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Immunogenicity and Safety of a Tetravalent Dengue Vaccine Administered Concomitantly or Sequentially With Tdap Vaccine

Randomized Phase IIIb Trial in Healthy Participants 9–60 Years of Age in the Philippines

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Background: Incorporating dengue vaccination into existing childhood vaccination programs could increase vaccine coverage. This study assessed the safety and immunogenicity of concomitant versus sequential administration of the combined tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine and the tetravalent dengue vaccine (CYD-TDV).

Methods: This phase IIIb, randomized, open-label, multicenter study was conducted in the Philippines in individuals 9–≤60 years of age (NCT02992418). Participants were to receive 3 CYD-TDV doses 6 months apart, the first dose administered either concomitantly or sequentially (28 days post-Tdap). Antibody levels were measured at baseline and 28 days post-first doses of Tdap vaccine and CYD-TDV, using enzyme-linked immunosorbent assay (pertussis, tetanus), micrometabolic inhibition test-toxin neutralization assay (diphtheria) and plaque reduction neutralization test (dengue). Immunogenicity was assessed for all participants, and statistical analysis reported for baseline dengue seropositive participants. Safety was assessed throughout.

Results: Among 688 randomized participants, 629 (91.4%) were baseline dengue seropositive (concomitant group, n = 314 and sequential group, n = 315). After the first dose, non-inferiority of immune responses between concomitant and sequential vaccination was achieved; between-group geometric mean antibody concentration ratios were close to 1 for anti-PT, anti-FHA, anti-PRN and anti-FIM, between-group differences in percent achieving seroprotection (titers ≥0.1 IU/mL) were 0.26% (diphtheria) and 0.66% (tetanus), and between-group geometric mean antibody titer ratios were close to 1 for dengue serotypes 1–4. Safety profiles in both study groups were comparable.

Conclusions: CYD-TDV and Tdap vaccine administered concomitantly or sequentially in baseline dengue seropositive participants elicited comparable immunogenicity and safety profiles.

Key Words: dengue vaccine, immunogenicity, Philippines, Tdap vaccine, safety

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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, 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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IMPORTANCE

In dengue-endemic countries, integrating the dengue vaccine with national childhood immunization programs could help increase dengue vaccine coverage. The immunogenicity profiles of the combined tetanus toxoid (TT), reduced diphtheria toxoid (DT) and acellular pertussis (Tdap) vaccine and a tetravalent dengue vaccine (CYD-TDV) were unaffected when co-administered, either concomitantly or sequentially, in healthy participants between 9 and ≤60 years of age. Our study results demonstrate the feasibility of co-administration of CYD-TDV and Tdap without compromising the immunogenicity or safety of either vaccine. This could facilitate integrating the dengue vaccination schedule with preexisting national Tdap immunization programs in dengue-endemic countries.

Dengue ranges from mild, self-limiting disease resolving within 7–10 days, to severe dengue hemorrhagic fever and dengue shock syndrome, which lead to the hospitalization of an estimated 500,000 people/year and about 22,000 deaths/year worldwide.[1,2] The annual global incidence of dengue infections (asymptomatic and symptomatic) was estimated to be 390 million in 2018, of which 70% were in South-East Asia and Western Pacific regions.[3] However, in 2019, an unprecedented increase in dengue symptomatic cases was reported, with over 2,000,000 cases recorded in Brazil,[4] and about 420,000 in the Philippines.[5]

Preventive measures, such as vector control and personal protection to prevent transmission are limited in efficacy. A safe and effective vaccine against all 4 dengue serotypes is considered the best method of prevention.[6] The CYD-TDV (Dengvaxia; Sanofi Pasteur, Swiftwater, PA) is a live-attenuated, chimeric vaccine.[7,8] The efficacy and safety of a 3-dose series was assessed in phase IIb and phase III studies,[9–11] and a retrospective analysis of the inferred serostatus of participants at the time of vaccination concluded that CYD-TDV protected against severe or hospitalized virologically-confirmed dengue (VCD) among baseline dengue seropositive participants, but not seronegative participants, who had a higher risk of developing severe dengue.[12] The World Health Organization recommends that CYD-TDV should be used in individuals living in dengue-endemic regions with evidence of previous dengue infection.[13]

Pertussis, tetanus and diphtheria are major health concerns globally.[14–16] Diphtheria (D) toxoid, tetanus (T) toxoid and pertussis (P) antigens have been combined to develop a range of combination vaccines; with DTwP (whole-cell pertussis), DTaP (acellular pertussis) and DT vaccines, for children <7 years, and Tdap and Td for individuals ≥7 years.[17]

Co-administration of vaccines is perceived as an efficient strategy to introduce new vaccines to immunization schedules; however, supporting safety and immunogenicity data may be limited or inconclusive.[18] Given the severe impact on public health of dengue, diphtheria, tetanus and pertussis infections, co-administration of CYD-TDV with Tdap could facilitate the implementation of a school-based dengue vaccination program in those ≥9 years old in dengue-endemic countries. This study investigated the immunogenicity and safety of CYD-TDV when administered either concomitantly or sequentially with a booster dose of Tdap.

MATERIALS AND METHODS

Design and Participants

This was a phase IIIb, randomized, open-label, multicenter non-inferiority trial of the immunogenicity and safety of concomitant or sequential administration of CYD-TDV and Tdap vaccines in healthy participants 9–≤60 years of age in the Philippines (NCT02992418). The study was conducted between December 2016 and December 2019.

Inclusion criteria were: 9–≤60 years of age, healthy and receipt of at least 4 previous doses of DTaP vaccine (participants 9–11 years of age) or at least 3 previous doses of DTwP vaccine (participants ≥12 years of age), with the last dose of either vaccine not within 5 years of enrolment. Exclusion criteria included: being pregnant or lactating or of childbearing potential, unless surgically sterile or using an effective method of contraception; participating or planned participation in another clinical trial during this study; and previous vaccination with CYD-TDV (see Methods, Supplemental Digital Content 1, http://links.lww.com/INF/E419).

The informed consent form (ICF) and/or assent form was obtained from the participants or parent(s) or another legally acceptable representative before any study procedures were performed. The conduct of this study was consistent with the standards established by the Declaration of Helsinki and compliant with the International Council for Harmonisation guidelines for Good Clinical Practice as well as with all local and/or national regulations and directives. The protocol was approved by applicable independent ethics committees/institutional review boards and the regulatory agency as per local regulations.

During the study, following reports of excess risk of severe dengue and hospitalization among dengue-seronegative participants,[12] the Independent Data Monitoring Committee (IDMC) concluded that only baseline dengue seropositive participants should receive further doses of CYD-TDV. This trial was paused to allow for the protocol amendment and serostatus determination. Baseline seronegative participants did not receive further CYD-TDV doses but, once consent was given, continued the 6-month safety follow-up. As a consequence of the study pause, the vaccination schedule was substantially delayed and the decision was made to prematurely terminate the study (see Methods and Figure 1, Supplemental Digital Content 1, http://links.lww.com/INF/E419 and 2, http://links.lww.com/INF/E420).

Procedures, Vaccines and Vaccinations

Participants were randomized 1:1 with stratification on center and age (9–11 years, 12–17 years, 18–45 years and 46–60 years), using scratchable randomization lists (one per site and per age group), to receive the Tdap vaccine dose at inclusion (day 0) and the first dose of CYD-TDV 28 days later at month 1 (sequential group), or to receive the first dose of CYD-TDV concomitantly with the dose of Tdap vaccine at month 1 (concomitant group). The second and third doses of CYD-TDV were to be administered at month 7 and month 13 in both groups (see Figure 1, Supplemental Digital Content 2, http://links.lww.com/INF/E420).

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 contained 4.5–6.0 $\log_{10}$ cell-culture infectious dose 50% ($CCID_{50}$) of each live, attenuated and recombinant dengue serotype 1-4.

Participants received a single 0.5 mL dose of Tdap vaccine (Adacel; powder and solvent for suspension for injection) by intramuscular injection in the deltoid region of the upper arm, in the opposite arm to that receiving CYD-TDV.[19] One dose contained 5 limes flocculation dose (Lf) of TT, 2 Lf of DT, 2.5 μg of pertussis toxoid (PT) and 5 μg each of filamentous hemagglutinin (FHA), pertactin (PRN) and fimbriae types 2 and 3 (FIM).

Immunogenicity Assessment

Participants were to provide blood samples for immunogenicity assessments at baseline and 28 days after the first (Tdap and CYD-TDV) and third (CYD-TDV) vaccine doses (see Figure 1, Supplemental Digital Content 2, http://links.lww.com/INF/E420).

Neutralizing antibody titers were measured for each of the 4 dengue serotypes by a 50% plaque reduction neutralization test ($PRNT_{50}$).[20] Participants with $PRNT_{50}$ titers <10 (1/dil) for all 4 serotypes at baseline or after any vaccine dose were classed as dengue seronegative, and those with titers ≥10 (1/dil) for ≥1 serotype at baseline or after any vaccine dose were dengue seropositive. Participants with test results that were undetermined were classified as seronegative.

Antibody levels against pertussis antigens (PT, FHA, PRN, FIM) and TT were measured by an enzyme-linked immunosorbent assay (ELISA), and those against DT were measured by a micrometabolic inhibition test-toxin neutralization assay. Seroprotection to DT or TT was defined as antibody concentrations ≥0.1 IU/mL. The lower limit of quantitation for the anti-PT, PRN and FIM ELISA was 4 EU/mL, the anti-FHA ELISA was 3 EU/mL, and the anti-TT ELISA was 0.01 IU/mL. For the anti-DT micrometabolic inhibition test-toxin neutralization assay the lower limit of quantitation was 0.005 IU/mL. All assays were performed by Global Clinical Immunology (Sanofi Pasteur).

The co-primary objectives for the evaluation of immunogenicity were to demonstrate the non-inferiority of concomitant administration of Tdap [based on geometric mean concentrations (GMCs) of antibodies against PT, FHA, PRN, FIM and seroprotection rates for TT and DT] and CYD-TDV [based on geometric

mean titers (GMTs) of antibodies against serogroups 1–4] vaccines as compared with sequential administration, measured 28 days after Tdap and the first CYD-TDV dose.

The planned secondary objectives of this study were to demonstrate the non-inferiority of the dengue immune response following the third CYD-TDV dose in the concomitant versus sequential administration groups, to describe dengue immunogenicity at baseline and 28 days after the first and third doses of CYD-TDV, and to describe immunogenicity of Tdap antigens at baseline and 28 days after vaccination.

Safety

Safety objectives were determined in all participants who received a study vaccine, regardless of baseline dengue serostatus. Records were kept in a diary card or memory aid provided to each participant. Safety outcomes were occurrence of immediate adverse events (AEs) or adverse reactions within 30 minutes after injection; solicited injection site reactions (pain, erythema and swelling) within 7 days; solicited systemic reactions (fever, headache, malaise, myalgia and asthenia) within 14 days; unsolicited or spontaneously reported AEs within 28 days; non-serious AESIs (hypersensitivity/allergic reactions) within 7 days; and SAEs, including serious AESIs (serious viscerotropic or serious neurotropic disease, and hospitalization for dengue) throughout the trial. Hospitalized dengue was defined as an acute febrile illness with diagnosis of dengue requiring hospitalization, and confirmed by dengue non-structural protein 1 antigen ELISA and/or dengue reverse transcriptase-polymerase chain reaction. The IDMC regularly reviewed hospitalized VCD cases, including assessment of severity. Investigators assessed the potential relationship between vaccination and systemic AEs and non-serious AESIs. The IDMC reviewed any related SAE or death.

Statistics

The planned sample size was 688 participants (n = 344 in each group; n = 86 in each age group [9–11 years, 12–17 years, 18–45 years and 46–60 years]), to provide a global power of >90% for the co-primary objectives. Following protocol amendments, the minimum number of expected dengue-seropositive participants was reduced to 510 for the co-primary objectives (255 per group), and 324 (162 per group) for the secondary objective. Statistical analysis was performed on baseline dengue-seropositive participants. Descriptive analyses were conducted on all participants. 95% confidence intervals [CIs] were calculated based on the Wilson score method without continuity correction as quoted by Newcombe[21] for seroprotection rates, and using normal approximation of log-transformed titers for GMCs/GMTs.

Non-inferiority for the pertussis antigens (PT, FHA, PRN and FIM) was demonstrated if the lower limit of the 2-sided 95% CI of the GMC ratio (GMCR; concomitant/sequential) was >0.667 for each; overall non-inferiority was demonstrated if all achieved non-inferiority. Non-inferiority for the DT and TT antigens was demonstrated if the lower limit of the 95% CI of the between-group difference was ≥–10%, with overall non-inferiority if both achieved non-inferiority. Non-inferiority for each of the dengue serotypes was demonstrated if the lower limit of the 2-sided 95% CI of the between-group GMT ratio (concomitant/sequential) was >0.5 for each serotype; overall non-inferiority was demonstrated if all achieved non-inferiority. Early termination of the study before the third CYD-TDV dose prevented testing non-inferiority of secondary outcomes. All safety analyses were descriptive; no hypotheses were tested.

The full analysis set was comprised of all participants who received ≥1 dose of study vaccines, of which baseline dengue-seropositive participants were a subset. Non-inferiority analyses were performed on per-protocol analysis sets, for the Tdap dose (PPT set) and for the first dose of CYD-TDV (PPC1 set). The main criteria for including participants in the PPT and PPC1 sets were: baseline dengue seropositive, meeting all inclusion and none of the exclusion criteria, completing the vaccination schedule, receiving the correct doses of vaccine within the specified times, and a valid post-injection antibody test. Safety was evaluated in the safety analysis set, defined as participants who received ≥1 dose of the study vaccines, assessed by the vaccine they received.

RESULTS

Study Population

Enrolled participants (n = 688) were randomized to receive concomitant (n = 346) or sequential vaccination (n = 342; see Figure 2, Supplemental Digital Content 3, http://links.lww.com/INF/E421). At the study pause, 688/688 (100%) and 676/688 (98%) participants had received Tdap and the first CYD-TDV dose, respectively, and 640/688 (93%) had received Tdap and 2 doses of CYD-TDV, none received the third CYD-TDV dose.

Among the enrolled participants, 629/688 (91.4%) were baseline dengue seropositive [concomitant: 314/346 (90.8%); sequential: 315/342 (92.1%)]. As the expected minimum number of evaluable participants (>255 per group) was reached, non-inferiority analysis was performed. The PPT set included 626/688 (91.0%) participants [concomitant: 312/346 (90.2%); sequential 314/342 (91.8%)]. The PPC1 set included 620/688 (90.1%) participants [concomitant: 312/346 (90.2%); sequential: 308/342 (90.1%)]. Demographic and baseline characteristics were balanced between both groups (Table 1).

Immunogenicity

Tdap

The non-inferiority of the humoral immune response to the pertussis antigens (PT, FHA, PRN and FIM), DT and TT with concomitant versus sequential administration of Tdap and CYD-TDV was achieved when measured 28 days post-Tdap in baseline dengue seropositive participants (Table 2; see Table 1, Supplemental Digital Content 4, http://links.lww.com/INF/E422 and 5, http://links.lww.com/INF/E423). Both the GMCs of the pertussis antibodies, and the seroprotection rates of DT and TT antibodies, increased from baseline to 28 days post-Tdap, and were comparable between groups (Fig. 1). At 28 days post-Tdap, the GMCs (95% CI) of DT antibodies were similar in the concomitant and sequential groups [2.85 (2.22–3.67) EU/mL and 2.80 (2.13–3.67) EU/mL, respectively], as were the GMCs (95% CI) of TT antibodies [13.6 (11.4–16.2) EU/mL and 15.2 (12.9–17.9) EU/mL, respectively]. When examined by age group, the GMCs of pertussis antibodies 28 days post-Tdap dose showed some variations, with the highest levels seen in the 12–17 year age group, particularly for the Anti-FIM2 + 3 antigen (see Table 3, Supplemental Digital Content 6, http://links.lww.com/INF/E424).

CYD-TDV

The non-inferiority of the responses to each of the dengue serotypes for concomitant versus sequential administration of the first dose of CYD-TDV with Tdap vaccine in baseline dengue seropositive participants was achieved (Table 2). The baseline titers for each serotype were similar between groups in the dengue baseline seropositive participants, and increased 28 days post-CYD-TDV dose 1 (Fig. 2); with comparable GMT ratios between groups (see Table 4, Supplemental Digital Content 7, http://links.lww.com/INF/E425), and across the age groups (see Table 5, Supplemental Digital

TABLE 1. Baseline Demographic by Baseline Dengue Status in Baseline Dengue Seropositive Participants—FAS

	All			Dengue Seropositive		
	Concomitant (N = 338)	Sequential (N = 342)	All (N = 680)	Concomitant (N = 314)	Sequential (N = 315)	All (N = 629)
Sex, n (%)						
Male	154 (45.6)	149 (43.6)	303 (44.6)	142 (45.2)	136 (43.2)	278 (44.2)
Age (years)						
Mean (SD)	26.2 (16.3)	27.1 (16.7)	26.6 (16.5)	27.4 (16.3)	28.2 (16.7)	27.8 (16.5)
Min; max	9.0; 60.0	9.0; 60.0	9.0; 60.0	9.0; 60.0	9.0; 60.0	9.0; 60.0
Age, n (%)						
9–11 years	81 (24.0)	87 (25.4)	168 (24.7)	62 (19.7)	67 (21.3)	129 (20.5)
12–17 years	91 (26.9)	81 (23.7)	172 (25.3)	86 (27.4)	78 (24.8)	164 (26.1)
18–45 years	84 (24.9)	86 (25.1)	170 (25.0)	84 (26.8)	83 (26.3)	167 (26.6)
46–60 years	82 (24.3)	88 (25.7)	170 (25.0)	82 (26.1)	87 (27.6)	169 (26.9)

N indicates sample number; n, number of participants fulfilling the item listed.

Content 8, http://links.lww.com/INF/E426). The proportion of participants with seropositivity to each dengue serotype increased after the first CYD-TDV dose (see Table 6, Supplemental Digital Content 9, http://links.lww.com/INF/E427).

Safety

A summary of the safety outcomes is shown in Table 3. The rates of solicited injection site reactions and solicited systemic reactions were similar between both study groups (see Tables 7 and 8, Supplemental Digital Contents 10, http://links.lww.com/INF/E428 and 11, http://links.lww.com/INF/E429); pain after injection, and headache and malaise were the most common reactions, respectively. No immediate unsolicited systemic AEs or adverse reactions were reported during the study, and there were no early terminations due to an SAE.

In the concomitant group during the study period, 8/338 (2.4%) participants reported an SAE (one within 28 days post-dose) versus 11/342 (3.2%) in the sequential group (none within 28 days post-dose). No SAEs were considered related to study vaccination. There were no non-serious AESIs. Four participants developed serious AESIs, 1 in the concomitant group (baseline dengue seropositive) and 3 in the sequential group (2 baseline dengue seropositive and 1 seronegative), none of which were considered related to the study vaccines. All 4 participants with serious AESIs had suspected hospitalized dengue cases; 3 were assessed as VCD (all from the sequential group), of whom 2 were baseline dengue seropositive and 1 seronegative. The VCD case in the baseline dengue seronegative individual (a 13-year-old boy) occurred more than 2 years after the second dose of CYD-TDV and was

TABLE 2. Non-inferiority of the Antigens to Each of the Tdap Vaccine Components 28 Days After Administration (PPT Subset) and 28 Days After the First Dose of CYD-TDV (PPC1 Subset) in the Concomitant and Sequential Groups in Baseline Dengue Seropositive Participants

	Concomitant (N = 312)			Sequential (N = 314)			Concomitant/Sequential		
Pertussis Antigens (EU/mL)	M	GMC	95% CI	M	GMC	95% CI	GMC ratio	95% CI	Overall Non-inferiority
PT	300	65.2	57.7–73.8	310	76.0	67.9–85.1	0.848	0.721 to 0.997	Yes*
FHA	308	273	248–299	314	267	241–296	1.02	0.892 to 1.18	
PRN	311	50.6	41.4–61.9	314	44.9	36.7–55.0	1.11	0.836 to 1.46	
FIM	309	705	586–847	312	643	537–770	1.05	0.827 to 1.33	
Diphtheria seroprotection (%)	**n/M**	**Seroprotection**	**95% CI†**	**M**	**Seroprotection**	**95% CI†**	**Difference**	**95% CI‡**	
DT	281/312	90.1	86.2–93.1	282	89.8	85.9–92.9	0.26	–4.53 to 5.04	
Tetanus seroprotection (%)	**n/M**	**Seroprotection**	**95% CI†**	**M**	**Seroprotection**	**95% CI†**	**Difference**	**95% CI‡**	Yes§
TT	304/309	98.4	96.3–99.5	311	99.0	97.2–99.8	–0.66	–2.87 to 1.37	
Dengue antigens, 1/dil	**M**	**GMT**	**95% CI**	**M**	**GMT**	**95% CI**	**GMTR**	**95% CI**	
Serotype 1	312	513	427–617	308	461	384–552	1.11	0.86 to 1.44	Yes¶
Serotype 2	312	677	588–780	308	568	489–661	1.19	0.97 to 1.47	
Serotype 3	312	653	558–765	308	706	603–828	0.925	0.74 to 1.16	
Serotype 4	312	378	324–442	308	472	404–551	0.802	0.64 to 1.00	

*The non-inferiority of the GMC of antibodies against pertussis antigens was met if the lower limit of the 2-sided 95% CI of the GMC ratio (concomitant/sequential) was >0.667 for each antigen; overall non-inferiority was met if all 4 antigens achieved non-inferiority.

†Exact binomial method (Clopper-Pearson method, quoted by Newcombe) used for the single proportion 95% 2-sided CIs

‡The 95% CI was calculated based on the Wilson score method without continuity correction as described by Newcombe

§The non-inferiority of seroprotection rates of antibodies against diphtheria and tetanus toxoids was met if the lower limit of all the 95% CI of the difference in proportions of seroprotection rates was greater than –10% for both antigens.

¶The non-inferiority of geometric mean neutralizing antibody titers for each dengue serotype was met if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups (concomitant/sequential) was >0.5 for each serotype. Overall non-inferiority was met if all 4 serotypes achieve non-inferiority.

GMTR indicates GMT ratio; M, number of participants with available data for the relevant endpoint; N, sample number; n, number of participants fulfilling the item listed; PPC1, per-protocol analysis set after CYD-TDV dose 1; PPT, per-protocol analysis set.

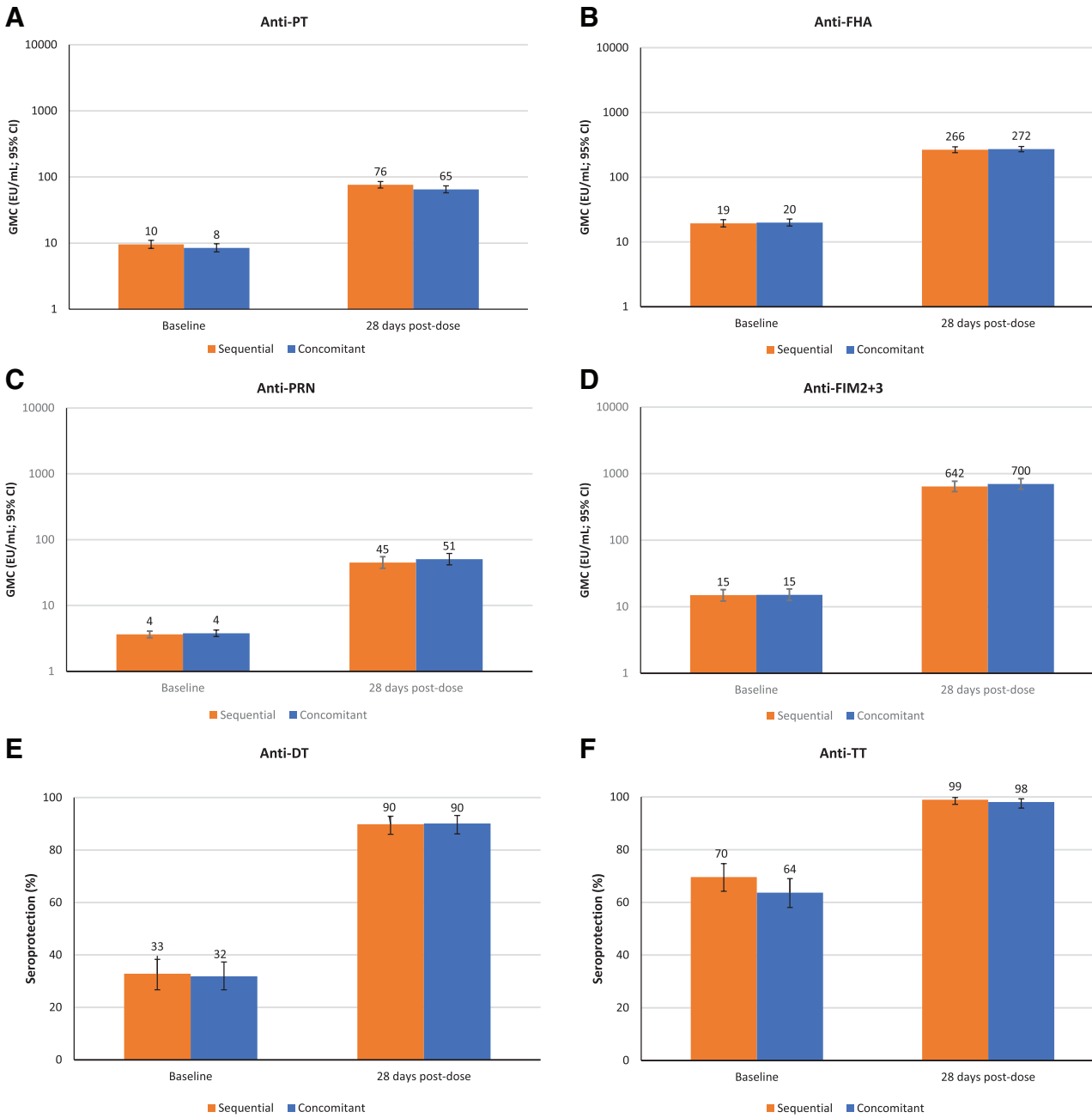

FIGURE 1. GMCs of antibodies against pertussis antigens (PT, FHA, PRN and FIM; A–D) and seroprotection* rates (E and F) of antibodies against diphtheria and tetanus toxoids at baseline (pre-Tdap dose) and 28 days post-Tdap dose given concomitantly or sequentially with CYD-TDV in baseline dengue seropositive participants—FAS. *Seroprotection of antibodies against DT or TT was defined as antibody concentrations ≥0.1 IU/mL. FSA indicates full analysis set.

adjudicated as severe by the IDMC. The participant, who had a medical history of primary tuberculosis and dengue hemorrhagic fever, for which he was previously admitted to hospital, fully recovered after 7–8 days and continued in the trial. This event of severe dengue was reported by the investigator as serious and unrelated to the vaccine. There were no deaths during the study.

DISCUSSION

This study demonstrated that, in baseline dengue seropositive participants 9–≤60 years of age, concomitant administration of Tdap with the first CYD-TDV dose resulted in a non-inferior humoral immune response against the antigen components of each vaccine compared with sequential administration. The safety profiles of both vaccines were comparable when administered sequentially or concomitantly.

Previous studies of the co-administration of CYD-TDV with human papillomavirus vaccines in children 9–14 years of age (NCT02979535 and NCT02993757), or with DTaP inactivated polio vaccine and *Haemophilus influenzae* type b vaccine in toddlers 15–18 months of age,[22] have demonstrated that CYD-TDV

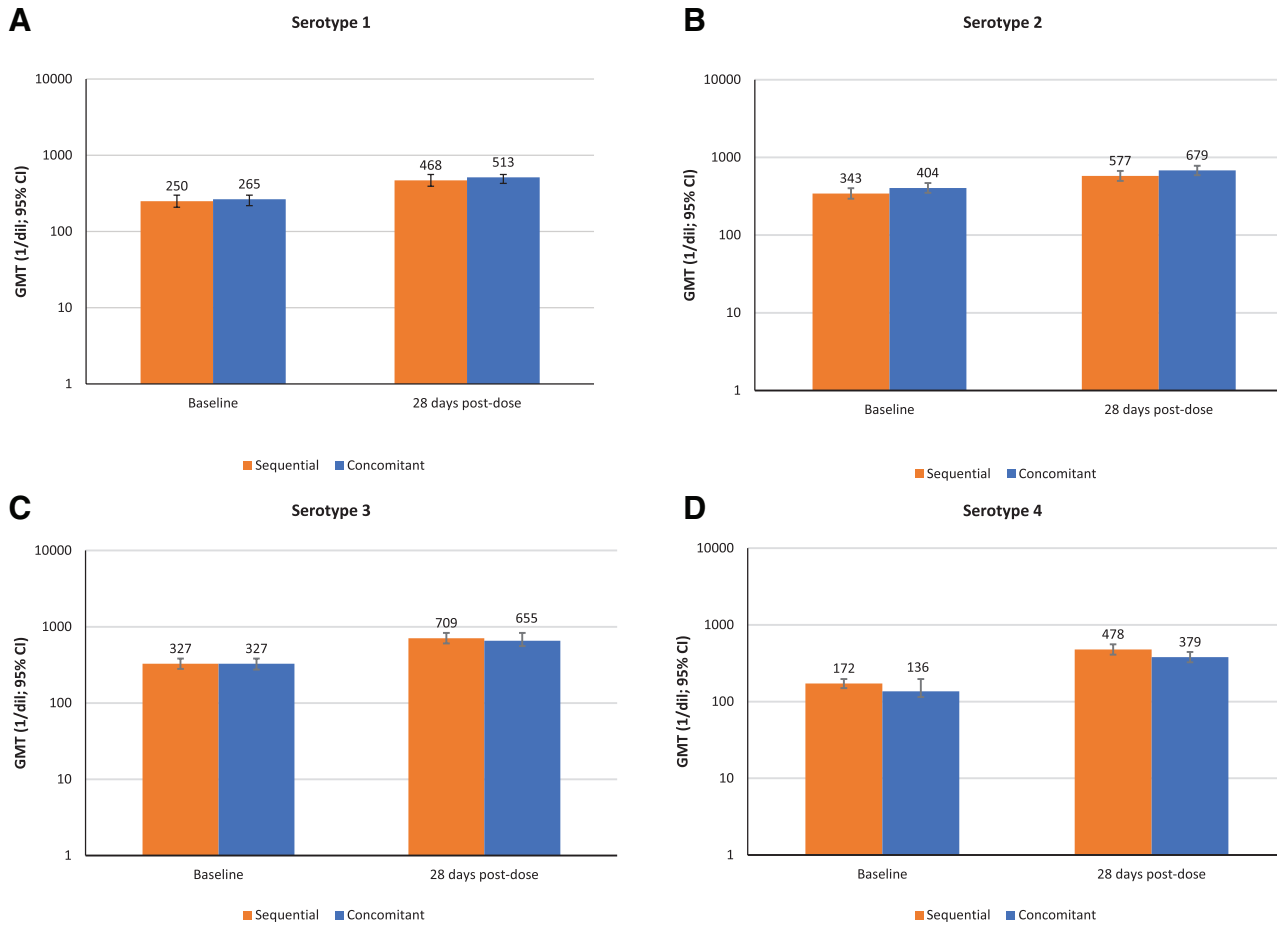

FIGURE 2. Dengue geometric mean neutralizing antibody titers for each serotype at baseline (pre-dose 1) and 28 days post-dose 1 of CYD-TDV administered concomitantly or sequentially with Tdap vaccine in baseline dengue seropositive participants—FAS. FSA indicates full analysis set.

could be administered concomitantly with other vaccines, safely and without affecting immunogenicity.

In participants who were baseline dengue seropositive, the neutralizing antibody responses at 28 days post-first CYD-TDV dose for serotypes 1-4, were consistent with those reported in the previous pivotal trials of CYD-TDV in highly endemic countries.[9,23,24] The GMCs of antibodies reported against Tdap vaccine antigens in the present study are aligned to values reported in previous studies investigating the immunogenicity of the first Tdap vaccine dose, in adults[25,26] and adolescents.[27]

Seroprotection rates of antibodies against DT and TT (close to 90% for both groups) were lower than the expected >99% seroprotection used for sample size calculations. A possible explanation for the lower seroprotection is the inclusion of older adults, who have been shown to have lower rates.[28,29,30] As results were not assessed by age group in this study, we cannot confirm if seroprotection declines with age.

Concomitant or sequential administration of CYD-TDV or Tdap vaccine was well tolerated in this study, with no immediate systemic AEs, related SAEs, AEs leading to early termination or deaths. Four suspected hospitalized dengue cases were reported and were considered unrelated to the study vaccines; 3 of these were VCD (all in the sequential group), all participants recovered. Among the 3 hospitalized VCD cases, 1 in a baseline dengue seronegative participant was assessed as severe by the IDMC. The proportion of severe VCD cases observed among baseline dengue seronegative participants was 1.96% (1/51), occurring ≥2 years after the second CYD-TDV dose. In the case-cohort study of 3 CYD-TDV efficacy studies, the cumulative incidence of severe VCD over a period of 60 months was 0.40% among dengue seronegative participants, who had received all 3 CYD-TDV doses,[12] where the third dose has been shown to further increase the immune response in baseline dengue seronegative participants.[31,32] The proportion of hospitalized VCD cases in seropositive participants were similar between this [0.32% (2/629)] and the case-cohort (0.38%) studies.[12] Overall, the reported safety outcomes were generally consistent with published safety profiles.[7,19,33–36]

The sudden increase in incidence and mortality rates of dengue worldwide in 2019, with the declaration of an epidemic in the Philippines during the same year,[37] highlights the need for an effective vaccine. Diphtheria, pertussis and tetanus vaccination is part of an ongoing national vaccination program in the Philippines Expanded Program on Immunization with an estimated vaccination coverage of 65% in 2019.[38,39] Integrating the dengue vaccine with immunization programs could help reduce the morbidity and mortality rates on future epidemics. Furthermore, the findings of this study are consistent with reports indicating that vaccines, such as meningococcal[40] and human papillomavirus,[41] can be safely and effectively co-administered with other vaccines in adolescents and adults to improve vaccination rates and reduce the burden of vaccinations.

TABLE 3. Overview of Safety Outcomes—SafAS

	All						Dengue Seropositive					
	Concomitant (N = 338)			Sequential (N = 342)			Concomitant (N = 314)			Sequential (N = 315)		
Participants experiencing at least one	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	0/338	0.0	0.0–1.1	0/342	0.0	0.0–1.1	0/314	0.0	0.0–1.2	0/315	0.0	0.0–1.2
Solicited reaction	245/338	72.5	67.4–77.2	262/341	76.8	72.0–81.2	229/314	72.9	67.7–77.8	244/315	77.5	72.4–82.0
Solicited injection site reaction	232/338	68.6	63.4–73.6	241/341	70.7	65.5–75.5	218/314	69.4	64.0–74.5	223/315	70.8	65.4–75.8
Solicited systemic reaction	139/338	41.1	35.8–46.6	183/341	53.7	48.2–59.1	128/314	40.8	35.3–46.4	168/315	53.3	47.7–58.9
Unsolicited AE	56/338	16.6	12.8–21.0	70/342	20.5	16.3–25.1	54/314	17.2	13.2–21.8	64/315	20.3	16.0–25.2
Unsolicited AR	2/338	0.6	0.1–2.1	1/342	0.3	0.0–1.6	2/314	0.6	0.1–2.3	1/315	0.3	0.0–1.8
Unsolicited non-serious systemic AE	54/338	16.0	12.2–20.3	70/342	20.5	16.3–25.1	52/314	16.6	12.6–21.1	64/315	20.3	16.0–25.2
Unsolicited non-serious systemic AR	0/338	0.0	0.0–1.1	1/342	0.3	0.0–1.6	0/314	0.0	0.0–1.2	1/315	0.3	0.0–1.8
Unsolicited non-serious AESI	0/338	0.0	0.0–1.1	0/342	0.0	0.0–1.1	0/314	0.0	0.0–1.2	0/315	0.0	0.0–1.2
AE leading to study discontinuation	0/338	0.0	0.0–1.1	0/342	0.0	0.0–1.1	0/314	0.0	0.0–1.2	0/315	0.0	0.0–1.2
SAE	1/338	0.3	0.0–1.6	0/342	0.0	0.0–1.1	1/314	0.3	0.0–1.8	0/315	0.0	0.0–1.2
During the follow-up period (6 months)												
SAE	7/338	2.1	0.8–4.2	10/342	2.9	1.4–5.3	4/314	1.3	0.3–3.2	8/315	2.5	1.1–4.9

AR indicates adverse reactions; M, number of participants with available data for the relevant endpoint; n, number of participants with the endpoint listed; SAE, serious AEs; SafAS, safety analysis set.

A limitation to this study was its termination before the third CYD-TDV dose, and therefore the inability to test the non-inferiority of this dose.

The co-administration of CYD-TDV with Tdap in participants who were baseline dengue seropositive elicited a non-inferior immune response compared with sequential administration, with a consistent safety profile. The study results demonstrate the feasibility of co-administration of CYD-TDV and Tdap vaccine.

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