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Immunogenicity and safety of a tetravalent dengue vaccine during a five-year follow-up period

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ABSTRACT

This study assessed the safety and persistence of dengue neutralising antibodies for five years after administration of a recombinant live, attenuated, tetravalent dengue vaccine (TDV). Participants aged 2–45 years ($n = 126$) were randomised at a single centre in the Philippines to receive TDV vaccinations at months 0, 3–4, and 12 (TDV–TDV–TDV group) or licensed typhoid vaccination (TyVi) at month 0 and TDV at months 3–4 and 12 (TyVi–TDV–TDV group). Dengue antibodies were measured annually (plaque reduction neutralisation test). Participants with suspected dengue underwent laboratory testing. No safety concerns were reported throughout the study. Six dengue cases were virologically confirmed, but assessed as non-severe dengue disease. Geometric mean titres throughout the follow-up period remained 2- to 4-fold higher than at baseline for all serotypes, ages and study groups. Approximately 10% of participants annually were exposed to wild-type dengue, which contributed to persistently higher titres compared with non-infected participants. In conclusion, TDV appears to have good safety and persistence of antibodies over five years.

Introduction

Dengue is an important vector-borne infectious disease globally, and represents a significant health burden in tropical and subtropical regions of the world where it is endemic [1]. An estimated 50–100 million dengue infections occur annually worldwide, resulting in over 2 million cases of dengue disease. There are currently no specific antiviral treatments for dengue, and infection control measures are mainly limited to environmental risk reduction such as elimination of mosquito populations. A recombinant yellow fever-17D–dengue virus, live, attenuated, tetravalent dengue vaccine (TDV) is currently in development and has already undergone extensive clinical trials to date [2–10].

A Phase I study was conducted in the Philippines, a country endemic for dengue, to assess the safety and immunogenicity of TDV over a five-year follow-up period. The aim of this study was to describe safety and persistence of antibodies up to five years following administration of TDV, as well as the number of dengue cases through passive surveillance of febrile episodes and the incidence of dengue infection. Safety and immunogenicity data during the 12 month vaccination schedule and up to 28 days after the last vaccination has previously been reported [11]. Here we report follow-up to five years after the last vaccination.

Methods

The study design, inclusion and exclusion criteria, and vaccination schedule have been described in detail elsewhere [11]. In brief, 126 participants aged 2–45 years were randomised at a single study centre in the Philippines to receive three TDV injections at 0, 3–4 and 12 months (TDV–TDV–TDV group; $n = 84$) or one injection with a licensed control typhoid vaccine (TyphimVi®) at month 0, followed by two TDV injections at 3–4 and 12 months (TyVi–TDV–TDV group; $n = 42$). Participants were followed-up for five years after the last study injection. Serious adverse events (SAEs) were recorded throughout the study. Pregnancy outcomes were reported for the first two years of follow-up. Diagnostic tests for laboratory-confirmation of dengue infection (dengue NS1 antigen Enzyme-Linked Immunosorbent Assay [ELISA](Platelia™, Bio-Rad Laboratories), serotype-specific dengue reverse transcriptase

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polymerase chain reaction [RT-PCR], dengue IgM/IgG ELISA) [7] were performed in participants with suspected dengue i.e., participants with febrile episodes (temperature ⩾38 °C for ⩾48 h) during the first four years of follow-up and hospitalised cases only during the fifth year. Serological confirmation of dengue infection was defined as presence of dengue IgM and/or IgG, and virologically confirmed by detection of dengue NS1 antigen and/or amplified genomic sequences. Serum samples for immunogenicity analyses were taken at baseline, 28-days after each study injection and annually after the last injection. Serum neutralising antibody levels to each of the four parental wild-type dengue virus strains were determined using a 50% plaque reduction neutralisation test ($PRNT_{50}$) [12]. Exposure to wild-type dengue was defined as a 4-fold increase in $PRNT_{50}$ antibody titre (and with a resultant titre ⩾40) for at least one serotype between two consecutive years (with no missing data for any serotype at both time points). No hypothesis testing was carried out in this study; descriptive statistics were used to summarise the data. Geometric mean titres (GMTs) were determined with and without exclusion of participants who had been exposed to wild-type dengue.

It should be noted that an optimised PRNT assay was developed and validated for assessment of vaccine immunogenicity during the follow-up period. Baseline, post-vaccination and follow-up samples from the study were then tested with this single assay to generate a complete dataset, [12] as such the GMTs reported here for baseline and after the third vaccination differ from those reported previously [11].

Results

A total of 126 participants received study vaccination at month 0 of the study, of whom 113 completed the five year follow-up. The baseline characteristics of the participants are summarised elsewhere [11].

There were no vaccine-related SAEs reported during the five year follow-up period in either study group. Only two SAEs were reported; both occurred during the fifth year of follow up in the TDV–TDV–TDV group. The first was a hospitalisation for myofascial pain syndrome in a 19 year old female participant, and the second a dengue episode in a 10 year old boy who was hospitalised with fever, abdominal pain, and vomiting. The hospitalised boy had virologically-confirmed dengue (serotype 1), but did not have severe dengue according to the World Health Organization 2009 classification (i.e. no sign of shock, haemorrhage, plasma leakage, or thrombocytopenia) and recovered four days after fever onset and discharged two days later (6 days after fever onset). Four women became pregnant during follow up; none of these pregnancies were exposed to vaccination. There were no complications with the pregnancies and the women delivered healthy babies.

During the first four years of follow up, 53 febrile episodes (suspected dengue disease) were reported by 34 participants (20 in the TDV–TDV–TDV group and 14 in the TyVi–TDV–TDV group), most of whom ($n = 28$) were children aged 2–11 years. Among the suspected dengue disease cases in the first four years (three in the TDV–TDV–TDV group and three in the TyVi–TDV–TDV group), six were laboratory confirmed and of these, five were virologically confirmed (Table 1). In the case where dengue was laboratory confirmed but not virologically confirmed, the subject was positive for anti-dengue IgG and IgM but negative for RT-PCR and NS1 Ag. During the fifth year of follow-up, one additional dengue case (virologically confirmed) was reported in a boy in the 2–5 year old group (Table 1). Overall, of the seven dengue cases that occurred during this study, four subjects were dengue seropositive and three subjects were seronegative at baseline (prior to vaccination).

Fig. 1 summarises the serotype specific seropositivity rates (titres >10) during follow up across the two study groups. The GMTs for the four dengue serotypes decreased during follow up. The decrease was most pronounced within the first year post-vaccination, but remained 2- to 4-fold higher than at baseline over the five years of follow-up for all serotypes, age groups and study groups. There was little difference in GMTs for each serotype between the two groups for the duration of follow up (Supplementary Fig. 1). Natural exposure to wild-type dengue, as determined by a 4-fold increase in $PRNT_{50}$ titre (and with a resultant titre ⩾40), occurred in approximately 10% of participants each year (35 out of 77 participants in the TDV–TDV–TDV group had evidence of at least one episode of exposure to wild-type dengue). Participants with no evidence of natural exposure to wild-type dengue in the TDV–TDV–TDV group had generally lower seropositivity rates (data not shown), particularly over time, and lower GMT levels for all dengue serotypes compared with all participants throughout follow up (Fig. 2), suggesting that natural exposure to wild-type dengue boosted immunogenicity of all serotypes. The same trends regarding antibody persistence and natural exposure

Table 1
Laboratory-confirmed dengue cases during the five-year follow-up period.

Time of occurrence*	Group	Age	Pre-infection $PRNT_{50}$ antibody titres to infecting serotype	Serology		NSI Ag	RT-PCR	Virologically confirmed	Hospitalised
				IgM	IgG				
1st year follow-up	TDV–TDV–TDV	6–11 years	DEN-1: 41; DEN-2: 96; DEN-3:143; DEN-4: 19	Positive	Positive	Positive	Negative	Yes	No
2nd year follow-up	TDV–TDV–TDV	2–5 years	DEN-1: < 10; DEN-2: 43; DEN-3:<10; DEN-4: 87	Positive	Positive	Positive	Negative	Yes	No
3rd year follow-up	TyVi–TDV–TDV	2–5 years	DEN-1: 53; DEN-2: 215; DEN-3: 5659; DEN-4: 303	Positive	Positive	Negative	Negative	No	No
4th year follow-up	TDV–TDV–TDV	2–5 years	DEN-1:<10; DEN-2: 36; DEN-3: 37; DEN-4: 36	Positive	Positive	Positive	Serotype 1	Yes	No
4th year follow-up	TyVi–TDV–TDV	6–11 years	DEN-1:<10; DEN-2:<10; DEN-3:<10; DEN-4:<10	Positive	Positive	Positive	Serotype 2	Yes	No
4th year follow-up	TyVi–TDV–TDV	12–17 years	DEN-1: 88; DEN-2: 86; DEN-3: 2057; DEN-4: 86	Negative	Negative	Positive	Serotype 1	Yes	No
5th year follow-up	TDV–TDV–TDV	2–5 years	DEN-1:<10; DEN-2:<10; DEN-3: 51; DEN-4: 31	Positive	Positive	Positive	Serotype 1	Yes	Yes

IgG, Gamma immunoglobulin; IgM, M immunoglobulin; N/A, not available; $PRNT_{50}$, 50% plaque reduction neutralising test; RT-PCR, reverse transcriptase polymerase chain reaction.

* During the first four years of follow-up, laboratory tests to confirm dengue infection were performed in all participants with suspected dengue i.e. with febrile episodes (temperature ⩾38 °C for ⩾48). In the 5th year of the follow-up, these tests were performed in hospitalised cases only.