

Theme: Immunization **Immunogenicity and safety of Takeda's tetravalent dengue vaccine (TDV) in healthy children in Asia and Latin America** (*Lancet Infect Dis.* 2018;18:162-70).

This study presents 18-month interim data of Takeda's tetravalent dengue vaccine (TDV) candidate from an ongoing phase-2, multicentre, randomized, double-blind, placebo-controlled study at three sites in the Dominican Republic, Panama and the Philippines to assess the immunogenicity and safety over 48 months in healthy children aged 2-17 years. 1800 children were randomly assigned to receive either two TDV doses 3 months apart (group 1), one TDV dose (group 2), one TDV dose and a booster dose 1 year later (group 3), or placebo (group 4).

Antibody titers remained elevated 18 months after vaccination in all TDV groups against all four dengue serotypes, irrespective of baseline dengue serostatus. Limited differences were observed between groups 1 and 2. In baseline-seronegative participants, a 1-year booster increased antibody titers. Vaccine-related unsolicited adverse events occurred in 14 (2%) of 562 participants, but no vaccine-related serious adverse events were observed. Symptomatic, virologically-confirmed dengue was recorded in 21 (1.3%) of 1596 participants vaccinated with TDV compared with 9 (4.5%) of 198 placebo recipients.

Comments: The need for a second generation, more refined Dengue vaccine cannot be overstated considering the huge burden of the disease and the unsatisfactory performance of the first-generation dengue vaccine, Dengvaxia. In the Takeda's trial, the serostatus at the time of vaccination was measured, but follow-up is too short to detect risks associated with being seronegative. For licensure, in the absence of an accepted correlate of protection or risk, the immunogenicity study will not suffice and the efficacy will need to be demonstrated based on clinical outcomes collected over multiple dengue seasons that support durable benefit.

 **Can single dose of human papillomavirus (HPV) vaccine prevent cervical cancer?** (*Vaccine.* 2018 Mar 15. pii: S0264-410X(18)30286-X).

In a multi-center cluster randomized trial of two vs three doses of quadrivalent human papilloma virus (qHPV) vaccine in India, suspension of the vaccination led to per protocol and partial vaccination of 10-18/ year old girls leading to four study groups, two by design and two by default. Of the 17,729 vaccinated girls, 4348 (25%) received three doses on days 1, 60, 180 or later, 4979 (28%) received two doses on days 1 and 180 or later, 3452 (19%) received two doses on days 1 and 60, and 4950 (28%) received one dose. One dose recipients demonstrated a robust and sustained immune response against HPV 16 and 18, albeit inferior to that of 3- or 2-doses, and the antibody levels were stable over a 4-year period. The frequencies of cumulative incident and persistent HPV 16 and 18 infections up to 7-years of follow-up were similar and uniformly low in all the vaccinated study groups; the frequency of HPV 16 and 18 infections were significantly

higher in unvaccinated age-matched control women than among vaccine recipients. The researchers conclude that a single dose of HPV vaccine is immunogenic and provides lasting protection against HPV 16 and 18 infections similar to the three- and two-dose vaccine schedules.

Comments: The single-dose schedule would not only be more economical but would have programmatic advantages over multiple-dose schedule. Though the above study has some limitations like the participants were not randomized nor blinded to the number of doses received, the distribution of the participants by the study sites was different across the vaccinated dose groups. In fact, the trial was not designed in the first place to prospectively assess the effectiveness of one-dose of HPV vaccine. Nevertheless, this trial has significant number of participants (around 5000) than other single dose trials. More trials with longer follow-ups on HPV infection and cervical precancerous lesions are needed before single-dose schedule replace the existing ones.

 **Immunogenicity and safety of a novel liquid hexavalent DTwP-Hib/Hep B-IPV vaccine to licensed combination vaccines in healthy infants** (*Vaccine.* 2018;36:2378-84).

Immunogenicity and safety of a newly developed liquid DTwP-Hib/HepB-IPV hexavalent vaccine (EasySix) was evaluated and compared with administration of licensed Pentavac SD (DTwP-HepB/Hib) and Imovax Polio (IPV) vaccine among 284 participants, aged 6-10 weeks in an open-label, randomized multicentric trial.

Post-vaccination, seroprotection was achieved against all six vaccine antigens in both vaccine groups. The seroresponse rate and antibody titers for all vaccine components were comparable between two groups. Both vaccines had similar reactogenicity profiles and were well tolerated; all adverse events resolved completely without any sequelae. Only one serious adverse event was reported that completely resolved; it was regarded unconnected to the vaccine administered. This study demonstrated that immunogenicity and safety profiles of this new combination vaccine are non-inferior to the commercially available vaccines.

Comments: This combination vaccine is the only available hexavalent vaccine employing whole-cell pertussis (wP) antigen in Indian market. Though the reported seroconversion rates for the pertussis component was slightly lower (around 68% and 76% for pertussis IgG and anti-PT, respectively) than other antigens, but was comparable to the comparator vaccine's figures. In an earlier trial of a pentavalent vaccine from the same manufacturer, almost similar titers were reported for the pertussis component (65% and 72%). However, relying solely on immunogenicity data for pertussis efficacy/protection would not be an ideal way since till date no known single correlate of protection for pertussis exists, nor any established protective antibody levels are known.

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