ORIGINAL ARTICLE

Efficacy of a Tetravalent Dengue Vaccine in Healthy Children and Adolescents

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ABSTRACT

BACKGROUND

Dengue, a mosquito-borne viral disease, was designated a World Health Organization top 10 threat to global health in 2019.

METHODS

We present primary efficacy data from part 1 of an ongoing phase 3 randomized trial of a tetravalent dengue vaccine candidate (TAK-003) in regions of Asia and Latin America in which the disease is endemic. Healthy children and adolescents 4 to 16 years of age were randomly assigned in a 2:1 ratio (stratified according to age category and region) to receive two doses of vaccine or placebo 3 months apart. Participants presenting with febrile illness were tested for virologically confirmed dengue by serotype-specific reverse-transcriptase polymerase chain reaction. The primary end point was overall vaccine efficacy in preventing virologically confirmed dengue caused by any dengue virus serotype.

RESULTS

Of the 20,071 participants who were given at least one dose of vaccine or placebo (safety population), 19,021 (94.8%) received both injections and were included in the per-protocol analysis. The overall vaccine efficacy in the safety population was 80.9% (95% confidence interval [CI], 75.2 to 85.3; 78 cases per 13,380 [0.5 per 100 person-years] in the vaccine group vs. 199 cases per 6687 [2.5 per 100 person-years] in the placebo group). In the per-protocol analyses, vaccine efficacy was 80.2% (95% CI, 73.3 to 85.3; 61 cases of virologically confirmed dengue in the vaccine group vs. 149 cases in the placebo group), with 95.4% efficacy against dengue leading to hospitalization (95% CI, 88.4 to 98.2; 5 hospitalizations in the vaccine group vs. 53 hospitalizations in the placebo group). Planned exploratory analyses involving the 27.7% of the per-protocol population that was seronegative at baseline showed vaccine efficacy of 74.9% (95% CI, 57.0 to 85.4; 20 cases of virologically confirmed dengue in the vaccine group vs. 39 cases in the placebo group). Efficacy trends varied according to serotype. The incidence of serious adverse events was similar in the vaccine group and placebo group (3.1% and 3.8%, respectively).

CONCLUSIONS

TAK-003 was efficacious against symptomatic dengue in countries in which the disease is endemic. (Funded by Takeda Vaccines; TIDES ClinicalTrials.gov number, NCT02747927.)

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*A list of the members of the TIDES Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Dengue is a pandemic-prone viral disease, the incidence of which has increased by a factor of 30 over the past 50 years.[1] Nearly half of the world's population lives in dengue-endemic areas in more than 100 countries worldwide, where approximately 390 million cases of dengue virus infection are estimated to occur each year.[2,3] Dengue can range from asymptomatic infection to severe disease with a mortality rate of 20% if untreated.[4-7] Four serotypes of dengue virus (DENV-1 through DENV-4) frequently cocirculate in areas in which the disease is endemic.[8] Although infection provides decades of protective immunity against the infecting serotype, secondary infection with a different serotype increases the risk of severe disease.[9]

A tetravalent dengue vaccine based on a yellow fever virus "backbone," CYD-TDV (Dengvaxia, Sanofi Pasteur), has been licensed in several countries on the basis of a 56 to 61% vaccine efficacy against virologically confirmed dengue among children in Asia and Latin America.[10,11] CYD-TDV is associated with an increased risk of severe dengue and dengue leading to hospitalization in seronegative persons,[12] which has led to recommendations that it be provided only to persons with evidence of past infection.[13] This leaves a substantial unmet need.

A new tetravalent dengue vaccine candidate, TAK-003 (Takeda), is based on a live attenuated DENV-2 virus that provides the genetic backbone for all four of the viruses in the vaccine, which were originally designed and constructed by scientists at the Division of Vector-Borne Diseases of the Centers for Disease Control and Prevention (CDC).[14] The DENV-2 strain (TDV-2) is based on an attenuated laboratory-derived virus, DEN-2 primary dog kidney (PDK)–53.[15] The other three virus strains (TDV-1, TDV-3, and TDV-4) are chimeras that were generated by replacing the premembrane and envelope genes of TDV-2 with those from wild-type DENV-1, DENV-3, and DENV-4 strains.[16,17]

The efficacy, safety, and immunogenicity of two doses of TAK-003 are currently being assessed in a large-scale, phase 3, randomized clinical trial (Efficacy, Safety and Immunogenicity of Takeda's Tetravalent Dengue Vaccine in Healthy Children [TIDES]) involving children and adolescents 4 to 16 years of age living in Latin America and Asia. We report the primary findings from the first part of this ongoing trial.

METHODS

TRIAL OVERSIGHT

In this phase 3, double-blind, randomized, placebo-controlled trial, we enrolled healthy children and adolescents at 26 sites in which dengue is endemic in Brazil (4 sites), Colombia (4), the Dominican Republic (2), Nicaragua (1), Panama (4), the Philippines (4), Sri Lanka (4), and Thailand (3); participants received their first injections between September 2016 and March 2017. The trial is being conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Tripartite Guidelines for Good Clinical Practice, as well as in accordance with applicable local regulations. Informed assent or consent forms and the trial protocol and its amendments (available with the full text of this article at NEJM.org) were reviewed and approved by institutional review boards, independent ethics committees, and health authorities. Written informed assent or consent was obtained from all participants or their parents or legal guardians before enrollment. During the trial, consent was obtained again from participants when they legally became adults. At the time of this analysis, the process of obtaining repeat consent for some participants was ongoing. Should any of these participants decline to provide repeat consent, data that were collected after they had reached legal adult age will be removed from future analyses.

The trial sponsor, Takeda Vaccines, is responsible for the overall trial design (taking into consideration the investigators' input), trial site selection, and data analysis. The trial investigators are responsible for data collection and day-to-day trial site management. To maintain blinding in this ongoing trial, certain authors employed by the sponsor, including a statistician, and the medical writers had access to group- and individual-level trial data and vouch for the accuracy and completeness of the data. Other authors had access only to the data presented in this article. All the authors vouch for the fidelity of the trial to the protocol. Medical writers at OLC Bioscience who were paid by the sponsor prepared the first draft of the manuscript on the basis of an

outline previously agreed on by all the authors. All the authors provided critical input during manuscript preparation and approved the submitted version. An independent data and safety monitoring committee has access to unblinded safety data on request.

PARTICIPANTS, RANDOMIZATION, AND BLINDING

Children and adolescents 4 to 16 years of age who met the trial entry criteria were randomly assigned in a 2:1 ratio to receive two doses of vaccine or placebo, 3 months apart. Randomization was stratified according to region (Asia-Pacific region or Latin America) and age (4 to 5 years, 6 to 11 years, or 12 to 16 years). A subpopulation of 4000 of the 20,099 participants who underwent randomization was randomly selected for additional safety and immunogenicity assessments. During the trial, investigators, participants and their parents or guardians, and representatives of the sponsor who advise on trial conduct remain unaware of the trial-group assignments. One or more designated pharmacists or vaccine administrators at each site are aware of the trial-group assignments but have no role in the collection or assessment of participant safety data.

TRIAL VACCINE AND PLACEBO

The lyophilized vaccine formulation was reconstituted before administration. One 0.5-ml dose of TAK-003 contained approximately 3.6, 4.0, 4.6, and 5.1 $\log_{10}$ plaque-forming units of TDV-1, TDV-2, TDV-3, and TDV-4, respectively. The placebo was a 0.5-ml injection of saline. Vaccine and placebo were administered subcutaneously into the upper arm. The lyophilized vaccine kits were kept at 2 to 8°C during shipping and storage.

TRIAL PROCEDURES

This ongoing trial consists of three parts for each participant, with active surveillance during parts 1 and 2 and modified active surveillance during part 3 (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Participants or their parents or guardians are contacted at least weekly for the entire trial duration to remind them to present for evaluation of febrile illness (defined as body temperature ≥38°C in any 2 of 3 consecutive days) to ensure identification of dengue cases. Part 1 was complete after 120 cases of virologically confirmed dengue had been confirmed for the analysis of the primary end point and participants had had 12 months of follow-up after the second vaccination. Data from part 1 are reported here. Part 2 lasts for another 6 months for the assessment of secondary efficacy end points, to be followed by an additional 3 years in part 3 for the evaluation of long-term efficacy and safety.

During active surveillance, participants presenting with febrile illness or clinically suspected dengue have blood samples taken in the acute phase (i.e., as soon as possible and preferably within 5 days after fever onset) and convalescent phase (i.e., 7 to 14 days after the acute-phase specimen is obtained). Testing includes quantitative serotype-specific reverse-transcriptase polymerase chain reaction (RT-PCR); enzyme-linked immunosorbent assay (ELISA) for dengue NS1, IgM, and IgG; and assessment of hematocrit, liver enzymes (aspartate aminotransferase and alanine aminotransferase), and platelet counts. RT-PCR and NS1 ELISA are performed only on the acute-phase specimen. Febrile illnesses are evaluated clinically, and additional tests can be performed in accordance with the local standard of care.

For the efficacy analyses, virologically confirmed dengue is defined as febrile illness or illness clinically suspected to be dengue by the investigator in association with a positive serotype-specific RT-PCR result. The severity of virologically confirmed dengue is assessed with the use of two approaches: blinded review by the dengue case adjudication committee, using predefined criteria, and with a program for analyzing data in accordance with World Health Organization (WHO) 1997 criteria for dengue hemorrhagic fever.[7] Blood specimens were obtained from all participants on day 1 (before vaccination) and day 120 to measure levels of dengue-neutralizing antibodies by microneutralization testing. Additional blood specimens for microneutralization testing are obtained on days 30, 90, 270, and 450 and then annually from the participants in the safety subpopulation. Safety assessments in the safety subpopulation included assessment of local reactions and systemic adverse events for 7 or 14 days, respectively, and of unsolicited adverse events for 28 days after each vaccination. Data on serious adverse events were collected for

all trial participants. Additional details of our methods and procedures are provided in the Supplementary Appendix and the protocol.

OUTCOMES

The primary end point was the vaccine efficacy of two doses of TAK-003 for the prevention of virologically confirmed dengue induced by any dengue virus serotype from 30 days after the second injection until the end of part 1 of the trial. Secondary vaccine efficacy end points included efficacy against individual dengue virus serotypes, efficacy according to baseline serostatus, and efficacy for the prevention of dengue leading to hospitalization and the prevention of severe dengue until the end of part 2 of the trial. Although the full assessment of these secondary end points is planned to occur after part 2, we report here on a planned exploratory analysis of vaccine efficacy in subgroups of interest based on cases of virologically confirmed dengue that occurred during part 1.

STATISTICAL ANALYSIS

Analysis of the primary end point was performed with the per-protocol population, which included all participants who did not have any major protocol violations. Vaccine efficacy is defined as 1 minus the hazard ratio (vaccine vs. placebo). Hazard ratios and corresponding 95% confidence intervals were estimated with a Cox proportional-hazards model that included trial group as a factor, with adjustment for age and stratification according to region. The primary vaccine efficacy objective was considered to be met if the lower bound of the 95% confidence interval for vaccine efficacy was above 25%. Additional analyses were performed with the per-protocol population, safety population, full analysis population, or safety and immunogenicity subpopulations (definitions are provided in the Supplementary Appendix). The sample size calculation was based on the assumption of a true vaccine efficacy of 60% and a background annual dengue incidence of 1%. We calculated that a sample of 20,100 participants undergoing randomization in a 2:1 ratio (TAK-003:placebo) would enable identification of 120 cases of virologically confirmed dengue from 30 days after the second vaccination to the end of part 1, providing at least 90% power to rule out a vaccine efficacy of 25% or less (with a two-sided significance level of 0.05).

Figure 1 (facing page). Randomization, Vaccination, and Follow-up.

Participants who never received a dose are included in the total numbers of participants who discontinued the trial before the second dose. Some participants (3 in the vaccine group and 2 in the placebo group) did not receive the second dose but continued to participate in the trial. Four participants (3 who had originally been assigned to the vaccine group and 1 who had been assigned to the placebo group) received both vaccine and placebo because of an administrative error and were excluded from the vaccine and placebo groups in the safety population, and 1 participant who had been assigned to the vaccine group received placebo and was included in the placebo group in the safety population. Participants had 12 months of follow-up after the second dose at the time of completing part 1 of the trial.

RESULTS

PARTICIPANTS

After screening, 20,099 participants underwent randomization, and 20,071 received at least one injection; 97.3% of vaccine recipients and 97.4% of placebo recipients completed part 1 (Fig. 1). Baseline characteristics were similar in the two treatment groups (Table 1). The mean age of the participants in the per-protocol population was 9.6 years, 27.7% of participants were seronegative at baseline, and enrollment was broadly balanced between the Asia-Pacific region (46.5%) and Latin America (53.5%). The highest percentage of seronegative participants was in Panama (62.2%), followed by Sri Lanka (38.5%), Thailand (34.4%), Brazil (28.8%), Nicaragua (22.3%), Colombia (15.4%), the Philippines (12.4%), and the Dominican Republic (2.8%). The percentages of participants who were seropositive at baseline according to dengue virus serotype are shown in Table S6.

FEBRILE ILLNESSES AND VIROLOGICALLY CONFIRMED DENGUE

During part 1 in the safety population, 5754 episodes of febrile illness were reported at Asian sites and 4663 were reported at Latin American sites. Acute-phase specimens were obtained in

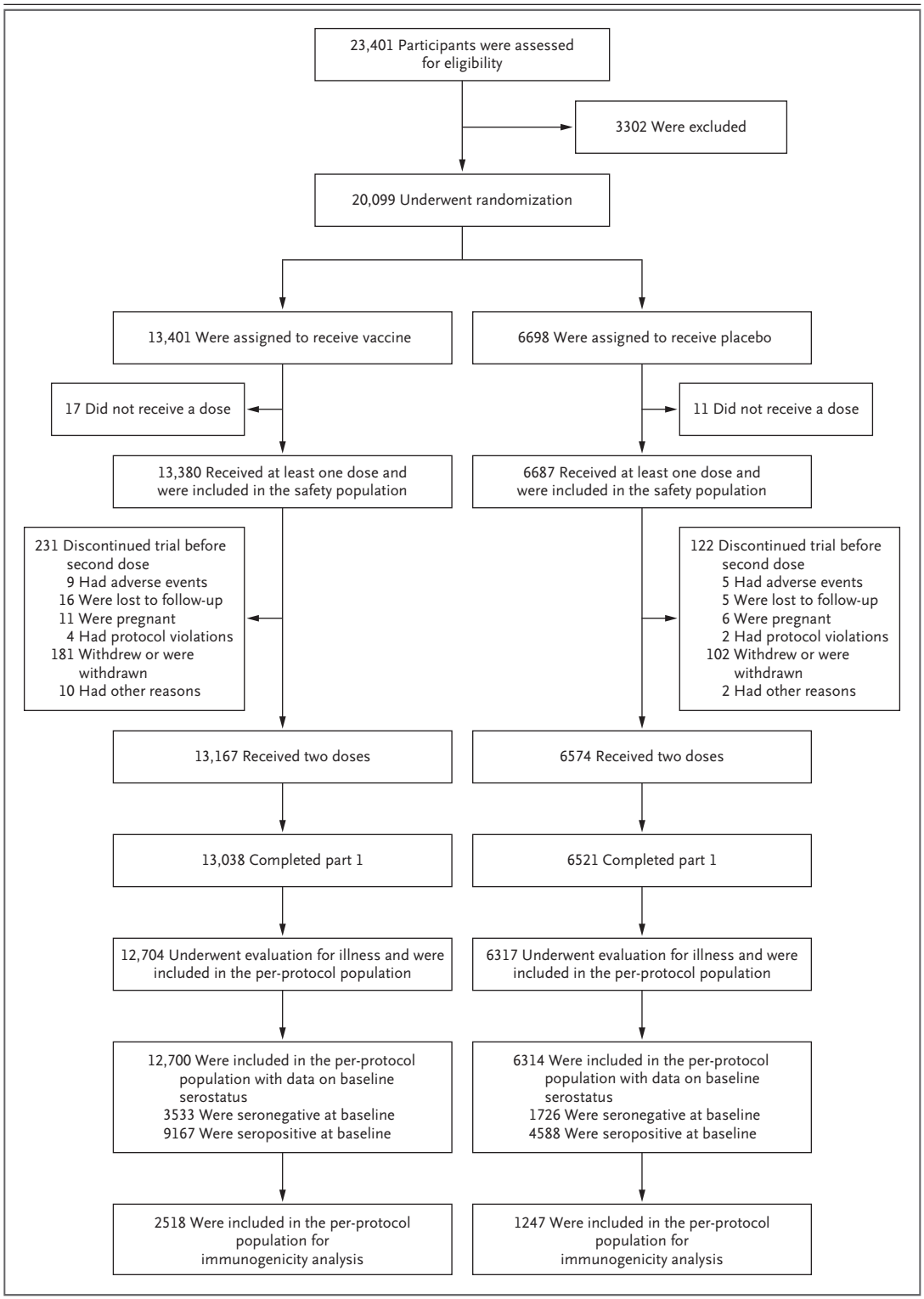


Table 1. Characteristics of the Participants at Baseline.*

Population and Characteristic	Vaccine Group	Placebo Group	Total
Per-protocol population			
No. of participants	12,704	6317	19,021
Age — yr	9.6±3.35	9.6±3.34	9.6±3.35
Seronegative for dengue virus — no./total no. (%)†	3533/12,700 (27.8)	1726/6314 (27.3)	5259/19,014 (27.7)
Female sex — no. (%)	6314 (49.7)	3098 (49.0)	9,412 (49.5)
Asia-Pacific region — no. (%)	5896 (46.4)	2942 (46.6)	8,838 (46.5)
Seronegative for dengue virus — no./total no. (%)†	1503/5895 (25.5)	773/2940 (26.3)	2276/8835 (25.8)
Latin America — no. (%)	6808 (53.6)	3375 (53.4)	10,183 (53.5)
Seronegative for dengue virus — no./total no. (%)†	2030/6805 (29.8)	953/3374 (28.2)	2983/10,179 (29.3)
Safety population‡			
No. of participants	13,380	6687	20,071
Age — yr	9.6±3.36	9.6±3.34	9.6±3.35
Seronegative for dengue virus — no./total no. (%)†	3714/13,375 (27.8)	1832/6684 (27.4)	5547/20,063 (27.6)
Female sex — no. (%)	6651 (49.7)	3276 (49.0)	9,929 (49.5)
Safety subpopulation‡§			
No. of participants	2663	1329	3993
Seronegative for dengue virus — no. (%)†	740 (27.8)	369 (27.8)	1,109 (27.8)

* Plus–minus values are means ±SD.
† Category includes participants who were seronegative for all dengue virus serotypes at baseline. Participants were considered to be seropositive at baseline if they had a reciprocal neutralizing antibody titer of 10 or higher to at least one dengue virus serotype.
‡ The total column includes participants who received both vaccine and placebo because of administrative errors; these participants are not included in the vaccine and placebo groups.
§ The safety subpopulation includes participants who were randomly selected for additional safety and immunogenicity assessments.

99.5% and 96.6% of these cases, respectively, with 98.3% and 85.1% of specimens obtained within 5 days. During the part 1 period, there were 278 cases of virologically confirmed dengue in the safety population (76 of which led to hospitalization [6 DENV-1, 59 DENV-2, 10 DENV-3, and 1 DENV-4]); 210 of these cases (58 leading to hospitalization [5 DENV-1, 43 DENV-2, and 10 DENV-3) occurred 30 or more days after the second vaccination in the per-protocol population (Table 2, and Tables S1 and S5) and were included in the analysis of the primary end point.

DISTRIBUTION OF DENGUE VIRUS SEROTYPES INCLUDED IN THE PRIMARY END-POINT ANALYSIS

DENV-1 was reported in all countries with virologically confirmed dengue and accounted for all 21 cases in Panama. In Sri Lanka, 54 of 60 cases of virologically confirmed dengue were caused by DENV-2, and 87 of 109 cases in the Philippines were caused by DENV-3. All 7 cases of virologically confirmed dengue caused by DENV-4 were reported in the Philippines. No cases were reported in Nicaragua or the Dominican Republic. Of the 58 cases of virologically confirmed dengue that led to hospitalization, 43 were reported in Sri Lanka. A total of 2 cases of severe dengue (both DENV-3) and 5 cases of dengue hemorrhagic fever (3 DENV-2 and 2 DENV-3) were reported (Table 2). These 7 cases were also the only such cases in the part 1 safety population.

VACCINE EFFICACY

The vaccine efficacy against virologically confirmed dengue caused by any serotype was 80.2% in the per-protocol population (95% confidence interval [CI], 73.3 to 85.3; P<0.001; 61 cases of virologically confirmed dengue in the vaccine group and 149 in the placebo group) (Table 2). Similar results were obtained in a sensitivity analysis involving the full analysis population (i.e., all participants who received at least one dose, analyzed according to the intention-to-treat principle), in which vaccine efficacy was 80.6% (95% CI, 73.8 to 85.6; 61 cases of virologically confirmed dengue in the vaccine group

Table 2. Vaccine Efficacy against Any Dengue Virus Serotype.

End Point and Population	Incidence				Vaccine Efficacy (95% CI)
	Vaccine Group		Placebo Group		
	*no./total no. (%)**	*cases/100 person-yr*	*no./total no. (%)**	*cases/100 person-yr*	%
Primary end point: virologically confirmed dengue from 30 days after second dose to end of part 1 of trial					
All participants in per-protocol population†	61/12,700 (0.5)	0.5	149/6316 (2.4)	2.6	80.2 (73.3 to 85.3)
Virologically confirmed dengue from first dose to end of part 1 of trial					
All participants in safety population‡	78/13,380 (0.6)	0.5	199/6687 (3.0)	2.5	80.9 (75.2 to 85.3)
Cases contributing to primary end point (per-protocol population)					
Virologically confirmed dengue					
Baseline serostatus§					
Seropositive	41/9165 (0.4)	0.5	110/4587 (2.4)	2.7	82.2 (74.5 to 87.6)
Seronegative	20/3531 (0.6)	0.6	39/1726 (2.3)	2.5	74.9 (57.0 to 85.4)
Dengue virus serotype					
DENV-1	16/12,700 (0.1)	0.1	30/6316 (0.5)	0.5	73.7 (51.7 to 85.7)
DENV-2	3/12,700 (<0.1)	<0.1	64/6316 (1.0)	1.1	97.7 (92.7 to 99.3)
DENV-3	39/12,700 (0.3)	0.3	51/6316 (0.8)	0.9	62.6 (43.3 to 75.4)
DENV-4	3/12,700 (<0.1)	<0.1	4/6316 (0.1)	<0.1	63.2 (–64.6 to 91.8)
Age group					
4–5 Yr	13/1619 (0.8)	0.9	23/801 (2.9)	3.2	72.8 (46.2 to 86.2)
6–11 Yr	34/7009 (0.5)	0.5	85/3491 (2.4)	2.7	80.7 (71.3 to 87.0)
12–16 Yr	14/4072 (0.3)	0.4	41/2024 (2.0)	2.2	83.3 (69.3 to 90.9)
Region					
Asia-Pacific region	54/5894 (0.9)	1.0	127/2942 (4.3)	4.9	79.5 (71.8 to 85.1)
Latin America	7/6806 (0.1)	0.1	22/3374 (0.7)	0.7	84.3 (63.1 to 93.3)
Virologically confirmed dengue leading to hospitalization					
Baseline serostatus§					
Seropositive	4/9165 (<0.1)	<0.1	35/4587 (0.8)	0.8	94.4 (84.3 to 98.0)
Seronegative	1/3531 (<0.1)	<0.1	18/1726 (1.0)	1.2	97.2 (79.1 to 99.6)
Dengue hemorrhagic fever¶					
All participants	1/12,700 (<0.1)	<0.1	4/6316 (0.1)	<0.1	87.3 (–13.5 to 98.6)
Severe virologically confirmed dengue‖					
All participants	1/12,700 (<0.1)	<0.1	1/6316 (<0.1)	<0.1	50.8 (–686.9 to 96.9)

* Percentages were calculated on the basis of the number of participants who underwent evaluation for virologically confirmed dengue.
† In the per-protocol population, 12,700 of 12,704 participants in the vaccine group and 6316 of 6317 in the placebo group were included in the evaluation of the primary end point. The per-protocol population was determined after exclusion of participants in a blinded manner before database lock in accordance with prespecified criteria (see the Supplementary Appendix). For analyses involving the per-protocol population, data from participants who discontinued were censored at the day of discontinuation.
‡ One participant had two instances of virologically confirmed dengue during part 1; only the first case was included in the efficacy calculation. For the analysis involving the safety population, data from participants who discontinued but agreed to continue surveillance to detect febrile illness for safety monitoring were not censored at the time of discontinuation. All cases of virologically confirmed dengue that were reported until either the last contact or the end of part 1 (whichever came first) were included in the safety population analysis of part 1.
§ Participants were considered seronegative if they were seronegative for all dengue virus serotypes at baseline. Participants were considered to be seropositive at baseline if they had a reciprocal neutralizing antibody titer of 10 or higher to at least one dengue virus serotype.
¶ Category includes cases of virologically confirmed dengue that met World Health Organization 1997 criteria for dengue hemorrhagic fever.
‖ Neither of the two cases of severe virologically confirmed dengue was classified as dengue hemorrhagic fever.

and 152 in the placebo group). The efficacy was also similar during the period between the two doses of vaccine in the per-protocol population (81%; 95% CI, 64.1 to 90.0; 13 cases of virologically confirmed dengue in the vaccine group and 34 in the placebo group).

Exploratory analysis of the secondary efficacy end points showed that the vaccine had 97.7% efficacy against DENV-2, 73.7% efficacy against DENV-1, and 62.6% efficacy against DENV-3; however, the results for efficacy against DENV-4 were inconclusive (63.2%; 95% CI, −64.6 to 91.8). Overall, efficacy was broadly similar across age ranges (72.8% to 83.3%) and among participants who were seronegative at baseline (74.9%) and those who were seropositive at baseline (82.2%) (Fig. 2A). The vaccine efficacy against DENV-1 was 79.8% among participants who were seropositive at baseline (95% CI, 51.3 to 91.6; 7 cases in the vaccine group vs. 17 in the placebo group) and was 67.2% among those who were seronegative at baseline (95% CI, 23.2 to 86.0; 9 cases in the vaccine group vs. 13 in the placebo group); against DENV-2, the corresponding vaccine efficacy values were 96.5% (95% CI, 88.7 to 98.8; 3 cases vs. 42 cases) and 100% (0 cases vs. 22 cases). The results for DENV-3 among participants who were seronegative at baseline were inconclusive but did not suggest efficacy (−38.7%; 95% CI, −335.7 to 55.8; 11 cases in the vaccine group vs. 4 cases in the placebo group), whereas the efficacy among participants who were seropositive at baseline was 71.3% (95% CI, 54.2 to 82.0; 28 cases in the vaccine group vs. 47 in the placebo group). No cases of virologically confirmed dengue caused by DENV-4 were observed among participants who were seronegative at baseline.

Among the 210 cases of virologically confirmed dengue that were included in the analysis of the primary end point, 5 in the vaccine group led to hospitalization, as compared with 53 in the placebo group, for a vaccine efficacy against dengue leading to hospitalization of 95.4% (95% CI, 88.4 to 98.2; 97.2% among participants who were seronegative at baseline and 94.4% among those who were seropositive at baseline) (Table 2 and Fig. 2B). In the safety population, the vaccine efficacy against virologically confirmed dengue leading to hospitalization was 93.3% (95% CI, 86.7 to 96.7; 9 cases vs. 67 cases) from the first dose onward (Table S1).

SAFETY

The percentage of participants with serious adverse events was similar in the vaccine group and the placebo group (3.1% and 3.8%, respectively) (Table 3). One vaccine recipient and four placebo recipients had serious adverse events that were considered by the investigator to be related to vaccine or placebo (two had hypersensitivity, two received a diagnosis of dengue, and one had dengue hemorrhagic fever). There were five deaths during part 1 of the trial (the causes were asphyxia, cerebrovascular arteriovenous malformation, malignant ependymoma, gunshot wound, and aseptic meningitis). All deaths were considered by the investigators to be unrelated to the trial. Nine vaccine recipients and five placebo recipients discontinued participation in the trial before the second dose of vaccine, with an adverse event as the primary reason (the events were angioedema, asphyxia, autoimmune hepatitis, disseminated tuberculosis, drug abuse, hypersensitivity, hyperthyroidism, influenza, malaise, aseptic meningitis, patent ductus arteriosus, seizure, septic shock, and urticaria). The percentages of participants with unsolicited adverse events were similar in the vaccine and placebo groups. The most commonly reported unsolicited adverse events (reported by ≥1% of vaccine recipients) within 4 weeks after any dose according to *Medical Dictionary for Regulatory Activities*, version 21.0, preferred term were nasopharyngitis (2.7% in the vaccine group and 3.0% in the placebo group), upper respiratory tract infection (2.6% and 2.9%, respectively), and viral infection (1.1% and 0.9%). Solicited local reactions were reported more frequently in the vaccine group. Additional details are provided in the Supplementary Appendix.

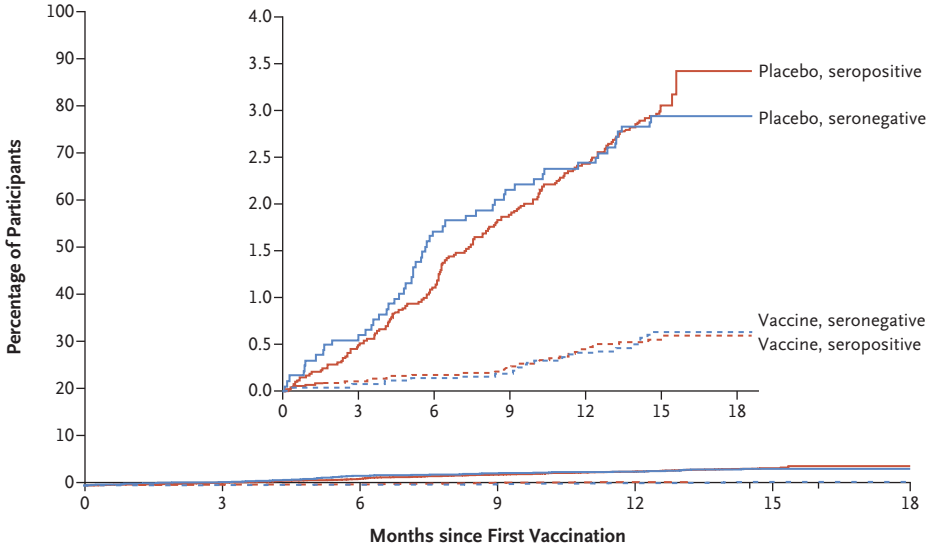
IMMUNOGENICITY

As in previous studies, the highest geometric mean titers of neutralizing antibodies were observed against DENV-2, regardless of baseline serostatus. Geometric mean titers were similar to those observed in previous studies of the same vaccine formulation,[18] and 99.5% of participants who were seronegative at baseline had tetravalent seropositivity 1 month after the second dose of vaccine (Tables S7 and S8).

DISCUSSION

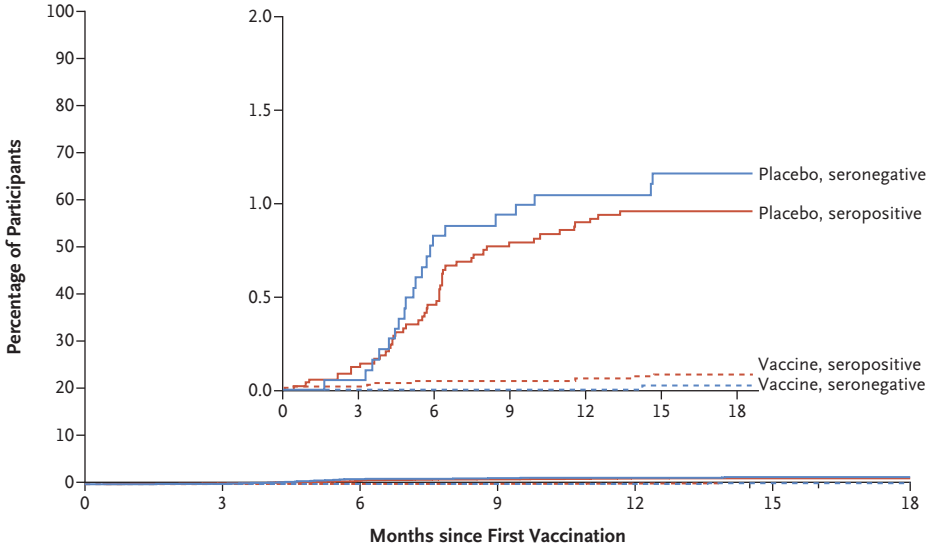
In part 1 of this trial, we found an overall vaccine efficacy of approximately 80% against viro-

A Virologically Confirmed Dengue



No. of Participants						
Placebo						
Seronegative	1832	1817	1755	1744	94	7
Seropositive	4852	4805	4637	4607	218	6
Vaccine						
Seronegative	3714	3690	3625	3615	157	10
Seropositive	9661	9591	9412	9391	417	10

B Virologically Confirmed Dengue Leading to Hospitalization



No. of Participants						
Placebo						
Seronegative	1832	1827	1780	1776	94	7
Seropositive	4852	4823	4710	4700	220	6
Vaccine						
Seronegative	3714	3693	3640	3635	157	10
Seropositive	9661	9599	9449	9435	417	10

Figure 2. Cumulative Incidence of Virologically Confirmed Dengue According to Baseline Serostatus.

Insets show the same data on an expanded y axis. The tables below the graphs show numbers of participants under follow-up at various time points to the end of the part 1 trial period.

Table 3. Safety Analysis (Safety Population).*

Adverse Event	Vaccine Group (N=13,380)	Placebo Group (N=6687)
Serious adverse event — no. (%)	409 (3.1)	255 (3.8)
Serious adverse event not related to vaccine or placebo — no. (%)†	408 (3.0)	251 (3.8)
Serious adverse event related to vaccine or placebo — no. (%)†	1 (<0.1)	4 (0.1)
Serious adverse event leading to withdrawal of vaccine or placebo or to trial discontinuation — no. (%)	18 (0.1)	8 (0.1)
Death — no. (%)	4 (<0.1)	1 (<0.1)
Death related to vaccine or placebo — no. (%)	0	0
Adverse events in the safety subpopulation — no./total no. (%)		
Unsolicited adverse event within 4 wk after either dose	487/2663 (18.3)	249/1329 (18.7)
Unsolicited adverse event related to vaccine or placebo within 4 wk after either dose†	23/2663 (0.9)	18/1329 (1.4)
Solicited systemic adverse event within 2 wk after either dose‡	1107/2635 (42.0)	501/1317 (38.0)
Solicited systemic adverse event related to vaccine or placebo within 2 wk after either dose†‡	821/2635 (31.2)	371/1317 (28.2)
Solicited local reaction within 1 wk after either dose‡§	967/2633 (36.7)	338/1317 (25.7)

* Data are numbers and percentages of participants with at least one adverse event after any injection (vaccine or placebo); the denominators for the calculation of percentages were the numbers of participants who underwent evaluation in the analysis set.
† The determination of whether an adverse event was related to vaccine or placebo was made by the investigator.
‡ Only participants with available diary card data were included in the evaluation.
§ All injection-site (solicited local) reactions were considered to be related to vaccine or placebo.

logically confirmed dengue among children and adolescents 4 to 16 years of age. The vaccine efficacy was 74.9% among participants who were seronegative at baseline and was 95.4% against dengue leading to hospitalization. Some evidence for the onset of protection after the first dose was seen, with an 81% efficacy during the period between doses, although the numbers were small. These results support a potential benefit regardless of previous dengue exposure or age, and the onset of some protection after the first dose suggests that the vaccine may be useful in the context of outbreak control or travel vaccination; however, reported variation in serotype-specific efficacy needs careful consideration.

Enrollment of trial participants in diverse settings across eight countries enabled identification of cases caused by all four dengue virus serotypes during part 1 of the trial. The number of cases identified was sufficient to provide estimates of vaccine efficacy against three of the serotypes but not against DENV-4. The trial design includes an additional 6 months of follow-up (part 2) before the formal secondary efficacy analysis, in anticipation of limitations in power. The analyses of secondary efficacy end points reported here were planned as exploratory at this point. Nevertheless, they provide information about how TAK-003 performs beyond overall efficacy. Vaccine efficacy was highest against DENV-2 (97.7%), the serotype that provides the genetic "backbone" of TAK-003. Efficacy was modest (62.6 to 73.7%) against the other three serotypes, which are represented as chimeric strains in TAK-003. It will be important to monitor whether the efficacy of the vaccine against these non–DENV-2 serotypes persists beyond 12 months after the second vaccination. The indication of a lack of efficacy against DENV-3 among participants who were seronegative at baseline warrants longer-term observation.

These efficacy data support the ongoing efforts to characterize the antibody- and cell-mediated responses to TAK-003 beyond the recommended neutralizing antibody assay. Although the efficacy against DENV-2 is associated with high antibody responses, the antibody response to DENV-3 did not predict efficacy against this serotype among participants who were seronegative at baseline. Further analyses to explore immune correlates of protection are planned.

The efficacy of the vaccine against dengue

leading to hospitalization is encouraging. However, this finding may be confounded by the high proportion of cases of dengue that led to hospitalization in which DENV-2 was the causal serotype (43 of 58 overall cases leading to hospitalization in the analysis of the primary end point), mainly in Sri Lanka. The distribution of severe dengue and dengue hemorrhagic fever remained favorable for the vaccine, although the small number of cases limits any meaningful conclusion.

In conclusion, TAK-003 was efficacious against virologically confirmed dengue fever among healthy children and adolescents 4 to 16 years of age, irrespective of previous dengue exposure. This trial is ongoing, and longer-term data will be important in better defining the efficacy and safety profile of this vaccine candidate.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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