

Safety and Reactogenicity of a Novel DTPa-HBV-IPV Combined Vaccine Given Along With Commercial Hib Vaccines in Comparison With Separate Concomitant Administration of DTPa, Hib, and OPV Vaccines in Infants

Fred Zepp, MD*; Anne Schuind, MD*; Claudius Meyer, PhD*; Roland Sanger, MD†; Achim Kaufhold, MD‡; and Paul Willems, MD‡

ABSTRACT. *Objective.* Combination vaccines simplify vaccine administration and have the potential to promote compliance and cost-effectiveness by decreasing the number of injections needed to immunize a child. The objective of this study was to assess the safety and reactogenicity of the diphtheria-tetanus toxoid-acellular pertussis-hepatitis B virus-inactivated polio virus (DTPa-HBV-IPV) vaccine when coadministered with different *Haemophilus influenzae* type B (Hib) vaccines in comparison with separate, commercially available, control vaccines in a 3-dose primary vaccination series.

Methods. An open-label, randomized, parallel-group study in 5318 infants who were 8 to 16 weeks of age at enrollment was conducted in 90 centers in Germany. The incidence of adverse events that occurred in infants who received the DTPa-HBV-IPV candidate vaccine coadministered with 1 of 4 different Hib vaccines (given in separate sites; groups 1–4) was compared with the incidence that occurred in infants who received commercially available control vaccines (DTPa, Hib, and oral polio virus [OPV] vaccine; group 5) administered separately. The vaccines were given as a 3-dose primary series at 3, 4, and 5 months of age. Infants were assessed for solicited local and general adverse events for 4 days and for unsolicited adverse events for 30 days after each vaccine dose. The primary endpoint was to rule out a 7.5% increase in infants who experienced grade 3 (defined as preventing normal everyday activities unless otherwise specified) solicited local and general adverse events over the 3-dose primary course after the combined DTPa-HBV-IPV vaccine coadministered with Hib as compared with commercially available vaccines.

Results. During the 3-dose primary course, 490 of 3029 infants (16.2%) in the pooled DTPa-HBV-IPV vaccine groups and 151 of 744 (20.3%) in the control vaccine group experienced a grade 3 adverse event (rate difference [control minus combination] 4.1%; 90% confidence interval, 1.41–7.13). The lower limit of the 90% confidence interval of the observed difference remained above the prespecified –7.5% limit for noninferiority, thereby meeting the primary endpoint. The incidences of

local injection-site reactions were similar for the DTPa-HBV-IPV and DTPa injection sites. Significant differences in the incidence of both local and general adverse events were observed depending on which of the Hib vaccines was coadministered. Infants who received Hib N meningitidis outer-membrane complex protein conjugate vaccine had greater incidences of fever and, to a lesser extent, greater reactions at the Hib injection site than did infants who received other Hib vaccines.

Conclusions. The combination DTPa-HBV-IPV vaccine administered concomitantly with Hib vaccine at separate sites was at least as safe as coadministration of individual DTPa, Hib, and OPV vaccines in terms of the defined endpoints for safety. *Pediatrics* 2002;109(4). URL: <http://www.pediatrics.org/cgi/content/full/109/4/e58>; combination vaccine, diphtheria, pertussis, tetanus, hepatitis B virus, *Haemophilus influenzae* type b, polio.

ABBREVIATIONS. DTPa, diphtheria-tetanus toxoid-acellular pertussis; HBV, hepatitis B virus; Hib, *Haemophilus influenzae* type b; IPV, inactivated polio virus; OPV, oral polio virus; ATP, according-to-protocol; ITT, intention-to-treat; CI, confidence interval; PRP-OMP, *Haemophilus influenzae* type b *Neisseria meningitidis* outer-membrane complex protein conjugate.

Vaccine recommendations for children are becoming more complex as new vaccines are added to an already elaborate immunization schedule. There are 2 ways to accommodate the increased number of vaccines recommended, increase the number of injections at each visit or increase the number of office visits. In the United States, infants receive up to 5 injections per visit to meet the current recommendations using vaccines presently available on the market (diphtheria-tetanus toxoid-acellular pertussis [DTPa], hepatitis B virus [HBV], *Haemophilus influenzae* type b [Hib], inactivated polio virus [IPV], and pneumococcal conjugate vaccines).¹ Both increasing the number of office visits or negative perception of increasing the number of injections per visit may adversely affect compliance because of missed appointments. Combination vaccines provide an opportunity to simplify vaccine administration, reduce missed opportunities, and potentially reduce costs.

Because DTPa, HBV, and IPV vaccines can be administered at the same age, development and investigation of a combination vaccine containing these components is justified. The World Health Organi-

From the *Children's Hospital, Pediatric Immunology and Infectious Diseases, Johannes Gutenberg University, Mainz, Germany; and †GlaxoSmithKline Biologicals S.A., Rixensart, Belgium.

Dr Schuind is currently an employee of GlaxoSmithKline but had no financial affiliation with the company at the time of this study.

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Reprint requests to (F.Z.) Johannes Gutenberg University, Department of Pediatrics, Langenbeckstr 1, D-55131 Mainz, Germany. E-mail: zepp@kinder.klinik.uni-mainz.de

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zation has recommended development of combined DTPa-HBV vaccines,² and a combination DTPa-HBV vaccine had been previously developed and is registered in the European Union and in other countries outside the United States, although it was not yet licensed when this study was conducted.^{3,4} Routine immunization with oral polio virus (OPV) has been replaced with IPV in various regions of the world because the risk to the child of vaccine-associated paralytic poliomyelitis is greater than the risk of contracting wild-type disease.⁵ In addition, there is a contamination risk from strains reverted to neurovirulence excreted by OPV recipients.^{6,7} Widespread use of IPV is key in protecting populations from both wild-type poliovirus and persisting vaccine strains.⁸ The DTPa-HBV-IPV combination vaccine and other such combinations allow for use of IPV without adding another injection.

Hib vaccines are routinely recommended as part of infant vaccination schedules in many countries and have tremendously decreased the incidence of invasive Hib disease in those countries.^{9–11} Three different Hib conjugate vaccines, each unique with regard to the carrier protein, are licensed for primary vaccination in the United States. These 3 vaccines were used in the present trial, as was a Hib tetanus conjugate vaccine manufactured by GlaxoSmithKline Biologicals (Rixensart, Belgium) and licensed for use outside the United States.

For a combination vaccine to become licensed and widely accepted, the combination should not be more reactogenic or less effective than vaccines administered separately. Previous studies^{12,13} established the immunogenicity of a novel combined DTPa-HBV-IPV vaccine and reported the vaccine to be safe and well tolerated. The purpose of this trial was to assess the safety and reactogenicity of the combined DTPa-HBV-IPV vaccine when coadministered as separate injections with commercially available Hib conjugate vaccines in comparison with coadministration of DTPa, Hib, and OPV as separate products in a large cohort of infants. A secondary objective was to determine the frequency of less common adverse events.

METHODS

Study Design

This was an open-label, randomized, parallel-group study of the combination DTPa-HBV-IPV vaccine administered as a separate injection concomitantly with Hib vaccine in comparison with commercially available control vaccines, DTPa, Hib, and OPV (Table 1). Vaccines were administered at 3, 4, and 5 months of age. The study was initiated as a comparative trial with all infants receiving the DTPa-HBV-IPV vaccine with 1 of 4 commercially available Hib vaccines (groups 1–4). After 1569 infants were enrolled, the protocol was amended to add a control group receiving DTPa, Hib, and OPV as separate products at the same visit (group 5). Infants in the control group were not given HBV and received OPV rather than IPV because a combination DTPa-HBV vaccine was not available on the German market and parents and investigators believed that the number of injections would be unacceptably high. For the according-to-protocol (ATP) analysis, only infants who were enrolled in the postamendment period were considered, to avoid any potential bias in the comparison with the control group because of improper randomization. An intention-to-treat (ITT) analysis that included all infants enrolled into the trial (ie, infants enrolled during the pre- and postamendment

TABLE 1. Vaccines Administered by Group

Group	Combination/Control Vaccine(s)	Hib Vaccine
1	DTPa-HBV-IPV*	PRP-T _{GSK}
2	DTPa-HBV-IPV	PRP-T _{AP}
3	DTPa-HBV-IPV	HbOC
4	DTPa-HBV-IPV	PRP-OMP†
5	DTPa, OPV	PRP-T _{AP}

PRP-T_{GSK} indicates PRP-T_{GlaxoSmithKline}; PRP-T_{AP}, PRP-T_{Aventis Pasteur}; HbOC, *Haemophilus influenzae* type b diphtheria CRM₁₉₇ protein conjugate.

* Candidate vaccine manufactured by GlaxoSmithKline.

† Given at 3 and 5 months of age only.

periods) was performed. The study was conducted according to good clinical practice and in accordance with the Declaration of Helsinki, as amended September 1989. The ethics committee at each center reviewed the protocol, and written informed consent was obtained from each parent or guardian before entry of his or her child into the study.

Infants

A total of 5472 healthy infants between the ages of 8 and 16 weeks were enrolled at 90 centers in Germany. Infants were excluded if they had a history of allergic disease likely to be stimulated by the vaccination; previous diphtheria, tetanus, pertussis, hepatitis B, polio, or Hib vaccination or disease; history of progressive neurologic disease, major congenital defect, serious chronic illness, acute febrile illness at the time of the vaccination, or immunosuppressive condition; or if they were undergoing immunosuppressive therapy or had received immunoglobulin therapy or blood products. Infants were withdrawn from the study if they experienced fever $\geq 40.5^{\circ}\text{C}$ (104.9°F rectal); persistent, inconsolable screaming or crying for more than 3 hours within 48 hours of vaccination; seizures; encephalopathy; or hypersensitivity reaction to the vaccine.

Vaccines

Vaccine compositions and manufacturers are provided in Table 2. Vaccines were administered as a 3-dose primary series at 3, 4, and 5 months of age by intramuscular injection in the anterolateral aspect of the thigh (with the exception of OPV). Infants always received the DTPa-containing vaccine in the right thigh and the Hib vaccine in the left thigh. Infants who received *Haemophilus influenzae* type b N meningitidis outer-membrane complex protein conjugate (PRP-OMP) vaccine (group 4) received the Hib vaccine at 3 and 5 months of age only.

Reactogenicity Analysis

Diary cards were used by parents or guardians to solicit local reactions at each injection site individually (pain, redness, and swelling) and general adverse events (diarrhea, fever, restlessness, unusual crying, vomiting, and loss of appetite) on the day of vaccination and for 3 subsequent days. For the analysis, adverse events were graded from 1 to 3 in intensity. For local reactions, grade 3 redness or swelling was defined as areas >20 mm in diameter and grade 3 pain preventing normal daily activities. Fever was defined as rectal body temperature $\geq 38^{\circ}\text{C}$ (100.4°F) and grade 3 fever as a rectal temperature $>39.5^{\circ}\text{C}$ (103.1°F). For all other general adverse events, grade 3 was defined as preventing normal daily activities. In addition, unsolicited adverse events that occurred during the 30 days after each vaccine dose were recorded, and serious adverse events were collected for the entire study period.

Statistical Analysis

The primary objective of this study was to determine whether administration of the DTPa-HBV-IPV vaccine resulted in a clinically significant increase in the proportion of infants who experienced any solicited adverse event graded 3 in intensity compared with the control vaccines over the 3-dose primary course. Noninferiority testing compared pooled data from the 4 DTPa-HBV-IPV + Hib vaccine groups with the control vaccine group for the ATP cohort. The pooled group (groups 1–4, DTPa-HBV-IPV + Hib)

TABLE 2. Vaccine Composition

Vaccine	Composition
DTPa-HBV-IPV	Diphtheria toxoid ≥ 30 IU (25 Lf), tetanus toxoid ≥ 40 IU (10 Lf), PT 25 μg , FHA 25 μg , PRN 8 μg , HBsAg 10 μg , 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, aluminum as salts 0.7 mg in 0.5 mL
Infanrix Penta, GlaxoSmithKline Biologicals)	
Hib vaccines	
HbOC: <i>Haemophilus influenzae</i> type b diphtheria CRM ₁₉₇ protein conjugate (HibTITER, Lederle)	PRP 10 μg , CRM ₁₉₇ protein 25 μg , NaCl 0.9% in 0.5 mL (liquid)
PRP-T _{CSK} : <i>Haemophilus influenzae</i> type b tetanus toxoid conjugate (Hiberix, GlaxoSmithKline Biologicals)	PRP 10 μg , tetanus toxoid ≈ 30 μg , lactose 10 mg in 0.5 mL (lyophilized; saline diluent 9 mg/mL NaCl)
PRP-T _{AP} : <i>Haemophilus influenzae</i> type b tetanus toxoid conjugate vaccine (Act-HIB, Aventis Pasteur)	PRP 10 μg , tetanus toxoid 24 μg , sucrose 42.5 mg in 0.5 mL (lyophilized; saline diluent 4 mg/mL NaCl)
PRP-OMP: <i>Haemophilus influenzae</i> type b <i>Neisseria meningitidis</i> outer-membrane complex protein conjugate vaccine (PedvaxHIB, Merck & Co, Inc)	PRP 15 μg , Group B meningococcal outer membrane 250 μg , lactose 2 mg, Al (OH) ₃ 225 μg in 0.5 mL (lyophilized)
DTPa (Infanrix, GlaxoSmithKline Biologicals)	Diphtheria toxoid ≥ 30 IU (25 Lf), tetanus toxoid ≥ 40 IU (10 Lf), PT 25 μg , FHA 25 μg , PRN 8 μg , and aluminum as salts 0.5 mg in 0.5 mL
OPV vaccine (ORIMUNE, Lederle Laboratories)	Poliovirus type 1 10 ^{5.4} to 10 ^{6.4} TCID ₅₀ , poliovirus type 2 10 ^{4.5} to 10 ^{5.5} TCID ₅₀ , poliovirus type 3 10 ^{5.2} to 10 ^{6.2} TCID ₅₀ in 0.5 mL

PT indicates pertussis toxoid; FHA, filamentous hemagglutinin; PRN, pertactin; HBsAg, hepatitis B surface antigen; PRP, polyribose ribitol phosphate

was determined to be clinically noninferior to the control group (group 5, DTPa + Hib + OPV) if the lower limit of the 90% confidence interval (CI) of the treatment difference (control minus combination) remained above the prespecified -7.5% limit considered clinically acceptable, thereby ruling out a 7.5% increase in the combination group.

All analyses were performed with SAS (version 6.08 or version 6.12; SAS Inc, Cary, NC) and Stat Xact (version 3.0; Cytel Software Corporation, Cambridge, MA). The target sample size was established at 2880 assessable infants in the pooled DTPa-HBV-IPV vaccine group and 720 in the control group to have 99% power to reach the primary objective. This was established on the basis of the expected range for the percentage of infants with grade 3 adverse reactions between 7.2% and 12.5% from previous studies. A 10% attrition rate was anticipated.

RESULTS

Of the 5472 infants enrolled, 5318 completed the protocol. A total of 1569 infants were entered before protocol amendment and 3903 after amendment. For avoiding any bias in the comparison with the separate vaccines caused by a nonrandomized study design, only infants who were enrolled during the post-amendment period (ie, after introduction of the control group) were considered for the ATP analysis. A total of 3773 infants were included in this analysis; 3029 received DTPa-HBV-IPV + Hib vaccines and 744 received the control vaccines. Data on solicited adverse events presented here are limited to the ATP analysis. An ITT analysis was performed, and results were consistent with those for the ATP cohort (data not shown).

Reactogenicity Data for Pooled DTPa-HBV-IPV + Hib Group Versus Control Group

During the entire 3-dose primary course, 16.2% of infants (95% CI, 14.9–17.5) in the pooled DTPa-HBV-IPV + Hib vaccine group and 20.3% (95% CI, 17.5–23.4) in the control vaccine group experienced a solicited adverse event graded 3 in intensity. The difference (control minus combination) in the inci-

dence of grade 3 solicited adverse events between the 2 groups was 4.1% (90% CI, 1.41–7.13). The lower limit of the 90% CI of the observed difference remained above the prespecified -7.5% limit for non-inferiority. The incidences in the pooled DTPa-HBV-IPV group and the control group over a 3-dose primary course were 10.5% and 12.6%, respectively, for grade 3 general adverse events; 7.8% and 12.1%, respectively, for grade 3 local adverse reactions regardless of injection site; 2.0% and 3.6%, respectively, for grade 3 pain regardless of injection site; and 1.4% and 0.8%, respectively, for grade 3 fever. Because noninferiority was demonstrated, the DTPa-HBV-IPV + Hib vaccine group can be considered to be at least as good as the control group with respect to the incidence of grade 3 solicited adverse events.

Unsolicited Adverse Events

Unsolicited adverse events that occurred within 30 days of each vaccination were reported in 1790 infants (59%) in the DTPa-HBV-IPV + Hib vaccine group and 434 (58%) in the control vaccine group. Unsolicited adverse events that occurred in >1% of infants included somnolence, nervousness, fatigue, injection-site reaction, bronchitis, fever, otitis media, viral infection, and upper respiratory tract infection. There was no difference between groups, and the majority of adverse events were graded 1 (easily tolerated) in intensity and were considered unrelated to vaccination.

Reactogenicity Analysis for Individual Treatment Groups

The percentages of infants who experienced solicited local and general adverse events in each treatment group (groups 1–5) during the 3-dose vaccination course also were tabulated.

Local Reactions

Most local adverse reactions were mild or moderate in intensity and resolved within the 4-day follow-up period. Differences in the incidence of pain, swelling, or redness at the DTPa-HBV-IPV vaccine injection sites (groups 1–4) and at the DTPa injection sites (group 5) were reported (Table 3). There was significant variation in local injection-site reactions to the 4 different Hib vaccines. Infants in group 4 who received PRP-OMP vaccine had significantly greater incidences of redness at the Hib injection site than did children who received the other Hib vaccines used in this study (Table 3). The incidences of pain and swelling after the last dose of study vaccines were also significantly greater in infants who received the PRP-OMP vaccine compared with infants who received the other Hib vaccines. However, no differences in the incidence of grade 3 reactions were reported between the groups, and the main differences between groups at the DTPa-HBV-IPV injection site for a given dose suggest that some of the differences observed may be from chance alone.

General Adverse Events

The majority (>97%) of general events reactions resolved within the 4-day follow-up period. It should be noted that the control group received 1 less antigen (HBV vaccine) than did the DTPa-HBV-IPV + Hib groups. Thus, the comparison for general adverse events may be biased in favor of the control group. Even so, rates of restlessness, loss of appetite, vomiting, and diarrhea were similar between groups (Table 4). Significant differences in the incidence of fever (ie, temperature $\geq 38^{\circ}\text{C}$ [100.4°F]) were found according to which Hib vaccine was administered. The incidence of fever was significantly greater in infants in group 4 who received the PRP-OMP vaccine compared with infants who received the other Hib vaccines (Table 4). After the first dose of study vaccines, fever was reported in 41.2% of infants (95% CI, 37.6–44.8) in group 4, and after the third dose of vaccines, the incidence of fever in group 4 was 28.6% (95% CI, 25.0–32.0). This is in contrast to the incidence of fever reported in group 4 after the second vaccine dose (18.0%; 95% CI, 15.0–20.9), which was similar to incidences reported in the other study groups. It must be noted that infants in group 4 did not receive Hib vaccine at this time. Overall, the rates of antipyretic use were low and similar among the groups. During the entire vaccination course, a total of 16.1%, 16.5%, 15.7%, 17.5%, and 17.1% of infants in groups 1 to 5, respectively, received antipyretic medication within 30 days after vaccination.

Serious Adverse Experiences

A total of 112 serious adverse experiences were reported in 100 infants in the total ITT cohort of 5318 infants. Of these, 107 were judged by the investigator to be unrelated to vaccination, 3 were considered to be related to vaccination, and 2 were considered to be possibly related to vaccination. Of the 3 infants who had serious adverse experiences deemed related to vaccination, 1 child had 3 episodes of unusual

crying (defined as crying for >1 hour) that lasted for several hours with pain, redness, and swelling at the Hib injection site after the first doses of DTPa-HBV-IPV and PRP-T_{Aventis Pasteur} vaccines. Additional doses were administered uneventfully. A second infant developed restlessness, fever, and severe pain on pressure at the Hib injection site associated with redness of the entire outer thigh after the first doses of DTPa-HBV-IPV and PRP-OMP vaccines. Additional doses were given without similar events. A third infant developed a high fever associated with restlessness and sleeping more than usual after his second doses of DTPa-HBV-IPV and PRP-OMP vaccines, and the vaccine course was discontinued. Of the 2 infants who were judged to have serious adverse experiences that were possibly related to the vaccination, 1 infant experienced a change in behavior with a fever after the second doses of DTPa-HBV-IPV and *Haemophilus influenzae* type b diphtheria CRM₁₉₇ protein conjugate vaccines, resulting in hospitalization and discontinuation of the vaccine series. A second infant developed fever and tachycardia 1 day after the third doses of DTPa-HBV-IPV and PRP-T_{Aventis Pasteur} vaccines possibly related to concurrent viral infection. Four deaths occurred; none was related to vaccination (2 were attributed to sudden infant death syndrome and 1 was attributed to an underlying convulsive disorder, and 1 infant had a congenital immunodeficiency and died from respiratory arrest resulting from a viral infection).

Adverse Events Associated With B Pertussis-Containing Vaccines

Special attention was paid to serious adverse events that have been described in association with pertussis-containing vaccines: anaphylaxis, febrile and afebrile convulsions, hypotonic hyporesponsive episodes, and encephalopathy. No cases of anaphylaxis were reported during the study. Eighteen cases of allergy or allergic reaction were reported; however, only 1 case, a dermatologic reaction that occurred after the third dose, was judged to be probably related to vaccination. Seven cases of seizures (6 afebrile, 1 febrile) were reported in 6 infants (all in DTPa-HBV-IPV recipients; difference not statistically significant). On the basis of the identified underlying conditions and temporal relationship, none of these cases was considered to be related to the vaccination. Two cases occurred within 4 days of vaccination (1 case associated with idiopathic West syndrome and 1 with an underlying convulsive disorder). Of the remaining 5 episodes in 4 infants, all occurred >2 weeks (up to 40 days) after vaccination, within the context of hypoxic cerebral damage, gastroenteritis with dehydration, rhinopharyngitis with acute dyspnea (convulsions suspected), and cerebral tuberculous sclerosis. No cases of hypotonic-hyporesponsive events or encephalopathy were reported. Although there was a higher incidence of low-grade fever ($\geq 38.5^{\circ}\text{C}/101.3^{\circ}\text{F}$) in DTPa-HBV-IPV vaccine recipients as compared with control vaccine recipients (40.6% vs 27.0%), no significant differences were found in incidence of grade 3 fever ($>39.5^{\circ}\text{C}/103.1^{\circ}\text{F}$; 1.4% vs 0.8%) or duration of fever (the epi-

TABLE 3. Incidence of Solicited Local Adverse Reactions by Dose and Vaccine for Groups 1 to 5 in the ATP Cohort During the 4-Day Follow-up Period

Group: Vaccines	Pain at Injection Site (%) (95% CI)		Redness		Swelling	
	DTPa or DTPa- HBV-IPV	Hib	DTPa or DTPa- HBV-IPV	Hib	DTPa or DTPa- HBV-IPV	Hib
Dose 1						
1: DTPa-HBV-IPV + PRP-T _{CSK} (N = 765)	12.0 (9.8–14.5)	8.4 (6.5–10.6)	17.8 (15.1–20.7)	12.3 (10.0–14.8)	13.2 (10.9–15.8)	5.8 (4.2–7.6)
2: DTPa-HBV-IPV + PRP-T _{AP} (N = 762)	17.8 (15.2–20.8)	18.1 (15.4–21.0)*	18.5 (15.8–21.4)	17.8 (15.2–20.8)*	15.2 (12.7–18.0)	14.6 (12.1–17.3)*
3: DTPa-HBV-IPV + HbOC (N = 764)	9.4 (7.4–11.7)	7.6 (5.8–9.7)	16.0 (13.4–18.8)	11.5 (9.3–14.0)	10.5 (8.4–12.9)	5.5 (4.0–7.4)
4: DTPa-HBV-IPV + PRP-OMP (N = 736)	17.7 (15.0–20.6)	19.4 (16.6–22.5)	22.6 (19.6–25.7)	24.7 (21.6–28.0)†	15.5 (12.9–18.3)	15.6 (13.1–18.5)
5: DTPa + OPV + PRP-T _{AP} (N = 744)	14.4 (11.9–17.1)	17.3 (14.7–20.3)*	16.4 (13.8–19.3)	17.9 (15.2–20.8)*	9.7 (7.6–12.0)	13.0 (10.7–15.7)*
Dose 2						
1: DTPa-HBV-IPV + PRP-T _{CSK} (N = 763)	10.1 (8.0–12.5)	6.0 (4.4–8.0)	25.4 (22.4–28.7)	14.5 (12.1–17.3)	20.4 (17.6–23.5)‡	9.6 (7.6–11.9)
2: DTPa-HBV-IPV + PRP-T _{AP} (N = 757)	11.6 (9.4–14.1)	9.8 (7.8–12.1)	27.9 (24.7–31.2)	17.6 (14.9–20.5)	19.2 (16.4–22.1)‡	9.0 (7.0–11.2)
3: DTPa-HBV-IPV + HbOC (N = 761)	10.1 (8.1–12.5)	6.3 (4.7–8.3)	23.8 (20.8–27.0)	13.7 (11.3–16.3)	16.8 (14.2–19.7)	7.0 (5.3–9.0)
4: DTPa-HBV-IPV + PRP-OMP (N = 735)	9.9 (7.9–12.3)	—	28.8 (25.6–32.3)‡	—	19.2 (16.4–22.2)‡	—
5: DTPa + OPV + PRP-T _{AP} (N = 738)	9.9 (7.8–12.3)	8.4 (6.5–10.6)	21.7 (18.8–24.8)	15.6 (13.0–18.4)	13.1 (10.8–15.8)	7.0 (5.3–9.1)
Dose 3						
1: DTPa-HBV-IPV + PRP-T _{CSK} (N = 755)	9.7 (7.7–12.0)	4.6 (3.2–6.4)	25.4 (22.4–28.7)	15.2 (12.7–18.0)	20.5 (17.7–23.6)	7.9 (6.1–10.1)
2: DTPa-HBV-IPV + PRP-T _{AP} (N = 753)	9.7 (7.7–12.0)	6.6 (5.0–8.7)	24.8 (21.8–28.1)	17.7 (15.0–20.6)	17.4 (14.8–20.3)	8.1 (6.3–10.3)
3: DTPa-HBV-IPV + HbOC (N = 756)	8.2 (6.3–10.4)	5.2 (3.7–7.0)	23.5 (20.6–26.7)	13.9 (11.5–16.6)	17.6 (14.9–20.5)	7.3 (5.5–9.4)
4: DTPa-HBV-IPV + PRP-OMP (N = 725)	13.7 (11.2–16.4)§	13.1 (10.7–15.8)†	30.1 (26.7–33.6)‡	27.4 (24.2–30.9)†	21.7 (18.7–24.8)‡	16.0 (13.4–18.9)†
5: DTPa + OPV + PRP-T _{AP} (N = 731)	8.1 (6.2–10.3)	6.3 (4.6–8.3)	20.9 (18.0–24.1)	17.0 (14.3–19.9)	14.0 (11.5–16.7)	8.6 (6.7–10.9)

* Significantly higher as shown by a nonoverlap of the 95% CI compared with groups 1 and 3.
 † Significantly higher as shown by a nonoverlap of the 95% CI compared with groups 1, 2, 3, and 5.
 ‡ Significantly higher as shown by a nonoverlap of the 95% CI compared with group 5.
 § Significantly higher as shown by a nonoverlap of the 95% CI compared with groups 3 and 5.

TABLE 4. Incidence of Solicited General Adverse Reactions by Dose for Groups 1 to 5 in the ATP Cohort During the 4-Day Follow-up Period

Group: Vaccines	Diarrhea	Loss of Appetite	Restlessness	Temperature $\geq 38^{\circ}\text{C}$	Temperature $> 39.5^{\circ}\text{C}$	Unusual Crying	Vomiting
Dose 1							
1: DTPa-HBV-IPV + PRP-T _{CSK}	15.0 (13.0–18.0)	14.0 (12.0–17.0)	42.0 (38.0–45.0)	16.0 (13.0–19.0)	0.0 (0.0–0.5)	22.0 (19.0–25.0)	12.0 (9.3–14.0)
2: DTPa-HBV-IPV + PRP-T _{AP}	14.0 (11.5–16.6)	13.0 (17.7–23.5)*	45.0 (41.4–48.6)†	22.0 (19.2–25.2)‡	0.3 (0.0–0.9)	32.0 (28.3–35.1)*	12.0 (9.5–14.2)
3: DTPa-HBV-IPV + HbOC	12.6 (10.3–15.1)	21.9 (11.5–16.5)	35.1 (31.7–38.6)	12.0 (9.8–14.6)	0.1 (0.0–0.7)	17.0 (14.4–19.9)	7.2 (5.5–9.3)
4: DTPa-HBV-IPV + PRP-OMP	15.5 (12.9–18.3)	23.1 (20.1–26.3)*	49.6 (45.9–53.3)†	41.2 (37.6–44.8)§	4.8 (3.3–6.6)	32.2 (28.8–35.7)*	8.3 (6.4–10.5)
5: DTPa + OPV + PRP-T _{AP}	16.8 (14.2–19.7)	19.5 (16.7–22.5)	46.4 (42.7–50.0)†	13.4 (11.1–16.1)	6.5 (4.8–8.5)	36.6 (33.1–40.1)*	12.0 (9.7–14.5)
Dose 2							
1: DTPa-HBV-IPV + PRP-T _{CSK}	9.3 (7.3–11.6)	14.5 (12.0–17.3)	33.3 (30.0–36.8)	19.0 (16.0–22.0)	0.3 (0.0–0.9)	16.5 (14.0–19.3)	8.7 (6.8–10.9)
2: DTPa-HBV-IPV + PRP-T _{AP}	10.8 (8.7–13.3)	14.4 (12.0–17.1)	35.7 (32.3–39.2)	19.8 (17.0–22.8)	0.5 (0.1–1.3)	19.9 (17.2–23.0)	7.0 (5.3–9.1)
3: DTPa-HBV-IPV + HbOC	10.5 (8.4–12.9)	13.3 (10.9–15.9)	32.6 (29.3–36.0)	16.0 (13.5–18.8)	0.5 (0.1–1.3)	16.2 (13.6–19.0)	7.1 (5.4–9.2)
4: DTPa-HBV-IPV + PRP-OMP	8.3 (6.4–10.5)	13.6 (11.0–16.3)	31.0 (28.0–34.5)	18.0 (15.0–20.9)	0.5 (0.1–1.4)	17.6 (15.0–20.5)	7.1 (5.3–9.2)
5: DTPa + OPV + PRP-T _{AP}	10.6 (8.4–13.0)	16.3 (13.7–19.1)	34.7 (31.3–38.2)	13.3 (10.9–15.9)	0.1 (0.0–0.8)	19.9 (17.1–23.0)	8.4 (6.5–10.6)
Dose 3							
1: DTPa-HBV-IPV + PRP-T _{CSK}	9.3 (7.3–11.6)	12.8 (11.0–15.4)	24.8 (22.0–28.0)	17.5 (15.0–20.4)	0.7 (0.2–1.5)	11.3 (9.1–13.7)	7.0 (5.3–9.1)
2: DTPa-HBV-IPV + PRP-T _{AP}	9.7 (7.7–12.0)	11.8 (9.6–14.3)	25.9 (22.8–29.2)	15.5 (13.0–18.3)	0.8 (0.3–1.7)	13.8 (11.4–16.5)	4.9 (3.5–6.7)
3: DTPa-HBV-IPV + HbOC	8.9 (6.9–11.1)	10.1 (8.0–12.4)	25.8 (22.7–29.1)	15.1 (12.6–17.8)	0.8 (0.3–1.7)	13.1 (10.8–15.7)	6.0 (4.4–7.9)
4: DTPa-HBV-IPV + PRP-OMP	6.9 (5.2–9.0)	15.4 (13.0–18.3)†	31.7 (28.0–35.3)	28.6 (25.0–32.0)§	1.0 (0.4–2.0)	15.6 (13.0–18.4)	4.6 (3.2–6.3)
5: DTPa + OPV + PRP-T _{AP}	6.0 (4.4–8.0)	11.2 (9.0–13.7)	27.5 (24.3–30.9)	11.2 (9.0–13.7)	0.5 (0.1–1.4)	14.2 (11.8–17.0)	5.2 (3.7–7.1)

PRP-T_{CSK} indicates PRP-T_{ClaxoSmithKline}; PRP-T_{AP}, PRP-T_{Aventis Pasteur}

* Significantly higher as shown by a nonoverlap of the 95% CI compared with groups 1 and 3.

† Significantly higher as shown by a nonoverlap of the 95% CI compared with group 3.

‡ Significantly higher as shown by a nonoverlap of the 95% CI compared with groups 1, 3, and 5.

§ Significantly higher as shown by a nonoverlap of the 95% CI compared with groups 1, 2, 3, and 5.

|| Significantly higher as shown by a nonoverlap of the 95% CI compared with group 5.

sodes in general lasting for only 1–2 days), use of antipyretics (ranging from 15.7% to 17.5% of infants per group), and hospitalizations associated with fever (0.23% of infants receiving DTPa-HBV-IPV vs 0.39% of control subjects).

DISCUSSION

In this trial, the combination DTPa-HBV-IPV candidate vaccine administered concomitantly with 1 of 4 different Hib vaccines (given in separate sites) was at least as safe as coadministration of commercially available control vaccines (DTPa, Hib, and OPV) in terms of the defined endpoints for safety. During the 3-dose vaccination series, 16.2% of infants in the pooled DTPa-HBV-IPV + Hib vaccine group and 20.3% in the control vaccine group experienced a solicited adverse reaction graded 3 in intensity (rate difference [control minus combination] 4.1%; 90% CI, 1.41–7.13). The lower limit of the 90% CI of the observed difference remained above the prespecified –7.5% limit for noninferiority, thereby meeting the primary objective of the study.

The development of new vaccine products leads to the challenge of ensuring vaccine safety, convenience, and cost effectiveness. For simplifying vaccine schedules, vaccine products are becoming more complex, with greater numbers of antigens delivered in a single injection. This trial demonstrates the safety of a novel combination vaccine, DTPa-HBV-IPV, which has the potential to reduce the number of injections per visit currently given during childhood in the United States from as many as 5 down to 3.

Infants in the control group were not given HBV vaccine because the injection burden was believed to be unacceptable to parents and investigators. For the same reason and even more so because IPV vaccine was not yet recommended in Germany at the time that the study was conducted, infants in the comparison group were given OPV vaccine. The potential bias introduced by these 2 factors is likely to play in favor of the comparison group, reducing the incidence of local reactions as well as some general reactions such as fever in the comparison group.

This study was designed to use a range of commercial Hib vaccines that could be given concomitantly with the combination DTPa-HBV-IPV vaccine. Differences in rates of adverse experiences between the groups associated with the different Hib vaccines were unexpected. Any impact on the comparison of pooled groups would not be in favor of the candidate vaccine. Although the 3-, 4-, 5-month schedule used in this study differs from the 2-, 4-, 6-month schedule recommended in the United States, we expect that our data can be extrapolated, because the large age slots allowed in our protocol for each visit overlap the 2-, 4-, 6-month time points. Also, the incidence found in our study for key symptoms such as local reactions and fever of grade 3 intensity is similar to that reported in a US study conducted according to the 2-, 4-, 6-month schedule.¹⁴

There was considerable variation in the local reactogenicity of the 4 Hib vaccines. Data from the individual groups show that after the first dose, infants who received either PRP-T_{GlaxoSmithKline} or *Haemophi-*

lus influenzae type b diphtheria CRM₁₉₇ protein conjugate had lower incidences of local reactions; however, this was not found after the second or third vaccine doses. The incidences of local reactions after administration of PRP-OMP seemed higher after the first dose and reached statistical significance after the second dose. Similar differences in reactogenicity between commercial Hib vaccines were reported previously in a study that compared the immunogenicity and reactogenicity profiles of the same 4 Hib vaccines administered concomitantly, but in the opposite thigh, with the combination DTPa-HBV-IPV vaccine.¹⁵ The PRP-OMP vaccine is different from the other Hib vaccines not only from an immunogenicity perspective, as reflected by its own vaccination schedule, but also by its composition (eg, carrier protein, higher PRP content, presence of Al(OH)₃); therefore, the reasons for our findings are probably complex and could only be speculated on.

With regard to general adverse reactions, the incidence of fever (ie, temperature $\geq 38^{\circ}\text{C}$ [100.4°F]) was slightly higher in the groups that received the DTPa-HBV-IPV combination vaccine compared with the control group. Unexpectedly, the incidences of fever were significantly higher when PRP-OMP was coadministered. In all groups, grade 3 fever ($>39.5^{\circ}\text{C}$ [103.1°F]) was reported in $<1\%$ of infants after each individual dose over the entire vaccination course. Moreover, there were no differences in the duration of fever, use of antipyretics, and hospitalizations associated with fever between groups that received the combination vaccine and the control group. We therefore conclude that this increased incidence of low-grade fever does not lead to clinically significant consequences.

The combination DTPa-HBV-IPV vaccine coadministered with Hib was safe and well tolerated. Only 5 serious adverse events were related or possibly related to vaccination, resulting in noncompletion of the vaccine series in only 2 infants. The trial demonstrates that a more complex vaccine strategy with simultaneous administration of up to 6 different antigens can be achieved without increased risk of clinically relevant adverse events.

CONCLUSION

The 3-dose primary vaccination course of the combination DTPa-HBV-IPV vaccine coadministered with Hib vaccine given at a separate site is a safe approach for immunizing infants in a cost-effective and convenient manner. Rates of solicited local and general adverse reactions, as well as unsolicited adverse reactions, were similar in the DTPa-HBV-IPV with Hib vaccine group and the control vaccine group.

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