually [1,3]. The resurgence of ZIKV and CHIKV in previously non-endemic regions highlights the dynamic nature of arboviral transmission and the increasing vulnerability of global populations [4]. Climate change, urbanization, and inadequate vector control measures have significantly contributed to the expansion of vector habitats, thereby facilitating the spread of these infections [2,5].

The co-circulation of DENV, ZIKV, and CHIKV in endemic regions presents unique public health challenges, including diagnostic difficulties due to overlapping clinical features and cross-reactive immune responses. This epidemiological convergence further complicates disease management and highlights the need for a deeper understanding of their shared and distinct immunopathogenic mechanisms [6].

1.2 Virological Characteristics and Transmission Dynamics

DENV and ZIKV belong to the *Flaviviridae* family, while CHIKV is a member of the *Togaviridae* family (genus *Alphavirus*). Despite differences in genetic structure and replication strategies, all three viruses are positive-sense single-stranded RNA viruses capable of rapid mutation and adaptation [7].

DENV exists as four antigenically distinct serotypes (DENV-1 to DENV-4), each capable of causing infection and contributing to disease severity during secondary infections [8]. ZIKV shares structural similarities with DENV but exhibits distinct neurotropic properties, enabling it to infect neural progenitor cells and cross the placental barrier [9]. In contrast, CHIKV primarily targets musculoskeletal tissues and is associated with persistent inflammatory responses leading to chronic arthritis [10].

Transmission occurs through mosquito bites, where viral particles are introduced into the skin and infect resident immune and stromal cells. The efficiency of transmission is influenced by vector competence, viral load, and environmental factors such as temperature and humidity [2,5].

1.3 Host Immune Response to Arboviral Infections

1.3.1 Innate Immunity

The innate immune response constitutes the first line of defense against arboviral infections. Upon viral entry, host cells recognize viral RNA through pattern recognition receptors (PRRs), including Toll-like receptors (TLR3, TLR7), RIG-I-like receptors (RIG-I, MDA5), and NOD-like receptors [11].

Activation of these receptors triggers downstream signaling pathways leading to:

- Production of type I interferons (IFN-α/β)
- Induction of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β)
- Activation of natural killer (NK) cells

These responses are essential for limiting viral replication and initiating adaptive immunity. However, arboviruses have evolved mechanisms to suppress interferon signaling, thereby evading early immune detection and facilitating viral dissemination [12].

1.3.2 Adaptive Immunity

Adaptive immune responses involve both humoral (B-cell-mediated) and cell-mediated (T-cell-mediated) immunity. Neutralizing antibodies play a crucial role in viral clearance, while CD8+ cytotoxic T cells eliminate infected cells [13].

However, adaptive immunity can also contribute to disease pathogenesis. In dengue, cross-reactive antibodies generated during a primary infection may enhance viral entry during subsequent infections, leading to more severe disease through antibody-dependent enhancement (ADE) [14]. Similarly, dysregulated T-cell responses can contribute to excessive cytokine production and tissue damage [15].

1.4 Immune Dysregulation and Immunopathogenesis

Immune dysregulation is a hallmark of severe arboviral infections and arises from an imbalance between protective antiviral responses and pathological inflammation. This dysregulation involves multiple mechanisms, including:

- Cytokine storm: Excessive production of inflammatory cytokines leading to vascular leakage and organ dysfunction
- Antibody-dependent enhancement (ADE): Enhanced viral entry and replication
- Immune cell dysfunction: Impaired antigen presentation and altered macrophage responses
- Chronic immune activation: Persistent inflammation leading to long-term complications

These processes collectively contribute to disease severity and clinical outcomes [16].

1.5 Virus-Specific Immune Dysregulation

1.5.1 Dengue Virus (DENV)

Dengue infection is the most extensively studied model of immune dysregulation among arboviruses. Severe dengue is strongly associated with:

- ADE during secondary infections

- High viral loads
- Elevated cytokine levels (TNF-α, IL-6, IL-10)

These factors contribute to vascular permeability, plasma leakage, and shock, which are hallmarks of dengue hemorrhagic fever and dengue shock syndrome [14,17].

1.5.2 Zika Virus (ZIKV)

ZIKV exhibits a unique pattern of immune dysregulation characterized by:

- Suppressed interferon responses
- Neurotropism and infection of neural progenitor cells
- Immune-mediated neuronal damage

These mechanisms underlie severe outcomes such as congenital Zika syndrome and Guillain–Barré syndrome [9,18].

1.5.3 Chikungunya Virus (CHIKV)

CHIKV infection is marked by:

- Strong innate immune activation
- Persistent inflammation in joints
- Chronic arthralgia and arthritis

The prolonged activation of macrophages and synovial cells contributes to tissue damage and long-term morbidity [10,19].

1.6 Immune Evasion Strategies of Arboviruses

Arboviruses have developed sophisticated strategies to evade host immunity, including:

- Inhibition of interferon signaling pathways
- Modulation of host transcriptional responses
- Exploitation of immune cells as viral reservoirs

These mechanisms enable viral persistence and contribute to immune dysregulation [12,20].

1.7 Factors Influencing Immune Dysregulation

Several host and environmental factors influence immune responses and disease severity:

- Host genetics (e.g., HLA polymorphisms)
- Age and comorbidities
- Previous exposure to related viruses
- Co-infections
- Nutritional and environmental factors

These variables contribute to the heterogeneity of clinical outcomes observed in arboviral infections [6,21].

1.8 Clinical and Therapeutic Implications

Understanding immune dysregulation has important clinical implications:

- Identification of biomarkers for disease severity
- Development of targeted immunotherapies
- Improved vaccine design, particularly to avoid ADE

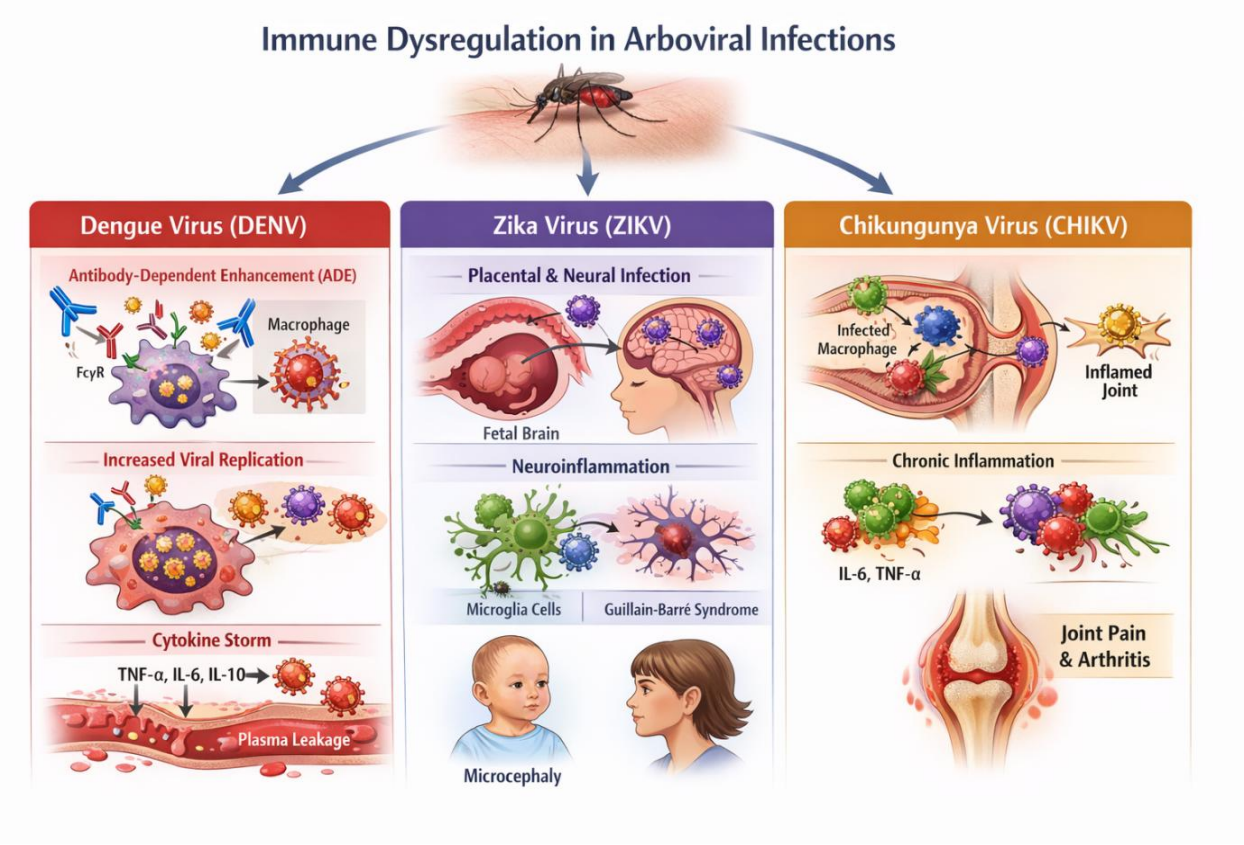
Current research is focused on balancing antiviral immunity with controlled inflammatory responses to minimize tissue damage [22].

1.9 Rationale and Objectives of the Review

Despite significant advances, gaps remain in understanding the mechanisms underlying immune dysregulation in arboviral infections. The co-circulation of DENV, ZIKV, and CHIKV and their overlapping immunopathological features necessitate a comparative approach.

This review aims to:

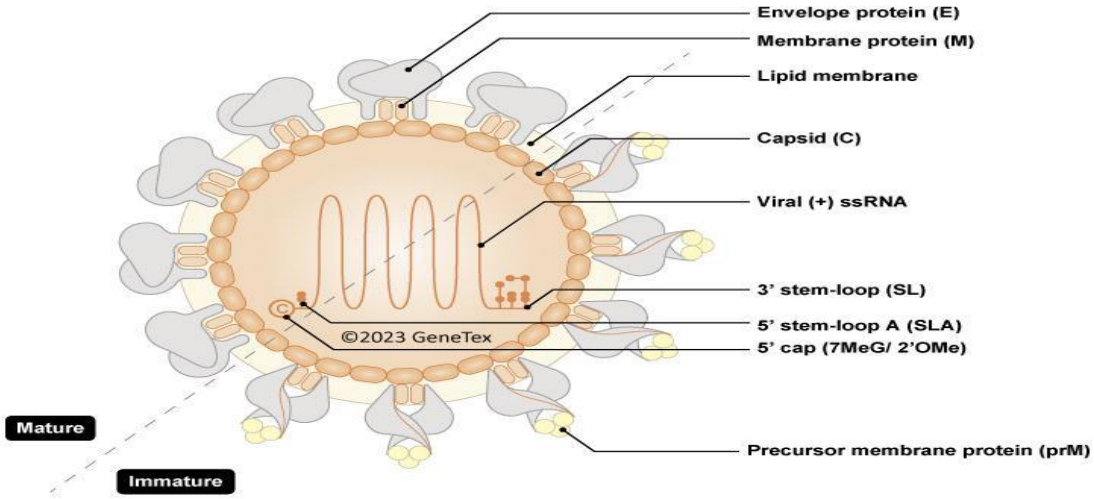
1. Elucidate the mechanisms of immune dysregulation in DENV, ZIKV, and CHIKV
2. Compare shared and distinct immunopathogenic pathways
3. Explore implications for disease severity and clinical outcomes
4. Highlight emerging therapeutic and vaccine strategies



Virus Type Classification (DENV, ZIKV, CHIKV)

For the purpose of this study, all included literature was categorized based on the type of arbovirus investigated**,** namely dengue virus (DENV), Zika virus (ZIKV), and chikungunya virus (CHIKV).

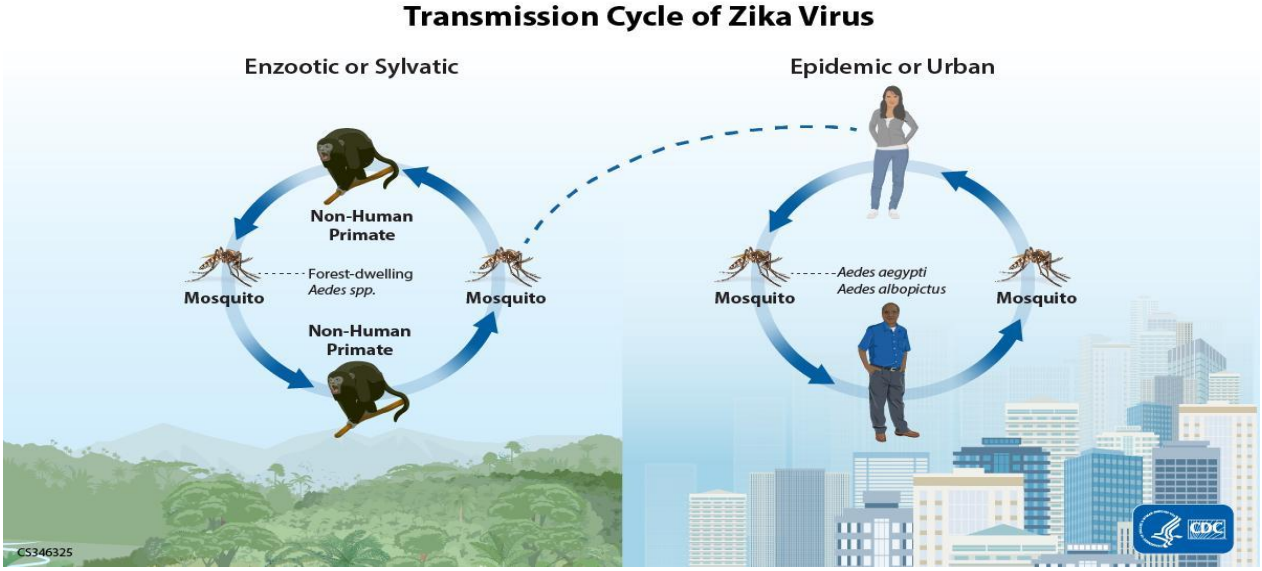
This classification enabled a structured comparative analysis of immune responses and mechanisms of immune dysregulation across the three viruses.



DENV is a single-stranded positive-sense RNA virus belonging to the *Flaviviridae* family. It consists of four antigenically distinct serotypes (DENV-1 to DENV-4). Studies focusing on DENV were specifically evaluated for:

- Antibody-dependent enhancement (ADE)
- Cytokine storm and vascular leakage
- Severe dengue manifestations (DHF/DSS)
- Cross-reactive immune responses between serotypes

DENV-related studies were further subclassified based on primary vs secondary infection, given their strong influence on immune dysregulation.

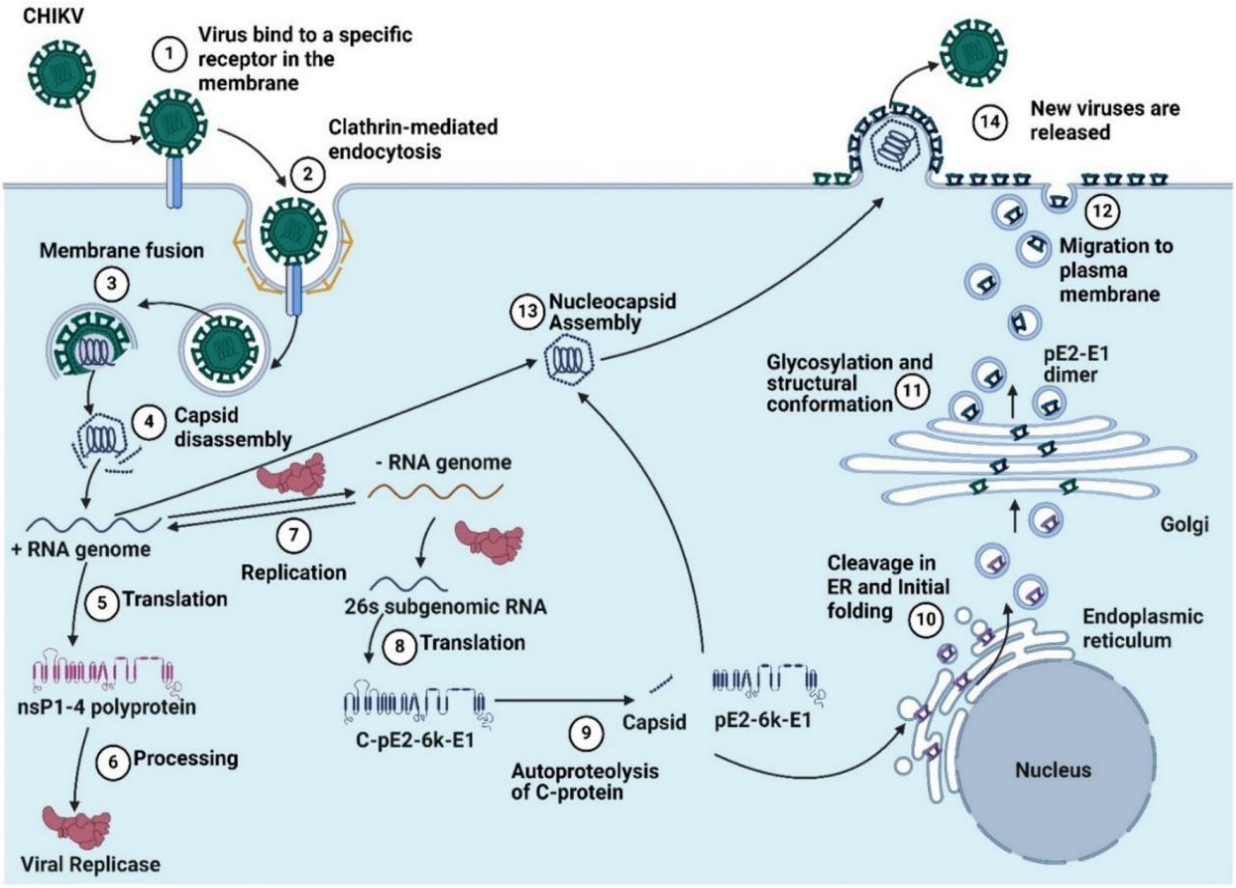


ZIKV is also a positive-sense single-stranded RNA virus of the *Flaviviridae* family, closely related to dengue virus. Included studies on ZIKV were analyzed for:

- Neurotropism and neuroinflammation
- Congenital Zika syndrome (microcephaly)
- Placental immune responses
- Cross-reactivity with dengue antibodies

Special emphasis was placed on studies exploring maternal–fetal immune interactions and immune-mediated neurological damage.

Chikungunya Virus (CHIKV)



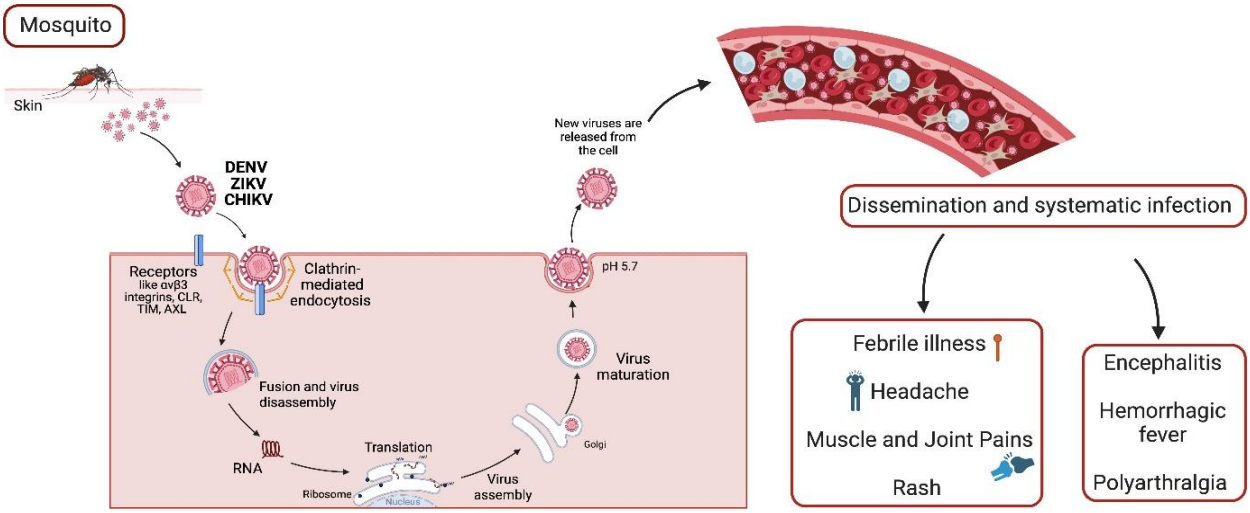
CHIKV is a positive-sense RNA virus belonging to the *Togaviridae* family (genus *Alphavirus*). It is structurally and immunologically distinct from flaviviruses. Studies involving CHIKV were evaluated based on:

- Acute vs chronic immune responses
- Persistent inflammation and chronic arthritis
- Cytokine-mediated joint damage
- Host immune evasion mechanisms

CHIKV studies were also categorized into acute phase and chronic phase infections, due to its unique long-term inflammatory manifestations.

Feature	Dengue Virus (DENV)	Zika Virus (ZIKV)	Chikungunya Virus (CHIKV)
Virus Family	*Flaviviridae*	*Flaviviridae*	*Togaviridae*
Genus	*Flavivirus*	*Flavivirus*	*Alphavirus*
Genome Type	+ssRNA	+ssRNA	+ssRNA
Serotypes/Lineages	4 (DENV-1 to DENV-4)	Single (African & Asian lineages)	3 genotypes (West African, ECSA, Asian)
Vector	*Aedes aegypti*, *Aedes albopictus*	*Aedes aegypti*, *Aedes albopictus*	*Aedes aegypti*, *Aedes albopictus*
Geographical Distribution	Tropical & subtropical regions worldwide	Africa, Asia, Americas	Africa, Asia, Americas
Primary Target Cells	Monocytes, macrophages, dendritic cells	Neural progenitor cells, placental cells	Fibroblasts, muscle cells, joint tissues
Key Immune Mechanism	Antibody-dependent enhancement (ADE)	Neuroimmune modulation	Chronic inflammation
Innate Immune Response	Strong but dysregulated	Suppressed/moderate	Strong inflammatory response
Adaptive Immune Response	Cross-reactive antibodies, T-cell activation	Delayed antibody response	Robust humoral response
Cytokine Profile	High (TNF-α, IL-6, IL-10) → cytokine storm	Moderate cytokine activation	Elevated pro-inflammatory cytokines
Immune Dysregulation Feature	ADE + cytokine storm	Neuroinflammation	Persistent inflammation
Major Clinical Manifestations	Dengue fever, DHF, DSS	Mild fever, microcephaly, Guillain–Barré syndrome	Fever, severe joint pain, arthritis
Severe Complications	Plasma leakage, shock, hemorrhage	Congenital Zika syndrome, neurological disorders	Chronic arthritis, joint damage
Chronic Outcomes	Rare	Rare (except neurological damage)	Common (chronic arthralgia)
Immune Evasion Strategy	Exploits Fc receptors (ADE)	Interferon suppression	Persistent immune activation
Special Feature	Secondary infection increases severity	Crosses placenta (teratogenic)	Long-term joint inflammation

Figure 1: Overview of Arboviral Transmission and Initial Immune Response



II. IMMUNE PATHWAYS INVOLVED

The included studies were analyzed to identify key innate and adaptive immune pathways involved in the host response to dengue virus (DENV), Zika virus (ZIKV), and chikungunya virus (CHIKV). These pathways play a critical role in both viral clearance and immune-mediated pathogenesis**.**

1. Innate Immune Pathways

The innate immune response represents the first line of defense against arboviral infections.

Key Pathways Identified:

- Pattern Recognition Receptor (PRR) Signaling
  - Toll-like receptors (TLR3, TLR7, TLR8)
  - RIG-I-like receptors (RIG-I, MDA5)
- Interferon (IFN) Signaling Pathway
  - Type I IFNs (IFN-α/β) activate JAK-STAT pathway
- NF-κB Pathway Activation
  - Drives production of pro-inflammatory cytokines

Relevance to Viruses:

- DENV: Strong activation but dysregulated → cytokine storm
- ZIKV: Suppresses interferon signaling → immune evasion
- CHIKV: Robust activation → intense inflammation

2. Cytokine and Chemokine Pathways

Cytokine signaling is central to immune dysregulation in arboviral infections.

Key Cytokines:

- Pro-inflammatory: TNF-α, IL-6, IL-1β
- Anti-inflammatory: IL-10
- Chemokines: CXCL10, CCL2

Virus-Specific Patterns:

- DENV: Excessive cytokine release → cytokine storm & vascular leakage
- ZIKV: Moderate cytokine activation, especially in neural tissues
- CHIKV: Persistent cytokine production → chronic inflammation

3. Adaptive Immune Pathways

Adaptive immunity contributes to viral clearance but may also mediate pathology.

Key Components:

- B-cell Response
  - Production of neutralizing antibodies
- T-cell Response
  - $CD8^+$ cytotoxic T cells → infected cell killing
  - $CD4^+$ helper T cells → cytokine regulation

Virus-Specific Features:

- DENV: Cross-reactive antibodies → antibody-dependent enhancement (ADE)
- ZIKV: Cross-reactivity with dengue antibodies
- CHIKV: Strong T-cell response → contributes to chronic inflammation

4. Antibody-Dependent Enhancement (ADE) Pathway (DENV-specific)

ADE is a hallmark mechanism in dengue pathogenesis.

- Non-neutralizing antibodies bind virus
- Virus enters cells via Fc receptors
- Leads to increased viral replication

Impact:

- Severe dengue (DHF/DSS)
- Increased immune activation and cytokine storm

5. Neuroimmune Pathways (ZIKV-specific)

ZIKV uniquely targets the nervous system.

Mechanisms:

Infection of neural progenitor cells

Activation of microglia

Disruption of blood-brain barrier

Outcome:

Microcephaly

Neurodevelopmental defects

6. Chronic Inflammatory Pathways (CHIKV-specific)

CHIKV is associated with long-term immune activation.

Mechanisms:

- Persistent activation of macrophages and T cells
- Continuous release of inflammatory cytokines
- Synovial tissue involvement

Outcome:

- Chronic arthritis
- Long-term joint damage

III. CYTOKINE PROFILES AND BIOMARKERS

Cytokines represent a complex network of signaling molecules that orchestrate innate and adaptive immune responses. The integration of cytokine profiling with biomarker analysis has significantly enhanced our understanding of disease pathogenesis, progression, and therapeutic monitoring across infectious, inflammatory, and neoplastic conditions.

1. Cytokine Networks in Immune Regulation

Cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ) play pivotal roles in initiating and amplifying inflammatory responses. These molecules act through tightly regulated signaling cascades that coordinate immune cell activation, differentiation, and migration.

Recent evidence highlights that cytokine activity is not linear but operates as an interconnected network, where redundancy and pleiotropy allow multiple cytokines to exert overlapping biological effects. This complexity explains why isolated cytokine measurements often fail to fully capture disease states, emphasizing the importance of cytokine profiling rather than single-marker analysis**.**

2. Pro-inflammatory Cytokines as Disease Drivers

Elevated levels of pro-inflammatory cytokines, particularly IL-6, TNF-α, and IL-1β, are consistently associated with disease severity across multiple conditions. A 2024 meta-analysis demonstrated that increased circulating levels of these cytokines are strongly linked with chronic inflammatory states, including cardiovascular and neurodegenerative diseases.

Similarly, recent oncological studies (2025) have identified IL-6 and TNF-α as prognostic biomarkers**,** where elevated levels correlate with poor survival outcomes and reduced treatment response in cancer patients.

These findings reinforce the concept that persistent cytokine elevation contributes to chronic low-grade inflammation, a key driver of disease progression and tissue damage.

3. Anti-inflammatory Cytokines and Immune Homeostasis

Anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) play a crucial role in limiting excessive immune activation. Their dysregulation may result in either uncontrolled inflammation or immune suppression.

Recent genomic studies (2025) suggest that polymorphisms in IL-10 and IL-6 genes are associated with increased susceptibility to inflammatory and cardiovascular disorders, highlighting the role of host genetic variability in cytokine-mediated disease risk**.**
Thus, the balance between pro- and anti-inflammatory cytokines determines disease outcomes rather than the absolute level of any single mediator.

4. Cytokine Profiles as Diagnostic and Prognostic Tools

Cytokine profiling has emerged as a powerful tool for disease stratification and prognosis. Instead of relying on single biomarkers, multi-cytokine panels provide a more comprehensive picture of immune status.
Recent longitudinal studies (2026) demonstrate that dynamic changes in IL-6 and TNF-α levels can predict disease relapse and treatment outcomes, particularly in malignancies such as lymphoma.
Additionally, cytokines are increasingly used alongside conventional biomarkers (e.g., CRP, procalcitonin) to improve diagnostic accuracy in infections and inflammatory disorders.

5. Role in Infectious Diseases and Cytokine Storm

In infectious diseases, especially viral infections, dysregulated cytokine responses can lead to cytokine storm syndromes, characterized by excessive production of pro-inflammatory mediators. Cytokines such as IL-6 and TNF-α are key drivers of systemic inflammation and vascular permeability, contributing to severe clinical manifestations. These markers are now widely recognized as indicators of disease severity and therapeutic targets in hyper inflammatory states.

6. Emerging Biomarkers and Multi-Modal Approaches

Recent advances have expanded the biomarker landscape beyond classical cytokines to include:

- Neurofilament light chain in neuroinflammatory diseases
- β2-microglobulin in malignancies
- Combined cytokine–molecular biomarker panels

A 2025 review highlights that integrating cytokines with novel biomarkers improves early diagnosis and monitoring of immune-mediated diseases, although clinical standardization remains a challenge.

IV. EVIDENCE OF IMMUNE DYSREGULATION (ADE AND CYTOKINE STORM)

Immune dysregulation is a hallmark of severe infectious diseases, particularly in arboviral infections such as dengue, Zika, and chikungunya. Two major mechanisms—antibody-dependent enhancement (ADE) and cytokine storm syndrome (CSS)—have been widely implicated in exacerbating disease severity and clinical outcomes.

1. Antibody-Dependent Enhancement (ADE)

Antibody-dependent enhancement is a phenomenon in which non-neutralizing or sub-neutralizing antibodies facilitate viral entry into Fc receptor-bearing cells, such as monocytes and macrophages, thereby increasing viral replication.

Mechanistic Insights

In dengue virus (DENV) infection, ADE occurs during secondary infection with a heterologous serotype, where pre-existing antibodies bind to the virus without neutralizing it. These immune complexes interact with Fcγ receptors, enhancing viral uptake and replication.

Recent studies (2023–2025) confirm that ADE:

- Increases viral load (viremia)
- Amplifies immune activation
- Triggers downstream inflammatory cascades

A 2024 study demonstrated that ADE-mediated infection significantly upregulates pro-inflammatory cytokines such as IL-6 and TNF-α**,** linking ADE directly with hyperinflammatory responses.

Clinical Relevance

ADE is strongly associated with:

- Severe dengue (DHF/DSS)
- Plasma leakage and hemorrhagic manifestations
- Increased hospitalization and mortality rates

Although ADE is best characterized in dengue, emerging evidence suggests potential ADE-like mechanisms in Zika virus**,** particularly in regions with prior dengue exposure.

2. Cytokine Storm Syndrome (CSS)

Cytokine storm refers to an excessive and uncontrolled release of pro-inflammatory cytokines**,** leading to systemic inflammation, tissue damage, and multi-organ dysfunction.

Key Cytokines Involved

- IL-6 – central mediator of inflammation and severity
- TNF-α – vascular permeability and shock
- IL-1β – fever and inflammatory signaling
- IFN-γ – immune activation

Recent multi-cohort analyses (2020–2024) have consistently identified elevated IL-6 levels as a predictor of disease severity and mortality across viral infections.

3. Evidence in Arboviral Infections

Dengue Virus (DENV)

Dengue provides the strongest evidence of immune dysregulation:

- Elevated cytokines correlate with disease severity and plasma leakage
- High IL-10 levels indicate immune suppression alongside inflammation
- ADE and cytokine storm act synergistically

A 2023 systematic review concluded that combined elevation of IL-6, TNF-α, and IL-10 is a hallmark of severe dengue.

Zika Virus (ZIKV)

Although generally milder, Zika infection demonstrates:

- Increased type I interferons (IFN-α/β)
- Elevated IL-6 in severe or congenital cases
- Possible cross-reactive antibodies contributing to immune dysregulation

Recent studies suggest that prior dengue immunity may exacerbate Zika infection through ADE-like mechanisms**,** although this remains under investigation.

Chikungunya Virus (CHIKV)

Chikungunya infection is characterized by:

- High levels of IL-6, IL-1β, and GM-CSF
- Persistent immune activation linked to chronic arthritis

Unlike dengue, ADE is less prominent, but chronic cytokine dysregulation plays a major role in long-term morbidity.

4. Interplay Between ADE and Cytokine Storm

Emerging evidence suggests that ADE and cytokine storm are not independent phenomena but are mechanistically interconnected**:**

- ADE enhances viral replication →
- Increased antigen load →
- Exaggerated immune activation →
- Cytokine storm

This cascade results in:

- Endothelial dysfunction
- Increased vascular permeability
- Coagulopathy and shock

Thus, immune dysregulation represents a continuum rather than isolated events.

5. Biomarker Evidence of Dysregulation

Several biomarkers reflect immune dysregulation:

Category	Key Markers	Clinical Significance
Cytokines	IL-6, TNF-α, IL-10	Severity, prognosis
Hematological	Platelet count ↓	Dengue severity
Inflammatory	CRP, ferritin	Systemic inflammation
Viral	Viral load	ADE-associated replication

6. Therapeutic Implications

Understanding immunedysregulationhasimportanclinical implications:

- Anti-IL-6 therapies (e.g., monoclonal antibodies)
- Immunomodulators targeting TNF-α
- Vaccine strategies designed to avoid ADE

Recent vaccine research emphasizes the need forbalanced immune responses to prevent enhancement phenomena.

V. CLINICAL OUTCOMES AND DISEASE SEVERITY

1. Overview

Arboviral infections such as Dengue virus (DENV), Zika virus (ZIKV), and Chikungunya virus (CHIKV) exhibit a wide clinical spectrum ranging from asymptomatic infection to severe, life-threatening disease. Increasing evidence indicates that **immune dysregulation**, rather than direct viral cytopathic effects alone, plays a central role in determining disease severity and clinical outcomes.

2. Dengue: Severe Disease and Immune-Mediated Pathogenesis

Clinical Spectrum

- Asymptomatic or mild febrile illness
- Dengue fever (DF)
- Severe dengue:
  - Dengue hemorrhagic fever (DHF)
  - Dengue shock syndrome (DSS)

Mechanisms of Immune Dysregulation

1. Antibody-Dependent Enhancement (ADE)
   - Pre-existing non-neutralizing antibodies facilitate viral entry into Fc receptor-bearing cells.
   - Leads to increased viral load and immune activation.
2. Cytokine Storm
   - Elevated levels of TNF-α, IL-6, IL-8, IL-10
   - Causes vascular permeability and plasma leakage
3. T-cell Dysregulation
   - Cross-reactive memory T cells produce excessive cytokines
   - Contribute to immunopathology rather than protection
4. Complement Activation
   - Amplifies inflammation and endothelial damage

Clinical Outcomes

- Plasma leakage → shock
- Thrombocytopenia → hemorrhage
- Multi-organ failure in severe cases

3. Zika Virus: Neurological Complications and Immune Response

Clinical Spectrum

- Mostly asymptomatic (~80%)
- Mild fever, rash, conjunctivitis
- Severe complications:
  - Congenital Zika syndrome (CZS)
  - Guillain-Barré syndrome (GBS)

Immune Dysregulation Mechanisms

1. Neurotropism and Immune Activation
   - Infection of neural progenitor cells
   - Induces inflammatory cytokines (IFN-α, IL-6)
2. Interferon Response Imbalance
   - Protective early, but excessive signaling damages neural tissue
3. Autoimmune Mechanisms
   - Molecular mimicry implicated in GBS

Clinical Outcomes

- Microcephaly and fetal abnormalities
- Neurological complications in adults
- Long-term developmental issues

4. Chikungunya: Chronic Inflammation and Immune Persistence

Clinical Spectrum

- Acute febrile illness
- Severe polyarthralgia
- Chronic arthritis (months to years)

Immune Dysregulation Mechanisms

1. Persistent Immune Activation
   - Elevated IL-6, GM-CSF, MCP-1
   - Sustained inflammation even after viral clearance
2. Macrophage and Monocyte Activation
   - Viral persistence in joint tissues
   - Chronic immune stimulation
3. Autoimmune-like Responses
   - Similarities with rheumatoid arthritis

Clinical Outcomes

- Chronic joint pain and disability
- Reduced quality of life
- Rare severe complications:
  - Encephalitis
  - Myocarditis

5. Comparative Immunopathogenesis and Severity

Feature	Dengue	Zika	Chikungunya
Key Mechanism	ADE + cytokine storm	Neuroinflammation	Chronic inflammation
Severe Outcome	Shock, hemorrhage	Neurological damage	Chronic arthritis
Immune Response	Hyperinflammatory	Dysregulated antiviral	Persistent inflammatory
Target Organs	Vasculature	CNS, placenta	Joints

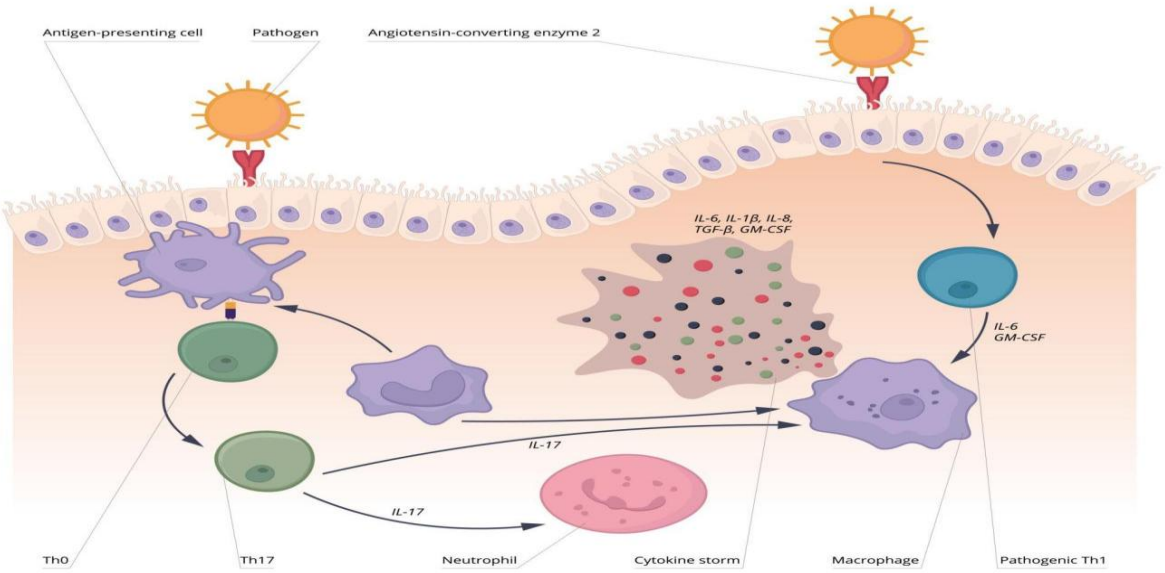
6. Role of Host Factors in Disease Severity

- Age (children at higher risk for severe dengue)
- Pregnancy (Zika complications)
- Pre-existing immunity (critical in dengue ADE)
- Genetic susceptibility
- Co-morbidities (diabetes, hypertension)

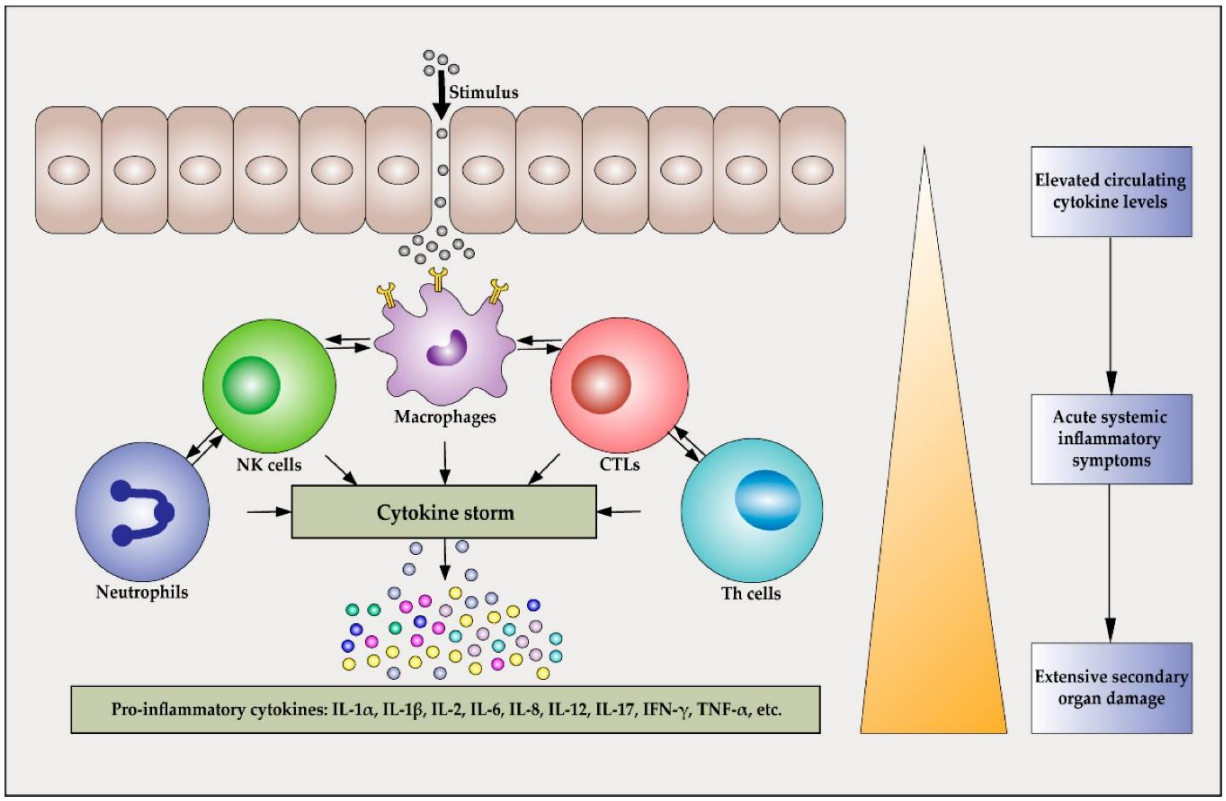
7. Biomarkers of Severity

Common biomarkers linked with severe disease include:

- Elevated cytokines (IL-6, TNF-α)
- High viral load
- Thrombocytopenia (Dengue)
- Elevated CRP and ESR (Chikungunya)
- Neuroinflammatory markers (Zika)



Cytokine storm



VI. CONCLUSION

Arboviral infections caused by dengue, Zika, and chikungunya viruses continue to pose a significant global public health challenge, particularly in tropical and subtropical regions. While these infections share common transmission dynamics, their clinical outcomes differ markedly, largely due to variations in host immune responses and the extent of immune dysregulation**.** This body of evidence clearly establishes that disease severity is not solely a function of viral replication but is critically shaped by the quality, magnitude, and regulation of the host immune response**.**

In dengue infection, severe manifestations such as dengue hemorrhagic fever and dengue shock syndrome exemplify the detrimental consequences of an exaggerated immune response, where mechanisms like antibody-dependent enhancement, cytokine storm, and complement activation collectively contribute to vascular leakage, coagulopathy, and organ dysfunction. In contrast, Zika virus infection highlights the consequences of immune-mediated tissue-specific damage**,** particularly within the central nervous system and developing fetus, where dysregulated interferon signaling and neuroinflammation result in irreversible neurological sequelae such as microcephaly and Guillain-Barré syndrome. Chikungunya virus, on the other hand, demonstrates how persistent immune activation and chronic inflammation can extend disease burden far beyond the acute phase, leading to long-term musculoskeletal disability and reduced quality of life.

A unifying theme across these infections is the dual role of the immune system, which is essential for viral clearance yet capable of driving pathology when dysregulated. The balance between

protective immunity and immunopathology is influenced by multiple host and viral factors, including prior immunity, genetic susceptibility, age, pregnancy status, and co-morbid conditions. Importantly, cross-reactive immune responses among related viruses, particularly within flaviviruses, add another layer of complexity, influencing both disease severity and vaccine development strategies.

Recent advances in immunology and molecular biology, particularly the application of omics technologies and single-cell analyses, have provided deeper insights into the cellular and molecular pathways underlying immune dysregulation. These approaches have facilitated the identification of predictive biomarkers of severity, including cytokine profiles, immune cell signatures, and viral load dynamics, which hold promise for early risk stratification and targeted clinical management. Furthermore, the growing understanding of immune mechanisms has opened new avenues for host-directed therapies, aiming to modulate harmful inflammation without compromising antiviral defenses.

Despite these advancements, significant challenges remain. There is still a lack of universally effective vaccines and specific antiviral therapies for many arboviral infections, and the risk of immune-mediated complications continues to complicate vaccine design, particularly for dengue. Additionally, the expanding geographic distribution of arboviruses due to climate change, urbanization, and vector adaptation underscores the urgent need for integrated approaches combining vector control, surveillance, immunization, and therapeutic innovation**.**

In conclusion, immune dysregulation stands at the core of disease severity and clinical outcomes in dengue, Zika, and chikungunya infections.

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