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Review

The dengue vaccine pipeline: Implications for the future of dengue control

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ABSTRACT

Dengue has become the most rapidly expanding mosquito-borne infectious disease on the planet, surpassing malaria and infecting at least 390 million people per year. There is no effective treatment for dengue illness other than supportive care, especially for severe cases. Symptoms can be mild or life-threatening as in dengue hemorrhagic fever and dengue shock syndrome. Vector control has been only partially successful in decreasing dengue transmission. The potential use of safe and effective tetravalent dengue vaccines is an attractive addition to prevent disease or minimize the possibility of epidemics. There are currently no licensed dengue vaccines. This review summarizes the current status of all dengue vaccine candidates in clinical evaluation. Currently five candidate vaccines are in human clinical trials. One has completed two Phase III trials, two are in Phase II trials, and three are in Phase I testing.

1. Introduction

Q3 Dengue virus (DENV) is a mosquito-borne flavivirus that infects at least 390 million people per year [1]. It is estimated that nearly half the world's population is at risk for dengue infection [1]. A recent report from the Pan American Health Organization points out that reported dengue cases in the America rose by a factor of five in the last ten years [2]. The primary mosquito vector for dengue, *Aedes aegypti*, continues to spread widely and into new habitats due to increased urbanization and climate change. The less efficient vector *A. albopictus* is also rapidly expanding its habitat [3]. Dengue has become the most rapidly expanding mosquito-borne infectious disease on the planet, surpassing malaria.

Dengue infection and illness are caused by four distinct DENV serotypes that cross-react immunologically. Infection with a particular serotype is believed to result in life-long immunity to that serotype and cross-protection to the other serotypes for up to two years [4]. People who have had a single primary infection have been observed to have a higher risk of severe dengue including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) upon a second infection, a phenomenon often attributed to antibody enhancement [5]. Infants with waning maternal dengue antibodies have been observed to be at higher risk of DHF and DSS compared to infants with no maternal dengue antibodies [6]. There is no specific effective antiviral treatment for dengue illness other than supportive care, especially for severe cases. Good case management of severe dengue cases can greatly reduce the death rate. The only current means for dengue control are various forms of vector control. However, vector control has been only partially successful in reducing dengue disease burden [7,8]. More effective vector control measures such as integrated vector control, the use of Wolbachia infection in mosquitoes [9], or genetically modified mosquitoes [10] could eventually prove effective, but implementation of these methods is probably years into the future. Against this backdrop of an expanding dengue pandemic and no effective means to mitigate spread, the potential use of safe and effective tetravalent dengue vaccines is a very attractive addition to dengue control. Even if only partially effective, the use of dengue vaccines could be highly beneficial in blunting dengue epidemics, and for increasing population-level immunity to the level where vector control could be more effective.

Dengue vaccines could have beneficial individual-level effects by reducing the probability of infection given exposure to an infected mosquito, i.e., vaccine efficacy (VE) for susceptibility to

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Table 1
Summary of dengue vaccine candidates in clinical development.

Vaccine candidate	Manufacturer	Vaccine type	Mechanism of attenuation or inactivation	Clinical phase	References
CYD	Sanofi Pasteur	Live attenuated	Yellow fever vaccine backbone, premembrane and envelope proteins from wildtype dengue virus	III	[11–34]
DENVax	Takeda	Live attenuated	Wildtype DEN2 strain attenuated in primary dog kidney cells and further attenuated by mutation in NS3 gene	II	[35–43]
TV003/TV005	NIAID and Butantan Institute	Live attenuated	Wildtype strains with genetic mutations	II	[44–59]
TDENV PIV	GSK and WRAIR	Purified inactivated	Formalin inactivated	I	[60–63]
V180	Merck	Recombinant subunit	Wildtype premembrane and truncated envelope protein via expression in the *Drosophila* S2 cell expression system	I	[64,65]
D1ME100	NMRC	DNA	Premembrane and envelope proteins of DENV1 are expressed under control of the human cytomegalovirus promoter/enhancer of the plasmid vector VR1012	I	[66,67]

infection, reducing the probability of clinical disease given infection or the probability of severe disease, i.e., VE for disease progression, or reducing the probability that an infected vaccinated person will transmit virus to a mosquito that bites him or her, i.e., VE for direct transmission. In addition, with increasing vaccine coverage in a population, vaccines could reduce the overall transmission in the entire community, even to unvaccinated people, and thus have indirect or herd effects. All of these individual-level and community-level vaccine effects need to be taken into account when assessing the potential effectiveness and impact of dengue vaccines. In this paper, we summarize properties of the dengue vaccine candidates that are currently in some stage of clinical development with vaccine trials in phases I–III (Table 1). We note that only one vaccine has made it to double-blinded, placebo-control, phase III vaccine trials, the Sanofi Pasteur tetravalent chimeric yellow-fever dengue (CYD) vaccine, as summarized below.

2. Overview of vaccines in clinical development

2.1. CYD (Sanofi Pasteur)

Sanofi Pasteur's CYD vaccine is a live attenuated tetravalent chimeric vaccine. For each of the four dengue serotypes the premembrane and envelope proteins from a wild type dengue virus are substituted into the yellow fever (YF) 17D vaccine backbone [11]. The first CYD clinical trial in healthy adults, which only assessed the serotype 2 vaccine strain, found a high dose ($5 \log_{10}$ plaque forming units (PFU)) elicited a strong neutralizing antibody response to DENV2. Participants previously given YF vaccine seroconverted to all 4 dengue serotypes [12]. This multivalent neutralizing antibody response was further observed in a phase IIa study in Australian adults. To safely mimic the dengue endemic target population, participants were vaccinated with YF vaccine or monovalent DENV1 or DENV2 vaccines one year before vaccinating with one dose of tetravalent CYD. In flavivirus-naïve participants, no participant seroconverted to DENV1 by day 28 and only ~22% had seroconverted to DENV2 (compared to ~60% who seroconverted to DENV3 and ~70% who seroconverted to DENV4). The pre-existing flavivirus immunity increased neutralizing antibody response to all four serotypes compared to flavivirus-naïve participants [13].

The first phase I study in children was conducted in the dengue non-endemic region of Mexico City. Children aged 2 to 17 years received three doses at 0, 3.5 and 12 months. Seropositivity rates after the first dose were lowest for DEN1 and DEN2 [14]. A phase I trial conducted in the Philippines, where both dengue and Japanese encephalitis are endemic, compared the immunogenicity of three doses of CYD at 0, 3.5 and 12 months to only two doses of CYD at 3.5 and 12 months. 85% of participants were seropositive to all four serotypes regardless of the dosing schedule [15]. Early studies in flavivirus-naïve adults compared a 0, 4, and 12–15 month dosing schedule to a 2-dose schedule at 4 and 12–15 months. In the three-dose group all participants seroconverted to all four serotypes, while in the two dose group 92% seroconverted to DENV1 and 100% seroconverted to DENV2–4 [16]. To limit viral interference and subsequently increase immunogenicity and balance the immune response in naïve populations, Sanofi moved forward with a 0, 6, and 12 month dosing schedule.

Several phase II studies have been conducted throughout the world in adults and children. In the dengue-naïve population of Singapore, immunogenicity data on 600 participants found that after three doses of CYD at 0, 6, and 12 months 66.5% of those vaccinated were seropositive to all four serotypes, though seroconversion rates were higher in children [17]. A study of 300 2–11 year olds in Peru with 82% of children YF seropositive at baseline found 94.1% to be seropositive to all four serotypes after the third CYD dose. The overall antibody geometric mean titer (GMT) was higher in participants who were dengue seropositive at baseline compared to participants who were dengue seronegative at baseline [18]. A trend of higher seroconversion and GMT antibody response in baseline *Flavivirus* seropositive participants has also been seen in phase II studies in Brazil [19], Malaysia [20], and Latin America (Colombia, Honduras, Mexico, Puerto Rico) [21]. A phase IIb proof-of-concept trial was conducted in 4002 Thai children aged 4–11. Children were randomized to placebo or vaccine with three doses at 0, 6, and 12 months. This was the first trial with a primary endpoint of vaccine efficacy and secondary endpoints including safety and immunogenicity. In this study the per-protocol vaccine efficacy of CYD against all serotypes was 30.2% and not statistically significant (95% confidence interval (CI): −13.4–56.6%) [22]. Efficacy after at least one injection against serotypes DENV1, DENV3, and DENV4 was statistically significant (VE = 61.2%, 81.9%, 90.0%, respectively), though the trial was not designed or powered for this post-hoc analysis. Vaccine efficacy against DENV2 was not significant (VE = 3.5%, 95%CI: −59.8–40.5%). The immunogenicity sub study in only 296 subjects found increased GMT (as measured by plaque reduction neutralization test (PRNT)) after the first, second and third doses for all serotypes. Investigators suggest that immunogenicity as measured by PRNT may not indicate protection, the GMTs were not high enough to protect this particular lineage of viruses, or there was an antigenic mismatch between the vaccine serotype 2 virus and the circulating DENV2 causing disease in Thailand. Further investigations showed that antigenic diversity between vaccine virus and wild type did not impact neutralization and was likely not a cause of the low efficacy [23]. Additional phase II safety and immunogenicity studies have been completed in Vietnam [24], the Philippines