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Hexavalent vaccines for immunization in paediatric age

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Abstract

Despite the potential for protection against a broad spectrum of pathogens, the availability of an increased number of effective vaccines could lead to a significant reduction in vaccination coverage as the result of issues with implementation of new vaccines within existing protocols. To overcome these problems, the development of combined vaccines has been promoted. The use of combined vaccines offers a number of potential benefits, including a reduction in the number of patient visits, reduced complications associated with multiple intramuscular injections, decreased costs of stocking and administering separate vaccines, and a lowering of the risk of delayed or missed vaccinations. The hexavalent vaccine includes antigens against diphtheria, tetanus, acellular pertussis (DTaP), hepatitis B (HBsAg), poliomyelitis (P1, P2, P3) and *Haemophilus influenzae* type B (Hib) infections. The primary goal of this review is to discuss the immunogenicity, efficacy, safety and tolerability of several hexavalent preparations that are either commercially available or still under development.

Keywords: Anti-HBs, combined vaccines, hepatitis B, hexavalent vaccine, pertactin, pertussis
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Introduction

Over the last 20 years a significant number of new effective vaccines against infectious diseases have become available. Most of these have been adopted worldwide for use in children, with a relevant increase in the complexity of paediatric immunization schedules [1]. However, these regimens also increase the number of injections administered in a single visit, leading many immunization providers and parents to refuse one or more immunizations because of the child's fear of needles [2] and pain [3–7] in addition to a number of unsubstantiated concerns regarding safety [8,9]. Consequently, the availability of more vaccines could lead to a significant reduction in vaccination coverage through greater difficulties in implementing programmes for new vaccines. To overcome these issues, the development of combined vaccines was promoted. The use of combined vaccines, which include several antigens in a single administration, have a number of potential benefits including a reduction in the number of visits and complications related to multiple intramuscular injections, decreased costs of stocking and administering separate vaccines, and reduced risk of delayed or missed vaccinations [10]. The combined diphtheria, tetanus and pertussis vaccine, which includes a whole cell pertussis component (DTwP) or two or more pertussis antigens (DTaP), has already been incorporated into the national immunization schedules of several countries worldwide. This served as the core formulation to which other vaccines were added. To gain acceptance by health authorities, combination products had to demonstrate that their use was not associated with any significant decrease in immunogenicity or efficacy, or increase in reactogenicity with any component compared with the individual vaccine given separately [11].

One formulation known as the hexavalent vaccine combines DTaP with antigens against hepatitis B (HBsAg), poliomyelitis (P1, P2, P3) and *Haemophilus influenzae* type B (Hib) infection. A number of similar but not identical hexavalent preparations have been developed by pharmaceutical companies. The primary goal of this review is to discuss the immunogenicity, efficacy, safety and tolerability of several hexavalent preparations that are either commercially available or still under development.

Hexavac

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 [12]. 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 [13]. In particular, it was found that although >95% of children vaccinated with Hexavac seroconverted and had protective antibody concentrations (≥10 IU/L) 1 month after primary immunization, 5–20% of them had relatively low antibody titres (≤100 IU/L) [14–16]. Moreover, these children had a significantly diminished response to a subsequent booster dose compared with children with greater antibody titres after the primary series [14–16]. Data confirming the low immunogenicity of the hepatitis B component of Hexavac were further collected when this vaccine was administered in conjunction with the heptavalent pneumococcal conjugate vaccine (PCV7) or with the meningococcal type C conjugate vaccine. In both cases, vaccinated children had lower than expected anti-HB seroconversion rates and antibody geometric mean titres (GMTs) [16,17]. Because peak antibody levels achieved after primary and booster immunizations condition the length of the period during which concentrations remain within the protective range, it was assumed that in a proportion of children immunized with Hexavac the vaccine might not have assured protection against hepatitis B during adolescence and adulthood. Consequently, the vaccine lost authorization for use in children and was withdrawn from the market. Moreover, although the European Medicines Agency did not mandate the immediate revaccination of children that had received Hexavac, some health authorities recommended the administration of a booster dose of hepatitis B vaccine to ensure long-term adequate protection [18].

However, further studies have clarified the characteristics of the immune response evoked by the hepatitis B component of Hexavac, apparently reducing the importance of its lower antibody production for children in the first years of life. Initial surveillance studies did not report evidence of breakthrough HBV infections in children vaccinated with Hexavac. In Italy, a country where this vaccine was largely used, no case was reported between 2000 and 2009, i.e. at least 3–4 years after the last vaccine dose [19]. Moreover, it was demonstrated that in healthy vaccinated children the immunological memory for HBsAg might persist regardless of the presence of protective antibodies, providing effective protection even in those showing waning or undetectable concentrations of anti-HBs after primary vaccination [19–21]. In the study carried out by Zanetti *et al.*, which included 831 children 5–6 years old who had received Hexavac at 3, 5 and 11–12 months of age. The study noted that despite the fact that over 60% of them did not have protective anti-HBs concentrations at the moment of administration of the booster dose, a protective antibody response (≥10 IU/L) was evoked in 92.1% of study participants [21]. This was considered the best evidence that even in the absence of protective antibody levels, children who had received Hexavac maintained T-cell memory and were able to trigger anti-HBs production by B cells when exposed to the viral antigen. The study concluded that because hepatitis B has a long incubation period, the effective immune memory of primed children assures the possibility of developing adequate protection against acute disease and the development of a chronic carrier state, independent of the antibody level [21]. Consequently, a booster dose of hepatitis B vaccine was considered not mandatory in immunocompetent participants who were given Hexavac [21]. However, a recent meta-analysis of studies that have evaluated the persistence of protection after hepatitis B vaccination identified maternal carrier status (OR 2.37; 95% CI 1.11–5.08), administration of a lower vaccine dosage than presently recommended (OR 0.14; 95% CI 0.06–0.30) and the gap time between the last and preceding doses of the primary vaccine series (OR 0.44; 95% CI 0.22–0.86) as determinants for persistence of anti-HBsAg antibodies ≥10 IU/L [22]. A lower vaccine dosage was also associated with failure to respond to booster (OR 0.20; 95% CI 0.10–0.38) [22]. Because Hexavac HBsAg content was only 5 μg, the possibility that children who received this vaccine could be at higher risk of losing immune memory and developing infections of HBV in adolescence or in adulthood cannot be excluded. On the other hand, recent studies showed that immune memory may diminish during the second decade post-vaccination (particularly in children vaccinated at birth), suggesting the need for a booster dose