ORIGINAL ARTICLE

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease

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ABSTRACT

BACKGROUND

A candidate tetravalent dengue vaccine is being assessed in three clinical trials involving more than 35,000 children between the ages of 2 and 16 years in Asian–Pacific and Latin American countries. We report the results of long-term follow-up interim analyses and integrated efficacy analyses.

METHODS

We are assessing the incidence of hospitalization for virologically confirmed dengue as a surrogate safety end point during follow-up in years 3 to 6 of two phase 3 trials, CYD14 and CYD15, and a phase 2b trial, CYD23/57. We estimated vaccine efficacy using pooled data from the first 25 months of CYD14 and CYD15.

RESULTS

Follow-up data were available for 10,165 of 10,275 participants (99%) in CYD14 and 19,898 of 20,869 participants (95%) in CYD15. Data were available for 3203 of the 4002 participants (80%) in the CYD23 trial included in CYD57. During year 3 in the CYD14, CYD15, and CYD57 trials combined, hospitalization for virologically confirmed dengue occurred in 65 of 22,177 participants in the vaccine group and 39 of 11,089 participants in the control group. Pooled relative risks of hospitalization for dengue were 0.84 (95% confidence interval [CI], 0.56 to 1.24) among all participants, 1.58 (95% CI, 0.83 to 3.02) among those under the age of 9 years, and 0.50 (95% CI, 0.29 to 0.86) among those 9 years of age or older. During year 3, hospitalization for severe dengue, as defined by the independent data monitoring committee criteria, occurred in 18 of 22,177 participants in the vaccine group and 6 of 11,089 participants in the control group. Pooled rates of efficacy for symptomatic dengue during the first 25 months were 60.3% (95% CI, 55.7 to 64.5) for all participants, 65.6% (95% CI, 60.7 to 69.9) for those 9 years of age or older, and 44.6% (95% CI, 31.6 to 55.0) for those younger than 9 years of age.

CONCLUSIONS

Although the unexplained higher incidence of hospitalization for dengue in year 3 among children younger than 9 years of age needs to be carefully monitored during long-term follow-up, the risk among children 2 to 16 years of age was lower in the vaccine group than in the control group. (Funded by Sanofi Pasteur; ClinicalTrials.gov numbers, NCT00842530, NCT01983553, NCT01373281, and NCT01374516.)

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A recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV) has been assessed in two phase 3 randomized efficacy trials involving more than 31,000 children between the ages of 2 and 14 years in the Asian–Pacific region (CYD14 trial) and between the ages of 9 and 16 years in Latin America (CYD15 trial).[1,2] The vaccine was administered in three doses: at baseline, at 6 months, and at 12 months. Vaccine efficacy against virologically confirmed dengue and safety were assessed during a 25-month efficacy surveillance phase (i.e., until 13 months after the third dose was administered). Reactogenicity and immunogenicity were also assessed in a subgroup of participants.[1,2] Vaccination significantly reduced the incidence of virologically confirmed dengue and showed acceptable safety and reactogenicity profiles, findings that were consistent with earlier results.

In the ongoing longer-term follow-up (from year 3 to year 6) to assess safety, we are monitoring the incidence of hospitalization for dengue as a surrogate end point for disease severity in order to evaluate a potential predisposition in vaccinated persons to increased severity of disease.[3] In addition, we invited the 4002 children between the ages of 4 and 11 years from a single-center phase 2b trial (CYD23) in Thailand that had a study design similar to that of the CYD14 and CYD15 trials to participate in a separate study (CYD57) of 4 years of follow-up in which we are assessing safety in a similar way to the way it is being assessed in the two phase 3 trials.[4] Here we report the interim analyses of data from the long-term safety phase and integrated analyses of data from the efficacy surveillance phase to provide a global view of the clinical profile of the CYD-TDV dengue vaccine.

METHODS

TRIAL PROCEDURES AND OVERSIGHT

Interim Long-Term Safety Analyses

The long-term safety analyses are based on data collected during year 3 of two phase 3 trials in five Asian–Pacific countries (CYD14) and five Latin American countries (CYD15) and during years 3 and 4 of the CYD23 extension study (CYD57) in Thailand (Fig. 1). The participants were originally randomly assigned in a 2:1 ratio to the vaccine group or the control group, stratified according to age, with a subgroup of participants assigned to a study of immunogenicity.[1,2,4] Representatives of the sponsor of the trials, Sanofi Pasteur, were

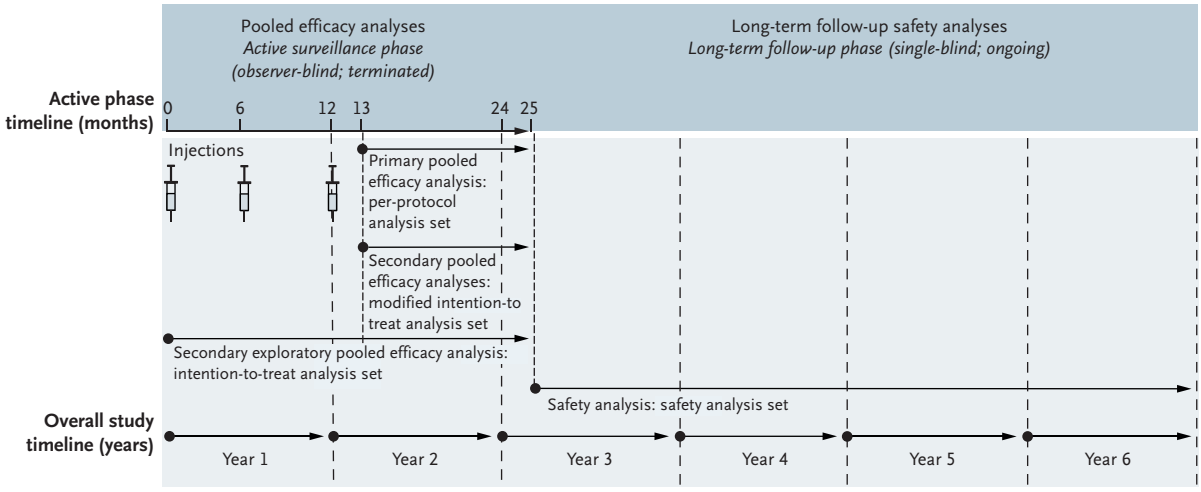


Figure 1. Overview of the Surveillance Phase and Long-Term Follow-up Phase of the CYD-TDV Candidate Vaccine Trials.

CYD-TDV is a candidate recombinant, live, attenuated, tetravalent dengue vaccine that has been assessed in two phase 3 randomized efficacy studies (called CYD14 and CYD15) involving a total of more than 31,000 participants between the ages of 2 and 16 years in Asian–Pacific and Latin American countries. In addition, 3203 of 4002 participants (80%) who were between the ages of 4 and 11 at initial enrollment in the phase 2b CYD23 trial in Thailand are being followed in the CYD57 trial. The trials had similar designs. According to the study designs, the long-term follow-up phase will continue for a total of 6 years after enrollment.

informed about study-group assignments after the analyses for the efficacy surveillance phase were performed. However, all participants, their parents, and staff members at the study sites remain unaware of the study-group assignments. Full details regarding the three studies are provided in the study protocol, available with the full text of this article at NEJM.org.

Participants attended yearly clinic visits, with regular contact (≥1 contact every 3 months by telephone, text message, or home visit) between visits. Hospitalization for acute fever was recorded during study contacts and visits, as well as by self-report and surveillance at nonstudy hospitals. Blood samples during the acute phase of illness were obtained for virologic confirmation of dengue infection (see the Methods section in the Supplementary Appendix, available at NEJM.org).

Pooled Efficacy Analyses

In the pooled efficacy analyses, we evaluated data from the 25-month efficacy surveillance phase in the CYD14 and CYD15 trials (Fig. 1).[1,2] The study designs, objectives, vaccine formulation and schedules, hypotheses, and end points were identical in the two trials. Sample sizes differed to account for local incidence data.

Trial Oversight

The sponsor designed the trials and performed sample testing and data analyses. The investigators collected the data, and the sponsor and the investigators interpreted the data and collaborated in the preparation of the manuscript. Representatives of the sponsor had complete access to the trial data and vouch for the completeness and accuracy of the data and the analyses. The nonsponsor authors had access to the statistical analyses but not to participant-level data, so that blinding in the ongoing trials could be maintained. The first draft of the manuscript was written by a medical writer who was employed by MediCom Consult and was paid by the sponsor. All the authors provided critical input in the preparation of the manuscript and approved the submitted version.

STUDY OUTCOMES

All analyses that are presented here were prespecified, except for post hoc analyses of data from participants younger than 9 years of age and those 9 years of age or older in the CYD14 and CYD23/57 trials. Ages refer to the ages at initial enrollment.

Long-Term Follow-up Analyses

The objective of the follow-up analyses was to describe the long-term safety of the dengue candidate vaccine, as recommended by the World Health Organization (WHO), to verify that the immune response to vaccination does not confer a predisposition to severe disease and that the risk of severe disease does not increase with time owing to waning titers of vaccine-induced antibodies in persons in whom immunity has not been naturally boosted. We are assessing the incidence of hospitalization for virologically confirmed dengue (of any severity or any serotype) for 4 years after the end of the 25-month efficacy surveillance periods as a surrogate outcome for severe disease. (For details, see the Methods section in the Supplementary Appendix.) In addition, among the hospitalized participants, we are assessing the occurrence of severe dengue using the criteria of the independent data monitoring committee and the 1997 WHO criteria for dengue hemorrhagic fever. We are recording clinical signs and symptoms of the hospitalized participants to describe the disease profile and are collecting data regarding serious adverse events that occur during the 4-year safety follow-up.

Pooled Efficacy Analyses

The objective of the pooled CYD14 and CYD15 analyses was to assess the efficacy of CYD-TDV against virologically confirmed dengue, hospitalization for dengue, and severe illness (defined according to the criteria of the independent data monitoring committee and the WHO criteria for dengue hemorrhagic fever) associated with any serotype. We repeated the analyses according to age and, in participants in the immunogenicity subgroups, according to baseline dengue serostatus.

DATA SETS INCLUDED IN ANALYSES

For the interim analysis of long-term follow-up, the safety analysis set included participants who had received at least one dose of vaccine; participants were analyzed in the group corresponding to the first injection received, regardless of group assignment. For the pooled efficacy analysis of the primary outcome (i.e., symptomatic,

virologically confirmed dengue of any severity or any serotype), the analysis was performed in the per-protocol efficacy population, which included participants who had received three doses of vaccine and who had no prespecified protocol deviations. For all other outcomes, the analyses were performed in the intention-to-treat efficacy population, which included all participants who had received at least one injection and who were evaluated in the group to which they had been randomly assigned, regardless of per-protocol criteria (see the Methods section in the Supplementary Appendix).

STATISTICAL ANALYSIS

We calculated annual incidence rates and 95% confidence intervals for hospitalization for virologically confirmed dengue and for severe disease (as defined according to the criteria of the independent data monitoring committee and the WHO criteria for dengue hemorrhagic fever) for any and for all serotypes, for all participants, and according to age group at enrollment. We calculated incidence rates (expressed as percentages) as the number of participants who had at least one event divided by the number of participants present at the start of the study period. Since data were collected for 11 months during year 3 (from month 25 to month 36), the annual incidence was calculated as the number of cases divided by the total number of participants divided by 11 and multiplied by 12. We calculated relative risk as the annual incidence rate ratios in the vaccine and control groups.[1,2]

The statistical methods that were used for the calculations of estimates of vaccine efficacy have been reported previously.[1,2] We used a Cox regression model to estimate pooled vaccine efficacy, with vaccine group and trial included as fixed effects. An analysis of interaction was added in the model to test for heterogeneity, with a P value of less than 0.10 considered to indicate statistical significance. Suspected interactions were assessed for their clinical and statistical relevance.[5]

RESULTS

STUDY PARTICIPANTS

A total of 3203 of the 4002 participants (80%) in the CYD23 trial who were between the ages of 4 and 11 years at enrollment were subsequently enrolled in the extension trial, CYD57 (2131 in the vaccine group and 1072 in the control group). A total of 10,165 of 10,275 participants (99%) in the CYD14 trial and 19,898 of 20,869 participants (95%) in the CYD15 trial who were between the ages of 2 and 16 years are being followed (6778 in the vaccine group and 3387 in the control group in the CYD14 trial and 13,268 and 6630, respectively, in the CYD15 trial). The vaccine and control groups were well balanced with respect to age and sex (Table S1 in the Supplementary Appendix). More participants in the CYD15 trial than in the CYD14 trial were seropositive for dengue at baseline, although the numbers were similar among those who were 9 years of age or older (Fig. S1 in the Supplementary Appendix).

INTERIM LONG-TERM SAFETY ANALYSES

All Participants

During year 3, the annual incidence of hospitalization for virologically confirmed dengue was 0.4% (27 of 6778 participants) in the vaccine group and 0.4% (13 of 3387) in the control group in the CYD14 trial, 0.1% (16 of 13,268 participants) in the vaccine group and 0.2% (15 of 6630) in the control group in the CYD15 trial, and 1.1% (22 of 2131 participants) in the vaccine group and 1.1% (11 of 1072) in the control group in the CYD57 trial (Table 1). The relative risk of hospitalization for virologically confirmed dengue in the vaccine group as compared with the control group was 1.04 (95% confidence interval [CI], 0.52 to 2.19) in the CYD14 trial, 0.53 (95% CI, 0.25 to 1.16) in the CYD15 trial, and 1.01 (95% CI, 0.47 to 2.30) in the CYD23/57 trial (Table 1). The pooled relative risk for the three trials was 0.84 (95% CI, 0.56 to 1.24). The majority of patients had serotype 1 or 2 infection; serotype 4 was the least frequently identified serotype (Table 1).

The length of hospitalization, duration of fever, and clinical symptoms were similar in the three trials (Tables S2A, S2B, and S2C in the Supplementary Appendix). No clinically important differences in the frequencies of signs and symptoms were observed between the vaccine and control groups, suggesting that there were no vaccine-related changes in the clinical picture of hospitalized participants. Similar levels of viremia were observed among hospitalized participants in the vaccine group and the control group (Table S3 in the Supplementary Appendix).

Table 1. Annual Incidence of Hospitalization for Virologically Confirmed Dengue, According to Trial, Age Group, and Study Period.*

Trial, Age Group, and Study Period	Vaccine Group			Control Group			Relative Risk (95% CI)
	Cases of Dengue	Total Participants†	Annual Incidence Rate‡	Cases of Dengue	Total Participants†	Annual Incidence Rate‡	
		no.	*% (95% CI)*		*no.*	*% (95% CI)*	
CYD14							
All participants§	27	6,778	0.4 (0.3–0.6)	13	3387	0.4 (0.2–0.7)	1.04 (0.52–2.19)
2–5 yr	15	1,636	1.0 (0.6–1.6)	1	813	0.1 (0.0–0.7)	7.45 (1.15–313.80)
6–11 yr	10	3,598	0.3 (0.1–0.6)	8	1806	0.5 (0.2–1.0)	0.63 (0.22–1.83)
12–14 yr	2	1,544	0.1 (0.0; 0.5)	4	768	0.6 (0.2–1.4)	0.25 (0.02–1.74)
<9 yr	19	3,493	0.6 (0.4–0.9)	6	1741	0.4 (0.1–0.8)	1.58 (0.61–4.83)
≥9 yr	8	3,285	0.3 (0.1–0.5)	7	1646	0.5 (0.2–1.0)	0.57 (0.18–1.86)
CYD15							
All participants¶	16	13,268	0.1 (0.1–0.2)	15	6630	0.2 (0.1–0.4)	0.53 (0.25–1.16)
9–11 yr	10	6,029	0.2 (0.1–0.3)	9	3005	0.3 (0.1–0.6)	0.55 (0.20–1.54)
12–16 yr	6	7,239	<0.1 (0.0–0.2)	6	3625	0.2 (0.1–0.4)	0.50 (0.13–1.87)
CYD57							
All participants							
Year 3‖	22	2,131	1.1 (0.7–1.7)	11	1072	1.1 (0.6–2.0)	1.01 (0.47–2.30)
Year 4‖	16	2,131	0.8 (0.4–1.2)	17	1072	1.6 (0.9–2.5)	0.47 (0.22–1.00)
4 or 5 yr							
Year 3	5	393	1.4 (0.5–3.2)	1	192	0.6 (0.0–3.1)	2.44 (0.27–115.54)
Year 4	5	393	1.3 (0.4–2.9)	3	192	1.6 (0.3–4.5)	0.81 (0.16–5.24)
6–11 yr							
Year 3	17	1,738	1.1 (0.6–1.7)	10	880	1.2 (0.6–2.3)	0.86 (0.37–2.10)
Year 4	11	1,738	0.6 (0.3–1.1)	14	880	1.6 (0.9–2.7)	0.40 (0.16–0.94)
<9 yr							
Year 3	19	1,338	1.5 (0.9–2.4)	6	665	1.0 (0.4–2.1)	1.57 (0.60–4.80)
Year 4	13	1,338	1.0 (0.5–1.7)	12	665	1.8 (0.9–3.1)	0.54 (0.23–1.29)
≥9 yr							
Year 3	3	793	0.4 (0.1–1.2)	5	407	1.3 (0.4–3.1)	0.31 (0.05–1.58)
Year 4	3	793	0.4 (0.1–1.1)	5	407	1.2 (0.4–2.8)	0.31 (0.05–1.58)

* CYD14 and CYD15 are two phase 3 randomized efficacy studies involving a total of more than 31,000 participants between the ages of 2 and 16 years in Asian–Pacific and Latin American countries, respectively. In addition, 3203 of 4002 participants (80%) who were between the ages of 4 and 11 at initial enrollment in the phase 2b CYD23 trial in Thailand are being followed in the CYD57 trial. The trials had similar designs. Listed are virologically confirmed cases of any serotype of dengue during year 3 in the CYD14 and CYD15 trials and in years 3 and 4 in the CYD57 trial.

† Listed is the number of participants at the beginning of each year or the mean number of participants who were followed during the years included in the period.

‡ Since data were collected for 11 months during year 3 (from month 25 to month 36), the annual incidence was calculated as the number of cases divided by the total number of participants divided by 11 times 12.

§ During year 3 in the CYD14 trial, the numbers of participants with disease caused by each serotype at baseline in the vaccine group versus the control group (with patients randomly assigned in a 2:1 ratio) were as follows: serotype 1, 11 vs. 1; serotype 2, 3 vs. 0; serotype 3, 13 vs. 7; and serotype 4, 0 vs. 5.

¶ During year 3 in the CYD15 trial, the numbers of participants with disease caused by each serotype at baseline in the vaccine group versus the control group were as follows: serotype 1, 5 vs. 5; serotype 2, 8 vs. 11; serotype 3, 3 vs. 0; and serotype 4, 0 vs. 0.

‖ During years 3 and 4 in the CYD57 trial, the numbers of participants with disease caused by each serotype at baseline in the vaccine group versus the control group were as follows: year 3: serotype 1, 5 vs. 5; serotype 2, 17 vs. 4; serotype 3, 1 vs. 1; and serotype 4, 0 vs. 0; year 4: serotype 1, 4 vs. 3; serotype 2, 4 vs. 6; serotype 3, 6 vs. 3; and serotype 4, 2 vs. 4.

Overall, during year 3, severe dengue, defined according to the criteria of the independent data monitoring committee, was reported in 18 of 22,177 participants in the vaccine group and in 6 of 11,089 in the control group (Table S4 in the Supplementary Appendix). In the CYD23/57 trial during year 4, severe dengue occurred in 1 participant in the vaccine group and in 2 participants in the control group. All the cases that were classified as severe according to the criteria of the independent data monitoring committee were classified as WHO grade I or II, except for the cases in 2 participants in the vaccine group during year 3 of the CYD23/57 trial, which were classified as grade III. All the participants who were hospitalized for virologically confirmed dengue during follow-up had a full recovery after receiving appropriate supportive treatment.

Long-Term Follow-up According to Age Group

In the CYD14 trial, prespecified age-specific analyses showed a clear trend toward a higher relative risk for hospitalization for virologically confirmed dengue among younger children, although the number of cases was low; the relative risks were 7.45 among children between the ages of 2 and 5 years, 0.63 among those between the ages of 6 and 11 years, and 0.25 among those between the ages of 12 and 14 years (Table 1). The prespecified age-specific analyses in the CYD23/57 trial showed a relative risk of 2.44 (95% CI, 0.27 to 115.34) among participants who were 4 or 5 years of age during year 3 (Table 1). In year 4 of the CYD23/57 trial, the relative risk among children who were 4 or 5 years of age was 0.81, but the upper boundary of the 95% confidence interval remained more than 1 (95% CI, 0.16 to 5.24). Further analyses in the CYD15 trial, in which participants between the ages of 9 and 16 years were enrolled, showed no trend according to age group among those who were between the ages of 9 and 11 years and those who were between the ages of 12 and 16 years.

In year 3, the relative risks among participants younger than 9 years of age were similar in the CYD14 and CYD23/57 trials, with a pooled estimated relative risk of 1.58 (95% CI, 0.83 to 3.02), which suggests an overall trend to increased risk in the vaccine group, although the lower boundary of the 95% confidence interval was less than 1 (Table 1). The relative risk among those who were 9 years of age or older was 0.57 (95% CI, 0.18 to 1.86) in the CYD14 trial and 0.31 (95% CI, 0.05 to 1.58) in the CYD23/57 trial, findings that were similar to the results in the CYD15 trial, in which all the participants were 9 years of age or older (relative risk, 0.53; 95% CI, 0.25 to 1.16). The pooled relative risk among participants who were 9 years of age or older was 0.50 (95% CI, 0.29 to 0.86). An exploratory analysis in the CYD14 trial showed that among participants between the ages of 9 and 11 years, the relative risk was 1.01 (95% CI, 0.22 to 6.23), as compared with a relative risk of 0.25 (95% CI, 0.02 to 1.74) among those between the ages of 12 and 14 years. This trend was not observed in the CYD15 trial (Table 1). In year 4 in the CYD57 trial, the relative risk among participants who were 9 years of age or older was similar to that in year 3 (relative risk, 0.31; 95% CI, 0.05 to 1.58), whereas the relative risk among the younger participants had decreased to 0.54 (95% CI, 0.23 to 1.29) (Table 1).

In the CYD14 trial, among participants younger than 9 years of age who were hospitalized for dengue, severe disease (according to the criteria of the independent data monitoring committee) occurred in 8 of 19 participants in the vaccine group and in none of 6 participants in the placebo group (relative risk could not be calculated). Among those who were 9 years of age or older, severe disease occurred in 3 of 8 participants in the vaccine group and in 1 of 7 participants in the control group (relative risk, 1.50; 95% CI, 0.12 to 78.9). The three cases in the vaccine group occurred in participants who were between the ages of 9 and 11 years at enrollment. In the CYD23/57 trial, all the severe cases occurred in participants who were younger than 9 years of age. In year 3, the two participants in the vaccine group in whom the illness was classified as grade III dengue hemorrhagic fever according to the WHO criteria had clinical shock.

For year 3, the overall pooled estimate of the relative risk of hospitalization for severe dengue was 1.50 (95% CI, 0.60 to 3.79) for all the participants, as compared with 0.50 (95% CI, 0.16 to 1.55) for participants who were 9 years of age or older. Among participants under the age of 9 years, there were 12 cases of severe dengue (8 in the CYD14 trial and 4 in the CYD23/57 trial) in the vaccine group and none in the control group; consequently, the relative risk for this analysis

could not be calculated. The pooled relative risk was driven mainly by the cases occurring in participants younger than 9 years of age.

Hospitalization since Vaccination

Although the relative risk of hospitalization for dengue varied in the three studies, within-trial estimates showed reductions in risk in the vaccine group during years 1 and 2 of the efficacy surveillance phase. With the exception of year 1 in the CYD23/57 trial, the upper boundaries of the 95% confidence intervals were all less than 1 (Table S5 in the Supplementary Appendix). Cumulative relative risks for hospitalizations that occurred more than 3 years after vaccination were 0.46 (95% CI, 0.32 to 0.65) in the CYD14 trial, 0.28 (95% CI, 0.18 to 0.44) in the CYD15 trial, and 0.66 (95% CI, 0.43 to 1.02) in the CYD23/57 trial (Table S5 in the Supplementary Appendix). Cumulative relative risks during this period in the CYD14 trial were 0.61 (95% CI, 0.39 to 0.95) among participants younger than 9 years of age and 0.27 (95% CI, 0.14 to 0.48) among those who were 9 years of age or older. A Kaplan–Meier plot showed that there was greater protection among participants who were 9 years of age or older than among those who were under the age of 9 years, and the incidence appeared to be stable (Fig. S2 in the Supplementary Appendix). Cases occurred throughout the follow-up, with similar accrual patterns over time.

The length of hospitalization and duration of fever and clinical symptoms were similar for those hospitalized during the efficacy surveillance phase and the long-term follow-up phase in all three trials (Tables S2A, S2B, and S2C in the Supplementary Appendix). No clinically important differences in the frequencies of various signs and symptoms in the hospitalized participants were seen between the efficacy surveillance phase and the long-term follow-up phase in any of the studies or between the vaccine and control groups, which suggests there were no changes in the clinical picture of hospitalized cases during long-term follow-up. The levels of viremia were similar to those in the efficacy surveillance phase and similar between groups (Table S3 in the Supplementary Appendix).

POOLED ANALYSES FOR VACCINE EFFICACY

Vaccine efficacies for dengue caused by any and each serotype were generally consistent in the per-protocol and intention-to-treat analyses in the individual trials and in the pooled analyses for all outcomes, but multivariate analyses including age as a categorical variable (age group) or as a continuous variable showed significant interaction between age and vaccine group (Fig. S3 through S6 in the Supplementary Appendix). As compared with vaccine efficacies among all participants, for all outcomes, efficacies were higher among participants who were 9 years of age or older and lower among participants who were under 9 years of age. Vaccine efficacies against dengue in participants who were 9 years of age or older were similar in the individual trials, with a pooled estimate of 65.6% (95% CI, 60.7 to 69.9) (Fig. 2A), as compared with 44.6% (95% CI, 31.6 to 55.0) among participants under the age of 9 years (Fig. 2B).

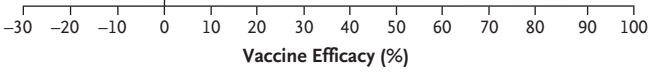
The pooled serotype-specific vaccine efficacies for this outcome ranged from 47.1% (95% CI, 31.3 to 59.2) for serotype 2 to 83.2% (95% CI, 76.2 to 88.2) for serotype 4 among participants who were 9 years of age or older (Fig. 2A). Among those under the age of 9 years, the range was from 33.6% (95% CI, 1.3 to 55.0) for serotype 2 to 62.1% (95% CI, 28.4 to 80.3) for serotype 3 (Fig. 2B).

Approximately 80% of the participants 9 years of age or older in the immunogenicity subgroup in the CYD14 and CYD15 trials were seropositive for dengue at baseline (Fig. S1 in the Supplementary Appendix). Pooled vaccine efficacy among seropositive participants was 81.9% (95% CI, 67.2 to 90.0) among those who were 9 years of age or older (Fig. 2A), as compared with 70.1% (95% CI, 32.3 to 87.3) among those who were younger than 9 years of age (Fig. 2B). In each study, vaccine efficacies were lower among seronegative participants who were 9 years of age or older than among seropositive participants in the same age group, and the lower boundaries of the 95% confidence intervals were less than 0. However, the pooled vaccine efficacy in this age group was 52.5%, with a lower boundary of the 95% confidence interval of more than 0 (Fig. 2A), as compared with a vaccine efficacy of 14.4% (95% CI, –111.0 to 63.5) among participants under the age of 9 years (Fig. 2B).

Vaccine efficacies against hospitalization for dengue were more than 80% in the individual trials among participants who were 9 years of age or older, with a pooled vaccine efficacy of

A Participants 9 Yr of Age or Older

Serotype and Trial	Vaccine Group	Control Group	Vaccine Efficacy (95% CI)
	no. of cases/total no.		
All serotypes			
CYD14	90/3316	136/1656	67.8 (57.7 to 75.6)
CYD15	277/13,914	385/6940	64.7 (58.7 to 69.8)
CYD14+CYD15			65.6 (60.7 to 69.9)
Serotype 1			
CYD14	36/3316	52/1656	65.7 (46.6 to 78.2)
CYD15	99/13,914	109/6940	54.8 (40.2 to 65.9)
CYD14+CYD15			58.4 (47.7 to 66.9)
Serotype 2			
CYD14	33/3316	26/1656	36.8 (–10.1 to 63.3)
CYD15	84/13,914	84/6940	50.2 (31.8 to 63.6)
CYD14+CYD15			47.1 (31.3 to 59.2)
Serotype 3			
CYD14	11/3316	18/1656	69.5 (31.9 to 87.0)
CYD15	55/13,914	106/6940	74.2 (63.9 to 81.7)
CYD14+CYD15			73.6 (64.4 to 80.4)
Serotype 4			
CYD14	10/3316	41/1656	87.9 (75.5 to 94.6)
CYD15	32/13,914	83/6940	80.9 (70.9 to 87.7)
CYD14+CYD15			83.2 (76.2 to 88.2)
Seropositive at baseline			
CYD14	7/487	17/251	79.2 (47.2 to 92.7)
CYD15	8/1073	23/512	83.7 (62.2 to 93.7)
CYD14+CYD15			81.9 (67.2 to 90.0)
Seronegative at baseline			
CYD14	7/129	8/59	61.6 (–21.1 to 88.1)
CYD15	9/258	9/149	43.2 (–61.6 to 80.0)
CYD14+CYD15			52.5 (5.9 to 76.1)



B Participants under 9 Yr of Age

Serotype in Trial CYD14	Vaccine Group	Control Group	Vaccine Efficacy (95% CI)
	no. of cases/total no.		
All serotypes	196/3532	173/1768	44.6 (31.6 to 55.0)
Serotype 1	80/3532	74/1768	46.6 (25.7 to 61.5)
Serotype 2	64/3532	48/1768	33.6 (1.3 to 55.0)
Serotype 3	19/3532	25/1768	62.1 (28.4 to 80.3)
Serotype 4	30/3532	31/1768	51.7 (17.6 to 71.8)
Seropositive at baseline	11/414	17/193	70.1 (32.3 to 87.3)
Seronegative at baseline	13/295	10/157	14.4 (–111 to 63.5)

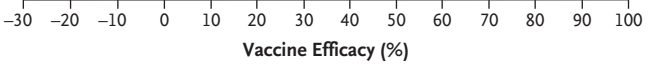


Figure 2 (facing page). Vaccine Efficacy, According to Serotype and Age Group.

Panel A shows a forest plot indicating vaccine efficacy against virologically confirmed dengue according to serotype and serostatus at baseline among participants who were 9 years of age or older at baseline in the CYD14 trial (which enrolled children between the ages of 2 and 14 years), the CYD15 trial (which enrolled children between the ages of 9 and 16 years), and the meta-analysis of these trials. There was no significant interaction between the vaccine group and the trial. Panel B shows vaccine efficacy among participants who were under the age of 9 years in the CYD14 trial.

80.8% (95% CI, 70.1 to 87.7) (Fig. 3A), as compared with 56.1% (95% CI, 26.2 to 74.1) among participants under the age of 9 years (Fig. 3B). Pooled vaccine efficacies for severe dengue, as defined according to the criteria of the independent data monitoring committee, were 93.2% (95% CI, 77.3 to 98.0) among participants who were 9 years of age or older and 44.5 (95% CI, −54.4 to 79.7) among those under the age of 9 years. The vaccine efficacies against dengue hemorrhagic fever, as defined according to the WHO criteria, were 92.9% (95% CI, 76.1 to 97.9) and 66.7% (95% CI, −4.7 to 90.2) in the two groups, respectively (Fig. 3A and 3B).

DISCUSSION

The three clinical trials assessing the CYD-TDV candidate vaccine include a 4-year long-term follow-up safety phase, which was designed in line with WHO guidelines.[6] During year 3 in the CYD14 trial, 40 participants were hospitalized for virologically confirmed dengue (27 in the vaccine group and 13 in the control group). However, the relative risk in the vaccine group shifted to 1.0, driven by the 15 cases that occurred among younger children in the vaccine group, particularly those who were 5 years of age or younger. The combined analysis of the CYD14, CYD15, and CYD57 trials during year 3 showed a lower risk of hospitalization for dengue among participants who were 9 years of age or older in the vaccine group than among those in the control group. This reduction in risk was not observed among children under the age of 9 years. However, variability in the relative risks between year 3 (1.01; 95% CI, 0.47 to 2.30) and year 4 (0.47; 95% CI, 0.22 to 1.00) in the CYD23/57 trial suggests that results from year 3 in the CYD14 and CYD15 trials should be interpreted with caution.

Hospitalization for dengue was used as an end point to minimize the risk of underreporting during long-term follow-up, since participants with more severe febrile illness are more likely to be hospitalized than are those with mild illness. Although hospitalization practices vary among countries and among health care centers in the same country, randomization should have assured a similar likelihood of hospitalization among vaccinated and unvaccinated participants in each center. Data are limited regarding markers of dengue severity, and some of such markers (e.g., plasma leakage) rely on variable, imprecise clinical assessment that is dependent on the time since onset. Since the methods that were used to capture hospitalization for dengue in the CYD14 and CYD15 trials differ between the efficacy surveillance phase and the long-term follow-up phase, the comparisons of relative risks for the two phases and the relative risks for the entire studies should be interpreted with caution as well.

Although there were more hospitalizations and cases of severe dengue reported among participants under the age of 9 years than among those older than 9 years of age in the vaccine group, the clinical pattern of these cases during the long-term follow-up safety phase was similar to that reported for hospitalization during the efficacy surveillance phase, with no observed differences in clinical severity or viremia. In all cases, the participants had a complete recovery. In addition, there were no significant differences between cases occurring in the vaccine group and the control group among participants under the age of 9 years. Ongoing safety review during long-term follow-up monitors cases between the planned interim analyses. Available clinical data are insufficient for drawing definitive conclusions about the observed imbalance in younger children. However, on-site investigations have shown that major forms of bias (e.g., unblinding) are unlikely to explain the imbalance.

Several interrelated plausible biologic hypotheses could explain the imbalance among the

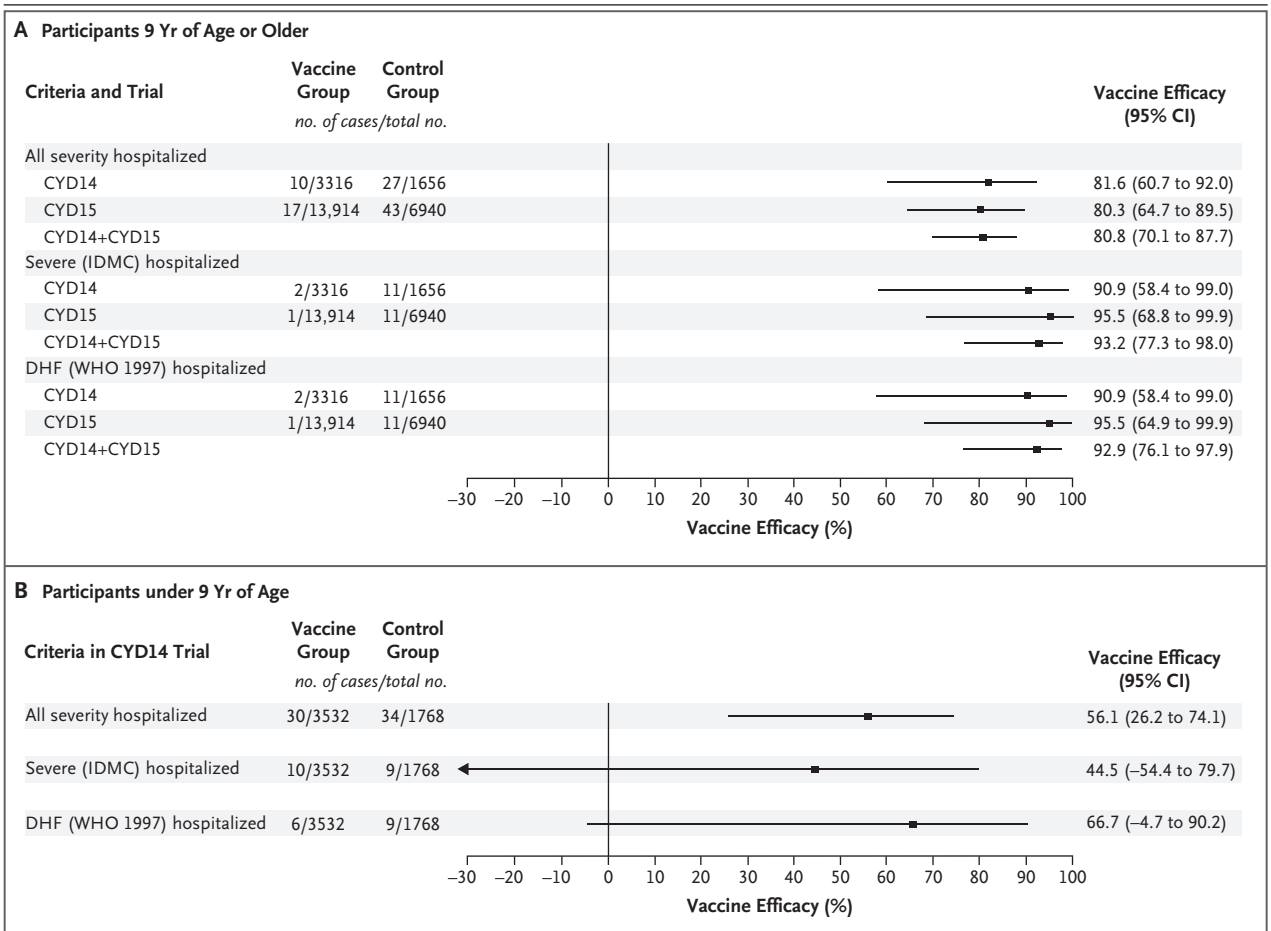


Figure 3. Vaccine Efficacy, According to Group Criteria and Trial.

Panel A shows a forest plot indicating vaccine efficacy among children who were 9 years of age or older at baseline according to rates of hospitalization for dengue in the intention-to-treat population; rates of severe dengue, as defined according to the criteria of the independent data monitoring committee (IDMC); and rates of dengue hemorrhagic fever (DHF), as defined according to the 1997 criteria of the World Health Organization (WHO). Shown are data for the CYD14 trial (which enrolled children between the ages of 2 and 14 years), the CYD15 trial (which enrolled children between the ages of 9 and 16), and the meta-analysis of these trials. There was no significant interaction between the vaccine group and the trial. Panel B shows the same results for children under the age of 9 years in the CYD14 trial.

younger participants. Some of these children may have had a lower-quality cross-reactive immune response to vaccination that is prone to waning; this may have been the case particularly among children who were seronegative at the time of vaccination and therefore more likely to be younger. Subsequent first wild-type infection (which is typically less severe) may have occurred in a vaccination-induced immunologic setting, which is more analogous to a secondary infection (which is associated with an increased risk of severe disease).[7] Vaccination during the condensed enrollment period could have clustered these children, as compared with the unvaccinated controls, who would be primed naturally over a longer period. Further surveillance is required to assess whether there is equalization over time. However, if an immune-enhancement hypothesis explains our observations, we would have expected elevated clinical viremia and an altered cytokine profile, which we did not observe. Age per se may also be important, because younger children have less-developed vascular physiology and partially immature immune

responses, which could explain the observed imbalance of events among younger vaccinees in the CYD14 trial during year 3.[8-10] Statistical and clinical investigations are ongoing to explore these hypotheses. Since it is essential to continue evaluating long-term vaccine efficacy and safety, the protocols for the CYD14 and CYD15 trials were amended to allow for the documentation of cases of dengue among both hospitalized and nonhospitalized participants as safety and efficacy end points during the 4-year long-term follow-up.

Even though the trials were performed in different geographic areas and among different age groups, point estimates of vaccine efficacy were similar across the trials in the majority of the analyses. Pooled vaccine efficacy against dengue of any severity and any serotype from the efficacy surveillance phase among participants who were 9 years of age or older was 65.6%; pooled vaccine efficacies for serotype-specific dengue were all higher than the nonpooled vaccine efficacies. On the basis of a limited number of participants in the immunogenicity subgroups, pooled analyses of data from participants who were 9 years of age or older showed that the vaccine efficacies were 81.9% (95% CI, 67.2 to 90.0) among seropositive participants and 52.5% (95% CI, 5.9 to 76.1) among seronegative participants.

Data from the CYD23 trial were not included in the pooled analyses because although the CYD23 trial had a similar design to that in the CYD14 and CYD15 trials, there were some notable differences — in particular, the definition of acute fever. However, sensitivity analyses that included data from the CYD23 trial showed results similar to those reported here, although with higher heterogeneity.

In addition to evidence from efficacy trials, long-term safety and efficacy data from these studies and others (including potential post-authorization studies of safety and effectiveness) in an integrated risk-management plan will provide a more complete clinical profile of the CYD-TDV candidate dengue vaccine. Although further follow-up of children under the age of 9 years is needed to provide more information regarding the observed imbalance, our results show a lower risk of hospitalization for dengue during year 3 among vaccinated children who were 9 years of age or older than among controls.[1,2] The population at risk for dengue varies depending on local epidemiology, with the highest disease burden generally observed in age groups representing the largest population (i.e., adolescents and adults).[11,12]

In conclusion, available data from the efficacy and long-term follow-up surveillance periods across three studies in Asian–Pacific and Latin American tropical and subtropical regions in which dengue is endemic showed a reduction in dengue disease in the efficacy surveillance phase among children who received the vaccine. In addition, there was a lower risk of hospitalization for dengue overall for up to 2 years after completion of the three-dose vaccination schedule among children between the ages of 9 and 16 years.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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