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Review

A dengue vaccine whirlwind update

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***Abstract*:** Dengue virus (DENV) is a mosquito-borne single-stranded RNA virus of the *Flaviviridae* family with four serotypes (DENV1, DENV2, DENV3, and DENV4) circulating many tropical and subtropical regions of the world. Endemic in more than 100 countries, DENV results in over 400 million cases annually, a subset presenting with severe or life-threatening illnesses such as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). While no specific treatments outside of supportive management exist, vaccines are an area of major research with two vaccines, Dengvaxia® (CYD-TDV) and Denvax® (TAK003), recently licensed for clinical use. CYD-TDV is highly efficacious in children 9 years or older who have had prior DENV infection due to the high risk of severe disease in seronegative children aged 2–5 years. Meanwhile, TAK003 has shown efficacy at 97.7% and 73.7% against, DENV2 and DENV1, respectively, in phase 3 clinical trials across Latin America and Asia in healthy children aged 4–16 with virologically confirmed dengue. Other vaccines including TV003 and TV005 continue to be developed across the world, with the hopes of entering clinical trials in the near future. We discuss the current state of vaccine development against dengue, with a focus on CYD-TDV and TAK003 as promising novel vaccines to target this neglected tropical disease (NTD).

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Epidemiology

Dengue is a mosquito-borne viral infection of the genus *Flavivirus*, primarily transmitted by the bite of infected female *Aedes aegypti* mosquitoes from human and non-human primate reservoirs.[1] This virus is prevalent in tropical regions and influenced by seasonal variations of precipitation, humidity, travel, and urbanization.[1] Dengue is endemic in more than 100 countries including the Americas, South Asia, Africa, and the Mediterranean, with an approximate of 400–500 million cases annually.[2] The virus consists of four individual serotypes, DENV1, DENV2, DENV3, and DENV4; with DENV2 and DENV3 most associated with severe infection.[1,2] Dengue presents similarly to other flaviviruses including Yellow Fever, West Nile Virus and St. Louis encephalitis.[3] The onset of fever is observed within days of infection and the virus circulates the human host's blood stream for 2 to 7 days. Combined with high fever, other symptoms experienced by patients include headache, muscle and joint pain, nausea, vomiting, or rash.[4] Typically, recovery occurs over a week; however, a small proportion of cases progress to severe or life-threatening stages. Severe dengue may presents as dengue hemorrhagic fever (DHF), resulting in bleeding, low platelet counts and blood plasma leakage, or dengue shock syndrome (DSS), where patients present with dangerously low blood pressure.[3] Mortality rates of patients with DHF and DSS are approximately 2–10%, but with early detection and intervention, they can be as low as 1%.[3] The higher mortality rates associated with DSS are attributable to different factors. In countries with limited resources, hospitals are overburdened, preventing the close assessment and management of patients.[5] Furthermore, several patients arrive for critical care at later stages of infection due to a lack of awareness and external factors leading to poor outcomes.[5]

Dengue infection is diagnosed through serological tests and laboratory confirmation of dengue antibodies or viral isolation. For virus detection, serum has the highest yield if tested by molecular assays within 5 days of symptom onset.[3] For antibody detection, on the contrary, serum to detect IgM antibodies has the highest yield if collected following 6 days of symptom onset.[3]

While there is no specific antiviral treatment for dengue, measures are taken to provide supportive and symptomatic relief as well as life-saving interventions. If the patient is monitored and accordingly treated during the danger phase, which lasts between 48 and 72 hours post infection, the chances of casualty can be minimized.[5] Dengue infection provides some future immunity against the homologous serotype, however not against the others (i.e. heterologous serotypes).[5] Due to challenges in diagnosis and specific management of patients as well as the risk of hospitalization and death with DENV1-4, dengue prevention remains a global health priority. Vector control tactics have been used to control disease transmission; however, these come with their own challenges and varying preventive efficacy.[5] Dengue vaccine development has also been a major area of research, with two vaccines, Dengvaxia (CYD-TDV) being licensed for clinical use in 2015 and Denvax® (TAK003) currently being assessed in Latin America and Asia.

Dengvaxia (CYD-TDV)

Dengvaxia (CYD-TDV) is a recombinant, live, attenuated tetravalent dengue vaccine developed by Sanofi Pasteur licensed for clinical use in 2015 and recently US Food and Drug Administration (FDA)-approved for the prevention of dengue caused by DENV1-4 in individuals aged 9–45 years with previously laboratory-confirmed dengue and residing in endemic areas.[6–8] The vaccine is based on the Yellow fever (YF) 17D vaccine virus backbone, replacing the YF premembrane (prM) and envelope (E) proteins with proteins from DENV1-4.[6] CYD-TDV has been evaluated in two Phase 3 clinical trials in Asia and Latin America (CYD14 in Malaysia, Philippines, Thailand and Vietnam; CYD15 in Colombia, Brazil, Mexico, Puerto Rico and Honduras) involving more than 35,000 school-aged children between the ages of 2 and 16 years using a three-dose series on a 0-, 6-, and 12-month schedule.[7,9] Participants were randomized at a 2:1 ratio to receive the vaccine or placebo using a computer-generated permutation block of six and included active phase follow-up for 25 months after the first injection and a hospital-based follow-up for 4 additional years totalling 5 years.[10,11] Primary outcome measures included time from study enrollment to laboratory-confirmed onset of dengue symptoms, regardless of severity.[10,11]

Pooled vaccine efficacy (VE) was 59.2% across both trials in the year following the per-protocol analysis, varying by serotype, age at vaccination and baseline serostatus.[7] VE among baseline seropositive children was higher than baseline seronegative children, where the risk of hospitalization dengue was highest (7.45 [95% confidence interval (CI): 1.15, 313.80]) among the seronegative group, particularly in vaccinated children aged 2–5 years in the CYD14 trial.[9] Given that children in the 2–5 years age group are at greater risk for vascular permeability and antibody-dependent enhancement (ADE), the CYD15 trial recruited participants 9 years and older.[9] VE in the seronegative group was 38.1%, majority observed in the context of DENV4.[9] However, in the seropositive group, overall VE was 78.2% with VE highest against DENV3 and DENV4 (89.9% and 75.4%, respectively) compared to DENV1 and DENV2 (70.2% and 67.9%, respectively) with a trend of higher efficacies among older age groups, particularly those 9 years or older.[9]

With the goal of reducing dengue morbidity and mortality by at least 25% and 50%, respectively by 2020, the World Health Organization (WHO)'s Strategic Advisory Group of Experts (SAGE) has recommended the administration of CYD-TDV using the three-dose series scheduling, in seropositive individuals within the indicated age range of 9 to 45 years.[12] Target age groups will be age before which severe dengue is highest and will depend on country and district-level dengue transmission intensities.[12] Screening tests including conventional serological testing and rapid diagnostic tests (RDTs) are recommended tools for the pre-vaccination screening strategy, subject to appropriate sensitivities and specificities depending on transmission settings (i.e low to moderate, high etc.).[12] This pre-vaccination screening strategy is recommended for countries considering vaccination as part of

dengue control programs only if minimization of risk is assured for seronegative individuals.[7,12] If pre-vaccination screening is not feasible, vaccination without screening is considered in areas where documented seroprevalence rates of DEN is at least 80% by 9 years of age.[12] CYD-TDV is currently contraindicated for pregnant or lactating women, immunocompromised persons and travelers with documented dengue illness or seropositivity, given the lack of data at this current time.[12] Overall, CYD-TDV is highly efficacious in children 9 years or older who have had prior DENV infection due to the high risk of severe disease in seronegative children aged 2–5 years.

Since initial implementation of the vaccine in the Philippines in 2016, a number of scientists raised concerns after reviewing hospitalization data in young children, whereby the vaccine almost doubled the risk of severe disease including DHF in seronegative children aged 2–16 (hazard ratio = 1.75, 95% CI: 1.14–2.70).[13,14] As such, the WHO published an interim position statement addressing the new information in 2017, with the SAGE group making new recommendations after their meeting in April 2018 including population seroprevalence criteria and pre-vaccination screening strategies.

Denvax (TAK003)

Denvax (TAK-003) by Takeda is a live attenuated tetravalent dengue vaccine initially developed by the Division of Vector-Borne Diseases of the Centers for Disease Control and Prevention (CDC).[15] TAK-003 contains a DENV-2 backbone whereby the pre-membrane (prM) and envelope (E) structural genes are substituted with the chimeric viruses for DENV1, DENV3, and DENV4.[15] Although the trials for TAK-003 are still being assessed on a large scale, part 1 of its phase 3 has been deemed to be efficacious against 'virologically confirmed dengue fever' present in endemic areas like Latin America and Asia among healthy children and teens aged 4–16.[15] TAK-003 has been evaluated in a phase 3, double-blind, randomized, placebo-controlled trial in 26 sites including Brazil, Columbia, the Dominican Republic, Nicaragua, Panama, the Philippines, Sri Lanka, and Thailand.[15] A total of 20,099 participants (healthy children aged from 4 to 16) were recruited to receive their first injections between September 2016 and March 2017.[15] These participants were randomly subjected to receive either two doses of vaccine or placebo (saline) in a 2:1 ratio, 3 months apart. The participants were also given a 12- and 27-month follow-up, which includes the data from part 1 presented here.[15,16] Part 2 lasts for 6 months for assessing the secondary efficacy end points, and 3 more years in part 3 for looking over long-term efficacy and safety. The primary end point of the VE of two doses of TAK-003 for the prevention of dengue induced by any dengue virus serotype from 30 days after the second injection until the end of part 1 of the trial.[15]

In per-protocol population, VE against virologically confirmed dengue cause by any type of serotype was 80.2%.[15] Furthermore, exploratory analysis demonstrated that the vaccine was most effective against DENV2 and DENV1, displaying results of 97.7% and 73.7% for its effectiveness, respectively.[15] It was less-effective against the DENV3 (62.6 %) and inconclusive to display results for DENV4 [13]. Overall efficacy was similar across different age groups, regardless of baseline serostatus (72.8–83.3%).[15] VE was highest against DENV2, whereby VE among seronegative individuals was 96.5% compared to 100% of seropositive individuals.[15] VE against DENV1 was 79.8% among seronegative individuals compared to 67.2% among seropositive individuals.[15] Finally, VE against DENV3 were inconclusive and did not suggest efficacy among seronegative individuals, whereas VE for seropositive individuals was 71.3%.[15] Virologically confirmed DENV4 cases were not observed among seronegative participants at baseline.[15] Moreover, among 210 cases confirmed dengue that were included in the analysis of the primary end point, five in the vaccine group led to hospitalization, whereas the 53 cases in the placebo group led to hospitalization, resulting in a VE of 87.2% among participants who were seronegative at baseline compared to 94.4% of those who were seropositive at baseline.[15]

Recently, Takeda's Biologics License Application (BLA) to the FDA was accepted and granted priority review, given recent data from the phase 3 parts 1–3 Tetravalent Immunization against Dengue Efficacy Study (TIDES), highlighting that primary and secondary endpoints were met.[17] Currently, TAK-003 is only approved for use in Indonesia for individuals between ages 6 and 45 years.[14] A 2-year update whereby 19,330 (96.3%) participants were evaluated for cumulative efficacy 27 months after first dose and

24 months after second dose has shown 72.7% (50.4–90.8% cumulative serotyping-specific efficacy), 74.8%, and 67% efficacy in dengue-naïve, previously dengue infected, and hospitalized dengue, respectively.[17] Fifteen cases of severe dengue were reported according to the DHF definition by the WHO or the Dengue Case Severity Adjunction Committee (DCAC), resulting in overall cumulative efficacy of 81.2% against DHF.[17] Immunogenicity studies have shown a decrease in antibody titers to DENV-2 as opposed to DENV-1, DENV-3, and DENV-4 indicating a potential need for booster dosing if data post-3 years reflects the same trends.[17]

TV003 and TV005

The U.S. National Institutes of Health (NIH) has developed two live-attenuated single-dose vaccine candidates known as TV003 and TV005, based on deletions in the 3′ untranslated region and structural gene chimerization.[18,19] TV003 and TV005 contains DENV-1, DENV-3, and DENV-4 strains with 30 nucleotide deletions for attenuations followed by a DENV-4 backbone with replacements with DENV-2 prM and E proteins with a higher dose of the DENV-2 component in TV005.[6,18,19] TV005 has shown a higher tetravalent response in vaccinated individuals compared to TV003.[18,20] Phase 1, three-arm, randomized, placebo-controlled, multicenter blinded trials have shown no difference in AEs (i.e rashes, headaches, fatigue, and myalgias) between TV003, TV005, and placebo groups with 18- to 50-year-old healthy adults from the United States and Puerto Rico. Vaccine viremia was detected in 63.9% and 25.6% of baseline-flavivirus-naïve (BFN) TV003 and TV005 group, respectively, after dose 1. More importantly, seropositivity was 92.6% and 74.2% after dose 1 in BFN given TV003 and TV005, respectively, and 100% in both vaccine groups including flavivirus-experienced (BFE) healthy adults.[20] Currently, phase 2 and phase 3 trials are underway in Taiwan and Brazil, respectively, with very good safety profiles and immunogenicity against all strains and high tolerability in the 50- to 70-year-old populations.[18]

Other vaccines in development

Other non-attenuated chimera vaccine candidates in phase I development include a purified formalin–inactivated virus (PIV) with formulated adjuvants from WRAIR/GSK, a monovalent DEMV-1 prM/E delivered by needle-free biojector, and a tetravalent prM/E formulated with Vaxfectin by US Naval Medical Research Command (NMRC).[6] A subunit vaccine known as V180, which contains 80% of an N-terminal E protein produced in insect cell formulated with ISOCOMATRIX and alhydrogel by Hawaii Biotech Inc. and Merck and a heterologous prime boost known as TLAV-prime/PIV-boost by the US Army Medical Research and Material Command.[6]

Summary

Given that CYD-TDV is not recommended for use in populations with less than 50% seroprevalence and lowest efficacy against DENV2, TAK-003 proves to be efficacious against virologically confirmed dengue fever for healthy children aged 4–16 years.[1,9] With no serious adverse effect signals, TAK003 is well tolerated and immunogenic against all four dengue serotypes, regardless of baseline serostatus with a recent priority review of the BLA to the FDA[15,21] Overall, both Dengvaxia and Denvax are promising vaccines that have the potential to change the overall prevention and treatment of DENV infection around the world through a multimodal approach. In addition, TAK-003 has the potential to be used for travelers to endemic areas regardless of serostatus.

In conclusion, Dengvaxia currently remains the only licensed and FDA-approved live-attenuated vaccine for use in the prevention of all dengue serotypes in individuals aged 9–45 years in persons previously confirmed to have had dengue. One major caveat to this vaccine is worsened infection in seronegative individuals as well as a decreased VE against DENV2. On the contrary, TAK-003 is a promising live-attenuated vaccine currently in phase 3 trials with no safety concerns in seronegative individuals, with the highest VE against DENV2 and recent BLA to the US FDA which is currently under priority review. Along with TK003 and TK005, TAK-003 is a promising novel vaccine to combat dengue with initial results becoming available in the coming months. Vaccine development for dengue virus is very promising, with many formulations in the pipeline which will accelerate efforts to effectively reduce transmission and meet WHO's global strategy for dengue prevention and control.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Ruwandi Kariyawasam: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

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Sumontra Chakrabarti: Conceptualization; Data curation; Formal analysis; Supervision; Writing – review & editing.

Andrea K. Boggild: Conceptualization; Data curation; Project administration; Resources; Supervision; Writing – review & editing.

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