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PEARLS

# Understanding antibody-dependent enhancement in dengue: Are afucosylated IgG1s a concern?

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Dengue is a mosquito-borne infection caused by dengue virus (DENV) of the Flaviviridae family. There are four distinct serotypes, DENV-1,-2,-3,-4, which cause outbreaks globally. Infection is often self-resolving, and lifelong immunity against the infecting serotype can be achieved after exposure. However, in some individuals, homologous infection may still result in symptomatic dengue [1]. There is usually limited protection against heterotypic infections by three other DENV serotypes, as cross-protection is short-lived [2]. After this window of "protection", subsequent infection with a different serotype may increase the risk of developing severe dengue [3,4]. Antibody-dependent enhancement (ADE) in dengue, a process mainly mediated by immunoglobulin G (IgG), is believed to be one of the major underlying mechanisms leading to increased severity in secondary DENV infection. ADE was shown to enhance viral entry into immune cells via their Fcγ receptors (FcγR), which promotes viral replication, leading to increased viremia and pro-inflammatory responses. These contribute to disease pathologies including vascular hyperpermeability, a common cause of severe dengue [5]. Although this pathological link was first reported about six decades ago, the inherent molecular mechanisms are still not fully understood. Here, we discuss the current model of ADE in dengue and provide new perspective on the possible roles of afucosylated IgG1s in ADE-mediated severe dengue.

## Viral and host factors in influencing ADE in dengue

DENV has a positive-sense RNA genome that encodes for seven nonstructural proteins and three structural glycoproteins (the capsid shell, envelope (E) and premembrane (prM) proteins) that are responsible for virus attachment, entry, and maturation [6]. Although all serotypes are closely related, a significant degree of sequence diversity exists [4]. As a result, a subset of IgGs that target viral proteins from one serotype may cross-react with those from other serotypes and exhibit poor neutralising function. For instance, the noninfectious immature virions have a "spiky" appearance, because of higher surface exposure of immunodominant epitopes (pr fragment of the prM proteins and fusion loop in the E proteins) [7]. These epitopes are recognised by low levels of cross-reactive IgGs, promoting entry into FcγR-bearing cells that lead to infectious virus maturation and immune suppression that favours viral replication [4,8,9]. Additionally, decreased neutralising antibody concentrations due to waning immunity may