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Insights into Dengue Vaccine Development: Highlighting Serotype Diversity, Safety Concerns, and the Promise of AI

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Dengue is the most prominent virus in terms of morbidity and mortality, which is carried by mosquitoes and infects over 100 million people per year in tropical and subtropical zones of the world [1]. An effective vaccination is a burning issue globally, and its formulation is mainly hindered by the biological complexity of the virus and the intricacy of the human immune system. The major setback of the dengue vaccine development process is not just to induce an effective immune response but also to avoid unintended risks of immunization during secondary heterotypic infection, leading to worse outcomes as observed in the antibody-dependent enhancement (ADE) [2].

Dengue virus is present as four different serotypes, namely DENV-1, DENV-2, DENV-3, and DENV-4. Each of them has the potential to cause the entire disease spectrum. Although there is about 65-70 percent genetic similarity among these serotypes, they differ in antigenicity enough to demand balanced immunological protection [3]. Primary infections are likely to manifest clinically as a mild or moderate dengue fever, whereas secondary infections, particularly with some of the strains of DENV-2 and DENV-3, are more likely to be linked with severe disease outcomes such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [4]. The infection of a single serotype provides long-term protection against the same serotype but only temporary cross-protection to others. Whereas, the risk of severe dengue is substantially increased by a heterologous reinfection, due to immunopathological responses like ADE, where pre-existing antibodies do not neutralize a virus; on the contrary, the antibodies support viral entry to the cells [5].

The introduction of Dengvaxia as the first licensed live-attenuated dengue vaccine in the market reflected the trade-off between efficacy and safety. Although it offered protection to the dengue-infected individuals, it enhanced the risk of severe dengue to seronegative recipients. This experience has underlined the importance of careful pre-vaccination screening, site-specific deployment strategies, and vaccines that can be safely utilized to offer protection to the population irrespective of serostatus [6]. The latest advances in vaccinations have been promising, yet drawbacks are present in the form of critical limitations. Live attenuated vaccine TAK-003 (Qdenga), which was WHO prequalified in 2024, received a license to be used in children 6-16 years old in high-transmission settings. When tested in a phase 3 trial, after 4.5 years

of follow-up, efficacy against hospitalization was 85.9 percent and 79.3 percent against symptomatic dengue, including those who were seronegative to DENV-1 and DENV-2 [7].

Besides these orthodox solutions, new generation technologies are bringing themselves to the equation. Subunit vaccines, DNA-based constructs, and mRNA platforms hold advantages in increasing the safety and specificity [8]. mRNA vaccines, particularly, add the advantages of quick adaptation and multivalent targeting. These advances, however, are faced with technical obstacles to real-world manufacturing capability, regulatory readiness, and the necessity to be capable of maintaining balanced immunity against all serotypes [9].

The current gold standard is measuring neutralizing antibody titers to estimate protective immunity, which is not a reliable predictor of long-term correlates of protection and/or risk of ADE. Vaccine performance also varies because of geographic variation of serotype prevalence, predisposed host genetic backgrounds, and pre-existing immunity. The immunity raised against current vaccine candidates is not durable, and the efficacy is highly variable over time and among different serotypes [10]. Moreover, human immune reaction to candidate vaccines could be modelled with predictive modelling to predict ADE risks before clinical trials [11]. Real-time genomic surveillance can be applied when tracking the evolution of the dengue virus using AI, which would allow the vaccine formulations to be updated as quickly as possible. Also, AI analytics of large, multi-site trial data can help identify early signs of efficacy or safety issues, thereby speeding decision-making and mitigating risks in the development process [12].

The way forward towards a safe and effective dengue vaccine must be accompanied by a novel AI-based strategy for vaccine formulation, safety evaluation, and implementation planning. Dengue is on the move, catalyzed by climate change, population growth, and urbanization, and by the spreading geographic footprint of its vectors, the mosquitoes. The teachings of Dengvaxia should not discourage us; we must be more vigilant in vaccine design, more cautious in its implementation, and more prompt in correction. Coupled with new technologies and the determination to do science that is rigorous, transparent, we can escape the cycle of uncertain breakthroughs and shift towards something alternative to an enduring, equitable fix. Communities that are most vulnerable in the world should get nothing less.

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