Immunogenicity and safety of a tetravalent dengue vaccine in healthy adults in India: A randomized, observer-blind, placebo-controlled phase II trial

Anand Prakash Dubey1, Sharad Agarkhedkar2, Jugesh Chhatwal3, Arun Narayan4, Satyabrata Ganguly5, T Anh Wartel6, Alain Bouckenooghe6, and Josemund Menezes6*

1Maulana Azad Medical College & Hospital; New Delhi, India; 2Dr DY Patil Medical College & Hospital; Pimpri, Pune, India; 3Christian Medical College & Hospital; Ludhiana, India; 4Sr Professor of Medicine; MS Ramaiah Medical College & Hospitals; Bangalore, India; 5Medical College; Kolkata, India; 6Clinical Research & Development; Sanoﬁ Pasteur, Singapore

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Dengue is a mosquito-borne viral disease that is endemic in India. We evaluated the immunogenicity and safety of recombinant, live-attenuated, tetravalent dengue vaccine (CYD-TDV) in Indian adults. In this observer-blind, randomized, placebo-controlled, Phase II study, adults aged 18–45 years were randomized 2:1 to receive CYD-TDV or placebo at 0, 6 and 12 months in sub-cutaneous administration. Immunogenicity was assessed using a 50% plaque reduction neutralization test (PRNT50) at baseline and 28 days after each study injection. 189 participants were enrolled (CYD-TDV [n = 128]; placebo, [n = 61]). At baseline, seropositivity rates for dengue serotypes 1, 2, 3 and 4 ranged from 77.0% to 86.9%. Seropositivity rates for each serotype increased after each CYD-TDV injection with a more pronounced increase after the first injection. In the CYD-TDV group, geometric mean titres (GMTs) were 2.38 to 6.11-fold higher after the third injection compared with baseline but remained similar to baseline in the placebo group. In the CYD-TDV group, the GMTs were 1.66 to 4.95-fold higher and 9.23 to 24.6-fold higher after the third injection compared with baseline in those who were dengue seropositive and dengue seronegative, respectively. Pain was the most commonly reported solicited injection site reaction after the first injection in both the CYD-TDV (6.3%) and placebo groups (4.9%), but occurred less frequently after subsequent injections. No serious adverse events were vaccine-related, no immediate unsolicited adverse events, and no virologically-confirmed cases of dengue, were reported during the study. The immunogenicity and safety of CYD-TDV was satisfactory in both dengue seropositive and seronegative Indian adults.

Introduction

Dengue is a mosquito-borne viral disease that is endemic in tropical and subtropical countries and represents a global pandemic threat.1 The virus is endemic in India, with several known hyper-endemic sub-regions.2-3 Dengue is a notifiable disease, that is of significant public health concern in India due to annual outbreaks and all 4 dengue virus serotypes circulate in the country. In 2013, more than 75,000 cases and 167 deaths were reported to the Indian national surveillance program.2-4 However, dengue is believed to be significantly under-reported in India and the average annual number of cases has been estimated to vary widely up to 33 million apparent cases annually (which would represent 34% of the global total).7-9

In addition, the economic burden of dengue illness in India is considerable with annual medical and non-medical and indirect costs estimated at US$1.11 billion.8

There is no specific treatment for dengue and current control measures have involved promoting the principles of integrated vector management and deploying locally-adapted vector control measures, but they have in general failed to reduce the occurrence of dengue epidemics.1 Vaccination is acknowledged as a potentially effective strategy for the control of dengue, but there is no registered vaccine currently available.

A recombinant, yellow fever-17D–dengue virus, live-attenuated, tetravalent dengue vaccine (CYD-TDV) is in late phase of development for the control of dengue disease with a 3 dose-schedule regimen, with vaccinations given 6 months.
Two landmark phase III studies with CYD-TDV, in children aged 2–14 years in 5 countries in Asia and those aged 9–16 years in 5 countries in Latin America, have shown that, over the 25 month active surveillance period, the vaccine was efficacious against virologically-confirmed dengue and severe disease and there were fewer hospitalizations in the vaccine group compared to control.12,13 In the Latin American study CYD-TDV vaccination was associated with overall efficacy of 60.8% against symptomatic dengue and efficacy against hospitalization was 80.3% over the 25 month active surveillance period.13 Similarly, in the Asian study, CYD-TDV vaccination was associated with overall efficacy against symptomatic dengue of 56.5%, prevented 80% of cases of dengue hemorrhagic fever (during the 13 month period after the third dose), and led to a clinically important reduction in the risk of hospitalization due to dengue (during the 25 month active surveillance period).12 The favorable vaccine safety profile observed during the 25 month active surveillance period was consistent with that documented in prior studies in Asia.10,11,14-16 As a first step before evaluating the vaccine in children in India, we conducted a clinical trial in Indian adults. Here we describe the immunogenicity and safety profiles of CYD-TDV in healthy Indian adults (ClinicalTrials.gov NCT01550289 and CTRI/2012/03/002518).

Results

A total of 189 participants were enrolled and randomized (128 in the CYD-TDV group and 61 in the placebo group) with a 2:1 ratio between 27 March 2012 and 28 June 2012. Among the 128 participants randomized in the CYD-TDV group, 127 (99.2%) received the first injection and one participant was excluded due to chronic type 2 diabetes mellitus and did not receive study injection. One hundred and 17 participants (91.4%) received the second injection, and 115 (89.8%) received the third injection. A total of 17 participants (9.0%) discontinued the study, but none were withdrawn from the study due to an SAE or AE. Overall, 172 participants completed the study (115 in the CYD-TDV group and 57 in the placebo group). The flow of participants through the study is shown in Figure 1.

The demographics and baseline characteristics are summarized in Table 1. All of the participants were of Asian ethnicity with an overall mean (±SD) age of 29.5 ± 6.9 years at enrolment. However, there was a higher proportion of male participants (151/187 [80.7%]) than female participants (36/187 [19.3%]) in the FAS and this was reflected in the composition of both vaccination groups (Table 1).

Immunogenicity

At baseline, the percentages of participants who were seropositive (PRNT<sub>50</sub> antibody titer ≥10 1/dil) for each dengue serotype were high and similar in both groups. In the CYD-TDV group, the seropositivity rate ranged from 77.0% (97/126) for serotype 4 to 84.9% (107/126) for serotype 3; in the placebo group, the seropositivity rate ranged from 80.3% (49/61) for serotypes 1 and 4 to 86.9% (53/61) for serotypes 2 and 3. The percentages of participants in the CYD-TDV and placebo groups

![Figure 1. Participant flow chart: summary of dispositions and discontinuations.](image-url)
who were seropositive at baseline and after the third injection for at least one dengue virus serotype are presented in Table 1 and Figure 2.

Balanced immune responses against all 4 serotypes were noted in the CYD-TDV group. Seropositivity rates for each dengue virus serotype increased after each injection with a more pronounced increase after the first injection (Fig. 3). GMTs in the CYD-TDV and placebo groups at baseline and after the first, second and third injections are presented in Figure 4. In the CYD-TDV group, GMTs were 2.38 to 6.11-fold higher after the third dengue injection compared with baseline. In the placebo group, GMTs remained similar to baseline after each injection with increases from baseline from 1.05 to 1.44-fold 28 days after the third injection.

GMTs after each CYD-TDV injection are summarized by baseline dengue serostatus in Figure 5 (data for the placebo-injected group are not shown). The GMTs in the dengue seropositive and dengue seronegative groups were 1.66 to 4.95-fold higher and 9.23 to 24.6-fold higher, respectively, after the third injection compared with baseline. In contrast, in the placebo groups, GMTs remained similar to baseline after each injection in both the dengue seropositive and seronegative groups but, overall, were higher in dengue seropositive participants than dengue seronegative participants 28 days after the third injection.

### Safety and Reactogenicity

A total of 188 participants (127 in the CYD-TDV group and 61 in the placebo group) received at least one injection and were included in the SAS (Table 2). One participant in the CYD-TDV group (0.8%) and one participant in the placebo group (1.6%) experienced at least one SAE (megaloblastic anemia and viral upper respiratory tract infection, respectively). Both participants recovered and neither of these events were considered related to study vaccination.

No immediate unsolicited AEs were reported during the study. However, solicited injection site reactions and solicited systemic reactions were reported by higher percentages of participants in the CYD-TDV group (9.5% and 19.0%, respectively) compared to the placebo group (4.9% and 6.6%, respectively) (Table 2). No action was taken and both reactions resolved spontaneously.

No Grade 3 solicited injection site reactions were reported after the first injection. Similarly, pain was the only reported solicited injection site reaction after the second injection in the CYD-TDV and placebo groups (2/115 [1.7%] vs 2/58 [3.4%, respectively] and after the third injection in the CYD-TDV group (3/115 [2.6%]). Erythema and swelling were not reported within 7 days after any injection.

Unsolicited AEs within 28 days after any injection were also reported by a slightly higher proportion of participants in the CYD-TDV group (9.4%) compared to the placebo group (6.6%) (Table 2). There were no immediate unsolicited AEs in either the CYD-TDV or placebo group. All unsolicited AEs were considered as non-serious in both groups and did not lead to participant discontinuation. There were no unsolicited adverse reactions and no deaths reported during the study and no virologically-confirmed cases of dengue. In the CYD-TDV group, 3/127 (2.4%) participants reported at least one non-serious AESI, suggestive of an allergic reaction (Grade 1 pruritus on the day of the first injection which resolved spontaneously on the same day (n = 2) and Grade 1 papular rash on the day of the first injection which resolved spontaneously 2 days after vaccination (n = 1)). None of these 3 participants had a medical history of

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### Table 1. Demographic characteristics and seropositivity rates for each dengue virus serotype of randomized participants at baseline (FAS)

| Characteristic                          | CYD-TDV (n = 126) | Placebo (n = 61) |
|-----------------------------------------|-------------------|-----------------|
| Mean ± SD age, years                    | 29.5 ± 7.17       | 29.6 ± 6.41     |
| Male, n (%)                             | 99 (78.6)         | 52 (85.2)       |
| Ethnicity, n (%)                        |                   |                 |
| Asian                                   | 126 (100)         | 61 (100)        |
| Flavivirus seropositive, n (%)          |                   |                 |
| CYD-TDV, tetravalent dengue vaccine; SD |                   |                 |
| Flavivirus seropositive, n (%)          |                   |                 |
| Dengue seropositive, n (%)              |                   |                 |
| Participants with PRNT50 antibody       |                   |                 |
| titer ≥ 10 l/dil against each           |                   |                 |
| dengue serotype, n (%)                  |                   |                 |
| Serotype 1                              | 105 (83.3)        | 49 (80.3)       |
| Serotype 2                              | 105 (83.3)        | 53 (86.9)       |
| Serotype 3                              | 107 (84.9)        | 53 (86.9)       |
| Serotype 4                              | 97 (77.0)         | 49 (80.3)       |

*aParticipants with at least one dengue virus serotype ≥ 10 l/dil or Japanese Encephalitis serology ≥ 10 l/dil.

*bParticipants with at least one dengue virus serotype ≥ 10 l/dil.

### Figure 2. Seropositivity rates (PRNT50 antibody titer ≥ 10 l/dil [95% CI]) against one, 2, 3 or 4 dengue virus serotypes at baseline and 28 days after each study injection given at 0, 6 and 12 months (FAS).
For all of them the suspected allergen was unknown and these AESIs were considered as not related to study vaccination. No AESIs were observed in the placebo group and no other occurrences of these AESIs were observed after the second and third injections.

**Discussion**

This was the first clinical trial of CYD-TDV in India, a country which in 2010 was estimated to have contributed approximately 34% of the global total of dengue infections. The high dengue seropositivity rates (80–87% against all 4 serotypes) at enrolment in this study in healthy Indian adults confirm the high degree of endemicity of dengue disease in India.

Overall, CYD-TDV administered at 0, 6 and 12 months produced a balanced humoral immune response against all 4 dengue serotypes in Indian adults regardless of baseline dengue immune status and displayed a satisfactory safety profile, comparable to that observed in similar trials elsewhere in Asia. The majority of participants completed the study and no safety issues with CYD-TDV were reported during vaccine administration and subsequent 6 month safety follow-up. The safety results during the 6 month observation period Indian adults are consistent with the previous phase I and II studies and the long term safety follow-up is ongoing in the Asia and Latin America efficacy trials to assess severe disease due to subsequent heterologous dengue infections.

Data published recently from the Philippines study by Capeding et al. shows the tetravalent dengue vaccine appears to have good safety within the observation period and persistence of antibodies over 5 years after the 3-dose schedule.

GMTs for neutralizing antibodies against all 4 dengue serotypes in this study in Indian adults increased irrespective of baseline dengue serostatus, but the GMTs were highest in those who were dengue seropositive at baseline in line with previous studies. Moreover, GMTs in this study were comparable with or seemed rather higher than those reported for other Asian countries where dengue endemicity is high e.g. Vietnam (adults and children) and the Philippines (adults).

Phase III lots of CYD-TDV were used in this study. The safety profile of CYD-TDV does not appear to be adversely affected by previous dengue exposure. Reactogenicity with CYD-TDV was comparable to the placebo injection and, in terms of solicited reactions and unsolicited AEs tended to be lower in both CYD-TDV and placebo groups after the second and third injection compared to the first injection. The trend toward a lower incidence of AEs with subsequent injections has also been observed in previous trials with both Phase II lots of CYD-TDV and Phase III lots. (CYD17 study, manuscript in preparation). Moreover, there was a lack of vaccine-related SAEs in line with the findings of previous studies in high endemic regions.

In conclusion, the overall immunogenicity and safety profile of CYD-TDV administered at 0, 6, 12 months was satisfactory in both dengue seropositive and dengue seronegative Indian adults.
Patients and Methods

Study design and participants

This was a multi-center, observer-blind, randomized, placebo-controlled, Phase II study of CYD-TDV in healthy adult participants in India (endemic population). The study was conducted at centers in New Delhi, Pune, Ludhiana, Bangalore and Kolkata between 27 March 2012 and 10 June 2013. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on the Harmonization-Good Clinical Practice. Written informed consent was obtained from all participants before study entry. An independent data monitoring committee (IDMC) oversaw the conduct of the study and was involved in the review of all deaths, related serious adverse events (SAEs) and virologically-confirmed dengue cases.

Individuals aged 18 to 45 years in good health based on medical history and physical examination, able to attend all study visits and to comply with study procedures, were eligible for participation in this study. Participants were ineligible if they: had febrile illness (temperature $\geq 38.0^\circ$C) or moderate or severe acute illness/infection on the day of vaccination; had known seropositivity for human immunodeficiency virus (HIV), hepatitis B, and hepatitis C; had known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy within the previous 6 months, or long-term systemic corticosteroid therapy (prednisone or equivalent for $>2$ consecutive weeks within the previous months); had receipt of blood or blood-derived products in the previous 3 months that might interfere with assessment of immune responses; were in receipt of (or planned receipt of) any vaccine in the 4 weeks preceding or following any trial vaccination. Pregnant or lactating women were also ineligible for inclusion and all female participants were required to be of non-child-bearing potential (i.e., post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or

Table 2. Solicited and unsolicited adverse events and adverse reactions after any injection (SAS).

| Participants experiencing at least one: | CYD-TDV group | Placebo group |
|----------------------------------------|--------------|--------------|
|                                       | n/N | % (95% CI) | n/N | % (95% CI) |
| Immediate unsolicited AE               | 0/127 | 0 (0.0; 2.9) | 0/61 | 0 (0.0; 5.9) |
| Immediate unsolicited AR               | 0/127 | 0 (0.0; 2.9) | 0/61 | 0 (0.0; 5.9) |
| Solicited reaction                     | 27/126 | 21.4 (14.6; 29.6) | 5/61 | 8.2 (2.7; 18.1) |
| Solicited injection site reaction      | 12/126 | 9.5 (5.0; 16.0) | 3/61 | 4.9 (1.0; 13.7) |
| Solicited systemic reaction            | 24/126 | 19.0 (12.6; 27.0) | 4/61 | 6.6 (1.8; 15.9) |
| Unsolicited AE*                        | 12/127 | 9.4 (5.0; 15.9) | 4/61 | 6.6 (1.8; 15.9) |
| Unsolicited AR*                        | 0/127 | 0 (0.0; 2.9) | 0/61 | 0 (0.0; 5.9) |
| SAE†                                   | 1/127 | 0.8 (0.0; 4.3) | 1/61 | 1.6 (0.0; 8.8) |
| SERIOUS AESI†                          | 0/127 | 0 (0.0; 2.9) | 0/61 | 0 (0.0; 5.9) |
| Non-serious AESI**                     | 3/127 | 2.4 (0.5; 6.7) | 0/61 | 0 (0.5; 6.7) |

n: number of subjects experiencing the endpoint listed in the first column; N: number of subjects with available data for the relevant endpoint.
AE, adverse event; AR, adverse reaction; AESI, adverse event of special interest; SAE, serious adverse event.
*Within 28 days after injection.
†Includes serious adverse events and serious adverse events of special interest throughout the trial.
‡Throughout the trial.
**Within 7 days after injection.
were abstinence from at least 4 weeks prior to the first vaccination and until at least 4 weeks after the last vaccination. Women who became pregnant during the study were not to be vaccinated further. Contraindications for the second or third CYD-TDV doses included: evidence of anaphylactic or other significant allergic reaction to the previous study vaccination; an ongoing clinical adverse event (AE) related to the previous study vaccination or SAE following the previous study vaccination.

Participants were randomized 2:1 at enrolment by study site personnel via an interactive voice response system/interactive web response system (IVRS/IWRS), using a permuted block method with block size of 9 and stratification by site. A double randomization system was used, such that the participant treatment allocation was separated from dose dispensing. Each dose had both a code number and a dose number. The code number was used by the IVRS while the dose number was entered in the participant’s eCRF. The unique dose numbers were defined according to a random list to ensure that dose numbers could not be used to distinguish between treatment groups.

Participants received a 3-dose primary series of subcutaneous injections of CYD-TDV or an inactive placebo (0.5 mL NaCl 0.9% solution) in the deltoid region of the upper arm at visits 0, 6, and 12 months, followed by a 6-month safety follow-up. Observers, investigators, the sponsor and participants were all blinded to the allocation of study injections. Phase III lots of CYD-TDV (Sanofi Pasteur S.A., France) were supplied as powder and solvent for suspension for subcutaneous injection. Each 0.5 mL injection of reconstituted vaccine contained 4.5–6.0 log10 cell-culture infectious dose 50% (CCID50) of each live, attenuated, recombinant dengue serotype 1, 2, 3, 4 virus. The solvent consisted of NaCl 0.4%.

**Immunogenicity**

Blood samples were taken for determination of antibody responses at baseline and 28 days after each study injection. Serum levels of neutralizing antibodies against each of the 4 parental dengue strains of CYD-TDV were determined using a 50% plaque reduction neutralization test (PRNT50) as described elsewhere. The lower limit of quantitation (LLOQ) of the assay was 10 (1/dilution [dil]). Geometric mean titres (GMTs) were calculated.

**Safety and reactogenicity**

Participants were kept under observation for 30 minutes after each trial injection to assess the occurrence of any immediate AEs. AEs monitored throughout the study included: unsolicited systematic AEs within 30 minutes of each injection; solicited injection site reactions (tenderness, redness, and swelling) up to 7 days after each injection; solicited systemic reactions (headache, fever, malaise, myalgia and asthenia) up to 14 days after each injection; unsolicited AEs up to 28 days after each vaccination; SAEs throughout the trial; and adverse events of special interest (AESIs) considered to be relevant for the monitoring of the safety profile of CYD-TDV. AESIs included: hypersensitivity/allergic reactions within 7 days; serious viscerotropic disease and serious neuropsychiatric disease within 30 days; and serious dengue disease at any time during the study. AE data after the initial 30-minute observation period were collected using diary cards with the specific solicited adverse reactions and an open field for unsolicited AEs. AEs were classified according to the following scale: Grade 1, no interference with activity; Grade 2, some interference with activity; and Grade 3, significant (prevents daily activity). Investigators assessed the causal relationship of each unsolicited systematic AE and vaccination and the participants rated the intensity of solicited and unsolicited AEs on their diary cards. SAEs were defined as events that were life-threatening or resulted in death, required in-patient hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability or incapacity, resulted in a congenital anomaly or birth defect, or were regarded as an important medical event. Participants were followed up at 6 months after the last injection for information on AEs occurring since the last visit.

**Detection of symptomatic cases**

Participants with suspected dengue, defined as febrile episodes (temperature ≥38°C) on at least 2 consecutive days, were assessed for dengue infection. The following tests were performed to virologically confirm any potential dengue case: dengue reverse transcriptase polymerase chain reactions (RT-PCRs), dengue non-structural protein (NS) 1 antigen (Ag) enzyme-linked immunosorbent assay (ELISA) and immunoglobulin (Ig) M/IgG ELISA. If a sample was positive for the wild type (WT) dengue RT-PCR and/or the NS1 assay was positive, then it was classified as a virologically-confirmed dengue infection.

**Statistical Methods and Analysis Populations**

Analyses were descriptive and no hypotheses were tested. The sample size was set to 126 participants for the CYD-TDV group to provide a 95% probability of observing an event that had a true incidence of 2.38% in this group. For the main parameters, 95% confidence intervals (CI) of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions. Analyses were performed on all available data, with no replacement of missing data. The full analysis set (FAS) for immunogenicity included all participants who received at least one dose of CYD-TDV or placebo and had at least one valid serology result after study injection. The safety analysis set (SAS) comprised of participants who received at least one dose of CYD-TDV or placebo injection.

**Disclosure of Potential Conflicts of Interest**

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