

Protection against six childhood diseases with a hexavalent vaccine

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Background

There is an urgent call for combined vaccines, containing multiple antigens, to ensure compliance by physicians and parents with the increasing number of vaccines recommended for children. To address this need, GlaxoSmithKline (GSK) Biologicals has developed a range of acellular pertussis-based diphtheria, tetanus, pertussis (DTPa) combination vaccines, the cornerstone of which is *Infanrix™* (DTPa-GSK). These combination vaccines allow for flexibility and variations in schedules and recommendations in different countries. GSK's hexavalent vaccine (DTPa-HBV-IPV/Hib) covers six main diseases against which vaccination is recommended in many countries: diphtheria, tetanus, pertussis, hepatitis B, polio and *Haemophilus influenzae* type b.

Clinical development

In extensive clinical trials, the hexavalent GSK vaccine was well-tolerated and induced protective antibody levels against diphtheria, tetanus, hepatitis B and polio. Decreased levels of antibody against *H. influenzae* type b were not considered clinically relevant mainly because they were compensated for by the induction of immune memory. The three pertussis antigens (PT, FHA and PRN) produced levels of antibodies that were equivalent to those specifically generated in efficacy trials with DTPa-GSK vaccine. Further support for the protective capacity of the hexavalent vaccine against pertussis came from mouse model data and post-marketing effectiveness studies.

Conclusions

This manuscript provides an overview of the clinical characteristics, immunogenicity, efficacy and reactogenicity of the hexavalent GSK vaccine. The safety and effectiveness of this combination will permit vaccination against six diseases with single injections, minimize the distress to infants and children, improve cost-effectiveness, and extend vaccine coverage. In addition, the hexavalent combination lends itself as the vaccine of choice for parents and healthcare providers for childhood vaccination schedules.

Key words:

Vaccines. Diphtheria-tetanus-acellular pertussis vaccines. Hepatitis B. Poliomyelitis. Haemophilus influenzae type b.

INTRODUCTION

Childhood vaccination is becoming a challenging undertaking for healthcare providers and parents as more and more new vaccines become available. With the ever-increasing number of injections required to fully immunize a child against all of the vaccine-preventable diseases, there is a great need to simplify the administration of existing vaccines.

Combined vaccines that protect against several diseases in single injections are a welcome accomplishment that have improved the acceptance of and simplified the implementation of childhood immunization. Scientific advances in immunology have and will continue to result in more new vaccines in the future. It will be a daunting task to add them to the already busy vaccination schedules without the benefit of combined vaccines.

In response to the need for simplification, GlaxoSmithKline Biologicals has developed a range of DTPa based combination vaccines. The cornerstone, *Infanrix™*, referred to hereinafter as DTPa-GSK, was first licensed in 1994 and is available in more than 60 countries, including the United States. More than 70 million doses have been distributed; half of the children in Europe and the United States receive GSK DTPa for their primary vaccination.

During the initial development of GSK's DTPa combinations in the early 1990's, there was no agreement throughout Europe regarding vaccination schedules or which vaccines to combine. From this initial stage arose what is now referred to as the DTPa-based family of vaccines (table 1), to accommodate the recommendations in different countries. The combinations cover six main diseases against which vaccination is recommended in many

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TABLE 1. DTPa-based pediatric combination vaccines

DTPa-GSK	DTPa/Hib
DTPa-HBV	DTPa-HBV/Hib
DTPa-IPV	DTPa-IPV/Hib
DTPa-HBV-IPV	DTPa-HBV-IPV/Hib

DTPa: diphtheria, tetanus, and the acellular pertussis antigens, PT, FHA and pertactin; Hib: lyophilized PRP-T conjugate; HBV: recombinant HBsAg; IPV: inactivated enhanced-potency poliomyelitis.

TABLE 2. DTPa-GSK hexavalent vaccine: primary immunization trials

Author (reference number)	Country	Principal investigator	Schedule (months)	Number of infants vaccinated
Blatter et al ²	USA	Blatter	2,4,6	134
Blatter et al ³	USA	Blatter	2,4,6*	525
Schmitt et al ⁴	Germany	Schmitt	3,4,5	179
Cohen et al ⁵	France	Cohen	2,3,4	166
Black ^{6**}	USA	Black	2,4,6	1,076
Avdicova et al ^{7**}	Slovakia	Avdicova	3,5,11	155
Nolan ^{8**}	Australia	Nolan	2,4,6	182
Meyer et al ^{9,10}	Germany	Zepp	3,4,5	49
Jahn et al ¹¹	Germany	Zepp	3,4,5	1,581
Bravo ^{12**}	Philippines	Bravo	1 ^{1/2} ,2 ^{1/2} ,3 ^{1/2} *	144
Heininger et al ¹³	Germany	Heininger	3,4,5	555
Total				4,746

*One study group received HBV at birth; **principal investigator.

TABLE 3. Hexavalent vaccine seroprotection rates for antigens with established surrogate markers of protection; summary of all studies and schedules

Antibody	Definition of minimal seroprotective titre	% of subjects with seroprotective titres
Anti-diphtheria	0.1 IU/ml	≥ 98.5
Anti-tetanus	0.1 IU/ml	≥ 99.2
Anti-HBs	10 mIU/ml	≥ 98.5
Anti-polio serotype 1	1:8	≥ 99.2
Anti-polio 2 serotype 2	1:8	≥ 94.5
Anti-polio 3 serotype 3	1:8	≥ 98.8

developed countries: diphtheria, tetanus, *pertussis*, hepatitis B, polio and *Haemophilus influenzae*.

Depending on local recommended schedules and individual preferences, the combinations respond to changing needs offering greater flexibility. New developments in immunization in the past decade such as *a*) the acellular pertussis vaccine, which is unquestionably better tolerated than the whole cell pertussis vaccine, *b*) the introduction of Hib and hepatitis B vaccines in the World

Health Organisation's Expanded Programme on Immunization, *c*) an increasing shift in the use of IPV vaccine over the oral polio vaccine in developed countries and *d*) the arrival of new vaccines such as the conjugate pneumococcal vaccine against *Streptococcus pneumoniae* infection and conjugate meningococcal vaccine against type C bacterial meningitis, all have, or will have an effect on local vaccination schedules within a particular country or region.

The hexavalent vaccine, the most comprehensive combination vaccine to date, contains antigens against all six diseases and offers maximal comfort by reducing the number of injections. Since approval of GSK's DTPa-HBV-IPV/Hib vaccine in Europe by the European Medicine Evaluation Agency (EMEA), in October 2000, more than two million doses have been distributed.

CLINICAL DEVELOPMENT OF THE HEXAVALENT VACCINE

The hexavalent vaccine combines the antigens with hepatitis B virus surface antigen (HBV) and three serotypes of inactivated polio virus in a 0.5 ml liquid formulation that is used to reconstitute a lyophilized conjugated *H. influenzae b* antigen (Hib). This combination is referred to as DTPa-HBV-IPV/Hib.

The recombinant hepatitis B surface antigen is the same as in Engerix[®]-B, which was licensed in 1986 and is the leading hepatitis B vaccine worldwide. The enhanced potency inactivated polio vaccine was developed by GSK Biologicals and contains the formalin inactivated strains: Type 1: Mahoney strain, Type 2: MEF-1 strain, and Type 3: Saukett strain. The Hib antigen, developed by GSK, is a capsular polyribosylribitol phosphate polysaccharide (PRP), chemically conjugated to a T-cell dependent protein (tetanus) carrier¹, is the basis of the Hiberix[™] vaccine and the DTPa-based Hib combination vaccines. Sixty million doses of Hiberix[™] vaccine have been distributed in 76 countries, more than 10 million of which are DTPa-based Hib combination vaccines.

The DTPa-HBV-IPV/Hib hexavalent vaccine has been extensively studied: more than 4700 children (between 6 and 16 weeks at the time of the first immunization) have been enrolled in primary vaccination studies designed to evaluate the hexavalent vaccine's immunogenicity and reactogenicity using different vaccination schedules, as shown in table 2²⁻¹³.

IMMUNOGENICITY OF THE HEXAVALENT VACCINE

Most of the vaccinated children reached protective antibody titres for diphtheria, tetanus, hepatitis B and polio; vaccine antigens for which there are reference titres that act as a surrogate marker of protection (table 3). Regarding the response to Hib antigen and the immunogenicity of pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin (PRN), the hexavalent vaccine was com-

pared to separate administration of vaccines². A total of 268 patients were randomized to two treatment arms in the same schedule that is used in Spain (2, 4, 6 months): 134 children were vaccinated with the hexavalent vaccine and 134 were vaccinated with four separate injections: DTPa, HBV, OPV and Hib. The results are presented in table 4.

After the third vaccination, all children who received the hexavalent vaccine had anti-PRP titres ≥ 0.15 $\mu\text{g/ml}$ and 84% had antibody concentrations ≥ 1.0 $\mu\text{g/ml}$. Compared to separate administration, Hib conjugated vaccine when given as a mixed administration with DTPa elicits a lower antibody response to PRP. However, it is able to mount a large and rapid immune response to a booster with plain PRP (unconjugated), indicating that the extemporaneous combination provides good priming and successful induction of immunological memory^{14,15}. The lower Hib concentration was of no clinical relevance and the DTPa-based Hib combination vaccines provide substantial benefit to the recipient¹⁶. This was since confirmed by a population-based effectiveness surveillance in Germany, that showed a continued trend of lower Hib disease in the population since the introduction of universal Hib vaccination without any change since introduction of DTPa-based Hib combinations¹⁷. Antibodies against the three pertussis antigens were detected in 100% of the vaccinated infants, which is similar to other immunogenicity studies^{4,7,13}.

There were no clinically significant differences in serum antibody responses in the children who received the hexavalent vaccine compared to those who received the separate vaccine components concomitantly at different sites^{2,4,7,13}.

VACCINE EFFICACY AGAINST PERTUSSIS

The efficacy of the DTPa-GSK vaccine used as the basis for the hexavalent vaccine is well documented, having been tested in two large pertussis efficacy trials of different designs. The first of the two trials was a German household contact study designed to evaluate the efficacy of a three-dose primary vaccination with the DTPa-GSK vaccine against "typical" pertussis (defined as a spasmodic cough of 21 days or longer with confirmation of *B. pertussis* infection by culture or serology)¹⁸. Surveillance in Germany was conducted for suspected first household cases of typical pertussis, comprising 22,505 children who were vaccinated with the DTPa vaccine at 3, 4 and 5 months of age. Four hundred fifty-three households with index cases comprising 360 evaluable contacts were analysed. Vaccine efficacy was 88.7% (95% CI, 76.6-94.6%).

The second pertussis efficacy study was a double-blind, prospective, cohort study of 14,751 infants conducted in Italy by the Istituto Superiore di Sanita and the United States National Institutes of Health¹⁹. In this trial infants

TABLE 4. Hexavalent vaccine Hib seroprotection rates and pertussis seropositivity compared to licensed vaccines in USA

Antibody	Hexavalent vaccine			Comparator group (DTPa + HBV + Hib + OPV)		
	N	% SP	GMT (95% CI)	N	% SP	GMT (95% CI)
Anti-PT	106	100	67.4 (59.6-76.3)	93	100	41.8 (36.6-47.6)
Anti-FHA	97	100	288 (257-322)	98	100	302.8 (267-343)
Anti-PRN	106	100	168.2 (147-193)	98	100	136.9 (116-162)
Anti-PRP	106			98		
≥ 0.15 $\mu\text{g/ml}$		100	2.65 (2.16-3.24)	96.9		5.53 (4.14-7.38)
≥ 1.0 $\mu\text{g/ml}$		84	-	91.8		-

N: number of subjects with available results; SP: seropositivity rate, for pertussis (% of subjects with titres > 5 EL.U/ml); Infanrix Hexavalent Product Monograph. GlaxoSmithKline 2001.

were randomly assigned to vaccination with DTPa-GSK, a second (genetically engineered) acellular pertussis vaccine (Chiron-Biocine), a DTPw (Connaught whole-cell pertussis vaccine) or a DT vaccine (without pertussis antigens). The vaccines were given at 2, 4 and 6 months of age. The cases included in the analysis were children with cough that began 30 days or more after the completion of immunization. The primary case definition of pertussis vaccine efficacy was a laboratory-confirmed *B. pertussis* infection (a cough episode that lasted ≥ 7 days with confirmation by culture or serology), plus ≥ 14 days of spasmodic cough or ≥ 21 days of any cough. For both of the DTPa vaccines, the efficacy was 84% (95% CI, 76-89%), which was comparable to that observed in the household contact study. Children in this study were under active surveillance up to six years of age with no further pertussis boosters given²⁰. Protective efficacy remained high at 78% (95% CI, 71-83%), indicating that immunological memory was induced.

The potential for protection against pertussis by the hexavalent vaccine was evaluated by comparing the reverse cumulative distribution curves (RCC) of the hexavalent vaccine to the RCC derived from the German household contact efficacy study⁴. The RCCs for PT, FHA and PRN antibodies for the hexavalent vaccine showed extensive overlap with those for DTPa-GSK confirming that the additional antigens did not affect the immune response to the pertussis antigens indicating that the efficacy of the hexavalent vaccine can be expected to be similar to that of the DTPa-GSK vaccine^{4,21}.

Further evidence of efficacy of DTPa-GSK has also been demonstrated in an established and validated animal model to provide a means of testing the overall effect of vaccination on respiratory clearance of *B. pertussis* based on the analysis of lung clearance of *B. pertussis*

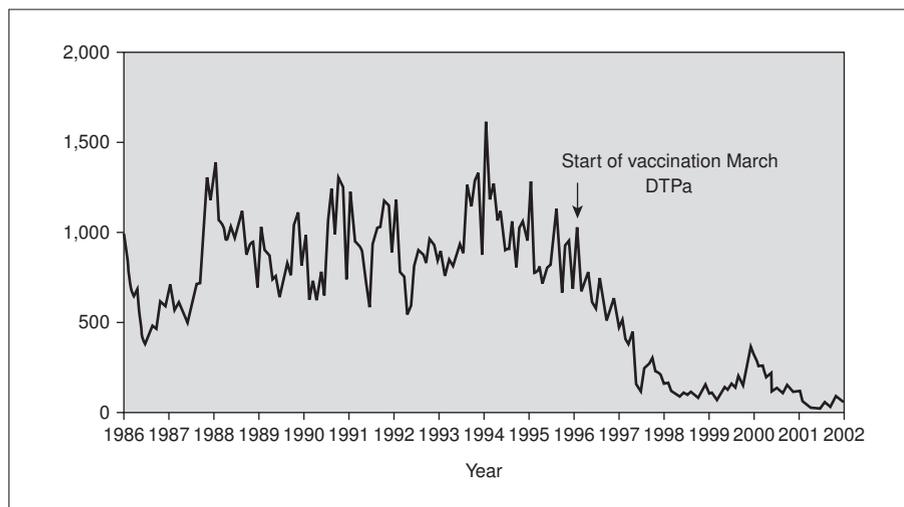


Figure 1. Pertussis surveillance: Sweden 1986-2001. Culture-confirmed cases of pertussis per month.

following a standard intranasal challenge in vaccinated and unvaccinated mice²². Because of ethical and practical difficulties in performing clinical studies of pertussis vaccine efficacy, the use of such animal models has been encouraged. Increasingly complex DTPa-based combination vaccines have been tested in these models in order to observe the overall effect these vaccines have on bacterial clearance, to complement clinical trials on their immunogenicity and safety. The intranasal model is reproducible and accurate in reflecting the protective capacity of acellular pertussis vaccines previously observed in clinical trials in infants. The model also offers the opportunity to dissect the individual components of acellular pertussis vaccines to determine their relative contribution to protection. This aerosol model demonstrated a significant correlation between bacterial clearance activity and the efficacy of the individual vaccines from clinical trials and it has shown that tri-component acellular pertussis vaccines are more effective than mono- or bi-component vaccines thus reflecting observations in clinical practice^{22,23}.

In addition to the evidence from the mouse model and to the well-established efficacy of acellular pertussis vaccines in clinical trials, efficacy has also been evaluated in clinical practice. A postmarketing surveillance study was conducted by the Swedish Institute for Infectious Disease Control²⁴. Repeated epidemics of pertussis were occurring in Sweden in the absence of vaccination prior to introduction of general childhood acellular pertussis vaccination in 1996.

In 1996-97, primarily infants were vaccinated at 3, 5 and 12 months of age using DTPa-GSK. Within a few months of the initiation of the programme, vaccine coverage reached 95%. The incidence of pertussis dropped by 90% in the following three years as shown in figure 1²⁴. Furthermore, in the few vaccinated children who developed disease, the clinical course was less severe than in unvaccinated children. Combined DTPa-IPV/Hib vaccines are now being used in Sweden and monitoring is continuing.

Post vaccination surveillance was also conducted in Germany in order to assess the efficacy of universal acellular pertussis vaccination in infants. Vaccine coverage of children born between 1996 and 1998 was assessed by telephone survey. Data from children hospitalized with pertussis in 1997-1998 and those with pertussis complications in 1997-2000 were acquired by hospital-based active surveillance. Vaccine effectiveness was as high as 91.8% (95% CI 84.7-95.7) after the second dose, establishing the fact that the vaccine was highly effective in preventing pertussis-related hospitalizations²⁵.

REACTOGENICITY OF THE HEXAVALENT VACCINE

The overall reactogenicity profile of a primary course of the hexavalent vaccine evaluated in clinical studies show that the incidence of local and general symptoms are comparable to those observed after separate administration of individual components or other DTPa-based vaccines, while requiring fewer injections^{5,26}. In a study by Cohen et al, the hexavalent vaccine was compared to a commercial combined DTPw-IPV/HIB vaccine⁵. Despite the fact that there are more antigen components in the hexavalent vaccine, the hexavalent was much less reactogenic than the whole-cell combined vaccine (fig. 2)⁵.

The post-marketing safety profile of the DTPa-GSK hexavalent vaccine and other DTPa-based combinations are shown in table 5. The numbers of adverse events and serious adverse events reported following the hexavalent combination vaccine is similar to that of the DTPa-GSK vaccine²⁶.

CONCLUSION

In extensive clinical trials, the hexavalent GSK vaccine was well tolerated and induced protective antibody levels against diphtheria, tetanus, hepatitis B and polio. The lower levels of antibody against *H. influenzae* were compensated for by the induction of immune memory and therefore not considered clinically relevant. The three pertussis antigens (PT, FHA and PRN) generated levels of

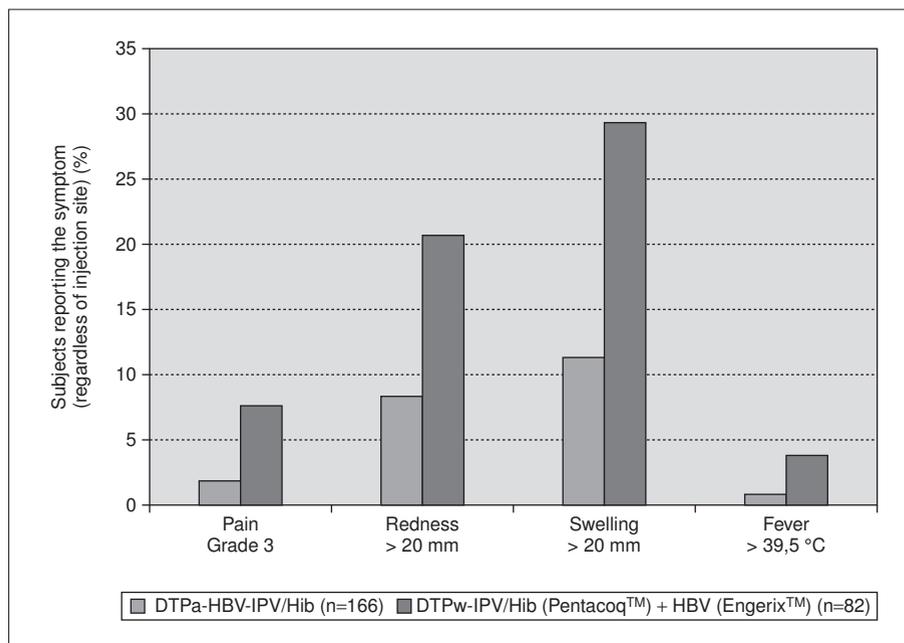


Figure 2. Reactogenicity of GSK hexavalent vaccine vs. a whole-cell pertussis-containing combination vaccine.

TABLE 5. DTPa-based combinations: post-marketing safety profile up to 30 June 2002

Vaccine combinations	Adverse events (AE) reported	Serious adverse events (SAE) reported	SAE/AE (%)
DTPa (Infanrix™) licensed in 1994 > 54 million doses administered	2141	481	22.5
Infanrix combinations* > 26.5 million doses administered	2145	408	19.0
DTPa-based hexavalent licensed in 2000 .2.1 million doses distributed	276	68	24.6

*DTPa-HBV, DTPa-IPV, DTPa-HBV-IPV, DTPa/Hib, DTPa-HBV/Hib, DTPa-IPV/Hib.

antibodies that were equivalent to those specifically generated in efficacy trials with DTPa-GSK vaccine. Further support to the protective capacity of the hexavalent vaccine against pertussis came from mouse model data as well as postmarketing effectiveness studies.

The safety and effectiveness of the hexavalent GSK vaccine combination will enable vaccination against six diseases with a single injection, thus minimizing the distress to infants and children, improving cost-effectiveness, and improving vaccine coverage. The obvious convenience of this acellular pertussis-based hexavalent vaccine lends itself to being the choice of parents and healthcare providers for childhood vaccination schedules. The use of the hexavalent vaccine will certainly facilitate better compliance and therefore, higher immunization rates.

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