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Dengue vaccines: dawning at last?

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The need for a dengue vaccine is more pressing than ever. Dengue, a mosquito-borne viral infection caused by any of the 4 dengue virus serotypes (DENV 1-4), is currently regarded as the most important arboviral disease globally, as over 50% of the world's population lives in areas at risk of the disease, and all evidence points towards further geographical and numerical expansion.¹ Hence, the results of the first multi-centre efficacy trial for a recombinant, chimeric, live attenuated tetravalent dengue vaccine (CYD-TDV), published in this issue,² have been awaited with great anticipation and with some trepidation, as earlier results of a single centre trial with the same vaccine were disappointing.³

Conducted in five Asia-Pacific countries, this pivotal trial was a randomized controlled, multicenter, phase 3 trial amongst more than 10,000 healthy children aged 2-14 years. The primary endpoint was defined as protective efficacy against symptomatic, virologically-confirmed dengue (VCD) after the completion of 3 doses given 6 months apart. The incidence density of VCD during the 25 month surveillance was 1.8 % (95% CI 1.5 to 2.1) in the vaccinees and 4.1 % (95% CI 3.5 to 4.9) in the controls, translating into an overall protective efficacy of 56.5% (95% CI 43.8 to 66.4). The overall vaccine efficacy in the per-protocol analysis (PP) was similar the intention-to-treat analysis (ITT).

Efficacy was serotype specific. Consistent with the previous single-centre Phase 2b trial in Thailand,³ efficacy against dengue virus serotype 2 was low with the confidence interval (CI) crossing zero (35.0; 95% CI -9.2 to 61.0) in the PP and 34.7% in the ITT (95% CI 10.4 to 52.3). But the estimates on serotype-specific efficacy were more robust in this trial due to the larger sample size and multiple sites at different epidemiological settings. Confidence intervals were therefore

narrower, and hence previous doubts about the true efficacy for serotypes 1, 3 and 4 can be put at rest: efficacy against serotypes 3 and 4 was consistently more than 75% and was 50% for serotype 1 (Serotype 1: 50%, 95% CI 24.6 to 66.8; serotype 3: 78.4, 95% CI 52.9 to 90.8; serotype 4: 75.3, 95% CI 54.5 to 87.0). The efficacy against all 4 serotypes combined will always depend on the serotype distribution at any given time. In this trial the lower prominence of serotype 2 explains the higher overall efficacy of 56% compared to the Thai trial³ where the overall efficacy was only 33%.

The apparent failure to protect against DENV-2 despite high geometric mean titres (GMT) following vaccination (as measured by the plaque reduction neutralization test-PRNT) remains an enigma; in particular as GMT were even higher than for the other three serotypes. Are we measuring the “wrong” antibodies? Or are we measuring the antibodies wrongly? The lessons learnt from these trials are that neutralizing antibodies measured by the traditional PRNT (based on Vero cells) correlate poorly with clinical protection.⁴ The antibody response in dengue is much more complex than we previously thought. Recent studies propose that human antibodies neutralize DENV infection by binding to a quaternary structure epitope that is expressed only when E proteins are assembled on a virus particle.^{5,6} In other words, the antibody repertoire may be different after natural infection than after vaccination. Identifying an appropriate immune correlate is now the most crucial issue in dengue vaccine development.⁷

The overall good safety profile in this trial is consistent with previous trials.⁸ In particular, the lack of more severe disease due to the feared antibody dependent enhancement (ADE) is reassuring. However, the observation time was only up to 25 months. Experiences from Cuba show that the incidence of severe dengue disease increased as the interval between heterologous infections increased from 4 to 20 years⁹, yet another enigma in this complex disease. Longer observation times are needed to conclusively rule out an increased risk of ADE in vaccinees.¹⁰ Indeed, a follow-up study is ongoing in this trial.

Perhaps the most interesting finding of this trial was the fact that efficacy after at least one dose was almost as high as after 3 doses. This is most likely due to an excellent priming effect in a population with high flavivirus exposure (about 78% in this trial).¹¹ As three doses six months apart is an inconvenient and costly immunization schedule for scaling up in national programmes, the question whether sufficient efficacy can be achieved with lower number of doses definitely deserves further evaluation.

The observation that efficacy in younger age groups was far lower (33.7% for children aged 2-5) than in older children (74.4% for children aged 12 to 14) needs to be highlighted. Yet younger children have a higher incidence of dengue (in most dengue endemic countries including in the cohort of this trial) and are often at higher risk for more severe disease, although a shift towards older age groups has been reported in most countries in the past decade.¹ Of greater concern was the lack of vaccine efficacy in DENV-naïve subjects (35.5%, and the 95% CI included 0: 95% CI -26.8 to 66.7) suggesting that this vaccine boosts and broadens pre-existing immunity rather than raising protective immunity which would also explain the better efficacy in DENV-exposed older children. This means that the CYD-TDV vaccine may be of limited use in countries with low dengue endemicity, or in international travellers from non-dengue endemic countries for that matter. However, due to the exploratory nature of the covariate analyses, and the limited sample size of the baseline serostatus data in the immunogenicity subset, no firm conclusions can be made.

Does an overall efficacy of 56% justify introduction of this dengue vaccine into national immunization programs in dengue endemic countries? With an estimated 96 million clinically apparent dengue infections annually¹², a reduction by half would present a significant public health benefit that would support dengue vaccine introduction. Furthermore, given that this trial showed an impressive vaccine efficacy against dengue haemorrhagic fever (DHF) of 80% (95% CI 52.7 to 92.4) after one or more injections and 88.5% (95% CI 58.2 to 97.9) after three injections, the main indication for this vaccine should be to protect against severe disease, reduce hospitalization and hence health care

costs and potentially prevent deaths. Even a trivalent vaccine (eg a vaccine effective only against DENV-1, 3 and 4) would have a substantial benefit in terms of reducing severe disease, which is probably the best news from this trial.¹³

Many questions remain to be answered: What is the epidemiological threshold of dengue activity upon which national dengue vaccination programs are justified and cost effective given that this vaccine is likely not going to be inexpensive? What about countries with high DENV-2 dominance? Should only high-risk age groups or age groups with the highest vaccine efficacy be targeted?

This phase 3 trial signifies the dawn of a new era in dengue control. But the morning fog is not yet lifted as dengue continues to puzzle because of its complex immunology. It remains to be seen whether the armamentarium of alternative vaccine candidates that are currently in the pipeline (including inactivated, live attenuated, chimeric, recombinant, subunit and DNA vaccines)¹⁴ will better efficacy beyond 56%. For the moment, the CYD-TDV vaccine is the best we have. With a 56% efficacy it will never be a single solution. Continued support for the development of other novel strategies (drugs, improved case management, insecticides, and new approaches to vector control) is needed before effective dengue control becomes a credible prospect.¹⁵

Conflict of interest: No conflict of interest in the past 3 years. Annelies Wilder-Smith was the Principal Investigator of the adult cohort in the Phase 2 dengue vaccine trial by Sanofi Pasteur at the National University Hospital Singapore in 2008 and 2009. Since 2011, she is the Scientific Coordinator of a European Commission funded international consortium called DengueTools (www.denguetools.net).

References:

1. Murray NE, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. *Clin Epidemiol* 2013; **5**: 299-309.
2. Capeding MR. Clinical efficacy and safety of a novel tetravalent dengue vaccine

in healthy children aged 2 to 14 years in Asia: a phase III randomised observer-masked, placebo-controlled trial. *Lancet* 2014.

3. Sabchareon A, Wallace D, Sirivichayakul C, 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**(9853): 1559-67.
4. Sirivichayakul C, Sabchareon A, Limkittikul K, Yoksan S. Plaque reduction neutralization antibody test does not accurately predict protection against dengue infection in Ratchaburi cohort, Thailand. *Virol J* 2014; **11**: 48.
5. de Alwis R, Smith SA, Olivarez NP, et al. Identification of human neutralizing antibodies that bind to complex epitopes on dengue virions. *Proc Natl Acad Sci U S A* 2012; **109**(19): 7439-44.
6. Teoh EP, Kukkaro P, Teo EW, et al. The structural basis for serotype-specific neutralization of dengue virus by a human antibody. *Sci Transl Med* 2012; **4**(139): 139ra83.
7. Halstead SB. Identifying protective dengue vaccines: guide to mastering an empirical process. *Vaccine* 2013; **31**(41): 4501-7.
8. Leo YS, Wilder-Smith A, Archuleta S, 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**(9): 1259-71.
9. Guzman MG, Kouri G, Valdes L, Bravo J, Vazquez S, Halstead SB. Enhanced severity of secondary dengue-2 infections: death rates in 1981 and 1997 Cuban outbreaks. *Rev Panam Salud Publica* 2002; **11**(4): 223-7.
10. Lam SK, Burke D, Capeding MR, et al. Preparing for introduction of a dengue vaccine: recommendations from the 1st Dengue v2V Asia-Pacific Meeting. *Vaccine* 2011; **29**(51): 9417-22.
11. Qiao M, Shaw D, Forrat R, Wartel-Tram A, Lang J. Priming effect of dengue and yellow fever vaccination on the immunogenicity, infectivity, and safety of a tetravalent dengue vaccine in humans. *Am J Trop Med Hyg* 2011; **85**(4): 724-31.
12. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. *Nature* 2013; **496**(7446): 504-7.
13. Gubler D. 70 years on: progress in dengue vaccine development. *The Vaccine Companion* 2011; **4**: 1-3.
14. Thomas SJ, Endy TP. Current issues in dengue vaccination. *Curr Opin Infect Dis* 2013; **26**(5): 429-34.
15. Wilder-Smith A, Macary P. Dengue: challenges for policy makers and vaccine developers. *Curr Infect Dis Rep* 2014; **16**(5): 404.