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Short communication

Dengue vaccine safety signal: Immune enhancement, waning immunity, or chance occurrence?

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ABSTRACT

A new dengue vaccine was associated with increased risk of hospitalized virologically-confirmed disease during year 3 of follow-up among children age 2–5 years. Among hypotheses to explain this finding, we could not distinguish definitively between antibody dependent enhancement, waning immunity, or chance occurrence. However, any theory must account for the following: (a) the signal occurred mainly because of decreased dengue among controls rather than increased dengue among vaccinees; (b) among 48 data points, a statistically significant increase in hospitalization among vaccinated children occurred for only one age group, during one year, and in one region; (c) cumulative risk was similar for vaccinated vs. control children age 2–5 years at the end of year 5 and lower for vaccinated vs. control children among older age groups; (d) the protective effect of vaccine against hospitalization decreased from years 1–2 to years 3–5 of follow-up for all age groups and regions.

1. Background

A live, attenuated tetravalent dengue vaccine showed efficacy against virologically confirmed dengue (VCD) in a phase 2b trial [1] and phase III trials [2,3] and has now been licensed in 13 countries. Unlike Latin American countries, where enrollment age was 9–16 years, participating trial sites in Asian countries enrolled children from age 2 to 14 years. In the Asian setting, an increase in hospitalized cases – and the subset that were severe – occurred among the youngest age group during the third year of follow-up. Some authors have questioned whether these findings resulted in part from immune enhancement, such as antibody dependent enhancement (ADE), where incomplete vaccine induced priming of seronegative patients led to subsequent severe disease after natural infection [4]. The lead clinical trial investigators have disputed this interpretation [5]. Here we review the clinical trial data and assess potential explanations for the unexpected findings. We did not conduct any modeling.

We have based our analysis on published methods, including relative risk – rather than vaccine efficacy [VE] – of hospitalization in vaccinated versus control populations [2,3] (Table 1). Age groups were defined by age at enrollment and not age at outcome.

2. Data summary

The protective effect of dengue vaccine against hospitalization for virologically-confirmed dengue (VCD) decreased from the first two to the last three years of follow-up in all age groups and both regions (Fig. 1 and Table 1). Nevertheless, cumulative relative risk for vaccinated versus control children was <1.0 for all groups except children age 2–5 years in both Asia (CYD14) and Thailand (CYD23/57).

Among the 48 individual year data points reported in Table 1, only one involved a relative risk >1.0 that was significant at the 95% confidence level. Specifically, during analysis of the Asian data, a 7.5-fold increase in risk was identified in vaccinated compared to control children age 2–5 years during year 3 of follow-up, a risk that subsequently decreased during years 4–5 (Fig. 1 and Table 1). When adjusted for the 2:1 vaccinated:control design, the increased risk of dengue during year 3 among children enrolled at age 2–5 years appeared to occur primarily because of a decrease in the number of cases among control children from year 2 to 3, not an increase in cases among vaccinated children (Fig. 2a).

Abbreviations: ADE, antibody dependent enhancement; CI, confidence interval; CYD14, Asian phase 3 clinical trial; CYD15, Latin America phase 3 clinical trial; CYD23/57, Thailand phase 2b clinical trial; VCD, virologically-confirmed dengue; VE, vaccine efficacy.

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Table 1
Hospitalized confirmed dengue cases in Asia and Latin America among vaccinated and control children by age at study enrollment and study year. In Asia children were ages 2–14 years at enrollment and in Latin America age 9–16 years. The study design involved a 2:1 vaccinated to control enrollment ratio. Data are reproduced from Ref. [3], Table 8.

	ASIA (CYD14)		LATIN AMERICA (CYD15)		THAILAND (CYD23/57)	
Age group and study year	Cases in vaccinated vs. controls	Relative risk (95% CI)	Cases in vaccinated vs. controls	Relative risk (95% CI)	Cases in vaccinated vs. controls	Relative risk (95% CI)
2–5 years						
1	8:6	0.64 (0.20–2.32)	Not in study	Not in study	1:2	0.24 (0.0–4.6)
2	9:7	0.64 (0.21–2.02)	Not in study	Not in study	3:1	1.4 (0.11–74)
3	15:1	7.5 (1.15–313.8)	Not in study	Not in study	5:1	2.4 (0.27–116)
4	20:7	1.4 (0.58–3.99)	Not in study	Not in study	5:3	0.81 (0.16–5.2)
5	6:2	1.5 (0.27–15.15)	Not in study	Not in study	4:0	Inf (0.32–inf)
6	Not available	Not available	Not in study	Not in study	11:4	1.3 (0.40–5.8)
Cumulative	58:46	1.26 (0.76–2.13)	Not in study	Not in study	29:11	1.3 (0.62–2.8)
6–8 years						
1	5:12	0.21 (0.06–0.64)	Not in study	Not in study	4:3	1.3 (0.62–2.8)
2	8:9	0.45 (0.15–1.3)	Not in study	Not in study	18:13	0.67 (0.11–4.6)
3	4:5	0.40 (0.08–1.86)	Not in study	Not in study	14:5	0.71 (0.33–1.6)
4	18:9	1.0 (0.43–2.53)	Not in study	Not in study	8:9	1.4 (0.48–5.0)
5	5:3	0.83 (0.16–5.37)	Not in study	Not in study	3:1	0.45 (0.15–1.3)
6	Not available	Not available	Not in study	Not in study	15:4	1.9 (0.60–7.8)
Cumulative	40:76	0.54 (0.34–0.87)	Not in study	Not in study	62:35	0.89 (0.058–1.4)
9–11 years						
1	5:5	0.50 (0.12–2.18)	2:8	0.13 (0.01–0.63)	3:2	0.76 (0.09–9.1)
2	2:13	0.077 (0.01–0.34)	6:14	0.21 (0.07–0.59)	3:9	0.17 (0.03–0.68)
3	6:3	1.01 (0.22–6.23)	10:9	0.55 (0.20–1.54)	3:5	0.31 (0.05–1.6)
4	12:3	2.01 (0.54–11)	6:5	0.60 (0.15–2.5)	3:5	0.31 (0.05–1.6)
5	3:2	0.76 (0.09–9.0)	1:1	0.50 (0.01–39)	1:3	0.17 (0.0–2.1)
6	Not available	Not available			11:5	1.2 (0.36–4.1)
Cumulative	28:52	0.54 (0.32–0.96)	25:37	0.34 (0.19–0.58)	24:29	0.42 (0.24–0.75)
12–14/16 years						
1	2:5	0.14 (0.02–1.22)	3:7	0.21 (0.04–0.94)	Not in study	Not in study
2	1:7	0.071 (0–0.55)	7:14	0.25 (0.09–0.66)	Not in study	Not in study
3	2:4	0.25 (0.02–1.74)	6:6	0.50 (0.13–1.9)	Not in study	Not in study
4	7:10	0.35 (0.11–1.01)	0:2	0 (0–2.67)	Not in study	Not in study
5	1:2	0.25 (0–4.79)	0:0	–	Not in study	Not in study
Cumulative	13:56	0.24 (0.11–0.48)	16:29	0.28 (0.14–0.52)	Not in study	Not in study

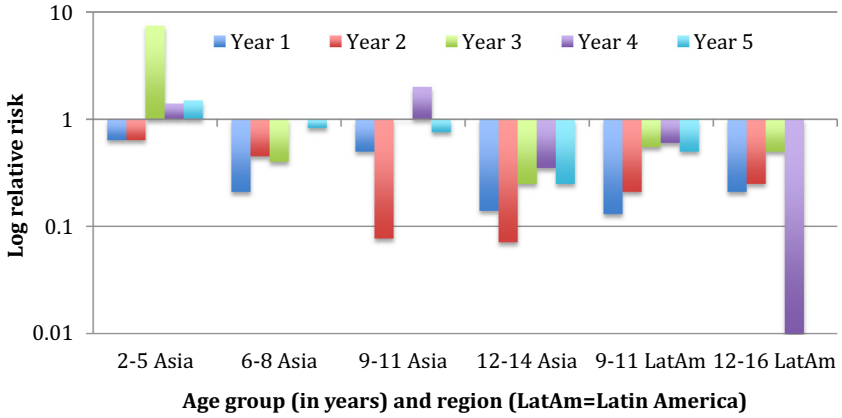

Fig. 1. Log relative risk of hospitalization for confirmed dengue for vaccinated versus unvaccinated persons, by follow-up year.

A second possible signal of increased risk among vaccinated children was seen during year 4 among Asian children age 9–11 years, with a non-significant relative risk of 2.0 (95% CI, 0.54–11). Unlike children age 2–5 years, this increase occurred primarily from an increase in cases among vaccinated children; also, unlike children aged 2–5 years, the relative level of cumulative cases remained lower among vaccinated children for each study year (Fig. 2c).

Baseline serostatus was obtained for a subset of study subjects. The data set was too small to assess correlation between baseline serostatus and risk of dengue-associated hospitalization or severe disease. However, vaccine provided protection against all VCD among baseline seropositive persons in Asia (VE, 79%; 95% CI 47–93%) and Latin America (VE, 81%; 95% CI, 71–88%) and also provided protection to seronegative persons in Asia (VE, 62%; 95% CI −21 to 88%) and Latin America (VE, 43%; 95% CI 62–80%). Cumulative efficacy across both regions was 82% (95% CI, 67–90%) for seropositive persons, and 53% (95% CI, 6–76%) for seronegative persons. On a population level, no correlation existed between baseline seropositivity prevalence and vaccine efficacy (Fig. 3).

3. Explanatory hypotheses

1. Waning immunity. Waning immunity with a subsequent rebound in disease in the vaccinated group was proposed as

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