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Immunogenicity and Safety of a Tetravalent Dengue Vaccine Administered Concomitantly or Sequentially With Quadrivalent Human Papillomavirus Vaccine in Boys and Girls 9–13 Years of Age in Malaysia

A Phase IIIb, Randomized, Open-label Study

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Data Sharing Statement: Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

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Background: Incorporating dengue vaccination within existing vaccination programs could help improve dengue vaccine coverage. We assessed the immunogenicity and safety of a quadrivalent human papillomavirus (HPV) vaccine administered concomitantly or sequentially with a tetravalent dengue vaccine (CYD-TDV) in healthy children 9–13 years of age in Malaysia.

Methods: In this phase IIIb, open-label, multicenter study (NCT02993757), participants were randomized 1:1 to receive 3 CYD-TDV doses 6 months apart and 2 doses of quadrivalent HPV vaccine concomitantly with, or 1 month before (sequentially), the first 2 CYD-TDV doses. Only baseline dengue-seropositive participants received the 3 doses. Antibody levels were measured at baseline and 28 days after each injection using an enzyme-linked immunosorbent assay for HPV-6, -9, -16 and -18, and the 50% plaque reduction neutralization test for the 4 dengue serotypes; immunogenicity results are presented for baseline dengue-seropositive participants. Safety was assessed throughout the study for all participants.

Results: At baseline, 197 of 528 (37.3%) randomized participants were dengue-seropositive [n = 109 (concomitant group) and n = 88 (sequential group)]. After the last HPV vaccine dose, antibody titers for HPV among baseline dengue-seropositive participants were similar between treatment groups, with between-group titer ratios close to 1 for HPV-6 and 0.8 for HPV-11, -16, and -18. After CYD-TDV dose 3, dengue antibody titers were similar between treatment groups for all serotypes [between-group ratios ranged from 0.783 (serotype 2) to 1.07 (serotype 4)]. No safety concerns were identified.

Conclusions: The immunogenicity and safety profiles of CYD-TDV and quadrivalent HPV vaccines were unaffected when administered concomitantly or sequentially in dengue-seropositive children.

Key Words: dengue vaccine, human papillomavirus vaccine, immunogenicity, Malaysia, safety

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Dengue is a mosquito-borne viral disease that is endemic in regions with tropical and sub-tropical climates.[1,2] Dengue disease can present as mild and self-limiting flu-like symptoms, but some individuals develop complications such as severe dengue or dengue shock syndrome (DSS) resulting in an estimated 500,000 hospitalizations and 22,000 deaths globally.[3] Travel acquired dengue is playing an increasingly important role in dengue transmission with, dengue now the leading cause of febrile illness in returning travelers and the second highest cause of traveler hospitalizations in Europe.[4,5]

The recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV, Dengvaxia, Sanofi Pasteur) is registered in 22 countries plus the European Union,[6,7] and the efficacy of a 3-dose schedule has been demonstrated against symptomatic and hospitalized virologically confirmed dengue (VCD) in 2 phase III studies.[8,9] Pooled vaccine efficacy estimates for participants ≥9 years of age were 65.6% [95% confidence interval (CI): 60.7–69.9] against symptomatic VCD of any serotype and 80.8% against dengue-related hospitalizations.[10] The pooled vaccine efficacy against VCD was 81.9% (95% CI: 67.2–90.0) for seropositive participants and 52.5% (95% CI: 5.9–76.1) for seronegative participants 9–16 years of age.[10] In a reevaluation of vaccine efficacy data across 1 phase IIb trial[11] and the 2 phase III trials, CYD-TDV protected against severe and hospitalized VCD among seropositives, but there was an increased risk of these outcomes among participants who were seronegative before vaccination.[10,12] As part of the global strategy to prevent and control dengue, the World Health Organization recommends CYD-TDV for individuals ≥9 years living in dengue-endemic regions with evidence of previous dengue infection.[1,13]

Three human papillomavirus (HPV) vaccines have been licensed for the prevention of cervical cancer associated with infection by HPV: a bivalent, a quadrivalent and a nonavalent vaccine. In countries achieving high vaccination coverage, the prevalence of these infections has decreased by about 80%.[14,15] The USA Advisory Committee on Immunization Practices recommends routine HPV vaccination for girls and boys at the age of 11 or 12 years,[16] and a 2-dose HPV vaccine schedule is part of the National Immunization Program in numerous dengue-endemic countries.[17]

The co-administration of dengue and HPV vaccines could facilitate the introduction of dengue vaccination to existing immunization schedules. The current study assessed the immunogenicity and safety of 2 doses of a HPV vaccine given either concomitantly or sequentially with 3 CYD-TDV doses in children 9–13 years of age.

MATERIALS AND METHODS

Design and Participants

This was a phase IIIb, open-label, multicenter study of the immunogenicity and safety of CYD-TDV and quadrivalent HPV vaccine given concomitantly or sequentially in healthy boys and girls 9–13 years of age (NCT02993757). The current study was conducted in Malaysia, where vaccination with the bivalent or quadrivalent HPV vaccine is offered as a 2-dose schedule, 6 months apart, to 13-year-old school girls as part of a national school-based program. CYD-TDV was conditionally approved in Malaysia for the prevention of dengue disease in 9–45 years olds at the time of study, for use in postregistration phase IV studies only, and was registered as an investigational product specific to the current study. Study participants were randomized to receive 3 doses of CYD-TDV, 6 months apart, and 2 doses of HPV vaccine given either at the same time (concomitant group) or 1 month before (sequential group) the first and second CYD-TDV doses (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E383). The study was conducted at 5 centers in Malaysia between December 1, 2016 and December 24, 2018, followed by a 6-month safety follow-up (last contact, May 27, 2019).

Participants were excluded if they had previous vaccination against dengue or HPV; a history of HPV infection, confirmed either clinically, serologically, or microbiologically as reported by participant or parent/legal representative; self-reported hepatitis B or hepatitis C infection, known or suspected congenital or acquired immunodeficiency; if they had received any other vaccine within 4 weeks, immunosuppressive therapy within the preceding 6 months or long-term systemic corticosteroid therapy within the preceding 3 months of the study; or if they were pregnant or lactating.

Participants were randomized (1:1) to receive concomitant or sequential vaccinations, stratified in a 2:1 female:male ratio, through a scratch-off randomization list provided by the study sponsor.

Informed written consent and assent were obtained from the participants and their parents/legal guardians before any study procedures were performed. The study was undertaken in compliance with the International Conference on Harmonization guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol and amendment were approved by the Ministry of Health Malaysia Medical Research and Ethics Committee (NMRR-16-1352-31227) and University of Malaya Institutional Review Board (MRECID-201696-4218).

Following evidence reported in November 2017 of reduced efficacy and excess risk of severe dengue and hospitalization among dengue seronegative participants,[12] the Independent Data Monitoring Committee (IDMC) recommended that all vaccinated participants be informed of their baseline dengue serostatus and further vaccination with CYD-TDV be ceased for dengue seronegative participants. The study was paused and the protocol was amended. Baseline seronegative participants did not receive further CYD-TDV doses; if consent was given, these participants could continue for the 6-month safety follow-up. Dengue-seropositive participants received the third CYD-TDV dose only after providing additional informed consent. Due to the study pause (up to 6 months), the interval between the second and third CYD-TDV doses exceeded 6 months (see Methods, Supplemental Digital Content 2A, http://links.lww.com/INF/E383).

Vaccines and Vaccinations

Recombinant quadrivalent HPV vaccine (types 6, 11, 16 and 18; Gardasil; Merck Sharp & Dohme Corp, West Point, PA) was administered by intramuscular injection.[18] Each 0.5 mL dose contained 20 μg of HPV-6 L1 protein, 40 μg of HPV-11 L1 protein, 40 μg of HPV-16 L1 protein and 20 μg of HPV-18 L1 protein. CYD-TDV was presented as a powder for immediate reconstitution in 0.4% NaCl and administered by subcutaneous injection into the deltoid region of the upper arm. Each 0.5 mL dose of reconstituted vaccine contained 4.5–6.0 $\log_{10}$ cell-culture infectious dose 50% ($CCID_{50}$) of each live, attenuated, recombinant dengue virus serotype 1, 2, 3 and 4.

Immunogenicity Assessment

Participants provided blood samples for immunogenicity assessments before the first vaccination and 28 days after each dose (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E383). Neutralizing antibody levels against HPV-6, -11, -16 and -18 were measured using competitive Luminex immunoassay performed by Merck Sharp & Dohme Corp. The lower limit of quantification (LLOQ) values were 11 milli-Merck Units (mMU)/mL for HPV-6 and HPV-16, 8 mMU/mL for HPV-11 and 10 mMU/mL for HPV-18. Geometric mean titers (GMTs) and seroconversion rates were calculated, with seroconversion defined as a post-vaccination titer ≥LLOQ for participants with a pre-vaccination titer <LLOQ or a ≥4-fold increase in titer for participants with a pre-vaccination titer ≥LLOQ.

Neutralizing antibody titers against the 4 dengue serotypes were measured using the 50% plaque reduction neutralization test, performed by Sanofi Pasteur, GCI, Swiftwater, as previously described.[19] Participants with 50% plaque reduction neutralization test titers ≥10 (1/dil) for at least 1 dengue serotype were dengue seropositive and those with titers <10 (1/dil) for all 4 dengue

serotypes were seronegative; all other participants (with unavailable or invalid results) were deemed, "undetermined."

In-line with the statistical analysis plan following the protocol amendment, immunogenicity endpoints were presented for those who were seropositive at baseline only. After the protocol amendment, the co-primary endpoints for the evaluation of immunogenicity were: antibody levels against each HPV type 28 days after the last dose of HPV vaccine in dengue-seropositive participants, and neutralizing antibody levels against each of the 4 dengue serotypes 28 days after the last CYD-TDV dose in dengue-seropositive participants in each group. The secondary outcomes were antibody levels against each HPV type at baseline and 28 days after each HPV vaccine dose, seroconversion against each HPV type 28 days after each dose, neutralizing antibody titers against each dengue serotype at baseline and 28 days after each CYD-TDV dose, and the proportion with neutralizing antibody titers ≥10 (1/dil) against each dengue serotype at baseline and 28 days after each CYD-TDV dose, in dengue-seropositive participants only.

Safety

Safety outcomes were determined in all participants who received any study vaccine, regardless of dengue serostatus. Participants were observed for 30 minutes after each vaccine dose to monitor for immediate adverse events (AEs). Solicited injection-site reactions (pain, erythema and swelling) were assessed for 7 days and solicited systemic reactions (fever, headache, malaise, myalgia and asthenia), for 14 days postvaccination. Unsolicited AEs were assessed for 28 days after each vaccination.

Serious AEs (SAEs) and AEs of special interest (AESIs) were assessed throughout the study and for 6 months following any injection. AESIs included serious or nonserious hypersensitivity/allergic reactions occurring within 7 days after injection, serious viscerotropic or serious neurotropic disease occurring within 30 days postinjection, and serious dengue disease requiring hospitalization throughout the trial. Investigators assessed the potential relationship between vaccination and systemic AEs and nonserious AESIs, and any SAE or death considered to be vaccine-related was reviewed promptly by the IDMC. The IDMC regularly reviewed hospitalized VCD cases, including an assessment of severity.

Statistics

The sample size of 528 participants (264 in each group) was established before protocol amendment to provide 98.4% power for the planned co-primary noninferiority objectives based on GMTs, and 90.2% power for secondary non-inferiority objectives based on HPV seroconversion rates (see Methods, Supplemental Digital Content 2, http://links.lww.com/INF/E383). Following protocol amendment, the evaluable population of dengue-seropositive participants did not provide sufficient power for noninferiority testing, therefore, immunogenicity analyses remained descriptive.

GMTs and GMT ratios (GMTRs) were calculated for HPV and dengue, assuming that $\log_{10}$ transformation of the titers followed a normal distribution; the mean and the 95% CI of the $\log_{10}$ transformed titers were calculated using the Student's *t*-distribution with n − 1 degree of freedom. Anti-log transformations were then applied to provide GMTs and their 95% CI. Safety was described for each dose of vaccine, for each group, by baseline dengue serostatus. 95% CIs were calculated using the Clopper-Pearson method.

The safety analysis set (SafAS) included participants who received ≥1 dose of CYD-TDV or HPV vaccine, regardless of baseline dengue serostatus. The FAS included participants who received ≥1 dose of either CYD-TDV or HPV vaccine; those who were dengue-seropositive at baseline were included in a subset.

RESULTS

Participants

Enrolled participants (n = 528) were randomly allocated to receive concomitant (n = 266) or sequential vaccinations (n = 262) (Figure, Supplemental Digital Content 3, http://links.lww.com/INF/E383). Five participants did not meet inclusion criteria or refused the allocated vaccine after randomization and were excluded; thus, 263 participants from the concomitant group and 260 from the sequential group received the first scheduled injection and were included in the FAS and SafAS. The FAS included 342 (65.4%) girls and 181 (34.6%) boys, with a mean (SD) age of 10.5 (1.2) years. Baseline demographics were balanced between the concomitant and sequential groups (Table 1).

At the time of the study pause, all participants (except 8 from the sequential group) had received the second CYD-TDV dose, and all participants had completed HPV vaccination. Among the enrolled participants, 197 of 528 (37.3%) were dengue seropositive at baseline and were invited to receive CYD-TDV dose 3. Of these, 186 received 3 CYD-TDV doses (concomitant group, n = 102; sequential group, n = 84); 11 dengue-seropositive participants withdrew from the study, mostly due to voluntary withdrawal, and none due to an AE (Fig. 1). Immunogenicity outcomes are presented in those who were dengue seropositive at baseline only.

In the SafAS, 260 (97.7%) participants in the concomitant group and 256 (97.7%) in the sequential group completed the 6-month safety follow-up.

TABLE 1. Age and Baseline Dengue Serostatus in the Full Analysis Set

	All			Seropositive			Seronegative or Undetermined		
Baseline Dengue Status	Concomitant (N=263)	Sequential (N = 260)	All (N = 523)	Concomitant (N = 109)	Sequential (N = 88)	All (N = 197)	Concomitant (N = 154)	Sequential (N = 172)	All (N = 326)
Sex, n (%)									
Male	91 (34.6)	90 (34.6)	181 (34.6)	36 (33.0)	29 (33.0)	65 (33.0)	55 (35.7)	61 (35.5)	116 (35.6)
Female	172 (65.4)	170 (65.4)	342 (65.4)	73 (67.0)	59 (67.0)	132 (67.0)	99 (64.3)	111 (64.5)	210 (64.4)
Mean age, years									
Mean (SD); range	10.4 (1.2); 8.0–13.0	10.5 (1.2); 8.0–13.0	10.5 (1.2); 8.0–13.0	10.5 (1.2); 8.0–13.0	10.5 (1.2); 9.0–13.0	10.5 (1.2); 8.0–13.0	10.4 (1.2); 9.0–13.0	10.5 (1.2); 8.0–13.0	10.4 (1.2); 8.0–13.0
Age group, n (%)*									
9–11 years	208 (79.1)	207 (79.6)	415 (79.3)	83 (76.1)	71 (80.7)	154 (78.2)	125 (81.2)	136 (79.1)	261 (80.1)
12–13 years	54 (20.5)	52 (20.0)	106 (20.3)	25 (22.9)	17 (19.3)	42 (21.3)	29 (18.8)	35 (20.3)	64 (19.6)

The full analysis set included n = 263 (concomitant) and n = 260 (sequential) participants who received the first scheduled injection.
*Note that percentages across age groups may not add up to 100% as 2 participants were <9 years of age (8 years old).
n, number of participants fulfilling the item listed; N, the number of participants per group, in the FAS.

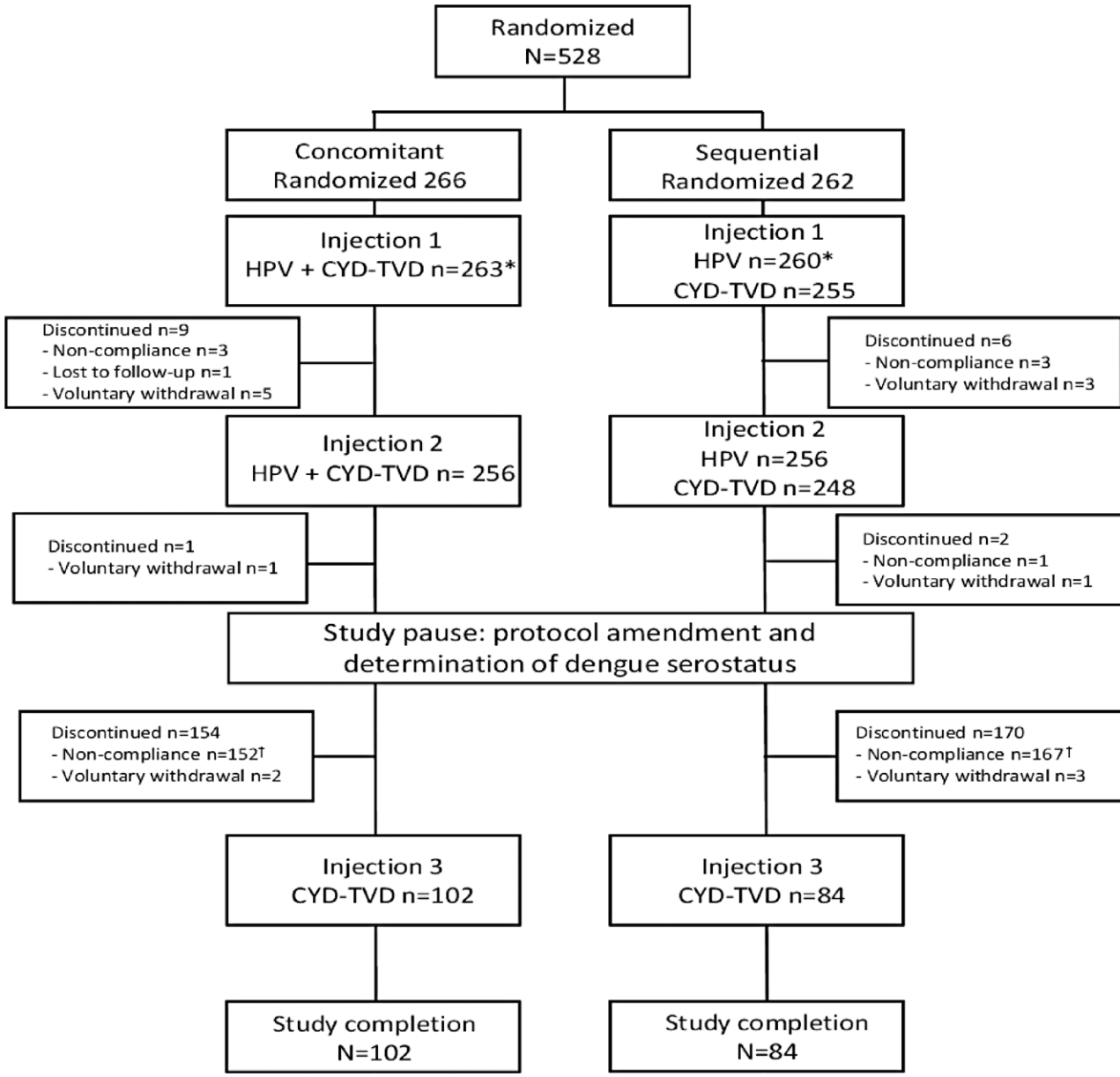

FIGURE 1. Flow of participants through the study. *Five participants did not meet inclusion criteria or refused vaccine after randomization. †After protocol amendment, participants who were seronegative for dengue at baseline were discontinued for "noncompliance with protocol."

Immunogenicity

HPV-6, -11, -16, -18

In baseline dengue-seropositive participants, HPV antibody GMTs (1/dil) at 28 days after the last HPV vaccine dose were comparable between the concomitant and the sequential group (Table 2A). The between-group GMTRs were 0.8 for HPV-11, -16 and -18, and close to 1 for HPV-6 (Table 2A). At 28 days after the last HPV vaccine dose, the seroconversion rates were 100% for all HPV types in both groups, except for HPV-6 in the sequential group which was 98.1% (Table, Supplemental Digital Content 3, http://links.lww.com/INF/E383). The lower bounds of the 95% CI of the differences in the antibody titers and seroconversion rates were above the noninferiority margins that were to be tested in the original protocol, for all but the seroconversion rate for HPV-6. GMTs increased after each dose for each HPV type, and were comparable across treatment groups (Fig. 2 and Table, Supplemental Digital Content 4, http://links.lww.com/INF/E383).

Dengue Serotypes

In dengue-seropositive participants, GMTs at 28 days after CYD-TDV dose 3 were similar between treatment groups across all 4 dengue serotypes (Table 2B). In both concomitant and sequential groups, the GMTs for each dengue serotype increased after the first CYD-TDV dose; levels stabilized thereafter (Fig. 3).

The between-group GMTRs (95% CI) were 0.987 (0.574–1.70) for serotype 1, 0.783 (0.500–1.22) for serotype 2, 0.836 (0.568–1.23) for serotype 3 and 1.07 (0.813–1.40) for serotype 4 (Table 2B). For

TABLE 2. HPV Antibody (A) and Dengue Neutralizing Antibody (B) GMTs 28 Days After the Last Dose of Vaccine Administered Concomitantly or Sequentially—Full Analysis Set, Dengue-Seropositive Participants

	Concomitant (N = 109)		Sequential (N = 88)		Concomitant/Sequential Ratio (95% CI)
	M	GMT (95% CI)	M	GMT (95% CI)	
A. HPV					
HPV-6	104	420 (327–539)	86	428 (314–583)	0.982 (0.664–1.45)
HPV-11	104	1288 (1089–1522)	86	1601 (1323–1937)	0.804 (0.626–1.03)
HPV-16	104	6221 (5093–7598)	86	7629 (6142–9475)	0.815 (0.608–1.09)
HPV-18	104	829 (682–1007)	86	1042 (858–1266)	0.795 (0.603–1.05)
B. Dengue					
Serotype 1	102	447 (303–659)	84	453 (313–656)	0.987 (0.574–1.70)
Serotype 2	102	561 (408–771)	84	717 (526–977)	0.783 (0.500–1.22)
Serotype 3	102	460 (354–596)	84	549 (411–734)	0.836 (0.568–1.23)
Serotype 4	102	323 (263–398)	84	303 (255–359)	1.07 (0.813–1.40)

N, number in the full analysis set; M, number with antibody data available.

dengue serotypes 1, 3 and 4, the lower bounds of the 95% CIs were all greater than 0.5, which was the noninferiority margin to be tested in the original protocol; the lower bound for serotype 2 was 0.5.

GMTRs postinjection 2/preinjection 1 and postinjection 3/preinjection 1 were similar between groups (Table, Supplemental Digital Content 5, http://links.lww.com/INF/E383).

Safety

In the SafAS (dengue seropositive and seronegative at baseline), 3 participants, all from the sequential group, had immediate unsolicited systemic AEs. These included vomiting after the first CYD-TDV dose, not considered related to the study vaccine, and pallor of lips after the first HPV vaccine dose and cough after the second CYD-TDV dose, both considered related to the study vaccine; all resolved within 1 day (Table 3). Solicited outcomes were reported by 88.5% and 90.3% of participants in the concomitant and sequential groups, respectively (Table 3). The frequency of injection site reactions was higher after any HPV vaccine injection than after any CYD-TDV injection, with pain being the most frequently reported (Table 3 and Table, Supplemental Digital Content 6, http://links.lww.com/INF/E383). The most frequent solicited systemic reactions were myalgia and headache in both groups (Table, Supplemental Digital Content 6, http://links.lww.com/INF/E383).

Unsolicited non-SAEs were reported less frequently in the concomitant group (20.5%) than in the sequential group (34.6%; Table 3).

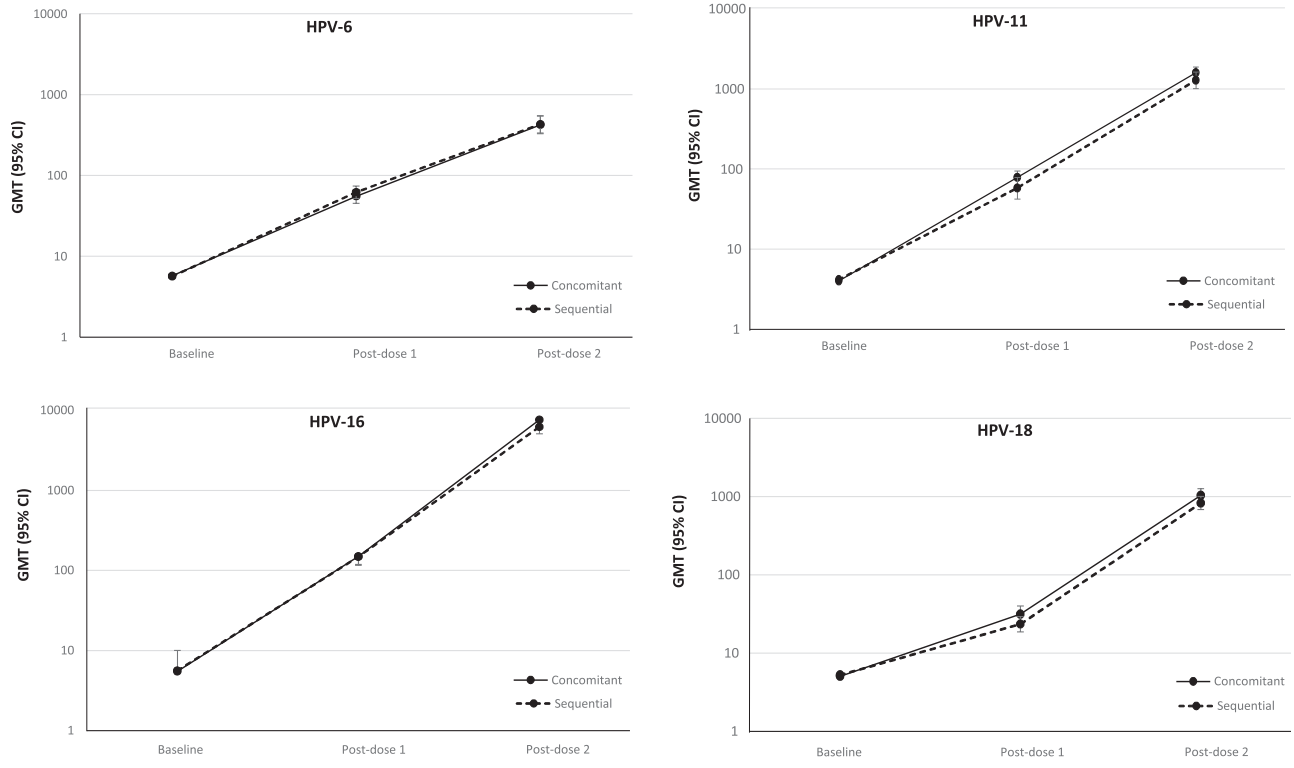

FIGURE 2. GMTs of neutralizing antibodies against HPV types 6, 11, 16 and 18 28 days after each dose of quadrivalent HPV vaccine given concomitantly or sequentially with CYD-TDV (full analysis set, dengue-seropositive participants).

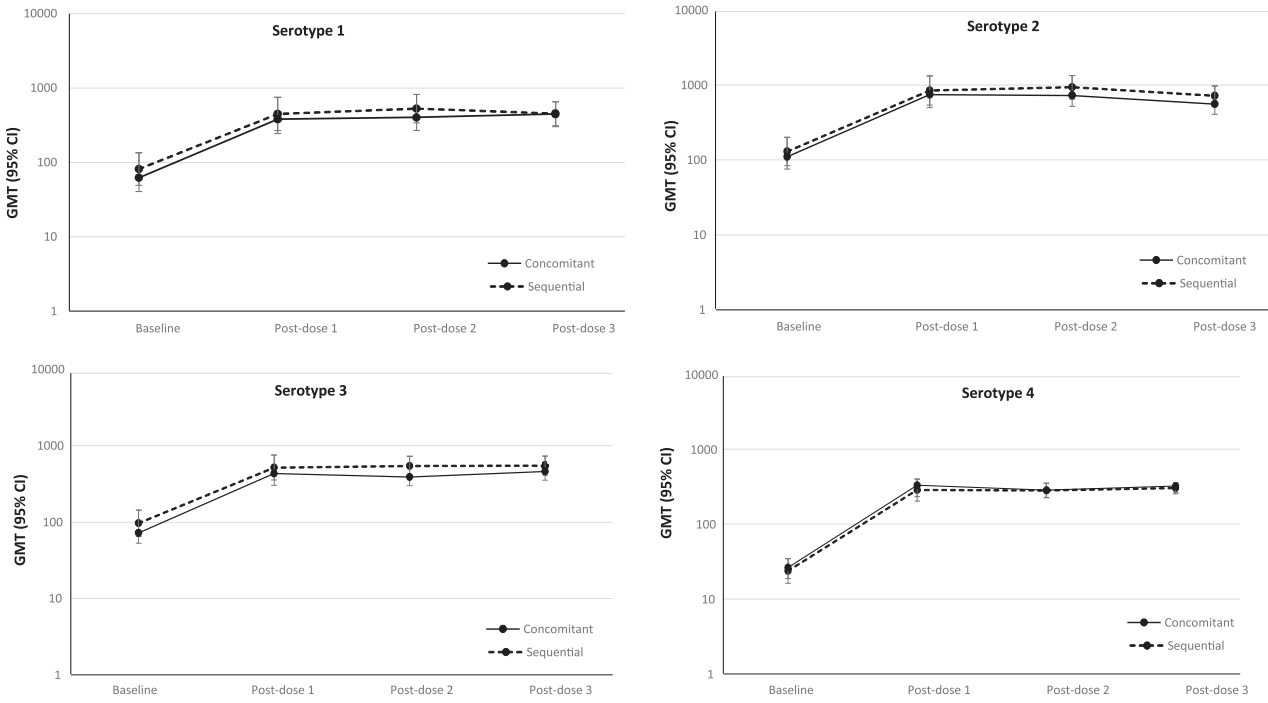

FIGURE 3. GMTs of neutralizing antibody for each dengue serotype, 28 days after each dose of CYD-TDV administered concomitantly or sequentially with quadrivalent HPV vaccine (full analysis set, dengue-seropositive participants).

Overall, during the study and the 6-month follow-up period, there were no nonserious AESIs reported; 11 of 263 (4.2%) participants in the concomitant group reported 12 SAEs, and 8 of 260 (3.1%) in the sequential group reported 9 SAEs (Table 3). There were 3 serious AESIs, all of which were hospitalized cases of dengue fever. One of these (dengue fever with decompensated DSS occurring 268 days after the second CYD-TDV dose in a baseline dengue seronegative participant from the sequential group) was considered related to study vaccination by the investigator, was virologically confirmed and assessed as severe by the IDMC. The 2 other cases, assessed as unrelated by the investigator, occurred in a seronegative participant from the sequential group (could not be confirmed virologically due to the nonavailability of a blood sample), and in a seropositive participant from the concomitant group (virologically confirmed and assessed as nonsevere by the IDMC). All recovered within 5–14 days. After the end of the study, 2 further baseline seronegative participants (1 in each group) experienced severe dengue with DSS and recovered after 7–8 days. Both were SAEs, assessed by the IDMC as severe and considered by the investigator to be related to CYD-TDV. There were no early withdrawals due to an AE or SAE, and there were no deaths reported.

The safety profiles for each vaccine were similar between dengue baseline seropositive and all participants (Table 3).

DISCUSSION

In this descriptive analysis, a 2-dose schedule of quadrivalent HPV vaccine given either concomitantly or sequentially with a 3-dose CYD-TDV schedule to baseline dengue seropositive children 9–13 years of age, elicited humoral immune responses 28 days after the last dose of each vaccine that were consistent with their established immunogenicity profiles.

The immunogenicity profile of the 2-dose quadrivalent HPV vaccine schedule in the mixed population of girls and boys in our study was consistent with the established profiles previously reported.[18] At 28 days after the last HPV vaccine dose, almost all participants were seropositive for all 4 HPV vaccine antigen types, with 100% seroconversion rates for HPV types 11, 16 and 18. A similar study of a bivalent HPV vaccine administered concomitantly or sequentially with CYD-TDV in Mexico has also been conducted (NCT02979535), and with the similarities between these and the 9-valent HPV vaccine components it may be possible to extrapolate these findings to concomitant or sequential administration of CYD-TDV and the 9-valent HPV vaccine.

In baseline dengue-seropositive participants, the neutralizing antibody responses at 28 days after the third dose of CYD-TDV against all 4 dengue serotypes were consistent with those reported in the previous pivotal efficacy trial in Asia.[8] Although an immune correlate of protection threshold has not been established for dengue disease, vaccine efficacy was correlated with higher antibody responses in CYD-TDV trials.[20]

Five cases of dengue fever were reported during the study. Three participants, who were seronegative for dengue at baseline and who received 2 CYD-TDV doses, experienced severe dengue with decompensated DSS which required hospitalization and resolved within 7–14 days. The 2 remaining cases of dengue fever, 1 in a dengue seronegative participant and the other in a seropositive participant, were nonsevere. The cases of severe dengue in participants who were seronegative for dengue at baseline were deemed to be related to CYD-TDV, consistent with the safety profile of the vaccine in children who are seronegative for dengue.[10] A number of dengue outbreaks have been reported in the Americas and South-East Asia during recent years, with high numbers of cases reported in Malaysia 2019, when this study was conducted[2]; the cases of dengue fever reported during our study occurred in affected areas.

The HPV vaccine and CYD-TDV were well-tolerated in this study; no differences in reactogenicity or AEs were observed between the concomitant and sequential groups, whether assessed

TABLE 3. Summary of Safety Outcomes After Any Dose of CYD-TDV or Quadrivalent HPV Vaccine for All Participants and Baseline Dengue-seropositive Participants—SafAS

	All				Seropositive			
	Concomitant (N = 263)		Sequential (N = 260)		Concomitant (N = 110)		Sequential (N = 87)	
Experiencing ≥1:	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)	n/M	% (95% CI)
Within 28 days after any vaccine injections								
Immediate unsolicited systemic AE	0/263	0.0 (0.0–1.4)	3/260	1.2 (0.2–3.3)	0/110	0.0 (0.0–3.3)	1/87	1.1 (0.0–6.2)
Immediate unsolicited systemic AR	0/263	0.0 (0.0–1.4)	2/260	0.8 (0.1–2.8)	0/110	0.0 (0.0–3.3)	0/87	0.0 (0.0–4.2)
Solicited reaction	230/260	88.5 (83.9–92.1)	233/258	90.3 (86.0–93.6)	97/108	89.8 (82.5–94.8)	83/87	95.4 (88.6–98.7)
Solicited injection site reaction	211/260	81.2 (75.9–85.7)	196/258	76.0 (70.3–81.1)	90/108	83.3 (74.9–89.8)	69/87	79.3 (69.3–87.3)
After injection of HPV vaccine	193/260	74.2 (68.5–79.4)	182/258	70.5 (64.6–76.0)	78/108	72.2 (62.8–80.4)	64/87	73.6 (63.0–82.4)
After injection of CYD dengue vaccine	170/260	65.4 (59.3–71.2)	128/256	50.0 (43.7–56.3)	77/108	71.3 (61.8–79.6)	47/87	54.0 (43.0–64.8)
Solicited systemic reaction	187/260	71.9 (66.0–77.3)	208/258	80.6 (75.3–85.3)	79/108	73.1 (63.8–81.2)	73/87	83.9 (74.5–90.9)
Unsolicited AE	54/263	20.5 (15.8–25.9)	91/260	35.0 (29.2–41.1)	19/110	17.3 (10.7–25.7)	26/87	29.9 (20.5–40.6)
Unsolicited AR	13/263	4.9 (2.7–8.3)	12/260	4.6 (2.4–7.9)	2/110	1.8 (0.2–6.4)	2/87	2.3 (0.3–8.1)
Unsolicited non-SAE	54/263	20.5 (15.8–25.9)	90/260	34.6 (28.8–40.7)	19/110	17.3 (10.7–25.7)	26/87	29.9 (20.5–40.6)
Unsolicited nonserious AR	13/263	4.9 (2.7–8.3)	12/260	4.6 (2.4–7.9)	2/110	1.8 (0.2–6.4)	2/87	2.3 (0.3–8.1)
Unsolicited nonserious injection site AR	0/263	0.0 (0.0–1.4)	3/260	1.2 (0.2–3.3)	0/110	0.0 (0.0–3.3)	1/87	1.1 (0.0–6.2)
After injection of HPV vaccine	0/263	0.0 (0.0–1.4)	2/260	0.8 (0.1–2.8)	0/110	0.0 (0.0–3.3)	1/87	1.1 (0.0–6.2)
After injection of CYD dengue vaccine	0/263	0.0 (0.0–1.4)	1/260	0.4 (0.0–2.1)	0/110	0.0 (0.0–3.3)	0/87	0.0 (0.0–4.2)
Unsolicited nonserious systemic AE	54/263	20.5 (15.8–25.9)	89/260	34.2 (28.5–40.3)	19/110	17.3 (10.7–25.7)	26/87	29.9 (20.5–40.6)
Unsolicited nonserious systemic AR	13/263	4.9 (2.7–8.3)	9/260	3.5 (1.6–6.5)	2/110	1.8 (0.2–6.4)	1/87	1.1 (0.0–6.2)
Unsolicited nonserious AESI	0/263	0.0 (0.0–1.4)	0/260	0.0 (0.0–1.4)	0/110	0.0 (0.0–3.3)	0/87	0.0 (0.0–4.2)
SAE	1/263	0.4 (0.0–2.1)	3/260	1.2 (0.2–3.3)	1/110	0.9 (0.0–5.0)	0/87	0.0 (0.0–4.2)
Serious AESI	0/263	0.0 (0.0–1.4)	0/260	0.0 (0.0–1.4)	0/110	0.0 (0.0–3.3)	0/87	0.0 (0.0–4.2)
Death	0/263	0.0 (0.0–1.4)	0/260	0.0 (0.0–1.4)	0/110	0.0 (0.0–3.3)	0/87	0.0 (0.0–4.2)
Up to 28 days post-dose 3								
SAE	7/263	2.7 (1.1–5.4)	5/260	1.9 (0.6–4.4)	5/110	4.5 (1.5–10.3)	0/87	0.0 (0.0–4.2)
Serious AESI	0/263	0.0 (0.0–1.4)	1/260	0.4 (0.0–2.1)	0/110	0.0 (0.0–3.3)	0/87	0.0 (0.0–4.2)
Death	0/263	0.0 (0.0–1.4)	0/260	0.0 (0.0–1.4)	0/110	0.0 (0.0–3.3)	0/87	0.0 (0.0–4.2)
During the 6-month follow-up period								
SAE	4/263	1.5 (0.4–3.8)	3/260	1.2 (0.2–3.3)	2/110	1.8 (0.2–6.4)	0/87	0.0 (0.0–4.2)
Serious AESI	1/263	0.4 (0.0–2.1)	0/260	0.0 (0.0–1.4)	1/110	0.9 (0.0–5.0)	0/87	0.0 (0.0–4.2)
Death	0/263	0.0 (0.0–1.4)	0/260	0.0 (0.0–1.4)	0/110	0.0 (0.0–3.3)	0/87	0.0 (0.0–4.2)
During the entire study								
SAE	11/263	4.2 (2.1–7.4)	8/260	3.1 (1.3–6.0)	7/110	6.4 (2.6–12.7)	0/87	0.0 (0.0–4.2)
Hospitalized VCD cases	1/263	0.4 (0.0–2.1)	1/260	0.4 (0.0–2.1)	1/110	0.9 (0.0–5.0)	0/87	0.0 (0.0–4.2)
Serious AESI	1/263	0.4 (0.0–2.1)	2/260	0.8 (0.1–2.8)	1/110	0.9 (0.0–5.0)	0/87	0.0 (0.0–4.2)
AE leading to study discontinuation	0/263	0.0 (0.0–1.4)	0/260	0.0 (0.0–1.4)	0/110	0.0 (0.0–3.3)	0/87	0.0 (0.0–4.2)
Death	0/263	0.0 (0.0–1.4)	0/260	0.0 (0.0–1.4)	0/110	0.0 (0.0–3.3)	0/87	0.0 (0.0–4.2)

M, number in the full analysis set with data available for that outcome; n, number reporting outcome.

for all (baseline dengue seropositive and seronegative) participants or for dengue-seropositive participants alone.

In November 2017, based on the findings of an increased risk of hospitalizations in children who were dengue seronegative before vaccination, the IDMC recommended that participants who were dengue seronegative at baseline, should not receive the third CYD-TDV dose. Therefore, the immunogenicity analysis provided here was based on a limited proportion (37%) of enrolled participants who were dengue seropositive at baseline. A major limitation of the study was thus the consequent lack of power for the co-primary non-inferiority endpoints described in the original statistical analysis plan. However, the GMTs and seroconversion rates against the 4 HPV types were similar in the concomitant and sequential groups, and for each dengue serotype, the GMTR between the groups was close to 1, with a 95% CI lower bound within the inferiority margin specified in the original protocol.

In baseline dengue-seropositive participants, HPV antibody GMTs 28 days after the last HPV vaccine dose and dengue GMTs 28 days after CYD-TDV dose 3 (for all 4 dengue serotypes) were comparable between the concomitant and the sequential treatment groups. Furthermore, the quadrivalent HPV vaccine and CYD-TDV were well-tolerated in both groups. Our findings therefore support the feasibility that CYD-TDV could be given concomitantly with quadrivalent HPV, without compromising the immunogenicity or safety of either vaccine. Due to protocol amendment, the evaluable population of dengue-seropositive participants lacked sufficient power for noninferiority testing, therefore these findings remain descriptive. In dengue-endemic countries with existing HPV school-based vaccination programs based on World Health Organization recommendations, giving CYD-TDV and HPV vaccine together could facilitate the implementation of dengue vaccination and maximize dengue vaccine coverage without disrupting the National Immunization Program.

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