Clinical Evaluation of a DTaP-HepB-IPV Combined Vaccine

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Abstract

Objective: To provide an overview of prelicensure clinical data for a new pediatric vaccine that combines diphtheria, tetanus, acellular pertussis, hepatitis B, and inactivated poliovirus vaccines into a single injection (DTaP-HepB-IPV combined vaccine; Pediarix, GlaxoSmithKline Biologicals, Rixensart, Belgium).

Methods: The safety and immunogenicity of DTaP-HepB-IPV combined vaccine have been evaluated extensively in clinical trials in infants. To date, DTaP-HepB-IPV combined vaccine has been administered to more than 7000 infants as a 3-dose primary series during the first year of life.

Results: Studies show that DTaP-HepB-IPV combined vaccine is generally safe, well tolerated, and has not caused any significant serious adverse events. The rates of solicited and unsolicited reports of adverse reactions following vaccination were similar between groups receiving DTaP-HepB-IPV combined vaccine and comparator groups receiving the vaccine components separately. DTaP-HepB-IPV combined vaccine induces immunogenicity (as measured by seroprotection or vaccine response rates to each of the vaccine components [diphtheria, tetanus, 3 pertussis antigens, hepatitis B, and poliovirus types 1, 2, and 3]) similar to licensed vaccine components administered separately.

Conclusion: In prelicensure clinical studies, DTaP-HepB-IPV combined vaccine was safe and immunogenic when given to infants as a primary 3-dose series. As a single injection of multiple vaccine components, DTaP-HepB-IPV combined vaccine may provide a safe and effective alternative to the current multiple-injection immunization regimen.

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With the increasing number of recommended vaccines in the US childhood immunization schedule,[1] there is an urgent need to develop safe and effective vaccines that combine multiple antigens into a single injection. In the United States and worldwide, there is a long history of incorporating combination vaccines into routine pediatric practice. One of the first combination or multivalent vaccines (trivalent diphtheria, tetanus toxoids, and pertussis), DTP, became available in the 1940s. Other combination vaccines, such as measles-mumps-rubella, and poliovirus (poliovirus types 1, 2, and 3) were developed more than 40 years ago, and have been a standard part of the childhood vaccine schedule.

During the past decade, there has been a gradual increase in the number of vaccines added to the recommended immunization schedule.[1] With licensure of a pneumococcal conjugate vaccine (Prevnar, Lederle Laboratories, Pearl River, NY) in 2000, and the change in 1999 from an orally administered live poliovirus vaccine to an all injectable inactivated poliovirus vaccine (IPV) schedule, the number of injections required to comply with current immunization recommendations has increased even further. Infants today may receive up to 5 injections during an immunization visit and up to a total of 20 injections during the first 2 years of life. These advances in the immunization schedule have resulted in an acute need to develop new combination vaccines for infants. In 1999, the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians recommended that combination vaccines be used whenever possible and encouraged further research on the development of combination vaccines.[2] It is anticipated that

combination vaccines will not only help alleviate discomfort for infants and their parents, but will reduce vaccine administration and storage costs, simplify the immunization schedule, and potentially improve immunization compliance. Simplification of the immunization schedule with combination vaccines is essential to accommodate newly developed vaccines against other serious infectious diseases not currently being prevented.

Recently, a diphtheria and tetanus toxoids, acellular pertussis vaccine adsorbed, hepatitis B (recombinant), and inactivated poliovirus (DTaP-HepB-IPV combined) vaccine has been licensed by the US Food and Drug Administration (FDA) (Pediarix, GlaxoSmithKline Biologicals, Rixensart, Belgium). This new combination vaccine has been extensively evaluated in prelicensure clinical studies as a 3-dose primary series given to infants during the first year of life. This article reviews the results of studies with this DTaP-HepB-IPV combined vaccine and implications for further evaluation.

Evaluation of Combination Vaccines

The development of combination vaccines is not a simple process of mixing currently licensed products together. Combining vaccine antigens into a single injectable product requires an evaluation of how this process impacts vaccine potency (immunogenicity of the antigen), stability, safety (adverse reactions), and immune response. These issues differ for every combination vaccine evaluated, and prior studies have shown that some combinations of antigens, preservatives, and adjuvants may have a negative impact on vaccine potency. Examples of such interactions include diminished antibody response to the *Haemophilus influenzae* type b (Hib) vaccine when combined with DTaP vaccine[3-6] and diminished polio antibody levels when IPV is combined with a thimerosal-containing vaccine.[7,8] Clinical studies of combination vaccines are targeted at demonstrating that the combination is generally comparable to available separate vaccine components. The new combined vaccine cannot be more reactogenic or less immunogenic than the separately administered licensed vaccines. In addition, before licensure, studies must demonstrate that the new combination vaccine does not impact the safety of or immune response to other recommended vaccines that may be administered at the same visit.

Evaluation of immunogenicity (antibody response) to a combination vaccine can present challenges. For some diseases, a certain level of measurable antibody is associated with protection (referred to as a correlate of protection), and those levels can be used to evaluate serologic end points and vaccine immunogenicity.[9] Correlates of protection exist for hepatitis B, diphtheria, tetanus, Hib, and poliovirus. Diminished immunogenicity occurs when there is a decrease in the amount of antibody induced by the vaccine, or when the proportion of individuals with induced antibody levels higher than the correlate of protection is less than expected.

For diseases without correlates of protection, such as pertussis, serologic end points are more difficult to define. Lack of serologic correlates may limit the ability to interpret a potential reduction in immunogenicity for the pertussis components in a combination vaccine. A test of equivalence that compares the immune responses to the combination vaccine with those of the vaccines given separately is required by the FDA.[10] The accuracy of this test is dependent on the ability to define an acceptable difference between the combination vaccine and its components prior to conducting the study.

Development and Composition of a DTaP-HepB-IPV Combined Vaccine

In the United States and many other countries, DTP or DTaP, oral or inactivated poliovirus, and HepB vaccines are recommended for routine childhood immunization. Because these vaccines can be administered on the same schedule, the availability of a vaccine that combines these antigens would result in fewer injections at each infant immunization visit and further the goals set forth for combination vaccine products.

The backbone of DTaP-HepB-IPV combined vaccine (Pediarix) (**Table 1**) is a DTaP vaccine (Infanrix, GlaxoSmithKline Biologicals,

Rixensart, Belgium) currently licensed in 69 countries worldwide and routinely given at 2, 4, and 6 months of age in the United States. The hepatitis B component of this combination vaccine is similar to Engerix-B (GlaxoSmithKline Biologicals, Rixensart, Belgium), which is a recombinant HepB vaccine licensed in 147 countries (in 74 countries for pediatric use) and routinely administered to infants in the United States. The hepatitis B component in this DTaP-HepB-IPV combined vaccine undergoes 1 additional purification step prior to adsorption. The IPV component is an enhanced-potency preparation containing the same types, strains, and quantity of poliovirus and manufactured in a manner similar to the vaccine currently licensed in the United States (IPOL, Aventis Pasteur SA, Lyon, France). The enhanced IPV in this DTaP-HepB-IPV combined vaccine is included in several combination vaccines licensed outside of the United States. The preservative used in the manufacturing of this combined vaccine is 2-phenoxyethanol, which is the same preservative currently used in Havrix (GlaxoSmithKline Biologicals, Rixensart, Belgium), Infanrix, and IPOL (poliovirus vaccine inactivated). Thimerosal is used early in the manufacturing process of the hepatitis B component, but is then removed through purification and not detectable in the final product. This DTaP-HepB-IPV combined vaccine is supplied as a 0.5-mL single-unit dose. It is a turbid white suspension that must be shaken well and administered intramuscularly.

Clinical Evaluation of a DTaP-HepB-IPV Combined Vaccine

DTaP-HepB-IPV combined vaccine has been evaluated in 16 clinical studies in Europe and the United States involving 7693 infants who received a primary series of the vaccine during the first year of life (Data on file, GlaxoSmithKline). Data from 6 clinical studies of DTaP-HepB-IPV combined vaccine have been published[11-16] (**Table 2**). In each study, the safety of DTaP-HepB-IPV combined vaccine when given concurrently with a Hib conjugate vaccine was assessed. Serologic responses to the vaccine were evaluated in most of the studies.

The methods for safety assessment were similar in all studies.[11-16] Following administration of DTaP-HepB-IPV combined vaccine, infants were observed for 15 to 30 minutes for any immediate reactions. Parents or guardians of infants were asked to complete diary cards and answer questions about local (injection-site) and systemic reactions on the day of vaccination and for the following 3 days. In all studies, the local reactions of pain, redness, and swelling were solicited for DTaP-HepB-IPV combined vaccine and separate vaccine injection sites. General symptoms solicited included fever, diarrhea, loss of appetite, restlessness, vomiting, irritability/fussiness, unusual crying, and drowsiness/sleepiness. Adverse reactions were graded from 1 to 3 in intensity. For local reactions, grade 3 was defined as swelling or redness of 20 mm or more, pain that prevented

Table 1. Composition of DTaP-HepB-IPV Combined Vaccine (Pediarix, GlaxoSmithKline Biologicals, Rixensart, Belgium)

Antigen/Ingredient	Vaccine Component	Amount in Each 0.5-mL Dose
Diphtheria (D)	Diphtheria toxoid	≥2 U/mL (25 Lf)
Tetanus (T)	Tetanus toxoid	≥2 U/mL (10 Lf)
Pertussis, acellular (aP)	Pertussis toxoid (PT)	25 µg
	Pertactin (PRN)	8 µg
	Filamentous hemagglutinin (FHA)	25 µg
Hepatitis B (HepB)	Recombinant HBsAg protein	10 µg
Inactivated poliovirus (IPV)	Poliovirus type 1 (Mahoney strain)	40 D-antigen units
	Poliovirus type 2 (MEF-1 strain)	8 D-antigen units
	Poliovirus type 3 (Saukett strain)	32 D-antigen units
Preservative	2-phenoxyethanol	2.5 mg
Adjuvant	Aluminum	≤0.85 mg

The amount of thimerosal is below the detectable limit.
Lf indicates limit of flocculation.

Table 2. Summary of Published Clinical Studies of DTaP-HepB-IPV Combined Vaccine in Infants

Description	Age at Vaccination (mo)	N	Reference
Safety, immunogenicity of DTaP-HepB-IPV combined vaccine compared with vaccine components given separately (including comparison of separate OPV) and given concurrently with Hib vaccine	2, 4, 6	200 (groups 1 and 4)	11
Safety, immunogenicity of 3 consistency lots of DTaP-HepB-IPV combined vaccine given concurrently with Hib vaccine	2, 4, 6	363	12
Safety, immunogenicity of DTaP-HepB-IPV combined vaccine given concurrently with Hib vaccine compared with DTaP-HepB-IPV/Hib vaccine	2, 3, 4	179	13
Safety, immunogenicity of DTaP-HepB-IPV combined vaccine given concurrently with 1 of 4 Hib conjugate vaccines	3, 4.5, 6	549	14
Safety, immunogenicity of DTaP-HepB-IPV combined vaccine given concurrently with Hib vaccine compared with DTwP-IPV/Hib given concurrently with HepB vaccine	1.5, 2.5, 3.5	160	15
Safety of DTaP-HepB-IPV combined vaccine given concurrently with 1 of 4 Hib conjugate vaccines and compared with the vaccine components given separately (including separate OPV and IPV)	3, 4, 5	3029	16

DTaP indicates diphtheria-tetanus-acellular pertussis vaccine; DTwP, diphtheria-tetanus-whole-cell pertussis vaccine; HepB, hepatitis B virus vaccine; Hib, *Haemophilus influenzae* type b vaccine; IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine.

normal activities, or pain when the limb was moved. Fever was defined as rectal body temperature of 38°C (100.4°F) or higher, and grade 3 fever as higher than 39.5°C (103.1°F). For all other general adverse events, grade 3 was defined as preventing normal daily activities. Reports of unsolicited adverse events were collected for 30 days following each vaccine dose and were similarly graded as 1 to 3 in intensity. Serious adverse events (including any illness or event that was life threatening, resulted in or prolonged hospitalization, or resulted in death or significant disability) were collected for the duration of the study.

For evaluation of immunogenicity,[11-15] previously described and standard assays were performed for diphtheria, tetanus, poliovirus types 1, 2 and 3, hepatitis B surface antibody, pertussis antigens, and *Haemophilus influenzae* type b-polyribosyl ribitol phosphate (Hib-PRP).[17-22] Cutoff levels used to define seroprotection were as follows: ≥0.1 IU/mL for diphtheria and tetanus, ≥10 mIU/mL for hepatitis B, and ≥1:8 for polioviruses 1, 2, and 3. For seroprotection against Hib, 2 cutoffs are reported when available: ≥0.15 µg/mL and ≥1.0 µg/mL. Because there are no known serologic correlates of protection for pertussis, in all but

Table 3. Incidence of Solicited Reports of Systemic Reactions Following Any Dose of DTaP-HepB-IPV Combined Vaccine or Separately Administered Component Vaccines

Reference	Vaccine Doses	Fever (%)		Restlessness (%)	Loss of Appetite (%)	Vomiting (%)	Diarrhea (%)	Sleepiness (%)	Unusual Crying (%)	Fussiness (%)
		≥38ºC	>39.5ºC							
11 (Control)	269	14.1	0.7	22.3*†	18.2*	7.8*	14.9	34.2	2.2	53.9
11	291	19.2	1.0	19.6*†	18.2*	5.2*	11.0	33.3	2.1	55.0
12	1058*	28.6*	0.8	29.3*	20.6*	11.1*	13.7*	35.4*	NS	61.2*
13	533*	17.7	0.4	22.8	16.5*	9.4*	10.7*	22.8	NS	19.2
14	1635*	8.7*	0.1*	41.8*	16.2*	6.7*	9.0*	NS	19.0*	NS
15	475	10.3	0.2	10.9	6.3*	4.0*	4.0*	9.5*	NS	21.5
16	9034*	20.0*	1.4	34.3*	14.8*	7.6*	10.9*	NS	18.6*	NS

Control group (administration of separate vaccine components) from reference 11; subjects received diphtheria-tetanus-acellular pertussis vaccine (DTaP [Infanrix, GlaxoSmithKline Biologicals, Rixensart, Belgium]), hepatitis B virus vaccine (HepB [Engerix-B, GlaxoSmithKline Biologicals, Rixensart, Belgium]), oral poliovirus vaccine (OPV [Orimune, Lederle Laboratories, Pearl River, NY]), and *Haemophilus influenzae* type b vaccine (Hib [OmniHIB, Aventis Pasteur SA, Lyon, France]).
IPV indicates inactivated poliovirus; NS, not solicited.
*Data on file, GlaxoSmithKline.
†Solicited as sleeping less than usual.

1 study,[11] a vaccine response to each of the pertussis antigens was based on an infant's prevaccination antibody level. If the infant was previously seronegative to a pertussis antigen, vaccine response was demonstrated if the infant had an antibody level equal to the cutoff of the assay (5 EU/mL) or higher 1 month after completion of the primary series. If the infant had antibodies to a pertussis antigen prior to vaccination, a positive vaccine response was defined as an equivalent or higher antibody level 1 month after completion of the primary vaccine series. In the study by Yeh and colleagues,[11] 2 cutoff levels were used to define response to each of the pertussis antigens: ≥10 EU/mL and ≥20 EU/mL, which are 2- and 4-fold higher, respectively, than the highest minimum level of quantitation for the pertussis assays.

Safety Results

Currently, safety and reactogenicity data are available for 22 961 doses of DTaP-HepB-IPV combined vaccine given to infants as part of the primary vaccination series (Data on file, GlaxoSmithKline). Safety data from published studies involving administration of 13 295 doses of DTaP-HepB-IPV combined vaccine are available, including the percentage of infants with a systemic adverse reaction after any dose (**Table 3**), and the percentage of infants with local reactions (**Table 4**). Overall, the rates of reports of solicited systemic and local reactions were similar between infants receiving DTaP-HepB-IPV combined vaccine and those receiving separate vaccinations, and reactions generally resolved within the 4-day follow-up period.

A study by Zepp and colleagues[16] provides the largest set of safety data in infants given DTaP-HepB-IPV combined vaccine as a primary vaccine series. In this large-scale safety study conducted at multiple pediatric clinics in Germany, investigators found that 490 of 3029 infants (16.2%) given DTaP-HepB-IPV combined vaccine, and 151 of 744 infants (20.3%) in the control group, experienced a grade 3 adverse event (a 4.1% difference, 90% confidence interval [CI], 1.41-7.13, which met pre-established criteria for noninferiority). With regard to solicited

Table 4. Incidence of Solicited Reports of Local Reactions Following Any Dose of DTaP-HepB-IPV Combined Vaccine or Separately Administered Component Vaccines

Reference	Vaccine Doses	Pain (%)		Redness (%)		Swelling (%)	
		Any	Grade 3*	Any	Grade 3*	Any	Grade 3*
11 (Control)	269	25.3	1.9†	13.0	0.0†	9.3	0.7†
11	291	27.8	0.7†	18.2	1.0†	13.7	2.1†
12	1056†	26.9†	3.4	31.7†	4.5	18.4†	3.6
13	533†	24.0	1.1	43.0	3.9	36.9	5.6
14	1635†	15.8†	0.3†	45.4†	5.7†	34.0†	6.9†
15	475	19.4	1.9	43.6	2.9	22.3	4.6
16	9034†	11.6†	2.0	23.7†	1.1†	17.2†	1.5†

Control group (administration of separate vaccine components) from reference 11; subjects received diphtheria-tetanus-acellular pertussis vaccine (DTaP [Infanrix, GlaxoSmithKline Biologicals, Rixensart, Belgium]), hepatitis B virus vaccine (HepB [Engerix-B, GlaxoSmithKline Biologicals, Rixensart, Belgium]), oral poliovirus vaccine (OPV [Orimune, Lederle Laboratories, Pearl River, NY]), and *Haemophilus influenzae* type b vaccine (Hib [OmniHIB, Aventis Pasteur SA, Lyon, France]).

*Grade 3 indicates "for swelling and redness"; grade 3 was defined as ≥20 mm. For pain, grade 3 was defined as preventing normal activities.

†Data on file, GlaxoSmithKline.

systemic reactions of any intensity, the rates of restlessness, loss of appetite, vomiting, and diarrhea were similar between groups.

In some studies, the percentage of infants reporting fever was greater in the group that received DTaP-HepB-IPV combined vaccine than in the comparator, separate vaccine group. Yeh and colleagues[11] found that the rate of fever (temperature ≥38°C) following all 291 doses in the DTaP-HepB-IPV combined vaccine group was 19.2% compared with 14.1% following the 269 doses in the control group, but this was not statistically significant. Although Zepp and colleagues[16] reported a higher incidence of fever of 38°C or higher in DTaP-HepB-IPV combined vaccine recipients following all vaccine doses compared with control vaccine recipients (20.0% vs 12.7%) (Data on file, GlaxoSmithKline), there were no significant differences in the incidence of grade 3 fever (1.4% vs 0.8%).[16] The groups were similar with respect to duration of fever (episodes lasting 1 to 2 days), use of antipyretics (ranging from 15.7% to 17.5% of infants depending on which 1 of the 4 Hib vaccines used in the study the infant received), or hospitalizations associated with fever (0.23% of infants receiving DTaP-HepB-IPV combined vaccine vs 0.39% of control subjects).[16] The authors noted that the higher rate of fever was in the study group that received the combination vaccine concurrently with PRP-OMP (PRP conjugated to *Neisseria meningitidis* outer-membrane protein) Hib conjugate vaccine, compared with other groups that received the combination vaccine concurrently with other US-licensed Hib conjugate vaccines (PRP-T [PRP conjugated to tetanus toxoid] or HbOC [oligosaccharides conjugated to diphtheria CRM_{197} protein]; significantly higher with 95% CIs not overlapping for dose 1 and dose 3).[16]

Overall rates of solicited local reactions such as pain, redness, and swelling were similar between groups receiving DTaP-HepB-IPV combined vaccine versus separate components (local reactions were measured at the DTaP injection site). In 12 of the 16 available studies, there were 2 reports of thigh swelling with DTaP-HepB-IPV combined vaccine (Data on file, GlaxoSmithKline). Both cases occurred in the German safety study, with the first case occurring after dose 1 and graded as mild (easily tolerated), and the sec-

Table 5. Summary of Immunogenicity Data With DTaP-HepB-IPV Combined Vaccine or Separately Administered Component Vaccines

		Diphtheria		Tetanus		Hepatitis B		Polio 1		Polio 2		Polio 3		Hib		
Reference	N	% SP (≥0.1 IU/mL)	GMC (IU/mL)	% SP (≥0.1 IU/mL)	GMC (IU/mL)	% SP (≥10 mIU/mL)	GMC (mIU/mL)	% SP (≥1:8)	GMT	% SP (≥1:8)	GMT	% SP (≥1:8)	GMT	% ≥ 0.15 μg/mL	% ≥ 1.0 μg/mL	GMC (μg/mL)
11 (Control)	73-78	100	0.8	100	2.3	100	805	98.6	819	100	1262	100	453	100*	94.9	7.8
11	86-91	98.9	1.3	100	3.7	100	1661	100	415	98.8	514	100	1729	98.9*	94.4	6.2
12	325-328*	99.7	1.0	100	2.7	99.1	1681	100	328*	100	319	100	895	100	90.9*	5.4
13	97-141	100	1.81	100	1.96	98.6	524.9	100	404.7	100	165.7	100	913.9	100	88.6	4.45
15	150	98.7	0.54	100	1.8	98.7	1016.2	98.7	535.1	98.0	154.0	98.7	731.1	96.0	65.3	1.9

Control group (administration of separate vaccine components) from reference 11. Subjects received diphtheria-tetanus-acellular pertussis vaccine (DTaP [Infanrix, GlaxoSmithKline Biologicals, Rixensart, Belgium]), hepatitis B virus vaccine (HepB [Engerix-B, GlaxoSmithKline Biologicals, Rixensart, Belgium]), oral poliovirus vaccine (OPV [Orimune, Lederle Laboratories, Pearl River, NY]), and *Haemophilus influenzae* type b vaccine (Hib [OmniHIB, Aventis Pasteur SA, Lyon, France]).
GMC/GMT indicates geometric mean concentration/titer; NA, not available; % SP, percentage of subjects with seroprotective antibody levels. *Data on file, GlaxoSmithKline.

ond case occurring after dose 2 and rated as moderate (sufficiently uncomfortable to interfere with normal everyday activities). Each infant received subsequent doses of DTaP-HepB-IPV combined vaccine without sequelae.

Reports of serious adverse events occurring among study subjects were collected in all 16 studies that evaluated DTaP-HepB-IPV combined vaccine, including several that are unpublished. Of the 7693 infants who received DTaP-HepB-IPV combined vaccine, 231 reported at least 1 serious adverse event (Data on file, GlaxoSmithKline). Of those, 9 events were thought to have a causal relationship to DTaP-HepB-IPV combined vaccine. In all but 1 of the cases, the infant received a concurrently administered Hib conjugate vaccine, and all of the infants recovered following the event. Six of the serious adverse events involved onset of fever within 4 days of vaccination with DTaP-HepB-IPV combined vaccine (classified as related or possibly related); 2 of these events included concurrent viral illness. One infant developed hyperpyrexia, diarrhea, and vomiting on day 3 following the second dose of DTaP-HepB-IPV combined vaccine. Two infants enrolled in the large-scale German safety study developed pain and redness at the Hib vaccination site on day 0 following the first dose of DTaP-HepB-IPV combined vaccine: 1 of the infants also developed fever and restlessness, and the other had an onset of symptoms within 30 minutes, which included site swelling and unusual crying. One infant in the large US trial[11] developed exanthema (skin eruption) macular and urticaria on day 3 following the third dose of DTaP-HepB-IPV combined vaccine. Finally, 1 infant developed obstructive bronchitis and rhinitis, wheeze, persistent crying, and cough after the first dose of DTaP-HepB-IPV combined vaccine was given. Among the 7693 infants who received DTaP-HepB-IPV combined vaccine in 16 clinical trials, as part of a primary series, there have been 5 deaths, none of which was thought to be causally related to vaccination (Data on file, GlaxoSmithKline).

Table 6. Summary of Vaccine Response Rates and Antibody Concentrations to Pertussis Antigens 1 Month Following Primary Vaccination Series With DTaP-HepB-IPV Combined Vaccine

		PT		PRN		FHA	
Reference	N	% VR*	GMC (EU/mL)	% VR*	GMC (EU/mL)	% VR*	GMC (EU/mL)
11 (Control)	73-78	93.8	47.5	91.7	108.6	100	153.2
11	86-91	100	97.1	100	150.4	100	119.1
12	303-328†	99.7	99.1	89.0†	111.8	98.3†	167.7
13	127-130	98.4	58.1	97.7	170.8	99.2	154.4
15	144-148	97.7	53.1	93.4	105.1	86.8	60.8

FHA indicates filamentous hemagglutinin; GMC, geometric mean concentration; PRN, pertactin; PT, pertussis toxin.
*% VR, vaccine response defined as appearance of antibodies ≥5 EU/mL in initially seronegative subjects and at least maintenance of prevaccination antibody levels in initially seropositive subjects for references 12, 13, and 15. % VR response defined as antibody concentration ≥20 EU/mL in all subjects for reference 11.
†Data on file, GlaxoSmithKline.

Immunogenicity Results

Immunogenicity results of the 4 studies that performed serologic analyses of each vaccine component 1 month following primary vaccination with DTaP-HepB-IPV combined vaccine and concomitant Hib are presented in **Tables 5** and **6**. There were 3 different vaccination schedules among the 4 studies. The data demonstrate that 98% or more of infants in each study had seroprotective antibody levels for diphtheria, tetanus, hepatitis B, and polioviruses 1, 2, and 3 at 1 month following the third dose of DTaP-HepB-IPV combined vaccine. For Hib, 96% or more of infants had antibody concentrations of 0.15 µg/mL or higher. The proportion of infants with antibody concentrations of 1.0 µg/mL or higher was not available in 1 study, and was variable among the other 3 studies. It is important to note that not all of these studies used the same Hib vaccine. In the studies by Blatter and colleagues[12] and Yeh and colleagues,[11] the Hib vaccine administered was OmniHib (Aventis Pasteur SA, Lyon, France). In the other 2 studies,[13,15] the Hib vaccine that was administered was Hiberix (GlaxoSmithKline Biologicals, Rixensart, Belgium). For the pertussis antigens, more than 97% of infants responded to pertussis toxoid, 89% or more to pertactin, and more than 86% to filamentous hemagglutinin.

Of the 4 studies, only 2 evaluated the noninferiority of DTaP-HepB-IPV combined vaccine compared with licensed products given separately.[11,15] Gylca and colleagues[15] compared DTaP-HepB-IPV combined vaccine with diphtheria-tetanus-whole-cell pertussis-IPV/Hib (Pentacoq, Aventis Pasteur, Lyon, France; licensed in Europe) with HepB vaccine given as a separate injection. For both the seroprotection rates and geometric mean concentrations/titers, DTaP-HepB-IPV combined vaccine was equivalent to the comparator group for diphtheria, tetanus, hepatitis B, and poliovirus types 1, 2, and 3. The DTaP-HepB-IPV combined vaccine group had a higher proportion of vaccine responses to each pertussis antigen than the comparator group. Response to Hib was not subject to the test of noninferiority in this study. Yeh and colleagues[11] published the primary US phase 3 study of DTaP-HepB-IPV combined vaccine, which compared the combination with separately administered licensed DTaP (Infanrix), oral poliovirus vaccine (Orimune, Lederle Laboratories, Pearl River, NY), and hepatitis B (Engerix-B) vaccines. For all antigens, the DTaP-HepB-IPV combined vaccine group was similar to the groups receiving separate

vaccines with respect to seroprotection or vaccine response rates, although there were minor differences with respect to antibody levels for some antigens.

Usonis and Bakasenas[14] evaluated the reactogenicity and immunogenicity of 3 licensed Hib vaccines when given concomitantly with DTaP-HepB-IPV combined vaccine. As such, antipolyribosylribitol phosphate responses were reported, but responses to each of the vaccine antigens in DTaP-HepB-IPV combined vaccine were not reported, and therefore are not included in Tables 5 and 6. The study demonstrated that DTaP-HepB-IPV combined vaccine did not interfere with the immunogenicity of Hib vaccines when given at a separate injection site.

Conclusion

When DTaP-HepB-IPV combined vaccine is given as a primary 3-dose series, rates of reports of solicited and unsolicited adverse reactions are similar to those seen in infants receiving separate vaccines. Although a higher incidence of fever occurred with DTaP-HepB-IPV combined vaccine, severe (grade 3) fever was not significantly increased, and the higher rate of fever did not result in clinically significant consequences. The immunogenicity of DTaP-HepB-IPV combined vaccine is similar to administration of licensed components given separately.

In published studies, DTaP-HepB-IPV combined vaccine was administered at the same time as Hib conjugate vaccine at a different injection site and there was no evidence that DTaP-HepB-IPV combined vaccine interfered with the response to Hib vaccine. At the time these studies were conducted, pneumococcal conjugate vaccine was not available. Coadministration of DTaP-HepB-IPV combined vaccine with pneumococcal conjugate vaccine does not appear to affect reactogenicity rates,[23] and studies to further evaluate this regimen are ongoing. As with all newly licensed products, postlicensure evaluations will need to be conducted.

Based on the results of safety and immunogenicity studies conducted to date, DTaP-HepB-IPV combined vaccine appears to be well tolerated and immunogenic and may provide an acceptable alternative to separate administration of multiple vaccines. Use of DTaP-HepB-IPV combined vaccine is an efficient way to vaccinate infants against 5 serious diseases with a 3-dose primary series and would allow for introduction of newer vaccines into the recommended pediatric immunization schedule.

NOTE: Questions regarding unpublished data may be addressed by calling GlaxoSmithKline at (888) 825-5249.

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