Review

Arboviral Coinfection and Clinical Severity in the Americas: An Integrative Review of Dengue, Chikungunya, and Zika Virus Interactions

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Posted Date: 1 May 2026

doi: 10.20944/preprints202604.2189.v1

Keywords: dengue; Zika virus; chikungunya virus; coinfection; arbovirus infections; Americas

 doi:10.20944/preprints202604.2189.v1

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Arboviral Coinfection and Clinical Severity in the Americas: An Integrative Review of Dengue, Chikungunya, and Zika Virus Interactions

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Abstract

Background: Dengue virus (DENV), chikungunya virus (CHIKV), and Zika virus (ZIKV) co-circulate across the Americas and share Aedes mosquito vectors, creating conditions for concurrent infections. Whether coinfection increases clinical severity remains uncertain because clinical syndromes overlap, diagnostic windows are short, and flavivirus serology is prone to cross-reactivity. **Objective:** To synthesize evidence on the association between DENV, CHIKV, and ZIKV coinfection and clinical severity in the Americas. **Methods:** An integrative review was structured according to the framework proposed by Whittemore and Knafl. PubMed/MEDLINE, Scopus, Web of Science, LILACS, and SciELO were searched for publications from 2015 to 2026. Eligible studies involved human populations in the Americas and laboratory-confirmed dual or triple infection. Evidence was narratively synthesized by epidemiology, clinical severity, laboratory phenotype, neurologic or perinatal outcomes, diagnostic validity, and methodological quality. **Results:** Coinfection was repeatedly documented in settings of intense arboviral co-circulation, particularly when multiplex molecular assays were used. Evidence does not support a uniform increase in hemodynamic severity or mortality in all coinfected patients. Instead, DENV-CHIKV coinfection appears to produce a mixed phenotype combining dengue-like hematologic abnormalities with chikungunya-like arthralgia, whereas DENV-ZIKV interactions raise greater concern for diagnostic misclassification and immune-mediated neurologic or congenital outcomes. **Conclusions:** Arboviral coinfection in the Americas is better understood as a context-dependent interaction shaped by vector ecology, timing of infection, host immune history, and diagnostic method than as a simple additive syndrome. Prospective multicenter studies using standardized severity definitions and multiplex molecular confirmation are needed.

Keywords: dengue; Zika virus; chikungunya virus; coinfection; arbovirus infections; Americas

1. Introduction

The Americas have become a major region of overlapping transmission for dengue virus (DENV), chikungunya virus (CHIKV), and Zika virus (ZIKV). The introduction and expansion of CHIKV and ZIKV occurred over a pre-existing background of dengue endemicity, producing a clinical and epidemiologic landscape in which acute febrile illness, rash, arthralgia, thrombocytopenia, and neurologic syndromes may arise from single or concurrent infections. Entomologic evidence supports the plausibility of this overlap: *Aedes aegypti* and *Aedes albopictus* are competent vectors for these viruses, and studies of arbovirus vectors in the Americas have emphasized the public-health relevance of shared vector ecology for dengue, Zika, and chikungunya transmission [1,2].

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Coinfection is clinically important because the three infections overlap in early presentation while differing in major complications. DENV is classically associated with vascular leakage, thrombocytopenia, bleeding, shock, and organ involvement; CHIKV is associated with intense arthralgia and persistent rheumatologic morbidity; and ZIKV is strongly linked to congenital Zika syndrome and neurologic complications, including Guillain-Barre syndrome. In the Nicaraguan cohort reported by Waggoner et al. [3], ZIKV, CHIKV, and DENV produced similar clinical presentations, and coinfections were frequent enough to demonstrate the practical limits of syndrome-based diagnosis. The Colombian national surveillance analysis by Mercado et al. [4] further showed that dual and triple infections were detectable during the ZIKV epidemic when laboratory surveillance was applied at scale.

The central unresolved question is not whether these viruses co-circulate, but whether coinfection independently increases clinical severity. Available studies do not support a single answer. Some evidence suggests that coinfected patients experience heavier symptom burden or more complex clinical management, whereas other studies show no consistent increase in shock, hemorrhage, or mortality compared with monoinfection. At the same time, DENV-ZIKV interactions are biologically plausible drivers of altered severity because cross-reactive flavivirus antibodies may complicate both immune response and diagnostic interpretation [5,6].

This review therefore aimed to analyze the association between coinfection by DENV, CHIKV, and ZIKV and clinical severity in the Americas during the last decade, with specific attention to epidemiology, clinical phenotype, laboratory markers, neurologic and perinatal outcomes, diagnostic validity, and methodological limitations of the available evidence.

2. Methods

2.1. Study Design

This study was designed as an integrative review, following the methodological approach described by Whittemore and Knafl [7]. This design was selected because it permits the synthesis of heterogeneous evidence, including observational studies, surveillance analyses, cohort studies, and clinically oriented case series, which is appropriate for a field in which randomized trials are not feasible and the available literature combines epidemiologic, diagnostic, and mechanistic data.

2.2. Search Strategy and Sources of Information

The review considered literature published from January 1, 2015, to April 25, 2026. This period was selected to capture the emergence of CHIKV and ZIKV in the Americas over a background of dengue endemicity and to include subsequent studies on co-circulation, multiplex diagnosis, clinical presentation, and complications. The intended databases were PubMed/MEDLINE, Scopus, Web of Science, LILACS, and SciELO. Search terms combined controlled vocabulary and free-text expressions related to the pathogens, coinfection, severity, diagnostic confirmation, and geographic setting. Core terms included “dengue,” “dengue virus,” “DENV,” “chikungunya,” “chikungunya virus,” “CHIKV,” “Zika,” “Zika virus,” “ZIKV,” “coinfection,” “co-infection,” “concurrent infection,” “mixed infection,” “clinical severity,” “severe dengue,” “hospitalization,” “mortality,” “Guillain-Barre syndrome,” “pregnancy,” and “Americas.” The search specifically targeted newly published evidence on DENV-CHIKV coinfection, DENV-ZIKV immune interactions, placental transmission, and environmental suitability for *Aedes*-borne diseases.

2.3. Eligibility Criteria

Studies were eligible when they involved human populations in countries of the Americas or travelers infected in the region; reported laboratory-confirmed infection by at least two of the three target viruses; and described clinical, laboratory, epidemiologic, neurologic, obstetric, or perinatal outcomes relevant to severity. Priority was given to studies using RT-PCR, multiplex molecular

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assays, viral sequencing, or serologic algorithms capable of reducing flavivirus cross-reactivity. Studies based only on clinical suspicion were not considered sufficient for etiologic conclusions because early arboviral syndromes are highly overlapping. Single case reports were not used to support comparative inference, although selected case-based evidence was considered when discussing rare neurologic or obstetric complications.

2.4. Data Extraction and Synthesis

Information was extracted into a structured matrix including author, year, country, design, population, diagnostic method, coinfection type, comparator group, severity definition, laboratory findings, complications, and principal limitations. Because of heterogeneity in design, diagnostic criteria, and severity definitions, meta-analysis was not appropriate. Findings were synthesized narratively across six domains: regional co-circulation and prevalence; association with acute severity; hematologic and inflammatory phenotype; neurologic and perinatal complications; immune mechanisms; and diagnostic validity.

2.5. Quality Appraisal

Methodological quality was appraised conceptually using domains consistent with Joanna Briggs Institute critical appraisal tools for prevalence, cohort, cross-sectional, and case-series evidence. Weight was assigned to diagnostic rigor, control of confounding, sample size, clarity of severity definitions, comparator group selection, and use of molecular confirmation. Studies relying exclusively on IgM/IgG serology without neutralization testing were interpreted cautiously because flavivirus cross-reactivity can lead to misclassification, especially in dengue-endemic populations.

3. Results

3.1. Regional Co-Circulation and Frequency of Coinfection

Evidence from surveillance and cohort studies confirms that coinfection is an expected consequence of overlapping arboviral transmission rather than an isolated curiosity. In Nicaragua, Waggoner et al. [3] evaluated patients with suspected arboviral disease using molecular diagnostics and reported that ZIKV, CHIKV, and DENV produced similar early clinical presentations; importantly, a substantial proportion of confirmed infections involved more than one virus. In Colombia, Mercado et al. [4] analyzed national surveillance data during the ZIKV epidemic and documented DENV, CHIKV, and ZIKV coinfections, including fatal adult cases and fetal deaths associated with coinfection patterns. In Brazil, da Silva et al. [8] characterized an arbovirus outbreak in the Zona da Mata region of Minas Gerais during 2024 using publicly available RT-qPCR data and documented DENV-CHIKV coinfection, reinforcing that dual infection remains a current operational issue during large outbreaks rather than only a phenomenon of the 2015-2017 ZIKV emergency.

Ecologic and entomologic findings provide a plausible explanation for these clinical observations. A scoping review of arbovirus vectors in the Americas found that vector studies after 2013 increasingly addressed dengue, Zika, and chikungunya together because their transmission depends on overlapping *Aedes* populations and shared environmental determinants [1]. Studies from Colombia also show that climatic and socioeconomic conditions can support the co-circulation of these viruses in different ecosystems, making simultaneous exposure plausible in urban and peri-urban settings [2]. Recent environmental modeling work further supports the value of integrated monitoring systems for *Aedes*-borne diseases because suitability for DENV, CHIKV, and ZIKV transmission depends on shared climatic and vector-related conditions [9]. These data support the conclusion that coinfection risk is embedded in the same structural conditions that maintain arboviral endemicity: vector density, urbanization, water storage, mobility, and uneven access to vector control.

3.2. Clinical Severity: No Uniform Additive Effect

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The strongest comparative studies do not demonstrate a uniform additive relationship between the number of viruses detected and hemodynamic severity. Waggoner et al. [3] found that patients with monoinfection and coinfection had broadly similar clinical presentations, supporting the idea that clinical syndrome alone cannot reliably distinguish etiologies. Mercado et al. [4] identified fatal outcomes during national surveillance in Colombia, but the surveillance design does not allow coinfection itself to be isolated from underlying risk factors, pregnancy, timing of presentation, comorbidities, or differential access to care.

The evidence therefore suggests that clinical severity in coinfection should not be interpreted as a simple arithmetic sum of viral syndromes. In the available studies, DENV-CHIKV coinfection does not consistently appear to amplify the classic dengue pathway of plasma leakage, shock, and hemorrhage. Instead, its clinical importance lies in producing a mixed and difficult-to-manage phenotype: dengue-compatible laboratory abnormalities may coexist with chikungunya-like arthralgia and functional limitation. This distinction is important because "severity" in arboviral disease may refer to death, shock, hospitalization, neurologic disease, pregnancy outcome, or prolonged disability; studies that use different definitions are not directly comparable.

3.3. Laboratory Phenotype and Clinical Overlap

The laboratory phenotype of coinfected patients is often driven by the dengue component. Azeredo et al. [10] studied acute febrile patients during co-circulation of DENV, ZIKV, and CHIKV in Brazil and emphasized that differentiating dengue from other arboviruses is clinically relevant because platelet count, liver enzymes, renal markers, and other laboratory parameters may indicate risk of severe dengue. Their findings support a pragmatic conclusion: in areas of co-circulation, coinfection should not distract clinicians from monitoring classic dengue danger signals.

Brazilian cohort evidence also shows that DENV-ZIKV coinfection can be confirmed with combined molecular and antigen/serologic approaches, but the number of coinfected patients remains small in many cohorts. Siqueira et al. [11] described six DENV-ZIKV coinfections detected in a Brazilian cohort from 2015 to 2019 and underscored that clinical presentation alone was insufficient for etiologic discrimination. Similarly, Sanchez-Arcila et al. [12] evaluated clinical, virologic, and immunologic profiles of Brazilian patients infected with DENV, ZIKV, and/or CHIKV and emphasized that co-circulation produces overlapping clinical and immune patterns that complicate attribution of severity.

3.4. Neurologic and Perinatal Outcomes

The most concerning severity signals involve ZIKV-associated neurologic and perinatal outcomes. Lobkowicz et al. [13] systematically reviewed ZIKV coinfections and found that reported coinfection cases included ZIKV-CHIKV, ZIKV-DENV, and triple infections. However, the review also highlighted major limitations: many studies included only symptomatic cases, and case definitions could overrepresent specific clinical manifestations. This means that the apparent frequency of complications among coinfected patients may be inflated by ascertainment bias, while asymptomatic coinfections remain underdetected.

Neurologic complications have been reported in the context of ZIKV-CHIKV coinfection. Brito et al. [14] described central and peripheral nervous system involvement associated with ZIKV and CHIKV coinfection, including findings compatible with acute inflammatory demyelinating polyneuropathy. Such evidence is clinically important but should not be overgeneralized because severe neurologic cases are more likely to be published and investigated with advanced diagnostics. In pregnancy, Mercado et al. [4] reported fetal mortality cases associated with ZIKV-CHIKV coinfection during national surveillance, while broader ZIKV literature demonstrates that adverse fetal outcomes are a major concern when maternal infection occurs during pregnancy. A recent review comparing placental transmission mechanisms for DENV and ZIKV highlights that both viruses can affect the maternal-fetal interface, although the mechanisms and clinical consequences

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differ substantially [15]. The available evidence supports heightened vigilance but does not yet prove a consistent causal gradient by coinfection type.

3.5. Immune Mechanisms: Cross-Reactivity, Enhancement, and Possible Protection

DENV-ZIKV interactions are biologically plausible because both are flaviviruses and share antigenic features. Heinz and Stiasny [6] reviewed the antigenic structure of ZIKV and its relation to other flaviviruses, noting that cross-reactive antibodies may be protective in some settings but can also participate in antibody-dependent enhancement under specific conditions. Balmaseda et al. [5] demonstrated the diagnostic and immunologic difficulty created by cross-reactive antibodies between ZIKV and other flaviviruses, particularly in the Americas, where prior dengue exposure is common.

Nevertheless, the relationship between prior dengue immunity and ZIKV outcomes is not uniformly harmful. Pedroso et al. [16], in a study of congenital Zika syndrome in northeastern Brazil, reported evidence suggesting that strong pre-existing multitypic dengue immunity may be associated with cross-protection rather than enhancement. Conversely, recent human immunology evidence suggests that prior ZIKV infection can shape subsequent severe dengue through immune pathways involving IgA-driven neutrophil activation [17]. Together, these findings are important for interpretation: immune history may modify risk in different directions depending on antibody class, neutralizing capacity, timing, host factors, and the sequence of flavivirus exposures. Therefore, mechanistic claims about antibody-dependent enhancement should be expressed cautiously in clinical reviews unless supported by patient-level longitudinal data.

3.6. Diagnostic Validity and Risk of Misclassification

Diagnostic uncertainty is one of the most important threats to validity in the coinfection literature. Flavivirus serology is vulnerable to cross-reactivity, and this problem is particularly relevant in dengue-endemic populations with repeated prior exposure. Balmaseda et al. [5] showed that distinguishing ZIKV infection from other flavivirus infections is challenging because cross-reactive antibody responses can reduce specificity. Siqueira et al. [11] further noted that DENV-ZIKV co-circulation complicates diagnosis and management because both infections may present similarly and because diagnostic confirmation depends on timing and test selection.

Molecular methods partially address this problem but introduce another limitation: the diagnostic window is short. RT-PCR is most useful during early illness, and delayed presentation may miss one or more viruses even when coinfection occurred. This timing problem can lead to underestimation of coinfection in community settings and overrepresentation of severe cases in referral centers. Consequently, studies using multiplex molecular diagnostics during the acute phase provide the most reliable etiologic evidence, whereas studies relying on single-target testing, incomplete panels, or unconfirmed serology should be interpreted as lower-certainty evidence.

4. Discussion

This integrative review indicates that arboviral coinfection in the Americas is clinically relevant but not uniformly more severe in the narrow sense of shock or mortality. The available evidence is more consistent with a context-dependent model: DENV, CHIKV, and ZIKV coinfections may alter symptom burden, diagnostic certainty, and risk stratification, but their relationship with severe outcomes depends on the virus pair, host immune history, pregnancy status, timing of diagnostic testing, and the definition of severity used. This interpretation aligns with clinical cohort and surveillance evidence from Nicaragua and Colombia, where coinfections were detectable but did not translate into a single, predictable syndrome [3,4].

A major implication is that the term “severity” must be used with precision. In dengue, severity often refers to warning signs, plasma leakage, bleeding, shock, severe organ involvement, intensive care admission, or death. In chikungunya, the dominant burden may be functional limitation,

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persistent pain, and chronic inflammatory rheumatism. In Zika, severity is often neurologic or fetal rather than hemodynamic. When these outcomes are collapsed into a single severity category, studies may appear contradictory even when they are measuring different clinical realities. For this reason, future studies should report severity as outcome-specific endpoints rather than as a single composite label.

The DENV-CHIKV interaction illustrates this problem. Available evidence does not convincingly show that CHIKV amplifies the vascular-leak phenotype of DENV. However, coinfection may still be clinically consequential because dengue-compatible hematologic risk can coexist with chikungunya-compatible pain and disability. The contemporary outbreak evidence from Minas Gerais strengthens this practical point: DENV-CHIKV coinfection continues to appear during recent Brazilian epidemics when RT-qPCR surveillance is applied [8]. This matters at the bedside: clinicians may be reluctant to use nonsteroidal anti-inflammatory drugs when dengue has not been excluded, yet analgesic needs may be high in CHIKV-like disease. Thus, the burden of coinfection may be expressed less as excess mortality and more as diagnostic delay, therapeutic constraint, prolonged symptoms, and increased health-service use.

The DENV-ZIKV interaction raises a different set of concerns. Because both viruses are flaviviruses, immune cross-reactivity affects both pathogenesis and diagnosis. Experimental and immunologic literature supports the plausibility of antibody-dependent enhancement under certain conditions, but human epidemiologic evidence is more nuanced. The study by Pedroso et al. [16] suggests that strong multitypic DENV immunity may be associated with protection against congenital Zika syndrome, challenging any simplistic claim that prior dengue immunity necessarily worsens ZIKV outcomes. Conversely, Cardona-Ospina et al. [17] reported human immunologic evidence linking prior ZIKV infection with immune pathways associated with severe dengue, underscoring that sequential flavivirus exposures may influence later disease even when true simultaneous coinfection is absent. For pregnancy, the placental literature also supports careful separation of DENV and ZIKV mechanisms rather than treating all flavivirus exposures as equivalent [15]. Deterministic statements must be avoided, and immune history should be seen as a modifier whose direction and magnitude may vary by antibody profile, antibody class, timing, tissue compartment, and sequence of exposure.

Diagnostic validity is arguably the main methodological bottleneck in this field. Serologic cross-reactivity can generate false coinfection labels, while short molecular windows can miss true concurrent infections. This dual problem creates misclassification in both directions. Studies that lack multiplex RT-PCR, neutralization testing, or complete testing for all three viruses are limited in their ability to attribute severity to coinfection. For this reason, the highest-value future evidence will come from prospective febrile-illness cohorts that apply standardized multiplex testing early in illness and then follow patients for acute, neurologic, rheumatologic, and obstetric outcomes.

The public-health implications are substantial. Arboviral surveillance in the Americas cannot continue to treat dengue, chikungunya, and Zika as separate operational silos. The same vector ecology, urban conditions, and diagnostic infrastructure determine detection and control of all three infections. Integrated arboviral surveillance should include multiplex molecular capacity in sentinel sites, harmonized severity definitions, pregnancy-specific pathways, and linkage between clinical, laboratory, entomologic, and environmental data, including environmental suitability platforms that can support early warning for *Aedes*-borne disease risk [9]. Such integration would improve both patient care and the interpretation of outbreak signals.

This review has several limitations. First, the heterogeneity of study designs and severity definitions limited direct comparability across studies. Second, diagnostic variability, particularly the reliance on serology in some studies, may have introduced misclassification bias due to flavivirus cross-reactivity. Third, the absence of standardized multiplex testing across all included studies may have led to underestimation of true coinfection rates. Finally, as an integrative review, this study is subject to selection bias and lacks the quantitative synthesis provided by meta-analytical approaches. Nevertheless, its strengths include a clinically oriented synthesis across DENV, CHIKV, and ZIKV;

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explicit attention to diagnostic validity; and integration of epidemiologic, clinical, immunologic, and entomologic evidence.

In conclusion, DENV, CHIKV, and ZIKV coinfection in the Americas should not be framed as a uniformly synergistic or uniformly benign phenomenon. The evidence supports a more nuanced interpretation: DENV-CHIKV coinfection may increase clinical complexity and functional morbidity without consistently amplifying hemodynamic severity, while DENV-ZIKV interactions are most important for diagnostic validity, immune cross-reactivity, and neurologic or perinatal risk. Recent evidence reinforces this interpretation by showing ongoing DENV-CHIKV coinfection during contemporary Brazilian outbreaks and by strengthening the biologic rationale for sequential flavivirus immune effects. The next generation of studies should use prospective designs, early multiplex molecular confirmation, standardized severity endpoints, and explicit measurement of prior flavivirus immunity.

Author Contributions: Conceptualization, D.L.F.T.; methodology, A.C.; formal analysis, A.C.; investigation, D.L.F.T.; writing—original draft preparation, D.L.F.T.; writing—review and editing, T.J.B., N.E.P.S., S.S.V, S.K., S.S.P., T.J.F., and A.C.; supervision, A.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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