EDITORIAL

Hepatitis B Vaccination Strategies Using Combination Vaccines for Low Birthweight Infants

ASHOK KUMAR DUTTA

Emeritus Consultant, Department of Pediatrics, Indraprastha Apollo Hospital, New Delhi, India.
drdutta@gmail.com

The concept of combining different antigen mixture in a single vaccine is not new and the first combination of a trivalent influenza viral vaccine was produced way back in 1945. Diphtheria-Pertussis-Tetanus (DPT), oral trivalent and bivalent polio, Inactivated trivalent polio and pneumococcal vaccines are some of the examples of the combination vaccines in use for a long time [1]. Recently, pentavalent vaccine containing DPT, *Hemophilus influenzae* b (Hib) and hepatitis-B (HBV) antigenic components, has been introduced in the universal immunization schedule of many countries of the world, including India [2]. There is a general fear that mixing several antigens to produce a single vaccine would lead to less immunogenicity and more reactogenicity. However, with modern manufacturing techniques, epitopic suppression and antigenic interaction is almost negligible making product immunogenic, safe and effective. In the present era, when several antigens are included in the immunization schedule, combination vaccine is the natural choice of both physicians and parents. It reduces the number of injections, pain, anxiety and visits to health centers, and results in minimal drop-out leading to several programmatic benefits.

There are many studies published regarding the immunogenicity of each component of pentavalent vaccines containing either whole cell- (wP) or acellular- (aP) pertussis component along with diphtheria, tetanus, *Hemophilus influenzae* b and hepatitis-B components. Several schedules (6, 10, 14 weeks; 2, 3, 4 months; 2, 4, 6 months) have been studied, and almost all the studies showed adequate immunogenicity to prevent the disease. Although the geometric mean titers of antibodies in these studies were very variable, these were much above the critical protective level [3,4]. In one of the study, when birth dose of hepatitis-B vaccine was not used, the seroresponse following three primary pentavalent doses yielded >10 IU/mL in 88.5% compared to 94% in whom birth dose was also administered [5]. All available pentavalent vaccines containing DwPT-Hib-HBV have undergone immunogenicity and safety trials in India before being approved by regulatory authority (Drug Controller General of India). Most of the developed countries in the world recommend a schedule of 0, 1, 6 months or 2, 4, 6 months. It has been observed that the antibody titer obtained in these two schedules are very high and expected to wane slowly compared to the schedule of 6, 10, 14 weeks or 0, 6, 10, 14 weeks. The interval between second and third dose, if kept at two months, the seroresponse is higher. However, World Health Organization (WHO) recommends a schedule of 0, 6, 14 weeks or 0, 6, 10, 14 weeks (if there is no shortage of vaccine) so that the coverage rate is high, and the infants develop immunity at an earlier age. India follows the four-dose schedule.

There is confusion regarding administration of hepatitis-B vaccine in term low birthweight (LBW) babies. In most of the Western world, preterms constitute majority of LBW babies in contrary to developed countries, including India, where most of the LBW babies are born at term. Most of the studies have observed poor antibody response to HBV vaccine in preterm infants weighing <2000 g, and based on these reports, guidelines for HBV vaccine in preterm babies have been framed. However, in term very low birthweight babies, no clear guideline exists. Few trials done in the past in term low birthweight babies have shown good immunogenicity. In one of the study to compare immunogenicity of term LBW *vs* preterm babies, authors observed the seroconversion (>10 IU/mL) in 86.6% in preterm- compared to 96.7% in term babies [6]. In another recent publication, Kashyap, *et al*. [7] reported that at 9-12 months of age there was no difference in the protective antibody titers among Neonatal intensive care graduates weighing >1800 g or <1800 g at birth. However, in this study, the gestational age of included infants has not been reported. In a study published in this issue of *Indian Pediatrics*, Verma, *et al*. [8] reported no statistically

significant difference in mean geometric titers of HBV antibodies in babies weighing 1800-2499 g or >2500 g, thereby reinforcing the fact that term LBW babies do not differ from normal birthweight term babies in term of antibody response to HBV vaccine.

The present policy of hepatitis B vaccination in term LBW babies should follow as for normal weight term babies provided they are hemodynamically stable. On the contrary, the practice of delay in first dose of HBV vaccine should be followed in preterm infants weighing <2000 g at birth to HBsAg negative mothers. However, in babies born to HbsAg positive mothers, the policy of HBV vaccine and HB immunoglobulin within 12 hours of birth should be practiced, irrespective of birthweight and gestation. The first dose should not be counted in these cases, and three doses as pentavalent vaccine containing HBV as per National schedule should be followed thereafter.

Funding: None; *Competing interest*: None stated.

REFERENCES

1. Dutta AK, Dutta R, Pemde H. Combination vaccines. In: Dutta AK, editor. Childhood Vaccination: A Guide for the Pediatrician. New Delhi: IJP, 2014. p. 58-74.
2. Pentavalent Vaccine: Guide for Health Workers with Answers to Frequently Asked Questions. Ministry of Health and Family welfare Government of India. 2012. Available from: *http://www.searo.who.int/india/topics/routine_immunization/Pentavalent_vaccine_ Guide_for_HWs_with_answers_to_FAQs.pdf.* Accessed April 21, 2018.
3. Rao R, Dhingra MS, B avdekar S, Behera N, Daga SR, Dutta AK, *et al*. A comparison of immunogenicity and safety of an indigenously developed liquid (DTwP-Hib-HBV) pentavalent vaccine with Easy Five and Tritanrix HB + Hiberix in Indian infants administered according to EPI schedule. Hum Vaccine. 2009; 5:425-9.
4. Sharma HJ, Yadav S, Lalwani SK, Kapre SV, Jadhav SS, Chakravarty A, *et al*. Immunogenicity and safety of an indigenously manufactured reconstituted pentavalent (DTwP-Hib- HBV) vaccine in comparison with a foreign competitor following primary and booster immunization in Indian Children . Hum Vaccine. 2011;7:451-7.
5. Gatchalian S, Reyes M, Bernal N, Lefevre I, David MP, Han HH, *et al*. A new DTPw-HBV/Hib vaccine is immunogenic and safe when administered according to the EPI (Expanded Programme for Immunization) schedule and following hepatitis B vaccination at birth. Hum Vaccin. 2005;5:198-203.
6. Arora NK, Ganguly S, Agadi SN, Irshad M, Kohli R, Deo M, *et al*. Hepatitis B immunization in low birth weight infants: do they need an additional dose? Acta Pediatr. 2002;91:995-1001.
7. Kashyap B, Dewan P, Kaur T, Kashyap A, Faridi MMA, Kaur IR. Effect of birth weight on immunogenicity of hepatitis B vaccine among newborn intensive care graduates. Tropical J Med Res. 2017;20:31-35.
8. Verma C, Faridi MMA, Narang M, Kaur IR. Anti-HBs titers following pentavalent immunization (DTwP-HBV-Hib) in term normal weight *vs* low birthweight infants. Indian Pediatr. 2018;55:395-9.