



Dengue: Vaccines at a glance

Dr. Ajay Kumar Saini, Dr. Neha Mali, Dr. Susheel Kumar Saini

(Dnb pediatrics, sanjay gandhi memorial hospital, delhi-83)

(3rd year resident md pathology, spmc bikaner, rajasthan)

(assistant professor paediatrics, nims medical college, jaipur, rajasthan)

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I. INTRODUCTION

First recommendation on June 24, 2021 of a dengue vaccine (Dengvaxia) in the United States made by Advisory Committee on Immunization Practices (ACIP), marking an historic moment for dengue control following decades of global efforts to develop a safe and effective vaccine. Two other vaccines, TAK-003 developed by Takeda and TV003 developed by the National Institutes of Health, are in late-stage trials with efficacy results published or expected in 2022.

Principles of Live-Attenuated Dengue Vaccines –

Dengvaxia, TAK-003 & TV003 are live vaccines and contain four different attenuated vaccine viruses (tetraivalent) targeting each of the dengue virus serotypes (Fig. 1) with the goal of achieving balanced protective immunity against all 4 serotypes, in both those who are DENV naïve and those who have been previously infected with DENV. Vaccine virus replication (infectivity) of each vaccine serotype after immunization will lead to antigenic stimulation, which then results in homotypic immunity. Infectivity by vaccine virus serotype differed among the 3 vaccines. Table 1.

These differences in vaccine serotype specific infectivity mirrored the induction of neutralizing homotypic antibody titers. Dengvaxia induced approximately 70% homotypic antibody for DENV-4 but < 50% for DENV-1, DENV-2, and DENV-3.^[1] Antibodies induced by TAK-003 were 83% homotypic for DENV-2 and 5%, 12%, and 27% homotypic for

DENV-1, DENV-3, and DENV-4, respectively.^[2] TV003 induced a balanced homotypic antibody response to DENV-1 (62%), DENV-2 (76%), DENV-3 (86%), and DENV-4 (100%).^[3] Although homotypic antibody titers are associated with serotype specific vaccine efficacy, immune correlates that reliably predict vaccine efficacy have not yet been identified and remain an area of active research.^[8]

DENGVAXIA –

History of Dengvaxia –

Dengvaxia uses a 3-dose schedule with each dose given 6 months apart (at months 0, 6, and 12). It was developed by Washington and St Louis Universities and Acambis and licensed to Sanofi Pasteur in the 2000s, entered phase 3 trials in the 2010s, and was first recommended by WHO in 2016 for persons aged 9 years and older living in highly endemic areas. Long-term follow-up data (over 5 years) from the phase 3 trials and further analyses of the efficacy results^[4-7] demonstrated that children with evidence of previous DENV infection were protected from virologically confirmed dengue illness, including severe dengue if they were vaccinated with Dengvaxia. However, risk of hospitalization for dengue and severe dengue was increased among children without previous dengue infection who were vaccinated with Dengvaxia and had a subsequent dengue infection in the years after vaccination. In children without a previous dengue infection, the vaccine acts as a silent primary dengue infection



Live attenuated dengue vaccines

	Dengvaxia (Sanofi Pasteur)	TAK-003 (Takeda)	TV003 (NIH/Butantan)
Status	Licensed	Phase 3	Phase 3
# Doses	3 doses over 12 months (0, 6, 12)	2 doses (0, 3 months)	Single dose
Indicated age	9 - 45	Phase 3 age range 4 - 16	Phase 3 age range 2 - 59
Other	Requires documented previous DENV immunity	?	?
Construct			
Dengue proteins	8	16	32

[Fig. (1) - Key features of the 3 live attenuated dengue vaccines. Each DENV serotype is represented by a color (DENV-1 = green, DENV-2 = gray, DENV-3 = crimson, and DENV-4 = blue). Dengvaxia is comprised of 4 chimeric viruses in which the prM and E of each DENV serotype replaces those of yellow fever

17D (yellow).³⁴ TAK-003 is comprised of 1 fulllength DENV-2 and 3 chimeric viruses (prM and E of DENV-1, DENV-3, and DENV-4 on a DENV-2 background).³⁵ TV003 is comprised of 3 full-length DENV and 1 chimeric virus.²⁵ The total number of dengue proteins in each vaccine is also shown.]

Table 1 - Percentage of Vaccine Recipients with Detectable Vaccine Virus Serotype by RT-PCR after a Single Dose of the Indicated Vaccine in Persons without Previous Dengue Virus Infections.

	DENV-1	DENV-2	DENV-3	DENV-4
Dengvaxia(n=95)	7.4	0	12.6	44.2
TAK-003(n=74)	0	68.9	0	0
TV003 (n=36)	63.9	69.4	52.8	52.8

resulting in a “secondary-like” infection upon their first infection with wild-type DENV and an increased risk of severe disease due to ADE (Fig 2).^[9-10]

After these findings, WHO revised their recommendations for the vaccine to only be given to children with laboratory-confirmed evidence of a past infection. Following WHO’s recommendation, the FDA licensed Dengvaxia in 2019, and in 2021, ACIP recommended routine use of Dengvaxia for children aged 9–16 years with laboratory confirmation of previous

DENV infection and living in areas where dengue is endemic. Dengvaxia is the first dengue vaccine recommended for use in the United States.

Safety and Efficacy –

9 to 16 years old aged children with evidence of previous dengue infection, Dengvaxia has an efficacy of about 80% against the outcomes of symptomatic virologically confirmed dengue (VCD) followed over 25 months as well as hospitalization for dengue and

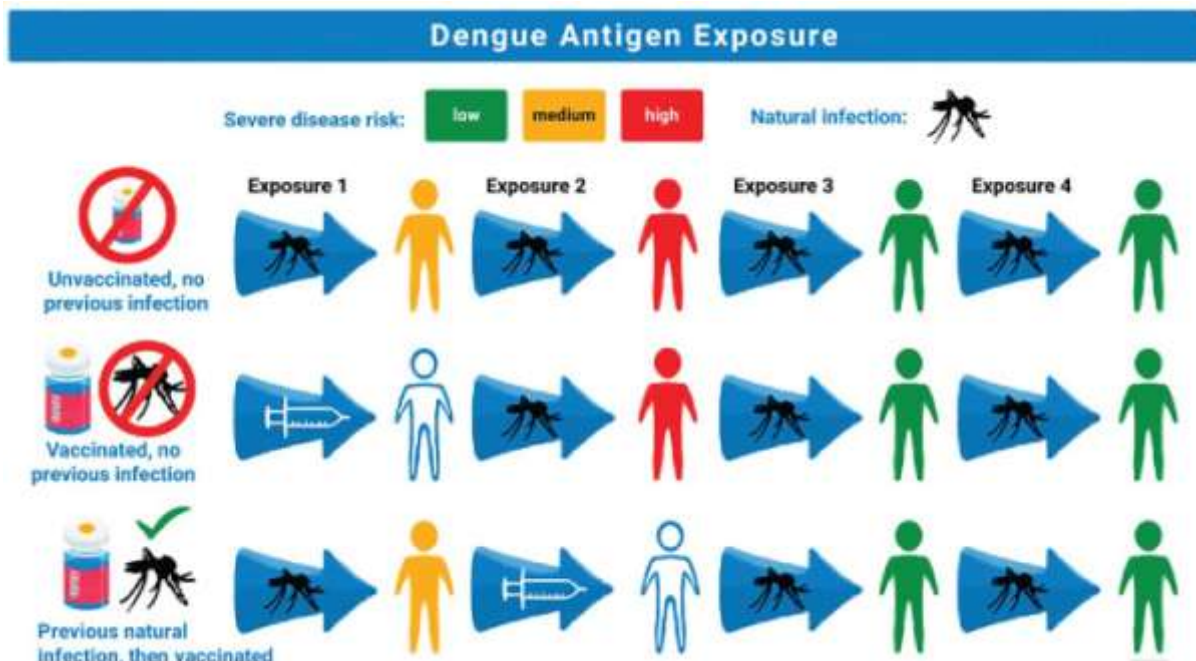


severe dengue as defined by criteria set by the trial's independent data monitoring committee and followed over 60 months (Table 2).^[5,6] The efficacy by serotype mirrored its induction of a homotypic immune response^[1] with highest protection against DENV-4 (89%), followed by DENV-3 (80%), and lowest against DENV-1 (67%) and DENV-2 (67%) (Table 3).^[6] Protection against mortality could not be reported because there were no dengue related deaths in the phase 3 trials.

The most frequently reported side effects (regardless of the dengue serostatus before vaccination) were headache (40%), injection site pain (32%), malaise (25%), asthenia (25%), and myalgia (29%) (n 5 1333).^[9] Serious adverse events (ie, life-

threatening events, hospitalization, disability or permanent damage, and death) within 28 days were rare in both vaccinated participants (0.6%) and control participants (0.8%) and were not significantly different. At 6 months, fewer severe adverse events were reported in the vaccine (2.8%) than in the control arm (3.2%).^[9]

Children who were seronegative for dengue at the time of vaccination had increased risk of severe illness on subsequent dengue infections. Risk of dengue-related hospitalization was approximately 1.5 times higher, and risk of severe dengue was approximately 2.5 times higher among seronegative children aged 9 to 16 years who were vaccinated than control participants over a 5-year period.^[6]



[Fig. 2 - Proposed mechanism of Dengvaxia efficacy based on prior dengue antigen exposure. Risk of severe disease is represented by color (low 5 green, medium 5 yellow, and high 5 red). Exposure to dengue antigens is represented by mosquito figure for wild-type exposure and by a syringe for Dengvaxia exposure. The first row shows an unvaccinated individual exposed to 4 different dengue serotypes in their life with highest risk for severe disease with second infection and low risk of severe disease in the third and fourth

infection. The second row shows an individual without previous dengue exposure who receives Dengvaxia, which acts as a silent primary infection, and then has higher risk for severe disease upon their first exposure to wildtype dengue, the equivalent of the second exposure to dengue antigen. The third row shows an individual with previous wild-type infection who receives Dengvaxia which acts as a silent second dengue exposure with lower risk for severe disease in subsequent exposures to wild-type dengue.]



Table 2. Dengvaxia Efficacy by Outcome and by Serotype in Persons 9–16 Years Old with Evidence of Previous Dengue Virus Infection.

Outcome	VE	95% CI
Virologically confirmed disease (all serotypes) ^{a,5}	81.9	67.2 to 90.0
By Serotype ^{a,5}		
DENV-1	67.4	45.9 to 80.4
DENV-2	67.3	46.7
DENV-3	80.0	To 79.9
DENV-4	89.3	67.3 to 87.7
Hospitalization (all serotypes) ^b	79	69 to 86
Severe disease (all serotypes) ^b	84	63 to 93

Pooled vaccine efficacy data are from CYD14 and CYD15 (clinical trial registration: NCT01373281, NCT01374516). CI, confidence interval; VE, vaccine efficacy.

Data are presented as percentages.

a Follow-up over 25 mo.

b Follow-up over 60 mo.

Prevaccination Laboratory Testing –

The requirement for a laboratory test before administration creates a unique challenge for Dengvaxia implementation. In areas with ongoing transmission of flaviviruses other than dengue, qualifying laboratory tests include a positive NAAT or NS1 test performed during an episode of acute dengue or a positive result on prevaccination screening tests for serologic evidence of previous infection that meet specific performance characteristics. In areas without other ongoing flavivirus transmission, a positive dengue IgM assay during an episode of acute dengue is also considered a qualifying laboratory test.^[11]

Prevaccination screening is critical because many DENV infections are asymptomatic or do not result in medical visits and testing. Thus, a significant proportion of previously infected individuals who could benefit from the vaccine will not be aware of or have laboratory documentation of their previous dengue infection.^[12–15] One of the most challenging aspects in selecting a prevaccination test is defining benchmarks for test performance, as explored by several international working groups.^[16,17] To reduce the risk of vaccinating someone without previous DENV infection, test specificity is a priority. Although test specificity and sensitivity are independent of seroprevalence, positive predictive value (PPV) and negative predictive value are dependent on seroprevalence and describe the likelihood of a true positive if a

patient tests positive or the likelihood of a true negative if a patient tests negative.

In areas with moderate or low seroprevalence (eg, 30%–50%), high test specificity (>98%) is required to achieve a PPV of 90% and therefore reduce the risk of misclassifying seronegative individuals. In these settings, nearperfect specificity at the expense of sensitivity is preferred to minimize the risk of vaccinating a misclassified negative individual and subsequently increasing their risk of severe dengue. However, highprevalence areas (eg, >60%) would benefit from a higher test sensitivity and more moderate specificity (eg, 95%), which would increase identification of children who would benefit from the vaccine.^[18]

Because dengue seroprevalence at age 9 to 16 years is estimated to be approximately 50% in Puerto Rico^[19,20] (where most of the eligible population for Dengvaxia in the United States and its territories and freely associated states reside), the CDC recommends that tests have a minimum sensitivity of 75% and a minimum specificity of 98%. The recommendations also specify that the test performance in the population should achieve a PPV of 90% and a negative predictive value of 75%.^[11] These test characteristics were used to model the risks and benefits of implementing Dengvaxia. Using Puerto Rico’s population and an estimated seroprevalence of 50%, the model found that Dengvaxia vaccination would avert approximately 4148 symptomatic disease cases and 2956 hospitalizations over a 10-year period. This implementation would also result in an additional 51 hospitalizations caused by vaccination of people without previous dengue infection who were misclassified by the screening test.¹¹⁹ The most common cause of hospitalization among vaccinated children will be breakthrough disease because the vaccine is not 100% efficacious.



TAK-003 -

TAK-003, developed by Takeda, consists of 2 doses given 3 months apart. The clinical trial population was primarily composed of children aged 4 to 16 years. At 18 months after vaccination, vaccine efficacy was found to be 80.2% against VCD, which waned to 62.0% by 3 years after vaccination.^[21,22] Efficacy against hospitalization for dengue remained higher, at 83.6% at 3 years after vaccination. Differences in efficacy were observed by history of previous dengue infection, with higher efficacy among persons with previous infection compared with those without previous infection (65.0%–54.3%), and by age, with higher efficacy in older children. In contrast to findings from Dengvaxia at 25 months, children who were seronegative at the time of TAK-003

vaccination did not show an overall increased risk for hospitalization and severe disease compared with the placebo group at 3 years, although efficacy varied by DENV serotype and an age effect could not be ruled out (Table 3).^[6,21] Efficacy against both VCD and hospitalization varied by serotype and corresponded to the homotypic antibody titers,^[2] with highest efficacy against DENV-2 and lowest against DENV-3 and DENV-4. Among children without previous DENV infection, there was no observed efficacy for VCD against DENV-3 or DENV-4. In the safety analysis, the number of serious adverse events was similar between vaccine (2.9%) and placebo (3.5%) groups. In March 2021, Takeda submitted TAK-003 to the European Medicines Agency for prevention of dengue from any DENV serotype among people

Table 3 :- TAK-003 Efficacy by Serostatus, Outcome, Serotype, and Age Group in Persons Aged 4–16 Years Over 36 Months of Follow-Up^[21]		
Outcome	VE	95% CI
Vaccinees with evidence of previous dengue virus infection (seropositives)		
Virologically confirmed disease (all serotypes)	65	58.9 to 70.1
Virologically confirmed disease by serotypes		
DENV-1	56.2	43.7 to 66.0
DENV-2	83.4	76.4 to 88.3
DENV-3	52.3	36.6 to 64.2
DENV-4	60.7	16.0 to 81.6
Vaccinees with no evidence of previous dengue virus infection (seropositives)		
Virologically confirmed disease (all serotypes)	54.3	41.9 to 64.1
Virologically confirmed disease by serotypes		
DENV-1	43.5	21.5 to 59.3
DENV-2	91.9	83.6 to 96.0
DENV-3	-23.5	-125.3 to 32.4
DENV-4	-105.5	-867.5 to 56.4
Hospitalization (all serotypes)	77.1	58.6 to 87.3
Virologically confirmed disease by age group (all serotypes, serostatus combined)		
4-5 year	42.3	22.5 to 57.0
6-11 year	64.6	57.8 to 70.4
12-16 year	68.9	58.7 to 76.6
Hospitalization by age group (all serotypes, serostatus combined)		
4-5 year	50.6	-13.9 to 78.6
6-11 year	85.7	77.3 to 91.0
12-16 year	89.1	76.6 to 94.9

Vaccine efficacy data are from clinical trial NCT02747927. CI, confidence interval; VE, vaccine efficacy. Data presented as percentage.

aged 4 to 60 years.^[23] The company will also be submitting filings to regulatory agencies

in Argentina, Brazil, Colombia, Indonesia, Malaysia, Mexico, Singapore, Sri Lanka, and



Thailand during 2021 and has future plans to submit to the FDA.

TV003 –

TV003 was developed by the National Institutes of Health and was formulated by selecting serotype-specific components that were determined to provide the most balanced safety and immunogenicity profile based on an evaluation of multiple monovalent and tetravalent candidates.^[24,25] Because antibody titers failed to predict the efficacy of Dengvaxia, a human infection model was developed to assess the protective immunity induced by TV003 against DENV-2 challenge. Forty-eight volunteers were enrolled and randomized to receive TV003 (24) or placebo (24). Six months later, volunteers were administered a naturally attenuated DENV-2 challenge virus.^[26] The primary efficacy endpoint was protection against detectable viremia after challenge. After challenge, DENV-2 was recovered by culture or reverse transcription-polymerase chain reaction (RT-PCR) from 100% of placebo recipients (n 5 20) and 0% of TV003 recipient (n 5 21) ($P < .0001$). Postchallenge, rash was observed in 80% of placebo recipients compared with 0% of TV003 recipients ($P < .0001$). TV003 has been licensed to several manufacturers globally, including Merck & Co in the United States and the Instituto Butantan in Brazil. Phase 3 trials in Brazil are underway with efficacy and safety results expected in late 2022 (Clinical trial registration: NCT02406729).

II. CONCLUSION AND FUTURE DIRECTIONS –

Dengue is the most common arboviral disease worldwide and is projected to increase in range and global burden of disease. Although advancements in the field have progressed incrementally for decades, the recent approval of Dengvaxia for routine use marks a major step forward for control and prevention efforts in the United States and paves the way for future dengue vaccines.

Dengvaxia has several complexities that necessitate future research, including the possibility of fewer doses in the initial schedule followed by booster doses in later years.³⁰ Because it is the first vaccine to require laboratory testing before administration, public-private partnerships to develop more specific, sensitive, and accessible tests or testing algorithms will be key to minimize vaccination

of persons without previous DENV infection and maximize benefit to those with previous infection. Jurisdictions that wish to use Dengvaxia will need to gather seroprevalence data and ensure that prevaccination screening tests meet the requirements for positive and negative predictive values. Furthermore, behavioral science assessments to elicit community-level perceptions and concerns combined with health systems research on optimal “test-and-vaccinate” strategies will result in dengue vaccination programs that are well accepted, efficient, and tailored to individual communities.

TAK-003 and TV003 are in latestage trials and could soon be approaching licensure. An indication for use in travelers would offer clinicians in nonendemic areas of the United States a prophylactic therapeutic option for their patients. While awaiting the approval of a vaccine with balanced serotype immunity, a mix-and-match strategy guided by differences in serotype-dominant immune responses in each vaccine (TAK-003 followed by Dengvaxia, for example) could potentially lead to higher levels of protection against dengue, but it has yet to be evaluated for safety and efficacy in clinical trials.^[27] For all 3 vaccines, studies evaluating efficacy against emerging DENV serotype variants will be important to assess longterm protection induced by the vaccine strains.^{10,127}

Future vaccines against dengue could also benefit from the lessons learned from the COVID-19 pandemic, namely that new vaccine platform technologies plus political will can result in rapid development of safe and effective vaccines and that clear communication with the public is crucial to successful vaccine implementation.^{128–130} Dengue vaccines based on an mRNA platform are already under investigation.¹³¹ Vaccines are a powerful new tool in our arsenal against dengue, but they are only 1 of many interventions, including novel vector control strategies, to control a virus with a complex epidemiology, immunopathogenesis, and clinical picture influenced by climate change, urbanization, poverty, and human migration. Clinicians should remain vigilant in recognizing and diagnosing patients with dengue, because early treatment remains the cornerstone for reducing morbidity and mortality. However, with the recent approval of Dengvaxia, we are 1 step closer on the path to dengue elimination and can expect exciting new developments in dengue interventions in the near future.



ABBREVIATIONS –

ACIP: Advisory Committee on Immunization Practices
ADE: antibody dependent enhancement
CDC: Centers for Disease Control and Prevention
DENV: dengue virus
FDA: Food and Drug Administration
IgM: immunoglobulin M
NAAT: nucleic acid amplification test
NS1: nonstructural protein 1
PPV: positive predictive value
PRNT: plaque reduction neutralization test
VCD: virologically confirmed dengue
WHO: World Health Organization

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