ARTIKEL PENELITIAN

Candidate Antivirals and Immunomodulatory Therapies for Dengue in Indonesia: A Narrative Review of Clinical and Immunological Outcomes

[*]Ichwan Baihaki[1)], Niken Rahmah Ghanny[2)], Herera Rahajeng[3)], Afifa Radhina[4)], Assyafiya Salwa[5)], Bunga Anggreini Sari[6)]

[1]Department of Microbiology, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, 12450, Indonesia
[2]Department of Biochemistry, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, 12450, Indonesia
[3]Department of Anatomy Pathology, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, 12450, Indonesia
[4]Department of Physiology, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, 12450, Indonesia
[5]Department of Histology, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, 12450, Indonesia
[6]Department of Molecular Biology, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, 12450, Indonesia

***Corresponding author*:** Ichwan Baihaki, ichwan.baihaki@upnvj.ac.id, Jakarta, Indonesia

Abstract

Dengue remains a major public health challenge in Indonesia, where sustained transmission, seasonal increases, and geographical variation contribute to a substantial disease burden. Current clinical management remains primarily supportive, and no disease-specific antiviral therapy is recommended for routine use. This narrative review critically evaluates candidate antiviral, host-directed or immunomodulatory, and platelet-enhancing therapies for dengue, with emphasis on their virological, immunological, haematological, and patient-important clinical outcomes and their relevance to the Indonesian setting. A structured search of PubMed/MEDLINE, Scopus, and Web of Science was conducted from database inception to 7 October 2025 and supplemented with key evidence available during manuscript revision. Clinical, observational, and clinically relevant preclinical studies were selected using predefined eligibility criteria. Titles, abstracts, and full texts were screened by three authors, with disagreements resolved by consensus. The evidence indicates that antiviral candidates, including celgosivir, ivermectin, niclosamide formulations, and other investigational compounds, vary substantially in their stage of development and strength of evidence. Some agents have demonstrated changes in viraemia, viral clearance, or NS1 clearance, but these effects have not consistently translated into reduced progression to severe dengue, shorter hospitalisation, or lower mortality. Host-directed and immunomodulatory therapies have shown preliminary effects on inflammatory pathways and other biological markers, although evidence for patient-important clinical benefit remains insufficient. Platelet-enhancing interventions, including recombinant interleukin-11, anti-D, eltrombopag, and Carica papaya preparations, may accelerate platelet recovery, but increased platelet counts should not be interpreted as evidence of reduced bleeding, shock, intensive care admission, or mortality. Overall, no candidate therapy currently has sufficient evidence to replace supportive care. Future multicentre trials should use standardised formulations, enrol patients early in the disease course, assess safety systematically, and adopt the DEN-CORE outcome framework to distinguish biological effects from clinically meaningful benefits.

Keywords: *Antiviral, Dengue, Immunomodulator*

INTRODUCTION

Dengue remains a major public health concern in Indonesia, with sustained local transmission across most provinces and periodic increases in incidence associated with seasonal, ecological, and geographical factors. In this review, "endemic dengue" refers to the continued occurrence of locally acquired dengue transmission over time; it does not imply uniform transmission intensity across regions or the absence of seasonal outbreaks. Indonesia is particularly relevant to dengue therapeutic research because of its large and geographically dispersed population, year-round transmission in many areas, circulation of multiple dengue virus (DENV) serotypes, and substantial variation in access to early diagnosis and hospital-based care. According to the World Health Organization, Indonesia recorded more than 257,000 dengue cases and 1,400 deaths in 2024. These figures represent nationally reported surveillance data and should be interpreted according to the applicable reporting period, case definitions, and completeness of reporting (World Health Organization, 2026). Climatic variability, urbanisation, population mobility, and differences in vector density further contribute to marked spatial and temporal heterogeneity in dengue incidence across the country (Mamenun et al., 2024).

Dengue is caused by four antigenically distinct DENV serotypes. Although many infections are asymptomatic or self-limiting, a subset progresses to severe manifestations characterised by plasma leakage, shock, clinically significant bleeding, or organ impairment. Disease severity is influenced by interactions between viral replication and host responses, including antibody-dependent enhancement, dysregulated inflammatory signalling, endothelial dysfunction, and haemostatic disturbances (Kalimuddin et al., 2025). Viraemia generally peaks during the early phase of illness, whereas severe manifestations frequently emerge later, creating a narrow window in which antiviral treatment may meaningfully alter disease progression (Huyen et al., 2026). Current management therefore remains focused on careful clinical monitoring, appropriate fluid therapy, recognition of warning signs, and management of shock, bleeding, and organ dysfunction. No antiviral or host-directed therapy has yet demonstrated sufficiently consistent clinical benefit to replace supportive care (Adhikari et al., 2025; Huyen et al., 2026).

Therapeutic interventions for dengue can be organised into three conceptually distinct categories. The first comprises direct-acting or repurposed antivirals intended to

inhibit viral entry, replication, or maturation. The second includes host-directed or immunomodulatory therapies intended to modify excessive inflammation, endothelial dysfunction, vascular permeability, or other host pathways associated with disease severity. The third comprises platelet-enhancing or thrombopoietic interventions intended primarily to accelerate platelet recovery. These categories should not be interpreted as equivalent because they target different biological mechanisms and therapeutic goals. Moreover, changes in viraemia, NS1 clearance, cytokine concentrations, or platelet counts are biological or surrogate outcomes and do not necessarily indicate reductions in severe dengue, plasma leakage, shock, clinically significant bleeding, intensive care unit admission, duration of hospitalisation, or mortality.

Previous evidence syntheses have demonstrated that the dengue therapeutic literature is characterised by small studies, substantial variation in intervention types and treatment timing, inconsistent outcome definitions, and limited assessment of patient-important clinical outcomes (Aynekulu Mersha et al., 2025). A subsequent systematic mapping review identified 121 published or registered therapeutic clinical studies and reported that many available trials were small, methodologically heterogeneous, or at high or critical risk of bias. The heterogeneity of interventions and primary endpoints prevented meaningful quantitative synthesis, and no single intervention had sufficiently consistent evidence to support its use in clinical practice (Huyen et al., 2026).

The importance of distinguishing biological changes from meaningful clinical benefit is reinforced by the DEN-CORE initiative. Through a systematic literature review, interviews with people with lived experience, a modified Delphi process, and international consensus meetings, DEN-CORE developed a consensus-based core outcome measurement set for dengue clinical trials. The framework recommends standardised outcomes for early-stage, hospitalised, and critically ill patients and provides unified definitions for clinically relevant outcomes. Its adoption is expected to improve comparability across trials and strengthen the relevance of evidence for clinical and policy decisions (Yacoub et al., 2026).

The present review differs from previous evidence syntheses in three respects. First, it integrates foundational clinical trials with recent clinical and translational evidence, while emphasising developments relevant to current therapeutic research and integrates clinical findings with clinically relevant preclinical evidence for selected therapeutic candidates. Second, it distinguishes direct-acting and host-targeted antivirals, immunomodulatory

therapies, and platelet-enhancing interventions while separating virological, immunological, and haematological markers from patient-important clinical outcomes. Third, it interprets the available therapeutic evidence in relation to Indonesia's disease burden, diagnostic capacity, therapeutic window, health-care infrastructure, and research priorities. Accordingly, this review aims to: (1) identify major antiviral, host-directed or immunomodulatory, and platelet-enhancing candidates investigated for dengue; (2) critically evaluate their effects on virological, immunological, haematological, and patient-important clinical outcomes; and (3) identify priorities for context-appropriate therapeutic research in Indonesia using the DEN-CORE framework.

METHOD

This narrative review was supported by a structured literature search and predefined eligibility criteria. A narrative approach was selected to facilitate an integrative and critical discussion of clinically and methodologically heterogeneous evidence encompassing different therapeutic categories, stages of development, study designs, populations, and outcome domains. The review was intended to map and interpret the available evidence rather than estimate a pooled treatment effect.

PubMed/MEDLINE, Scopus, and Web of Science were searched from database inception to 7 October 2025. The search was subsequently updated to include key evidence and consensus publications available during manuscript revision. No lower publication-date restriction was applied because several foundational clinical trials of dengue therapeutics were conducted before 2020 and remained directly relevant to the therapeutic candidates evaluated in this review. Publications were restricted to English or Indonesian. Controlled vocabulary, where available, and free-text terms were combined using Boolean operators. The principal search concepts included ("dengue" OR "DENV") AND ("antiviral" OR "direct-acting antiviral" OR "host-targeted therapy" OR "immunomodulator" OR "immunotherapy" OR "platelet-enhancing therapy" OR "thrombopoietin receptor agonist" OR "Carica papaya"). Supplementary searches incorporating the terms "Indonesia" and "endemic" were conducted to identify evidence specifically relevant to Indonesia and other endemic settings. The reference lists of relevant reviews and eligible articles were also examined to identify additional primary studies.

All retrieved records were compiled manually. Duplicate records were identified by comparing article titles, authors, publication years, and digital object identifiers, where available. Titles and abstracts were screened by three authors, followed by full-text assessment against the predefined eligibility criteria. Any disagreements regarding study eligibility were resolved through discussion among the three reviewers until consensus was reached.

Eligible studies included: (1) randomised or non-randomised controlled trials, prospective or retrospective cohort studies, and case-control studies involving at least 10 participants with confirmed dengue; (2) clinically relevant in vitro or in vivo studies evaluating therapeutic candidates relevant to clinical development; and (3) studies reporting at least one virological, immunological, haematological, or patient-important clinical outcome. The interventions of interest comprised direct-acting or host-targeted antivirals, host-directed or immunomodulatory therapies, and platelet-enhancing or thrombopoietic interventions.

Virological outcomes included viral load, viraemia, viral RNA, and NS1 clearance. Immunological outcomes included cytokines, chemokines, inflammatory mediators, and immune-cell responses. Haematological outcomes included platelet count, time to platelet recovery, and haematocrit. Patient-important clinical outcomes included fever duration, length of hospital stay, plasma leakage, clinically significant bleeding, shock, intensive care unit admission, progression to severe dengue, and mortality. Editorials, commentaries, case reports, very small case series, studies with outcomes unrelated to the review objectives, and language restrictions were excluded. Recent evidence syntheses were retained only to contextualise the findings and identify potentially relevant primary studies; they were not treated as primary evidence of therapeutic efficacy.

Data from eligible studies were extracted using a standardised form that captured the author and publication year, study location, population characteristics, dengue severity, intervention and comparator, dose, timing of administration relative to symptom onset, study design, sample size, phase of clinical development, primary endpoint, principal findings, adverse events, and study limitations. The studies were grouped into three therapeutic categories: (1) direct-acting and host-targeted antivirals; (2) host-directed or immunomodulatory therapies; and (3) platelet-enhancing or thrombopoietic interventions. Outcomes were further classified as virological, immunological, haematological, or patient-

important clinical outcomes. This classification was applied to distinguish changes in biological or surrogate markers from evidence of meaningful clinical efficacy.

Methodological quality was appraised descriptively by considering the study design, sample size, participant selection, presence of a comparator, clarity and consistency of outcome definitions, completeness of safety reporting, and potential sources of bias. A formal risk-of-bias scoring instrument was not applied because the objective was to provide a critical narrative synthesis across diverse clinical and preclinical study designs. Reported outcomes were also compared with the dengue core outcome measurement set developed by the DEN-CORE initiative to assess their alignment with recently recommended standardised endpoints. Owing to substantial heterogeneity in interventions, populations, study designs, and outcome measures, meta-analysis was not performed. The findings were synthesised narratively and supported by a table of study characteristics.

RESULTS

The eligible evidence encompassed clinical trials, observational studies, and clinically relevant preclinical investigations evaluating three conceptually distinct therapeutic categories: (1) direct-acting or repurposed antivirals; (2) host-directed or immunomodulatory therapies; and (3) platelet-enhancing or thrombopoietic interventions. The studies varied substantially in developmental phase, population, treatment timing, intervention dose, comparator, and outcome selection. Virological outcomes included viraemia, viral RNA, and NS1 clearance; immunological outcomes included cytokine and inflammatory-marker responses; haematological outcomes included platelet counts and platelet recovery; and patient-important clinical outcomes included progression to severe dengue, plasma leakage, bleeding, shock, hospitalisation, intensive care admission, and mortality. This classification was used to prevent biological or surrogate outcomes from being interpreted as equivalent to clinical efficacy. The principal characteristics, intervention regimens, outcomes, findings, and limitations of the clinical and preclinical studies are summarised in Tables 1 and 2.

Table 1. Characteristics and principal findings of clinical studies evaluating therapeutic candidates for dengue

References	Category and developmental phase	Design and participants	Intervention and timing	Principal outcomes	Main findings and safety	Key limitations
Low et al. (2014)	Host-targeted antiviral; phase 1b	Randomised, double-blind, placebo-controlled proof-of-concept trial; 50 adults with laboratory-confirmed dengue, Singapore	Celgosivir: 400 mg oral loading dose within 6 h of randomisation, followed by 200 mg every 12 h; nine doses in total	Viral load; viraemia; fever burden; safety	Generally safe and well tolerated, but no significant reduction in viral load, viraemia, or fever burden	Small sample; early-phase trial; dose and timing may not have provided sufficient exposure during the narrow viraemic phase
Suputtamongkol et al. (2021)	Repurposed antiviral; combined phases 2 and 3	Consecutive randomised, double-blind, placebo-controlled trials; 203 adults in intention-to-treat analysis	Ivermectin 400 μg/kg orally once daily for 3 days versus placebo	NS1 clearance; viraemia clearance; dengue haemorrhagic fever; adverse events	Shorter NS1 clearance time, but no significant effect on viraemia clearance or dengue haemorrhagic fever; adverse-event incidence was similar between groups	Improvement limited to a surrogate virological outcome; no demonstrated clinical efficacy
Tam et al. (2012)	Host-directed therapy; clinical efficacy and safety trial	Randomised, blinded, placebo-controlled trial; 225 patients aged 5–20 years with fever for ≤72 h, Vietnam	Oral prednisolone 0.5 mg/kg or 2 mg/kg daily for 3 days versus placebo	Viraemia; NS1 clearance; plasma leakage; shock; bleeding; haematological outcomes; safety	No improvement in predefined virological, haematological, or clinical outcomes; adverse events were infrequent, but hyperglycaemia was more frequent with prednisolone	Primarily designed for safety; not powered for uncommon severe outcomes
Malavige et al. (2022)	Host-directed therapy; phase 2	Randomised, double-blind, placebo-controlled trial; 249 patients with acute dengue within 3 days of illness, Sri Lanka	Rupatadine 40 mg orally once daily for 5 days (n = 123) versus placebo (n = 126)	Progression to dengue haemorrhagic fever; shock; bleeding; liver failure; transfusion; hospitalisation; illness duration	Non-significant trend towards reduced dengue haemorrhagic fever (RR 0.68; 95% CI 0.41–1.08); shorter illness duration; generally safe and well tolerated	Prematurely terminated; underpowered for the primary endpoint; post-hoc power 43.3%

References	Category and developmental phase	Design and participants	Intervention and timing	Principal outcomes	Main findings and safety	Key limitations
Suliman et al. (2014)	Platelet-enhancing therapy; exploratory clinical trial	Randomised, double-blind, placebo-controlled trial; 40 hospitalised patients with platelet count ≤30,000/μL	Recombinant human IL-11, 1.5 mg subcutaneously, versus placebo	Platelet response at 48 h	Platelet response in 50% of the rhIL-11 group versus 20% of placebo recipients (p = 0.047)	Very small sample; short follow-up; platelet response was a surrogate outcome; insufficient clinical and safety assessment
Pannu et al. (2017)	Immunoglobulin/platelet-enhancing intervention	Open-label randomised trial; 30 RhD-positive adults with platelet count ≤20,000/μL, India	Single intravenous anti-D dose of 50 μg/kg (250 IU/kg) plus supportive care versus supportive care alone	Platelet count ≥50,000/μL at 48 h; platelet transfusion; bleeding manifestations	Target platelet count achieved by 60% versus 6.7% of controls; lower platelet-transfusion volume and improvement in minor bleeding	Very small sample; open-label design; short follow-up; restricted to RhD-positive patients; potential haemolytic risk
Chakraborty et al. (2020)	Thrombopoietin-receptor agonist; phase 2	Open-label randomised controlled trial; 109 randomised and 101 completing participants aged 15–65 years with DF or DHF, Bangladesh	Eltrombopag 25 mg/day, 50 mg/day, or standard care for 3 days	Platelet recovery; bleeding manifestations; liver enzymes; thrombocytosis; thrombosis	Both doses accelerated platelet recovery; no clear efficacy advantage with 50 mg; higher dose associated with more platelet counts >450 × 10^9/L and more transaminase elevations; no detected thrombosis	Open-label; small sample; emphasis on platelet recovery; not powered for severe clinical outcomes
Subenthiran et al. (2013)	Herbal platelet-enhancing intervention	Open-label randomised controlled trial; 290 enrolled and 228 analysed patients with DF or DHF, Malaysia	Juice prepared from 50 g fresh *Carica papaya* leaves once daily for 3 days plus standard care versus standard care	Platelet count monitored over 48 h; ALOX12 and PTAFR expression	Faster platelet increase at 40 and 48 h and increased expression of platelet-associated genes	Open-label; attrition from enrolment to analysis; non-standardised fresh-leaf preparation; limited patient-important clinical outcomes
Sathyapalan et al. (2020)	Herbal platelet-enhancing intervention; pilot trial	Double-blind, randomised, placebo-controlled	*Carica papaya* leaf extract 1,100 mg orally three times	Platelet recovery; transfusion; bleeding;	Greater platelet increase and one-day shorter median time to ≥50,000/μL;	Small pilot sample; uncommon transfusion and

References	Category and developmental phase	Design and participants	Intervention and timing	Principal outcomes	Main findings and safety	Key limitations
		pilot trial; 51 randomised and 50 analysed adults with platelet count ≤30,000/μL, India	daily for 5 days versus placebo	hospital stay; cytokines; NS1; safety	generally well tolerated; no significant reduction in hospital stay	bleeding events; not powered for severe outcomes; industry funded

Abbreviations: CI, confidence interval; DENV, dengue virus; DF, dengue fever; DHF, dengue haemorrhagic fever; h, hours; IL-11, interleukin-11; NS1, non-structural protein 1; RR, relative risk.

Table 2. Clinically relevant preclinical evidence for selected antiviral and immunomodulatory candidates

References	Candidate and model	Intervention	Outcomes	Principal findings	Translational limitations
Kao et al. (2018)	Niclosamide; DENV2-infected human and animal cell lines and mouse model	Niclosamide administered in experimental conditions	Viral replication; cell viability; experimental disease manifestations	Reduced DENV2 infection in multiple cell lines and inhibited infection and disease progression in vivo	No human dengue trial; poor aqueous solubility, oral absorption, and systemic bioavailability
Jung et al. (2019)	Niclosamide; DENV-infected cell models	Niclosamide administered during different stages of the viral life cycle	Viral entry; replication; intracellular-vesicle acidification	Inhibited multiple stages of the DENV life cycle by neutralising acidic intracellular compartments	In vitro evidence only; clinically achievable exposure and human safety for dengue remain uncertain
Kim et al. (2024)	Pimecrolimus; DENV2-infected cell lines and IFN-receptor-deficient mice, eight mice per group	Pimecrolimus 5–20 μM in vitro; 15 or 30 mg/kg orally twice daily for 14 days in mice	Viral internalisation; viral genome and protein; tissue viral load; necrosis; weight loss; survival	Reduced viral internalisation and replication; lowered tissue viral load and focal necrosis; improved weight and survival	Restricted to DENV2; experimental mouse model does not reproduce the full spectrum of human dengue; immunosuppressive safety requires evaluation
Giraldo et al. (2018)	Vitamin D; ex vivo monocyte-derived macrophages from healthy adults	Vitamin D supplementation at 1,000 or 4,000 IU/day for 10 days before macrophage differentiation	Susceptibility to DENV2 infection; pro- and anti-inflammatory cytokines	Macrophages from the higher-dose group showed lower susceptibility to DENV2 and reduced pro-inflammatory cytokine production	Healthy participants rather than patients with dengue; ex vivo immune outcomes; no patient-important clinical endpoints

References	Candidate and model	Intervention	Outcomes	Principal findings	Translational limitations
Tamayo-Molina et al. (2025)	Vitamin D; DENV-infected human macrophage model	Experimental vitamin D exposure	Early-response genes; antiviral protein expression; inflammatory responses	Modulated early antiviral gene expression and macrophage responses to DENV	In vitro evidence; no therapeutic clinical trial; biomarker changes cannot establish clinical efficacy

Abbreviations: DENV, dengue virus; IFN, interferon; IU, international units.

Direct-acting and repurposed antiviral candidates

Celgosivir, an iminosugar prodrug with proposed host-targeted antiviral activity, was evaluated in the CELADEN phase 1b randomised, double-blind, placebo-controlled proof-of-concept trial involving 50 adults with laboratory-confirmed dengue in Singapore. Treatment consisted of an oral loading dose of 400 mg administered within 6 hours of randomisation, followed by 200 mg every 12 hours, with nine doses administered in total. The principal efficacy outcomes included viral load and fever burden. Although celgosivir was generally safe and well tolerated, it did not significantly reduce viraemia, viral load, or fever burden compared with placebo. Interpretation was limited by the small sample size, the early developmental phase, and the possibility that the dose and timing of treatment were insufficient to achieve effective drug exposure during the narrow viraemic phase (Low et al., 2014). Thus, celgosivir demonstrated acceptable short-term tolerability but no established virological or clinical efficacy.

Ivermectin was evaluated in consecutive phase 2 and phase 3 randomised, double-blind, placebo-controlled trials involving a combined intention-to-treat population of 203 adults with dengue. Participants received oral ivermectin at 400 μg/kg once daily for three days or placebo. NS1 antigenaemia clearance, viraemia clearance, progression to dengue haemorrhagic fever, and adverse events were evaluated. Median NS1 clearance was shorter with ivermectin than with placebo (71.5 versus 95.8 hours), and a greater proportion of ivermectin-treated participants had undetectable NS1 at discharge. However, there was no significant difference in viraemia clearance or the incidence of dengue haemorrhagic fever, which occurred in 24.0% of the ivermectin group and 31.1% of the placebo group. The incidence of adverse events was also similar between groups (Suputtamongkol et al., 2021). Therefore, accelerated NS1 clearance should be interpreted as a virological or surrogate effect rather than evidence of clinical efficacy.

Niclosamide has shown antiviral activity against DENV in preclinical models by interfering with endosomal acidification and other intracellular processes required for viral entry and replication. In vitro studies demonstrated inhibition of DENV replication in several cell lines, while animal experiments reported reduced viral replication and disease manifestations following treatment (Kao et al., 2018; Jung et al., 2019). However, conventional niclosamide has poor aqueous solubility, limited oral absorption, and low systemic bioavailability, which constrain its clinical translation. More recent nanoengineered and

alternative formulations have attempted to improve drug delivery and systemic exposure, but clinical efficacy in patients with dengue has not been established. Consequently, niclosamide should be classified as a preclinical candidate rather than grouped with agents evaluated in phase 2 or phase 3 clinical trials.

Pimecrolimus, a calcineurin inhibitor with host-directed and antiviral properties, has been investigated only in preclinical models. In DENV2-infected cells, pimecrolimus at concentrations of 5–20 μM reduced viral internalisation, viral genome expression, plaque formation, and envelope-protein production. In an interferon-receptor-deficient mouse model, oral pimecrolimus administered at 15 or 30 mg/kg twice daily for 14 days reduced viral loads in several organs, limited focal necrosis in the liver and spleen, reduced weight loss, and improved survival. No cytotoxicity was observed at the tested experimental concentrations (Kim et al., 2024). Nevertheless, these findings were restricted to DENV2 and experimental models that do not fully reproduce human dengue pathophysiology. Pimecrolimus has not been evaluated for dengue treatment in human clinical trials, and its immunosuppressive properties require careful safety assessment before clinical translation.

Overall, the evidence supporting antiviral candidates remains limited and agent-specific. Celgosivir did not improve its predefined virological or clinical outcomes, whereas ivermectin accelerated NS1 clearance without reducing viraemia or demonstrating a statistically significant clinical benefit. Niclosamide and pimecrolimus remain preclinical candidates. These differences in developmental stage and evidence strength preclude a general conclusion that the antiviral class produces a consistent therapeutic effect.

Host-directed and immunomodulatory therapies

Corticosteroids have been investigated as host-directed therapies because excessive inflammatory responses and endothelial dysfunction contribute to severe dengue. One of the largest well-characterised studies was a randomised, placebo-controlled, blinded trial involving 225 Vietnamese patients aged 5–20 years who presented within 72 hours of fever onset. Participants received low-dose oral prednisolone at 0.5 mg/kg, high-dose prednisolone at 2 mg/kg, or placebo for three days. The predefined outcomes included plasma viraemia, NS1 clearance, haematological measures, plasma leakage, shock, bleeding, and other recognised dengue complications. Neither prednisolone regimen improved the clinical, haematological, or virological outcomes. Adverse events were infrequent, although hyperglycaemia occurred more

frequently among corticosteroid recipients. The study was primarily designed to assess safety and was not powered to demonstrate differences in uncommon severe outcomes (Tam et al., 2012).

Earlier trials of corticosteroids in dengue shock used different agents, doses, treatment durations, populations, and outcome definitions. These studies were generally small and had methodological limitations, including unclear allocation procedures, inadequate blinding, and incomplete reporting of baseline disease severity. Across the available evidence, corticosteroids have not consistently reduced mortality in dengue shock, improved platelet recovery in dengue-associated thrombocytopaenia, or prevented progression to severe dengue when administered during early infection (Huyen et al., 2026). Consequently, suppression of inflammatory responses alone has not been shown to produce a reliable patient-important clinical benefit.

Rupatadine is a histamine H1- and platelet-activating factor-receptor antagonist proposed to reduce inflammatory signalling and endothelial permeability. It should not be classified as a leukotriene antagonist. A phase 2 randomised, double-blind, placebo-controlled trial conducted in Sri Lanka enrolled 249 patients with acute dengue within three days of illness onset. Participants received rupatadine 40 mg once daily for five days (n = 123) or placebo (n = 126), in addition to standard supportive care. The primary endpoint was progression to dengue haemorrhagic fever, while secondary outcomes included shock, bleeding, liver failure, requirement for colloids or blood transfusion, hospital admission, and illness duration.

Rupatadine was associated with a non-significant trend towards a lower risk of dengue haemorrhagic fever compared with placebo (relative risk 0.68; 95% confidence interval 0.41–1.08). The duration of illness was shorter in the rupatadine group, but hospital-admission rates did not differ significantly. Shock and bleeding events were uncommon in both groups, and rupatadine was generally safe and well tolerated. However, the trial was terminated before reaching its planned sample size and had an estimated post-hoc power of only 43.3% for the primary endpoint. The findings therefore suggest a possible clinical signal but do not establish that rupatadine prevents severe dengue or other major complications (Malavige et al., 2022).

Vitamin D has also been investigated as a potential host-response modifier, although the evidence remains predominantly mechanistic. Experimental studies using DENV-infected human macrophages have reported reduced viral susceptibility, modulation of early-response gene expression, and changes in pro- and anti-inflammatory cytokine production following vitamin D exposure or supplementation (Giraldo et al., 2018; Tamayo-Molina et al., 2025).

These findings indicate a possible interaction between vitamin D signalling and antiviral immune responses. However, changes in macrophage infection, gene expression, or cytokine concentrations are immunological outcomes and cannot be interpreted as evidence that vitamin D reduces plasma leakage, shock, hospitalisation, or mortality. Controlled therapeutic trials in patients with confirmed dengue are required before vitamin D can be considered an effective immunomodulatory treatment.

Overall, host-directed therapies have not demonstrated consistent patient-important clinical benefits. Prednisolone did not improve virological, haematological, or clinical outcomes, while rupatadine showed a non-significant signal towards reduced progression to dengue haemorrhagic fever in an underpowered phase 2 trial. Evidence for vitamin D remains mechanistic and preclinical. These findings support further evaluation of pathway-specific host-directed therapies but do not justify their routine use in dengue treatment.

Platelet-enhancing and thrombopoietic interventions

Recombinant human interleukin-11 (rhIL-11) has been evaluated as a thrombopoietic intervention for dengue-associated thrombocytopaenia. A randomised, double-blind, placebo-controlled trial enrolled 40 hospitalised patients with dengue and platelet counts of ≤30,000/μL. Participants received a subcutaneous dose of rhIL-11 at 1.5 mg or placebo. The principal outcome was an increase in platelet count at 48 hours. A platelet response was observed in 50% of patients receiving rhIL-11 compared with 20% of those receiving placebo ($p = 0.047$) (Suliman et al., 2014). However, the study was small, focused on a short-term haematological outcome, and did not establish whether treatment reduced clinically significant bleeding, transfusion requirements, shock, hospitalisation, or mortality. Safety reporting was also insufficient to support routine use.

Anti-D immunoglobulin was examined in an open-label randomised study involving 30 RhD-positive adults with dengue and severe thrombocytopaenia, defined as a platelet count of ≤20,000/μL. Participants received a single intravenous dose of anti-D at 50 μg/kg (250 IU/kg) plus supportive care or supportive care alone. At 48 hours, 60% of anti-D recipients achieved a platelet count of ≥50,000/μL compared with 6.7% of controls. The intervention group also received a lower mean volume of platelet concentrate and showed improvement in minor bleeding manifestations (Pannu et al., 2017). Nevertheless, the open-label design, very small sample, short follow-up, and restriction to RhD-positive patients limit generalisability.

Furthermore, potential haemolytic and transfusion-related risks require assessment in larger blinded trials.

Eltrombopag, an oral thrombopoietin-receptor agonist, was evaluated in a phase 2 open-label randomised controlled trial involving 109 patients aged 15–65 years with dengue fever or dengue haemorrhagic fever. Participants were assigned to eltrombopag 25 mg once daily, eltrombopag 50 mg once daily, or standard care for three consecutive days; 101 participants completed the study. Both doses accelerated platelet recovery, with no clear efficacy advantage of 50 mg over 25 mg. However, seven participants receiving 50 mg developed platelet counts above 450×10^9/L by day 7, compared with three participants receiving 25 mg. Elevations in hepatic transaminases were also more frequent with the higher dose, although no thrombotic event was detected by ultrasonography (Chakraborty et al., 2020). The findings suggest that 25 mg may have a more favourable short-term safety profile, but the open-label design, small sample, and emphasis on platelet recovery prevent conclusions regarding major bleeding, plasma leakage, shock, or mortality.

Carica papaya leaf preparations have been evaluated in several clinical studies, but their formulations, doses, treatment durations, and methodological quality vary considerably. An open-label randomised trial involving 228 analysed patients reported that juice prepared from 50 g of fresh Carica papaya leaves once daily for three days accelerated platelet recovery at 40 and 48 hours compared with standard care (Subenthiran et al., 2013). However, the absence of placebo blinding and the focus on platelet counts limited interpretation of clinical efficacy.

A subsequent double-blind, placebo-controlled pilot trial evaluated Carica papaya leaf extract in 51 adults with laboratory-confirmed dengue and platelet counts of ≤30,000/μL. Participants received an 1,100 mg extract tablet or matched placebo three times daily for five days. Fifty participants were included in the final analysis. Platelet recovery was greater in the treatment group by day 3, and the median time to reach a platelet count of ≥50,000/μL was two days with the extract and three days with placebo. However, platelet transfusions were uncommon in both groups, and the length of hospitalisation did not differ significantly. The preparation was generally well tolerated, but the small pilot sample was not powered to detect differences in bleeding, shock, intensive care admission, or mortality. The study also received industry funding, which should be considered when interpreting its findings (Sathyapalan et al., 2020).

Overall, rhIL-11, anti-D immunoglobulin, eltrombopag, and Carica papaya preparations have demonstrated the capacity to increase platelet counts or accelerate platelet recovery in selected patients. Nevertheless, thrombocytopaenia in dengue commonly improves spontaneously during the recovery phase, and platelet count alone does not reliably represent bleeding risk or overall disease severity. The available studies do not provide sufficient evidence that these interventions reduce clinically significant bleeding, plasma leakage, shock, intensive care admission, or mortality. Their clinical value therefore remains uncertain despite favourable haematological signals.

Alignment with the DEN-CORE outcome framework

Comparison of the included studies with the DEN-CORE consensus framework demonstrated substantial inconsistency in outcome selection and reporting. DEN-CORE recommends a minimum set of seven core outcomes for trials involving hospitalised patients with dengue and eleven outcomes for early-stage dengue trials, with additional recommendations for critically ill patients. The framework prioritises standardised, clinically meaningful, and patient-centred outcomes to facilitate comparison across studies and support clinical and policy decisions (Yacoub et al., 2026).

Among the antiviral studies, the celgosivir trial assessed viral load and fever burden, while the ivermectin trial assessed NS1 clearance, viraemia clearance, and progression to dengue haemorrhagic fever. The ivermectin findings illustrate the importance of the DEN-CORE framework because improved NS1 clearance was not accompanied by a significant improvement in clinical disease progression. Similarly, preclinical findings for niclosamide and pimecrolimus were based on viral replication, cellular responses, tissue viral load, and survival in experimental models and therefore cannot be directly compared with patient-important outcomes in human trials.

Outcome selection was also inconsistent among host-directed and immunomodulatory studies. The prednisolone trial evaluated virological, haematological, and clinical complications, whereas the rupatadine trial included progression to dengue haemorrhagic fever and several relevant clinical complications. However, the rupatadine study was underpowered for its primary clinical endpoint. Vitamin D studies predominantly evaluated viral susceptibility, gene expression, and cytokine responses in experimental systems, without assessing clinical outcomes in patients.

The greatest discrepancy between biological and clinical outcomes was observed in studies of platelet-enhancing interventions. Most rhIL-11, anti-D immunoglobulin, eltrombopag, and *Carica papaya* studies used platelet count or time to platelet recovery as their principal efficacy outcome. Only a limited number assessed bleeding, transfusion requirements, plasma leakage, hospitalisation, or safety systematically, and none provided sufficiently robust evidence of reduced shock, intensive care admission, or mortality. Therefore, increased platelet counts should be regarded as haematological or surrogate outcomes unless accompanied by demonstrated improvement in patient-important clinical outcomes.

Most of the reviewed trials were conducted before publication of the DEN-CORE framework and therefore could not have prospectively adopted its recommendations. Nevertheless, retrospective comparison indicates that inconsistent outcome definitions and selective emphasis on surrogate markers substantially limit cross-study comparison and evidence synthesis. Future dengue therapeutic trials should prospectively adopt the DEN-CORE outcome measurement set, predefine patient-important primary outcomes, apply standardised measurement time points, and report adverse events consistently.

DISCUSSION

This review demonstrates that the dengue therapeutic landscape remains heterogeneous and that no antiviral, host-directed, immunomodulatory, or platelet-enhancing intervention currently has sufficiently consistent evidence to replace supportive care. The principal limitation across therapeutic categories is not the absence of biological activity, but the failure to demonstrate that changes in viral or haematological markers result in patient-important clinical benefits. This distinction is especially important because reduced viraemia, faster NS1 clearance, altered cytokine concentrations, and increased platelet counts do not necessarily indicate prevention of plasma leakage, severe bleeding, shock, intensive care admission, or mortality.

The antiviral findings illustrate the challenges of administering treatment within the narrow viraemic phase. Celgosivir was generally well tolerated but did not reduce viral load or fever burden, potentially because the dosing regimen and treatment timing did not provide sufficient exposure during peak viral replication (Low et al., 2014). Ivermectin accelerated NS1 clearance but did not significantly alter viraemia clearance or progression to dengue haemorrhagic fever (Suputtamongkol et al., 2021). These findings indicate that NS1 clearance

may demonstrate biological activity without establishing clinical efficacy. Future antiviral trials should therefore recruit patients as early as possible after symptom onset, use rapid virological confirmation, confirm adequate pharmacokinetic exposure, and select clinical endpoints appropriate to the expected mechanism of action.

Niclosamide and pimecrolimus demonstrate promising antiviral effects in experimental systems but remain at substantially earlier stages of development. Niclosamide inhibits DENV infection through effects on endosomal acidification and other intracellular processes, but poor oral bioavailability remains a major translational barrier. Pimecrolimus reduced DENV2 replication and experimental disease manifestations in cell and mouse models, but its immunosuppressive properties and activity against only a limited range of experimental DENV strains require further evaluation. These candidates should therefore not be presented as equivalent to agents already assessed in randomised human trials.

The findings for host-directed therapies were similarly inconsistent. Corticosteroids have a plausible biological rationale because dysregulated inflammation contributes to vascular dysfunction and severe dengue. Nevertheless, prednisolone did not improve virological, haematological, or clinical outcomes in early dengue, and older corticosteroid trials in dengue shock were limited by small samples and methodological weaknesses (Tam et al., 2012; Huyen et al., 2026). Broad immunosuppression may therefore be insufficiently targeted to interrupt the complex pathways responsible for severe disease.

Rupatadine represents a more pathway-specific approach through antagonism of histamine H1 and platelet-activating factor receptors. Its phase 2 trial showed a possible signal towards reduced progression to dengue haemorrhagic fever and shorter illness duration, but the primary endpoint was not statistically significant and the study was underpowered (Malavige et al., 2022). These findings justify further adequately powered investigation but do not support routine clinical use. Similarly, vitamin D has demonstrated effects on macrophage susceptibility, antiviral gene expression, and cytokine responses, but evidence remains mechanistic. Controlled clinical trials are required before these immunological findings can be interpreted as therapeutic benefit.

Platelet-enhancing interventions produced the most consistent changes in laboratory outcomes but also the clearest risk of overinterpretation. RhIL-11, anti-D immunoglobulin, eltrombopag, and *Carica papaya* preparations accelerated platelet recovery in selected studies. However, thrombocytopaenia commonly resolves spontaneously during dengue recovery, and bleeding is

influenced by platelet function, endothelial dysfunction, coagulation abnormalities, disease phase, and clinical severity rather than platelet count alone. Consequently, a faster rise in platelet count does not establish prevention of severe bleeding or other major complications.

Safety, feasibility, and applicability also differ substantially among platelet-enhancing therapies. RhIL-11 and anti-D immunoglobulin require parenteral administration and have limited evidence from small trials. Anti-D is applicable only to selected RhD-positive patients and carries potential haemolytic risks. Eltrombopag is orally administered but requires attention to hepatic safety, excessive platelet responses, and possible thrombosis. *Carica papaya* is relatively accessible in endemic settings, but studies have used fresh juice, tablets, capsules, and extracts with inconsistent compositions and doses. Standardisation of active constituents, manufacturing quality, dosing, and safety assessment is therefore necessary before clinical recommendations can be made.

The DEN-CORE international consensus provides an important framework for addressing these limitations. Its development incorporated systematic evidence review, input from people with lived experience, a modified Delphi process, and international consensus meetings. DEN-CORE recommends standardised core outcomes for early-stage, hospitalised, and critically ill patients with dengue (Yacoub et al., 2026). Although most studies included in this review were conducted before DEN-CORE was published, retrospective comparison demonstrates that many prioritised surrogate markers while inconsistently assessing clinical outcomes and safety. Prospective adoption of DEN-CORE should improve comparability, reduce selective outcome reporting, and facilitate future evidence synthesis.

For Indonesia, therapeutic research must account for the narrow treatment window, geographical differences in access to diagnostic testing, and variation in health-care capacity. Antiviral treatment is most likely to be effective when administered early, yet patients may present after peak viraemia or receive virological confirmation only after entering the critical phase. Future Indonesian trials should therefore integrate rapid diagnostics, standardised assessment of illness day, and early recruitment through coordinated primary-care and hospital networks. Multicentre designs are necessary to capture variation across regions and improve generalisability.

Indonesian studies should prioritise interventions with a clear biological rationale, adequate preclinical evidence, feasible administration, and a realistic pathway to clinical implementation. Trials should be sufficiently powered for DEN-CORE-aligned patient-

important outcomes, stratify participants by illness phase and disease severity, and report adverse events systematically. Virological, immunological, and haematological biomarkers remain valuable for explaining mechanisms, but they should complement rather than replace clinically meaningful endpoints. Children and adolescents should also be appropriately represented because they remain an important population affected by dengue but have been excluded from several antiviral trials.

Overall, the available evidence supports continued investigation rather than clinical adoption of the reviewed candidates. The most informative future studies will be those that intervene early, apply mechanism-appropriate dosing, use standardised formulations, assess safety rigorously, and distinguish biological activity from meaningful improvement in patient outcomes.

Strengths and limitations

This review has several strengths. It applied a structured literature search across PubMed/MEDLINE, Scopus, and Web of Science using predefined eligibility criteria. Study selection involved three authors, with disagreements resolved through discussion and consensus. The review also classified interventions according to their therapeutic rationale and developmental stage rather than treating antiviral, immunomodulatory, and platelet-enhancing agents as equivalent. Furthermore, virological, immunological, haematological, and patient-important clinical outcomes were evaluated separately, reducing the risk that changes in surrogate markers would be interpreted as evidence of clinical efficacy. The use of primary clinical and preclinical studies, supported by comparison with the DEN-CORE international consensus framework, enabled a clinically focused appraisal of the available evidence and its relevance to Indonesia.

Several limitations should also be acknowledged. First, this was a narrative review supported by structured search and selection procedures rather than a prospectively registered systematic review. Although eligibility criteria were predefined, a formal review protocol was not registered, and the review process did not include preparation of a PRISMA flow diagram. Second, the search was limited to three bibliographic databases and publications in English or Indonesian. Relevant studies indexed only in other databases, clinical-trial registries, regional databases, or other languages may therefore have been missed. Records and duplicates were managed manually, which may have introduced additional selection or data-management error.

Third, methodological quality was assessed descriptively rather than using formal study-design-specific instruments such as RoB 2 for randomised trials or ROBINS-I for non-randomised studies. Consequently, the review cannot provide standardised risk-of-bias ratings across the included evidence. Publication bias and selective outcome reporting also could not be assessed formally. Positive laboratory findings and platelet responses may be more likely to be published than neutral or unfavourable results.

Fourth, substantial heterogeneity was present in study populations, DENV serotypes, disease phases, intervention doses, treatment timing, comparators, follow-up periods, and outcome definitions. This heterogeneity, together with the limited number of studies for individual candidates, prevented meaningful quantitative synthesis. Direct comparisons between interventions should therefore be avoided. The inclusion of both clinical and preclinical studies provided a broader view of the therapeutic pipeline but also introduced differences in evidentiary strength. Findings from cell and animal models cannot be assumed to predict safety or efficacy in patients.

Finally, evidence directly generated in Indonesia was limited. The implications for the Indonesian health-care setting were therefore based partly on international studies conducted in other endemic countries and on consideration of Indonesia's epidemiological and health-system context. Differences in patient characteristics, circulating serotypes, diagnostic access, referral patterns, and clinical capacity may limit the direct transferability of these findings. These limitations should be considered when interpreting the conclusions and designing future Indonesian multicentre trials.

CONCLUSION

No antiviral, host-directed, immunomodulatory, or platelet-enhancing therapy currently has sufficiently consistent evidence to replace supportive care as the standard treatment for dengue. Celgosivir did not demonstrate virological or clinical efficacy, whereas ivermectin accelerated NS1 clearance without significantly improving viraemia clearance or clinical disease progression. Niclosamide and pimecrolimus remain preclinical candidates whose effectiveness and safety have not been established in patients. Prednisolone did not improve clinical, haematological, or virological outcomes, while rupatadine showed a preliminary but non-significant clinical signal that requires confirmation in an adequately powered trial. RhIL-11, anti-D immunoglobulin, eltrombopag, and *Carica papaya* preparations may accelerate

platelet recovery, but increased platelet counts should not be interpreted as evidence of reduced severe bleeding, plasma leakage, shock, intensive care admission, or mortality. Future multicentre trials in Indonesia should enrol patients early in the disease course, use standardised formulations and mechanism-appropriate dosing, include systematic safety assessment, and adopt the DEN-CORE consensus framework. Virological, immunological, and haematological biomarkers should be used to explain therapeutic mechanisms, while patient-important clinical outcomes should remain the principal basis for determining clinical efficacy.

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