

COMMENTARY



## Safety issues from a Phase 3 clinical trial of a live-attenuated chimeric yellow fever tetravalent dengue vaccine

Scott B. Halstead

Private Consultant, Bethesda, Maryland

### ABSTRACT

A tetravalent live-attenuated 3-dose vaccine composed of chimeras of yellow fever 17D and the four dengue viruses (CYD, also called Dengvaxia) completed phase 3 clinical testing in over 35,000 children leading to a recommendation that vaccine be administered to  $\geq 9$  year-olds residing in highly dengue-endemic countries. When clinical trial results were assessed 2 years after the first dose, vaccine efficacy among seropositives was high, but among seronegatives efficacy was marginal. Breakthrough dengue hospitalizations of vaccinated children occurred continuously over a period of 4–5 years post 3rd dose in an age distribution suggesting these children had been vaccinated when seronegative. This surmise was validated recently when the manufacturer reported that dengue NS1 IgG antibodies were absent in sera from hospitalized vaccinated children, an observation consistent with their having received Dengvaxia when seronegative. Based upon published efficacy data and in compliance with initial published recommendations by the manufacturer and WHO the Philippine government undertook to vaccinate 800,000-plus 9 year-olds starting in April 2016. Eighteen months later, dengue hospitalizations and a deaths were reported among vaccinated children. The benefits of administering Dengvaxia predicted by the manufacturer, WHO and others derive from scoring dengue hospitalizations of vaccinated children as vaccine failures rather than as vaccine enhanced dengue disease. Recommended regimens for administration of Dengvaxia should have been structured to warn of and avoid serious adverse events.

### ARTICLE HISTORY

Received 1 February 2018  
Accepted 21 February 2018

### KEY WORDS

dengue; severe dengue; antibody dependent enhancement; serious adverse event; vaccine

### Introduction

A six decade-long effort to develop a dengue vaccine culminated in the publication in September 2015 of a meta-analysis of 3-years of results from three vaccine efficacy trials leading to recommendations for use of Dengvaxia, a chimera constructed by inserting the structural genes for the pre-membrane and envelope proteins from each of the four dengue viruses (DENV) into the capsid and non-structural protein genes of yellow fever 17 D.<sup>1</sup> When efficacy data were reviewed at a June 2015 meeting, the WHO Global Advisory Committee on Vaccine Safety (GACVS) detected a “safety signal,” noting, “During the first year of long-term follow-up in CYD14 (Asian study), the risk of hospitalized dengue was significantly higher in the CYD vaccinated group compared to the control group in the 2–5 year age group (RR = 7.45, 95% CI: 1.15,313.80).”<sup>2</sup> This would appear to be evidence of “harm” or “serious adverse event” as defined by dengue vaccine clinical trial Guidelines.<sup>3</sup> But, the GACVS did not recommend a halt to vaccine distribution or any further investigation of this “signal” and instead accepted the manufacturer’s statement that in the “absence of identical risk in the group aged  $\geq 9$  years, the company decided, based on post hoc analysis, to set an age cut-off at  $\geq 9$  years for licensure request.” These recommendations, reinforced by favorable reports from WHO’s Scientific Advisory Group of Experts on Immunization (SAGE) and a WHO Position Paper, culminated in December 2015, with the licensing of

Dengvaxia in Mexico, Honduras, Brazil and the Philippines for individuals  $\geq 9$  years-old, and subsequently in a total of 19 countries.<sup>4,6</sup>

Within months of this publication a further analysis of these data linked hospitalizations to a unique age distribution of vaccinated children suggesting that these breakthrough dengue infections occurred in children given vaccine when seronegative.<sup>7</sup> It was also noted that a discriminant analysis of dengue vaccine efficacy data required that vaccine enhanced dengue disease be looked for specifically in seronegative children.<sup>8,9</sup> A dengue infection mathematical model commissioned by WHO found increased protection could be expected if Dengvaxia was given to seropositives rather than to populations that included seronegatives.<sup>10</sup> Despite these warnings, the Philippine government announced the purchase of 3 million doses of Dengvaxia to be used to vaccinate one million 9 year-old children, a plan implemented beginning in April 2016. ([www.sanofi-pasteur.com/.../World-s-First-Public-Dengue-Immunization-Program-Start.April](http://www.sanofi-pasteur.com/.../World-s-First-Public-Dengue-Immunization-Program-Start.April) 4, 2016 accessed 24 Jan 18). This plan adhered closely to a model of vaccine delivery described approvingly by GACVS, SAGE and WHO stating that “vaccination in early adolescence could reduce dengue hospitalizations by 10%–30% over a period of 30 years.”<sup>4</sup> In the Philippines, by late 2017, a total of 830,000 individuals, mostly 9 year-old school children had been given one or more doses of Dengvaxia.

**CONTACT** Scott B. Halstead  [halsteads@erols.com](mailto:halsteads@erols.com)  5824 Edson Lane, N. Bethesda, MD 20852.

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In response to the recognized vulnerability of seronegatives, on 29 November 2017, Sanofi issued a press release stating that “For individuals who have not been previously infected by dengue virus, vaccination should not be recommended.” ([www.media-room.sanofi.com/sanofi](http://www.media-room.sanofi.com/sanofi) updates information on vaccine. Nov 29, 2017) It soon was understood that this message signified that children vaccinated when seronegative were not protected but placed at risk to severe dengue and/or hospitalization during breakthrough dengue infections. ([www.cidrap.umn.edu/.../sanofi-restricts-dengue-vaccine-downplays-antibody-enhancement](http://www.cidrap.umn.edu/.../sanofi-restricts-dengue-vaccine-downplays-antibody-enhancement). Dec 1, 2017) Despite reassuring statements from Sanofi and the Philippine Department of Health, the Philippines quickly became embroiled in multiple controversies related to past events and future plans. ([www.dailymail.co.uk/wires/afp/.../Dengue-vaccine-not-deadly-Sanofi-Philippines.html](http://www.dailymail.co.uk/wires/afp/.../Dengue-vaccine-not-deadly-Sanofi-Philippines.html), Dec 4, 2017), ([www.dailymail.co.uk/wires/.../Philippines-plans-sue-Sanofi-dengue-vaccine-minister.html](http://www.dailymail.co.uk/wires/.../Philippines-plans-sue-Sanofi-dengue-vaccine-minister.html). Dec 7, 2017). Moreover there were press reports of fatalities among vaccinated children. ([www.channelnewsasia.com/news/asiapacific/philippines-exhumes-bodies-of-two-children-in-dengue-vaccine-probe-Dec 15, 2017](http://www.channelnewsasia.com/news/asiapacific/philippines-exhumes-bodies-of-two-children-in-dengue-vaccine-probe-Dec-15-2017)) The Philippine Department of Health has appointed a committee to investigate the cause of deaths in children receiving Dengvaxia ([www.philstar.com/headlines/2017/12/09/1766647/doh-forms-task-force-dengvaxia-dengue-vaccine](http://www.philstar.com/headlines/2017/12/09/1766647/doh-forms-task-force-dengvaxia-dengue-vaccine)) (<http://www.philstar.com/headlines/2018/01/12/1776969/doh-confirms-dengue-deaths-after-taking-dengvaxia>).

Here we examine some of the safety issues associated with use of Dengvaxia.

## Results

### *Hospitalization risks: Comparison of sensitization by Dengvaxia with wild-type dengue infection*

Recognizing possible adverse clinical outcomes of dengue virus (DENV) infections in individuals given Dengvaxia when seronegative, it may be useful to compare the risk of dengue hospitalizations in individuals who were naturally sensitized by one prior heterotypic dengue infection (secondary dengue infections) versus dengue hospitalizations in individuals sensitized by Dengvaxia. These estimates and calculations have been prepared for 9–11 year-old children in [Tables 1 and 2](#).

[Table 1](#) shows the numbers of children given vaccine by country<sup>11–13</sup> The numbers of 9 – 11 year-old vaccinated children in cells are estimates from larger age groups assuming that there was an even distribution of enrollees between age groups. The percent contribution of seronegatives to total vaccinated children are calculated using median 9 – 11 year country dengue antibody seroprevalence data from Coudeville et al.<sup>14</sup> These rates were used to estimate number of seronegatives ([Table 1](#)). The force of infection (FOI) data are median values from 10 years of reported dengue cases from each phase 3 geographic locale compiled by Coudeville et al.<sup>14</sup> [Table 8](#) of the Background Paper from the SAGE report provides numbers of vaccinated 9 – 11 year-olds.<sup>15</sup> These data were used to estimate the total 9 – 11 year-old seronegative children who had been vaccinated ([Table 2](#)). It was estimated that children in the entire group were exposed to an average annual force of DENV infection of 0.155 (15.5%). ([Tables 1 and 2](#))

The risk of dengue hospitalizations occurring in seronegative vaccinated 9 – 11 year-olds was higher than hospitalization risk for secondary DENV infections occurring in the open population, being observed approximately 3 times more frequently than the hospitalization rates of secondary DENV infection hospitalization rates from prospective and retrospective epidemiological studies.<sup>16</sup> The broadly reactive non-protective pan-DENV neutralizing antibodies raised by Dengvaxia are reminiscent of antibodies transferred from mothers with 2 or more lifetime dengue infections to their infants, first protective then enhancing.<sup>17</sup> Surprisingly, the hospitalization rate estimated for primary dengue infections in seronegative children receiving Dengvaxia is similar to estimated hospitalization rates during primary dengue infections for these infants.<sup>16</sup>

### *Risk of hospitalized dengue illness in vaccinated seronegative 9 year-olds, Philippines*

Although a full description of Dengvaxia distribution among the Philippine population is not available, there is value in estimating the expected number of hospitalized breakthrough DENV infections in vaccinated 9 year-olds. This has already been attempted by Sanofi based upon unpublished efficacy trial data identifying a risk over “a 5-year follow-up, [of] about 5 additional hospitalized dengue cases or 2 additional severe dengue cases per 1000 vaccinees with no previous dengue infection

**Table 1.** Background data needed to compile rates of hospitalization of vaccinated and wild-type dengue virus infected 9–11 year-old children.

Country	Vaccinated	9 – 11 y.o.	% seronegative	No. seronegative	Ave. FOI
Indonesia	1870	430	.21	90	.2
Malaysia	1401	322	.35	113	.1
Philippines	3501	805	.18	145	.2
Thailand <sup>a</sup>	2666	613	.30	184	.15
Thailand <sup>b</sup>	1170	269	.22	59	.15
Vietnam	2333	537	.35	188	.18
Brazil	2370	782	.34	266	.1
Colombia	6497	2144	.10	214	.22
Honduras	1866	616	.15	92	.18
Mexico	2312	763	.44	336	.08
Puerto Rico	875	289	.46	133	.15
Totals		7570		1820	1.71/11 = 0.155

<sup>a</sup>Capeding et al, Thailand component<sup>12</sup>

<sup>b</sup>Sabchareon et al<sup>11</sup>

**Table 2.** Comparative risk of hospitalization of 9–11 year-old vaccinated children during a first dengue infection versus estimated hospitalizations during secondary wild type infections.

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From Table 1. Estimated seronegative/ vaccinated 9–11 year-olds (SAGE table 8) <sup>15</sup> $1820/7570 = 0.24$
Seronegatives among actual vaccinated 9–11 year-olds <sup>11–13</sup> $\times \% 8161 \times 0.24 = 1959$
DENV-infected vaccinated 9–11 year-olds- 4 years (1959 $\times 0.155$ FOI $\times 4$ ) <sup>*</sup> = 1215
Observed hospitalizations, 9–11 year-olds, 4 years = 77
Hospitalization rate, vaccinated seronegative 9–11 year-olds, (first dengue infections) 4 year total, $77/1215 = 6.3\%$
Hospitalization rate, secondary DENV infections From literature <sup>16</sup> = 2–4%
Risk of dengue hospitalization in vaccinees vs controls (secondary DENV infections) = $\sim 3$ fold greater risk

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[i.e. seronegatives] could occur following vaccination compared to unvaccinated seronegative children.<sup>18</sup> It is implied that this is a “low risk,” but, when expanded to 830,000 vaccinees, becomes 4150 hospitalizations. As shown in Table 3, an estimate derived from Philippines phase 3 clinical trial data yielded a risk similar to that of Sanofi.<sup>14</sup> It should be noted that in these estimates the Force of Infection may be high. Future breakthrough DENV hospitalization rates should correlate directly with yearly DENV infection rates. And, these rates may differ significantly between different locales in the Philippines.

## Discussion

What is the explanation for the failure of authorities from multiple institutions to anticipate, identify, caution against or delay licensure of Dengvaxia pending complete investigation into instances or cause of vaccine enhanced disease? From statements made in many reports by the manufacturer, international agencies and dengue scientists there would appear to be at least two possibilities: 1) skepticism and 2) mislabeling.

1) Skepticism, when voiced, was frequently directed at antibody dependent enhancement (ADE). It should be noted that ADE is a mechanistic hypothesis consistent with the observed high frequency of severe dengue during primary dengue infections in infants born to dengue immune mothers and in individuals of any age accompanying a second heterotypic dengue infection.<sup>16</sup> In one egregious example of skepticism written by two members of Sanofi’s Scientific Advisory Board on Dengue Vaccine the authors doubted the concept of ADE and specifically of an “enhancing vaccine.”<sup>19</sup> Their conclusion was based partly upon the observation that acute phase blood cytokine levels or viremias did not differ between hospitalized vaccinees

**Table 3.** Hospitalization estimates, Philippines (4 years) per 100,000 vaccinated seronegative.

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9 year-olds Seronegative % <sup>14</sup> = 18.0
No. seronegatives = 18,000
Dengue infected* FOI $0.155 \times 4 \times 18,000 = 11160$
Hospitalized $0.063 \times 11160 = 703.1$

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\*The estimate of force of infection over 4 years is rather high. In all dengue-endemic areas FOI varies significantly from year to year. Also, children who arrive at age 9 who are seronegative likely belong to cohorts with lower than average risk of exposure to dengue viruses. This number that dictates the rate at which vaccinated seronegative children develop severe dengue during acquired dengue infections. If FOI is smaller, the risk increases.

and placebo controls.<sup>20,21</sup> As noted above, hospitalized placebo children predominantly are experiencing a second heterotypic wild-type DENV infection and are not the appropriate control for the first DENV infections in hospitalized vaccinated seronegative children. Others attributed the high rate of hospitalization of 2–5 year-old vaccinated children to “chance.”<sup>22</sup> SAGE reflected skepticism of safety data when it observed that “The biologic mechanism behind this increased risk is currently not understood but may be related to naïve serostatus and/or age.”<sup>4</sup> Or as suggested by the manufacturer to a “clustering” phenomenon.<sup>15,23</sup> SAGE frequently referred to ADE as a theory. “While there are currently no data to indicate an increased risk of hospitalization due to dengue in vaccine recipients in the indicated age range of 9–45 years, there is a theoretical possibility that vaccination may be ineffective or may even increase that risk in those who are seronegative at the time of first vaccination.”<sup>15</sup> WHO reflects the same sentiment, “Vaccination may be ineffective or may theoretically even increase the future risk of hospitalized or severe dengue illness in those who are seronegative at the time of first vaccination regardless of age.”<sup>24</sup>

2) Mislabeling. WHO, GACVS, SAGE, modelers, the manufacturer and multiple non-industry commentators have assessed hospitalized vaccinated children as no fault “vaccine failures” instead of as serious adverse events. At its April 2016 meeting WHO’s Scientific Advisory Group of Experts on Immunization (SAGE) concluded, “In those children vaccinated at ages 2–5 years in Asia, a statistically significant increased risk of hospitalized dengue was seen in vaccine recipients in the third year after the first dose, though this dissipated in years 4 and 5. The biologic mechanism behind this increased risk is currently not understood but may be related to naïve vaccine serostatus and/or age. A significant increase in hospitalizations was not seen in those older than 5 years. No other safety signal has been identified.” The report continued, “SAGE was presented with the results of comparative mathematical modelling evaluations of the potential public health impact of CYD-TDV introduction.” There was agreement that “The positive benefit of vaccination provided in moderate-to-high transmission settings of seroprevalence at 9 years of age of 50% or higher across 8 different mathematical models provides reassurance that use of the vaccine in these contexts will result in a population-level reduction in dengue, including for hospitalizations, which present an important burden on the health system. A reduction of 10–30% in dengue-hospitalizations was predicted over 30 years. Notably, impact was highest in transmission settings of 70% or higher seroprevalence at age 9 years.” Similar conclusions have been confirmed by the authors of models.<sup>25</sup>

In the Background paper accompanying the SAGE report it was noted, “The explanation for these findings in the 2–5 year age group is unclear based on available data. The hypotheses put forward by the Sponsor (Section 5.3) are plausible, in particular the suggestion that the immunological mode of action of the vaccine is to move individuals along the infection line. The clustering hypothesis may also help explain the initial elevated relative risk 7.45 in Year 3 that diminished to 1.4–1.5 with further follow-up. An age effect independent of serostatus, which would reduce the theoretical risk of predisposing older seronegative vaccinees to more severe forms of dengue, would

also be compatible with the available data but requires further investigation.”<sup>15</sup>

Perhaps failures to label hospitalizations as serious adverse events can partly be explained by inadequate preparations made to recognize and handle vaccine enhanced disease in WHO planning documents on vaccine efficacy and safety.<sup>3,26–28</sup> For example, the WHO Global Vaccine Safety Blueprint defines an Adverse Event Following Immunization (AEFI) broadly but does not specifically list as “cause specific,” vaccine enhanced disease. Further, vaccine enhanced disease does not fit with the adopted criterion as a “quality defect.”<sup>26</sup>

To be candid, the Guidelines on the Quality, Safety and Efficacy of Dengue Tetravalent Vaccines (live, attenuated) did warn “There is general agreement that DENV vaccines should ideally induce protective neutralizing antibodies to each of the four serotypes simultaneously. In theory, a tetravalent immune response would protect against all [dengue illnesses] and would also reduce or eliminate the risk of a phenomenon termed antibody-dependent enhancement of disease, which is thought to be one of the mechanisms that predispose to severe forms of dengue.”<sup>27</sup> The Guidelines on the Clinical Evaluation of Dengue Vaccines in Endemic Areas continues, “Each study should be of sufficient size and duration to provide a robust estimate of vaccine efficacy and to provide preliminary evidence that the vaccine does not predispose recipients to develop one of the severe forms of DFI following natural infection.... [A] risk that could 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.” “Studies should be designed to detect increased risk of severe dengue in vaccine recipients throughout the duration of the Phase 3 clinical trial and beyond.”<sup>3</sup>

Despite remonstrances made by those advising on public policies based upon outcomes of Dengvaxia clinical trials, the hospitalization of children given vaccine cannot be regarded as “A Zero Sum Game.”<sup>29–31</sup> Why were Dengue Vaccine Efficacy Trial Guidelines ineffective? Or could they hope to deal with the unbidden optimism expressed in Updated Questions and Answers Related to the Use of Dengvaxia by WHO, “Theoretically, based on the model that the vaccine acts like a silent primary infection, it is expected that the elevated risk of severe disease in vaccinated seronegative persons should disappear after they have had a natural infection.”<sup>6</sup>

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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