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Review

Protective and immunological behavior of chimeric yellow fever dengue vaccine

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ABSTRACT

Clinical observations from the third year of the Sanofi Pasteur chimeric yellow fever dengue tetravalent vaccine (CYD) trials document both protection and vaccination-enhanced dengue disease among vaccine recipients. Children who were 5 years-old or younger when vaccinated experienced a DENV disease resulting in hospitalization at 5 times the rate of controls. On closer inspection, hospitalized cases among vaccinated seropositives, those at highest risk to hospitalized disease accompanying a dengue virus (DENV) infection, were greatly reduced by vaccination. But, seronegative individuals of all ages after being vaccinated were only modestly protected from mild to moderate disease throughout the entire observation period despite developing neutralizing antibodies at high rates. Applying a simple epidemiological model to the data, vaccinated seronegative individuals of all ages were at increased risk of developing hospitalized disease during a subsequent wild type DENV infection. The etiology of disease in placebo and vaccinated children resulting in hospitalization during a DENV infection, while clinically similar are of different origin. The implications of the observed mixture of DENV protection and enhanced disease in CYD vaccinees are discussed.

1. Introduction

Sanofi Pasteur has conducted an evaluation of clinical responses to dengue vaccine of unparalleled size involving more than 35000 children, ages 2–16, resident in 10 dengue endemic countries [1]. From published reports on this extensive experience it has been established that the CYD live-attenuated tetravalent vaccine was asymmetrically protective and enhancing. The efficacy of vaccine in preventing severe dengue or dengue hemorrhagic fever among children 9 years or older who were hospitalized during year 3 was over 90%. However, in children of all ages severe dengue during hospitalizations occurred more often in vaccinated (18/65) than in placebo groups (6/39) [1]. More pointedly, among 2029 vaccinated children, 5 years or younger (1636 from CYD 14 + 393 from CYD 23/57) subsequent dengue hospitalization rate was significantly higher, 20/2029 (0.99%) than among controls 2/1005 (0.2%), a relative risk of 4.95, $p = 0.03$. In addition, among vaccinated young children during year 3 of the Thai trial (CYD 23/57), 5 of 22 hospitalized developed plasma leakage and 2 were in shock, while there were no shock cases among 11 controls. The authors explain hospitalized disease in vaccinated young children as a "cluster" immunization effect or an example of vascular or immunological immaturity [1]. A more extensive analysis re-emphasized these hypotheses with the added suggestion that seronegatives are initially protected by vaccination but during year 3 become at risk to enhanced disease [2]. Outside experts suggested that hospitalized disease in vaccinated seronegatives might be only "transient" [3].

Data from the three CYD clinical trials suggest that vaccine related antibody-dependent enhancement (ADE) may have occurred across all age groups during the first two and the third year after vaccination. Because only a small fraction of vaccinated children were bled for serological studies prior to administering vaccine, 8%, 19% and 9.3% for CYD23, 14 and 15, respectively, the pre-illness immunological status in relation to hospitalized dengue illnesses in vaccinated and controls must be inferred [4–6]. Here we examine and comment on the clinical outcomes among vaccinated children who were naturally challenged by wild-type DENV over a period of 3–4 years.

2. Evidence of vaccine-enhanced dengue disease

2.1. Clinical responses to DENV infection

Before attempting to interpret the outcome of the CYD clinical trials, it is important to describe the established outcomes

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of dengue infections of children that occur in differing immunological settings: seronegative (flavivirus susceptible), Japanese encephalitis (JE)-immune, monotypic DENV-immune and polytypic DENV-immune. Unlike most viral infections the clinical presentation and severity of a dengue virus infection is determined by the previous experience with flaviviruses. Infections in individuals who are seropositive due to a previous infection are at risk to more severe disease than seronegative dengue naïve individuals.

2.2. Flavivirus susceptible

The clinical responses of seronegative children to DENV infection has been extensively described in multiple prospective and retrospective cohort studies including a relevant study in the Thailand vaccine CYD vaccine test site in Rajaburi, Thailand [7–11]. Based upon these studies, around half of primary DENV infections in children are inapparent, the remainder are clinically mild or very mild. The ratio of apparent:inapparent infections varies inversely with age [12]. Infection severity varies by serotype. Primary DENV 1 and 3 infections in children, possibly in 10% of cases, result in a febrile illness diagnosed as dengue fever, occasionally admitted to hospital and scored as dengue hemorrhagic fever (DHF) grade I or II [13]. Primary DENV 2 and 4 infections in children are predominantly inapparent, a small percent result in mild disease [13,14].

2.3. JE immune

DENV infection in JE-immunes, either due to prior wild-type JE infection or immunization, upgrades the severity of subsequent primary DENV infection, but, mainly from inapparent to mild disease, quantitative effect unmeasured [15].

2.4. Monotypic DENV-immune

This is the "classical" group at risk to severe dengue disease. When infected with a different DENV, 2–4% of these children develop an illness requiring hospitalization [12]. The severity of disease is age-dependent, 3–4 year-old children were observed to be at greater risk of hospitalization and death than older children (Fig. 1) [16]. Young children are 6–7 times more likely to be hospitalized with a secondary DENV infection than are adults [16]. The severity of second DENV infections differs by sequence. Infections in the sequence DENV1 then DENV 2 or DENV 3 are more severe than DENV 2 then DENV 3[17–19]. In Tahiti, infections in the sequence DENV 2 then DENV 1 resulted in high rates of hospitalization and death in children [20]. A single DENV infection results in some degree of cross protection for a year or more [21]. On a population level, sustained high annual rates of DENV infection shortens the interval between first and second infection resulting in the hospitalization of children at a low modal age [22]. As average annual infection rates fall, the modal age of admission to the hospital increases. Today, throughout much of SE Asia, the modal age of hospital admission of children is 11–12 years [23].

2.5. Multitypic DENV-immune

Two prior DENV infections provide protective immunity against severe dengue disease accompanying infection with a third DENV [24]. Third DENV infections may result in mild-moderate febrile disease that rarely requires hospitalization [25].

2.6. DENV disease in placebo controls

All placebo groups contain three of the immunological categories with JE-immunes principally found in Thailand and Vietnam. Accordingly dengue infections in placebo recipients are expected

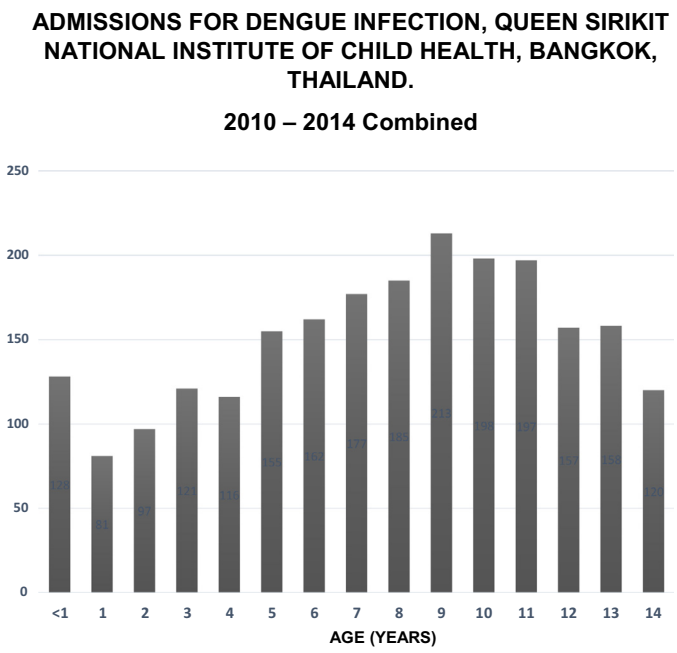

Fig. 1. Cumulative distribution of children hospitalized, ages <1–16 years, at the Queen Sirikit National Institute of Child Health, Bangkok, Thailand, 2010–2014.

to occur across the full spectrum of clinical responses. Among DENV-infected susceptibles and JE-immunes around half would be expected to experience mild disease, monotypic immunes somewhat less so [25]. Mild to moderate overt disease will occur more often in older than in younger children. Among DENV-infected monotypic immunes, around 50% will develop mild to moderate disease, some will be hospitalized for DF, a few for severe dengue or DHF. Hospitalized disease will occur at higher rates in young compared with older children. In the placebo groups during years 1–2, at the three geographic sites there were 636 mild-moderate illnesses (636/10,832 = 5.9% or 3.0%/year) and 134 children hospitalized, 134/10,832 = 1.2% or 0.6%/year, with a handful of severe cases [4–6,26].

2.7. DENV disease in vaccine recipients

2.7.1. Disease response in vaccinated serologically defined populations

In extensive pre-clinical experience and in all three clinical trials, seronegative children when vaccinated, developed neutralizing antibody immune responses [4–6]. Thus, it is expected that all vaccinated children will exhibit a secondary-type antibody responses accompanying all breakthrough DENV infections.

Based upon a selected sample of sera taken at enrolment, a high percentage of 2–16 year-old children in the three studies had evidence of one or more prior life-time DENV infections (Table 1). The prevalence of seropositives differed by country but the generally high prevalence of dengue antibodies is a function of the large

Table 1
Percentage of seropositives and seronegatives enrolled in CYD clinical trials. From Fig. S1 [1].

CYD trial	Sero-status			
	All ages		>/= 9 yrs	
	% neg	% pos	% neg	% pos
14	32	68	19	81
15			19	81