Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

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Summary

Background An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.

Methods We did an observer-masked, randomised controlled, multicentre, phase 3 trial in five countries in the Asia-Pacific region. Between June 3, and Dec 1, 2011, healthy children aged 2–14 years were randomly assigned (2:1), by computer-generated permuted blocks of six with an interactive voice or web response system, to receive three injections of a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV), or placebo, at months 0, 6, and 12. Randomisation was stratified by age and site. Participants were followed up until month 25. Trial staff responsible for the preparation and administration of injections were unmasked to group allocation, but were not included in the follow-up of the participants; allocation was concealed from the study sponsor, investigators, and parents and guardians. Our primary objective was to assess protective efficacy against symptomatic, virologically confirmed dengue, irrespective of disease severity or serotype, that took place more than 28 days after the third injection. The primary endpoint was for the lower bound of the 95% CI of vaccine efficacy to be greater than 25%. Analysis was by intention to treat and per procotol. This trial is registered with ClinicalTrials.gov, number NCT01373281.

Findings We randomly assigned 10 275 children to receive either vaccine (n=6851) or placebo (n=3424), of whom 6710 (98%) and 3350 (98%), respectively, were included in the primary analysis. 250 cases of virologically confirmed dengue took place more than 28 days after the third injection (117 [47%] in the vaccine group and 133 [53%] in the control group). The primary endpoint was achieved with 56·5% (95% CI 43·8–66·4) efficacy. We recorded 647 serious adverse events (402 [62%] in the vaccine group and 245 [38%] in the control group). 54 (1%) children in the vaccine group and 33 (1%) of those in the control group had serious adverse events that happened within 28 days of vaccination. Serious adverse events were consistent with medical disorders in this age group and were mainly infections and injuries.

Interpretation Our findings show that dengue vaccine is efficacious when given as three injections at months 0, 6, and 12 to children aged 2–14 years in endemic areas in Asia, and has a good safety profile. Vaccination could reduce the incidence of symptomatic infection and hospital admission and has the potential to provide an important public health benefit.

Funding Sanofi Pasteur.

Introduction

An estimated 390 million dengue infections take place every year and roughly 96 million people have clinically apparent disease.[1–3] About 70% of the overall disease burden, which has increased by 30 times in the past 50 years, is reported in the Asia-Pacific region.[1,3] Four viral serotypes cause disease in proportions that change unpredictably over time and from place to place, even within the same country. Incidence has increased in older age groups in many countries where dengue is endemic.[1,4]

No licensed vaccines and no specific treatments are available to prevent dengue infection. The vaccine candidate assessed here is a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV) that has been consistently well tolerated and immunogenic in clinical studies in Asia and Latin America.[5–9] A first, proof-of-concept efficacy trial[1] including 4002 Thai children aged 4–11 years, did not meet its primary outcome, with a vaccine efficacy of 30·2% (95% CI –13·4 to 56·6). In exploratory intention-to-treat analyses, the lower bound of the 95% CI for the serotype-specific vaccine efficacy for serotypes 1, 3, and 4 was greater than 0 after the first injection, but not after the third injection, possibly because of the lower number of cases.[10]

We did this phase 3 efficacy trial of dengue vaccine to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue, irrespective of serotype or disease severity. In an ongoing second study

phase, long-term safety surveillance for trial participants admitted to hospital for acute febrile illness will continue for an additional 4 years (ie, a total of 5 years follow-up after the third dose).

Methods

Study design and participants

We did a multicentre, randomised, observer-masked, placebo-controlled, phase 3 trial in five countries in the Asia-Pacific (three centres in Indonesia, two centres in Malaysia, two centres in the Philippines, three centres in Thailand, and two centres in Vietnam). We enrolled healthy children aged 2–14 years, whose parents or guardians were intending to stay in the trial's catchment area for the duration of the trial. We excluded children with acute febrile illness (until resolution), those who had received another vaccine (until 4 weeks after vaccination), those with congenital or acquired immunodeficiency, or those with other criteria listed in the protocol (appendix).

The trial was undertaken in compliance with good clinical practice guidelines and the principles of the Declaration of Helsinki. Ethics review committees approved the protocol, amendments, consent, and assent forms. Parents or legal guardians provided informed consent before participation, and written assent was obtained from older children, in compliance with the regulations of each country. An independent data monitoring committee regularly reviewed safety data and assessed the clinical severity of all cases of virologically confirmed dengue with criteria based on 1997 WHO guidance and an additional list of symptoms, such as visceral manifestations, as previously reported.[10,11]

Randomisation and masking

Eligible children were randomly assigned (2:1), by computer-generated permuted blocks of six with an interactive voice-response or web-response system, to receive CYD-TDV or placebo. Among participants enrolled during the first 2 months of the 6-month overall enrolment period, participants were also randomised (2:1) for inclusion in a subset for reactogenicity and immunogenicity assessment. This 2-month period was extended by up to 2 months in Malaysia and Indonesia.

The randomisation list was generated under the sponsor's responsibility with stratification by site and age (2–5 years, 6–11 years, and 12–14 years).

A observer-masked design was needed because the physical appearance of the vaccine and placebo differed. The unmasked trial staff, who were responsible specifically for the preparation and administration of injections, were not included in the follow-up of the participants. The sponsor was masked until the end of the active surveillance period and was unmasked to undertake the primary analysis. Study investigators and parents and guardians will remain masked until the hospital phase of the trial has been completed (appendix).

Procedures

The study sponsor supplied vaccine as a powder and solvent for suspension for injection (stored between 2°C and 8°C).[6,12] Qualified trial personnel administered injections subcutaneously in the deltoid region, promptly after reconstitution in 0·5 mL. Placebo was a 0·9% solution of sodium chloride, also supplied by the sponsor. Participants received three doses of vaccine or placebo at months 0, 6, and 12.

All participants attended five visits at months 0, 6, and 12 for vaccination and months 13 and 25 for follow-up; at month 18 participants had a follow-up phone call or home visit (appendix). Blood samples were taken from all participants at month 13. Participants randomised to the subset attended additional visits after injections one and two (at months 1 and 7) to document reactogenicity, as previously described, and to sample blood at month 7.[6,7,10] We actively monitored children via weekly contact with parents and guardians or participants, and by surveillance of school absenteeism. Parents were regularly reminded during phone calls and home visits to take their child to the trial or health-care centre in case of acute febrile illness (temperature ≥38°C on ≥2 consecutive days). Active surveillance started on the day of administration of dose one and continued until month 25. In the event of acute febrile illness, in addition to tests done according to the local standards of care, two blood samples were taken. One sample, taken during the acute phase within 5 days of fever onset, was tested for dengue non-structural protein 1 (NS1) antigen (Platelia Biorad Laboratories, Marnes-La-Coquette, France), and with a dengue screen PCR (quantitive reverse transcription PCR), and a serotype-specific PCR (Simplexa dengue real-time PCR assay, Focus Diagnostics, CA, USA). The Simplexa assay was introduced in a protocol amendment to improve sensitivity, on the basis of findings from a phase 2 study.[13] An episode was classified as virologically confirmed dengue if any of these tests were positive. Both the acute and a second, convalescent sample collected 7–14 days later, were tested for dengue IgM and IgG (findings not presented here). Assays were done under masked conditions at the sponsor's Global Clinical Immunology laboratories (Swiftwater, PA, USA) and at the Centre for Vaccine Development at Mahidol University (Bangkok, Thailand).

In the subset, concentrations of dengue neutralising antibody were measured with the plaque reduction neutralisation test ($PRNT_{50}$) at Global Clinical Immunology laboratories at baseline and after doses two and three.[14] Concentrations of neutralising antibody against Japanese encephalitis were also measured at baseline with $PRNT_{50}$ at the Centre for Vaccine Development.

We documented and assessed all serious adverse events that took place at any time during the trial.

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See Online for appendix

Outcomes

In accordance with WHO guidelines, the primary objective was to estimate vaccine efficacy against symptomatic, virologically confirmed dengue, irrespective of severity or serotype, that took place more than 28 days after the third dose (ie, at month 13) until month 25 in participants who received three injections according to protocol and without any of the criteria in a prespecified list (per-protocol population; appendix).[15] Our primary endpoint was for the lower bound of the 95% CI of vaccine efficacy to be greater than 25%. We assessed vaccine efficacy taking into account the number of cases (ie, participants with one or more episode of virologically confirmed dengue) and the cumulative person-time at risk to calculate the incidence density in each group, as described previously.[10]

Secondary efficacy analyses included the assessment of vaccine efficacy against virologically confirmed dengue that took place at any time from month 0–25 due to any and each serotype in the intention-to-treat population, and against each serotype occurring from 28 days after the third injection, irrespective of protocol deviations. Efficacy by age strata and country were also explored in the intention-to-treat population.

Statistical analysis

With the assumption of a true vaccine efficacy of 70% after three doses, a one-sided α risk of 2·5%, and a lower bound of the 95% CI of greater than 25%, 57 cases would be needed to have 90% power or more to show that vaccine efficacy was more than 25%. With an estimated disease incidence of 1·3%, and an overall dropout rate of 20%, 10 278 participants, randomised in a 2:1 ratio to the CYD-TDV (n=6852) and control groups (n=3426), were needed. Analyses were based on the lower bound of the 95% CI, calculated with the exact method.[16]

To assess the vaccine effect on severe dengue (independent data monitoring committee assessment) or dengue haemorrhagic fever of any grade according to the 1997 WHO criteria, vaccine efficacy was calculated against severe cases with the same method as described above, and the relative risk (RR) of hospital admissions for virologically confirmed dengue was calculated as the ratio of annual incidence in the vaccine group and control groups, and presented here as vaccine efficacy (ie, 1–RR).[11] To describe the effect of pre-existing dengue antibodies on vaccine efficacy in the subset, we calculated the RR of virologically confirmed dengue as the ratio of incidence density between groups, presented as vaccine efficacy (ie, 1–RR). We explored efficacy over time during the

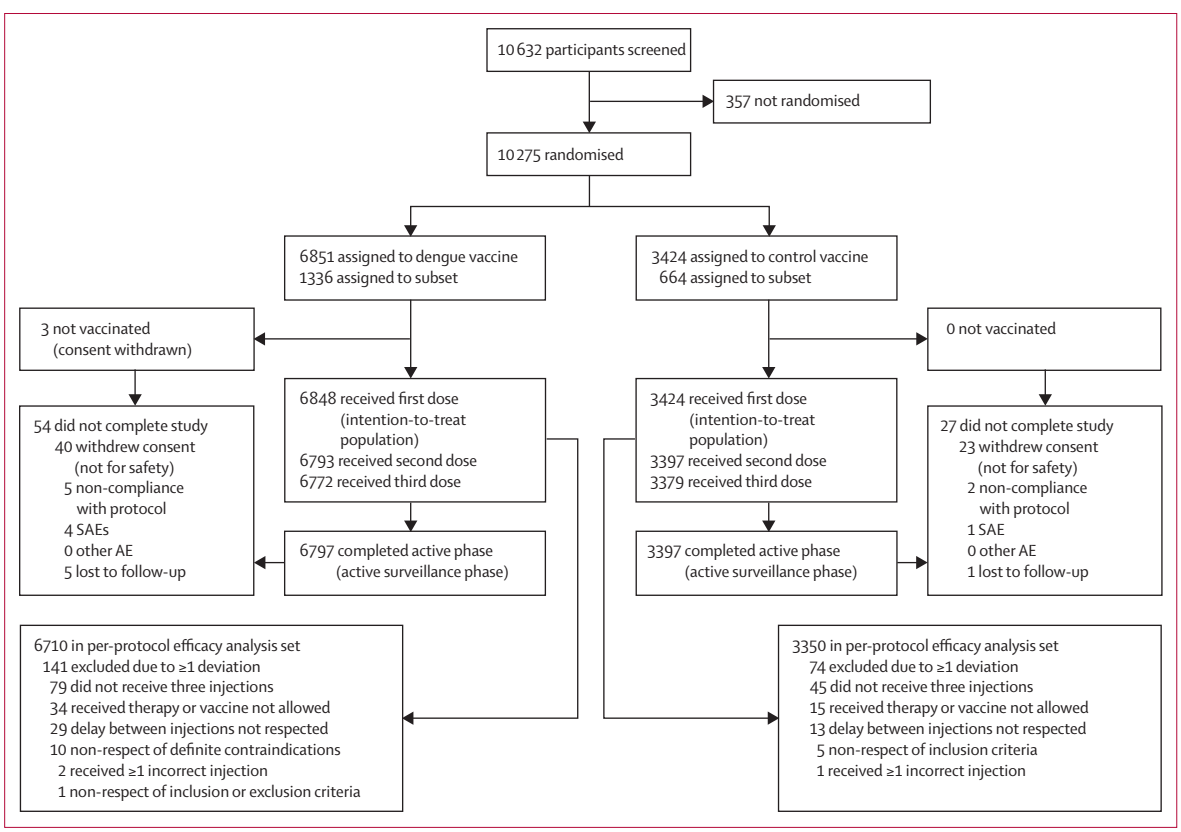

Figure 1: **Trial profile**
The safety analysis set included all participants who had received at least one injection, and participants were analysed in the group corresponding to the injection received. SAE=serious adverse event. AE=adverse event.

25-month active surveillance phase with Kaplan-Meier analysis. We assessed safety in all participants who had received one injection or more. All analyses were pre-defined and done by intention to treat and per protocol with SAS (version 9·3). This trial is registered with ClinicalTrials.gov, number NCT01373281.

Role of the funding source

The sponsor of the study had a role in study design, sample testing, data analysis, data interpretation, and writing of the report, but no role in data collection. DV, EL, TAW, NGT, MS, and AB (all employed by Sanofi Pasteur) had full access to the data in the study. Because the observer-masked phase for hospital admission is ongoing, the other authors had access to statistical analyses, but not participant-level data. All authors will have full access to all data at the end of the study. MRC, DvdV and NGT had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. We randomly assigned 10 275 children to receive either vaccine (n=6851) or placebo (n=3424). 6772 (99%) children in the vaccine group and 3379 (99%) of those in the placebo group received three injections, and 6710 (98%) and 3350 (98%), respectively, were included in the per-protocol analysis set for efficacy (figure 1).

At baseline, the two groups were similar in age and sex ratio (table 1). In the immunogenicity subset, 1340 (68%) of 1983 children tested positive for neutralising antibodies to dengue by $PRNT_{50}$ (table 1), increasing with age from 348 (51%) of 678 children aged 2–5 years, 507 (72%) of 706 children aged 6–11 years, and 485 (81%) of 599 children aged 12–14 years.

The incidence density of virologically confirmed dengue in children in the control group during the 25-month active surveillance period was 4·7% overall: 2·3% in Malaysia, 3·3% in Vietnam, 3·6% in Indonesia, 6·0% in Thailand, and 6·7% in the Philippines. We recorded 8927 episodes of fever (5816 [65%] in the vaccine group and 3111 [35%] in the control group), and obtained acute and convalescent blood samples according to protocol for 8786 (98%) and 8841 (99%) episodes, respectively. 595 (6%) children were diagnosed with virologically confirmed dengue, of whom 14 (2%) had two episodes: four in the vaccine group and ten in the control group. Sequences of these 28 episodes was: serotype 1/2 (n=5), serotype 2/1 (n=3), and serotype 1/4, 3/1, 3/4, 4/2, unserotyped/3, and unserotyped/unserotyped (n=1 case each).

On the basis of 250 cases of virologically confirmed dengue that took place more than 28 days after injection three in the per-protocol population, vaccine efficacy was 56·5% (95% CI 43·8–66·4; table 2), which met the primary endpoint because the lower bound of the 95% CI was greater than 25%. This result was confirmed in the intention-to-treat analysis of all dengue cases that happened between month 0 and month 25 in all participants who received at least one injection, and the calculated vaccine efficacy was similar (table 2). Table 3 shows serotype-specific vaccine efficacy after three injections and after one injection or more.

Kaplan-Meier analyses of virologically confirmed dengue due to any serotype from 28 days after the third dose in the per-protocol population, and from day 0 in the intention-to-treat population (more than 98% of whom received three injections) showed protection throughout the 25-month period (figure 2).

Efficacy was higher in participants with pre-existing dengue neutralising antibodies than in those who were seronegative, and in the older age cohorts than the younger ones in the intention-to-treat population (appendix). Efficacy by country was consistent with the overall estimate, ranging from 51·1% in Vietnam to 79·0% in Malaysia (appendix).

28 (5%) of 609 episodes of virologically confirmed dengue were classed as dengue haemorrhagic fever of any grade according to the 1997 WHO criteria (eight [29%] in the vaccine group and 20 [71%] in the control group); vaccine efficacy against dengue haemorrhagic

	Vaccine group (N=6851)	Control group (N=3424)
Per-protocol analysis set for efficacy		
n (%)	6710 (98%)	3350 (98%)
Age (years)	8·8 (3·4)	8·8 (3·4)
Sex		
Boys	3253 (48%)	1623 (48%)
Girls	3457 (52%)	1727 (52%)
Safety analysis set		
n (%)	6848 (100%)	3424 (100%)
Age (years)	8·8 (3·5)	8·8 (3·4)
Sex		
Boys	3324 (49%)	1657 (48%)
Girls	3524 (51%)	1767 (52%)
Full analysis set for immunogenicity		
n	1323	660
Age (years)	8·6 (3·8)	8·6 (3·8)
Sex		
Boys	652 (49%)	310 (47%)
Girls	671 (51%)	350 (53%)
Seroprevalence at baseline		
Dengue or Japanese encephalitis	1042 (79%)	509 (77%)
Dengue	896 (68%)	444 (67%)
Japanese encephalitis	702 (53%)	341 (52%)

Data are mean (SD), or n (%), unless otherwise indicated. Anti-dengue and anti-Japanese encephalitis seroprevalence defined as the proportion of participants with a plaque-reduction neutralisation test ($PRNT_{50}$) titre of 10 or higher. Per-protocol efficacy population included participants who had received three injections, according to protocol, and not presented with any of the criteria in a pre-specified list (appendix). Safety analysis set included all participants who received at least one injection, and participants were analysed according to which vaccine was given at first injection (accounting for any randomisation errors). Intention-to-treat efficacy population was similar to the safety analysis set, except that participants were analysed in the group to which they were randomised, irrespective of per-protocol criteria.

***Table 1*: Baseline characteristics**

fever was 80·0% (95% CI 52·7–92·4) after one or more injections (intention-to-treat population), and 88·5% (58·2–97·9) after three injections. Four additional cases in the vaccine group that were not classed as dengue haemorrhagic fever (two had <2 days of fever and one of these and two others presented with clinical shock without fever manifestations) were classed as clinically severe according to the independent data monitoring committee definition, and the corresponding vaccine efficacy was 70·0% (95% CI 35·7–86·6) after one or more injections (intention-to-treat population), and 80·8% (42·7–94·7) after three injections.

Breakthrough episodes of virologically confirmed dengue were milder in participants in the vaccine group than in those in the control group (intention-to-treat population; appendix). The proportion of episodes leading to hospital admission, and the median duration of admission for virologically confirmed dengue, were all lower in participants in the vaccine group than in those in the control group (appendix). 40 (<1%) of 6848 vaccine recipients and 61 (2%) of 3424 placebo recipients were admitted to hospital for virologically confirmed dengue, giving a vaccine efficacy of 67·2% (95% CI 50·3–78·6) against hospitalised dengue. Clinical signs of plasma leakage were reported for two (<1%) participants in the vaccine group and 12 (<1%) participants in the control group (RR 0·18, 95% CI 0·02–0·82) and thrombocytopenia (platelet count $\leq 50 \times 10^9$/L) was reported for eight (<1%) and 30 (1%) participants, respectively (RR 0·29, 95% CI 0·12–0·65).

We recorded 647 serious adverse events (402 in the vaccine group and 245 in the control group). 575 participants had one or more serious adverse event: (table 4). 54 (1%) participants in the vaccine group and 33 (1%) of those in the control group had serious adverse events that happened within 28 days of vaccination.

	Vaccine group (N=6848)			Control group (N=3424)			Vaccine efficacy (% [95% CI])
	Cases* (n)	Person-years at risk†	Incidence density‡ (95% CI)	Cases (n)	Person-years at risk	Incidence density (95% CI)	
Primary analysis (per-protocol)§	117	6526	1·8 (1·5–2·1)	133	3227	4·1 (3·5–4·9)	56·5% (43·8–66·4)
Intention-to-treat analysis¶	286	13 571	2·1 (1·9–2·4)	309	6623	4·7 (4·2–5·2)	54·8% (46·8–61·7)

Defined as a first episode of virologically confirmed dengue by either dengue non-structural protein 1 antigen ELISA, dengue screen PCR, or a serotype-specific PCR. †The cumulative time (in years) until the participant was diagnosed with virologically confirmed dengue or until the end of the active follow-up period, whichever came first. The person-years at risk presented in the tables is the sum of individual units of time for which the participants contributed to the analyses. ‡Calculated as the number of cases divided by the cumulative person-years at risk. §Per-protocol efficacy population included participants who received three injections, according to protocol, and did not present with any of the criteria in a pre-specified list (appendix); virologically confirmed dengue occurring at least 28 days after the third injection. ¶Intention-to-treat efficacy population included all participants who received at least one injection, and participants were analysed in the group to which they were randomised, irrespective of per-protocol criteria; virologically confirmed dengue occurring from baseline.

***Table 2*: Efficacy of CYD-TDV vaccination against symptomatic, virologically-confirmed dengue due to any serotype**

	Vaccine group (N=6848)			Control group (N=3424)			Vaccine efficacy (% [95% CI])
	Cases* (n)	Person-years at risk†	Incidence density‡ (95% CI)	Cases (n)	Person-years at risk	Incidence density (95% CI)	
Efficacy against VCD, more than 28 days after third injection in all participants who had received three injections							
Serotype 1	51	6548	0·8 (0·6 to 1·0)	50	3210	1·6 (1·2 to 2·0)	50·0% (24·6 to 66·8)
Serotype 2	38	6561	0·6 (0·4 to 0·8)	29	3253	0·9 (0·6 to 1·3)	35·0% (−9·2 to 61·0)
Serotype 3	10	6613	0·2 (0·1 to 0·3)	23	3281	0·7 (0·4 to 1·1)	78·4% (52·9 to 90·8)
Serotype 4	17	6605	0·3 (0·2 to 0·4)	34	3265	1·0 (0·7 to 1·5)	75·3% (54·5 to 87·0)
Unserotyped	2	6634	<0·1 (0·0 to 0·1)	3	3309	<0·1 (0·0 to 0·3)	66·7% (−190·3 to 97·2)
Efficacy against VCD, from baseline in all participants who had received at ≥1 injection (intention to treat)							
Serotype 1	116	13 742	0·8 (0·7 to 1·0)	126	6796	1·9 (1·5 to 2·2)	54·5% (40·9 to 64·9)
Serotype 2	97	13 766	0·7 (0·6 to 0·9)	74	6856	1·1 (0·8 to 1·4)	34·7% (10·4 to 52·3)
Serotype 3	30	13 835	0·2 (0·1 to 0·3)	43	6895	0·6 (0·5 to 0·8)	65·2% (43·3 to 78·9)
Serotype 4	40	13 826	0·3 (0·2 to 0·4)	72	6874	1·0 (0·8 to 1·3)	72·4% (58·8 to 81·7)
Unserotyped	7	13 858	<0·1 (0·0 to 0·1)	8	6926	0·1 (0·0 to 0·2)	56·3% (−38·0 to 86·5)

*Defined as a first episode of VCD by either dengue non-structural protein 1(NS1) antigen ELISA, dengue screen PCR, or a serotype-specific PCR. Unserotyped cases were those that were positive in either the dengue NS1 antigen ELISA, or the dengue screen PCR, but negative in the serotype-specific. †The cumulative time (in years) until the participant was diagnosed with VCD or until the end of the active period, whichever came first. The person-years at risk presented in the tables is the sum of individual units of time for which the participants contributed to the analyses. ‡Calculated as the number of cases divided by the cumulative person-years at risk.

***Table 3*: Serotype-specific vaccine efficacy against symptomatic, virologically-confirmed dengue (VCD), irrespective of protocol deviations**

Serious adverse events were consistent with medical disorders in this age group and were mainly infections and injuries (data not shown). One serious adverse event in a vaccine recipient (a case of acute disseminated encephalomyelitis) was reported as vaccine-related by the investigator because it happened on day 7 after the first injection. This child, without detectable vaccine virus in blood or cerebrospinal fluid, recovered 15 days later without clinical sequelae and there was no recurrence. The child was not withdrawn from the study, but no additional injections were given. Four deaths unrelated to vaccination were reported, all in participants in the vaccine group (table 4): three traffic accidents and one tracheal injury. No immediate hypersensitivity or allergic reactions, and no cases of viscerotropic or neurotropic disease, were reported.

In the subset, reactogenicity analyses showed similar reporting rates for adverse reaction in both groups (table 4). Geometric mean titres increased from baseline to 28 days after the second injection in the vaccine group (appendix). Concentrations 28 days after the third injection were similar to those after the second injection (appendix).

Discussion

Our findings show that CYD-TDV was safe and efficacious when given as a three-dose schedule to 2–14 year-olds. The per-protocol vaccine efficacy for the prevention of virologically confirmed dengue was greater than the predefined primary endpoint threshold, thus meeting the primary objective. The level of efficacy over the whole 25-month period of active surveillance in participants who had received one or more injections was similar to the per-protocol efficacy estimate. Notably, almost 99% of participants who received at least one injection went on to receive all three injections; therefore, we could not assess efficacy after only one or two doses.

In view of the high disease burden in endemic countries (as emphasised by the high rate of dengue seropositivity at enrolment, and the high incidence of dengue in the control group), this vaccine candidate, despite moderate overall efficacy, could have a substantial effect on public health (panel).[1,17] That vaccination provided clinically important reductions in hospital admissions and prevented 80% of cases of dengue haemorrhagic fever is particularly noteworthy in this context. The comparison of the symptomatology of disease between vaccine and placebo recipients suggests that disease was milder after vaccination, with no evidence of enhanced disease over the observation period.

A crucial observation in the previous phase 2b efficacy trial was that although there was some evidence of efficacy against serotypes 1, 3, and 4 in the intention-to-treat population, there was none against serotype 2—the main serotype in that study—despite the presence of neutralising antibodies against all four serotypes.[10] The large-scale trial reported here, done at several sites and in different epidemiological settings—provides a more robust estimate

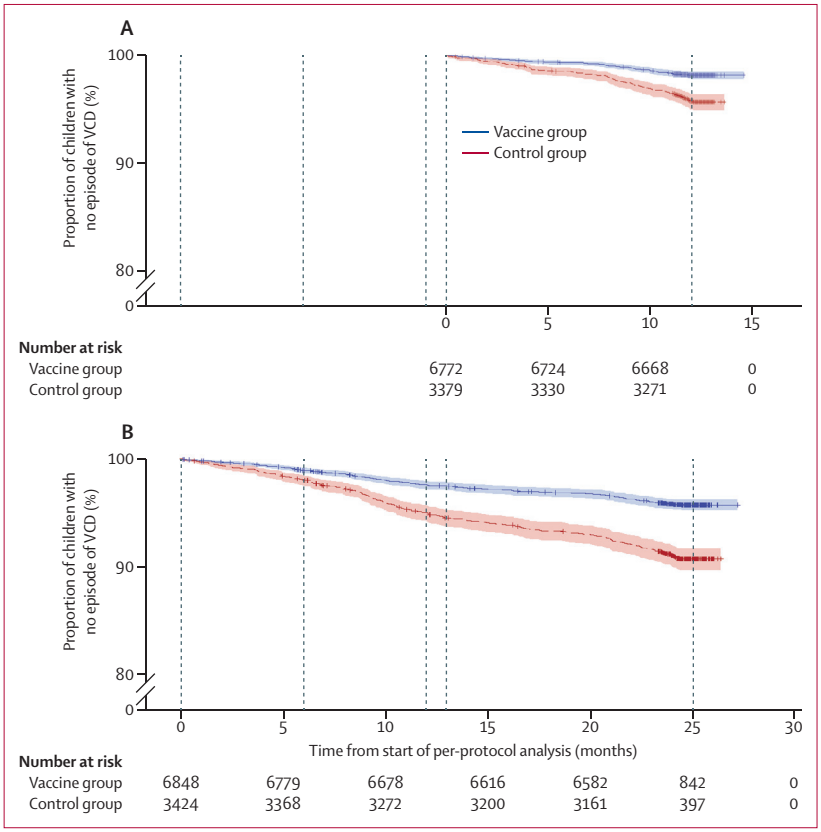

Figure 2: **Kaplan-Meier curve for symptomatic virologically-confirmed dengue (VCD) due to any serotypes taking place from 28 days after the third injection (ie, from month 13) in the per-protocol population (A) and at any time during the trial from day 0, irrespective of protocol compliance, in the intention-to-treat population (B)**

Dashed vertical lines show major study milestones: injections (at months 0, 6, 12); the start of the period for the primary, per-protocol analysis (month 13); and the end of the active phase of surveillance (month 25). Error bars show 95% CIs. Note breaks in y axes.

	Vaccine group		Control group	
	n (%)	95% CI	n (%)	95% CI
Safety analysis set (N)	6848	..	3424	..
SAE*	355 (5%)	4·7–5·7	220 (6%)	5·6–7·3
Death†	4 (<1%)	0·0–0·1	0	0·0–0·1
Subset (N)	1334	..	663	..
Immediate unsolicited non-serious AE	0	0·0–0·3	0	0·0–0·6
Solicited injection-site reaction‡	633 (47%)	44·8–50·2	285 (43%)	39·2–46·9
Solicited systemic reaction‡	760 (57%)	54·3–59·7	367 (55%)	51·5–59·2
Unsolicited non-serious AE	489 (37%)	34·1–39·3	268 (40%)	36·7–44·3
Unsolicited non-serious AR	19 (1%)	0·9–2·2	6 (<1%)	0·3–2·0
Unsolicited non-serious injection site AR	9 (<1%)	0·3–1·3	2 (<1%)	0·0–1·1
Unsolicited non-serious systemic AE	489 (37%)	34·1–39·3	268 (40%)	36·7–44·3
Unsolicited non-serious systemic AR	10 (<1%)	0·4–1·4	4 (<1%)	0·2–1·5

Data are n (%), unless otherwise indicated. Safety data were analysed according to the vaccine received at first injection. AE=adverse event. AR=adverse reaction. SAE=serious adverse event. *Includes SAEs due to virologically confirmed dengue. †Four (<1%) patients died in the vaccine group versus none in the control group; no deaths were vaccine related. ‡Data missing for two patients in the vaccine group.

Table 4: **Patients who had at least one AE and SAE reported from baseline to month 25 (safety analysis set) and reactogenicity events reported within 28 days after any injection (subset analysis)**

Panel: Research in context

Systematic review

We searched PubMed on June 5, 2014, with the terms "dengue", "vaccine", and "efficacy". Our search identified one previous clinical trial assessing efficacy of CYD tetravalent dengue vaccine.[1] We applied no date or language restrictions.

Interpretation

Our trial successfully showed efficacy against symptomatic dengue, irrespective of severity. Secondary analyses showed the contribution of each of the four serotypes to the overall efficacy. We noted high efficacy against dengue haemorrhagic fever, and clinically important reductions in severe disease and hospital admissions. The safety profile over the 25-month follow-up is consistent with the favourable safety profile reported in previous studies. These findings emphasise the potential of the candidate vaccine to reduce the burden of disease on health-care systems and to provide substantial public health benefit. Our results are particularly reassuring in the context of the theoretical potential for enhanced disease in partly or completely vaccinated individuals.

of serotype-specific efficacy. We noted that three CYD-TDV vaccinations prevented more than 75% of cases of serotype 3 and 4, and 50% of those caused by serotype 1, over the 12-month period following the 28th day after dose 3. Over this period, vaccine efficacy was 35% against serotype 2, but the 95% CI included 0 and therefore was not statistically significant. However, when the analysis set was extended to include all cases that happened during the observation period from day 0, the point estimate was similar and the lower bound of the 95% CI was greater than 0, improving the precision around the point estimate. The differences in the overall estimates for vaccine efficacy between the two trials could be explained by the difference in serotype distributions, particularly the lower prominence of serotype 2 in the present trial, or by strain characteristics. Studies are ongoing to further investigate the serotype-specific efficacy profiles.

About two-thirds of participants in the immunological subset were seropositive for dengue at baseline by $PRNT_{50}$, and the proportion of seropositivity increased with age. Within the limitations of this subset, the point estimate for vaccine efficacy was higher for participants who were seropositive for dengue than for those who were seronegative. Furthermore, vaccine efficacy increased with age, which could be a marker of previous exposure to dengue. Predictive models for vaccine efficacy, including population and epidemiological characteristics, might be needed to guide vaccine implementation in different settings around the world. However, efficacy was similar across the five countries in which the present study was done, despite difference in disease epidemiology between countries.

Consistent with previous studies, the safety profile was good after more than 2 years of follow-up in more than 6800 vaccine recipients. One case of acute disseminated encephalomyelitis was reported in a participant in the vaccine group, without evidence of vaccine virus in blood or cerebrospinal fluid. Acute disseminated encephalomyelitis is a rare event that mainly happens after an infection and has been temporally associated with several vaccines.[18,19] Data for the long-term safety of the vaccine are scarce, as such, we will continue to follow our trial population for safety for 5 years after the third vaccination in the hospital-based phase of our study. In the shorter term, a second phase 3 clinical trial (clinicaltrials.gov NCT01374516), done in five Latin American countries in more than 20 000 children and adolescents aged 9–16 years at the time of inclusion, is scheduled to conclude later this year. The results from Latin America are anticipated to complement those summarised in this report to provide a more global picture of the vaccine's potential to contribute to reaching the 2020 WHO target of reducing the global burden of dengue by decreasing morbidity by 25% and mortality by 50%.[20]

In summary, this trial was successfully done over more than 2 years in diverse dengue-endemic areas in Asia, a region that accounts for 70% of the global dengue burden. In this setting, we recorded promising results pointing to a substantial effect on severe disease manifestations. The safety and efficacy profile described here suggests that the CYD-TDV vaccine candidate, when given as three injections at months 0, 6, and 12 to 2–14 year-olds, has the potential to provide an important public health benefit in dengue-endemic countries.

Contributors

All authors contributed to the interpretation of the data, the drafting or critical review of the manuscript outline and drafts, and validation of the final version. MRC, SRSH, MNC, DNW, PP, UT, EL, TAW, NGT, MS, and AB contributed to the trial conception and design; NHT, CQL, I-KY, TL, YH, MB contributed to the trial design; MRC, NHT, SRSH, HIHJMI, TC, MNC, CQL, KR, DNW, RN, PP, UT, I-KY contributed to data acquisition; MRC, NHT, HIHJMI, TC, MNC, KR, PP, UT, DVDV, EL contributed to the data analyses; and DVDV was responsible for the management of the CYD14 trial. The manuscript was drafted by Grenville Marsh (Sanofi Pasteur) and Margaret Haugh (MediCom Consult).

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Declaration of interests
MRC, NHT, SRSH, HIHJMI, MNC, CQL, KR, DNW, RN, PP, UT, and I-KY received funds to their institutes from Sanofi Pasteur to support their work in the CYD14 trial and they did not receive any direct funds. TC received funds from Sanofi Pasteur for providing principle investigator services for CYD14 trial in Thailand and honoraria for lecturing activities. DVDV, EL, TL, YH, CF, MB, TAW, NGT, MS, AB are all employed by Sanofi Pasteur; additionally, DVDV, EL, YH, CF, MB, TAW NGT, MS, and AB have stocks or shares from Sanofi Pasteur.

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