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Tetravalent Dengue Vaccine: A Review in the Prevention of Dengue Disease

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Abstract Tetravalent, live-attenuated, dengue vaccine (Dengvaxia®; CYD-TDV) is the first vaccine approved for the prevention of dengue disease caused by dengue virus (DENV) serotypes 1–4 in individuals aged 9–45 or 9–60 years living in high dengue endemic areas. This narrative review discusses the immunogenicity, protective efficacy, reactogenicity and safety of CYD-TDV in the prevention of dengue disease. In Latin American and Asian phase 3 trials in children and adolescents ($n > 30{,}000$), the recommended three-dose CYD-TDV regimen was efficacious in preventing virologically-confirmed dengue (VCD) during the period from 28 days after the last dose (month 13) to month 25, meeting the primary endpoint criteria. Protective efficacy against VCD in the respective individual trials was 60.8 and 56.5 % (primary analysis). During the 25-month active surveillance phase, CYD-TDV also provided protective efficacy against VCD, severe dengue, any grade of dengue haemorrhagic fever and VCD-related hospitalization in children aged 9 years and older. CYD-TDV was generally well tolerated, with no safety concerns identified after up to 4 years' follow-up (i.e. from post dose 1) in ongoing long-term studies. Based on evidence from the dengue clinical trial program, the WHO SAGE recommended that countries with high dengue endemicity consider introducing CYD-TDV as part of an integrated disease prevention strategy to lower disease burden. Pharmacoeconomic considerations will be pivotal to implementing dengue vaccination prevention strategies in these countries. The availability of a dengue vaccine is considered essential if the 2012 WHO global strategy targets for reducing the burden of dengue disease by 2020 are to be attained. Hence, CYD-TDV represents a major advance for the prevention of dengue disease in high dengue endemic regions.

Tetravalent dengue vaccine (CYD-TDV): clinical considerations in the prevention of dengue disease

Robust immunogenic responses elicited against all DENV serotypes (1–4), with high DENV seropositivity rates after each CYD-TDV dose

Provides protective efficacy against VCD in children (aged ≥9 years), with similar or higher efficacy predicted in adults (aged 18–60 years)

Also provides protective efficacy against severe dengue disease and hospitalization for VCD

WHO recommends that countries with high dengue endemicity consider introducing CYD-TDV as part of an integrated disease prevention strategy to lower disease burden

Generally well tolerated; most adverse reactions are of mild to moderate intensity and transient, with no safety concerns identified after 4 years' follow-up

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1 Introduction

Dengue disease is one of the most important mosquito-borne viral diseases [1, 2]. The disease has reached epidemic proportions globally and imposes a significant disease and economic burden in endemic tropical and subtropical regions (e.g. Asia-Pacific and Latin American countries), with about 50 % of the world's population living in these at-risk areas (≈75 % of whom live in the Asia-Pacific region) [1, 2]. In 2013, the estimated total annual global costs of dengue illness was approximately $US9 billion, involving ≈58.4 million symptomatic dengue virus (DENV) infections [3]. Over the last five decades, the incidence of dengue has increased 30-fold, with the WHO estimating that 50–100 million infections occur annually [1]. However, the real burden of the disease is most likely much higher, reflecting factors such as under-reporting of the disease, the asymptomatic or mild nature of most cases and misdiagnosis of the disease in up to 50 % of cases [1, 2, 4, 5]. Indeed, recent epidemiological [6–13] and modelling [14] studies suggest that the incidence of dengue is markedly higher, with a disease distribution model estimating the annual incidence of dengue infections was ≈390 million [14].

About 5–10 % of patients with dengue infection (either with a primary or subsequent infection) develop potentially life-threatening, severe dengue haemorrhagic fever (DHF), which is characterized by increased capillary permeability leading to plasma leakage and ultimately, to haemodynamic shock and dengue shock syndrome [15, 16]. There are no specific treatments for dengue infections; however, with appropriate and timely triage of patients in hospital and relevant medical treatment (primarily maintenance of the patient's body fluid), the risk of death from severe dengue disease is reduced from more than 20 % to less than 1 % [2, 15]. In most Asian and Latin American countries, severe dengue infections are a leading cause of serious illness and death in children [1, 2], with dengue posing a substantial burden of disease in both regions, albeit this burden is highly variable between different countries [17].

Dengue infection is caused by one of four closely-related, but distinct, DENV serotypes (DENV1, DENV2, DENV3 and DENV4) of the genus Flavivirus [2, 15]. Natural infection with one of these DENV serotypes is hypothesized to provide life-long, serotype-specific protective immunity against a subsequent infection with that DENV serotype; however, only transient protection through cross-reactive immunity is provided against infection with any of the other DENV serotypes [2]. Moreover, subsequent infection with another DENV serotype is associated with the development of more severe disease, with T cell immunopathological responses initiated early in the course of the disease and antibody-dependent enhancement (ADE) amongst one of the factors involved in the pathogenesis of severe dengue disease [15, 18]. Hence, one of several challenges in developing an effective vaccine for the prevention of dengue was the necessity to provide protective immunity against all four serotypes simultaneously [15, 18]. Ideally, a dengue vaccine should be administered as one or two doses, provide protection against all four DENV serotypes (i.e. a tetravalent vaccine), exhibit long-term protective efficacy and have no significant side effects [1, 15].

Currently, the first and only vaccine approved for use in endemic populations for the prevention of dengue is the recombinant tetravalent, live-attenuated, yellow-fever-dengue virus vaccine (Dengvaxia®; hereafter referred to as CYD-TDV). CYD-TDV consists of live-attenuated CYD vaccine virus serotypes expressing the structural genes encoding the membrane protein and envelope protein of each of the four dengue serotypes and the attenuated yellow fever (YF) 17D virus strain genetic backbone [19–23]. This narrative review discusses the immunogenicity, protective efficacy, reactogenicity and safety of CYD-TDV in the prevention of dengue disease in endemic populations.

2 Immunogenicity of Tetravalent Dengue Vaccine

2.1 In Preclinical Studies

The recombinant, live-attenuated DENV vaccine for each specific serotype expresses the pre-membrane and envelope genes of that specific wild-type DENV on a YF 17D backbone, with each vaccine produced in serum-free Vero cells using recombinant DNA technology [23, 24]. The four recombinant DENV serotype viruses are combined into a single freeze dried vaccine (i.e. CYD-TDV) containing no preservative or adjuvant; the dose of each DENV serotype in the vaccine is 4.5–6 $\log_{10}$ of the 50 % cell culture infective dose ($CCID_{50}$) [23, 24]. The four wild-type DENVs used in the construction of CYD-TDV are the PUO-359/TVP-1140 Thai strain for serotype 1, the PUO-218 Thai strain for serotype 2, the PaH881/88 Thai strain for serotype 3 and the 1228 (TVP-980) Indonesian strain for serotype 4 [24].

In vitro and in vivo studies demonstrated high genetic and phenotypic stability of CYD1–4 viruses from early passages to bulk production stages [19, 24]. In cultured human monocyte-derived dendritic cells (mDC), each of the four CYD dengue virus serotypes induced high mannose, hybrid and complex glycosylation at the asparagine 67 and 153 residues of the envelope protein [25]. Envelope

protein glycosylation is pivotal for DENV-host cell receptor interactions [e.g. those with DC-specific intracellular adhesion molecule-3 grabbing non-integrin (DC-SIGN) molecules] and subsequent entry into host cells [25]. In mDC, the growth kinetics of CYD1–4 viruses were similar to those of their respective parent strains, with infection leading to maturation of cells and controlled immune responses involving limited inflammatory cytokine production and consistent expression of anti-viral type 1 interferon (IFN) [19, 24]. In monkeys, CYD-TDV induced effective immunogenic responses, with limited viraemia, and protected against infection with wild type DENV 1, 2, 3 and 4 [19, 24].

There are several hypothesized risks associated with the use of recombinant vaccine viruses, with potential key concerns including transmission by arthropod vectors, reversion to virulence, recombination with circulating viruses, the risk of viscerotropism (a rare serious adverse effect associated with YF 17D vaccination; incidence $\approx$0.4/100,000) and neurotropism (both related to the YF virus backbone), and sensitization/ADE effects [19, 24]. Given that YF 17D envelope genes are missing from CYD-TDV and numerous reversions in NS genes and the core protein gene would be required for reversion to a wild-type YF, it is not possible to create a wild type YF virus in CYD-TDV vaccinees [19]. The absence of recombinant viruses in forced in vitro systems suggests that it is highly unlikely that natural recombination of DENV will occur. Furthermore, should recombination with circulating viruses occur, they would not cause disease or spread in the environment based on evidence from artificial recombinants. The potential risks of viscerotropism and neurotropism occurring in CYD-TDV vaccinees and for ADE to occur were also addressed in CYD-TDV clinical trials, with ongoing assessment planned in postmarketing surveillance programs. In cell culture studies, dengue viruses in the CYD-TDV vaccine were less hepatotropic and less neurotropic than the YF 17D virus. Moreover, no serotype-specific differences that could be linked to variations in efficacy in phase 3 trials were identified in in vitro ADE assays [19].

2.2 In Clinical Trials

This section focuses on large ($n > 150$), observer-blinded, placebo-controlled, multicentre, phase 2 [26–28] or 3 [29] trials in healthy children and/or adults that evaluated the immunogenicity of the recommended three-dose regimen (given at 0, 6 and 12 months) of CYD-TDV (Table 1). All studies were conducted in line with WHO guidelines for the development of live-attenuated vaccines. These data are supported by results from phase 2b [30] and 3 [31, 32] protective efficacy trials ($n > 4000$ randomized/trial [30–32]) discussed in Sect. 3 (Table 1), and single-centre, phase 2 immunogenicity trials ($n \geq 150$) [13, 33, 34], all of which used the same three-dose CYD-TDV vaccination schedule. Evidence from phase 1 studies provides further support for the immunogenicity of CYD-TDV [35–37]. The equivalence of immune responses elicited by three consecutive batches of CYD-TDV from the scaled-up production process was shown in a placebo-controlled, multicentre study in flavivirus-naive adults [38].

Immunogenicity was assessed at baseline and 28 days after each dose using the plaque reduction neutralization test (PRNT), with geometric mean titres (GMTs) expressed as the highest reciprocal serum dilution (dil^{-1}) at which the mean number of plaques was reduced by 50 % compared with control wells (i.e. the $PRNT_{50}$ antibody titre) [26–32]. For each individual DENV serotype, a $PRNT_{50}$ antibody titre of $\geq$10 dil^{-1} was considered seropositive.

In multicentre phase 2 and 3 trials in children and/or adults living in various endemic countries/regions, robust immune responses were elicited against all DENV serotypes after each of the three doses of CYD-TDV, with GMTs at baseline and 28 days after the third dose summarized in Table 1 [26–32]. There were minimal changes in GMTs for all DENV serotypes in the control groups (Table 1). Robust immune responses against all DENV serotypes were elicited irrespective of the individual's flavivirus status [28, 29] or age at baseline [27, 29].

Factors influencing the immunogenic response to CYD-TDV were the flavivirus serostatus at baseline, the individual's age and the region, based on individual trials and pooled analyses [23, 28, 29, 39]. The flavivirus serostatus of an individual is a partially confounding factor of age, with older individuals in endemic areas more likely to have been exposed to DENV and consequently, more likely to be flavivirus seropositive [23, 29]. Indeed, the older the person, the higher the DENV GMT prior to the first dose and the greater the increase in DENV GMT 28 days after the third dose (i.e. GMTs 28 days after the third dose increase as a function of age) [23]. In a pooled analysis of five phase 2 trials, immune responses after the third dose of CYD-TDV were primarily determined by baseline immunological status against DENV serotypes and by trial region, with higher GMTs observed at baseline and after each CYD-TDV dose in individuals enrolled in Latin American trials than in Asian trials [39]. These data were confirmed in an integrated analysis of 11 trials evaluating the three-dose regimen of CYD-TDV in children, adolescents and adults (aged $\leq$60 years) living in the Asia-Pacific region and Latin America, with greater increases from baseline in DENV GMTs after the third dose observed with increasing age and with higher endemicity (abstract) [40]. In a subgroup analysis of participants from Australia,

Table 1 Immunogenicity of tetravalent dengue vaccine (CYD-TDV) in multicentre phase 2 [26–28, 30] or 3 [29, 31, 32] trials in healthy individuals aged 2–11 [29], 4–11 [30], 2–14 [31], 9–16 [26, 32], 2–45 [27] or 18–45 [28] years

Study (country/region)	Group (no. of individuals[a])	GMT (dil^{-1})[b]				Seropositivity (i.e. $PRNT_{50}$ titres ≥10 dil^{-1}) (% of individuals)			
		DENV1	DENV2	DENV3	DENV4	DENV1	DENV2	DENV3	DENV4
Capeding et al. [31] (Asia)	CYD-TDV BL (≤1313)	38.3	55.3	40.1	25.3				
	CYD-TDV post dose 3	166	355	207	151				
	PL BL (≤655)	42.1	62.1	40.7	26.2				
	Pl post dose 3	46.6	68.5	42.5	26.0				
Dubey et al. [28] (India)	CYD-TDV BL (126)	NE	NE	NE	NE	83	83	85	77
	CYD-TDV post dose 3	NE; 2.38-fold to 6.11-fold higher than BL				99[c]	99[c]	100[c]	100[c]
	PL BL (61)	NE	NE	NE	NE	80	87	87	80
	PL post dose 3	NE; 1.05-fold to 1.44 fold higher than BL				87[c]	90[c]	88[c]	83[c]
Hss et al. [29] (Malaysia)	CYD-TDV BL (196)	15.3	15.9	15.6	9.9	58[c,d]/0[d]	50[c,d]/0[d]	70[c,d]/0[d]	47[c,d]/0[d]
	CYD-TDV post dose 3	151	180	193	114	98[c,d]/98[c,d]	98[c,d]/98[c,d]	100[c,d]/100[c,d]	99[c,d]/98[c,d]
	PL BL (50)	18.6	18.6	15.9	12.3	32	30	36.7	30
	PL post dose 3	18.9	16.3	16.3	10.9	NR	NR	NR	NR
Leo et al. [27] (Singapore)	CYD-TDV BL (438)	8.1	9.0	8.5	6.9				
	CYD-TDV post dose 3	43	69.7	96	100				
	PL[e] BL (147)	8.3	8.5	9.2	6.8				
	PL[e] post dose 3	8.5	8.2	8.9	7.8				
Sabchareon et al. [30] (Thailand)	CYD-TDV BL (197)	42.8	56.8	31.5	28.1				
	CYD-TDV post dose 3	146.1	310	405	155				
	PL BL (99)	26.6	43.7	28.7	23.2				
	PL post dose 3	23.9	52.2	48.9	19.4				
Villar et al. [32] (Latin America)	CYD-TDV BL (1301)	128	138	121	44				
	CYD-TDV post dose 3	395	574	508	241				
	PL BL (643)	119	115	114	39.0				
	PL post dose 3	121	129	124	44.3				
Villar et al. [26] (Latin America)	CYD-TDV BL (401)	74.2	92.6	85.0	37.2	65[c]	70[c]	70[c]	63[c]
	CYD-TDV post dose 3	320	486	594	273	95[c]	99[c]	100[c]	99[c]
	PL BL (199)	81.9	100	88.8	40.1	68[c]	73[c]	72[c]	70[c]
	PL post dose 3	106	133	121	42.8	75[c]	76[c]	73[c]	70[c]

BL baseline, *DENV* dengue virus serotype, *GMT* geometric mean titre, *NE* not estimable from graph, *NR* not reported, *PL* placebo, *$PRNT_{50}$* 50 % plaque reduction neutralization test

[a] Full analysis set for immunogenicity

[b] At BL and 28 days post dose using $PRNT_{50}$ titres; expressed as the highest reciprocal (dil^{-1}) serum dilution at which the mean number of plaques was reduced by 50 % compared with control cells

[c] Value estimated from graph

[d] Data are for subjects who were seropositive at BL/seronegative at BL. In the overall CYD-TDV group, 31.1, 27.6, 36.7 and 24.0 % of subjects were seropositive at BL for DENV1, DENV2, DENV3 and DENV4, respectively

[e] A saline PL injection for the first dose; for subsequent doses, a Singapore licensed hepatitis A or influenza vaccine was given

increases from baseline in DENV GMTs after the third dose were similar in the overall adult population (aged 18–60 years; $n = 655$) to those in older adults (aged 45–60 years; $n = 241$) [40].

In general, seropositivity rates against DENV serotypes were relatively high at baseline and increased after each dose of CYD-TDV [26–29]. Where reported, seropositivity rates of ≥95 % for each of the DENV serotypes were achieved after the third dose of CYD-TDV (Table 1) [26, 28, 29]. DENV seropositivity rates were similar after the third dose of CYD-TDV, irrespective of the individual's baseline serostatus [26, 29].

A single dose of CYD-TDV elicited robust immune responses in adults participating in a phase 2a study [41]. Compared with flavivirus-naive individuals ($n = 12$), immune responses increased in those who had been previously been immunized with a YF vaccine ($n = 8$) or a monovalent dengue vaccine (DENV1 or DENV2 vaccines; $n = 15$) [41].

Antibody responses to CYD-TDV against each of the DENV serotypes persisted at 5 years' follow-up in a single-centre, phase 1 study conducted in the Philippines in individuals aged 2–45 years ($n = 126$) [42]. GMTs remained twofold to fourfold higher than baseline throughout the follow-up period, irrespective of the individuals age and flavivirus serostatus [42]. In the phase 1 study, participants had received three doses of CYD-TDV given at 0, 3–4 and 12 months or a dose of a licensed typhoid vaccine given at 0 months followed by doses of CYD-TDV given at 3–4 and 12 months [35].

In individuals 9 years of age and older living in endemic dengue regions, DENV GMTs for all serotypes decreased 1 year after the third injection, with a trend thereafter towards long-term stability of GMTs [23]. Reductions in DENV GMTs were affected by the individual's age and flavivirus serostatus prior to the initial vaccination, although long-term DENV GMTs remained higher than pre-vaccination levels in all individuals [23].

In clinical trials [43–45], CYD-TDV induced CYD-specific cell-mediated T helper 1 (Th1) immune responses and anti YF 17D NS3 specific CD8 responses in the absence of pro-inflammatory Th2 responses, with these data supported by preclinical studies [19, 24, 46]. For example, in a subgroup analysis of 80 adolescents and adults participating in a phase 2 trial (see Table 1 for trial design details [27]), CYD-TDV vaccination induced YF 17D NS3-specific CD8 cellular responses in all participants, with increased IFN-γ secretion relative to tumour necrosis factor-α and low levels of interleukin 13 secretion [43]. After the first dose of CYD-TDV, cell mediated responses were mainly elicited against DENV4 serotype, whereas responses against all DENV serotypes were elicited after the third dose. Cell-mediated immune responses to CYD-TDV were maintained at 1 year of follow-up, albeit at twofold to threefold lower levels [43].

3 Protective Efficacy of Tetravalent Dengue Vaccine

The protective efficacy of CD-TDV against virologically-confirmed dengue (VCD) infection was investigated in observer-blinded, placebo-controlled, multinational trials in healthy children and adolescents (aged 2–14 years [31] and 9–16 years [32]) living in endemic regions in Asia ($n = 10,275$ randomized) [31] and Latin America ($n = 20,869$) [32]. Protective efficacy data from these pivotal phase 3 trials are supported by results from a single-centre, phase 2, proof-of-concept trial [$n = 3673$ in per-protocol (PP) efficacy population] conducted in Thailand, in which the protective efficacy across all DENV serotypes was 30.2 % (95 % CI −13.4 to 56.6; $p = 0.034$) [30]. Pooled efficacy data from the two phase 3 trials are also discussed [47].

The pivotal phase 3 trials consisted of a 25-month active-surveillance, observer-blinded phase, followed by an ongoing single-blind, long-term, follow-up safety phase; the safety phase will continue for a total of 6 years after enrolment [47]. Key criteria for excluding participants included the presence of a contraindication for receiving CYD-TDV (see Sect. 5), having received another vaccine (until 4 weeks post vaccination), participation in another trial investigating a vaccine, drug, medical device or a medical procedure in the 4 weeks preceding the first vaccination in this trial, and receiving blood or blood-derived products in the previous 3 months that could interfere with the assessment of the immune response [31, 32]. Children were randomized (2:1) to vaccination with three doses of CYD-TDV or placebo (0.9 % saline) given at 6-monthly intervals [31, 32].

In accordance with WHO guidelines, the primary objective was to estimate vaccine efficacy against symptomatic VCD, irrespective of severity or DENV serotype, that occurred more than 28 days after the third dose (i.e. 13 months) until month 25 in children who received all three injections according to protocol and had no specified exclusion criteria (i.e. PP population) [31, 32]. Key secondary endpoints included vaccine efficacy against VCD caused by any serotype after the first injection (i.e. between month 0 and 25) in the intent-to-treat (ITT) population (i.e. participants who received ≥1 injection) and protective efficacy for each serotype for episodes occurring between 13 and 25 months in the modified PP (mPP) population (i.e. children who had received all three doses, irrespective of protocol deviations) [31, 32]. The algorithm for determining efficacy used a quantitative reverse transcriptase-polymerase chain reaction assay for virological confirmation of dengue infection and an enzyme-linked immunosorbent assay to determine the presence of dengue NS1 antigen [31, 32, 48].

In primary analyses in the PP population, the protective efficacy from month 13 to 25 after three doses of CYD-TDV was 56.5 [31] and 60.8 % [32], with the primary endpoint met as the lower bound of the 95 % CI exceeded 25 % (Table 2). These results were confirmed in ITT analyses of each individual trial (Table 2) [31, 32], and in prespecified pooled PP and ITT analyses

Table 2 Protective efficacy of CYD-TDV against symptomatic, virologically-confirmed dengue due to any serotype in phase 3 trials

Analysis	CYD-TDV group			Control group			CYD-TDV efficacy [% (95 % CI)]
	No. of VCD cases[a]	PY at risk[b]	Incidence density[c] (95 % CI)	No of VCD cases[a] (n)	PY at risk[b]	Incidence density[c] (95 % CI)	
In multinational trials							
Asia[d] [31] in children aged 2–14 years							
Primary PP analysis	117	6526	1.8 (1.5–2.1)	133	3227	4.1 (3.5–4.9)	56.5 (43.8–66.4)[e]
ITT analysis	286	13,571	2.1 (1.9–2.4)	309	6623	4.7 (4.2–5.2)	54.8 (46.8–61.7)
Latin America[f] [32] in children aged 9–16 years							
Primary PP analysis	176	11,793	1.5 (1.3–1.7)	221	5809	3.8 (3.3–4.3)	60.8 (52.0–68.0)[e]
ITT analysis	277	26,833	1.0 (0.9–1.2)	385	13,204	2.9 (2.6–3.2)	64.7 (58.7–69.8)
Pooled analyses [47]							
Overall PP analysis[g]	293			354			59.2 (52.3–65.0)
Overall ITT analysis[g]	563			694			60.3 (55.7–64.5)
Aged 9–16 years[h] (ITT)	367			521			65.6 (60.7–69.9)
Aged <9 years[h] (ITT)	196			173			44.6 (31.6–55.0)

CYD-TDV recombinant tetravalent, live-attenuated, chimeric yellow-fever-dengue virus vaccine, *ITT* intent-to-treat, *PP* per-protocol, *PY* person-years, *VCD* virologically-confirmed dengue

[a] Defined as a first episode of VCD: Cases occurring during month13–25 (PP primary analyses) or from baseline to month 25 (ITT analyses)

[b] Cumulative time until the participant was diagnosed with VCD or the end of the active follow-up period (i.e. at 25 months), whichever came first. PY at risk is the sum of individual units of time for which the participants contributed to the analysis

[c] Number of cases divided by the cumulative PY at risk

[d] In the PP population, $n = 6710$ in CYD-TDV group and 3350 in the control group; in the ITT populations, $n = 6848$ and 3424

[e] Primary objective (as defined in text); this was met as the lower bound of the 95 % CI was >25 %

[f] In the PP population, $n = 12{,}574$ in CYD-TDV group and 6261 in the control group; in the ITT populations, $n = 13{,}915$ and 6939

[g] Prespecified analysis (PP populations $n = 19{,}282$ in CYD-TDV group and 9611 in control group; ITT populations, $n = 20{,}762$ and 10,364)

[h] Pooled post hoc analysis of children aged 9–16 years at baseline in the two phase 3 trials ($n = 17{,}320$ in the CYD-TDV group and 8596 in the control group); subgroup analysis of participants aged <9 years at baseline in the Asian trial ($n = 3532$ and 1768)

(Table 2) [47]. Vaccine efficacy was maintained throughout the 25-month active-surveillance period in both trials [31, 32].

Prespecified pooled ITT analyses (0–25 month active-surveillance period) indicated that CYD-TDV protective efficacy for VCD infection was higher against DENV3 and DENV4 serotypes than against DENV1 and DENV2 serotype [47], which was consistent with results of ITT and mPP analyses in the individual trials [31, 32]. In pooled ITT analyses in children aged 2–16 years, respective serotype-specific vaccine efficacies for this outcome for DENV1, DENV2, DENV3 and DENV4 serotypes were 57.4 % (95 % CI 45.4–62.3), 43.0 % (95 % CI 29.4–53.9), 71.6 % (95 % CI 63.0–78.3) and 76.9 % (95 % CI 69.5–82.6) [47].

Pooled post hoc ITT analyses (period from 0–25 months) confirmed the protective efficacy of CYD-TDV against VCD infections in children 9 years of age and older, with higher vaccine efficacy for this outcome observed in these older children than in younger children (Table 2) [47]. Exploratory ITT analyses in individual trials support these data [31, 32].

In children aged 9 years and older, CYD-TDV provided protective efficacy against VCD irrespective of the individual's serostatus at baseline, based on pooled ITT analyses [47]. In this population, the protective efficacy of CYD-TDV against VCD was 81.9 % (95 % CI 67.2–90.0) in individuals who were DENV seropositive at baseline ($\approx$80 % of children) and 52.5 % (95 % CI 5.9–76.1) in those who were DENV seronegative at baseline [47].

CYD-TDV vaccination also provided protective efficacy against severe dengue fever [according to specified criteria of the Independent Data Monitoring Committee (IDMC)], any grade of DHF (based on 1997 WHO criteria) and hospitalization because of VCD during the 0–25 month active-surveillance phase in individual trials [31, 32] and in prespecified pooled ITT analyses [47]. For example, in the pooled ITT analyses in children aged 9 years and over, vaccine efficacy against hospitalization for VCD was 80.8 % (95 % CI 70.1–87.7), against severe dengue fever was 93.2 % (95 % CI 77.3–98.0) and against any grade of DHF was 92.9 % (95 % CI 76.1–97.9) [47].

In a post hoc pooled analysis of the phase 3 trials, CYD-TDV provided protective efficacy against asymptomatic

dengue infection during the 12-month period post dose 3, as assessed using a seroconversion algorithm as a surrogate marker of asymptomatic dengue infection [49]. CYD-TDV efficacy against asymptomatic dengue infections in children aged 9–16 years during the 12 months post dose 3 was 38.6 % (95 % CI 22.1–51.5). Seroconversion was defined as at least a fourfold increase in PRNT antibody titre from month 13 to 25 and a titre of $\geq$40 dil^{-1} at month 25 [49].

As similar or higher neutralizing antibody levels are anticipated after the third injection of CYD-TDV in adults to those in children in endemic areas, it is anticipated that a similar or higher level of protective efficacy to that in the pivotal efficacy trials in children and adolescents will be observed with CYD-TDV post dose three in persons aged 17–60 years in endemic areas [23].

4 Reactogenicity and Safety of Tetravalent Dengue Vaccine

CYD-TDV was generally well tolerated in children and adults participating in clinical trials discussed in Sects. 2.2 and 3. Discussion, for the most part, focuses on an integrated safety analysis [50] and interim long-term safety data [47] from the phase 2b [30] and 3 [31, 32] efficacy trials.

4.1 Reactogenicity

The integrated safety analysis included individuals aged 9–60 years who had participated in 13 main clinical trials (i.e. used the recommended CYD-TDV three-dose regimen and current formulation of $\approx$5 $\log_{10}$ $CCID_{50}$ of each of the four live-attenuated DENV) and 5 secondary clinical trials [50]. The main trials included 26,356 individuals who received 77,234 doses of CYD-TDV and 36,006 doses of placebo. No safety concerns were identified in terms of solicited reactions, unsolicited and serious adverse events, viraemia and biological parameters, with a similar clinical safety profile observed between DENV seropositive and DENV seronegative individuals. A similar tolerability and safety profile was observed between the CYD-TDV and placebo groups in terms of solicited systemic reactions (65.7 vs. 57.7 %), solicited injection site reactions (50.9 vs. 40.1 %) and immediate unsolicited adverse events (0.3 vs. 0.2 %) [50].

In CYD-TDV vaccinees, the incidence of solicited injection site and systemic reactions did not differ based on age (9–17 vs. 18–60 years), with no increase in reactogenicity with subsequent injections [50]. The majority of these reactions occurred within 3 days of vaccination, were of grade 1 intensity and transient (resolved within 3 days). In individuals aged 9–17 and 18–60 years, solicited injection site reactions occurred in 51.0 and 46.9 % of CYD-TDV vaccines, respectively (estimated from graph). Solicited injection site reactions of any grade reported in individuals aged 9–17 and 18–60 years were pain (49.2 vs. 45.2 %), erythema (8.4 vs. 7.9 %) and swelling (6.9 vs. 2.4 %). The respective incidences of solicited systemic adverse reactions in individuals aged 9–17 and 18–60 years were 67.0 and 65.6 % (estimated from graph). Solicited systemic adverse reactions reported in individuals aged 9–17 and 18–60 years were headache (54.1 vs. 51.4 %), malaise (40.9 vs. 44.3 %), myalgia (42.0 vs. 42.2 %), asthenia (34.2 vs. 28.3 %) and fever (16. 4 vs. 4.9 %) [50].

During the 25 months after the first injection, there was no excess of hospitalized or severe dengue cases between the CYD-TDV and control group [50]. There were no reports of severe or serious immediate anaphylactic reactions. Very few participants in the CYD-TDV (0.7 %) and placebo (0.5 %) groups experienced non-serious potential allergic reactions within 7 days of vaccination. No vaccine-related deaths and no confirmed cases of viscerotopic or neurotropic events were reported during this period. The frequency of serious adverse events was similar between the CYD-TDV and control groups [50].

4.2 Long-Term Safety

Interim long-term safety analyses [47, 50] from the ongoing 4-year safety phases of efficacy trials included data collected during year 3 of the Latin American [32] (19,898 children aged 9–16 years are being followed) and Asian [31] (10,165 children aged 2–14 years are being followed) trials, and during years 3 and 4 of the Thai trial (3203 children aged 4–11 years are being followed) [30]. All participants who received at least one dose of the vaccine were included in long-term safety analyses. The objective of these follow-up studies was to determine the long-term safety of CYD-TDV, to verify that the immune response to vaccination did not confer a predisposition to severe disease and that the risk of severe disease did not increase with time because of waning titres of vaccine-induced antibodies in persons in whom immunity has not been naturally boosted [47]. The outcome used as a surrogate marker for severe disease was the incidence of hospitalization for VCD of any severity or serotype during the 4 years after the end of the 25-month surveillance period of the efficacy trials, with severe dengue disease assessed using IDMC criteria and DHF assessed using 1997 WHO criteria [47].

In the overall populations, the relative risk (RR) of hospitalization for VCD in the vaccine versus the control group in the Asian, Latin American and Thai extension studies at year 3 was 1.04 (95 % CI 0.52–2.19), 0.53 (95 %

CI 0.25–1.16) and 1.01 (95 % CI 0.47–2.30), respectively [47], with a pooled RR for this outcome of 0.84 (95 % CI 0.56–1.24) [50]. In the Asian trial, the RR for this outcome at year 3 in those 9 years of age and older was 0.57 (95 % 0.18–1.86) [47] and at year 4 was 0.73 (95 % CI 0.34–1.61) [50]. The RR at year 3 in the Asian trial was similar to that observed at the same timepoint in the Latin American trial (RR 0.53; 95 % CI 0.25–1.16), which enrolled children aged 9–16 years [47]. The RR for VCD-related hospitalization at year 3 and 4 in those less than 9 years of age was 1.58 (95 % CI 0.0.83–3.02) and 1.19 (95 % CI 0.65–2.28), with a cumulative RR in the entire study of 0.79 (95 % CI 0.56–1.13) [50].

In participants hospitalized for VCD, there were no differences in terms of the length of hospitalization or the duration of fever and clinical symptoms of VCD between the CYD-TDV and control groups in individual trials or between the efficacy surveillance and the long-term safety phases, suggesting that there were no vaccine- or temporal-related changes in the clinical manifestations of VCD [47].

5 Dosage and Administration of Tetravalent Dengue Vaccine

CYD-TDV is indicated in several dengue-endemic countries in Asia and Latin America for the prevention of dengue disease caused by DENV serotypes 1, 2, 3 and 4 in individuals aged 9–45 or 9–60 years [21–23, 51, 52]. The primary vaccination schedule consists of three doses to be given at 6-month intervals, with no vaccination schedule or dose adjustments required based on age [23]. If flexibility in the vaccination schedule is necessary, a time window of ±20 days is acceptable [23, 52]. CYD-TDV should not be administered to individuals less than 9 or over 60 years of age, as there are insufficient data to determine the benefit/risk of CYD-TDV vaccination in these populations. As with any vaccine, CYD-TDV vaccination may not protect all individuals; after vaccination, it is recommended that personal protection measures against mosquito bites are continued [23].

CYD-TDV is contraindicated in individuals with a history of severe allergic reactions to any component of the vaccine or to a vaccine containing the same components [23]. Vaccination with CYD-TDV should be postponed in individuals with moderate to severe febrile or acute disease. It is contraindicated in immunocompromised individuals, pregnant women and in women who are breast feeding [23]. Local prescribing information should be consulted for detailed information, including precautions, warnings, interaction with other medicinal products and use in specific populations.

6 Place of Tetravalent Dengue Vaccine in the Prevention of Dengue Disease

The 2012 WHO global strategy for dengue prevention and control recommended implementing measures (e.g. integrated vector control, surveillance, case management and future vaccines) that reduced the morbidity and mortality of dengue disease from 2010 levels by at least 25 and 50 % by 2020 [1]. The development of a safe, efficacious and cost-effective dengue vaccine is considered imperative for achieving these goals, given the rapid global spread of dengue disease and, in the long-term, the relative ineffectiveness of current vector control methods (primarily involving eradication of the mosquito-borne vector) [1, 53]. The inability to sustain the success of vector control programs may, at least in part, reflect the high efficiency of the *Aedes aegypti* mosquito as a dengue vector, which means that entomological thresholds to avoid transmission are very low [54]. Implementation of a vaccine strategy in endemic countries poses numerous challenges, including costs, the ease of delivery and vaccination schedules, and deciding which populations to target (e.g. age groups, locations) and which strategic plan to utilize (e.g. routine immunization, catch-up campaigns) [1, 54]. The recent approval in several endemic countries of the first dengue vaccine, namely CYD-TDV, represents a major advance in the likelihood of achieving 2012 WHO global strategy targets for dengue disease by 2020 [55]. In April 2016, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommended that countries (including subnational regions) with high dengue endemicity (i.e. DENV seroprevalence of ≈70 % or greater in the age group targeted for vaccination, or other suitable epidemiologic criteria) should consider introducing CYD-TDV as part of integrated disease prevention strategy to lower disease burden [52], based on data from 25 clinical studies conducted in 15 endemic and non-endemic countries and involving more than 40,000 individuals [56]. SAGE did not recommend the use of CYD-TDV in countries or regions with seroprevalence rates that were less than 50 % [52]. Routine CYD-TDV vaccination should form part of a comprehensive dengue control plan, along with a communication strategy, sustained vector control, best evidence-based clinical care for all patients with dengue and a robust dengue surveillance plan [52]. Several other vaccines are also in various stages of clinical development, including other live-attenuated vaccines, DNA vaccines and inactivated vaccines [15, 55, 57].

CYD-TDV induced robust immune responses against all four DENV serotypes after each dose (three doses typically given at 6-month intervals) in several randomized, controlled trials in children and adults living in endemic

countries (Sect. 2.2). Robust immune responses were elicited irrespective of an individual's flavivirus serostatus or age at baseline (Sect. 2.2). However, these responses were higher in older (≥9 years of age) than younger participants and higher in flavivirus-seropositive individuals (majority of participants) than in flavivirus-seronegative individuals, with flavivirus status a partially confounding factor of age (Sect. 2.2). In addition, CYD-TDV induced CYD serospecific cell-mediated Th1 immune responses (Sect. 2.2).

In multinational phase 3 trials, the recommended three-dose CYD-TDV regimen was efficacious against VCD in children living in endemic countries in Asia and Latin America, with respective protective efficacy rates of 59 and 60 % in prespecified pooled analyses in the overall PP (13–25 month period; primary analysis) and ITT populations (0–25 month period), and of 66 % in those 9 years of age and over (0–25 month period) (Sect. 3). Vaccine efficacy against VCD was sustained throughout the 25-month active-surveillance period, with protective efficacy for this outcome higher against DENV3 and DENV4 serotypes than against DENV1 and DENV2 serotype, and higher in DENV-seropositive individuals than in DENV-seronegative individuals (Sect. 3). Although for the DENV2 serotype CYD-TDV efficacy against VCD was below 50 % (Sect. 3), a compartmental transmission model predicted that a partially effective vaccine (i.e. protective efficacy against three of the four DENV serotypes) would result in at least a 50 % reduction in the number of VCD cases [58]. CYD-TDV also provided protective efficacy against severe dengue fever (protective efficacy 93 %), any grade of DHF (93 %) and hospitalization due to VCD (81 %) during the 25-month active surveillance phase in pooled analyses of children 9 years of age and older (Sect. 3). For all efficacy outcomes, protective efficacy rates were higher in children aged 9–16 years than in younger children (<9 years of age). Albeit no efficacy trials have been conducted in adults, it is anticipated that protective efficacy levels will be similar to or higher than those observed in children in these phase 3 trials (Sect. 3), based on higher or similar DENV GMT levels in adults compared with those in children aged 9–16 year (Sect. 2.2). CYD-TDV also provided protective efficacy against asymptomatic dengue infection during the 12-month period post dose 3 in a post hoc pooled analysis (Sect. 3). Thus, with relevant dengue vaccination coverage rates, by simultaneously protecting against symptomatic and asymptomatic dengue infections, CYD-TDV may contribute to reduced transmission of the disease and thereby provide indirect protection against dengue [49].

CYD-TDV was generally well tolerated in clinical trials (Sect. 4), with no safety concerns identified after 4 years' follow-up (post dose 1) in ongoing long-term safety studies (Sect. 4.2). Adverse reactions occurring in clinical trials were usually mild to moderate in severity, with injection site reactions, headache, malaise, myalgia, asthenia and fever being the most common adverse reactions reported (Sect. 4.1).

In contemporary healthcare systems, pharmacoeconomic considerations play an important role in the allocation of healthcare resources, including in terms of implementing immunization programs [59, 60]. Vaccination is considered to be one of the most cost-effective prevention strategies for reducing the burden of a disease [59, 60]. In the pivotal efficacy trials, albeit CYD-TDV did not completely prevent transmission of dengue in individuals aged 9 years and older, it provided significant protective efficacy against severe disease and VCD-related hospital admissions (Sect. 3), thereby potentially reducing healthcare and societal costs. From a societal perspective, CYD-TDV vaccination was predicted to be a cost-effective prevention strategy in a country with a heterogeneous risk of dengue transmission such as Argentina, especially in endemic regions, based on a cost-utility analysis utilizing a Markov model and efficacy data from the phase 3 Latin American trial [61]. From a societal and healthpayer perspective in the Philippines, compared with the status quo, routine CYD-TDV vaccination of 9 year olds in a school-based vaccination program was predicted to reduce dengue cases by 24 % and disability-adjusted life years due to dengue by 26 % over a 5 year period (abstract) [62]. Targeted-hotspot (THS) and nationwide (NW) CYD-TDV vaccination strategies were predicted to significantly reduce dengue disease and economic burden over a 10-year horizon from a Malaysian healthpayer perspective and using a dynamic transmission mathematical model (abstracts) [63, 64]. These two studies were based on 2013 costing and efficacy data from phase 3 trials [63, 64]. The respective total dengue treatment costs saved with THS and NW vaccination strategies was predicted to be $US163,859,846 and $US386,962,641 [63]. THS and NW vaccination strategies were estimated to be cost-effective at CYD-TDV prices of up to $US71.78 and $US28.59, respectively [64]. From a third-party payer perspective in Colombia, the maximum price per CYD-TDV dose for vaccination to be cost effective was predicted to be $US66.65 if used in individuals aged 9–17 years and $US33.37 if used in those aged 9 years or older (abstract) [65]. An age-structured, host-vector, serotype-specific model predicted that a dengue vaccination program was likely to be cost effective (2015 $US costs; using WHO-criteria for cost effectiveness) from a societal perspective in the 10 endemic countries involved in the phase 3 efficacy trials (abstract) [66]. At the population level, routine CYD-TDV vaccination was estimated to prevent 20–30 % of dengue cases, with routine vaccination plus the broadest

catch-up campaigns reducing the number of dengue cases over a 10-year horizon by 70 %. Dependent on the country and vaccination strategy considered, the threshold price per dose for which vaccination was predicted to be cost-effective was $US20–100 [66]. Most of these studies are currently only available as abstract presentations, with fully published data awaited with interest.

Further evidence of the potential impact of CYD-TDV vaccination in individuals aged 9 years and over in terms of reducing the public health burden of disease comes from values for the vaccine preventable disease incidence (VPDI; considers vaccine efficacy and the underlying burden of disease) and number needed to vaccinate (NNV) [67]. In the Asian study, CYD-TDV vaccination prevented 2639 VCD cases per 100,000 persons vaccinated per year (i.e. a VPDI of 2639/100,000 vaccinated persons/year), corresponding to an NNV over the active study period (i.e. 2.1 years) of 18. In the Latin American study, the VPDI was 1707 VCD cases prevented per 100,000 vaccinated persons per year, giving an NNV of 28, with these higher VPDI and NNV values in Latin America reflecting the overall lower annual incidence of dengue in Latin America than in Asia. VPDI for VCD hospitalized cases in the Asian and Latin American trials (638 and 239 cases/1000,000 population/year, respectively) were higher than those for pneumococcal conjugate vaccine against all cause severe pneumonia or for *Haemophilus influenzae* type b (Hib) vaccination against Hib meningitis and lower than that for rotavirus vaccination against severe rotavirus gastroenteritis; these three vaccines are commonly used in most national immunization programs in Latin America [67].

In conclusion, in large well designed, phase 3 trials, a three-dose regimen of CYD-TDV was effective in preventing VCD during months 13–25 of the active surveillance phase, meeting the primary endpoint criteria. During the 25-month active surveillance phase, CYD-TDV also provided protective efficacy against VCD, severe dengue, any grade of DHF and VCD-related hospitalization in children aged 9 years and older. CYD-TDV was generally well tolerated, with no safety concerns identified after 4 years' follow-up in ongoing long-term safety studies. Based on these and other data from the dengue clinical trial program, the WHO SAGE group recommended that countries (including subnational regions) with high dengue endemicity consider introducing CYD-TDV as part of an integrated disease prevention strategy to lower disease burden. Pharmacoeconomic considerations will be pivotal to implementing dengue vaccination prevention strategies in these countries. The availability of a dengue vaccine is considered pivotal if the 2012 WHO global strategy targets for reducing the burden of dengue disease by 2020 are to be attained. Hence, CYD-TDV represents a major advance for the prevention of dengue disease in high dengue endemic regions.

Data selection sources: Database(s): Embase, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data [searches last updated 28 Jul 2016]. Records were limited to those in English language.
Search terms: Tetravalent dengue vaccine, CYD-TDV, Sanofi.

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Compliance with Ethical Standards

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