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Commentary

Ethics of a partially effective dengue vaccine: Lessons from the Philippines

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ABSTRACT

Dengvaxia, a chimeric yellow fever tetravalent dengue vaccine developed by SanofiPasteur is widely licensed in dengue-endemic countries. In a large cohort study Dengvaxia was found to partially protect children who had prior dengue virus (DENV) infections but sensitized seronegative children to breakthrough DENV disease of enhanced severity. In 2019, the European Medicines Agency and the US FDA issued licenses that reconciled safety issues by restricting vaccine to individuals with prior dengue infections. Using revised Dengvaxia efficacy and safety data we sought to estimate hospitalized and severe dengue cases among the more than 800,000 9 year-old children vaccinated in the Philippines. Despite an overall vaccine efficacy of 69% during 4 years post-vaccination we project there will be more than one thousand vaccinated seronegative and seropositive children hospitalized for severe dengue. Assisting these children through a program of enhanced surveillance leading to improved care deserves widespread support. Clinical responses observed during breakthrough dengue infections in vaccinated individuals counsel prudence in design of vaccine policies. Recommendations concerning continued use of this dengue vaccine are: (1) obtain a better definition of vaccine efficacy and safety through enhanced phase 4 surveillance, (2) obtain a valid, accessible, sensitive, specific and affordable serological test that identifies past wild-type dengue virus infection and (3) clarify safety and efficacy of Dengvaxia in flavivirus immunes. In the absence of an acceptable serological screening test these unresolved ethical issues suggest Dengvaxia be given only to those signing informed consent.

Over the past 50 years dengue viruses (DENV) have expanded from a geographic focus in Southeast Asia to achieve a global pandemic. These four mosquito-borne viruses circulate mostly in urban areas in more than 100 tropical and subtropical countries resulting in millions of infections and disease, mild to lethal, in young and old.[1,2] The disease exacts a horrific toll. As of 30 November, the cumulative number of dengue cases during 2019 in the Philippines was 414,532 with 1,546 deaths [3]. Failure to interrupt the transmission of dengue viruses using classical mosquito vector control has generated large scale efforts to develop dengue vaccines. This has been complicated by an immunopathological phenomenon, sensitization to a first DENV infection that increases the severity of a breakthrough DENV infection, antibody dependent enhancement (ADE) [4]. The 2013 WHO Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated) warned: "There is a risk that vaccination could predispose recipients to developing a severe form of dengue febrile illness (DFI). The risk may increase with time elapsed since vaccination in relation to waning titres of vaccine-induced antibodies in subjects who have not been naturally boosted in the interim period. The monitoring and investigation of all subjects who develop signs or symptoms potentially indicative of DFI during pre-licensure studies in endemic regions should provide a preliminary assessment of this

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risk.. . .it is essential that there is adequate follow-up of study subjects together with further assessment of the risk in the post-licensure period ."[5] A critical omission from the WHO Guidelines was a requirement that children be bled prior to vaccination permitting separate efficacy calculations for seronegative and seropositive individuals.

1. Dengvaxia

Beginning in 2006, Sanofipasteur tested a novel live-attenuated yellow fever chimeric tetravalent dengue vaccine (Dengvaxia) for efficacy and safety in placebo-controlled clinical trials enrolling nearly 35,000 children, ages 2–16 years, in ten dengue-endemic countries [6]. Less than 12% of these children had been bled prior to vaccination.[6,7] Early efficacy results were decidedly mixed. Through year 3 post-1st dose, vaccine protection against hospitalization of >/= 9 year-old children was 65.5% while among children ages 8 years or younger the rate was 44.6%.[6] For children with serostatus known at the time of immunization, in seronegatives vaccine protection of children 8 years and younger was 14.4% while for those 9 and older, it was 52.5%. Despite the warnings of the potential for vaccine-enhanced dengue disease in WHO Guidelines, in analyzing phase 3 results, advisory groups of the World Health Organization initially labeled breakthrough dengue disease in vaccinated children as "safety signals." [8] A high rate of hospitalization among vaccinated 2–5 year-olds was attributed to novel, unstudied pathogenic mechanisms such as young age, a temporal "clustering" of vaccine-related cases occurring in young children due to the large numbers given vaccine over a short period, or to the immunological immaturity of recipients [6,9]. These data led the manufacturer and advisory groups to recommend vaccine be restricted to children 9 years and older [6,10]. Further, it was recommended that vaccination be directed to populations in settings, national and regional, with a seroprevalence of 70% or greater [11]. To provide guidance for the deployment of vaccine, WHO described sampling and statistical methods for measuring population-based DENV seroprevalence [12,13].

Based upon vaccine efficacy, mathematical models and WHO recommendations, Dengvaxia achieved licensing in 20 dengue-endemic countries [10,11,14,15]. Recently, the European Union announced issuance of a license stipulating that "Dengvaxia® will be available in Europe to prevent dengue disease in individuals 9–45 years of age with a documented prior dengue infection and who are living in endemic areas" [16]. Subsequently, the U.S. Food and Drug Administration licensed Dengvaxia "for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas" [17]. Licensing decisions in the US and Europe were announced without identifying a marketed serological test capable of sensitively detecting a past dengue infection and distinguishing antibodies to dengue from other flavivirus infections.

The WHO Guidelines did not define vaccine enhanced severe dengue disease as a "serious adverse event" (SAE) and this position remains unchanged [15,18,19]. During phase 1 and 2 studies, vaccine adverse events (AE) were reported in children and adults. These were predominantly at needle inoculation sites and occurred at rates that did not differ between dengue-immunes or non-immunes or between controls and vaccinated [20,21]. A skin site focus for AEs also predominated in reports from phase 3 clinical trials. These were supplemented by additional solicited and unsolicited symptomatic events, including diverse systemic infections. Incidence rates of these events did not differ between vaccinated and controls [7,22–24]. No AEs were attributed to breakthrough DENV infections. Yet, a clinical diagnosis that can be made accurately in children, hospitalization for severe dengue, has been shown to occur at higher frequency after Dengvaxia administration to seronegatives than in unvaccinated controls. Severe dengue was a significant outcome of hospitalized breakthrough DENV infections in vaccinated seronegative 2–8 year-olds [25].

2. Vaccination of Philippine children

In one licensing country, the Philippines, beginning in 2016, Dengvaxia was given to 880,464 nine-year-old children (personal communication to LRD from Secretary of Health, Philippines, 4 September 2019). After this program was initiated a novel serological test, applied retrospectively, generated data for entire phase 3 population discovering that breakthrough dengue cases were related to pre-immunization serostatus [25]. Seronegative children given Dengvaxia were at significant risk to severe dengue. This news resulted in cancelation of the vaccination program in the Philippines and in widespread public alarm. We sought to understand the likely outcomes of this vaccination program.

To do this we estimated hospitalization and severe dengue rates in the phase 3 vaccinated and unvaccinated children, for both 9–16 and 2–8 year-olds based on revised data.[25] Estimating annual infection rates requires DENV force of infection (FOI) data but FOI was not measured during Phase 3 [25]. Fortuitously, prior to initiating phase 3, Sanofi measured DENV antibody prevalence in all 10 participating country vaccine sites. These data provided an estimate of average annual DENV FOI of 0.155 (15.5%) over a period of 14 years [26,27]. We applied the average annual FOI to obtain age-specific primary DENV infection rates for a post-vaccination period of 1 and 4 years. Observed and estimated figures for hospitalizations and severe dengue cases and rates in vaccinated and unvaccinated 9–16 year -old seronegative children are shown in Tables 1 and 2. Fifty-six dengue hospitalizations were observed among an estimated 1577 1st DENV infections in vaccinated seronegatives compared with 20 hospitalizations among 817 primary DENV infections among unvaccinated susceptibles. The 4-year hospitalization rate in vaccinated children is 3.55% versus 2.45% in controls, rates that do not differ (p greater than 0.05). Severe dengue was rare in dengue infected unvaccinated 9–16 year-olds. Only a single child among 817 primary DENV infections in this age group was hospitalized with severe dengue, 0.12%, compared with 12 severe hospitalizations among 1577 vaccinated seronegative children, 0.76%, chi square, $p < 0.05$, with Yates correction, $p = 0.0867$ N.S (Table 1).

Crucially, there is important confirmatory evidence of vaccine ADE among 2–8 year-old seronegatives, 25 severe dengue cases among an estimated 1820 vaccinated versus 4 cases among an estimated 1010 DENV-infected controls, $p = 0.024$ (Yates) (Table 3).[25] In the phase 3 population, over a period of 4 years, hospitalization

Table 1
Rates of hospitalization and severe dengue in 9–16 year-old seronegative children given Dengvaxia or placebo during months 13–60. Seronegative population has been expanded to 100% [25]. Estimates of 4 year DENV infections based on 15% annual DENV infection rate (47.8% cumulative) and seronegative prevalence rates from published data [26,27]. Month 13 serostatus is determined by dengue NS1 IgG ELISA test, threshold 9 [25].

Categories	Vaccinated	Placebo
Seronegatives (observed)	**3300**	**1710**
Primary DENV infections/4 years (est.)	1577	817
Hospitalizations (observed)	**56**	**20**
Severe cases (observed)	**12**	**1**
Hospitalization rate/4 years	3.55%	2.45%
Annual hospitalization rate	0.89%	0.6%
Severe case rate/4 years	0.76%	0.12%
Annual severe case rate	0.19%	0.03%

Bolded type signifies direct or inferred published observations [25].

Table 2
Rates of hospitalizations and severe dengue in 9–16 year-old seropositive children given Dengvaxia or placebo recorded for months 13–60. Seropositive totals have been expanded from the 10% sample. Estimates of 4 year DENV infections assume 15% annual DENV infection (47.8%, total) and seronegative prevalence rates using published data [26]. DENV monotypic immune prevalence of 33% is from published data [26]. M 13 serostatus is determined by dengue NS1 IgG ELISA test, threshold 9 [25].

Categories	Vaccinated	Placebo
Seropositives (observed)	**14,500**	**6870**
Monotypic immunes, est.	4833	2290
2° DENV infections/4 years est.	2310	1095
2° DENV hospitalizations, (observed)	**49**	**110**
2° DENV Severe cases, (observed)	**10**	**27**
Hospitalization rate/4 years	2.1%	10.05%
Annual hospitalization rate	0.525%	2.51%
Severe case rate/4 years	0.43%	2.5%
Annual severe case rate	0.108%	0.616

Bolded type signifies direct or inferred published observations [25].

Table 3
Rates of hospitalization and severe dengue in 2–8 year-old seronegative children given Dengvaxia or placebo during months 13–60. Seronegative population has been expanded to 100% [25]. Estimates of 4 year DENV infections based on 15% annual DENV infection rate (47.8% cumulative) and seronegative prevalence rates from published data [26,27]. Month 13 serostatus is determined by dengue NS1 IgG ELISA test, threshold 9 [25].

Categories	Vaccinated	Placebo
Seronegatives (observed)	**1820**	**1010**
Primary DENV infections/4 years (est.)	870	483
Hospitalizations (observed)	**131**	**33**
Severe cases (observed)	**25**	**4**
Hospitalization rate/4 years	15.1%	6.8%
Annual hospitalization rate	3.78%	1.7%
Severe case rate/4 years	6.8%	0.83%
Annual severe case rate	1.7%	0.21%

Bolded type signifies direct or inferred published observations [25].

and severe dengue occurred in 2.1% and 0.43%, respectively, of vaccinated seropositive (monotypic immune) 9–16 year-olds while in 2–8 year-old monotypic immunes these events occurred at the astonishing rates of 15.7% and 4.4%%, respectively. (Tables 2 and 4).

To better understand issues raised in the Philippines we applied these data to the population of nine year-olds vaccinated beginning in 2016 (Table 5). Prior to the phase 3 trial, Sanofi measured DENV seroprevalence in Philippine 9 year-olds at 85%.[26] Applying this figure to the 880,464 vaccinated children identifies 132,070 seronegatives. Of these, 63,129 would be expected to experience a DENV infection during the 4 years after completion of vaccination using our 4-year infection rate of 47.8%. Applying hospitalization and severe dengue rates from the phase 3 study (Table 1) to vaccinated seronegative Philippine children, yields 2241 hospitalized and 480 with severe dengue cases (Table 5).

Table 4
Rates of hospitalizations and severe dengue in 2–8 year-old seropositive children given Dengvaxia or placebo recorded for months 13–60. Seropositive totals have been expanded from the 10% sample. Estimates of 4 year DENV infections assume 15% annual DENV infection (47.8%, total) and seronegative prevalence rates using published data [26]. DENV monotypic immune prevalence of 33% is from published data [26]. M 13 serostatus is determined by dengue NS1 IgG ELISA test, threshold 9 [25].

Categories	Vaccinated	Placebo
Seropositives (observed)	**3000**	**1350**
Monotypic immunes, est.	1000	450
2° DENV infections/4 years est.	478	216
2° DENV hospitalizations, (observed)	**75**	**65**
2° DENV Severe cases, (observed)	**21**	**17**
Hospitalization rate/4 years	15.7%	30.0%
Annual hospitalization rate	3.9%	7.5%
Severe case rate/4 years	4.4%	7.9%
Annual severe case rate	1.1%	2.0%

Bolded type signifies direct or inferred published observations [25].

But, DENV disease also was observed in vaccinated seropositives. It is well established that nearly all hospitalizations of seropositive children occur during a second heterotypic dengue infection.[28] Seropositive children at risk to dengue hospitalization are monotypic immunes. From published measurements, 33% of Philippine 9 year olds were monotypic immunes.[26] Among an estimated 290,553 vaccinated monotypic immunes infected with DENV over 4 years (47.8%), there will be 138,884 secondary DENV infections resulting in 2917 hospitalizations and 597 severe cases (Table 5). Total hospitalizations and severe cases among seronegatives and seropositives are 5158, and 1077, respectively. Using a similar approach WHO staff and advisory groups recently estimated breakthrough clinical dengue disease among children vaccinated in the Philippines for a period of 5 years after the first dose.[29,30] Our data, for the 4 years after completion of vaccination are similar.

What are the trade-offs? How many hospitalizations and severe dengue cases were prevented by vaccine? Among an estimated 290,553 monotypic immunes infected over 4-years (47.8%) there would be 138,884 secondary DENV infections resulting in 13,958 hospitalizations and 3472 severe cases (Table 5). But, unvaccinated DENV-infected seronegatives (63,129) also experience DENV disease, 1547 hospitalizations and 75 severe cases. Totals for unvaccinated are 15,505 hospitalized and 3547 severe cases, compared with 5158 hospitalizations and 1077 severe cases in vaccinated children, a 67–69% vaccine efficacy, identical to other estimates. [30]

3. Dengvaxia, safety concerns

Based upon our estimates, during the first four years after complete Dengvaxia immunization a significant segment of children vaccinated in 2016 will have been protected from severe dengue disease. During that same period, however, nearly 500 vaccinated seronegative children are expected to acquire severe dengue. What do we owe them? Public health workers are confronted for the first time with a vaccine adverse event that can be predicted. A serological test used by Sanofi, the NS1dengue ELISA, was able retrospectively to identify seronegative vaccinated children based upon absence of DENV NS1 antibodies [25]. Accordingly, some of us recommended that high risk children be identified and placed on an "alert" status for clinical attention early after onset of a dengue like illness.[31] A panel, including the Chair of the WHO Scientific Advisory Group of Experts (SAGE) and the Director of the WHO Initiative for Vaccine Research describe this recommendation as "misguided." [32] It is explained the costs of serological testing would be "immense" and "totally disproportionate to the benefit." Using Philippine data, the expert panel found severe dengue disease in seronegative vaccinated children to be "rare" and, further, that "the vast majority of vaccinated children. . .will benefit from the vaccine." [30,32]

It should be noted the benefits cited by the WHO group are based on short term efficacy data. The biological reality is that seronegatives sensitized by Dengvaxia will be at risk to severe breakthrough dengue infections for the rest of their lives. In Cuba secondary DENV 2 disease occurred 20 years after DENV-1 infections. Persons infected at this long interval had significantly higher rates of severe disease and death than did those experiencing secondary DENV-2 infections at a shorter interval.[33] It has been noted that the phenomenon of heterotypic protection may have

Table 5
Four year projections of occurrence of dengue hospitalizations and severe cases among 880,464 Philippine children who were either given or not given Dengvaxia.

Serostatus	At risk	DENV infected	Vaccinated		Not Vaccinated	
			Hospitalized	Severe cases	Hospitalized	Severe Cases
Seroneg	132,070	63,129[a]	2241	480	1547	75
Seropos	290,553[b]	138,884[c]	2917	597	13,958	3472
Totals	422,623	202,013	5158	1077	15,505	3547

a = monotypic DENV infections.
b = monotypic-immunes.
c = secondary DENV infections.

contributed to an overestimation of Dengvaxia efficacy early in the phase 3 trials [34]. There is a growing consensus that generic short-term cross-protection that occurs with sequential DENV infections means that future dengue vaccine efficacy trials should monitor dengue illnesses for a period longer than that currently recommended.[15]

The full spectrum of long term risks of giving Dengvaxia either to dengue seronegative or seropositive individuals is as yet unknown. We and others have shown that when phase 3 results were applied to the Philippines, DENV-infection of vaccinated seropositives contributed the largest fraction of breakthrough disease.[29,30] Who are these "seropositives" specifically? To what degree did adverse outcomes occur in vaccinated children who were circulating non-dengue flavivirus antibodies? Such children are labeled "dengue-immune." [6] Is this label virologically correct? Is the risk of breakthrough severe disease related to any specific prior DENV infection? How do age of the vaccinee and the interval between vaccination and DENV infection alter outcomes? Phase 4 surveillance will be crucial to better understand these biological outcomes in real-life populations.

Reflecting on the risks associated with Dengvaxia, it has been noted that the administration of a dengue vaccine to healthy seronegative individuals is an ethical issue. This vaccine prevents serious disease in some while at the same time it places others at risk of severe dengue [35]. Despite numerous deliberations by expert groups, the full range of ethical issues associated with the identification and management of dengue vaccine SAEs has not been adequately defined.[15,36–39]

4. Recommendations

What can or should be done to assist vaccinated children who are at risk to severe dengue? Our position is that surveillance for identifiable adverse events is a phase 4 and public health responsibility. Although, undoubtedly expensive, organized surveillance of the large vaccinated Philippine population will contribute importantly to improving our understanding of dengue immunopathogenesis attributable to Dengvaxia. Regarding post-vaccination test costs, critics offered a lengthy negative evaluation of the reliability of the first generation dengue NS1 test applied retrospectively to phase 3 sera [32]. Missing from these comments was any call to mobilize the leadership and resources needed to improve and evaluate candidate serological screening tests [38,40]. Neither WHO nor the manufacturer have moved aggressively to call for the design of a booster vaccine that can remove vaccinated seronegative individuals from an "at risk" status. Booster doses of Dengvaxia are not likely to improve protection. Based upon published data, doses 2 and 3 did not augment efficacy above that of the first dose [6]

With respect to continued use of Dengvaxia in licensing countries we believe the following discussions or implementations be undertaken: 1) observers should be alert to the occurrence of dengue SAEs beyond a period of four years, 2) develop, evaluate and validate a serological test that sensitively, specifically and affordably detects immunity to wild-type dengue virus infection, 3) on emergence of such a test consider the public health importance of expanding immunization to children under the age of 9 years, 4) discuss whether Dengvaxia can be administered in high endemicity populations without individual serotesting, 5) considering the lessons learned from Dengvaxia, revise the WHO Guidelines for Design and Evaluation of Dengue Vaccine Efficacy Trials and 6) in the event a dengue serological test does emerge determine if the risks of Dengvaxia SAEs mandate signed consent prior to immunization? [41]

This report was written before the pandemic of COVID 19. Some of the same management issues raised here confront the public health community in attempting to moderate the burden of disease. Obtaining and making widely available tests that correctly identify coronavirus immune status is important. Hopefully, some of the resources and energy allocated to managing the coronavirus crisis can also be directed at achieving a full understanding of efficacy and safety issues accompanying Dengvaxia administration. Lessons should be applied to improve post-vaccination evaluation and decision-making for future generations of dengue vaccines.

5. Contributors

This manuscript resulted from months of discussion of the publication in July 2018 of data describing an increased risk of severe dengue in seronegative children given Dengvaxia. The manuscript was drafted by SBH, revised many times with contributions from each author.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SBH: Sanofipasteur, Takeda, GlaxoSmithKline and Merck within past 3 years. PKR: Inviragen

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References

[1] Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature 2013;496:504–7.
[2] Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, Abd-Allah F, Abera SF, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. Lancet 2015;386:2145–91.
[3] WPRO. Dengue in Phiippines, 2019. 2019.
[4] Halstead SB. Pathogenesis of dengue: challenges to molecular biology. Science 1988;239:476–81.

[5] WHO. Annex 2. Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated). Replacement of Annex 1 of WHO Technical Report Series, No. 932. WHO Technical Report Series, Annex 2, No 979, 2013. Geneva, Switzerland: World Health Organization; 2013.
[6] Hadinegoro SR, Arredondo-Garcia JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. N Engl J Med. 2015;373:1195–206.
[7] Sabchareon A, Wallace D, Sirivichayakul C, Limkittikul K, Chanthavanich P, Suvannadabba S, et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet 2012;380:1559–67.
[8] Secretariat. Background Paper on Dengue Vaccines, SAGE Working Group on Dengue Vaccine. Geneva: World Health Organization 2016.
[9] Guy B, Jackson N. Dengue vaccine: hypotheses to understand CYD-TDV-induced protection. Nat Rev Microbiol. 2016;14:45–54.
[10] WHO. Meeting of the Strategic Advisory Group of Experts on Immunization, April 2016, conclusions and recommendations. Weekly Epidemiological Record. 2016;91:265-84.
[11] WHO. Global Advisory Committee on Vaccine Safety, 15-16 June 2016. Weekly Epidemiological Record. 2016;91:341-8.
[12] WHO. A Toolkit for national dengue burden estimation. Geneva: World Health Organization; 2018.
[13] WHO. Informing vaccination programs: a guide to the design and conduct of dengue serosurveys. . Geneva: World Health Organization; 2017.
[14] WHO. Dengue vaccine: WHO position paper – July 2016. Weekly Epidemiological Record. 2016;91:349-64.
[15] Wilder-Smith A, Hombach J, Ferguson N, Selgelid M, O'Brien K, Vannice K, et al. Deliberations of the Strategic Advisory Group of Experts on Immunization on the use of CYD-TDV dengue vaccine. Lancet Infect Dis. 2019;19:e31–8.
[16] Dengvaxia El.
[17] Dengvaxia Fl.
[18] WHO. Guidelines for the clinical evaluation of dengue vaccines in endemic areas. In: Department of Immunization VaB, editor. Geneva, Switzerland: World Health Organization; 2008. p. 441.
[19] WHO. Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated). Geneva: WHO; 2011. p. 88.
[20] Guy B, Briand O, Lang J, Saville M, Jackson N. Development of the Sanofi Pasteur tetravalent dengue vaccine: One more step forward. Vaccine 2015;33:7100–11.
[21] Sin Leo Y, Wilder-Smith A, Archuleta S, Shek L, Chong CY, Nam Leong H, et al. Immunogenicity and safety of recombinant tetravalent dengue vaccine (CYD-TDV) in individuals aged 2–45 y: Phase II randomized controlled trial in Singapore. Hum Vaccin Immunother 2012;8:1259–71.
[22] Capeding MR, Tran NH, Hadinegoro SR, Ismail HI, Chotpitayasunondh T, Chua MN, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet 2014;384:1358–65.
[23] Gailhardou S, Skipetrova A, Dayan GH, Jezorwski J, Saville M, Van der Vliet D, et al. Safety Overview of a Recombinant Live-Attenuated Tetravalent Dengue Vaccine: Pooled Analysis of Data from 18 Clinical Trials. PLoS Negl Trop Dis 2016;10:e0004821.
[24] Arredondo-Garcia JL, Hadinegoro SR, Reynales H, Chua MN, Rivera Medina DM, Chotpitayasunondh T, et al. Four-year safety follow-up of the tetravalent dengue vaccine efficacy randomized controlled trials in Asia and Latin America. Clin Microbiol Infect 2018;24:755–63.
[25] Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med 2018;379:327–40.
[26] Coudeville L, Baurin N, Vergu E. Estimation of parameters related to vaccine efficacy and dengue transmission from two large phase III studies. Vaccine 2016;34:6417–25.
[27] Halstead SB. Safety issues from a Phase 3 clinical trial of a live-attenuated chimeric yellow fever tetravalent dengue vaccine. Hum Vaccin Immunother 2018;14:2158–62.
[28] Gibbons RV, Kalanarooj S, Jarman RG, Nisalak A, Vaughn DW, Endy TP, et al. Analysis of Repeat Hospital Admissions for Dengue to Estimate the Frequency of Third or Fourth Dengue Infections Resulting in Admissions and Dengue Hemorrhagic Fever, and Serotype Sequences. Am J Trop Med Hyg 2007;77:910–3.
[29] Wilder-Smith A, Flasche S, Smith PG. Vaccine-attributable severe dengue in the Philippines. Lancet 2019;394:2151–2.
[30] Flasche S, Wilder-Smith A, Hombach J, Smith PG. Estimating the proportion of vaccine-induced hospitalized dengue cases among Dengvaxia vaccinees in the Philippines. Wellcome Open Res 2019;4:165.
[31] Cohen J. Controversy over dengue vaccine risk. Science 2019;365:961–2.
[32] Wilder-Smith A, Hombach J, Cravioto A. Misguided approach to dengue vaccine risk. Science 2019;366:1082–3.
[33] Guzman MG, Kouri G, Valdes L, Bravo J, Vazquez S, Halstead SB. Enhanced severity of secondary dengue 2 infections occurring at an interval of 20 compared with 4 years after dengue 1 infection. PAHO J Epidemiol 2002;81:223–7.
[34] Anderson KB, Endy TP, Thomas SJ. The dynamic role of dengue cross-reactive immunity: changing the approach to defining vaccine safety and efficacy. Lancet Infect Dis 2018;18:e333–8.
[35] Rosenbaum L. Trolleyology and the Dengue Vaccine Dilemma. N Engl J Med 2018;379:305–7.
[36] Wichmann O, Vannice K, Asturias EJ, de Albuquerque Luna EJ, Longini I, Lopez AL, et al. Live-attenuated tetravalent dengue vaccines: The needs and challenges of post-licensure evaluation of vaccine safety and effectiveness. Vaccine 2017;35:5535–42.
[37] Vannice KS, Wilder-Smith A, Barrett ADT, Carrijo K, Cavaleri M, de Silva A, et al. Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines. Vaccine 2018;36:3411–7.
[38] Arien KK, Wilder-Smith A. Dengue vaccine: reliably determining previous exposure. Lancet Global Health 2018;6:e830–1.
[39] WHO. Dengue vaccine: WHO position paper - September 2018. Weekly Epidemiological Record. 2018;93:457-76.
[40] Goncalves A, Peeling RW, Chu MC, Gubler DJ, de Silva AM, Harris E, et al. Innovative and New Approaches to Laboratory Diagnosis of Zika and Dengue: A Meeting Report. J Infect Dis 2018;217:1060–8.
[41] Zagaja A, Patryn R, Pawlikowski J, Sak J. Informed Consent in Obligatory Vaccinations?. Med Sci Monitor Int Med J Experiment Clin Res 2018;24:8506–9.