Commentary

A new moment for facing dengue?

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Invited Commentary on Phase 3 dengue clinical trials in Asia and American countries articles by Capeding et al., and Villar et al.

After decades of research, results of the first two phase 3 dengue clinical trials were published in 2014.^{1,2} Efficacy studies of a schedule of three doses (administered at 0, 6 and 12 months) of the recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV) were performed in children from ten endemic countries of Asia and the Americas (Table 1). Vaccine efficacy against symptomatic virologically confirmed dengue (VCD) (independently of illness severity and infecting serotype) occurring between months 13 and 25 in children with a complete vaccination schedule was the primary outcome in both studies. Secondary outcomes included vaccine efficacy against VCD caused by each serotype (that occurred at any time from months 0 to 25 in the intention to treat population), dengue hemorrhagic fever (DHF), severe dengue and number of hospitalizations among others. Serious adverse events and immunogenicity (on the basis of neutralizing antibodies by PRNT₅₀ in a child subgroup) were also evaluated.

Vaccine efficacy fluctuated from 56.5% (Asian study) to 60.8% (American study) while the intention-treat analysis (with all children who received at least one injection and were followed from months 0 to 25) varied from 54.8% to 64.7%. Dengue 2 virus (DENV2) showed the lowest serotype specific efficacy while DENVs 3 and 4 showed figures around 74-78%. Highest vaccine efficacies were observed against dengue hospitalization, DHF and severe dengue as well as in individuals with a previous seropositive status. Safety and reactogenicity profiles showed no major concerns.

Overall efficacy increased when compared to results of the phase 2b trial in 2 669 Thai children.³ Probably, the higher size of the trials with several countries of

different epidemiological situations and potential serotype circulations, as well as the inclusion of volunteers with different dengue immune background, could explain the efficacy increment. Further studies are needed to define specifically the influence of each factor on vaccine efficacy.

With a moderate efficacy, results of these two studies open a new window of opportunity for a disease caused by four viruses with a global growing burden and where the immune enhancing phenomenon, the lack of an animal model and the undefined correlates of protection impose serious difficulties for vaccine development.

In principle, the vaccine could impact on the hospitalization reduction by dengue and in the prevention of DHF and severe dengue, and could potentially support the WHO aspiration of diminishing dengue morbidity and mortality by 2020.⁴ However, there are still important targets for consideration. These targets are: the efficacy determination in seronegative (the trials showed the lowest efficacy in these individuals) as well as in seropositive individuals immune to one, two or more serotypes; the vaccine efficacy by serotype with priority for type 2, the most pathogenic virus (still the lowest efficacy); the vaccine efficacy by vaccine doses and the implications of natural boosters; the long-term safety follow up (a higher severity has been associated to longer intervals among dengue infections). To achieve this, large studies in heterogeneous epidemiological settings and populations are needed, and over extended periods of time to identify adverse events following immunization.

There is no doubt that a new moment for facing dengue is ongoing. On one side, the CYD-TDV with a moderate efficacy but with possibilities of impact, and on the other is vaccine candidates at advanced stages of development, the new tools for vector control under evaluation as well as the increasing knowledge of dengue dynamic transmission among others results. In this context, some research is still pending. The impact of vaccination should be estimated considering vaccine efficacy, vaccine coverage, the dengue epidemiological situation and the dengue immunity of the target population and the vector control activities. Vaccine efficacy on clinical dengue but also on dengue infection should be studied.⁵ The application of mathematical models should allow estimates of the potential impact of the intervention strategies (vaccination and vector control) on clinical dengue and dengue transmission.

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Table 1 Summary of main results of the first two Phase 3 dengue clinical trials in Asia and the Americas.

	Asia*					Americas**				
	Vaccine group (n:6848)		Control group (n:3424)		Vaccine efficacy(%)	Vaccine group (n: 12574)		Control group (n: 6261)		Vaccine efficacy (%)
	Cases	Person-years at risk	Cases	Person-years at risk		Cases	Person-years at risk	Cases	Person-years at risk	
Primary analysis per protocol	117	6526	133	3227	56.5	176	11793	221	5809	60.8
Intention to treat analysis	286	13571	309	6623	54.8	277	26883	385	13204	64.7
Serotype efficacy against VCD after 28 days of the third injection in all children with a complete vaccination schedule										
DENV 1	51	6548	50	3210	50.0	66	12478	66	6196	50.3
DENV 2	38	6561	29	3253	35.0	58	12495	50	6219	42.3
DENV 3	10	6613	23	3281	78.4	43	12514	82	6213	74.0
DENV 4	17	6605	34	3265	75.3	18	12522	40	6206	77.7
Not defined	2	6634	3	3309	66.7	6	12540	3	6268	0.0
Efficacy against VCD from baseline in all children who received at least one injection (intention to treat analysis)										
DENV 1	116	13742	126	6796	54.5	99	27016	109	13434	54.8
DENV 2	97	13766	74	6856	34.7	84	27035	84	13461	50.2
DENV 3	30	13835	43	6895	65.2	55	27060	106	13459	74.2
DENV 4	40	13826	72	6874	72.4	32	27063	83	13442	80.9
Not defined	7	13858	8	6926	56.3	15	27079	14	13514	46.5
Countries	Indonesia, Malaysia, Philippines, Thailand, Vietnam					Brazil, Colombia, Honduras, Mexico, Puerto Rico				
Children	Healthy children 2-14 years					Healthy children 9-16 years				

* 1 ** 2

Finally, a priority must be given to research directed to better define the protective immunity to each serotype, including the role of the immune response in the course of a natural infection; the mechanism for achieving long-lasting protection; the mechanisms of protection of the vaccines; the evaluation of sequential rather than simultaneous immunization, and no less important: the implementation of new methods of assessing dengue immunity.^{6,7}

References

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