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I. Introduction

Dengue is a mosquito-borne viral disease (arboviral) caused by the dengue virus. Transmission occurs via the bite of mosquitoes - *Aedes aegypti* and *Aedes albopictus*, which thrive in tropical and sub-tropical regions. In 2023, WHO classified the worldwide surge in dengue cases as a Grade 3 public health emergency, its highest level of alert. In 2024, dengue cases worldwide rose to an unprecedented level, with approximately 14.6 million infections and more than 12,000 deaths reported to the World Health Organization [1]. Dengue has now become endemic in over 128 countries worldwide [2]. Singapore reported a total of 13,655 dengue cases in 2024, but lower than the record high of 35,315 cases reported in 2020 [3, 4]. Dengue is a notifiable disease in Singapore.

Dengue virus is an enveloped, positive-sense, single-stranded RNA virus from the *Flaviviridae* family. There are 4 serotypes of dengue – DENV-1, DENV-2, DENV-3, DENV-4. Infection with one serotype confers immunity to that serotype only. A secondary infection with a different serotype (heterologous infection) can lead to a more severe dengue infection due to antibody-dependent enhancement. Antibody-dependent enhancement (ADE) facilitates dengue virus entry into immune cells through Fcγ receptors, increasing viral replication and resulting in higher levels of viraemia and stronger pro-inflammatory immune responses [5]. Individuals at higher risk of severe dengue include young children, older adults, obese individuals, those with prior dengue infections, and people with chronic conditions such as diabetes, hypertension, cardiovascular or kidney disease [6-9].

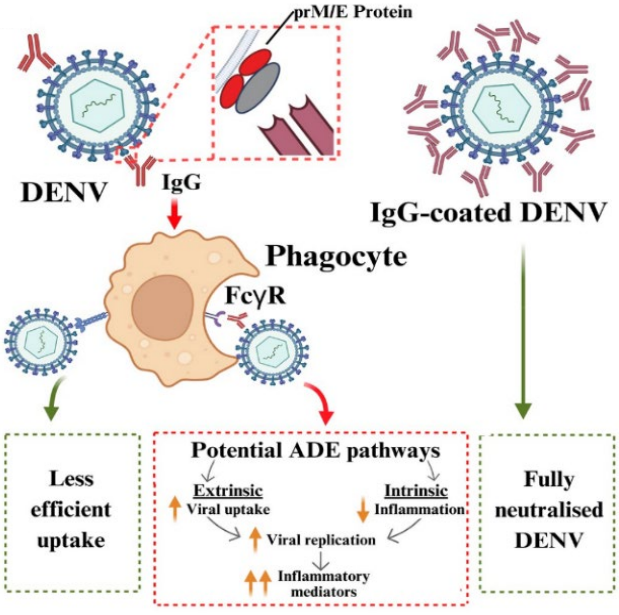

Figure 1: Schematic representation of IgG antibodies and the interaction with DENV. Anti-DENV IgGs can bind to DENV antigens including PrM and E proteins, which promotes interaction with FcγRs, such as FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16), expressed by phagocytes. When these antibodies are insufficient to neutralise the DENV, this may then result in enhanced immature virion uptake into the phagocytes (extrinsic pathway). In the phagocytes, the suppression of a pro-inflammatory response and induction of a Th2-type immune response can further enhance viral replication (intrinsic pathway), and subsequently cause excessive cytokine production. Together, this process is termed as antibody-dependent enhancement. On the other hand, in the absence of IgG, DENV is taken into the phagocytes less efficiently through canonical receptor-mediated endocytosis and is unlikely to contribute to ADE. When neutralising anti-DENV IgGs are present at high levels, DENV is fully neutralised and severe pathology can be prevented. Reproduced from [5]. Licensed under a Creative Commons Attribution 4.0 International License.

II. Clinical Features

Incubation period: Typically 4-7 days, range 3-14 days [10]. Infection presents a broad range of clinical manifestations, from mild to severe illness.

There are 3 phases of the symptomatic phrase – febrile, critical and convalescent (recovery) [11].

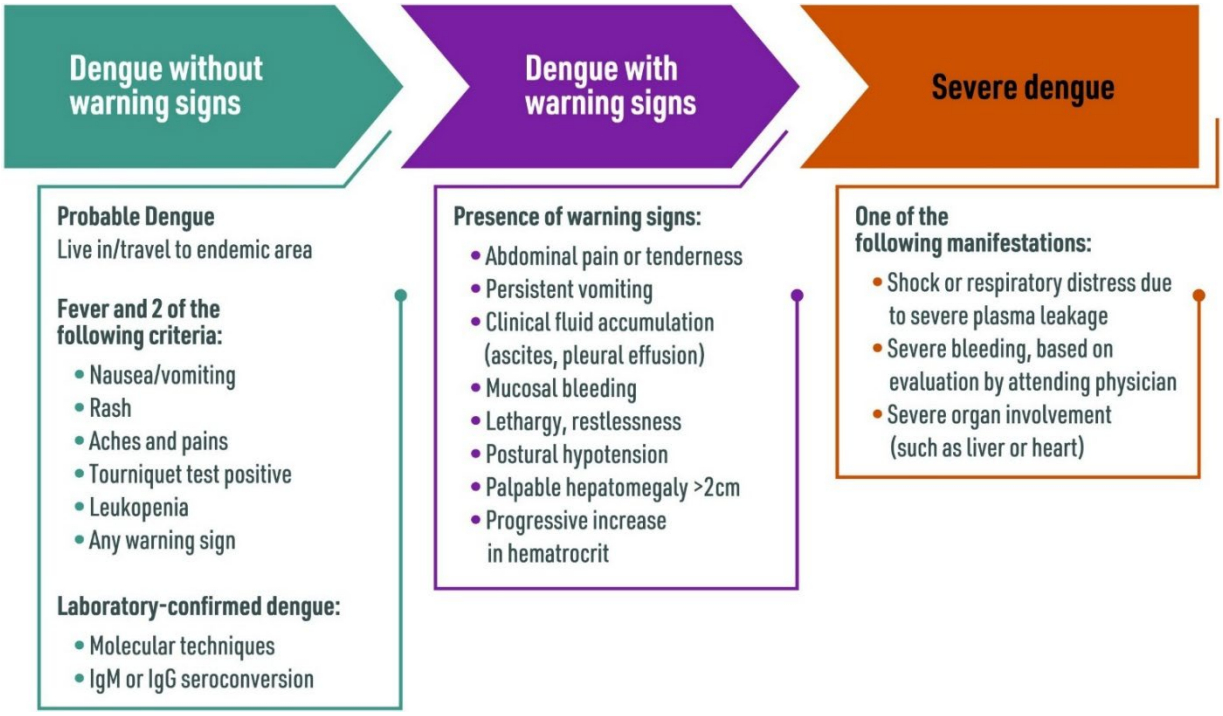

Figure 2: Dengue clinical classification (2009 WHO classification). Image reproduced from [11]. Severe organ involvement: Liver: AST or ALT $\geq$ 1000 IU, CNS: impairment of consciousness, Heart and other organs [12]

III. Detection and Diagnostic Methods

- **Interpretation of dengue diagnostic test results requires careful attention to the timing of symptom onset and specimen collection [13].**
  - Serum samples are preferred for DENV detection, although it can be detected in plasma, whole blood, capillary blood, urine, cerebrospinal fluid (CSF) [encephalitic cases], and tissue samples as well [13].
  - Presence of dengue non-structural protein 1 (NS1) and viral RNA will indicate current infection (early/acute phase: 0-7 days)
  - NS1 can be detected up to 9 days post illness, and up to 6-7 days in secondary infection [14]
  - Thus, the absence of NS1 detection after the first week of infection does not rule out dengue.
  - Serology testing after 7 days: IgM presence indicates recent infection, IgG appears later in primary infection, and quite rapidly in secondary infection (Figure 3)
  - Serological assays performed early in illness may be falsely negative
  - NS1 tests may fail in secondary infections (false negative result) because of the formation of antigen-antibody complexes with pre-existing antibodies [14].
  - Antibody cross-reactivity can also occur with other *orthoflaviviruses* (especially in co-endemic regions, or vaccinated individuals) [15-18]

- **Antigen rapid test kits**
  - Easy to perform and interpret, rapid results
  - Kits commercially available can detect NS1, IgM or IgG
  - Some kits allow detection of both NS1 and anti-dengue antibodies (IgM/IgG), which can increase sensitivity of the assay [19-21]
  - Can track stage of infection (Figure 3 and Figure 4)

NS1	IgM	IgG	Result
+	+	-	Early primary infection (acute phase)
-	-	+	Past infection or early convalescent secondary infection
+	+	+	Early secondary infection
-	-	-	Negative

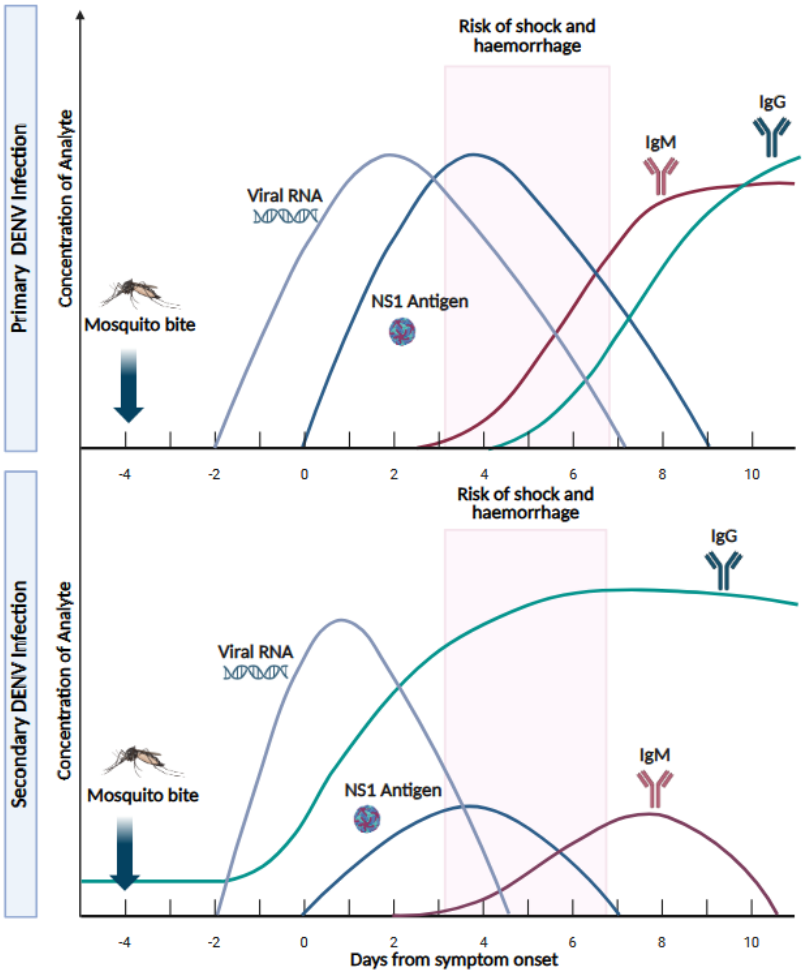

Figure 3: Progression of diagnostic markers in primary and secondary DENV infections in relation to days from symptom onset. Note that although the shaded areas indicating the risk of shock and haemorrhage appear similar for visual consistency, the actual risk is substantially higher during secondary dengue virus (DENV) infection than in primary infection. Reproduced from [13]. Licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO license.

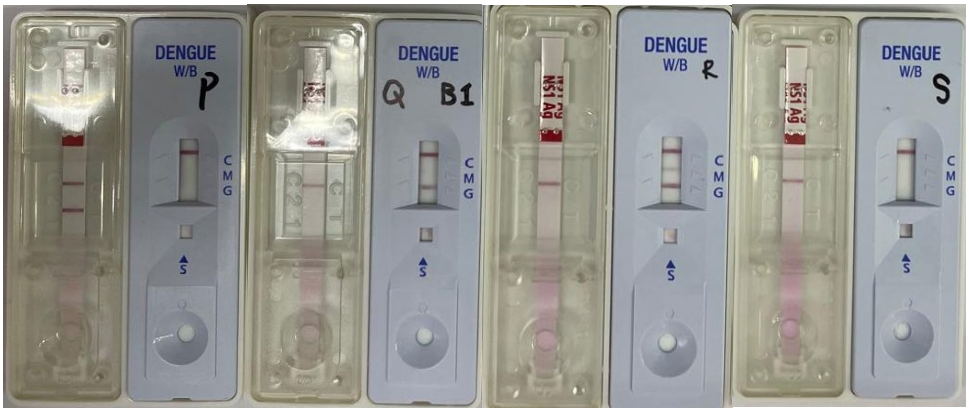

Figure 4: Results of ART test kits that can detect dengue NS1 and anti-dengue antibodies IgM and IgG. From left to right: Patient P is positive for NS1 (acute phase of dengue infection), Patient Q is positive for IgG (past dengue infection), Patient R is positive for IgM and IgG (Convalescent stage of dengue infection) while Patient S is negative for all three (non-dengue-infected). Figure kindly provided by Ms Rachel Chea, Department of Microbiology and Immunology, National University of Singapore.

- **RT-PCR**
  - Many assays designed to detect all 4 serotypes
  - Does not distinguish between primary and secondary infections
  - Suitable for detection in acute phase of infection, active viremia
  - High sensitivity and specificity
  - Requires specialized equipment and trained personnel

V. Prevention and Control Strategies

- **Vaccination**
  - A viable DENV vaccine requires potent protection across all four serotypes to prevent ADE triggered by inadequate, heterotypic antibody responses [22, 23]
  - Only dengue vaccine approved in Singapore is a live attenuated quadrivalent (target all four serotypes) called Dengvaxia, for individuals aged 12-45 years of age with a previous dengue infection (vaccination of dengue-naïve individuals are avoided as it can mimic a natural infection and predispose them to ADE and higher risk of severe dengue [24]). The vaccine will be phased out by late 2026 due to low global demand [25].
  - Another vaccine QDENGA/TAK-003 (Takeda) is not currently approved in Singapore although it has received prequalification from WHO [26]. TAK-003 (QDENGA, Takeda) has demonstrated efficacy against symptomatic and hospitalized dengue in both dengue-seropositive and seronegative children and adolescents, with no evidence of disease enhancement [27-29].
  - A Phase III clinical trial is currently underway in Singapore to evaluate safety and efficacy of a live-attenuated quadrivalent dengue vaccine V181, in children aged 2-17 [30].

- **Infection control strategies**
  - National Environment Agency (NEA) conducts inspections of houses and premises for mosquito breeding. Fines are also imposed [31].
  - Gravitrap surveillance systems are used to attract and trap female *Aedes* mosquitoes, helping reduce and monitor the local mosquito population [32].

- Project Wolbachia – release of male *Aedes aegypti* mosquitoes infected with the *Wolbachia* bacterium to suppress the local dengue-spreading mosquito population. The infection prevents the eggs produced by wild females mated with these males from hatching [33-35]. The project aims to cover 50% of all households by end 2026 [36].

- **Educational initiatives**
  - Public educational campaigns by NEA to prevent mosquito breeding which occurs in clean, stagnant water. This will reduce disease transmission.
  - Mnemonics – B-L-O-C-K and SAW
  - **B-L-O-C-K - B**reak up hardened soil, **L**ift and empty flowerpot plates, **O**verturn pails and wipe their rims, **C**hange water in vases, **K**eep roof gutters clear and place BTI insecticide inside
  - **S-A-W** (to prevent mosquito bites especially for residents in dengue cluster areas) - **S**pray insecticide in dark corners around the house, **A**pply insect repellent regularly (most effective: DEET (N,N-diethyl-m-toluamide), picaridin or IR3535 as the active ingredient), **W**ear long-sleeve tops and long pants
  - Public can check on information on the location of dengue clusters [37]

VI. Treatment Options

There are no anti-viral medications for dengue and treatment is normally only supportive.

Category	Details	Notes
Symptomatic treatment	Paracetamol for fever/pain	Avoid NSAIDs (inhibit platelet function and impair clotting, can increase risk of hemorrhagic complications [38]) Caution is advised when using paracetamol in patients with liver dysfunction or transaminitis (raised liver enzymes) [39].
Fluid management	Intravenous fluids for hypotension and dehydration	Avoid over-hydration, which can precipitate pulmonary oedema in dengue hemorrhagic fever (DHF)
Laboratory monitoring	Daily platelet and haematocrit measurement when platelets <100,000/mm^3	Monitor trends to guide fluid and clinical management.
Bed rest	Complete bed rest	Recommended when platelet count <50,000/mm^3 to reduce bleeding risk

Table summarized from [40].

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