Primary and booster vaccination with DTPw-HB/Hib pentavalent vaccine in Costa Rican children who had received a birth dose of hepatitis B vaccine

Idis Faingezicht,[1] *Maria Luisa Avila-Aguerro*,[1] *Yolanda Cervantes*,[2] *Marc Fourneau*,[3] *and Sue Ann Costa Clemens*[4]

ABSTRACT

Objective. *The DTPw-HB/Hib pentavalent combination vaccine has been developed following recommendations of the World Health Organization for the introduction of hepatitis B (HB) and* Haemophilus influenzae *type b (Hib) vaccines into routine childhood vaccination programs. The objectives of this study were to: 1) analyze the immunogenicity and the reactogenicity of the DTPw-HB/Hib pentavalent combination vaccine in comparison to separate injections of DTPw-HB and Hib vaccines as primary vaccination in a group of children who had received a dose of HB vaccine at birth and 2) in the second year of life to assess the antibody persistence as well as the response to a DTPw-HB/Hib or DTPw/Hib booster.*

Methods. *In the first part of the study (primary-vaccination stage), conducted in 1998–1999, we analyzed the immunogenicity and reactogenicity of the DTPw-HB/Hib combination vaccine in comparison to separate injections of DTPw-HB and Hib vaccines as primary vaccination at 2, 4, and 6 months of age in 207 Costa Rican children who had received a dose of HB vaccine at birth. Later, in the booster-vaccination stage of the study, in 1999–2000, in a subset of the children (69 toddlers, now 15–18 months old), antibody persistence was measured, and response to a DTPw-HB/Hib or DTPw/Hib booster was also assessed.*

Results. *In both primary-vaccination groups, at least 97.5% of the infants reached protective levels of antibodies (seropositivity) against the antigens employed in the vaccines. The DTPw-HB/Hib pentavalent combination vaccine did not result in more local reactions than did the DTPw-HB vaccine alone, and, in terms of general reactions, there was no clinically significant difference between the combination or separate injections, and with the pentavalent vaccine having the benefit of needing one less injection. Nine months after the third dose of the primary-vaccination course, antibody persistence was similar in both groups, with over 93% of children still having protective/seropositive titers for Hib, HB, and tetanus and about 50% for diphtheria and* Bordetella pertussis. *At 15 months of age, virtually all the toddlers responded with a strong boost response to all the vaccine antigens, whether they received the DTPw-HB/Hib pentavalent vaccine or the DTPw/Hib vaccine as a booster. Both booster regimens were equally well tolerated, indicating that up to five doses of the HB vaccine can be given without impact on safety.*

[1] Hospital Nacional de Niños, San José, Costa Rica.
[2] GlaxoSmithKline Biologicals, Mexico City, Mexico.
[3] GlaxoSmithKline Biologicals, Rixensart, Belgium.
[4] GlaxoSmithKline Biologicals, Rio de Janeiro, Brazil. Send correspondence to: Sue Ann Costa Clemens, GlaxoSmithKline Biologicals, Estrada dos Bandeirantes 8464 Jacarepagua CP 22783-110 Rio de Janeiro, Brazil; tel: 55-21-2444-6387; fax: 55-21-99-85-3155; email: sueann.a.costaclemens@gsk.com

Conclusions. *Our study confirms that the DTPw-HB/Hib pentavalent vaccine is highly immunogenic as a primary vaccination in children who received an HB vaccine at birth, with the pentavalent combination inducing both persisting immunity and boostable memory. The pentavalent vaccine was safe both for primary and booster vaccinations. Thus, this study in Costa Rican infants supports the routine use of the pentavalent DTPw-HB/Hib vaccine as part of childhood vaccination programs in Latin America and the Caribbean.*

Key words Vaccination; vaccines, combined; diphtheria-tetanus-pertussis vaccine; *Haemophilus influenzae*; hepatitis B.

Infectious diseases are still the second leading cause of death and the leading cause of disability-adjusted life years worldwide despite all the benefits realized from health education, better sanitation, antibiotics, and vaccines (1). However, the impact of infectious diseases varies widely among countries and world regions. It was estimated that in Latin America and the Caribbean in the year 2000 infectious diseases accounted for about 13% of all deaths and over 15% of all disability-adjusted life years (2).

Vaccines are considered the most powerful tool for preventing disease, disability, and death, and for controlling health care costs, especially when given in infancy (2–4). Since its introduction in the 1940s, the diphtheria-tetanus-pertussis (DTP) combined vaccine has been a backbone of infant vaccination programs, with a current coverage of over 80% worldwide (5). Hepatitis B infection is one of the most widespread viral diseases, with over 2 billion people worldwide having past or current evidence of hepatitis B infection and over 350 million being chronic virus carriers (6). In Latin America and the Caribbean, hepatitis B infections with vertical transmission are most prevalent in the Amazon basin as well as in parts of the Caribbean (7, 8). There is now convincing evidence that mass vaccination against hepatitis B results in dramatic reductions in the burden of the disease, including the incidence of hepatocellular carcinoma (9, 10). Because of the enormous public health importance of hepatitis B, the World Health Organization (WHO) endorsed universal vaccination of infants against hepatitis B in 1992 and recommended the addition of the hepatitis B (HB) vaccine to the Expanded Program on Immunization (EPI) in all countries, independently of endemicity levels (11). It is estimated that over 100 countries worldwide have implemented routine infant hepatitis B vaccination programs. With this step, the number of child carriers is expected to be reduced by more than 80% in the near future. To facilitate the introduction of hepatitis B vaccination into EPI programs, WHO recommended the use of the DTP-HB combination vaccine and established performance and quality criteria for it (12).

Haemophilus influenzae type b (Hib) has been the leading cause of bacterial meningitis in many parts of the world in the prevaccine era. In Latin America in the mid-1990s the incidence of Hib meningitis in children aged 0 to 4 years old was 35 per 100 000, and the incidence of any Hib disease was 60 per 100 000, with a peak incidence in the first year of life, according to published research (13) and a conference piece by Grinbaum et al.[5] There were estimated to be at least 40 000 cases of Hib disease and 5 000 deaths per year in Latin America and the Caribbean, along with auditory impairment and other lifelong sequelae and an increasing resistance to antimicrobials. On the other hand, there was evidence of the extremely high efficacy and effectiveness of the newly developed Hib conjugate vaccines (14–16). These various factors led the Pan American Health Organization (PAHO) and its Technical Advisory Group on Vaccine Preventable Diseases as early as 1997 to recommend regular Hib vaccination programs in the Americas (17). In 1998 the WHO recommended that the Hib vaccination be included in routine infant immunization programs, according to national capacities, preferably as a DTP-based combination (18).

The growing number of currently available and recommended vaccines for infant immunization, however, increases the complexity of childhood vaccination programs. Therefore, various combination vaccines have recently been developed, including a diphtheria-tetanus-(whole-cell) pertussis-hepatitis B and *Haemophilus influenzae* type b (DTPw-HB/Hib) pentavalent combination. Together with oral polio vaccine, that pentavalent combination covers all the vaccine antigens recommended by PAHO and WHO for administration between the first and sixth months of life.

Before a combination vaccine can be recommended in any immunization program, it is necessary to demonstrate that the combination does not adversely affect the immunogenicity of any of the components or lead to increased reactogenicity. Both the pentavalent DTPw-HB/Hib vaccine and an intermediate DTPw-HB combination have undergone extensive clinical testing and have proved free of any interference, according to published research (19–25) and a conference piece by Santos et al.[6]

[5] Grinbaum RS, Mendonca JS, Almeida ALSL, et al. Epidemiology of *Haemophilus influenzae* in Sao Paulo, Brazil, and implications for future routine immunisations (Abstract 103.010). 7th International Congress for Infectious Diseases, Hong Kong, 10–13 June, 1996.

[6] Santos JI, De Leon T, Rivera L, et al. Multicenter trial to evaluate the immunogenicity and reactogenicity of a novel pentavalent combined DTPw-HBV/Hib vaccine conducted in Latin America. Proc 2nd World Congr Pediatr Infect Dis Manila 1999, Vol. 40.

In 1997 the DTPw-HB combination vaccine was registered in Costa Rica. Costa Rica was also one of the first countries in the world to introduce the pentavalent DTPw-HB/Hib vaccine into its local Expanded Program on Immunization. Conducted between 1998 and 2000, this study was performed to address a number of questions that needed to be answered for the Costa Rica target population before the pentavalent could be integrated into the local immunization schedule. These questions included: 1) Is the immune response to Hib in the pentavalent vaccine as good as to Hib monovalent? 2) Can three doses of the pentavalent vaccine be given safely to children who have already received a birth dose of the hepatitis B vaccine? 3) What is the persistence of vaccine-induced antibodies into the second year of life, when children in Costa Rica are to receive a DTPw and Hib booster? 4) In order to reduce the complexity of the vaccination program, would it be safe and immunogenic to give a DTPw-HB/Hib pentavalent booster instead of a DTPw/Hib booster?

In order to provide answers to these questions, the study was designed with primary and secondary objectives for both the primary-vaccination phase and the booster-vaccination phase. In the primary-vaccination phase, the main objective was to compare the immune response to the polyribosyl ribitol phosphate (PRP) antigen after the third dose of Hib vaccine, when given either mixed with DTPw-HB or as a separate injection. Secondary objectives were: a) to assess the immune responses to all the other vaccine antigens (diphtheria, tetanus, *Bordetella pertussis*, and hepatitis B surface antigen (HBsAg)) and b) to assess the safety and reactogenicity of the two vaccination regimens after four doses of HB vaccine.

In the booster-vaccination phase, the primary objective was to evaluate the reactogenicity and safety of a total of five doses of HB vaccine (the DTPw-HB/Hib booster group) versus four doses of HB vaccine (the DTPw/Hib booster group). The secondary objective was to assess: a) the antibody persistence up to 15–18 months of age and b) the booster response to all vaccine antigens.

MATERIALS AND METHODS

The study was designed as a phase III observer-blind prospective randomized controlled trial in a single vaccination center in Costa Rica. The study was conducted according to the provisions of the Declaration of Helsinki in force at the time as well as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines in effect at study initiation. The study was performed in two parts: a) a primary-vaccination part, during which each child was in the study for approximately 5 months, and a booster-vaccination part of 6 weeks' duration. The primary-vaccination part extended from September 1998 to May 1999, and the booster part of the study was conducted from November 1999 to February 2000.

Subjects

Primary vaccination. Included in the primary-vaccination part of the study were healthy infants of either gender between 6 and 12 weeks of age at the time of first vaccination. All infants were to have received a documented dose of hepatitis B vaccine at birth, according to the Costa Rican immunization schedule. Exclusion criteria were: premature birth; moderate or severe acute disease; immunodeficient conditions or immunosuppressive therapy; neurological disorders, including previous seizures; previous allergic reactions; and a history of vaccination against diphtheria, tetanus, pertussis, or *Haemophilus influenzae* type b. As a precautionary measure, the child would be excluded from further vaccine dosing if after vaccine administration there was fever ≥40.5 °C, prolonged persistent crying, hypotonic-hyporesponsiveness, seizures, or a hypersensitivity reaction. That was done because those events might be attributed to the whole-cell *B. pertussis* component (26).

Booster vaccination. Included in the booster-vaccination part of the study were healthy children 15–18 months of age who had received a documented dose of hepatitis B at birth and who had completed the full primary-vaccination course of the study with three doses of DTPw-HB and Hib vaccines, at 2, 4, and 6 months of age. The same exclusion criteria as above were applied in this booster part of the study.

Ethics

The protocol, including a parent information sheet, was approved by the Committee on Bioethics and Research of the Dr. Carlos Saenz Herrera National Children's Hospital, in San José, Costa Rica, prior to the start of the study. Written informed consent was obtained from the parents or legal guardians before the children were enrolled.

Vaccines

All the vaccines used in the study were developed and manufactured by GlaxoSmithKline Biologicals (GSK) in Rixensart, Belgium. Vaccines were released, shipped, and stored according to the manufacturer's Good Manufacturing Practice protocols. As described below, the three vaccines used were: DTPw-HB (Tritanrix-HepB™), Hib (PRP-T, Hiberix™), and DTPw (Tritanrix™).

Each 0.5-mL dose of the DTPw-HB (Tritanrix-HepB™) vaccine contained purified diphtheria toxoid (≥30 international units (IU)), purified tetanus toxoid (≥60 IU), inactivated *B. pertussis* whole-cell suspension (≥2 IU), 10 mcg recombinant HBsAg protein, and 0.5 mg aluminum salt as well as 2-phenoxyethanol as preservative.

With the Hib (PRP-T, Hiberix™) vaccine, 10 mcg of *Haemophilus influenzae* type b capsular polysaccharide (PRP) are conjugated to 20–40 mcg tetanus toxoid as protein carrier and freeze-dried, to be reconstituted by DTPw-HB, DTPw, or its diluent.

The DTPw (Tritanrix™) was only used in the booster phase. It contained the same active ingredients as DTPw-

HB except for HBsAg, 0.4 mg aluminum salt, and 2-phenoxyethanol used to reconstitute Hib.

Study design and objectives

Primary study phase. Infants who had received a dose of hepatitis B vaccine at birth were randomly allocated to one of two study groups (P1 and P2), using an algorithm of pseudorandom numbers (Research Software 1, Bolt Beranek and Newman Inc., Cambridge, Massachusetts, United States of America). Infants in study group P1 received the DTPw-HB/Hib pentavalent combination vaccine as a single injection after extemporaneous mixing of the liquid DTPw-HB vaccine with the lyophilized Hib vaccine. The infants in group P2 received two separate but concomitant injections: the DTPw-HB vaccine and the Hib vaccine reconstituted with its own diluent. The vaccines were administered by deep intramuscular injection into the anterolateral thigh(s) at 2, 4, and 6 months of age.

Booster phase. Toddlers of 15–18 months who had completed their primary-vaccination course were eligible to be included in the booster part of the study. Upon enrollment into the primary study part, they had already been randomly allocated to receive either one dose of DTPw-HB/Hib vaccine (group B1) or one dose of DTPw/Hib vaccine (group B2) as a booster in the second year of life. Thus, all subjects in booster group B1 received a total of five doses of hepatitis B vaccine (birth dose HB monovalent, three doses of DTPw-HB and Hib either mixed or separate, and a booster with DTPw-HB/Hib). The children in booster group B2 received a total of four doses of hepatitis B vaccine (birth dose HB monovalent, three primary doses of DTPw-HB either mixed or separate, and a booster of DTPw/Hib).

To determine the primary immune response, blood samples were taken at two points: a) prior to the first study-vaccine dose, at 2 months of age and b) 1 month after the third study-vaccine dose, at age 7 months. With the toddlers, samples were taken shortly before the booster dose as well as 4–6 weeks after that booster dose, to assess antibody persistence as well as booster response.

Safety and reactogenicity

The parents/guardians received diary cards and were instructed by the study physicians to document any local reaction (pain, redness, swelling) or general reaction (fever, irritability, feeding problems, other), including the severity and duration of the event, for 4 days. In addition, parents were instructed to record on the diary card any other unsolicited adverse event (any local or general reaction beyond the four-day follow-up period and any other symptom) within 30 days after each vaccination, and to immediately report any serious event to the study investigator. The information that parents/guardians recorded on the diary cards was transcribed by the investigator onto symptom sheets included in the case report form for each subject.

Serology

Sera were stored at –20 °C until paired analyses were performed in a blinded fashion at GlaxoSmithKline Biologicals, Rixensart, Belgium. It is generally accepted that for both diphtheria and tetanus, titers >0.01 IU/mL, as measured by in vivo neutralization tests, are protective. A good correlation exists between in vivo neutralization tests and enzyme-linked immunosorbent assay (ELISA) test results, but this correlation may be reduced at antibody titers <0.1 IU/mL. For this reason, a titer of ≥ 0.1 IU/mL by ELISA was conservatively set as the cutoff for both anti-diphtheria and anti-tetanus. *B. pertussis* antibodies were determined using a whole-cell based commercial ELISA kit (Labsystems, Helsinki, Finland) with a cutoff at 15 ELISA units/mL. Antibodies to the hepatitis B surface antigen (anti-HBs) were determined using a commercial radioimmunoassay (AUSAB, Abbott, Wiesbaden, Germany) with an essay cutoff of 10 mIU/mL. Antibodies to the Hib polysaccharide PRP were measured by the ELISA technique, with a test cutoff of 0.15 mcg/mL.

For all components, antibody levels above the cutoff were considered to be protective and seroprotection rates were calculated, except for *B. pertussis*, for which no serological correlate for protection has been established. For anti-PRP antibodies, in addition to the seroprotection rate at the test cutoff level of 0.15 mcg/mL, the seroprotection rate at 1.0 mcg/mL was calculated.

Statistical methods

The statistical analyses were performed using two software packages, SAS 6.12 on Windows NT (Statistical Analysis System Inc., Cary, North Carolina, United States) and StatXact-3 (Cytel Software Corporation, Cambridge, Massachusetts, United States).

The sample size was calculated based on the primary objective of showing, one month after the third vaccine dose, non-inferiority of the anti-PRP response when Hib was mixed with DTPw-HB as compared to the separate administration of Hib and DTPw-HB. With the assumption of a 98% rate with titers ≥ 0.15 mcg/mL in the separate-administration group, 94 evaluable subjects per group were required to rule out the null hypothesis that the groups differ by more than 6% in the seroprotection rate (nQuery equivalence in proportions; one-sided test, $\alpha = 0.05$, $\beta = 0.1$) (nQuery software, Statistical Solutions Ltd., Cork, Ireland). Thus, if the lower confidence limit of the difference in the anti-PRP seroprotection rate at ≥0.15 mcg/mL between the mixed and the separate injection was above –6%, it was concluded that the mixed vaccine was at least as immunogenic as the separate administration for the anti-PRP response.

In addition, seroprotection/seropositivity rates as well as geometric mean titers (GMTs) with their 95% confidence intervals (using for GMTs the antilog of the mean of the log titer

transformations) were calculated for all vaccine-related antibodies at all blood samplings.

For safety and reactogenicity, the percentage of doses followed by a report of local or general adverse events was computed, with their 95% confidence intervals. Demographic comparability of the groups was tested by Fisher's exact test for the male/female ratio, and by analysis of variance (ANOVA) for age differences at the time of the first study-vaccine administration.

RESULTS

Primary vaccination

Demographics and study attrition. A total of 207 subjects were enrolled in the study, 103 females and 104 males. All were Caucasians, and their mean age at study entry was 8.8 weeks (standard deviation (SD) = 0.9 weeks). The 207 infants were randomly allocated to two groups: 103 of them were to receive DTPw-HB vaccine mixed with Hib vaccine in one injection (group P1), and 104 were to receive the DTPw-HB vaccine and the Hib vaccine separately (group P2). There were no significant differences in demographics between the two groups.

A total of 16 infants were excluded from both the reactogenicity and immunogenicity according-to-protocol analyses: 13 were lost to follow-up, and there were randomization failures with 3 others. Thus, the reactogenicity analysis included 191 infants, 96 in group P1 and 95 in group P2. In addition to these 16 subjects, a further 4 infants had to be excluded from the immunogenicity analysis due to protocol violation (age at study entry > 12 weeks), 14 others due to noncompliance with the vaccination schedule, and another 16 due to noncompliance with the blood sampling schedule. Thus, a total of 157 infants were included in the immunogenicity analysis, 78 in group P1 and 79 in group P2. The demographics of the cohorts included in the reactogenicity and the immunogenicity analysis did not differ significantly from the initial cohort of all the recruited children.

Immunogenicity. One month after the full primary-vaccination course, 100% of the infants in group P1 (receiving the DTPwHB/Hib pentavalent combination) and 98.7% in group P2 (receiving DTPw-HB and Hib vaccines) had anti-PRP antibody titers above the 0.15 mcg/mL cutoff level for protection. The difference in seroprotection rates between group P1 and group P2 was 1.3%, with a 90% confidence interval (CI) of –4.7% to 9.6%. Therefore, since the lower confidence limit of the group differences is above –6.0%, one can conclude that the DTPw-HB/Hib vaccine was as least as immunogenic as the separate injection of Hib in terms of anti-PRP protection at the 0.15 mcg/mL level, and therefore the primary study objective was met. Similarly, there was no significant difference between the two groups for anti-PRP seroprotection rates ≥ 1.0 mcg/mL or for GMTs, with widely overlapping confidence intervals for both measures. In addition, both vaccine regimens induced antibody titers above the protective level against diphtheria, tetanus, and hepatitis B as well as seropositivity for *B. pertussis* antibodies in at least 97.5% of the study population. Results in the intention-to-treat (ITT) cohort (i.e., all subjects enrolled for whom data are available), which included 93 subjects in group 1 and 86 in group 2, were similar for all vaccine antigens (data not shown).

Safety and reactogenicity. The safety and reactogenicity analysis was performed on a total of 191 subjects who received at least one dose of study vaccine: 96 in group P1 and 95 in group P2. In group P1, a total of 278 vaccine doses were given, with 230 of them (82.7%) (95% CI: 77.8%–87.0%) followed by a solicited or unsolicited local or general symptom during the four-day follow-up period (Table 1). In group P2, this figure was 223/272 (82.0%) (95% CI: 76.9%–86.4%), and thus very similar. There was no increase in reactogenicity with doses, either for local symptoms or for general symptoms. Local and systemic reactions were common in both groups, but most reactions were mild, and 97% of them resolved spontaneously within the four-day follow-up period.

For solicited local symptoms, it is important to keep in mind that group P1 received only one injection of the DTPw-HB/Hib pentavalent combination vaccine, whereas infants in group P2 received one injection of DTPw-HB vaccine and one injection of Hib vaccine, at separate sites. The pentavalent DTPw-HB/Hib combination did not result in more local or general reactions than did the separate DTPw-HB and Hib injections, and it had the benefit of needing one less injection.

Three serious adverse events were reported during the trial. A few hours after the first vaccine dose, one child in group P1 experienced seizures, which resolved spontaneously. Two weeks after the first vaccine dose another child in group P1 was diagnosed with acute bronchiolitis and subsequently died due to respiratory distress. The event was deemed unrelated to the vaccine. Another acute bronchiolitis case, due to respiratory syncytial virus infection, occurred in group P2 three days after the first vaccination. The child recovered after treatment and hospitalization. There were no cases of hypotonic-hyporesponsive reaction or of allergic reaction in either group. A total of 15 infants (6 in group P1 and 9 in group P2) received an antipyretic medication during the course of the study.

Antibody persistence

A total of 69 children from the primary-vaccination phase were recruited for the second part of the study; 39 were female and 30 were male. Their mean age at enrollment in the second study phase was 15.3 months (SD = 0.8 months). Of these 69 children, 68 could be analyzed for antibody persistence; 33 of the 68 were from group P1 (which had received DTPw-HB/Hib vaccine

TABLE 1. Local and general solicited adverse events with DTPw-HB/Hib pentavalent combination vaccine in comparison to separate injections of DTPw-HB and Hib vaccines, Costa Rica, 1998–1999

Symptom	Vaccine group[a]	Vaccine[b]	*n*[c]	Adverse events[d]					
				Total			Grade 3[e]		
				No.	%	95% CI	No	%	95% CI
Pain	P1	DTPw-HB/Hib	278	166	59.7	(53.7–65.5)	54	19.4	(14.9–24.6)
	P2	DTPw-HB	272	141	51.8	(45.7–57.9)	46	16.9	(12.7–21.9)
	P2	Hib	272	109	40.1	(34.2–46.2)	33	12.1	(8.5–16.6)
Redness	P1	DTPw-HB/Hib	278	165	59.4	(53.3–65.2)	12	4.3	(2.3–7.4)
	P2	DTPw-HB	272	146	53.7	(47.6–59.7)	14	5.1	(2.8–8.5)
	P2	Hib	272	87	32.0	(26.5–37.9)	5	1.8	(0.6–4.2)
Swelling	P1	DTPw-HB/Hib	278	130	46.8	(40.8–52.8)	18	6.5	(3.9–10.0)
	P2	DTPw-HB	272	115	42.3	(36.3–48.4)	14	5.1	(2.8–8.5)
	P2	Hib	272	61	22.4	(17.6–27.9)	7	2.6	(1.0–5.2)
Irritability	P1	DTPw-HB/Hib	278	153	55.0	(49.0–61.0)	27	9.7	(6.5–13.8)
	P2	DTPw-HB + Hib	272	142	52.2	(46.1–58.3)	30	11.0	(7.6–15.4)
Fever	P1	DTPw-HB/Hib	278	67	24.1	(19.2–29.6)	4	1.4	(0.4–3.6)
	P2	DTPw-HB + Hib	272	47	17.3	(13.0–22.3)	1	0.4	(0.0–2.0)
Loss of appetite	P1	DTPw-HB/Hib	278	72	25.9	(20.9–31.5)	10	3.6	(1.7–6.5)
	P2	DTPw-HB + Hib	272	52	19.1	(14.6–24.3)	9	3.3	(1.5–6.2)

[a] Vaccine groups: P1 = pentavalent DTPw-HB/Hib; P2 = DTPw-HB and Hib vaccines administered separately and concomitantly.
[b] Vaccines: DTPw = diphtheria-tetanus-(whole-cell) pertussis; HB = hepatitis B; Hib = *Haemophilus influenzae* type b.
[c] *n* = number of symptom sheets.
[d] Information for adverse events: No. = number of symptom sheets reporting a solicited symptom; % = percentage of symptom sheets reporting a solicited symptom; 95% CI = 95% confidence interval for the percentage of symptom sheets reporting a solicited symptom.
[e] Grade 3 adverse event = one that prevented normal everyday activities (pain, irritability, loss of appetite); redness, swelling >20 mm; fever >39 °C.

for priming), and the other 35 were from group P2 (which had received DTPw-HB and Hib vaccines separately). The results of the antibody persistence are shown in Table 2. In this part of the study, no formal statistical analysis was performed because of the power limitations of the small sample size. Nine months after the primary-vaccination third dose, all the children in group P1 (combined vaccine) and all but one child in group P2 (separate administration of Hib vaccine) still had anti-PRP antibody titers ≥0.15 mcg/mL. Also, for hepatitis B and tetanus nearly all the children still had titers above the cutoff. In contrast, for diphtheria and pertussis, about half of the children in both groups were below the cutoff.

Booster vaccination

Of the 69 children coming back to the booster part of this study, 29 had had been randomized to booster group B1 and received one dose of DTPw-HB/Hib vaccine as a booster (12 from primary-vaccination group P1, who had received the DTPw-HB/Hib vaccine; 17 from group P2, who had received the DTPw-HB and Hib vaccines separately). The other 40 children had had been randomized to booster group B2 and received DTPw/Hib vaccine as a booster (22 from group P1 and 18 from group P2). Of these 69 toddlers, 65 of them could be included in both the reactogenicity and immunogenicity analysis of the booster dose (28 from group B1 and 37 from group B2). The 4 other children had to be excluded as they were lost to follow-up for the final blood sampling and diary card collection.

Immunogenicity of booster. The response to the booster vaccination per vaccine antigen is given in Table 3. (In Table 2 the preboost cohorts were presented according to the primary vaccination, to identify any difference in antibody persistence. Here in Table 2, however, the same 68 children are presented according to their booster vaccine allocation.)

Both groups of vaccinees (B1 and B2) showed a similar boost response, by about a factor of 20 for anti-PRP antibody titers, with overlapping confidence intervals. In both groups, all the children had anti-PRP titers ≥1.0 mcg/mL after the booster. For hepatitis B, the children in the DTPw-HB/Hib group (group B1) all responded with an increase of GMTs by a factor of 40. For diphtheria, tetanus, and pertussis, all the children in both groups had antibody titers above the cutoff following the booster. In addition, the GMTs were similar for the two groups for tetanus and pertussis, but the diphtheria GMTs were somewhat higher in group B1.

Reactogenicity and safety of booster. Documented diary cards were returned for 28 of the 29 children in group B1 (DTPw-HB/Hib booster) and for 37 of the 40 children in group B2 (DTPw/Hib booster). Due to the small sample size, no formal com-

TABLE 2. Antibody persistence for children receiving DTPw-HB/Hib pentavalent combination vaccine (group P1) in comparison to children receiving separate injections of DTPw-HB and Hib vaccines (group P2), Costa Rica, 1999–2000

Antibody cutoff/GMT[a, b]	1 month after third dose (age = 7 months)		9 months after third dose (age = 15 months)	
	Group P1 (*n* = 78)	Group P2 (*n* = 79)	Group P1 (*n* = 33)	Group P2 (*n* = 35)
Anti-PRP				
% and 95% CI ≥ 0.15 mcg/mL[c]	100 (95.4–100)	98.7 (93.1–100)	100 (89.4–100)	97.1 (85.1–99.9)
% and 95% CI ≥ 1.0 mcg/mL	97.4 (91.0–99.7)	97.5 (91.2–99.7)	78.8 (61.1–91.0)	85.7 (69.7–95.2)
GMT and 95% CI, mcg/mL	15.95 (12.07–21.09)	25.51 (19.17–33.94)	2.89 (1.76–4.75)	3.01 (1.84–4.94)
Anti-HBs				
% and 95% CI ≥ 10 mIU/mL	100 (95.4–100)	100 (95.4–100)	93.9 (79.8–99.3)	100 (90.0–100)
GMT and 95% CI, mIU/mL	1 138 (866–1 495)	1 504 (1 236–1 831)	137.4 (86.1–219.3)	186.7 (122.2–285.4)
Diphtheria				
% and 95% CI with ≥ 0.1 IU/mL	98.7 (93.1–100)	97.5 (91.2–99.7)	48.5 (30.8–66.5)	54.3 (36.6–71.2)
GMT and 95% CI, mcg/mL	1.19 (0.93–1.52)	1.45 (1.14–1.85)	0.11 (0.08–0.14)	0.11 (0.08–0.14)
Tetanus				
% and 95% CI with ≥ 0.1 IU/mL	100 (95.4–100)	100 (95.4–100)	93.9 (79.8–99.3)	94.3 (80.8–99.3)
GMT and 95% CI, mcg/mL	3.87 (3.24–4.64)	2.11 (1.73–2.59)	0.41 (0.30–0.57)	0.41 (0.29–0.58)
Pertussis				
% and 95% CI with ≥ 15 EL U/mL	98.7 (93.1–100)	100 (95.4–100)	54.5 (36.4–71.9)	57.1 (39.4–73.7)
GMT and 95% CI, mcg/mL	94.7 (79.5–112.8)	112.5 (97.2–130.2)	17.9 (12.9–24.9)	19.6 (14.0–27.5)

[a] Antibody cutoffs are for seroprotection/seropositivity rates.
[b] GMT = geometric mean titer.
[c] 95% CI = 95% confidence interval.

parative statistical analyses were performed. The point estimates for severe solicited local symptoms were very similar for the two booster groups. Also, the point estimates for most of the solicited general symptoms were similar for the two groups, except for the loss of appetite, which was higher in group B1. In addition, compared to the primary vaccination, there seemed to be a tendency towards more fever reactions and pain in the toddlers for both of the booster vaccines. There were no serious adverse events reported following any booster dose. Thus, the addition of HB to a DTPw/Hib booster in the second year of life did not seem to negatively affect the reactogenicity profile.

DISCUSSION

Hib vaccination was introduced into Latin America in 1994, when Uruguay decided to include the Hib conjugates in its routine immunization program. While only 3.4% of all newborns in Latin America received a routine Hib vaccination in 1996, this situation has changed dramatically since then (27). In 2001, over 10 million (over 90%) of Latin Americas infants routinely received a Hib vaccine. This success of introducing a novel vaccine into routine immunization was triggered by various factors. These included the leadership role of PAHO; a surveillance network providing local disease burden data, thus increasing the disease awareness among both health care professionals and parents; local clinical-trial data; and the availability of vaccines in such combinations as DTPw/Hib and DTPw-HB/Hib.

Combination vaccines have numerous advantages, including a decreased number of injections, increased compliance, better coverage, and easier logistics. There is also a substantial reduction in program costs since the indirect costs of immunizing a child (e.g., logistics, materials involved, payment of medical staff, child transportation, etc.) are far greater than the vaccines themselves. These advantages have led scientific organizations such as the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians, as well as PAHO, to recommend the use of combination vaccines over the use of their single components wherever available (28, 29). DTPw/Hib or other combinations are used in about 10% of Latin American children, and about 40% of the infants receive Hib as a monovalent vaccine. Among those in the last group are infants in Brazil, who receive a locally produced Hib vaccine following a technology transfer from a private vaccine company to a manufacturer there.

Before a major change in a vaccine program and the introduction of a new vaccine, it is important to have data on the local target population. Our primary-vaccination study with the children in Costa Rica showed that there was no interference in immune response to the DTPw-HB/Hib pentavalent combination vaccine as compared to a separate immunization with Hib and DTPw-HB vaccines. Importantly, the Hib response in the DTPw-HB/Hib pentavalent combination was not inferior to that found with the separate administration of a monovalent Hib

TABLE 3. Immune response to the booster vaccination for children receiving DTPw-HB/Hib (group B1) and for children receiving DTPw/Hib (group B2), Costa Rica, 1999–2000

Antibody cutoff/GMT[a, b]	Prebooster (age = 15–16 months)		1 month after booster (age = 16–17 months)	
	Group B1 (*n* = 29)	Group B2 (*n* = 39)	Group B1 (*n* = 28)	Group B2 (*n* = 37)
Anti-PRP				
% and 95% CI ≥ 0.15 mcg/mL[c]	96.6 (82.2–99.9)	100 (91.0–100)	100 (87.7–100)	100 (90.5–100)
% and 95% CI ≥ 1.0 mcg/mL	93.1 (77.2–99.2)	74.4 (57.9–87.0)	100 (87.7–100)	100 (90.5–100)
GMT and 95% CI, mcg/mL	3.46 (1.96–6.11)	2.62 (1.69–4.06)	71.36 (43.84–116.16)	57.75 (38.31–87.06)
Anti-HBs				
% and 95% CI ≥ 10 mIU/mL	100 (88.1–100)	94.9 (82.7–99.4)	100 (87.7–100)	94.6 (81.8–99.3)
GMT and 95% CI, mIU/mL	190 (125–288)	142 (90–224)	7 971 (5 494–11 564)	151 (90–252)
Diphtheria				
% and 95% CI with ≥ 0.1 IU/mL	62.1 (42.3–79.3)	43.6 (27.8–60.4)	100 (71.5–100)	100 (76.8–100)
GMT and 95% CI, IU/mL	0.122 (0.090–0.165)	0.097 (0.075–0.127)	4.455 (3.211–6.181)	2.798 (1.930–4.059)
Tetanus				
% and 95% CI with ≥ 0.1 IU/mL	89.7 (72.6–97.8)	97.4 (86.5–99.9)	100 (87.7–100)	100 (90.5–100)
GMT and 95% CI, mcg/mL	0.469 (0.308–0.714)	0.375 (0.287–0.491)	6.638 (5.037–8.748)	5.259 (4.331–6.386)
Pertussis				
% and 95% CI with ≥ 15 EL U/mL	65.5 (45.7–82.1)	48.7 (32.4–65.2)	100 (87.7–100)	100 (90.5–100)
GMT and 95% CI, mcg/mL	22.0 (15.2–32.0)	16.7 (12.4–22.5)	263.0 (216.1–320.0)	258.1 (215.7–308.8)

[a] Antibody cutoffs are for seroprotection/seropositivity rates.
[b] GMT = geometric mean titer.
[c] 95% CI = 95% confidence interval.

vaccine, thus meeting the primary endpoint of the study. This is critical for the acceptance of the vaccine since it is known that Latin American children may react differently to Hib vaccines than do children from other parts of the world (30–32). In our study in Costa Rica, after the primary-vaccination three-dose course, 100% of the infants in group P1 and 98.7% of those in group P2 had anti-PRP titers above the conservative threshold of protection of 0.15 mcg/mL; in addition, 97.4% of those in group P1 and 97.5% of those in group P2 had titers above 1.0 mcg/mL. Our results in Costa Rica are very similar to the findings from two other studies performed in Latin America with this vaccine, one published (24) and the other the conference piece by Santos et al. Although the anti-PRP GMTs in the DTPw-HB/Hib group in our trial were lower than in the separate-administration group, this seemed to be of no clinical relevance. Persistence data nine months after the primary vaccination indicated that all the toddlers in the pentavalent group and all but one toddler in the separate-administration group had titers above 0.15 mcg/mL, with almost identical GMTs. Other than the Hib response, there were no significant differences in primary immune response and in antibody persistence for any of the vaccine antigens between the DTPw-HB/Hib pentavalent group and the DTPw-HB and Hib separate-administration group.

Although not tested here, the DTPw-HB and DTPw-HB/Hib combinations have one distinct advantage over the separate administration of hepatitis B monovalent vaccines in the first year of life. In the combinations with DTPw, the hepatitis B response reaches 95% seroprotection after two doses of vaccine, with GMTs of 95 mIU/mL. This compares with a 66% seroprotection rate, with a GMT of 25 mIU/mL, following the second dose of the monovalent HB vaccine in a study using a vaccination schedule of 6, 10, and 14 weeks (21). These results have been confirmed also after two doses in a schedule of 2, 4, and 6 months (25). Possible explanations for this potentiation of the anti-HBs response with the DTPw-HB/Hib pentavalent vaccine are differences in aluminum salts and that the whole-cell pertussis component exerts an adjuvant effect.

These findings of an enhanced HB immune response in the combination vaccine are important from a public health perspective. The goal for DTP, and also for HB and Hib in the DTPw-HB/Hib combination, is a vaccination coverage of close to 90%. However, there are still regions in many countries in Latin America where this is not achieved and children get only two or even fewer doses. If, however, children had received two doses of the DTPw-HB/Hib combination, the likelihood is high that about 95% of them would be protected against hepatitis B, compared to only about 65% if they had received the monovalent HB vaccine.

In our Costa Rica study, mild to moderate, spontaneously resolving local and systemic reactions were common in both groups with the three-dose primary-vaccination schedule. As expected, Hib monovalent was less locally reactogenic than the two DTPw-based combinations. Importantly, mixing DTPw-HB with Hib did not induce an increase in either local reactions or general reactions. The

incidence of those reactions after the pentavalent DTPw-HB/Hib combination was similar to what is seen when DTPw vaccines are given alone (33, 34) and also similar to what has been found in various other research performed with this vaccine, according to published studies (23–25), the Santos et al. conference piece already mentioned, and a conference piece by Gatchalian et al.[7] Also, there was no increase in reactogenicity with increasing number of doses during the primary-vaccination course in either group. One child experienced seizures with fever a few hours after vaccination, an event that most likely is to be attributed to the pertussis whole-cell component of the vaccine. For ethical reasons, no formal comparison could be made in this study between children who had or had not received the HB birth dose as part of the EPI schedule. However, we saw that the additional dose of hepatitis B at birth did not affect in any way the safety profile of the vaccines under study. This absence of effect of HB vaccine at birth on DTPw-HB/Hib vaccine safety has been clearly shown in a study performed in Asia, where there was a stratification done between children with an HB vaccine birth dose and those without (25).

One of the shortfalls of this trial was the relatively high attrition, with fewer than half of the children coming back for the booster vaccination. This might have introduced a selection bias. However, it appeared that both booster vaccines had a similar reactogenicity and safety profile, indicating that HB vaccine can be added safely to a DTPw/Hib booster. Both groups responded equally well to a Hib booster, with increases in GMTs by factors of 20 to 30. Likewise, the magnitude of the boost response for diphtheria, tetanus, and pertussis was similar for the pentavalent DTPw-HB/Hib combination and for the DTPw/Hib vaccine. The boost response to the fifth dose of HB vaccine in subjects belonging to group B1 induced a 40-fold increase in anti-HBs titers. Immunologically, the inclusion of HB vaccine in the second-year booster is not needed as all children are adequately primed. However, since the administration of DTPw-HB/Hib vaccine as booster is safe, one has to balance practical aspects with the need to store only one vaccine for both the primary and booster program versus the minimum medical need and program costs (26).

The pentavalent DTPw-HB/Hib vaccine has proven high immunogenicity and priming for all vaccine antigens in the first year of life, antibody persistence, excellent booster response, and an acceptable safety profile. Therefore, this vaccine meets all the criteria for a vaccine to be used as part of routine childhood vaccination programs in Latin America and the Caribbean.

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Note on conflict of interest. The Pan American Health Organization (PAHO) purchases vaccines from GlaxoSmithKline, and PAHO has also received contributions from GlaxoSmithKline. While the *Revista Panamericana de Salud Pública/Pan American Journal of Public Health* is affiliated with PAHO, the *Revista/Journal* is an independent scientific publication whose articles do not necessarily reflect the opinions or official positions of PAHO on specific issues. The mention of particular companies or of certain manufacturers' products in the *Revista/Journal* does not imply that they are endorsed or recommended by PAHO in preference to other ones of a similar nature. As with all other research articles published in the *Revista/Journal*, this article went through the regular process of peer review by outside experts.

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RESUMEN

Vacunación primaria y de refuerzo con la vacuna pentavalente DTPw-HB/Hib en niños costarricenses vacunados al nacer contra la hepatitis B

Objetivos. La vacuna combinada pentavalente DTPw-HB/Hib ha sido creada siguiendo la recomendación de la Organización Mundial de la Salud de añadir las vacunas contra la hepatitis b (HB) y el *Haemophilus influenzae* tipo b (Hib) a los programas de vacunación infantil. Los objetivos del presente estudio consistieron en: 1) analizar la inmunogenicidad y reactogenicidad de la vacuna combinada pentavalente DTPw-HB/Hib en comparación con las inyecciones separadas de las vacunas DTPw-HB e Hib como vacunación primaria en un grupo de niños que habían recibido al nacer una dosis de vacuna contra la HB, y 2) evaluar la persistencia de anticuerpos en el segundo año de vida, así como la respuesta a las dosis de recuerdo de DTPw-HB/Hib o DTPw/Hib.

Métodos. En la primera parte del estudio (fase de vacunación primaria), realizada en 1998–1999, se analizó la inmunogenicidad y reactogenicidad de la vacuna combinada DTPw-HB/Hib en comparación con inyecciones separadas de las vacunas DTPw-HB e Hib como vacunación primaria a los 2, 4 y 6 meses de edad en un grupo de 207 niños costarricenses que habían recibido al nacer una dosis de la vacuna contra la HB. Posteriormente, en la fase de vacunación de recuerdo, realizada en 1999–2000, se midió la persistencia de anticuerpos y se evaluó la respuesta a los

recuerdos de DTPw-HB/Hib o DTPw/Hib en un subgrupo de 69 niños que tenían entonces 15 a 18 meses.

Resultados. La vacunación primaria proporcionó concentraciones protectoras de anticuerpos frente a los antígenos empleados en las vacunas en al menos el 97,5% de los lactantes de ambos grupos. La vacuna combinada pentavalente DTPw-HB/Hib no originó más reacciones locales que la vacuna DTPw-HB aislada. Con respecto a las reacciones generales, no hubo diferencias clínicamente significativas entre ambas vacunas, y la combinada pentavalente tuvo la ventaja de necesitar una inyección menos. Nueve meses después de la tercera dosis de la vacunación primaria, la persistencia de anticuerpos fue similar en ambos grupos: más del 93% de los niños todavía tenían títulos protectores de anticuerpos frente al Hib, la HB y el tétanos, y cerca del 50% de ellos frente a la difteria y la tos ferina. A los 15 meses de edad, prácticamente todos los niños presentaron una fuerte respuesta de recuerdo a todos los antígenos de las vacunas, independientemente de que recibieran recuerdos de DTPw-HB/Hib pentavalente o DTPw/Hib. Ambos recuerdos fueron igualmente bien tolerados, lo cual indica que se pueden administrar hasta cinco dosis de vacuna contra la hepatitis B sin que haya problemas de seguridad.

Conclusiones. Este estudio confirma que la vacuna pentavalente DTPw-HB/Hib es altamente inmunogénica en la vacunación primaria de niños vacunados contra la HB al nacer, y que la combinación pentavalente produce inmunidad persistente y potenciable mediante la administración de dosis de recuerdo. La vacuna pentavalente fue segura en la vacunación tanto primaria como de recuerdo. Por consiguiente, este estudio respalda el uso rutinario de la vacuna pentavalente DTPw-HB/Hib como parte de los programas de vacunación en Latinoamérica y el Caribe.

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