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Review

Post-Dengue Syndrome: From Immunopathogenesis to Multisystemic Clinical Sequelae

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Abstract

Dengue virus (DENV) causes the most prevalent arboviral infection worldwide. Although classically regarded as an acute illness, growing evidence describes Post-Dengue Syndrome (PDS) as a chronic entity affecting a subset of patients, with pooled estimates placing post-infectious fatigue at 20.0% (95% CI 10–36) and no standardized case definition yet available. This narrative review analyzes its pathophysiology: the cytokine storm, antibody-dependent enhancement, and NS1-triggered molecular mimicry, together with the cells that execute them—dendritic cells, mononuclear phagocytes, NK cells, platelets, and complement on the innate side, and plasmablast expansion, follicular helper T cell activation, defective regulatory control, and PD-L1/PD-1-mediated exhaustion on the adaptive side. Almost all of these immunological mechanisms have been characterized during acute infection; few studies have sampled the same patients during convalescence, and even fewer have compared those who developed persistent symptoms with those who recovered. They are therefore established features of acute dengue and, at present, hypotheses about PDS rather than demonstrated features. Genetic susceptibility is examined through polymorphisms of HLA, FcγRIIa, Toll-like receptor, and cytokine genes. Multisystemic manifestations are described—persistent fatigue, fibromyalgia-like myalgia and arthralgia, alopecia, brain fog, and mood disturbance—alongside neurological complications, categorized into direct neuroinvasion and post-infectious immune-mediated damage such as Guillain–Barré syndrome and encephalomyelitis. Recent population-based data linking dengue to acute neurological events and to later cognitive decline are examined critically, as is the unsettled question of whether post-dengue neuroinflammation amounts to neurodegeneration. Finally, the authors address the influence of age and sex and outline therapeutic and research priorities, offering an immunoclinical perspective for the multidisciplinary management of these patients.

Keywords: dengue; post-dengue syndrome; immunopathogenesis; molecular mimicry; innate immunity; NK cells; HLA; T lymphocytes; neuroinflammation; cognitive decline

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1. Introduction

Dengue virus (DENV) is an arbovirus in the family Flaviviridae that causes a clinical spectrum ranging from undifferentiated fever to severe dengue hemorrhagic fever and dengue shock syndrome [1]. This classic terminology—dengue fever, dengue hemorrhagic fever (DHF, graded I–IV), and dengue shock syndrome (DSS)—corresponds to the 1997 World Health Organization classification. In 2009, the WHO revised this scheme, replacing it with a classification based on clinical warning signs: dengue without warning signs, dengue with warning signs, and severe dengue [1]. Because the large majority of the genetic association and pathophysiology studies discussed in this review were published under, or explicitly refer to, the earlier grading system, this article retains the classic DHF/DSS nomenclature when reporting original findings, while acknowledging that current WHO guidance frames these same clinical phenotypes within the revised warning-signs classification. Over recent decades, global incidence has increased dramatically, with millions of people exposed to prolonged sequelae after overcoming the acute phase of the illness [2]. Attention has traditionally focused on acute manifestations; however, a chronic clinical entity known as Post-Dengue Syndrome (PDS) has emerged, characterized by debilitating symptoms that persist for months or years after initial recovery [3–5]. This impression has recently been reinforced by a large population-based cohort study showing that dengue survivors carry a significantly elevated risk of new-onset autoimmune, endocrine, gastrointestinal, and renal complications for up to 300 days after the acute infection, underscoring that PDS is not a marginal phenomenon but a measurable, systemic burden on convalescent patients [6]. The parallel with other post-viral syndromes is difficult to ignore: the convalescent picture after dengue overlaps substantially with the one described after SARS-CoV-2 infection, and a direct comparison of the two infections shows that both combine antibody-dependent enhancement (ADE)-prone antibody responses, endothelial injury, and a protracted inflammatory tail, while differing in tropism and in the kinetics of viral clearance [7]. The comparison with SARS-CoV-2 drawn at several points in this review derives from that analysis unless another source is given, and Section 6.5 develops it systematically alongside other post-infectious syndromes. Understanding why some patients recover fully while others develop this protracted syndrome requires an integrated view of the virus–host interaction: the immune mechanisms triggered during acute infection, the genetic background that shapes their intensity, and the resulting clinical and neurological expression. This review details the underlying immunological and genetic mechanisms, clinical symptomatology, and nervous system sequelae that define PDS, following the same logical sequence from mechanism to manifestation.

Two points should be stated at the outset, because they shape how the whole review should be read. The first is the working hypothesis that organizes it: Post-Dengue Syndrome is not a separate disease beginning where dengue ends, but the tail of a single process in patients whose immune system does not return to baseline. Acute-phase mechanisms set the intensity of the response, cellular compartments determine the conditions under which it is mounted, the adaptive system converts it into a memory repertoire that may remain cross-reactive and imperfectly regulated, and host genotype modulates the amplitude of each step. The clinical picture described in the later sections is what that process looks like when it fails to resolve.

The second point is a limitation of the evidence base, not the argument. Nearly all of the immunological data reviewed in Sections 3–5 were generated during acute infection. Very few studies have sampled the same patients during convalescence, and fewer still have compared those who developed persistent symptoms with those who recovered. The mechanisms described therefore carry two different evidential weights: they are established features of acute dengue, and they are hypotheses about Post-Dengue Syndrome. Table 1

makes this explicit, and Section 6.4 consolidates the specific gaps. Readers should not take the presence of a mechanism in the acute phase as evidence that it operates during the persistent phase, and the text signals this distinction throughout.

2. Materials and Methods

This is a narrative literature review; it was not registered as a systematic review or meta-analysis, and we did not generate a PRISMA-type flow diagram. Nonetheless, we followed a structured search strategy to identify the primary and secondary literature underlying each section.

Data sources: We used PubMed/MEDLINE and Scopus as the primary bibliographic databases, complemented by targeted searches in Google Scholar and, for regional and Spanish-language clinical reports, SciELO and LILACS. We also hand-searched the reference lists of key articles and prior reviews (snowballing) to capture additional relevant studies, including several 2024–2026 publications not yet indexed under all search terms at the time of the initial search.

Search terms: Searches combined the terms "dengue," "post-dengue syndrome," "post-dengue fatigue syndrome," "dengue immunopathogenesis," "antibody-dependent enhancement," "molecular mimicry," "NS1 protein," "blood–brain barrier," "FcγRIIa," "HLA dengue," "dengue polymorphism," "dengue neurological complications," "post-dengue cognitive decline," "dengue dementia," "follicular helper T cells," "PD-1/PD-L1 dengue," "neonatal Fc receptor," and "Toll-like receptor polymorphism dengue," combined using Boolean operators (AND/OR) and adapted to the syntax of each database.

Time frame: The search covered January 2000 to August 2026, capturing both the foundational immunogenetic literature on dengue severity (much of which was published in the 2000s and early 2010s) and the most recent evidence on post-dengue syndrome, neurological sequelae, and long-term multi-organ outcomes (2024–2026).

Selection criteria: We considered original research articles, systematic reviews, meta-analyses, and case series/case reports (the latter used sparingly, mainly to illustrate rare neurological presentations such as isolated cranial nerve palsies) published in English or Spanish. Conference abstracts without peer-reviewed full text, non-peer-reviewed preprints, and articles not available in full text were excluded. Given the narrative nature of this review, the authors selected and synthesized studies based on relevance, methodological quality, and contribution to the mechanistic and clinical narrative, rather than through a predefined systematic screening protocol.

The decision to conduct a narrative review instead of a systematic review stems primarily from the inquiry's diverse nature rather than the process's complexity. Systematic reviews usually concentrate on a specific research question with clearly defined criteria, which facilitates quantitative synthesis. In contrast, this study spans fields such as immunology and neurology, where study design, endpoints, and reporting standards vary considerably. Consequently, establishing uniform eligibility criteria across these areas is impractical.

Additionally, the absence of a validated case definition for Post-Dengue Syndrome poses a significant challenge in selecting studies that share a common outcome. To avoid redundancy, we reference relevant reviews and meta-analyses when a specific question has previously been addressed, such as those examining the pooled prevalence of post-infectious fatigue and studies on candidate genes. Looking ahead, conducting a systematic review focused on the prevalence and predictors of persistent symptoms, once a standardized case definition is developed, represents an important future research direction that aligns well with the priorities outlined in Section 1.

3. Immunological Mechanisms

To understand why PDS develops in only a subset of patients, it is first necessary to examine the immune events that unfold during the acute infection itself, since these same mechanisms set the stage for chronic disease. The immunopathogenesis of acute and chronic dengue is multifactorial. A key feature is ADE, in which non-neutralizing antibodies generated during a primary infection facilitate entry of a heterologous viral serotype into monocytes, macrophages, and dendritic cells bearing Fc gamma receptors (FcγR) [8,9]. This amplifies viral replication and triggers a massive release of soluble factors known as the "cytokine storm," involving increased interleukin-6 (IL-6), IL-8, IL-10, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α), which directly cause vascular endothelial dysfunction [10].

The ADE model does not account for one consistent observation. During acute dengue, the largest population of infected cells in the circulation is not the FcγR-bearing phagocyte but the B lymphocyte, even though FcγRIIb on B cells cannot mediate enhancement and instead drives anergy and apoptosis when engaged. This discrepancy is resolved by B cell receptor-dependent enhancement (BDE), in which DENV-reactive B cells internalize virus through their own antigen receptor rather than through an Fc receptor [11]. The mechanistic requirements have since been defined: entry depends on the specificity and affinity of the BCR for the viral envelope protein, requires proximal BCR signaling and dynamin-mediated endocytosis, involves trafficking to late endosomes, and results in productive infection of DENV-reactive B cells [12]. This has a direct implication for the present review. The memory B cells that expand during infection, discussed in Section 5.1 as the source of persistent anti-NS1 specificities, are themselves susceptible to infection through the very receptor that defines their specificity, which offers a mechanism by which the humoral memory left behind by dengue may be qualitatively altered rather than merely enlarged.

Beyond the cytokine storm, long-term symptom persistence is strongly linked to molecular mimicry. DENV non-structural protein 1 (NS1) and the structural envelope (E) and premembrane (prM) proteins exhibit substantial structural homology with human proteins [13]. Cross-reactivity may result in autoantibodies that specifically target endothelial cells, platelets, and various coagulation molecules, including plasminogen, thrombin, and platelet factor 4. This activity can lead to cellular apoptosis and disrupt hemostatic function [14,15]. The repertoire of targets has been cataloged in detail: cross-reactive antibodies recognize plasminogen, thrombin, and other coagulation factors; platelet surface proteins; and endothelial antigens, inhibiting the coagulation cascade, promoting hyperfibrinolysis, and, through anti-endothelial cell antibodies, contributing to hepatic inflammation in severe infection [16]. Two mechanisms are particularly well documented for the platelet: anti-NS1 antibodies opsonize platelets and drive their phagocytosis by macrophages [17], and the degree of platelet activation itself determines the severity of the resulting thrombocytopenia [18]. Moreover, viral antigens have been detected in brain tissue, and viral RNA has been amplified from cerebrospinal fluid in patients presenting with encephalitis or encephalopathy, so the same cross-reactive repertoire may also engage neural and glial antigens, offering a direct link between mimicry and the neurological syndromes [19]. This persistent cross-reactivity prolongs the chronic post-viral inflammatory state and underlies tissue damage [3].

PDS is a multifaceted condition that encompasses various elements of the immune response, as delineated below. Nonetheless, significant research efforts are still needed to improve our understanding and treatment of the syndrome.

4. Innate Immune Response: Target Cells and Early Effector Mechanisms

The mechanisms discussed are not just theories; they involve specific cell populations, with genetic variants affecting molecules expressed by these cells. The innate immune response governs the early hours of infection and influences the subsequent adaptive response, so it warrants a detailed description before addressing B and T lymphocytes. This section focuses on what changes may persist after the acute phase of infection has resolved.

4.1. Dendritic Cells and Mononuclear Phagocytes

Cutaneous myeloid dendritic cells (DCs) represent the initial cellular responders to dengue virus (DENV) following a mosquito bite [9,20]. The principal entry receptor for DENV is DC-SIGN (CD209), which is why polymorphisms in the gene encoding this receptor frequently appear in the literature discussed in Section 6.3.1 [21,22]. Monocytes and macrophages are the second major reservoir and the cells in which antibody-dependent enhancement operates, since their FcγR internalizes virus–antibody complexes [8,9,23]. Beyond serving as targets, these cells behave abnormally in patients: flow-cytometric analysis of monocytes and of myeloid and plasmacytoid DC from dengue patients shows increased TLR3 and TLR9 early in uncomplicated dengue but poor TLR3 and TLR9 stimulation in those with severe manifestations, together with differences in TLR2 expression and in the co-stimulatory molecules CD80 and CD86 between clinical groups [20]. The functional implication is that antigen-presentation quality is already compromised during the acute episode, precisely when the adaptive repertoire is being selected. This compartment is one of those listed in Section 6.4 as uncharacterized beyond the acute phase.

4.2. Natural Killer Cells and the NKG2D–MICB Axis

NK cells are among the first lymphocytes to respond to DENV, with early activation markers (CD69, HLA-DR, CD38, CD44) observed in patients during the initial days of illness. This early activation is linked to milder disease, indicating a protective role [24]. A detailed analysis confirmed strong NK cell activation and proliferation during acute infection, dependent on IL-18 signaling [25]. Responding cells showed a less mature phenotype with chemokine receptors indicating skin homing, with a subset detectable in the skin early in infection [25]. The kinetics of responses [24,25] in $CD56^{bright}$ and CD56dim subsets, stratified by NKG2A and CD57, are well characterized for the acute and immediate post-febrile phases.

One dimension, however, remains notably underexplored, and genetic evidence directly indicates its relevance. NKG2D (CD314) is the primary activating receptor through which natural killer (NK) cells, as well as CD8+ and γδ T cells, recognize stress-induced ligands, with MICA and MICB being the most prominent [26,27]. This axis is worth stating plainly for readers outside NK biology. MICA and MICB are not expressed on healthy cells; they appear on the surface when a cell is infected, transformed, or otherwise stressed, signaling that the cell should be eliminated. NKG2D is the receptor that reads that signal. A genetic variant affecting the ligand therefore changes how efficiently stressed cells are recognized and killed, which is why a locus of this kind emerging from an unbiased genome-wide scan of severe dengue is mechanistically informative rather than incidental. Variants of the MICB gene are among the few loci consistently associated with dengue shock syndrome according to genome-wide analyses, as discussed in Section 6.3.4. Although the ligand has been genetically implicated, researchers have infrequently assessed patients' receptor expression levels. Furthermore, the potential for soluble MICA and MICB to be shed during acute infection, thereby downregulating NKG2D and diminishing cytotoxic function—a mechanism well established in tumor immunology and in other chronic viral infections [26,27]—has not yet been investigated in dengue, particularly during convales-

cence. This represents a feasible research opportunity: the receptor can be quantified using conventional flow cytometry in conjunction with degranulation markers such as CD107a. A persistent deficit in NKG2D would provide a definitive cellular correlate for the extended post-infectious phase.

4.3. Unconventional and Innate-like Lymphocytes

Between the innate and adaptive compartments are populations that activate rapidly and without conventional peptide–MHC restriction: γδ T cells, mucosal-associated invariant T (MAIT) cells, and NKT cells. All three have been reported to be activated in acute dengue, and their dysregulation contributes to the broader picture of disturbed immune cell responses in severe disease [28]. Innate cytokine profiling in patient cohorts has placed mediators of this compartment among the markers that discriminate clinical outcome [29]. NKT cells have since been shown to promote the Th1 bias that governs long-term protective antibody dynamics after DENV infection—a finding of particular interest here, because it links an innate-like population directly to the durability and quality of humoral memory [30]. The role of CD1d in modulating NKT cell activation suggests that variations within this axis may significantly contribute to the development of post-dengue syndrome [30]. Furthermore, a similar argument has been put forth regarding the persistence of altered innate immune compartments following other acute viral infections [30].

The γδ compartment adds a further layer. Analysis of T cell receptor repertoire dynamics in dengue patients shows that severity is accompanied by distinctive usage of TRGV and TRBV segments and by elongated δ-CDR3 sequences, a pattern consistent with specialized inflammatory function rather than with conventional antigen recognition [31]. Further research is necessary to comprehend the role of these cells in the syndrome.

Investigating this subject is essential for understanding the role of these cells in dengue chronicity and potentially in sustaining the inflammatory response associated with new viral infections and their resolution.

4.4. Neutrophils and Neutrophil Extracellular Traps

Neutrophils are the most abundant circulating leukocyte and, until recently, the least examined in dengue. They are recruited early after infection, and DENV activates them to release myeloperoxidase and to form neutrophil extracellular traps (NETs); both processes have been shown to increase vascular permeability and to mediate the cardiac impairment described in severe disease. Neutrophil-derived soluble products, among them olfactomedin 4 and the soluble urokinase plasminogen activator receptor, have been proposed as biomarkers of clinical progression, and attenuating the neutrophil response has been suggested as a therapeutic avenue [32]. For a syndrome defined by persistent inflammation, this compartment is conspicuously unstudied: whether NET formation resolves with convalescence, or whether a low-grade NETotic state accompanies persistent symptoms, is unknown.

4.5. Complement, Platelets, and the Amplification of Vascular Injury

The innate contribution to dengue is not confined to cells that present antigen or kill. Circulating NS1 activates complement locally and systemically, generating anaphylatoxins and the terminal SC5b-9 complex in proportion to disease severity; these products contribute to the plasma leakage that defines severe dengue [33]. At the same time, the virus subverts the same system: flavivirus NS1 antagonizes complement component C4 and binds C4b-binding protein, attenuating activation on the surface of infected cells [34]. Complement therefore appears twice in the pathogenesis, as an effector of tissue injury and as a target of viral evasion.

Platelets, for their part, are not simply the cells whose count falls. DENV triggers assembly of NLRP3 inflammasomes in platelets, with caspase-1 activation and release of IL-1β-rich microparticles; these microparticles increase endothelial permeability in an IL-1-dependent manner, and inflammasome activation in patients correlates with clinical signs of vascular leak [35]. Read alongside the anti-platelet autoantibodies generated through molecular mimicry (Section 3), this establishes platelets as active immune effectors in dengue rather than passive casualties of the infection—a point of direct relevance to the persistent hemostatic and vascular complaints reported by some convalescent patients, and one that has not been followed beyond the acute phase.

5. Adaptive Immune Response: B- and T-Lymphocyte Dynamics from Acute to Convalescent Phase

Beyond the innate and humoral mechanisms described above, the cellular arms of adaptive immunity—B and T lymphocytes—undergo dramatic, time-dependent changes during dengue infection that are directly relevant to understanding why some patients transition into PDS while others recover without sequelae.

5.1. B-Lymphocyte Responses

During the acute febrile phase, DENV infection triggers one of the most striking plasmablast expansions described for any human viral infection: antibody-secreting plasmablasts can transiently account for up to 30–50% of circulating B lymphocytes, particularly during secondary heterotypic infection [36]. This burst is largely polyclonal and cross-reactive across serotypes, predominantly targeting the envelope (E) glycoprotein, and resolves rapidly, returning to baseline levels within about one month after discharge [36,37]. Longitudinal studies indicate that the memory B cell (MBC) compartment established during convalescence is largely distinct from, rather than directly descended from, this acute plasmablast population; MBCs preferentially target prM and non-structural proteins, including NS1, whereas plasmablasts are almost exclusively E-specific [37]. This divergence is directly relevant to PDS: because anti-NS1 memory B cell clones persist into convalescence and NS1 is the principal driver of the molecular-mimicry mechanisms described in Section 3, a sustained or dysregulated memory B cell response could plausibly help maintain production of cross-reactive autoantibodies well beyond viral clearance. However, this link has not yet been tested directly in patients with confirmed PDS [38].

Two further aspects of the B cell compartment remain poorly defined in dengue and deserve explicit mention. The first is the contribution of innate-like B cells. B-1-like and marginal-zone-like B cells are the main source of natural, polyreactive IgM in other systemic viral infections, and polyreactive IgM is precisely the isotype expected to participate in the early cross-reactive responses described above; these populations have nonetheless rarely been examined in acute or convalescent dengue, and their behavior in patients who go on to develop persistent symptoms is unknown. The second is prior exposure to other flaviviruses. In Latin America, where DENV and Zika virus circulate together, and yellow fever vaccination is widespread, the pre-existing memory pool is rarely dengue-specific: antibodies elicited by Zika virus cross-react extensively with DENV envelope and prM epitopes and can enhance DENV infection in vitro, and the converse also applies, so the individual serological history—and not merely the number of previous dengue episodes—conditions the quality of the response mounted during a new infection [39].

The help that sustains the plasmablast burst comes largely from circulating follicular helper T cells. Peripheral Tfh (pTfh) subsets expand and acquire an activated PD-1^{high} CD38+ phenotype during acute DENV infection, reaching their highest frequencies during the critical phase; activated pTfh are more abundant in secondary than in primary infection,

are more abundant in patients with more severe disease, and their frequency correlates with the magnitude of the plasmablast response [40]. Because Tfh function governs affinity maturation and the composition of the memory pool, this axis is a plausible—though so far untested—determinant of whether the convalescent repertoire remains protective or drifts toward the cross-reactive, potentially autoreactive specificities associated with persistent symptoms.

5.2. T-Lymphocyte Responses

T cell responses follow a parallel but mechanistically distinct trajectory, and given their centrality to dengue immunopathogenesis, they are considered here in more detail across five complementary lines of evidence: serotype cross-reactivity, cytotoxic function, regulatory control, checkpoint-mediated exhaustion, and the interface with innate and unconventional lymphocytes.

5.2.1. Antigen Cross-Reactivity

According to this hypothesis, secondary infection with a heterologous serotype preferentially reactivates lower-affinity, serotype-cross-reactive memory CD8+ T cells from the primary infection rather than generating an optimal, serotype-specific response; these cross-reactive cells display a skewed activation phenotype, characterized by high production of TNF-α and IFN-γ with reduced cytotoxic degranulation, and undergo substantial activation-induced apoptosis during acute illness [41]. This phenomenon was originally proposed as a contributor to the systemic vascular disturbances of severe dengue, since excessive cytokine production by aberrantly activated T cells could compound the endothelial damage attributed to NS1 and the cytokine storm described in Section 3. More recent, comprehensive epitope-mapping studies have partly revised this model: dengue-specific CD8+ T cell responses are strongly restricted by HLA class I genotype, and several of the HLA alleles associated with disease severity discussed in Section 6.2 are now understood to shape not only antibody-mediated but also cell-mediated antiviral immunity, with some cross-reactive T cell populations behaving in a protective rather than a purely pathological manner [42]. A further caveat is that this discussion is almost always framed around HLA class I restriction of CD8+ T cells, whereas class II molecules—which control the CD4+ response and are themselves associated with severity—present epitopes broadly shared with other flaviviruses, including Zika virus. In populations exposed to both viruses, the cellular memory recalled during a dengue episode need not be dengue-specific at all [39,42].

5.2.2. Cytotoxic Function and Epitope Hierarchy

The non-structural protein NS3 is the immunodominant target of the human CD8+ T cell response across multiple HLA backgrounds. Functional studies using an HLA-A11–restricted NS3 epitope showed that CD8+ (and CD4+) T cells from patients with uncomplicated dengue fever were predominantly degranulating and cytotoxic (CD107a-^{positive}), whereas T cells from patients who progressed to DHF were skewed toward cytokine production without degranulation—a functional dichotomy that links the quality, and not merely the magnitude, of the T cell response to clinical severity [43]. CD4+ T cells contribute a complementary helper function, supporting both the B cell and CD8+ T cell responses described above, but subsets also act as direct cytotoxic effectors against NS1- and NS2a-derived epitopes, adding a further, less-studied cytotoxic layer to CD4+ T cell biology in dengue [44]. This cytotoxic CD4+ compartment deserves more attention than it usually receives: DENV-specific CD4+ T cells expressing granzyme B and perforin, with a highly differentiated phenotype, have been characterized in individuals from hyperendemic areas, where they appear to be associated with protection rather than with pathology, and they

represent a functional axis that conventional CD8+-centered epitope mapping does not capture [45].

5.2.3. Regulatory T Cells

CD4+CD25+FOXP3+ regulatory T cells (Tregs), whose normal role is to dampen excessive immune activation, are themselves dysregulated in acute dengue: Treg frequency and proliferation increase during acute infection, but these cells are abnormally activated, skewed toward a Th1-like phenotype, and functionally less suppressive than Tregs from healthy donors, particularly in patients who progress to more severe disease [46]. This suggests a failure of immune self-regulation that compounds, rather than restrains, the cytokine storm described in Section 3. Regulatory control, moreover, is not exercised by FOXP3+ Tregs alone. Dendritic cells, monocytes and macrophages, NK cells, γδ T cells, and NKT cells are all engaged early in dengue and shape the magnitude and quality of the subsequent adaptive response; their dysregulation in severe disease has been documented repeatedly, and it is at this innate–adaptive interface, rather than within any single cell type, that the balance between viral control and immunopathology appears to be decided [28].

5.2.4. T Cell Exhaustion and the Acute-to-Convalescent Transition

T cells in severe dengue also display features more typical of chronic viral infections, including elevated expression of the inhibitory receptors PD-1, TIM-3, and LAG-3, consistent with an exhaustion-like phenotype that correlates with reduced cytotoxic capacity [28]. Detailed kinetic studies show that CD4+ helper and CD8+ effector T cell activation peaks around defervescence and then declines over the following one to two weeks [47], but whether this decline is complete, or whether a residual, exhausted, or persistently activated T cell population extends further into convalescence—as has been documented for weeks to months after other acute viral infections—is essentially unstudied in dengue specifically. This is a notable gap, since sustained low-grade T cell activation is one of the mechanisms proposed, albeit not yet confirmed, to underlie post-dengue fatigue syndrome [48]. Two recent lines of work provide a more concrete mechanistic basis for this checkpoint biology. Extracellular vesicles recovered from the plasma of patients with severe dengue carry PD-L1 and suppress CD4+ T cell responses through PD-L1/PD-1 engagement, which provides a circulating, cell-free route by which checkpoint signaling can be sustained systemically [49]. In parallel, work in a clinically relevant mouse model has shown that the conserved N-linked glycan at position 207 of NS1 restrains T cell-mediated clearance: virus lacking this glycan is attenuated, produces milder lymphopenia and more functional DENV-specific CD8+ T cells, and is associated with reduced PD-L1 expression on innate immune cells and fewer PD-1+ T cells, while PD-1 blockade protects animals infected with wild-type viruses [50]. Together, these findings identify the PD-L1/PD-1 axis as an active mechanism of dengue immunopathogenesis rather than a passive marker of exhaustion, and they raise the possibility—untested in humans—that the same axis contributes to the incomplete immune restoration of convalescence. The existing literature on COVID-19 presents a closely related and similarly unexamined hypothesis: neutralizing autoantibodies targeting type I and type II interferons, together with functional impairments in the signaling pathways of IFN-α and IFN-γ, correlate with compromised viral control and prolonged illness following SARS-CoV-2 infection [7]. Furthermore, the potential emergence of analogous anti-cytokine autoantibodies subsequent to dengue infection, and their possible role in contributing to disease chronicity, remains to be thoroughly investigated.

Taken together, the adaptive cellular response to DENV is intense and functionally heterogeneous at its acute peak—spanning protective cytotoxicity, dysregulated cross-reactivity, defective regulatory control, and exhaustion—but it leaves behind an altered,

imperfectly characterized memory compartment in both the B and T cell lineages. Very few studies have examined how these adaptive compartments behave beyond the first weeks of convalescence. Essentially none have compared patients who go on to develop PDS with those who recover fully—a gap summarized in Table 1, which lists the populations discussed in this and the preceding section together with the markers used to identify them and the state of the evidence in each phase, and one that reinforces the mechanistic research priorities.

Table 1. Immune populations implicated in dengue immunopathogenesis.

Compartment/Population	Markers Commonly Used	Acute Phase	Convalescence and PDS
Myeloid and plasmacytoid DC, monocytes	Myeloid CD11c, CD135, CD1b/c, TLR1/2/3/4/5/6. Plasmacytoid CD123, CD303/304 and TLR7/9. HLA-DR, CD80/CD86 in both.	Primary targets: ADE via FcγR; altered TLR expression and co-stimulation [20]	Not characterized
NK cells	CD56, CD16, CD69, CD38, NKG2A, CD57, NKG2D (CD314), CD107a	Early activation associated with mild disease; IL-18-driven proliferation [25]	Not characterized in convalescence; NKG2D–MICB axis untested in patients
γδ T, MAIT and NKT cells	Vδ2 TCR, CD161, Vα7.2, CD1d multimers	Activation reported in small cohorts [29–31]	Not characterized
Plasmablasts	CD19, $CD27^{hi}$, $CD38^{hi}$	Expansion up to 30–50% of circulating B cells, mainly E-specific [36]	Return to baseline within about one month; link to autoantibody persistence untested
Memory B cells	CD19/CD20, CD27, IgD, NS1 and prM specificity	Distinct from the plasmablast pool; prM- and NS1-directed	Persist; contribution to cross-reactive autoantibodies hypothesized, not demonstrated
Peripheral follicular helper T cells	CD4, CXCR5, $PD\text{-}1^{high}$, CD38	Expanded and activated; correlate with plasmablasts and with severity [40]	Not characterized
CD8+ effector T cells	CD3, CD8, CD69, CD137, CD107a, granzyme B, IFN-γ	NS3-dominated response; functional quality tracks clinical severity [43]	Activation declines after defervescence; later kinetics unknown
Cytotoxic CD4+ T cells	CD3, CD4, CD107a, granzyme B, perforin	Associated with protection in hyperendemic settings	Not characterized
Regulatory T cells	CD4, $CD25^{high}$, $CD127^{low}$, FOXP3	Expanded but functionally impaired and Th1-skewed [46]	Not characterized
CD4+ helper subsets (Th1, Th2, Th17)	CD4, IFN-γ (Th1), IL-4 (Th2), IL-17 (Th17)	Th1 bias promoted by NKT cells and linked to protective antibody dynamics; Th2 and Th17 skewing reported in severe disease [30]	Not characterized
Checkpoint/exhaustion axis	PD-1, TIM-3, LAG-3, PD-L1 (including on extracellular vesicles)	Elevated in severe disease; PD-L1/PD-1 drives premature T cell apoptosis [49,50]	Not characterized in convalescence; proposed contributor to chronicity, untested in humans
Platelets and complement	CD41, CD62P, NLRP3/IL-1β; C3a, C5a, SC5b-9	Inflammasome activation, IL-1β microparticles, NS1-driven complement activation [35]	Not characterized in convalescence

6. Genetic Susceptibility: FcγR and HLA

The intensity of the immune events described above—the cytokine storm, ADE, and molecular mimicry—varies across individuals and is substantially shaped by host genetics, which helps explain why only a fraction of infected persons progress to severe acute disease or PDS. Host genetics strongly determines the degree of dengue-related damage and its long-term sequelae [51]. Polymorphisms in the gene encoding the FcγRIIa receptor (also known as CD32) play a critical role in modulating the host immune response, determining susceptibility to severe forms of the disease and to the development of chronic sequelae in Post-Dengue Syndrome [3,51].

6.1. FcγR

FcγRIIa is an activating receptor present on the surface of phagocytic cells such as monocytes, macrophages, and dendritic cells, which transduces signals through an immunoreceptor tyrosine-based activation motif (ITAM) [23]. This receptor mediates ADE by allowing binding and internalization of complexes formed by dengue virus and non-neutralizing antibodies. By facilitating viral entry into these target cells, it increases viral replication and infection severity [8].

FcγRIIa is not the only receptor that determines the fate of IgG–virus complexes. The neonatal Fc receptor (FcRn), classically described as the receptor that rescues IgG and albumin from degradation and extends their half-life several-fold, has emerged as an entry route exploited by structurally unrelated viruses, including echoviruses, astroviruses and—as shown by genome-wide CRISPR screening—the whole of the *Arteriviridae* family [52,53]. Two aspects of that work bear directly on dengue. The first is a negative result that should be stated plainly: in the same screening panel, yellow fever virus, a flavivirus, infected cells normally in the absence of FcRn, so there is no basis for proposing FcRn as an entry receptor for DENV, and none is proposed here.

The second is a corollary the authors themselves emphasize, and it is the one relevant to this review. Because FcRn continuously shuttles IgG and albumin between the cell surface and a non-degradative endosomal compartment, a virus that engages it in endothelial cells could be stored intracellularly alongside its physiological cargo and released slowly back into the circulation, constituting a semi-latent reservoir; conversely, antagonism of FcRn markedly shortens the half-life of circulating IgG and albumin. Persistence in the endothelium and disruption of IgG homeostasis relate to PDS, which has clinical correlates but lacks an established mechanism, with the endothelium most consistently injured by DENV. Neither possibility has been examined in dengue, and both are testable.

The clinical impact of this receptor is shaped by an important functional polymorphism at position 131 (nucleotide variation −393 A/G), which results in expression of either histidine (H) or arginine (R) [51]. The two variants generate markedly different phenotypes:

- Homozygous histidine genotype (HH131): This is a risk factor predisposing to susceptibility to dengue hemorrhagic fever (DHF). Individuals with this genotype show greater affinity for immunoglobulin IgG2, which triggers excessive monocyte activation and uncontrolled release of inflammatory mediators during dengue antigen clearance. Patients carrying the HH131 genotype also have a significantly higher probability of experiencing persistent symptoms associated with Post-Dengue Syndrome, even up to two years after infection [3,51].
- Homozygous arginine genotype (RR or Arg/Arg 131): in contrast, the arginine variant at this position acts as a protective factor against the more severe forms of the disease, reducing the risk of DHF and dengue shock syndrome (DSS), as observed in Vietnamese and Cuban population studies [54,55].

In sum, FcγRIIa polymorphisms directly modulate the immune system's capacity to process virus–antibody complexes, either conditioning a state of sustained hyperinflammation and damage (histidine variant) or conferring resistance to shock and plasma leakage (arginine variant).

6.2. HLA System

Several studies have confirmed the role of human leukocyte antigen (HLA) alleles in both susceptibility and protection against severe and prolonged disease [56]. Alleles such as HLA-A*24, HLA-A*0203, and DRB1*11 predispose individuals to greater severity, whereas HLA-A*33, DRB1*03, and DRB1*09 appear protective [56,57]. A recent multi-population meta-analysis corroborates these associations while underscoring substantial regional heterogeneity: HLA-A*02 and HLA-A*03 increase susceptibility to dengue fever and dengue hemorrhagic fever, respectively, predominantly in Southeast Asian cohorts, whereas HLA-A*33 and HLA-B*44 exert a protective effect whose magnitude varies markedly by population, a finding with direct implications for genetic risk stratification as dengue's geographic range expands under climate change [58]. These associations should be read with two caveats. Several of the alleles listed above are common, "public" alleles in the populations studied, so their apparent association with severity may partly reflect background allele frequency rather than a specific functional effect. Because class I and class II loci are inherited in linkage disequilibrium, the true unit of association is more likely the haplotype than any single allele [57,58]. Analyses reporting class I associations in isolation may therefore be capturing the effect of a linked class II allele. This distinction matters in settings where the same class II molecules present epitopes shared with other co-circulating flaviviruses [39].

6.3. Other Genetic Factors

Polymorphisms in the DC-SIGN gene (rs4804803 promoter), in NK-associated molecules (MICB), and in key cytokines such as TNF-α (−308A allele) also stand out, shaping cellular control and promoting pathogenic responses [59–61]. A broader case–control and meta-analytic evaluation of candidate genes in a pediatric cohort likewise confirms that this genetic layer contributes measurably to dengue severity in children specifically, reinforcing the relevance of these polymorphisms across age groups [62]. These are detailed below.

6.3.1. Viral Entry and Pathogen Recognition Receptors

DC-SIGN (CD209): This receptor is essential for viral entry into myeloid dendritic cells, and the widely studied rs4804803 (−336 A/G) promoter polymorphism significantly influences disease severity [21,22]. Notably, its effect depends strongly on ethnic background. In Asian populations, the G allele is associated with higher receptor expression, increased production of cytokines (such as TNF-α, IL-12, and IP-10), and a significant increase in DHF risk. In South American populations, however, this same G allele acts as a protective factor against severe dengue [21,22,59].

CLEC5A: A receptor expressed on monocytes and macrophages. The TT genotype of the rs1285933 polymorphism has been strongly associated with dengue severity. Patients with this genotype secrete significantly higher levels of TNF during the critical phase of infection, worsening vascular permeability [63].

MBL2 (mannose-binding lectin 2): variations in this gene, which encodes a key molecule in pathogen recognition and complement activation, have been associated with an increased risk of thrombocytopenia and DHF [64].

Toll-like receptors (TLR): The TLR family sits upstream of most of the responses described above. A recent systematic review of eight case–control studies from India,

Mexico, Colombia, and Indonesia, comprising 2525 individuals, found that polymorphisms in TLR3, TLR4, TLR7, TLR8, and TLR9 are associated with susceptibility to dengue, and that all of these except TLR4 and TLR9 also correlate with severity or with specific clinical outcomes [65]. The involvement of TLR4 is mechanistically coherent with the preceding sections, since NS1 itself activates immune cells through TLR4, whereas the endosomal receptors TLR3, TLR7, TLR8, and TLR9 act as sensors of viral nucleic acid. Two caveats accompany these findings: the direction of effect differs between populations, with one TLR3 variant carrying risk through one allele in a Colombian cohort and through the opposite allele in an Indian one, and no individual association has yet been replicated consistently enough to support clinical risk stratification.

One locus in this family deserves particular attention here. TLR3 is expressed in astrocytes, microglia, and T cells, and its functional L412F variant, which impairs dsRNA sensing and reduces type I interferon production, has been examined specifically in patients with dengue encephalitis [66]. The same variant has been implicated in Japanese encephalitis and tick-borne encephalitis, suggesting a susceptibility pathway shared across neurotropic flaviviruses rather than a dengue-specific effect. This makes TLR3 a plausible genetic link between innate nucleic acid sensing and the neurological syndromes discussed in Section 8, and one of the few points where the genetic and neurological studies on dengue converge.

6.3.2. Cytokine and Chemokine Gene Polymorphisms

The development of the "cytokine storm" is also genetically predisposed:

TNF-α: The polymorphism at position −308A promotes high production of this vasoactive cytokine and represents an important risk factor for severity and hemorrhagic manifestations in American and Latin American patients. In contrast, the −238A allele has demonstrated a protective effect [61,67].

IL-10 and TGF-β1: The ACC/ATA haplotype in the IL-10 promoter (positions −1082/−819/−592) is a significant risk factor for DHF and favors ADE [68]. Likewise, the −509 CC genotype of the TGF-β1 gene is associated with greater susceptibility to dengue hemorrhagic fever, a risk that increases when combined with the +49G allele of the CTLA-4 gene [51,69].

JAK1: polymorphisms in this gene (TT genotypes in introns 1 and 3, and GG in intron 2), which is crucial for the interferon signaling pathway, are associated with the development of DHF [70].

Other variants: Beyond the loci detailed above, candidate-gene studies have reported associations with interleukin genes (IL-1β, IL-6, IL-8/CXCL8), chemokines such as CCL2/MCP-1, IFN-γ (+874 A/T), and genes involved in complement activation and endothelial function. The catalogs compiled in recent reviews are considerably longer than can be usefully summarized here, and the recurring limitation is not a lack of candidate loci but limited replication across ethnically distinct cohorts [51,57,60].

6.3.3. Hemostasis and Endothelial Dysfunction Markers

Human Platelet Antigens (HPA): Variations in the HPA promoter region influence autoantibody-induced cross-reactive thrombocytopenia. The HPA 1a/1a and HPA 2a/2b genotypes are more prevalent in DHF patients, whereas the HPA 1b genotype is strongly associated with dengue shock syndrome (DSS) [51,71].

6.3.4. Other Regulatory Factors Identified by GWAS

Vitamin D Receptor (VDR): Vitamin D regulates immune interactions and can induce T-cell apoptosis after infection. The C allele at position −352 of the VDR promoter (associated with absence of the TaqI restriction site) confers clinical resistance to severe DHF [54].

TAP proteins (Transporter associated with Antigen Processing): polymorphisms in the TAP1 gene (heterozygous at position 333, Ile/Val), which influence processing of viral peptides for presentation by MHC class I, increase the risk of DHF [9,71].

MICB and PLCE1: variants in the MICB gene (associated with Natural Killer and T-cell activation) and in the PLCE1 gene (related to vascular endothelium), specifically the rs3132468 and rs3740360 genotypes, are directly associated with genetic susceptibility to dengue shock syndrome in children [60,72].

6.4. The Convalescence Gap

The convalescent gap presents significant challenges, highlighting the importance of understanding this phenomenon to support effective recovery. Sections 3–6 describe various mechanisms; however, a notable research gap remains regarding the convalescent and persistent phases across many compartments. For example, it remains unclear whether dendritic cells regain function after acute illness or whether alterations in lymphocyte characteristics persist into convalescence. Additionally, several questions remain unresolved, such as whether regulatory T cell impairment is reversible, whether the PD-1/PD-L1 axis contributes to the condition's chronicity, and whether specific cellular activations persist after viral clearance.

Two principal implications arise from the discussion: first, a mechanism present during the acute infection phase does not necessarily confirm its involvement in the persistent phase of the illness. Second, robust study designs are needed that prioritize paired sampling of the same patients during acute illness and at three-, six-, and twelve-month post-infection time points, with stratification by persistent symptoms. Although most assays required for such studies are routine, challenges persist because a clear case definition is needed to accurately stratify outcomes.

Sections 3–6 describe a single process. ADE and NS1 determine the intensity of the acute immune response, while dendritic cells, phagocytes, NK and NKT cells, platelets, and complement factors set the conditions for its development. The adaptive immune system then converts this response into memory, which may be cross-reactive and imperfectly regulated. The host's genetics also affect the strength of each stage.

Figure 1 provides a temporal overview of the key components of this review—namely, the acute phase, convalescence, and persistent disease—and links each mechanistic phase to its clinical manifestations.

6.5. Post-Dengue Syndrome in the Context of Other Post-Infectious Syndromes

By positioning these mechanisms alongside other post-infectious syndromes, one can elucidate which are likely specific to dengue and which conform to a broader post-viral pattern. Persistent fatigue after acute infection is not exclusive to dengue; it has also been documented after infections caused by Q fever, Epstein–Barr virus, Ebola virus, SARS-CoV-2, and chikungunya. The reported prevalence of persistent fatigue varies from 10% to 50%, depending on the specific pathogen and the assessment tools used [73–75]. The pooled figure for post-infectious fatigue after dengue, 20.0% (95% CI 10–36), falls within that range rather than above it, which argues against a mechanism unique to this virus and favors a final common pathway reached from several directions.

Three features recur across these syndromes. Persistent immune activation with a raised inflammatory tone during convalescence is common to post-COVID condition, post-Epstein–Barr fatigue, and the picture described here. Autoreactivity arising from cross-reactive antibody or T cell responses has been reported in each, although the target repertoires differ. Endothelial and microvascular dysfunction persisting beyond viral clearance has been described after SARS-CoV-2 and is mechanistically plausible after

dengue given the severity of the acute endothelial insult. A female predominance in the fatigue-predominant phenotype is also shared, and in dengue it is now supported by a pooled odds ratio rather than by individual series [73–75].

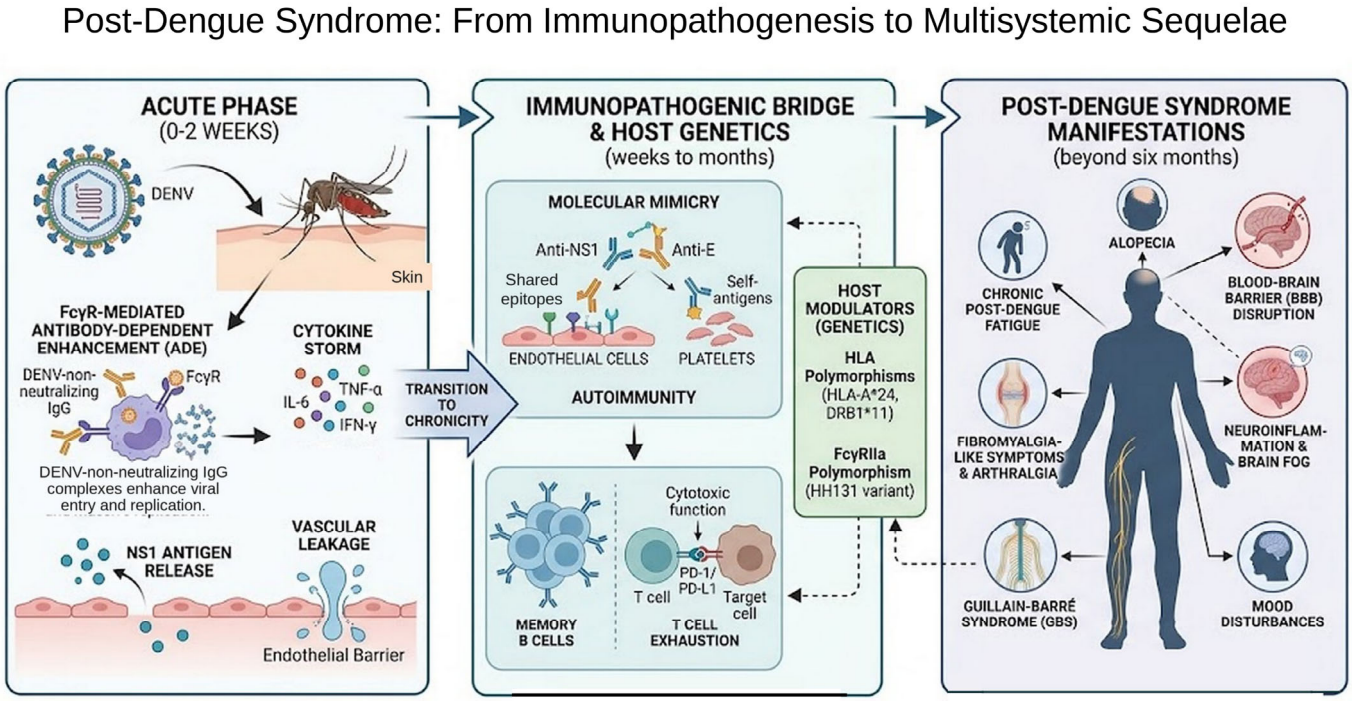


Figure 1. Integrated model of Post-Dengue Syndrome (PDS) pathogenesis, from acute infection to persistent disease. Left panel, acute phase (0–2 weeks): following the mosquito bite, non-neutralizing immunoglobulin G (IgG) from a previous heterotypic infection binds dengue virus (DENV) and promotes antibody-dependent enhancement (ADE) through the Fc gamma receptor (FcγR) in monocytes and macrophages, amplifying replication; the resulting cytokine storm—interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ)—together with the release of circulating non-structural protein 1 (NS1) antigen, disrupts the endothelial barrier and produces vascular leakage. Center panel, immunopathogenic bridge (weeks to months): antibodies directed against NS1 (anti-NS1) and against the viral envelope protein (anti-E) recognize epitopes shared with host structures, generating autoreactivity against endothelial cells and platelets; in parallel, memory B cells persist, and T cells acquire an exhausted phenotype in which engagement of programmed cell death protein 1 (PD-1) by its ligand (PD-L1) limits cytotoxic function. Host modulators—human leukocyte antigen (HLA) polymorphisms (HLA-A*24, HLA-DRB1*11) and the histidine/histidine variant at position 131 of the Fc gamma receptor IIa (FcγRIIa HH131)—act on the amplitude of these events rather than on any single one of them. Right panel, Post-Dengue Syndrome (beyond six months): the clinical expression of the process, comprising chronic fatigue, fibromyalgia-like symptoms and arthralgia, alopecia, mood disturbance, blood–brain barrier (BBB) disruption with neuroinflammation and brain fog, and immune-mediated neurological complications such as Guillain–Barré syndrome (GBS). Solid arrows denote the temporal progression and the mechanisms established in patients; dashed arrows denote proposed relationships inferred from acute-phase data but not demonstrated during convalescence.

Dengue appears to differ in the specificity of the molecular mimicry involved. NS1 has no counterpart in Epstein–Barr virus or SARS-CoV-2, and the cross-reactive repertoire it generates against plasminogen, thrombin, platelet surface proteins, and endothelial antigens is particular to flavivirus infection [76]. Dengue's serotype structure adds a second distinctive element, since antibody-dependent enhancement during heterologous secondary infection has no direct analog in the other syndromes [7,76]. Epstein–Barr virus, by contrast, is characterized by latency and reactivation, whereas dengue is not. However, in vitro studies

suggest a possible correlation between both viruses [77]. The practical implication is that the fatigue-predominant phenotype may be approachable with the tools being developed for post-viral syndromes generally. In contrast, the autoantibody-mediated and neurological manifestations are more likely to require dengue-specific investigation [78–81].

6.6. Antibody Fucosylation: A Host-Determined Modification of the Antibody Response

A determinant of severity that is neither genetic nor cellular but structural deserves mention alongside the polymorphisms discussed above. The Fc glycan of IgG1 modulates affinity for FcγRIIIa, and IgG1 lacking core fucose binds this receptor with markedly higher avidity. In secondary dengue, the proportion of afucosylated anti-DENV IgG1 predicts progression to severe disease and thrombocytopenia [82]. The same feature operates in early life: the fucosylation state of maternally transferred anti-dengue IgG predicts infants' susceptibility to symptomatic dengue [83]. This adds a post-translational layer to the ADE argument developed in Section 3—what matters is not only how much cross-reactive IgG persists after infection, but how it is glycosylated—and whether an afucosylation signature persists into convalescence, or tracks with prolonged symptoms, has not been investigated.

7. Symptomatology and Post-Dengue Fatigue Syndrome

Having outlined the molecular and genetic machinery that drives PDS, we now turn to how these mechanisms translate into the clinical picture seen at the bedside. The clinical manifestations of PDS encompass physical, neurological, psychiatric, and autonomic disturbances. The principal symptom is profound fatigue, also described as post-infectious fatigue, present in up to 25% of hospitalized adults, which differs from ordinary tiredness because of its incapacitating impact on everyday activities [84,85]. Other reported symptoms include headache, persistent retro-orbital pain, intense myalgia, arthralgia, memory loss, concentration difficulties, and sleep disturbances (depression and anxiety). Statistically significant predictors of this syndrome include female sex, older age, initial severe chills, and absence of the typical acute skin rash [84–86]. Researchers have tested the autoimmune dimension of this convalescent phase at the population level, with an instructive result. In a Taiwanese cohort of 63,814 laboratory-confirmed dengue patients matched to 255,256 controls, dengue was associated with an increased short-term risk of autoimmune encephalomyelitis but not with the other autoimmune diseases examined, contrary to earlier reports [87]. The distinction matters for how PDS is framed: the evidence supports discrete, immune-mediated neurological complications rather than a generalized predisposition to autoimmunity, and the persistent systemic symptoms described in this section should not be equated with the onset of classical autoimmune disease.

There are significant differences in the development and severity of post-dengue syndrome according to sex, with women showing greater vulnerability and a higher risk of these chronic sequelae [48].

- Greater prevalence and severity of fatigue: Female sex is an independent risk factor and a strong predictor for the development of post-infectious fatigue syndrome after dengue (pooled OR 1.65, 95% CI 1.27–2.14) [86,88,89]. Several studies have shown that women are significantly more likely to meet clinical criteria for fatigue and report much higher mean exhaustion scores compared with men [86,87].
- Rheumatologic complications and physical limitations: Joint and functional sequelae also disproportionately affect women. After the acute phase of illness, women report greater limitation, stiffness, and pain when performing everyday activities such as walking, standing, lying down, dressing, or climbing stairs. Similarly, women have a significantly higher incidence of persistent post-dengue joint inflammation and pain [90]. Persistent post-dengue arthropathy has been attributed to autoantibody-

mediated mechanisms rather than to ongoing viral replication: cross-reactive antibodies against endothelial and platelet antigens, and circulating immune complexes, have been detected months after viral clearance in patients with prolonged symptoms, which would also be consistent with the female predominance shared with classical autoimmune rheumatic disease [3,91].

Proposed mechanisms. The scientific literature attributes this greater predisposition of women to persistent symptoms to a combination of the following factors [86,88]:

- Biological and host factors: differences in genetic makeup, reproductive function, and hormonal imbalances are thought to play an important role in this vulnerability.
- Psychosocial and behavioral factors: differences in psychosomatic stress management may also influence predisposition to fatigue.
- Under-reporting in men: some authors note that part of the statistical gap between sexes may stem from men being more reluctant to report symptoms owing to cultural or gender norms in certain societies.

8. Neurological Sequelae and Nervous System Involvement

The nervous system warrants special attention due to severe complications from PDS. Recent studies confirm that neurological and psychiatric disorders are significant, yet likely under-recognized, consequences of dengue infection, occurring more frequently than previously thought [78–81,90,91]. The incidence of nervous system complications from dengue ranges between 0.5% and 20% of cases [88,92–94]. This range is wide because published series differ in case ascertainment (hospital-based versus population-based), whether they count encephalopathy of metabolic origin as a neurological complication, and the diagnostic criteria applied, so the figures are not directly comparable across studies. Neurotropism and immune-mediated damage from DENV occur through three main mechanisms, leading to different clinical syndromes [93–95]. Because these conditions differ fundamentally in timing and mechanism, this section is organized along the temporal axis rather than by syndrome. Section 8.1 covers acute neurological complications, which arise during or immediately after the febrile illness and include direct neuroinvasion and systemic and metabolic encephalopathy; Section 8.2 covers post-infectious immune-mediated complications, which appear weeks to months into convalescence through cross-reactive autoimmune mechanisms. Section 8.3 covers persistent neurological and cognitive sequelae, which are the only category that falls within Post-Dengue Syndrome as defined in this review. Evidence from one category should not be read as evidence for another, and the distinction is maintained throughout. Figure 2 sets out the three windows side by side, with the mechanism operating in each and the host factors that modulate all of them. The scale of the acute problem has recently been quantified. In a population-based cohort of 65,207 adults with confirmed dengue in Singapore, compared with more than 1.6 million uninfected individuals, the odds of a new neurological event within 30 days of infection were markedly elevated (adjusted odds ratio 9.69), with memory loss and movement disorders among the specific outcomes; the absolute excess burden was nevertheless small, since fewer than 1% of infected patients experienced such an event. Keep both figures in mind: dengue substantially increases relative risk while remaining neurologically uneventful for most patients [19]. The study window should be noted, because it determines what the finding can be used for. Events captured within 30 days of infection fall inside or immediately after the acute illness and are not, on that evidence alone, manifestations of Post-Dengue Syndrome. They belong to Section 8.1 below. Whether the same patients go on to develop persistent deficits is a separate question this design cannot answer, and Section 8.3 addresses it.

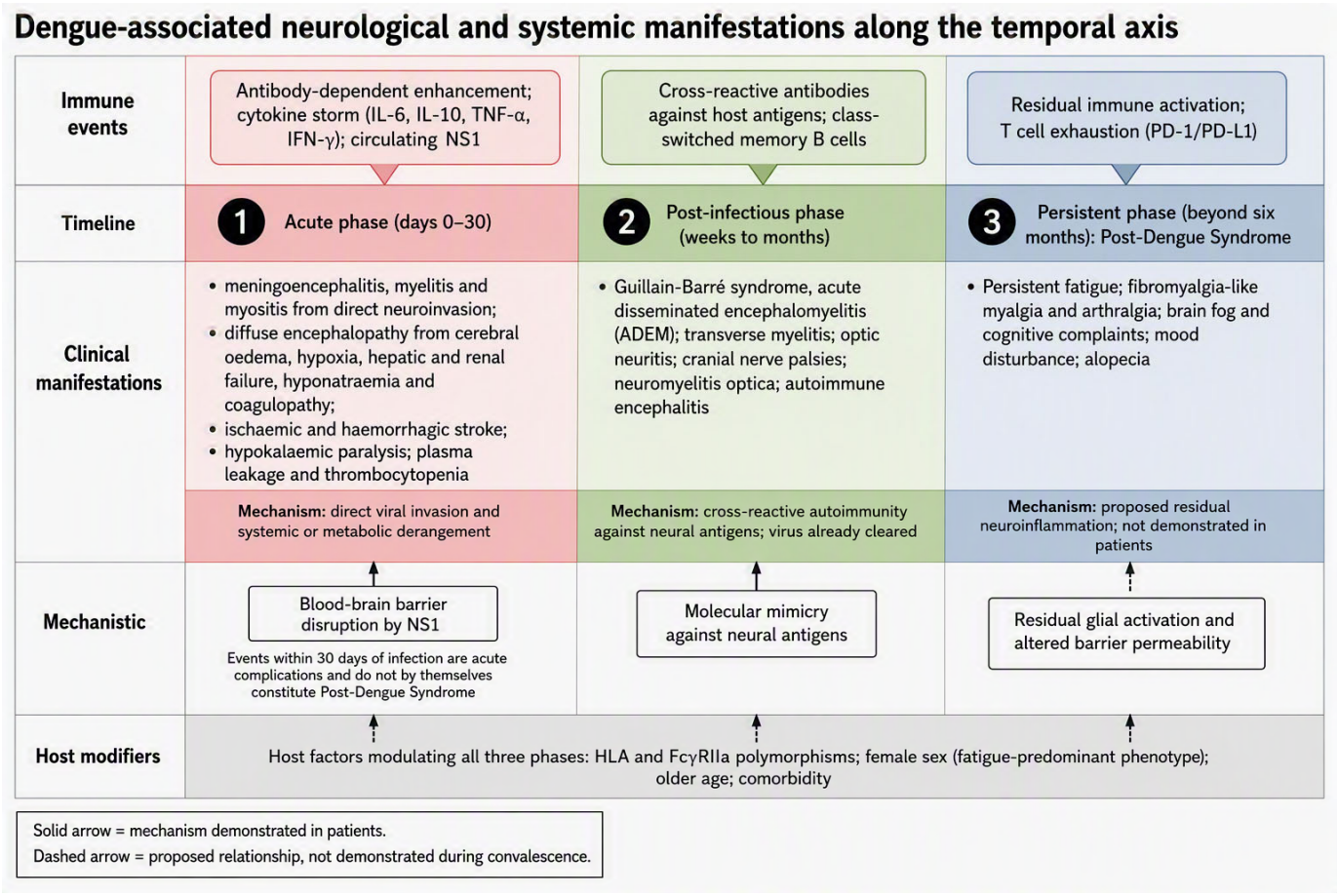


Figure 2. Illustrates the neurological and systemic manifestations associated with dengue fever along a temporal axis. The acute phase, spanning days 0 to 30, encompasses direct neuroinvasion as well as systemic or metabolic complications. The post-infectious phase, which extends from weeks to months, includes immune-mediated syndromes that emerge after viral clearance and are attributed to cross-reactive autoimmunity. The persistent phase, observed beyond six months, is characterized by fatigue-predominant and cognitive manifestations collectively referred to as Post-Dengue Syndrome, as outlined in this review. Neurological events documented within 30 days of infection, including those noted in population-based cohorts, fall within the acute phase and do not, in isolation, constitute Post-Dengue Syndrome. Host factors influence all three phases of the disease, not just a single phase. Solid arrows illustrate mechanisms established in patient populations, whereas dashed arrows represent proposed relationships derived from acute-phase data that have yet to be validated during convalescence. The Figure was created using Copilot AI (https://copilot.cloud.microsoft).

8.1. Acute Neurological Complications: Direct Neuroinvasion and Systemic Mechanisms

Direct neuroinvasion: Direct passage of the virus across the blood–brain barrier, or its transport via infected monocytes, induces meningoencephalitis, myelitis, and myositis [96–98]. Viral invasion promotes hyperintensities on magnetic resonance imaging in the thalamus, basal ganglia, and cerebellum [98]. Dengue virus non-structural protein 1 (NS1) profoundly and negatively affects the blood–brain barrier (BBB) through direct structural and indirect immune-mediated mechanisms, leading to vascular hyperpermeability and facilitating neuroinflammation. The principal mechanisms through which NS1 disrupts this barrier are:

- Cytokine storm and immune activation: NS1 acts as a potent immunological trigger by binding TLR4 on monocytes, macrophages, and endothelial cells. This interaction, together with activation of NK cells and T lymphocytes, provokes a massive release of pro-inflammatory cytokines such as IFN-γ, TNF-α, and interleukins IL-6, IL-8,

and IL-12. High circulating concentrations of these cytokines directly damage blood–brain barrier integrity, allowing abnormal passage of immune mediators into brain tissue [99–101].

- Destruction of the endothelial glycocalyx and tight junctions: NS1 stimulates destructive enzymes such as heparanase, cathepsin L, and sialidase. These enzymes degrade sialic acid and destroy the endothelial glycocalyx (the protective layer lining blood vessels), producing severe endothelial dysfunction and consequent hyperpermeability [102]. NS1 additionally promotes expression of matrix metalloproteinases (such as MMP-9), which degrade critical structural proteins such as β-catenin and zonula occludens-1 (ZO-1). Reducing these proteins disrupts the tight junctions that normally hold BBB endothelial cells together [100,103–105].
- Autoimmune damage (molecular mimicry) and apoptosis: Due to the phenomenon of molecular mimicry, the patient's immune system produces anti-NS1 antibodies that exhibit cross-reactivity with the patient's own endothelial cells. These antibodies interact with the endothelium, causing cellular stress and triggering apoptosis through nitric oxide production. This endothelial cell death and dysfunction further undermine vascular integrity [13,14,103–106].
- During the acute phase, NS1-mediated disruption of the blood–brain barrier allows dengue virus and inflammatory mediators to enter the central nervous system, which may lead to encephalitis and meningoencephalitis [107,108]. Whether this process continues beyond viral clearance remains unclear. Persistence of NS1 antigen or of NS1-dependent barrier injury during convalescence has not been demonstrated in patients, and the wording used here is deliberately restricted to the acute phase for that reason. What remains plausible, though untested, is that the downstream consequences of acute barrier injury (glial activation, local cytokine production and altered barrier permeability) outlast the antigen that initiated them, and that this residual state contributes to the long-term neuropsychiatric and cognitive complaints reported in Post-Dengue Syndrome. That hypothesis requires longitudinal studies with paired acute and convalescent sampling before it can be treated as a mechanism rather than an inference. The sex differences in neurological manifestations are set out below. They are retained at this point because they apply across all three temporal categories of this section rather than to any one of them, and because the contrast between the male predominance of the acute and post-infectious syndromes and the female predominance of the fatigue-predominant phenotype is itself informative; the broader discussion of sex as a determinant of Post-Dengue Syndrome is given in Section 7. The main sex-based differences in neurological manifestations are as follows:
- Neurological complications in general: Clinical studies indicate a male predominance in dengue-related neurological conditions, with men outnumbering women by a ratio of 1.7 to 1 [97], representing over 61% or 69% of affected patients in some reports [109].
- Transverse myelitis: A systematic review found that cases of this post-infectious inflammatory and demyelinating spinal cord condition were more common in men than women, at a ratio of 1.5 to 1 [98].
- Encephalitis: in prospective studies of large populations with dengue-related encephalitis, the proportion of affected men was 58% [101].
- Cranial nerve palsies: in complications such as isolated abducens nerve (sixth cranial nerve) palsy, only sporadic cases have been reported [88].
- Movement disorders: Emerging case reports and a recent review highlight dystonia, parkinsonism, chorea, tics, and ataxia as post-infectious complications of dengue encephalitis, expanding the recognized neurological manifestations beyond classical syndromes [110]. Dengue-associated autoimmune encephalitis can lead to dramatic

cases, such as a dystonic storm in an adolescent, highlighting that post-infectious autoimmunity against neural antigens can cause hyperkinetic movement disorders, not just the typical demyelinating syndromes [111].

- Post-dengue fatigue syndrome is the only neuro-systemic condition after infection in which women show a significantly higher risk [48,86].
- Systemic and metabolic complications: these give rise to diffuse encephalopathy resulting from a combination of cerebral edema, hypoxia, organ failure (hepatic and renal), hyponatremia, and coagulopathy (hemorrhage and ischemic or hemorrhagic stroke). Another crucial systemic manifestation is hypokalemic paralysis, an acute neuromuscular disorder secondary to intracellular potassium shift or transient renal tubular acidosis [112].

8.2. Post-Infectious Immune-Mediated Complications

These occur weeks to months into the convalescent phase, after the virus has been cleared, due to cross-reactive autoimmune reactions arising from molecular mimicry against neural antigens. Clinically, they include Guillain–Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), optic neuritis, cranial nerve palsies (oculomotor, abducens, facial), transverse myelitis and neuromyelitis optica [95,111,113]. They are separated here from the acute complications of Section 8.1 because the interval between the febrile illness and their onset provides evidence for an immune-mediated rather than a directly infectious mechanism, and because their management differs accordingly. They are also distinct from the persistent sequelae: these are discrete, self-limited neurological events with a defined onset, not a protracted symptomatic state.

8.3. Persistent Neurological Sequelae: Neuroinflammation, Cognitive Symptoms, and the Question of Neurodegeneration

The mechanisms mentioned—barrier disruption, cytokine-driven neuroinflammation, and cross-reactive autoimmunity—pose an unresolved question: does the neuroinflammatory state resolve with recovery, or does it contribute to progressive cognitive decline? A systematic review of five population-based studies involving around 200,000 participants from Taiwan, Brazil, and France found short-term cognitive impairment—such as confusion and memory loss—in some dengue patients. There was also a potential link to longer-term dementia, including Alzheimer's and vascular dementia, particularly in older adults. However, the authors stressed that the evidence is insufficient to establish a conclusive link [114,115].

The most careful attempt to test that link argues for caution. A Taiwanese cohort of 37,928 laboratory-confirmed dengue patients aged 45 years or older, matched to 151,712 uninfected individuals, found only a slight increase in the incidence of dementia. The corresponding E-values were small enough that modest unmeasured confounding—differences in comorbidity, health-seeking behavior, or surveillance intensity—could account for the association entirely [116]. Post-dengue cognitive complaints are real and often categorized as brain fog, similar to other post-viral syndromes. However, their long-term trajectory and potential link to neurodegeneration remain unclear. Distinguishing neuroinflammation from neurodegeneration necessitates prospective cohorts with baseline and serial cognitive testing, neuroimaging, and biomarkers, rather than relying on current administrative database studies.

9. Differences by Age Group

Neurological and systemic manifestations of PDS vary by age, influencing both likelihood and specific phenotypes. In pediatric and adolescent patients, dengue encephalopathy and acute symptomatic seizures are notably more common [98–100]. Greater severity of

primary capillary damage and differences in microvascular redistribution volume make infants especially vulnerable to ischemic or shock events [117]. In contrast, young or older adults show a greater predisposition to post-infectious demyelinating diseases (GBS, ADEM) and Post-Dengue Fatigue Syndrome, particularly in relation to comorbidities and baseline immune status [28,87,90]. Age, moreover, does not act on the nervous system alone; it acts on the immune system that responds to the virus. The pediatric immune system is highly plastic—broad naive repertoires, active thymic output, and a memory compartment still being assembled—which favors both vigorous, at times excessive, acute responses and a considerable capacity for functional recovery afterward. At the other extreme, immunosenescence and inflammaging narrow the repertoire, raise baseline inflammatory tone, and impair resolution in older adults. This contrast in immune plasticity offers a coherent explanation for the same age gradient observed at the bedside: encephalopathy and acute symptomatic seizures in the young, protracted fatigue and cognitive complaints in the old [28,118,119].

9.1. Encephalopathy and Encephalitis (Predominant in Pediatric and Adolescent Age Groups)

Encephalopathy is the most commonly described neurological syndrome in dengue, and its prevalence is significantly higher in children and adolescents. Within the pediatric population, infants (under one year of age) and children with obesity carry an especially high risk of developing this complication [117]. This heightened susceptibility to shock and encephalopathy in children is attributed to differences in baseline microvascular permeability compared with adults [117,118,120]. Additionally, infants born to dengue-immune mothers are at greatest risk of developing severe forms (dengue hemorrhagic fever and shock syndrome) during their first infection, between 6 and 9 months of age [117,120,121]. This results from an ADE mechanism, in which passively transferred maternal antibodies fall to sub-neutralizing levels and facilitate viral replication [117,120–122]. Encephalitis from direct viral invasion also predominantly affects younger populations; several studies report that between 52% and 68% of patients with dengue encephalitis are under 15 years of age [97,98,120]. This vulnerability carries lasting consequences: a retrospective pediatric cohort found measurable long-term neurologic sequelae, most commonly cognitive and behavioral impairment, in nearly 40% of children discharged after dengue-associated acute encephalitis, reinforcing the need for structured follow-up and rehabilitation in this age group rather than assuming full recovery once the acute illness resolves [120,123].

9.2. Neuromuscular Complications: Myositis and Rhabdomyolysis

Muscle involvement differs by age. In children, dengue-related muscle dysfunction or myositis typically presents as a relatively benign and self-limited condition (classically known as myalgia cruris epidemica), mainly involving calf pain and temporary difficulty walking [97,101,112]. In adult patients, by contrast, dengue-induced myositis tends to be a substantially more severe and aggressive entity, capable of triggering severe rhabdomyolysis, flaccid quadriparesis, and respiratory failure [97,98,101,112].

9.3. Myelitis

Unlike encephalopathy, which predominates in childhood, demyelinating spinal cord complications such as transverse myelitis (whether from acute direct invasion or post-infectious immune-mediated mechanisms) are more common in young adults, with a reported mean age of onset of 33 years in clinical cohorts [120,123,124]. Other autoimmune complications such as Guillain–Barré syndrome are frequently observed in adults, presenting weeks after the febrile phase resolves [78–80].

9.4. Post-Dengue Fatigue Syndrome (Commonly Found in Middle-Aged and Older Adults)

The development of persistent chronic symptoms, specifically Post-Dengue Fatigue Syndrome, is strongly and independently associated with older age. Older adults face a significantly higher risk of profound post-infectious fatigue that does not improve with rest, as well as memory loss, reasoning difficulties, hair loss, and persistent arthralgia. These chronic symptoms, which may last from several months to two years, impose severe physical and psychological limitations and are observed far more frequently in adults and older adults than in children [5,48,78–80,89].

10. Therapeutic Considerations and Future Perspectives

The evidence reviewed here converges on a coherent, if still incomplete, picture of Post-Dengue Syndrome as a genuine post-infectious entity rather than a diffuse or ill-defined complaint. Three lines of evidence support this view. First, the immunological mechanisms active during acute infection—antibody-dependent enhancement, the cytokine storm, and NS1-driven molecular mimicry—are not confined to the febrile phase; cross-reactive autoantibodies and endothelial injury plausibly persist beyond viral clearance, providing a mechanistic bridge to chronic symptoms [3,13–15]. Second, host genetics measurably shapes who develops severe or prolonged disease: FcγRIIa and HLA polymorphisms recur across genetically and geographically distinct cohorts—Vietnamese, Cuban, Thai, Brazilian, and Mexican—which strengthens confidence that these associations are biologically real rather than population-specific artifacts, even though effect sizes vary between studies [54,55,60,61,63,89,125]. Third, the clinical and epidemiological literature independently converges on the same risk architecture—female sex and older age for fatigue-predominant PDS, younger age for encephalopathy and direct neuroinvasion—suggesting that host factors operating at the level of both the adaptive immune system and end-organ vulnerability jointly determine phenotype [5,48,79,80,86–88,117–119].

At the same time, several limitations of the underlying evidence base deserve explicit comment, since they bound how confidently these findings can be generalized. Most of the genetic association studies discussed in Section 6 are candidate-gene, case–control designs conducted in single, often small, ethnic cohorts; replication across populations has been inconsistent, and few genome-wide association studies have specifically targeted PDS rather than acute severe dengue [60]. The clinical literature on PDS itself is dominated by hospital-based cohorts, which likely overrepresent more severe acute presentations and may not capture the full spectrum of illness seen in ambulatory or asymptomatic infections. Sex- and age-based differences, while consistently reported, largely come from observational studies without uniform case definitions for PDS or post-dengue fatigue syndrome, limiting direct comparison across studies and complicating pooled incidence estimates. Finally, because this is a narrative rather than a systematic review, article selection—while guided by the structured search strategy described in Section 2—inevitably involved subjective judgment regarding relevance and quality, and publication bias favoring positive or novel associations cannot be excluded.

Therapeutic considerations. No specific antiviral therapy exists for dengue, so PDS management is supportive and largely empirical. Key points include that immune-mediated neurological syndromes arising in the convalescent phase are clinically distinct entities and should not be grouped under a single therapeutic recommendation. Where dengue-associated cases have been reported, management has followed the established guidelines for the idiopathic form of each condition rather than any dengue-specific protocol. For Guillain–Barré syndrome, intravenous immunoglobulin and plasma exchange are the treatments of established benefit, and corticosteroids are explicitly not recommended, since randomized evidence shows no benefit from corticosteroid monotherapy. For acute

disseminated encephalomyelitis, high-dose intravenous corticosteroids are first-line, with immunoglobulin or plasma exchange reserved for refractory cases. Transverse myelitis is likewise treated with high-dose corticosteroids, followed by plasma exchange when the response is inadequate. Autoimmune encephalitis is managed according to antibody status, with corticosteroids, immunoglobulin, or plasma exchange as first-line immunotherapy and second-line agents as needed. The dengue literature supporting these approaches consists of case reports and small series; no controlled trial has been conducted in dengue-associated cases, and reported outcomes are therefore subject to publication bias favoring favorable results [112,121,123,124]. For the fatigue-predominant phenotype, no disease-modifying treatments exist. The management approach emphasizes a structured, symptom-guided activity framework that targets comorbid conditions such as sleep disturbances, pain, and mood-related symptoms. Additionally, it recognizes the biological underpinnings of these complaints as therapeutically significant. The checkpoint biology described in Section 5.2 is the most concrete pharmacological lead to have emerged recently, since PD-1 blockade protects mice infected with wild-type DENV [50]; the distance between an experimental model of acute infection and a chronic post-infectious syndrome in humans is nevertheless considerable, and manipulating immune checkpoints in a disease already characterized by autoreactivity would demand careful justification. Vaccination adds another layer, since the same ADE mechanism that governs severity in secondary natural infection also shapes the risk profile of dengue vaccines in seronegative recipients, and whether vaccine-primed immunity modifies PDS incidence remains unknown [119].

These gaps highlight priorities for future research and clinical practice. A standardized case definition for post-dengue syndrome (PDS) and post-dengue fatigue syndrome, validated across endemic regions, is needed for meaningful comparisons of incidence and risk factors. Population-based cohorts, like those reported in Singapore, should track multi-organ and neurological outcomes for at least a year post-infection to better understand the burden of PDS. Mechanistic studies linking genotype to autoantibody persistence or fatigue phenotypes are also needed. Clinically, a structured post-dengue follow-up for women, older adults, and children recovering from encephalitis should be integrated into routine care in endemic areas, even in the absence of specific treatment options.

Among these, the NKG2D–MICB axis set out in Section 4.2 is the most immediately testable, since it requires only conventional flow cytometry alongside existing genotype data, and it is not repeated here.

11. Conclusions

Persistent post-dengue sequelae occur in a subset of patients following an infection that engages multiple immune pathways and does not fully resolve in those individuals. Pooled estimates place post-infectious fatigue at 20.0% among dengue patients (95% CI 10–36), although heterogeneity between studies is substantial and no standardized case definition for Post-Dengue Syndrome exists yet [78,79]. Evidence links three factors: virological and innate mechanisms (including ADE and cytokine storms), an altered adaptive immune response (characterized by changes in plasmablasts and regulatory control), and genetic factors (like HLA haplotypes and cytokine variants) that influence individual responses. The resulting symptoms vary by sex and age, with fatigue in women and older adults, encephalopathy in children, and demyelinating syndromes in young adults. Clinicians in endemic areas should prioritize active follow-up during convalescence, especially for women, older adults, and children recovering from encephalitis. Research should focus on a validated case definition, prospective cohorts with immunological and cognitive assessments, and studies linking genotype to autoantibody persistence and fatigue. A significant question remains about whether identified mechanisms can be modified. As

dengue expands due to climate change, post-infectious sequelae (PDS) must be formally recognized, rather than treated as an afterthought.

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