***Editorial***

# A fresh look at dengue vaccines

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We wrote a previous editorial titled "Dengue vaccine: Light at the end of the tunnel?" in the September 2012 issue of the Sri Lanka Journal of Child Health[1]. At that time the Sanofi Pasteur dengue vaccine (CYD-TDV) had entered phase III clinical studies.

CYD-TDV (Dengvaxia) is a live recombinant tetravalent dengue vaccine given as a 3-dose series on a 0, 6 and 12 month schedule[2]. It has been evaluated in 2 Phase III clinical trials in 5 Asian countries[3] and 5 Latin American countries[4]. Results of each trial have been published separately, as well as together[5]. The Asian trial was carried out in 2-14 year old healthy children[3] whilst the Latin American trial comprised 9-16 year old healthy children[4]. Vaccine efficacy against confirmed dengue pooled across both trials was 59.2% in the year following the primary series[2]. During this year, pooled vaccine efficacy against severe dengue was 79.1%[2]. Vaccine efficacy was higher against serotypes 3 and 4 (71.6% and 76.9%, respectively) than for serotypes 1 and 2 (54.7% and 43.0%)[2]. The efficacy of Dengvaxia in preventing severe dengue or dengue haemorrhagic fever among children 9 years or older who were hospitalized during year 3 was over 90%[6]. However, among 2029 vaccinated children, 5 years or younger, subsequent dengue hospitalization rate was significantly higher than among controls ($p=0.03$)[6]. Efficacy was higher in seropositive individuals than in seronegative individuals irrespective of age[6]. In the Asian trial, vaccine efficacy was 74.3% in seropositive individuals versus 35.5% in seronegative individuals, and in the Latin American trial, efficacy was 83.7% in seropositive individuals versus 43.2% in seronegative individuals[3,4]. During the active phase of both trials, the safety profile for Dengvaxia was similar to that for placebo, with no marked differences in rates of adverse events[3,4].

In late 2015 and early 2016, Dengvaxia was registered in Mexico, Philippines, Brazil and El Salvador for use in 9-45 years old persons living in endemic areas[6]. Strategic Advisory Group of Experts on immunization convened by the World Health Organisation (WHO), reviewed Dengvaxia in April 2016 and recommended its use in highly endemic countries[2,7]. In a position paper issued on 29 July, 2016 WHO states that dengue seroprevalence "should be approximately 70% or greater in the age group targeted for vaccination in order to maximize public health impact and cost effectiveness. Vaccination of populations with seroprevalence between 50% and 70% is acceptable but the impact of the vaccination programme may be lower. The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination"[8].

Of the other dengue vaccines in the pipeline**,** DENVax is of special interest as Sri Lanka is among 10 countries which will participate in a multi-centre Phase III clinical trial involving it[9]. Clinical trials for DENVax, have been launched as a collaboration between Japan and the United States of America (USA). US Food and Drug Administration (FDA) has approved the study design which is based on the guidelines for clinical trials of dengue vaccine in endemic areas[10].

DENVax is a recombinant tetravalent, live-attenuated dengue vaccine the safety and immunogenicity of which was established in a randomised, placebo-controlled Phase 1 clinical trial in Colombia[10]. DENVax is based on an attenuated DEN-2 virus which produces long-lasting antibody and cellular immune responses to DEN-2. This attenuated DEN-2 virus was then engineered to express the structural proteins of DEN-1, DEN-3 or DEN-4 viruses. DENVax is a mixture of the original DEN-2 strain and the 3 engineered viruses[11]. An ongoing Phase II clinical trial is testing the safety and immunogenicity of DENVax in multiple age groups in Colombia, Puerto Rico, Thailand and Singapore[10].

At this point we should pause and take a reality check. DENVax has undergone Phase II clinical trials but is yet to commence Phase III clinical trials. In 2012, when we wrote our previous editorial, Dengvaxia was already undergoing Phase III clinical trials. However, it was only in April 2016 that Dengvaxia received WHO approval for use in 9-45 year old persons living in endemic areas. Thus, it is unlikely that DENVax will obtain WHO approval before 2020 even if the Phase III clinical trials are successful. In a study in the Colombo suburbs in 2014, dengue seroprevalence rate was found to be 52.9% in the 8-10 year age group,

64.6% in the 11-13 year age group, 70.5% in the 14-16 year age group and 95.4% in the 35-44 year age group[12]. Thus, as an interim measure, Sri Lanka should perhaps purchase Dengvaxia for use in children 14 years and over in the Colombo suburbs where the dengue seroprevalence rate is over 70%.

**References**


1. Lucas GN. Dengue vaccine: Light at the end of the tunnel? (Editorial). *Sri Lanka Journal of Child Health,* 2012; **41**(3): 107-8. http://dx.doi.org/10.4038/sljch.v41i3.4596

2. Questions and answers on dengue vaccines. Available from: file:///C:/Users/User/Downloads/Dengue%20vaccine/WHO%20_%20Questions%20and%20Answers%20on%20Dengue%20Vaccines.html

3. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial". *Lancet* 2014; **384** (9951): 1358–65. http://dx.doi.org/10.1016/S01406736(14)61060-6

4. Villar L, Dayan GH, Arredondo-Garcia JL, Rivera DM, Cunha R, Deseda C, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. *New England Journal of Medicine* 2015; **372**(2): 113-23. http://dx.doi.org/10.1056/NEJMoa1411037 PMid: 25365753

5. Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. *The New England Journal of Medicine* 2015; **373**: 1195–206. http://dx.doi.org/10.1056/NEJMoa1506223 PMid: 26214039

6. Halstead SB, Russell PK. Protective and immunological behaviour of chimeric yellow fever dengue vaccine. *Vaccine* 2016; **34**(14): 1643-7.

7. Dengue and severe dengue – Fact sheet Updated April 2016. Available from: file:///C:/Users/User/Downloads/Dengue%20vaccine/WHO%20_%20Dengue%20and%20severe%20dengue.html

8. Dengue vaccine: WHO position paper – 29th July, 2016. *WHO Weekly Epidemiological Record* 2016; **91**: 349-64 PMid: 27476189

9. Dengue breakthrough: Lanka agrees to preventive vaccine trial. 1st May 2016. Available from: file:///C:/Users/User/Downloads/Dengue%20vaccine/Dengue%20breakthrough_%20Lanka%20agrees%20to%20preventive%20vaccine%20trial%20_%20The%20Sunday%20Times%20Sri%20Lanka.html

10. Hombach J. Guidelines for clinical trials of dengue vaccine in endemic areas. *Journal of Clinical Virology* 2009; **46**(Suppl 2): S7-9. http://dx.doi.org/10.1016/S13866532(09)70287-2

11. Osorio JE, Velez ID, Thomson C, Lopez L, Jimenez A, Haller AA. Safety and immunogenicity of a recombinant live attenuated tetravalent dengue vaccine (DENVax) in flavivirus-naive healthy adults in Colombia: a randomised, placebo-controlled, phase 1 study. *The Lancet Infectious Diseases* 2014; **14**(9): 830-8. http://dx.doi.org/10.1016/S14733099(14)70811-4

12. Jeewandara C, Gomes L, Paranavitane SA, Tantirimudalige M, Panapitiya SS, Jayewardene A, et al. Change in dengue and Japanese encephalitis seroprevalence rates in Sri Lanka. *PLoS ONE* 2015; 10(12): e0144799 http://dx.doi.org/10.1371/journal.pone.0144799 PMid: 26696417 PMCid: PMC4687926


**G N Lucas**
*Joint Editor*

The author declares that there are no conflicts of interest.