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SAFETY OF DENGUE VACCINE (CYD-TDV) IN ASIA: A SYSTEMATIC REVIEW

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Abstract. The use of the vaccine in Asia is still very much limited and remained controversial due to its safety, which has yet been properly assessed and evaluated. Hence, the objective of this review is to assess the safety of the CYD-TDV dengue vaccine of the efficacy trials conducted in Asia. A total of 309 related articles were generated from the electronic database search using relevant keywords and only four of the articles were selected for the final review process. The seroprevalence at baseline of the participants involved in the studies was between 50 percent and 80 percent. In terms of the safety of the CYD-TDV vaccine, injection site reaction (pain, swelling, erythema) recorded a relative risk (RR) at 95% CI of (0.46–1.76) and systemic reactions (fever, headache, myalgia) also with RR at 95% CI of (0.89–1.81) were detected among the participants. Among the four studies reviewed, three studies reported some severe adverse effect experienced by the participants with RR at 95% CI of (0.92–2.11). In terms of the immunogenicity, high GMT values were reported for DENV-2 at 67.8 (95%CI of 64.8–70.8), DENV-3 at 73.1 (95% CI of 69.9–76.3) and DENV-4 at 65 (95%CI of 62–67.9) where even though lower values were reported it is consistent with other published studies on the immunogenicity of the CYD-TDV against the DENV serotypes. This review showed that the CYD-TDV can be considered for use in Asia, but with several conditions and following current safety recommendations.

Key words: *Dengue vaccine, CYD-TDV, safety, adults, children, Asia.*

БЕЗОПАСНОСТЬ ВАКЦИНЫ ОТ ЛИХОРАДКИ ДЕНГЕ (CYD-TDV) В АЗИИ: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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Резюме. Применение вакцины от лихорадки денге (CYD-TDV) в Азии в настоящее время остается достаточно ограниченным и противоречивым из-за вопросов безопасности, пока остающихся не оцененными должным образом. В связи с этим, целью нашего обзора стало проведение оценки безопасности вакцины CYD-TDV на основее анализа данных по эффективности ее применения в Азии. Поиск релевантных ключевых

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слов в электронных базах данных обнаружил 309 научных статей, из которых в обзор вошли лишь четыре публикации. Исходная распространенность серотипов среди участников исследований составляла 50–80%. В отношении безопасности вакцины CYD-TDV показано, что реакция в месте введения (боль, отек, эритема) отмечена с относительным риском (RR) 95% ДИ (0,46–1,76), как и системные реакции (лихорадка, головная боль, миалгия) [95% ДИ (0,89–1,81)]. Из четырех работ, включенных в обзор, три содержат данные о ряде тяжелых неблагополучных эффектов при RR 95% ДИ (0,92–2,11). В отношении иммуногенности показано, что для DENV-2 отмечено высокое среднее геометрическое значение титра в 67,8 (95% ДИ 64,8–70,8), DENV-3 — в 73,1 (95% ДИ 69,9–76,3), а для DENV-4 — в 65 (95% ДИ 62–67,9), когда при обнаружении даже меньших величин это согласуется с другими опубликованными работами по иммуногенности вакцины CYD-TDV в отношении серотипов DENV. В нашем обзоре показано, что вакцина CYD-TDV может рассматриваться для применения в Азии, но с учетом ряда условий и выполнения настоящих рекомендаций по безопасности.

Ключевые слова: *вакцина от лихорадки Денге, CYD-TDV, безопасность, взрослые, дети, Азия.*

Introduction

Dengue is an arthropod-borne viral disease caused by four distinct virus serotypes, namely DENV-1, DENV-2, DENV-3, DENV-4. It belongs to the family *Flaviviridae*, which is made up of positive-sense single-stranded RNA viruses. Dengue fever is caused by infection with one of four serotypes of the dengue flavivirus (DENV-1, DENV-2, DENV-3, and DENV-4) that usually manifests subclinically or with symptoms such as fever, headache, arthralgia, myalgia, retro-orbital pain, rash, bleeding, thrombocytopenia or leucopenia [5]. Dengue fever is endemic in more than 125 countries and it affects more than 100 million people and with 25,000 deaths reported annually worldwide. The virus is transmitted to a human host by the bite of an infected mosquito, namely *Aedes mosquito* of the *Aedes aegypti* and *Aedes albopictus*, which is the disease vector. Its ubiquitous transmission especially in the tropical countries contributed to the high incidence of reported cases in Asia and the Americas [2]. Treatment for dengue is mainly supportive and preventive measure such as environmental management, spraying insecticides and personal protective measures as there is no specific treatment available as well as no effective antivirals available [12]. There are several vaccines in the pipeline but CYD-TDV vaccine was recently licensed to be used in large population.

CYD-TDV is a recombinant, live, attenuated, tetravalent dengue vaccine and was licensed on the basis of three efficacy trials in the Asia Pacific region and Latin America [4]. WHO issued its stand on the use of the vaccine in July 2016 referring to the recommendations provided by SAGE in April 2016. According to them, the countries that are interested in introducing the vaccine should consider its use only in those of aged 9 years and above, and in areas with a seroprevalence of ≥ 70%, and not in areas below 50%. Besides that, SAGE also mentioned regarding evidence of the absence of a safety issue in seronegative individuals aged 9 and above was based on the limited data set of 10–20% of the trial population, and highlighted the urgent need to better describe the long-term benefit-risk ratio of CYD-TDV in seronegative individuals. On 29 November 2017, CYD-TDV manufacturer announced the results of additional studies to better describe the benefit-risk in seronegative individuals. This was made possible through the use of a newly developed NS1-based antibody assay applied to blood samples taken 13 months after vaccination to retrospectively infer dengue serostatus at the time of the first vaccination [19]. The objective of this review is to assess the safety of the CYD-TDV dengue vaccine of the efficacy trials conducted in Asia.

Materials and methods

Cochrane Library, Scopus, PubMed and Google Scholar were searched from 2012 through 2017 with language restricted to English. The search strategies, based on a combination of relevant Title/Abstract, text words and word variants for dengue vaccine, safety, adult, children and Asia. Research strategy followed the PICO strategy. Key search terms included Population: dengue fever, dengue hemorrhagic fever, severe dengue, adult, children and Asia; Intervention: dengue vaccine, CYD-TVD and Dengvaxia; Comparator: placebo and control group; and Outcome: safety, long term safety, dengue incidence and adverse effect. Eligibility criteria for studies to be included in the meta-analysis were as follows: (1) randomized controlled trial (RCT), (2) study on the safety of vaccines using the CYD-TDV (3) performed on children or adult and (4) reporting the safety of both the vaccine group and a control group (5) study with seroprevalence at the baseline (as recommended by SAGE) (6) original article, (7) English language, (8) study duration from 1.1.2012 till 31.12.2017. We excluded studies that did not assess CYD-TDV vaccine safety or did not use CYD-TDV vaccine and studies that used other than RCT. The search was done on 16 April 2018.

Two reviewers independently screened the titles and abstracts using the eligibility criteria. Any discrepancies were resolved by a third reviewer, where necessary. Two independent reviewers used a standardized data extraction form to collect all relevant data from the studies. The following data were extracted: study

ID, year, country of study, design of study, study period, participants (vaccine group and control group), age range, safety profile (cases/number of participants for pain, erythema, swelling, fever, headache, myalgia and severe adverse effect), and immunogenicity (GMTS). For CYD-TDV safety, the relative risk (RR) was measured and the immunogenicity is measured as Geometric Mean Titer (GMTs) was estimated using the Weighted Mean Difference (WMD). Relative risk was defined as the ratio of incidence in the CYD-TDV vaccine group divided by the ratio of incidence in the unvaccinated group. Mean Difference was defined as an absolute difference between the GMTs in the intervention and control groups.

Analyses were performed using Review Manager [14]. The forest plot was used to determine the possibility of combining data from studies in a meta-analysis. The I2 and chi squared were used to formally check for the presence of heterogeneity. Heterogeneity was classified as low, medium and high for I2 values corresponding to 25, 50, and 75%, respectively and chi squared testing with $p < 0.01$ denoting level of significance. The fixed effects model was preferred as we hypothesized that there is one true effect size which underlies all the studies in the analysis.

Results

Search results. The initial electronic search identified 117 abstracts from Cochrane Library, 104 from Scopus, 16 from PubMed and 72 from Google Scholar, added up to form 309 of total articles. 184 articles were removed for irrelevance of the titles. 125 potential relevant abstracts were then screened for eligibility and 68 abstracts were removed for not fulfilling the eligibility criteria. 57 full texts were extracted and reviewed but 53 were excluded for not explicitly displaying the outcome measurement and duplication. Four publications met our inclusion criteria and were included in the final analysis (Fig. 1).

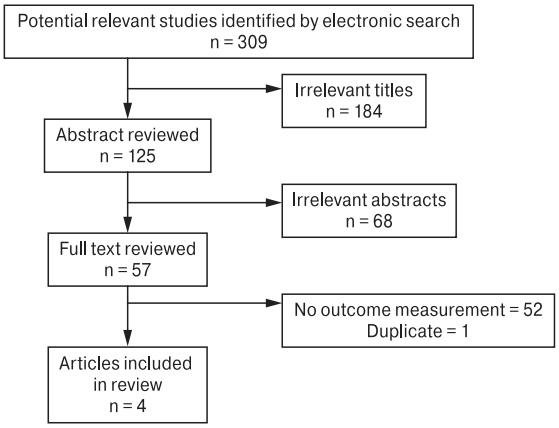

Figure 1. Process of study selection

Characteristics of the included studies are presented in Table 1. One study which is conducted in Malaysia is in phase III and other studies are in phase II. The number of participants in each included study varied from 90 to 1,198. Range of the participants' age varied between the studies with age range from 12 months to 45 years. Only children are participants in study conducted in Philippines with longest study duration which is to 24 months. The baseline seroprevalence of vaccine varies for dengue vaccine group (52 to 76%) and placebo group (50 to 60%).

Vaccine safety. Generally, severe adverse effect and systemic reaction showed an increased, but statistically insignificant risk in vaccinated participants compared

Table 1. Study characteristic

References	Country	Study design	Study duration	Sample size		Age range	Seroprevalence at baseline	
				CYD-TDV	Placebo		CYD-TDV	Placebo
Crevat et al. (2015) [6]	Philippines	RCT (II)	24 months	60	30	12 to 15 months	52%	50%
Hss et al. (2013) [9]	Malaysia	RCT (III)	18 monts	199	51	2 to 2 years	55.8%	60.8%
Leo et al. (2012) [10]	Singapore	RCT (II)	6 months	898	300	2 to 45 years	71%	67%
Tran et al. (2012) [17]	Vietnam	RCT (II)	6 months	120	60	2 to 45 years	76%	80%

Table 2. Main CYD-TDV findings

Safety Profile	No. of studies combined	Intervention (n/N)	Control (n/N)	Heterogeneity (p-value)	RR (95% CI)	p-value
Severe adverse effect	3	105/1076	26/390	15.0% (0.310)	1.39 (0.92; 2.11)	0.12
Injection site						
Pain (any)	4	665/1275	281/441	92.0% (< 0.0001)	0.79 (0.72; 0.86)	< 0.0001
Erythema (any)	4	169/1275	90/441	79.0% (0.002)	0.58 (0.46; 0.73)	< 0.0001
Swelling (any)	4	235/1275	60/441	92.0% (< 0.0001)	1.41 (1.13; 1.76)	0.003
Systemic reaction						
Fever (any)	4	193/1275	49/441	0.0% (0.570)	1.36 (1,01; 1.81)	0.04
Headache (any)	3	550/1215	153/411	0.0% (0.820)	1.20 (1.04; 1.38)	0.01
Myalgia (any)	3	496/1215	161/411	0.0% (0.650)	1.02 (0.89; 1.17)	0.75

Note. N, sample size; n, number of cases recorded; RR, relative risk.

with unvaccinated participants. Vaccinated participants have higher risk to develop swelling while reduced risk for pain and erythema. (Fig. 2 & Table 2).

Vaccine immunogenicity. Three studies were included for immunogenicity. Table 3 showed dengue serotype-specific antibody response before first dose and after third dose of CYD-TDV or control vaccine for the included studies.

The combined serotype-specific GMT levels found after resolving heterogeneity in descending order was: Serotype 3 (73.1 1/dil), Serotype 2 (67.8 1/dil), Serotype 4 (65 1/dil), and Serotype 1 (52.5 1/dil) (Table 4).

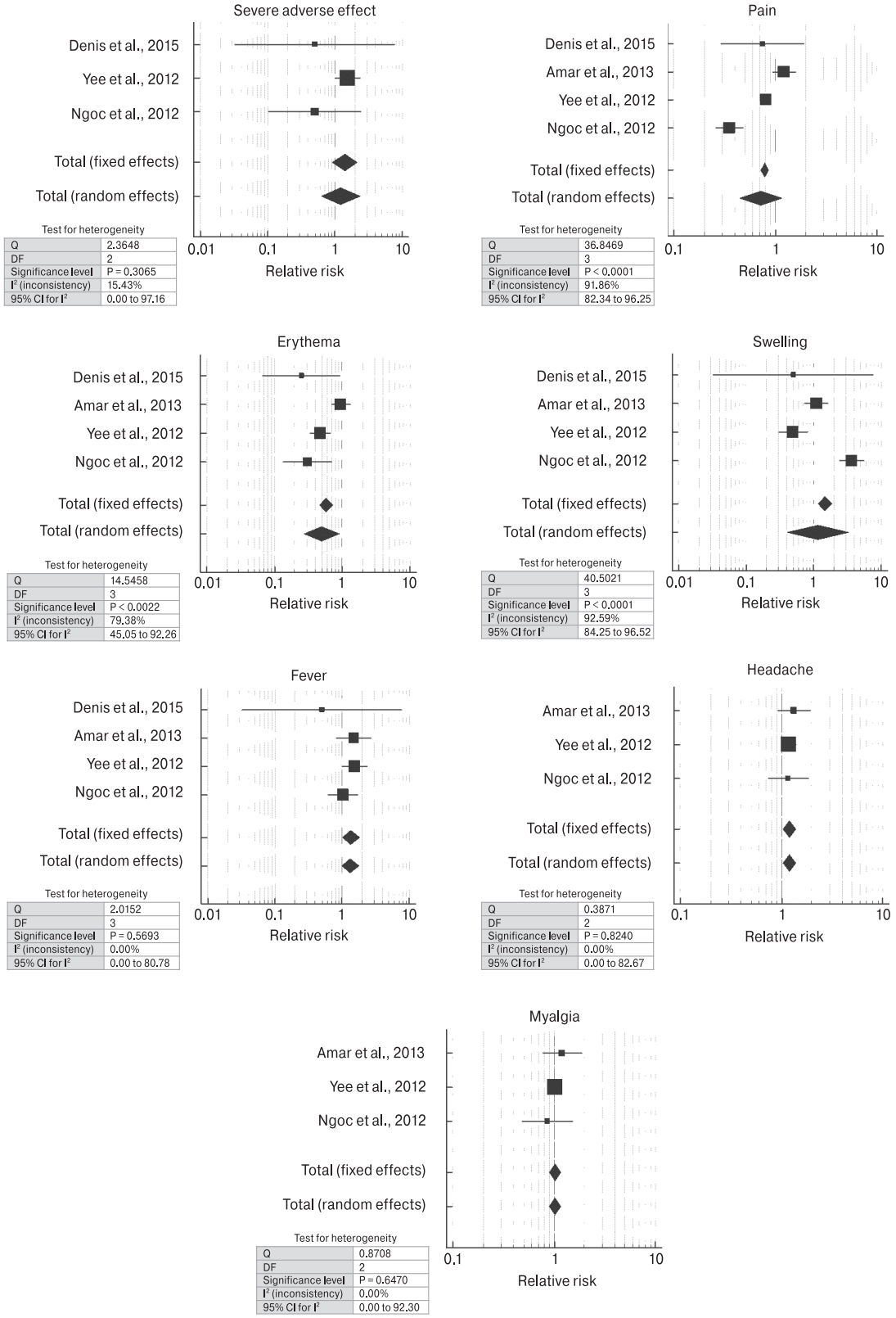

Figure 2. Forest plots of the meta-analysis of severe adverse effect, systemic and injection site reaction

Table 3. Comparison of dengue serotype-specific antibody response at baseline and after 3rd dose

	Hss et al. (2013) [9]							
	Dengue group, N = 196				Control group, N = 50			
	DENV 1	DENV 2	DENV 3	DENV 4	DENV 1	DENV 2	DENV 3	DENV 4
Baseline	15.3 (11.5; 20.4)	15.9 (11.8; 21.3)	15.6 (12.3; 19.9)	9.92 (8.17; 12.0)	18.6 (9.69; 35.8)	18.6 (10.0; 34.5)	15.9 (9.57; 26.5)	12.3 (7.96; 19.0)
After 3rd dose	151 (121; 188)	180 (146; 221)	193 (161; 231)	114 (97.0; 134)	18.9 (9.94; 35.8)	16.3 (9.59; 27.7)	16.3 (9.81; 27.0)	10.9 (7.34; 16.2)
	Leo et al. (2012) [10]							
	Dengue group, N = 438				Control group, N = 147			
	DENV 1	DENV 2	DENV 3	DENV 4	DENV 1	DENV 2	DENV 3	DENV 4
Baseline	8.13 (7.16; 9.24)	8.97 (7.80; 10.3)	8.48 (7.58; 9.50)	9.22 (7.33; 11.6)	8.34 (6.71; 10.4)	8.49 (6.73; 10.7)	9.22 (7.33; 11.6)	6.84 (5.88; 7.95)
After 3rd dose	43 (36.4; 50.8)	69.7 (59.6; 81.7)	96 (84.3; 109)	100 (88.7; 113)	8.51 (6.93; 10.4)	8.17 (6.60; 10.1)	8.89 (7.17; 11.0)	7.75 (6.55; 9.17)
	Tran NH et al. (2012) [17]							
	Dengue group, N = 120				Control group, N = 60			
	DENV 1	DENV 2	DENV 3	DENV 4	DENV 1	DENV 2	DENV 3	DENV 4
Baseline	32.8 (21.7; 49.5)	33.7 (23.0; 49.6)	32.5 (23.7; 44.5)	17.1 (12.9; 22.6)	19.6 (12.0; 31.8)	27.2 (15.3; 48.1)	20.5 (13.2; 31.9)	13.9 (9.28; 20.9)
After 3rd dose	129 (0.5; 183)	216 (163; 286)	169 (134; 214)	146 (115; 184)	25.3 (13.7; 46.8)	30.4 (16.7; 55.1)	25.2 (16.3; 39.1)	17.4 (11.2; 27.0)

Table 4. Main CYD-TDV Immunogenicity findings

Serotype	Number of studies combined	Heterogeneity (p-value)	WMD expressed as GMTs (95% CI)	p-value
DENV1	3	88.23% (0.0002)	52.5 (50.2–54.8)	< 0.0001
DENV2	3	0.00% (0.8797)	67.8 (64.8–70.8)	< 0.001
DENV3	3	88.7% (0.0001)	73.1 (69.9–76.3)	< 0.001
DENV4	3	97.92% (< 0.0001)	65.0 (62.0–67.9)	< 0.001

Discussion

Vaccine safety. The findings on vaccine safety is quite different when compared to other study in Malisheni et al. (2017). This might be due to the different of sample population taken in the study where the children age range is from 1 up to 17 years old and the baseline seroprevalence in that study is 37 to 91% for vaccination group and 48–91% for placebo group. The main concern in the vaccine safety is the severe adverse effects [1]. The relative risk is more than one but significant when compared to the other study. Due to high baseline seroprevalence in this study which range from 50 up to 80%, the number of severe adverse effects is expected to be high due to induced cross reaction with existing antibody. This might be due to small sample size taken in this review which is much lower compared to other study with nearly 40 thousand samples pooled for the review.

The injection of vaccine is supposed to cause pain due to the introduction of foreign substance which induces pain and also erythema. However, these findings show that the vaccination group does not cause pain and erythema as much as the placebo group. This might be due to the fact that the placebo group was given with many other different types of vaccine such as Hepatitis-A, Typhoid, Varicella and Inactivated-influenza vaccine which may have different reaction based on type of vaccine, dosage, repeated exposure, preservative used in the vaccine and many more [3]. The later health effects that tend to develop after period of time are swelling and fever. In this study, again has relative risk more than one and significant which might be due to several reasons. The first one is that the swelling and fever develop higher in vaccination group compared to the placebo group which might be due to the high seroprevalence of dengue in baseline. This high seroprevalence in the baseline of this study may induce cross reaction when vaccine due to some homologous structure that may enhance the inflammatory reaction. The second reason is that the placebo group is vaccine-naïve [7]. The vaccine injected in placebo group is relatively used to protect from getting severe fulminant disease or complication which most of the samples are not exposed to.

Vaccine immunogenicity. Our finding on immunogenicity of the vaccine are similar compared to Malisheni et al. 2017 [11]. The Geometric Mean Titres (GMTs) were higher among vaccinated study participants compared to unvaccinated study participants. Comparatively, study participants from Malaysia had higher GMT levels compared to those from Singapore and Vietnam. In contrast to the findings, we found that studies involving older participants

had lower GMT compared to others. This could be due to the smaller number of participants. Apart from mentioned findings, we also found that antibody response was higher during subsequent infection among those who had prior dengue virus exposure compared to others [11]. The observed GMTs were varied and the variation was most likely caused by the unequal burden of dengue infection across the countries. The other possible cause is the procedure of quantifying the neutralizing antibody titre of the infection. Even though Plaque Reduction Neutralization Test (PRNT) is considered as the gold standard, there are studies debating not only on discrepancies between laboratories and regions [15, 18], but also on inaccuracy of the test which depends on test conditions applied [13, 16]. The vaccine induces neutralizing antibodies against all four serotypes, but the outcome would differ according to seropositivity or seronegativity of vaccinees. Among seronegative vaccinees, responses to complete vaccine regimen are commonly homogenous, especially for Dengue Virus serotype four, whereby for the other serotypes, the responses are depending on the cross-reactive antibodies [8].

SAGE recommendation. In regards to the choice on a «pre-vaccination screening» strategy will indeed need an assessment at the country level including validity of available tests, local issues, dengue epidemiology, hospitalization rates as well as adequate finances for both CYD-TDV and screening tests. In terms of age, the vaccine should be used within the indicated age range, which is typically from 9 to 45 years. With recommendation as a three dose series given 6 months apart. However, there are currently no data on the use of booster doses. Some areas recommended to focus in the future would be development of a highly sensitive and specific rapid diagnostic test to determine serostatus, and assessment of simplified immunization schedules and booster needs should be prioritized [19].

Conclusion

Risk of some safety parameter noted to be increased with the administration of the vaccine, but the finding was not significant and a longer period of follow up focusing on the complications is required in order to generate better conclusion. Age group stratification is needed as other studies performed previously showed that immunogenicity of the vaccine among children was better compared to adolescents. Due to the burden of disease, especially in the area with high endemicity and no available treatment, the vaccine should be considered. CYD-TDV can be considered to use in Asia but with several conditions and following current safety recommendations.

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