*Review Article*

Pediatric Education and Research
Volume 5 Number 3, September - December 2017
DOI: https://dx.doi.org/10.21088/per.2321.1644.5317.10

# Hexavalent Vaccine

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**Abstract**

Combination vaccines that include multiple antigens in one vaccine are now a widely accepted as an effective means of eliciting protection against several disease at the same time. Owing to improvement in quality and convenient mode of administration, they have become part of routine paediatric practice. Hexavalent vaccine includes diptheria, tetanus, pertussis, hepatitis B, polio and Haemophilus influenzae type b antigens. The studies until now have shown that the vaccine is highly immunogenic and well tolerated. It is now a part of various primary and booster vaccination schedule as well as it is safely given with other vaccines.

**Keyword:** Hexavalent; Hemophilus Influenzae; Hepatitis B.; Pertussis.

## Introduction

The introduction of injectable vaccines targeting new diseases into childhood immunization programs has resulted in the need for combination vaccines to reduce the number of injections given during early childhood. In India and other similar countries, the successful implementation of IPV depends on many aspects of vaccine delivery, including the availability of an effective and affordable vaccine. Combination (multivalent) vaccines have the potential to simplify the currently complex childhood immunization schedules, improve caregiver compliance, and reduce healthcare costs [1].

Hexavalent vaccines containing Diphtheria (D), Tetanus (T), Pertussis (P), Hepatitis B (HBV), Haemophilus influenza B (Hib) and the three IPV antigens have been considered logically and scientifically sound charioteers of such a strategy, and have been touted to be the ultimate combination vaccine for routine immunization. The use of combined vaccine which include several antigen in a single administration, have a number of potential benefits including a reduction in the number of visits and complication related to multiple intramuscular injection, decreased costs of stocking and administering separate vaccine and reduced risk of delayed or missed vaccination [2].

The development of new hexavalent combination vaccines targeting established pathogens is likely to assist in improving compliance and timelines of vaccination in infants.These formulation will however need to be monitored for medium and long term effectiveness amidst growing concern of waning immunity against disease such as pertussis when using acellular pertussis vaccine and possibly hep B. When using combination vaccine the vaccine works by causing the body to produce it's own protection against the bacteria and viruses that causes these different infections-

- Diphtheria
- Tetanus
- Pertussis
- Hep B
- Poliomyelitis
- Haemophilus influenzae type B [3]

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**Received on** 12.07.2017, **Accepted on** 17.08.2017

*Content*

After shaking the normal appearance of the vaccine is a whitish cloudy suspension it contains:

- Each 0.5 ml dose contains
- At least 20 IU of diphtheria toxoid
- At least 40 IU of tetanus toxoid
- 25 microgm of pertussis toxoid and
- 25 microgm of pertussis filamentous hemagglutinin
- 10 microgm of hep B surface antigen
- 40 D antigen units of polio virus type 1
- 8 D antigen units of polio virus type 2
- 32 D antigen units of polio virus type 3
- 12 microgm of haemophilus type B
- Polysaccharides conjugated to 23-36 microgm of tetanus protein
- The other ingredients includes Sodium phosphate dibasic

Potassium phosphate monobasic Trometamol, sucrose, essential amino acids ( cysteine, tyrosine, arginine hydrochloride, Histidine, isoleucine, leucine, lysine hydrochloride, methionine, phenylalanine, threonine, tryptophan and valine) and water for injectionsn[4].

*Available Vaccines*

Hexavac® (Sanofi Pasteur MSD, Lyon, France) was licensed in Europe in October 2000 as a paediatric primary and booster immunization and is widely used in many European countries. One single dose is composed of D toxoid (≥20 IU), T toxoid (≥ 40 IU), pertussis toxoid (PT) (25 μg), pertussis filamentous haemagglutinin (FHA) (25 μg), HBsAg (produced from recombinant strain of the yeast *Saccharromyces cerevisiae*) (5.0 μg), P1 (Mahoney strain) (40 DAU), P2 (MEF 1 strain) (8 DAU), P3 (Saukett strain) (32 DAU) and Hib (polyribosylribitol phosphate) 12 μg conjugated to tetanus toxoid (24 μg). Several comparative, controlled clinical trials deemed Hexavac to be very effective in assuring long-term protection against all of the indicated target diseases with a high degree of safety and tolerance. It was also deemed non-inferior or equivalent to comparator vaccines, including both separate vaccine components and Infanrix hexa, the second hexavalent vaccine available in this time period. However, in September 2005 the European Medicines Agency recommended suspension of Hexavac marketing authorization because of the reduced immunization properties of the hepatitis B virus (HBV) component [5].

Infarix: ensed as Hexavac in 2000, Infanrix® (GSK, Riixensart, Belgium) hexa is the only hexavalent vaccine authorized for paediatric use in Europe. Its composition is similar to that of Hexavac with two main exceptions. In addition to the pertussis antigens PT and FHA, pertactin (PRN 8 μg) is also included. HBsAg is present in a doubled amount, 10 μg instead of 5 μg. Additionally, unlike Hexavac, Hib antigen needs to be reconstituted before use. Several studies have evaluated the immunogenicity, safety and tolerability of this vaccine after primary immunization (two or three doses in the first 6 months of age according to the schedules recommended for infants) and after a booster dose at 12–15 months of age in comparison with several DTaP-based pentavalent vaccines administered in conjunction with monovalent HBV or Hib vaccines. Several studies have also compared Infanrix hexa with Hexavac. Evaluation of immunogenicity was performed on blood samples drawn 1 month after the last primary series dose and 1 month after the booster administration. Antibody concentrations against D and T toxoids of ≥ 0.1 IU/mL, HBsAg of ≥ 10 IU/L, polyribosylribitol phosphate polysaccharide (PRP) of ≥ 0.15 mg/mL and/or ≥ 1 mg/mL (markers of short-term and long-term protective immunity, respectively) and against P1, P2 and P3 antigens of ≥ 1 : 8 were considered the cut-off values to evaluate seroconversion and seroprotection rates. Moreover, because no generally accepted seroprotective antibody levels for pertussis antigens were established, vaccine seroresponse/seropositivity rates against PT, FHA and PRN were assessed and vaccine response was defined as the proportion of patients with post-vaccination antibody titres of ≥ 5 U/mL in initially seronegative infants and minimal maintenance of pre-vaccination antibody titres in infants who were seropositive before vaccination (i.e. titres ≥ 5 U/mL). Seropositivity rates were defined as the proportion of infants with antibody titres ≥ 5 U/mL. Throughout all of the studies evaluating an immune response it was demonstrated that all components of Infanrix hexa were highly immunogenic and equivalent or non-inferior to comparators [6].

The same pharmaceutical company that produced Hexavac has developed a new hexavalent vaccine, Hexyon® (Sanofi Pasteur MSD, Lyon, France). It has the same composition against D, T, P, polio and Hib, but differs in hepatitis B content. Instead of 5 μg HBsAg produced from recombinant strain 2150-2-3 of the yeast *Saccharromyces cerevisiae*, it includes 10 μg of HBsAg produced in the yeast *Hansenula polymorpha.* Hexyon has been evaluated in several clinical trials and is currently registered in markets outside Europe for the primary immunization of children from 6

weeks of age and for booster vaccination up to 24 months of age. It is a liquid vaccine that does not require reconstitution of any component before injection, facilitating administration and reducing the risk of medication error. The immunogenicity of Hexyon used for primary vaccination has been evaluated after three doses of the vaccine, according to the recommended immunization schedules of the countries in which the trials were conducted When Hexyon was evaluated before and after booster dose, it was administered at 15–18 months of age. In all primary series trials. Hexyon immunogenicity and safety were compared with standard doses of licensed vaccines. Quadrivalent, pentavalent and hexavalent vaccines were used as comparators, with the addition of monovalent vaccines lacking in the combined preparations. Antibody concentrations against D, T, PT, FHA, P1, P2, P3 and Hib were generally evaluated with the same criteria and methods previously described for Infanrix hexa with the exception of pertussis antigens, for which an four-fold or greater increase from baseline in antibody concentration was predefined as the surrogate measure of seroconversion. Immune response was systematically similar to that obtained with comparators [7].

*Storage*

Keep it in refrigerator, store at 2°C to 8°C under these recommended storage conditions the vaccine is stable for 36 months after the date of manufacture. It should not be frozen.

Do not use vaccine after the expiry date which is stated on the carton after expiry. Do not use vaccine if the packaging is torn or show sign of tampering.

Keep out of reach and sight of children.

Keep vaccine in the original pack until it is time for it to be given.

Medicine should not be disposed of via waste water or household waste [8].

*Dosage and Schedule of Vaccination*

Vaccine should be administered intramuscularly. The recommended injection sites are generally the antero lateral aspect of upper thigh in infants and toddlers and deltoid muscle in older children. Primary vaccination schedule consists of three doses of 0.5 ml (such as 6,10,14 weeks) to be administered at an interval of at least 4 weeks. All vaccination schedules including the expand program on immunization can be used whether or not a dose of hep B vaccine has been given at birth where a dose of hep B vaccine is given at birth. The hexavalent vaccine can be used for supplementary doses of hep B vaccine from the age of 6 weeks. If a second dose of hep B vaccine is required before this age monovalent hep B vaccine should be used [9].

*Booster Vaccination*

After primary vaccination (e.g. 6, 10, 14 weeks; 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) with Hexaxim, a booster dose of HepB and Hib must be administered during the second year of life and at least 6 months after the last priming dose. In addition, if the priming schedule used is 6, 10 and 14 weeks a booster dose of polio vaccine should be given. Hexaxim or any other vaccine containing HepB, Hib and, if necessary, polio antigens may be used to accomplish boosting of the immune responses to these antigens.Booster doses should be given in accordance with the official recommendations [10].

*Side Effects*

1. Very common

   Pain redness loss of appetite sleeping vomiting Crying irritability fever
2. Common

   Abnormal crying diarrhea injection site hardness
3. Uncommon

   Allergic reaction lump at injection site high fever
4. Rare

   Rash large reaction at injection site
5. Very rare

   Pale flappy and unresponsive serious allergic reaction convulsions [11]

*Contraindication*

History of several allergic reaction to any component of the vaccine or to any pertussis vaccine after previous administration of vaccine or a vaccine containing the same component constituents. Encephalopathy of unknown etiology within 7 days of administration of a previous dose of any vaccine containing pertussis antigens [12]. In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria tetanus hep B polio and hib vaccine. Children suffering from progressive neurological disorders, uncontrolled epilepsy and progressive encephalopathy vaccination must be postponed in case of moderate or severe febrile and or acute disease [13].

*Seroconvertion*

The research paper by Chhatwal, et al. [7] published in this edition of Indian Paediatrics evaluates the efficacy of one such vaccine that is already approved in many countries, and is being used in their national schedules. The authors demonstrate very good seroconversion for all components even without a control group, and show how it can be integrated into the current immunization schedules. Moreover, the fully liquid preparations of hexavalent vaccines have distinct advantages over those which require reconstitution. Average preparation time is found to be almost half for the fully-liquid vaccine compared the non-fully-liquid vaccine. In the same study, almost all health care personnel (97.6%) stated that they would prefer the use of the fully-liquid vaccine in their daily practice [14].

*Current Status*

There have been a few issues with the combination vaccines themselves in the past. Hexavac (Sanofi Pasteur MSD, Lyon, France), which was licensed in Europe in 2000 as a pediatric primary and booster immunization, was recommended for suspension of marketing authorization by European Medicines Agency in September 2005 because of the reduced immunization properties of the HBV component [15]. However, the newer vaccine from the same manufacturers – Hexyon or Hexaxim – has a higher HBsAg content and uses a different method for its production. This seems to have resulted in higher immunogenicity compared to hexavac [16]. A possible temporal association between first immunization with hexavac and the occurrence of sudden unexpected death was also suspected. This claim was strongly refuted on further investigation. The other widely used hexavalent vaccine Infanrixhexa (GSK, Riixensart, Belgium), which contains three pertussis antigens (PT, FHA and PRN), has been demonstrated to be immunogenic, effective, safe and well tolerated in children regardless of gestational age at birth, and not significantly different from the vaccines used as comparators. The immunogenicity seems superior to Hexavac for hepatitis B until 7–9 years of age [17]. Furthermore, vaccination with this DTaP-HBV-IPV/Hib in infancy induces sustained seroprotection and immune memory against HBV even in 12-13 year-old adolescents . The comparison of this vaccine between two schedules in Indian infants has also been recently published. With regards to the current study, the immunological response with co-administration of PCV7 and rotavirus vaccine was not studied. Also, the persistence of seroprotection, especially with pertussis (having two antigens), and the effect of administration of rotavirus has not been studied [18].

## Conclusion

Hexavalent formulations are already a necessary component of the vaccination Schedule, and would be even more pertinent in the days ahead. Seroconversion or seroprotective titres of antibodies against all antigens were achieved in the majority of infants following a primary series of three doses administered at 1-2-month intervals from 2 months of age. Hexavalent vaccine also induced immunologic memory, as evidenced by the anamnestic response to booster vaccination at 12-18 months of age [19]. These responses were comparable with those seen following concomitant administration of Pentavac (DTaP-IPV//PRP-T) and monovalent hepatitis B vaccine (H-B-Vax II), and were also within the ranges observed for other relevant licensed vaccines. However, they would need to be monitored for long-term effectiveness in view of the growing concern of waning immunity against diseases such as pertussis when using acellular-pertussis vaccine, and possibly hepatitis B when using combination vaccine [20].

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