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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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 existing 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
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 (NCT029992418). 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 DTwP 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; or planned participation in another clinical trial during this study; and effective vaccine against all 4 dengue serotypes is consid-

Materials and Methods

Design and Participants

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.1 The CYD-TDV (Dengvaxia; Sanofi Pasteur, Swiftwater, PA) is a live-attenuated, chimeric vaccine.2,3 The efficacy and safety of a 3-dose series was assessed in phase IIB and phase III studies,2,11 and a retrospective analysis of the inferred serostatus of participants at the time of vaccination concluded that CYD-TDV protected against severe or hospitalized viremic 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 previ-

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 log10 cell-culture infectious dose 50% (CCID50) 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 intra-

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 (PRNT50).20 Participants with PRNT50 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 asthma) 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 Newcombe21 for the non-inferiority analysis. Investigators assessed the potential relationship between vaccination and systemic AEs and non-serious AESIs. The IDMC reviewed any related SAE or death.

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/E421). 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 antigens (see Table 3, Supplemental Digital Content 6, http://links.lww.com/INF/E422 and 5, http://links.lww.com/INF/E423).

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 Content 6, http://links.lww.com/INF/E426).
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/E426). The proportion of participants with seropositivity to each dengue serotype was >0.5 for each serotype. Overall non-inferiority was met if all 4 serotypes achieve non-inferiority.

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/E427 and 11, http://links.lww.com/INF/E429); pain after injection, and headache 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 1. Baseline Demographic by Baseline Dengue Status in Baseline Dengue Seropositive Participants—FAS |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Sex, n (%)                                      | Age (years)                                     | Mean (SD)                                       | Min; max | Age, n (%)                                      | 9–11 years | 12–17 years | 18–45 years | 46–60 years |
| Male                                           | 154 (45.6)                                      | 26.2 (16.3)                                     | 9.6; 60.0 | 9–11 years | 81 (24.0)  | 91 (26.9)  | 84 (24.9)  | 82 (24.3)  |
| Female                                         | 149 (43.8)                                      | 27.1 (16.7)                                     | 9.0; 60.0 | 12–17 years | 87 (25.4)  | 81 (23.7)  | 86 (25.1)  | 88 (25.7)  |
| All                                            | 303 (44.6)                                      | 26.6 (16.5)                                     | 9.0; 60.0 | 18–45 years | 168 (24.7) | 172 (25.3) | 170 (25.0) | 170 (25.0) |
| Sex, n (%)                                      | Age (years)                                     | Mean (SD)                                       | Min; max | Age, n (%)                                      | 9–11 years | 12–17 years | 18–45 years | 46–60 years |
| Male                                           | 142 (45.2)                                      | 27.4 (16.3)                                     | 9.0; 60.0 | 9–11 years | 62 (19.7)   | 86 (27.4)   | 84 (26.8)   | 82 (26.1)   |
| Female                                         | 136 (43.2)                                      | 28.2 (16.7)                                     | 9.0; 60.0 | 12–17 years | 67 (21.3)   | 78 (24.8)   | 83 (26.3)   | 87 (27.6)   |
| All                                            | 278 (44.2)                                      | 27.8 (16.5)                                     | 9.0; 60.0 | 18–45 years | 129 (20.5)  | 164 (26.1)  | 167 (26.6)  | 169 (26.9)  |

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

| 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 |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Pertussis Antigens (EU/mL)                       | Concomitant (N = 312)                           | Sequential (N = 314)                            | Concomitant/Sequential                          |
|                                                  | M      | GMC 95% CI | M      | GMC 95% CI | GMC ratio 95% CI | Overall Non-inferiority |
| DT                                                | 300    | 65.2      | 310    | 76.0       | 67.9–85.1        | 0.848 | 0.721 to 0.997 | Yes*        |
| FIM                                               | 308    | 273       | 314    | 267       | 241–296       | 1.02  | 0.892 to 1.18  |            |
| PRN                                               | 311    | 50.6      | 314    | 44.9       | 36.7–55.0      | 1.11  | 0.836 to 1.46  |            |
| FHA                                               | 309    | 705       | 312    | 643       | 537–770       | 1.05  | 0.827 to 1.33  |            |
| Tetanus seroprotection (%)                        | n/M    | 281/312   | 282    | 283/292   | 283/292       | 0.26  | –4.53 to 5.04  | Yes†       |
| Diphtheria seroprotection (%)                     | n/M    | 281/312   | 282    | 283/292   | 283/292       | –0.66 | –2.87 to 1.37  |            |
| PT                                                | 304/309| 98.4     | 311    | 99.0       | 97.2–99.8     | 0.26  | –4.53 to 5.04  | Yes†       |
| FHA                                               | 312    | 513       | 308    | 461       | 384–552       | 1.11  | 0.68 to 1.44   | Yes†       |
| PRN                                               | 312    | 677       | 308    | 568       | 489–661       | 1.19  | 0.97 to 1.47   |            |
| FIM                                               | 312    | 653       | 308    | 706       | 603–828       | 0.925 | 0.74 to 1.16   |            |
| Pertussis Antigens (EU/mL)                        | n/M    | 281/312   | 282    | 283/292   | 283/292       | 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.

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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, have demonstrated that CYD-TDV...
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. 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 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, 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 and the case-cohort (0.38%) studies. 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, 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. 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 and human papillomavirus, can be safely and effectively co-administered with other vaccines in adolescents and adults to improve vaccination rates and reduce the burden of vaccinations.

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.
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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