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Review

Dengue Fever: Comprehensive Review of Clinical Spectrum, Diagnostics and Management

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ABSTRACT

Background:

Dengue fever is the most prevalent mosquito-borne viral disease, with an estimated 390 million infections annually. It is caused by four antigenically distinct Dengue virus serotypes (DENV-1–4) and transmitted primarily by Aedes aegypti.

Main Findings:

The illness ranges from mild febrile episodes to severe Dengue characterized by plasma leakage, bleeding, or organ failure. Pathogenesis is driven by complex host–virus interactions, including antibody-dependent enhancement. Diagnosis relies on time-appropriate use of NS1 antigen, RT-PCR, and serology, complemented by haematocrit and platelet monitoring. Management is primarily supportive, with meticulous fluid therapy, avoidance of unnecessary transfusions, and close observation during the critical phase. Recent advances include WHO-endorsed TAK-003 vaccination, Wolbachia-based vector control, improved diagnostic algorithms, and emerging antiviral and monoclonal antibody candidates.

Implications:

Early recognition of warning signs, judicious fluid management, and implementation of vaccination and vector strategies are key to reducing morbidity and mortality. Research priorities include improved vaccines, therapeutics, and biomarkers for disease severity.

KEYWORDS: Arboviral disease, NS1 glycoprotein, Dengue Shock Syndrome

INTRODUCTION

Dengue fever is a rapidly expanding mosquito-borne viral infection that has become a major public-health concern across tropical and subtropical regions. Current estimates suggest 390 million infections annually, with ~96 million symptomatic cases, making Dengue the most prevalent arboviral illness worldwide[1,2].

Global Burden and Epidemiology

Once limited to sporadic outbreaks, Dengue has evolved into a global pandemic threat over the past five decades. Transmission is sustained in more than 120 countries, with the heaviest burden in South-East Asia, the Western Pacific, and the Americas[3]. Africa and the Eastern Mediterranean have also reported an increasing incidence, often linked to urbanisation, climate variability, and rapid human mobility[4].

Epidemics typically peak during the rainy season, when vector density and virus transmission intensify. The virus is primarily carried by *Aedes aegypti*, a highly anthropophilic, day-biting mosquito that thrives in peri-domestic habitats. *Aedes albopictus* has extended the disease range to temperate zones, including parts of Europe and North America[5].

Historical Perspective

The earliest reliable description of Dengue-like illness dates back to the late 18th century, but the isolation of the virus occurred only in 1943–44 during World War II. The classification of four antigenically distinct serotypes (DENV-1 to DENV-4) in the 1950s established the basis for modern understanding of pathogenesis and immunity. The introduction of the WHO 1997 classification (DF, DHF, DSS) and its revision in 2009 (Dengue, Dengue with warning signs, severe Dengue) reflected evolving clinical insight[6].

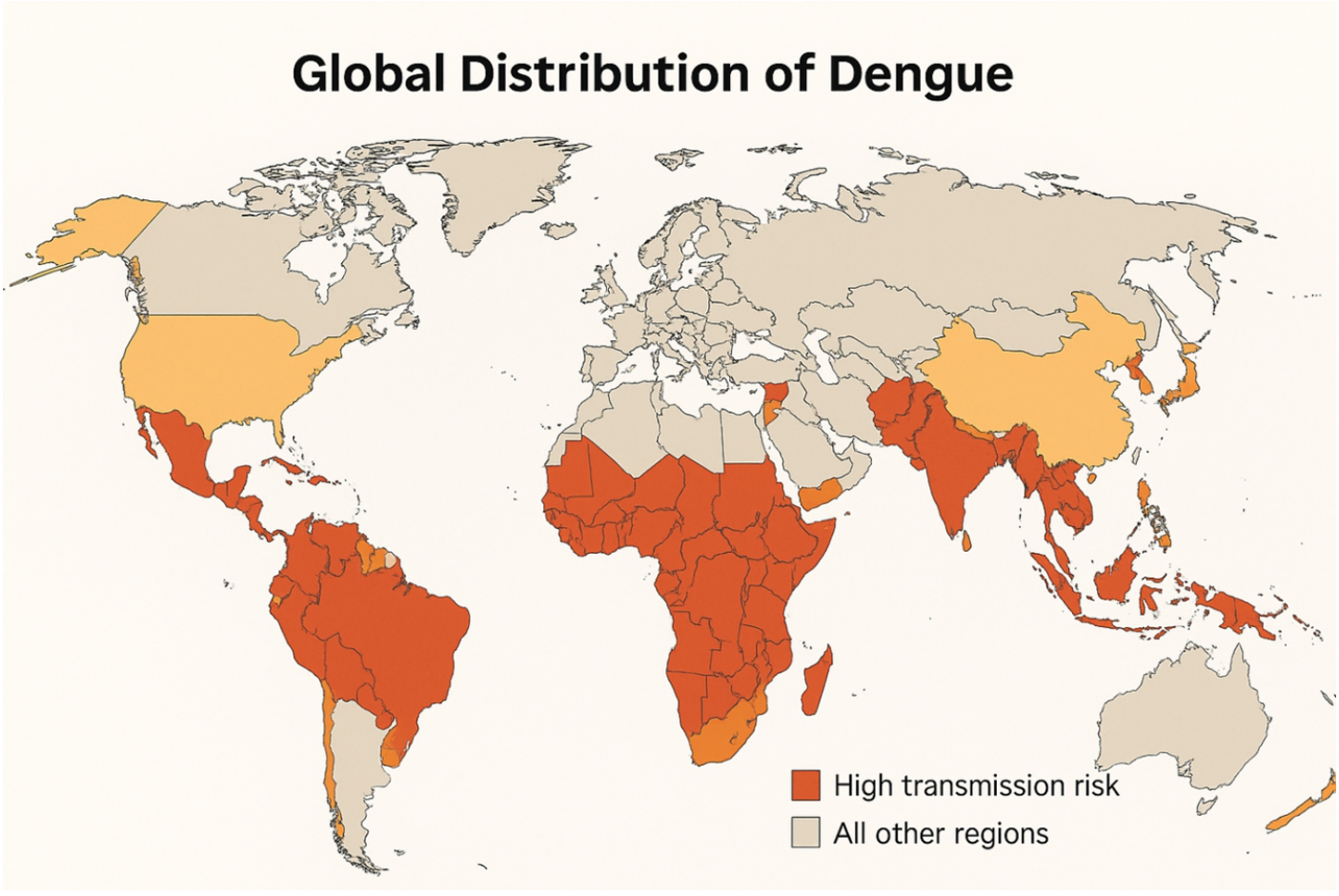

Figure 1: Global Distribution of Dengue Virus
World Map Showing Endemic and Epidemic Dengue Transmission; Shading indicates Intensity

Drivers of Resurgence

Several factors underpin Dengue's dramatic resurgence:

- Urbanisation & population growth: create favourable breeding environments for *Aedes*
- Climate change: expands mosquito habitats and prolongs transmission seasons
- Global travel & trade: facilitate importation of viral serotypes and genotypes
- Limitations in vector control: insecticide resistance, inadequate community participation
- Health-system gaps: delayed diagnosis, limited access to critical care during outbreaks

Scope and Objectives of this Review

This article provides a comprehensive narrative synthesis of Dengue fever and its complications. It covers:

- Etiological strains and molecular epidemiology
- Pathogenesis, including antibody-dependent enhancement (ADE) and host factors
- Clinical spectrum and complications across age groups and special populations
- Laboratory investigations, including novel biomarkers and imaging
- Evidence-based management, with emphasis on fluid therapy and organ support
- Prevention strategies: vaccination, vector control, and emerging interventions
- Research gaps and health-system priorities

Virology and Molecular Epidemiology

Taxonomy and Structural Biology

Dengue virus belongs to the genus *Flavivirus*, family *Flaviviridae*. It is an enveloped, positive-sense single-stranded RNA virus (~11 kb). The genome encodes a single polyprotein cleaved into three structural proteins (capsid [C], membrane [M], envelope [E]) and seven non-structural proteins (NS1–NS5)[7]. The envelope (E) protein mediates cell attachment and fusion and is the main target of neutralising antibodies.

Serotypes and Genotypes

Four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4 are antigenically distinct but share ~65% sequence homology. Each serotype has multiple genotypes, with geographic clustering and periodic lineage replacement. For example, DENV-2 Asian I and Cosmopolitan genotypes have repeatedly driven large epidemics in South-East Asia and the Americas[8].

Key Objectives of this Review

1. Integration of Pathobiology	Summaries current knowledge of viral biology, host responses, and mechanisms of disease.
2. Clinical Translation	Link basic science to bedside diagnosis, risk assessment, and therapeutic decision-making.
3. Recent Innovations	Highlight advances in diagnostics, antivirals, vaccines, and implementation strategies.
4. Pragmatic Focus	Provide clear, evidence-based guidance applicable to everyday practice and research settings.
5. Comprehensive Resource	Present a single, authoritative reference uniting foundational concepts with emerging data.

Table 1: **Dengue Serotypes and Genotypes**
Summary of the four serotypes, representative genotypes, and epidemiological features

Serotype	Representative Genotypes	Remarks
DENV-1	Genotype I, Genotype V	Common in Asia; often mild
DENV-2	Asian I, Cosmopolitan	Frequently linked to severe disease
DENV-3	Genotype I, Genotype III	Responsible for large epidemics in Asia and Latin America
DENV-4	Genotype II	Usually causes milder outbreaks

Replication Cycle

After inoculation by an infected mosquito, the virus binds to heparan-sulfate or DC-SIGN receptors on dendritic cells. Viral RNA is translated and replicated in the endoplasmic reticulum; progeny virions assemble and are released via exocytosis. The NS1 glycoprotein, secreted early, is an important diagnostic marker and contributes to immune evasion[9].

Evolution and Molecular Epidemiology

Phylogenetic analyses reveal frequent inter-serotype recombination and intra-serotype diversification. Globalisation has increased cross-border spread of lineages, occasionally introducing "virulent" clades associated with severe disease. Continuous sequencing of outbreak isolates informs vaccine strain selection and real-time surveillance[10].

Virus-vector Interactions

Aedes aegypti is the principal vector due to its preference for human blood and peri-domestic habitats. *Aedes albopictus*, with greater ecological plasticity enables transmission in subtropical climates. Vector competence varies by mosquito genotype and viral serotype, with higher susceptibility reported for DENV-2 and DENV-3 in several studies[11].

Implications for Control and Vaccine Design

Knowledge of serotype/ genotype dynamics is crucial for vaccine formulation. Balanced, durable immunity across all serotypes is required to avoid antibody-dependent enhancement (ADE). Genomic data also help identify introductions of new lineages that may outcompete resident strains, leading to outbreaks despite existing herd immunity.

Pathogenesis

Overview

The pathogenesis of Dengue is multifactorial, involving direct viral effects and host immune responses that culminate in plasma leakage, bleeding, and organ injury. While most infections are mild or asymptomatic, a subset progress to severe disease, typically at the time of defervescence.

Early Events after Inoculation

After the bite of an infected *Aedes* mosquito, the virus infects skin dendritic cells, keratinocytes, and Langerhans cells. Infected cells migrate to regional lymph nodes, spreading viremia within 24-48 hours. The virus primarily targets monocytes, macrophages, and endothelial cells [Figure 2].

Innate Immune Response

- Type I interferons (IFN-α/β): produced rapidly, limiting early replication
- Pattern-recognition receptors (e.g., TLR3, TLR7, RIG-I): activate NF-κB and IRF pathways
- Over-activation of innate immunity leads to a "cytokine storm," releasing TNF-α, IL-6, IL-8, IL-10, IFN-γ, and chemokines

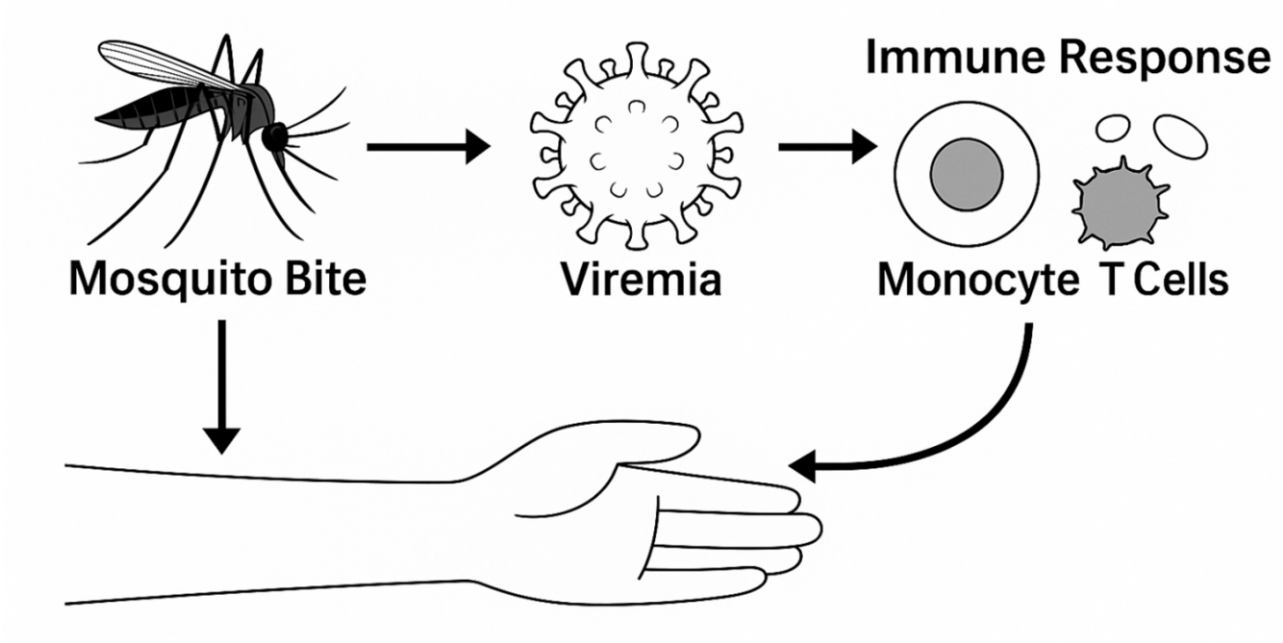

Figure 2: Pathogenesis of Dengue

Adaptive Immunity and Antibody-dependent Enhancement (ADE)

A hallmark of Dengue pathogenesis is antibody-dependent enhancement. Pre-existing, non-neutralising antibodies from a previous infection (or an imbalanced immune response after vaccination) facilitate viral entry via Fcγ receptors on monocytes/macrophages, amplifying viral replication and immune activation. This explains why secondary infection often carries higher risk of severe disease.

Endothelial Dysfunction and Plasma Leakage

Severe Dengue is characterised by capillary leak due to:

- Disruption of the endothelial glycocalyx by viral proteins (NS1) and cytokines
- Altered tight junctions and cytoskeletal rearrangement
- Complement activation and mast-cell degranulation releasing histamine, tryptase, and VEGF

The result is increased vascular permeability, leading to haemoconcentration, pleural effusions, ascites, and in extreme cases, Dengue shock syndrome (DSS).

Haemostatic Abnormalities and Bleeding

Multiple mechanisms contribute:

- Thrombocytopenia from bone-marrow suppression and peripheral destruction
- Platelet dysfunction (impaired aggregation, storage pool defects)
- Coagulation abnormalities: prolonged PT/aPTT, low fibrinogen (rarely frank DIC)
- Vascular fragility and liver dysfunction further increase risk

Organ Involvement

- Liver: direct viral injury, immune-mediated necrosis, and microcirculatory impairment; AST often exceeds ALT
- Kidneys: acute tubular necrosis or immune-mediated nephritis, occasionally requiring renal replacement therapy
- Heart: myocarditis or arrhythmias in severe cases
- Central nervous system: encephalopathy from hepatic failure or shock; encephalitis is rare but documented
- Bone marrow: suppression may contribute to cytopenias

Host and Viral Risk Factors for Severity

- Host: age (children, elderly), pregnancy, comorbidities (diabetes, asthma, CKD), genetic polymorphisms in TNF-α, HLA, Fcγ receptors
- Viral: serotype (DENV-2/3 linked to severe cases), genotype virulence, high viremia

Research Frontiers

- Role of endothelial glycocalyx biomarkers (syndecan-1, angiopoietin-2) in predicting plasma leakage
- Single-cell transcriptomics mapping immune cell phenotypes
- Investigational therapeutics targeting NS1, mast-cell stabilisers, and complement inhibitors

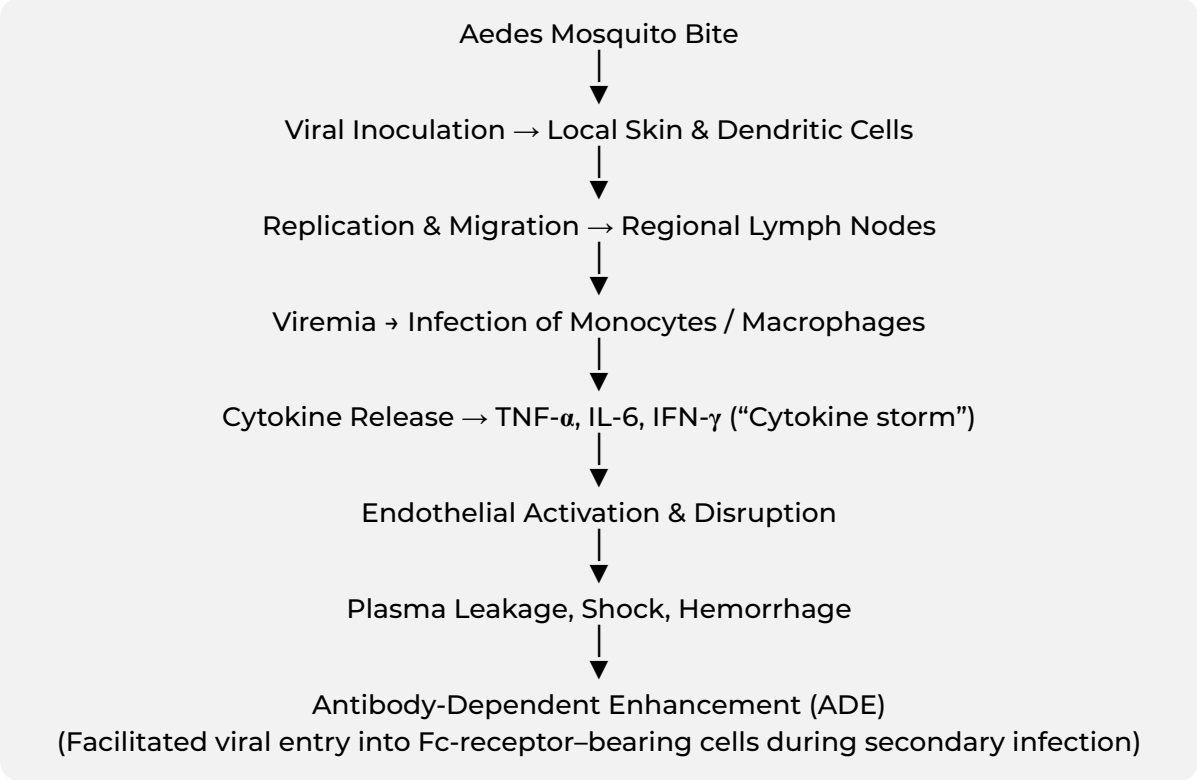

Figure 2: Pathogenesis of Dengue - from Mosquito Bite to ADE

Description*: Stepwise mechanisms in Dengue infection: inoculation by Aedes mosquito, viral replication in local dendritic cells, dissemination via lymphatics, viremia, cytokine storm, endothelial activation and capillary leakage, culminating in antibody-dependent enhancement during secondary infection.*

Clinical Spectrum and Complications[12,13]

Natural History and Phases

Dengue typically evolves through three overlapping phases:

Phase	Timing (Days of illness)	Clinical Features
Febrile	Day 0–3/4	Sudden high fever, intense headache, retro-orbital pain, myalgia ("breakbone fever"), arthralgia, rash (often flushing or maculopapular), mild mucosal bleeding
Critical (plasma-leak)	Day 3–7 (usually as fever subsides)	Warning signs appear: abdominal pain/tenderness, persistent vomiting, pleural effusion or ascites, mucosal bleed, lethargy/restlessness, hepatomegaly >2 cm, rising haematocrit with falling platelets
Recovery	Day 7–10	Reabsorption of extravasated fluid, gradual improvement in appetite, diuresis, bradycardia, pruritic rash

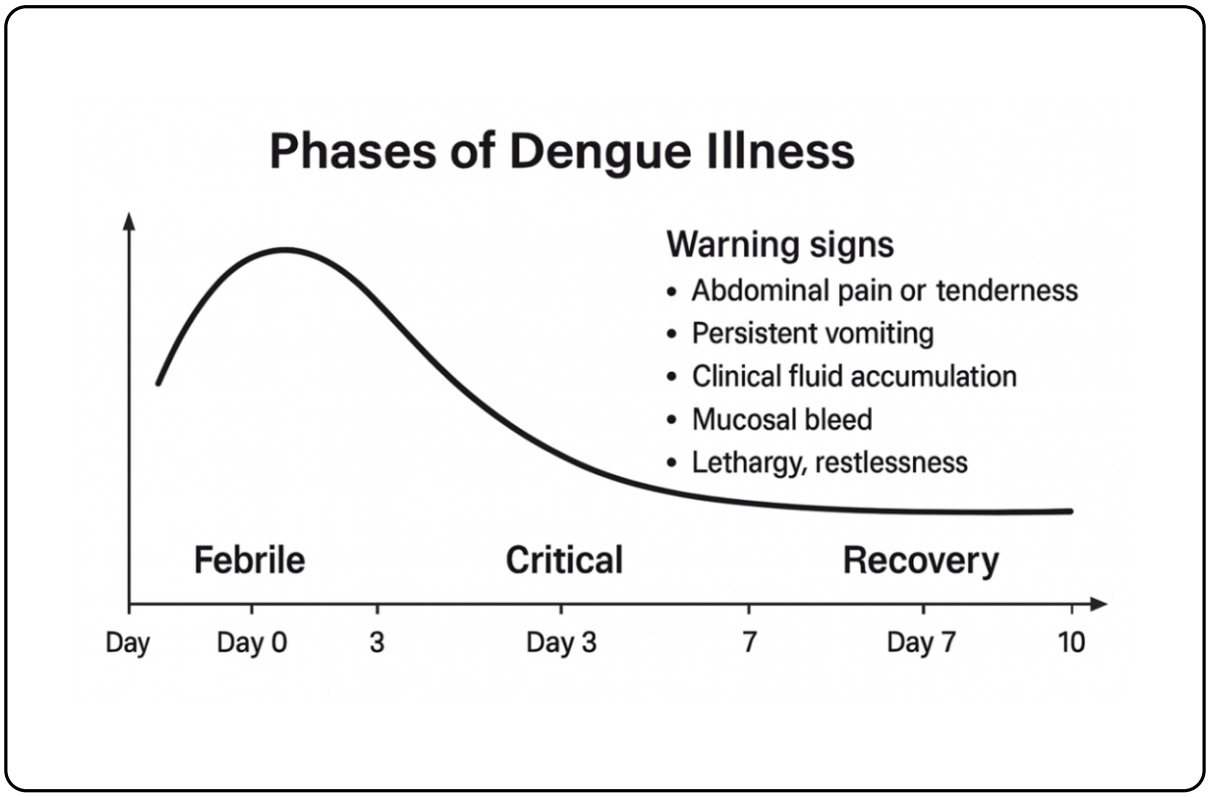

Figure 3: Phases of Dengue Illness

Timeline of Febrile, Critical and Recovery Phases with Warning Signs Highlighted

WHO Clinical Classification (2009)

- **Dengue without Warning Signs** - fever plus two of: nausea/vomiting, rash, aches and pains, positive tourniquet test, leucopenia
- **Dengue with Warning Signs** - presence of any sign listed above; indicates close monitoring/admission
- **Severe Dengue** - any of: severe plasma leakage (shock, respiratory distress), severe bleeding, or severe organ involvement (AST/ALT ≥1000 IU/L, impaired consciousness, heart failure)

Warning Signs and Admission Criteria

Key predictors of severe disease:

- Abdominal pain/ tenderness
- Persistent vomiting
- Clinical fluid accumulation (pleural effusion, ascites)
- Mucosal bleeding
- Lethargy or restlessness
- Enlarged liver (>2 cm)
- Rapid rise in haematocrit with precipitous platelet fall

Patients with any warning sign warrant hospital admission for serial monitoring.

Complications

Dengue Shock Syndrome (DSS)

- Characterised by narrow pulse pressure (<20 mmHg), tachycardia, cool extremities, delayed capillary refill
- May be "compensated" (normal BP) before progressing to hypotensive shock
- Plasma leakage is maximal at this stage; aggressive but carefully titrated fluids are lifesaving

Bleeding Manifestations

- Usually mucocutaneous (epistaxis, gum bleed, petechiae)
- Major bleeding (GI, intracranial) is uncommon and often accompanies profound plasma leakage or coagulopathy
- Platelet count alone is a poor predictor; clinical context and haematocrit trends are essential

Hepatic Involvement

- Elevated transaminases (AST > ALT) are common; levels >1000 IU/L suggest severe disease
- Fulminant hepatic failure, though rare, has high mortality

Renal Complications

- Acute kidney injury from hypoperfusion, rhabdomyolysis, or immune injury
- Requires vigilant fluid balance and renal replacement therapy when indicated

Neurological Manifestations

- Encephalopathy (from liver failure, shock, or hyponatraemia) is most frequent
- Encephalitis, Guillain–Barré syndrome, myelitis, cerebellitis[11] and intracranial haemorrhage have been reported

Cardiac Involvement

- Myocarditis[13], conduction disturbances, or pericardial effusion
- ECG and echocardiography recommended in severe Dengue or unexplained shock

Haematological & Immune

- Severe thrombocytopenia, bone-marrow suppression
- Haemophagocytic lymphohistiocytosis (HLH): persistent fever, cytopenias, hyperferritinaemia; high suspicion needed in prolonged illness

Others

- Pancreatitis, splenic rupture, secondary bacterial infections, chronic fatigue

Special Populations

- Children: Higher risk of shock with subtle symptoms; narrow pulse pressure may be the first clue
- Pregnant women: Increased risk of severe bleeding and obstetric complications (preterm birth, stillbirth)
- Elderly & comorbid patients: Prone to fluid overload during resuscitation; closer monitoring required
- Immunocompromised: Prolonged viraemia, atypical manifestations

Laboratory Investigations and Monitoring

General Principles

Laboratory testing in Dengue serves three purposes:

1. Confirm the diagnosis (especially early)
2. Assess severity by tracking haematocrit, platelets, and biochemical markers
3. Identify complications and guide therapy

Investigations should be timed according to the day of illness and repeated as the patient progresses through febrile, critical, and recovery phases.

Virological and Serological Tests

Day of illness	Preferred Test	Remarks
0–5	NS1 antigen or RT-PCR	High sensitivity in primary infection; NS1 less sensitive in secondary infection
3–7	Combined NS1 + IgM or RT-PCR	Improves diagnostic yield in transition phase
≥5	IgM ELISA ± IgG	Demonstrates seroconversion; useful for retrospective confirmation

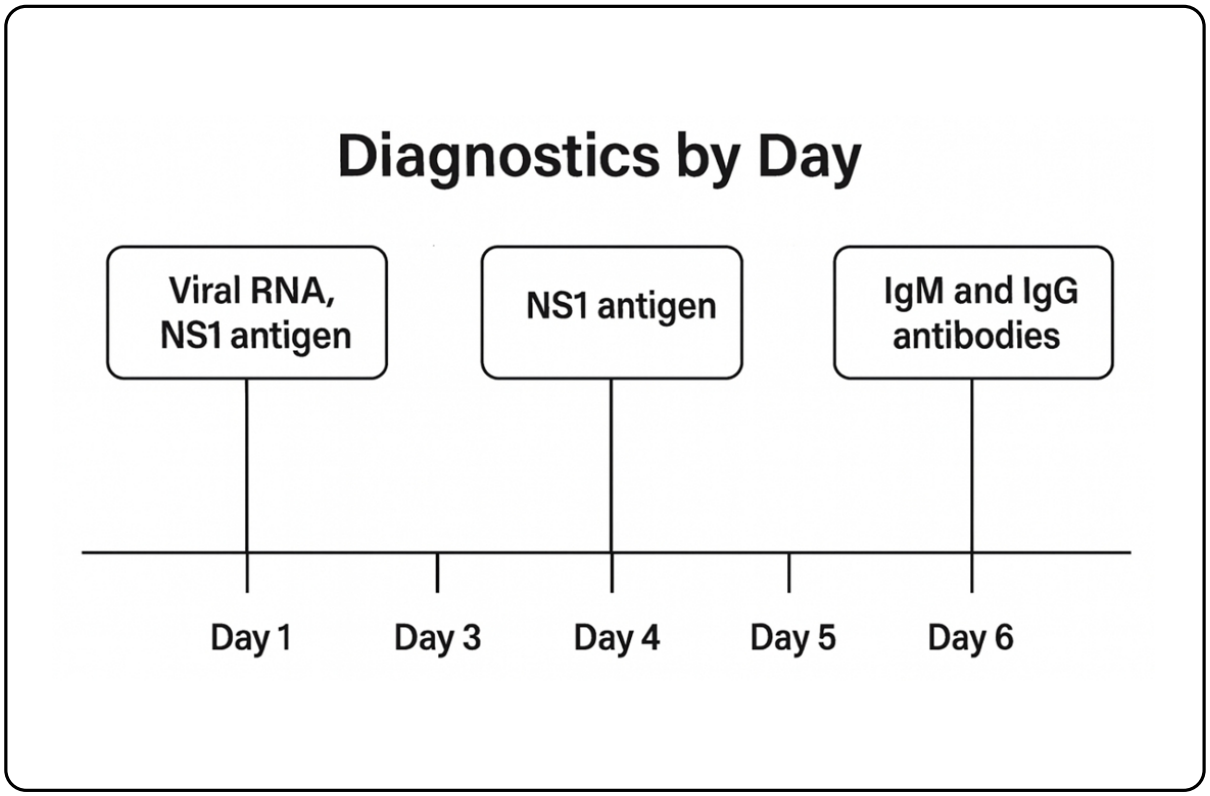

Figure 5: Diagnostic Approach by Day of illness
Flowchart Showing Recommended Laboratory Tests Aligned with Day of illness

Key Notes

- **NS1 antigen** is detectable during the viraemic phase and declines as antibodies appear
- **RT-PCR** provides serotype information, useful for surveillance and outbreak response
- **IgG avidity testing** can help distinguish primary from secondary infection in research or complex cases

Haematology

- **Complete blood count**: leukopenia (esp. lymphopenia) is common by day 2–3; progressive thrombocytopenia is typical
- **Haematocrit (Hct)**: rising Hct (>20% from baseline) indicates plasma leakage. Serial Hct is more useful than single values
- **Peripheral smear**: excludes malaria or other coinfections
- **Lactate**: early indicator of tissue hypoperfusion and risk of DSS
- Prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen if bleeding is significant
- D-dimer and fibrin degradation products: may be elevated but not specific for DIC
- Ferritin, triglycerides, soluble CD25: helpful in suspected HLH (Hemophagocytic Lymphohistiocytosis)

Imaging

- Chest Radiography & Abdominal Ultrasound: detect pleural effusion, ascites, and gallbladder wall thickening (an early sign of plasma leakage)
- Point-of-care Ultrasound (POCUS): dynamic tool for bedside assessment of fluid status (IVC collapsibility), serosal effusions, and cardiac function

Table 2: Biochemical Markers and Prognostic Implications in Severe Dengue

Parameter	Typical Change	Prognostic Message
Haematocrit ↑ > 20% from Baseline	Plasma leakage / haemoconcentration	Start IV fluids promptly; anticipate critical phase
Platelets ↓ < 100 × 10⁹/L	Marker of severity	Not an isolated trigger for transfusion (unless bleeding)
AST > ALT	Hepatic involvement	> 1000 IU/L suggests severe hepatic injury
Serum lactate ↑	Tissue hypoperfusion	Predicts shock, organ dysfunction
Albumin ↓	Capillary leakage	Early clue to plasma leakage
Coagulation & Inflammatory Markers	↑ aPTT, ↑ D-dimer, ↑ ferritin, ↑ CRP	Suggest progression to severe disease/ DIC; guide monitoring

[**Abbreviations:** AST – aspartate aminotransferase; ALT – alanine aminotransferase; aPTT – activated partial thromboplastin time; DIC – disseminated intravascular coagulation; CRP – C-reactive protein]

Biochemical Profile

- **Liver function tests**: AST often > ALT; marked elevations (>1000 IU/L) suggest severe disease or hepatic failure
- **Renal function**: serum creatinine, urea, electrolytes; monitor closely if shock or rhabdomyolysis suspected
- **Serum albumin**: low levels may indicate plasma leakage

Monitoring Schedule

- Stable Outpatients: daily platelet and Hct (or alternate-day if afebrile and improving)
- Hospitalised Patients: 6–12 hourly Hct and platelets during the critical phase; more frequent if shock suspected
- ICU Patients: continuous vitals, strict input–output, lactate, Hct, ABG, and bedside USG

Management

Guiding Principles

Management of Dengue is **supportive**, aimed at:

- Preventing progression to severe disease
- Managing plasma leakage and shock
- Treating bleeding and organ dysfunction
- Avoiding iatrogenic fluid overload and unnecessary transfusions

Early triage based on warning signs and daily assessment of haematocrit, platelet trends, and clinical status is essential.

Outpatient Care (Dengue without Warning Signs)

- Adequate oral fluids (2.5–3 L/day for adults; 50–70 mL/kg/day for children)
- Paracetamol for fever (≤60 mg/kg/day in divided doses)
- Avoid NSAIDs, aspirin, and corticosteroids
- Return immediately if warning signs or persistent vomiting occur

Hospital Care (Dengue with Warning Signs or Co-morbidities)

- Bed rest and close monitoring of vitals, Hct, platelets, urine output
- IV isotonic crystalloids for patients with rising Hct or early plasma leakage
- Maintain urine output ≥0.5 mL/kg/h

Management of Severe Dengue and Shock

Fluid Resuscitation is the Cornerstone.

Initial Resuscitation

- Start 0.9% saline or Ringer's lactate at 10–20 mL/kg over 15-30 min.
- Reassess: pulse pressure, capillary refill, BP, Hct.
- If improved → reduce rate to 5-7 mL/kg/h

Persistent Shock

- Repeat bolus; if Hct rises, plasma leakage predominates → continue crystalloids
- If Hct drops (suggesting bleeding) → transfuse packed RBCs

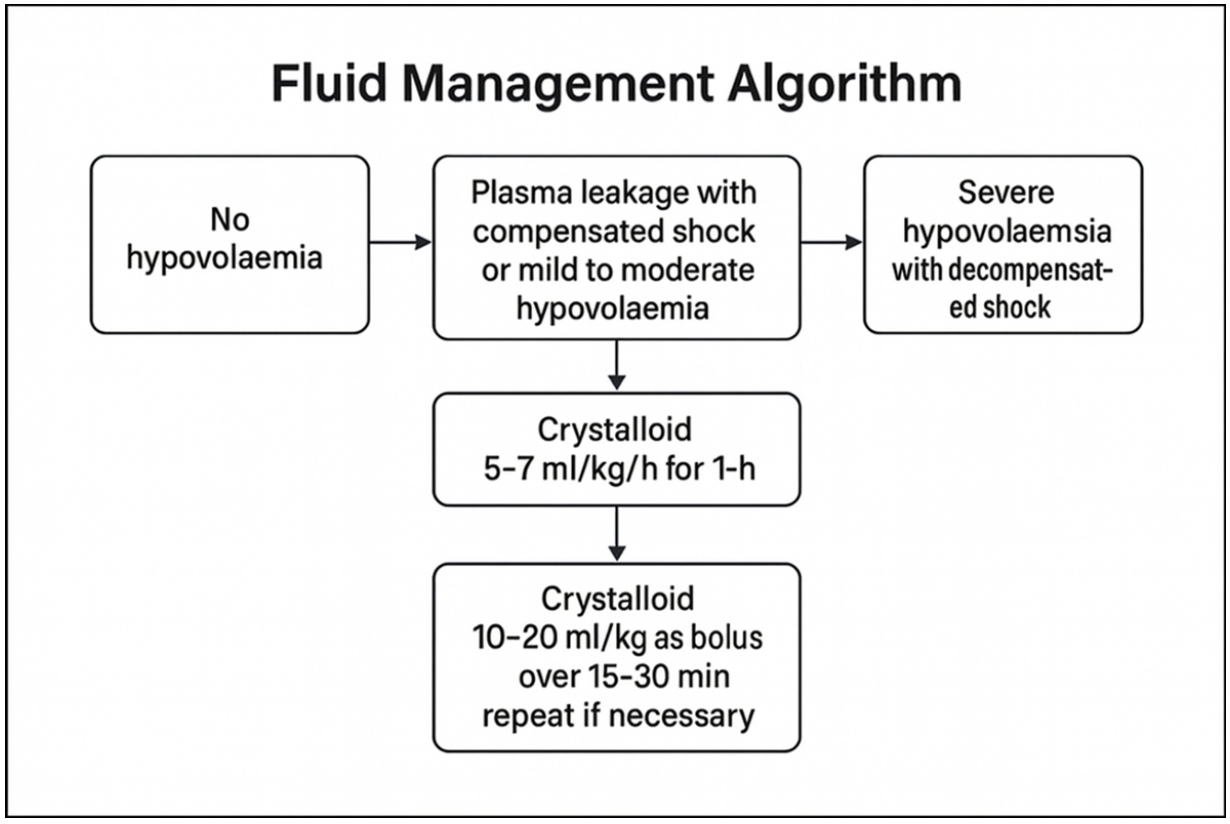

Figure 5: Algorithm for Fluid Management in Severe Dengue

Flowchart for Stepwise IV Fluid Therapy in Shock/ Plasma Leakage with Reassessment Points

Refractory Shock

- Consider colloids (dextran 40 or 5% albumin) if not responding after 2–3 crystalloid boluses
- Initiate vasopressors (e.g., norepinephrine) only after adequate fluid resuscitation

Bleeding and Transfusion Strategy

- Avoid prophylactic platelet transfusion in non-bleeding patients, regardless of count[13]
- Transfuse platelets only if:
  - Major bleeding, or
  - Invasive procedure required with very low counts (<10–20 ×10⁹/L)
- Packed RBCs for significant haemorrhage or Hct <30% with instability
- FFP or cryoprecipitate only if documented coagulopathy with active bleeding

Organ Support

- **Hepatic Failure:** manage coagulopathy, avoid hepatotoxic drugs, consider N-acetylcysteine in early acute liver injury
- **AKI:** maintain perfusion, avoid nephrotoxins, initiate dialysis for refractory acidosis, hyperkaliemia, or volume overload
- **Neurologic Complications:** correct metabolic derangements; mannitol or hypertonic saline if raised ICP
- **Cardiac Involvement:** ECG, troponin, echocardiography; manage arrhythmias and heart failure supportively

Convalescent Phase Management

- As leakage resolves, patients may develop diuresis and bradycardia
- Gradually reduce IV fluids to maintenance or stop when stable and drinking well
- Counsel regarding fatigue and mood changes that can persist for weeks

Discharge Criteria

- Afebrile for ≥24–48 h
- No warning signs
- Stable Hct, platelets rising (>50 ×10⁹/L)
- Good oral intake and urine output
- Reliable access to follow-up

Prevention and Recent Advances

Vaccines

TAK-003 (Qdenga)

- A live-attenuated, tetravalent vaccine derived from DENV-2 backbone expressing structural proteins of the other serotypes
- WHO prequalified (May 2024) for ages 6-45 in moderate–high transmission settings, irrespective of serostatus
- Phase 3 (CYD15) showed ~80% efficacy against symptomatic Dengue and ~90% against hospitalisation across serotypes
- Two-dose schedule (0, 3 months). Demonstrated good safety in seronegatives

CYD-TDV (Dengvaxia)

- Recommended only in seropositive individuals aged 9-45; not for seronegatives due to increased risk of severe disease after natural infection

Pipeline Candidates

- TV003/TV005 (NIH Butantan): phase 3 ongoing in Brazil
- Recombinant subunit and mRNA vaccines under early development

Table 3: Dengue Vaccines - Composition, Indications, and Efficacy

Vaccine	Platform/ Composition	Indication (Age/ Serostatus)	Efficacy vs. Symptomatic Dengue	Safety & Remarks
TAK-003 (Qdenga)	Live-attenuated tetravalent (DENV-2 backbone expressing prM/E of DENV-1,3,4)	6–45 yr, regardless of serostatus	≈ 80% overall efficacy (3–4 yr follow-up)	Generally well tolerated; mild injection-site reactions
CYD-TDV (Dengvaxia)	Chimeric vaccine (YF-17D backbone with Dengue prM/E)	9–45 yr, *only* in seropositive individuals	≈ 60% (higher in baseline-seropositive)	↑ risk of severe Dengue in seronegatives → pre-vaccination screening recommended
TV003 / TV005	NIH live-attenuated candidate (single-dose)	Phase 3 trials (Brazil, others)	Pending final results (≥ 80% in phase 2)	Good safety in early studies
Other pipeline vaccines	mRNA, VLP, recombinant subunit platforms	Early phase studies	Data awaited	Require further evaluation

[**Abbreviations:** prM/E – pre-membrane/ envelope proteins; VLP - virus-like particle]

Vector Control

Wolbachia-based Strategies

- Release of *Aedes aegypti* infected with Wolbachia (wMel strain) reduces mosquito susceptibility to Dengue
- Large cluster-RCT (Indonesia, NEJM 2021) showed 77% reduction in virologically confirmed Dengue and 86% fewer hospitalisations

Integrated Vector Management

- Source reduction: cover water containers, eliminate breeding sites
- Larvicides (temephos, pyriproxyfen) and adulticiding in outbreaks
- Community engagement and environmental sanitation

Gene-drive Mosquitoes

- CRISPR-based strategies under study to spread sterility or antiviral genes in wild populations

Personal Protection

- Long sleeves, trousers, permethrin-treated clothing
- Bed nets (esp. for infants)
- Household insect screens and repellents (DEET, picaridin)

Diagnostics and Surveillance

- Improved NS1 lateral-flow assays and multiplex RT-PCR for simultaneous detection of DENV, Zika, and chikungunya
- Digital tools: smartphone-linked RDT readers, GIS-based vector mapping, syndromic dashboards for outbreak prediction

Therapeutic Pipeline

- Monoclonal antibodies (e.g., VIS513, DN-01) show potent neutralising activity in early trials
- Small-molecule antivirals (e.g., Balapiravir analogues, nucleoside inhibitors) in phase 1-2
- Host-directed approaches: NS1 inhibitors, mast-cell stabilisers, complement pathway blockers

Health-system Strategies

- Early triage algorithms in emergency departments
- Surge-capacity planning for IV fluids, ICU beds, and blood components during outbreaks
- Training primary-care workers in recognition of warning signs

Key Practice Messages for Prevention and Health-System Preparedness

- Integrate vaccination (e.g., TAK-003 / Qdenga where eligible) with robust vector-control programmes
- Use Wolbachia-infected *Aedes* releases and community-based source reduction as sustainable, long-term strategies
- Maintain real-time surveillance by combining laboratory reporting, syndromic dashboards, and entomological data
- Prepare health-care surge capacity ahead of seasonal peaks: secure IV fluids, ICU beds, and blood products
- Train frontline staff in early triage and recognition of warning signs to prevent progression to severe Dengue
- Establish clear referral pathways and stockpiles for paediatric and obstetric emergencies
- Communicate clear public-health messages on personal protection (repellents, protective clothing, household screening)
- Strengthen multi-sector coordination (public health, environment, education, waste management) for sustained impact

Conclusions and Key Messages

Dengue fever has emerged as one of the most important global arboviral threats, with a steadily rising incidence, geographic expansion, and increasing frequency of severe manifestations. Advances in molecular virology, immunopathogenesis, and diagnostics have deepened understanding of disease biology, while refined fluid therapy and critical-care practices have significantly reduced case-fatality rates in specialised centres.

Yet, challenges persist: unpredictable outbreaks, heterogeneous health-system capacity, and the absence of widely deployed antivirals. The advent of TAK-003 vaccination and Wolbachia-based vector control marks a new era of integrated prevention, but sustainable implementation requires robust surveillance, supply chains, and community participation. Continued investment in vaccine innovation, host-targeted therapies, and biomarker discovery is essential to achieve durable control and improved clinical outcomes.

Practice Pearls: Early Recognition, Fluid Therapy, Transfusion, and Integrated Prevention

- **Link Diagnostics to Day of illness**: pair NS1 or RT-PCR in the first 5 days, then IgM/IgG serology after day 5 for confirmation
- **Watch for Warning Signs after Defervescence**: abdominal pain, persistent vomiting, mucosal bleed, rising haematocrit with falling platelets - herald the *critical phase*; admit and monitor closely
- **Fluids Save Lives**: begin isotonic crystalloids promptly, titrate to perfusion targets, and avoid fluid overload (monitor urine output, respiratory status)
- **Restrict Platelet Transfusion**: reserve for clinically significant bleeding or invasive procedures, not for low counts alone
- **Prevention is Integrated**: combine vaccination (e.g., TAK-003 where indicated) with sustained vector-control programmes

Research Priorities: Vaccines, Antivirals, Biomarkers, and Outbreak Preparedness

- **Advance Vaccine Science**: develop safe, broadly protective Dengue vaccines effective across serotypes and serostatus groups
- **Discover Novel Therapeutics**: pursue direct-acting antivirals and adjunctive immunomodulators to reduce viral replication and immune-mediated injury
- **Validate Predictive Biomarkers**: identify and test early markers of plasma leakage and severe disease for timely risk stratification
- **Strengthen Outbreak Preparedness**: conduct operational research on cost-effective surveillance, early warning, and response systems for low-resource and high-burden settings

CONFLICT OF INTEREST: None

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