Safety and Immunogenicity of a Diphtheria, Tetanus, and Acellular Pertussis-Inactivated Poliovirus Vaccine / *Haemophilus Influenzae* Type B Combination Vaccine Administered to Taiwanese Infants at 2, 4, and 6 Months of Age

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Background: Combined vaccines are urgently needed to ensure compliance with the increasing number of recommended vaccines for children. We evaluated the safety and antibody response to a diphtheria, tetanus, and acellular pertussis-inactivated poliovirus vaccine / *Haemophilus influenzae* type b (DTaP-IPV / Hib) combination vaccine administrated to infants at 2, 4, and 6 months of age.

Methods: Sixty healthy infants between 6 and 12 weeks of age were enrolled. One group of vaccines received the DTaP-IPV/Hib in a single injection, while another group concurrently received DTaP-IPV and Hib at separate injection sites. Solicited adverse events were monitored by parental observation and were recorded on a diary card. Levels of serum antibodies to DTaP and polyribosyl-ribitolphosphate-tetanus (PRP-T) antigens were collected before the first vaccine dose and 1 month after the third vaccine dose.

Results: The combined-injection group tended to have lower local reactions, and there was no increase in reactogenicity when compared with the separate-injection group. Seroconversion rates were 100% in both groups for all antigens, except for the anti-polio 2 antibody in the combined-injection group (96.4%). The combined-injection group had lower antibody levels of PRP (8.45 μg/ml) than did the separate-injection group (20.61 μg/ml). However, the percentage of vaccines achieving protective levels of antibody to PRP (≥ 0.15 μg/ml or ≥ 1.0 μg/ml) was similar in both groups.

Conclusions: DTaP-IPV/Hib may be safely and effectively administered to healthy infants, using a 2-, 4-, and 6-month vaccination schedule. This combined vaccine is cost-effective, more acceptable to parents and physicians, and minimizes distress to infants.

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Key words: **diphtheria, tetanus, and acellular pertussis, inactivated poliovirus vaccine, *Haemophilus influenzae* type b, reactogenicity, immunogenicity.**

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With the extensive use of routine pediatric vaccines, many infectious diseases in children have been controlled or even eradicated. It is widely accepted that an all-in-one combination vaccine is the preferred future delivery method for children. The main advantages of a combined vaccine are a fewer number of injections, improved compliance, lower costs, and consequently more-effective control of vaccine-preventable diseases.[1,2] However, many concerns have been expressed about the possibility of increased reactogenicity and interfering immunogenicity. The excellent tolerability, immunogenicity, and efficacy of the diphtheria, tetanus, and acellular pertussis vaccine (DTaP) makes it the cornerstone for additional pediatric components, such as Haemophilus influenzae type b (Hib), inactivated polio vaccine, or hepatitis B.[3-5] We evaluated the safety and antibody response to a 3-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids and an inactivated poliovirus vaccine (DTaP-IPV) given either separately or combined as a single injection with a lyophilized Hib-tetanus toxoid-conjugated vaccine. We administered our combinations to Taiwanese infants for their first 3 doses at 2, 4, and 6 months of age. In this study, we paid special attention to the antibody responses to the Hib polyribosyl-ribitolphosphate (PRP) antigen.

METHODS

Subjects and consent

Healthy infants between 6 and 12 weeks of age were enrolled in the study at Chang Gung Children's Hospital, Taoyuan, Taiwan. Infants were excluded from the study if they had a history of previous immunization or infection with 1 of the vaccine constituents used in the study, had had any chronic or neurological illness, or had received any blood products. Exclusions to a subsequent dose included a hypersensitivity reaction, seizures, encephalopathy, or an axillary temperature of $\geq 40^{\circ}C$ within 48 hours of a previous vaccine dose. The study was conducted according to Good Clinical Practice and in accordance with the Declaration of Helsinki. The study was approved by the Ethical Review Committee of Chang Gung Memorial Hospital on March 10, 1999 and by the Department of Health, Executive Yuan, Taiwan on July 19, 1999. Written informed consent was obtained from a parent or guardian of all participants prior to entry into the study.

Vaccines

Hib-tetanus toxoid-conjugate vaccine (Hiberix™) and DTaP-IPV (Infanrix™-IPV) (GlaxoSmithKline Biologicals, Rixensart, Belgium) were used in this study. The Hib-tetanus toxoid-conjugate vaccine was a lyophilized preparation containing 10 μg of purified capsular polysaccharide (polyribosyl-ribitolphosphate; PRP) conjugated to 20-40 μg of tetanus toxoids per 0.5-ml dose. The DTaP-IPV vaccine per 0.5 ml dose contained diphtheria toxoids (≥ 30 IU), tetanus toxoids (≥ 40 IU), acellular *Bordetella pertussis* antigens (pertussis toxoid (PT) 25 μg; filamentous hemagglutinin (FHA) 25 μg; and pertactin (PRN) 8 μg), inactivated poliovirus (40 D antigen units of poliovirus type 1 (Mahoney strain), 8 D antigen units of poliovirus type 2 (MEF-1 strain), and 32 D antigen units of poliovirus type 3 (Saukett strain). One lot of each vaccine was used.

Study design

The study was a randomized, open comparison trial. Sixty children were randomly assigned, according to a random-number table, to 1 of 2 groups: a combined-injection group or a separate-injection group. In the separate-injection groups, the vaccines were given as separate injections by means of a 25-gauge, 1-in (2.54 cm)-long needle in opposite limbs. In the combined-injection group, the lyophilized Hib-tetanus toxoid conjugate vaccine was reconstituted in liquid DTaP-IPV and given as a single injection. The DTaP-IPV or DTaP-IPV/Hib vaccine was given as an intramuscular injection in the left anterolateral thigh and Hib (in the separate-injection group) was given as an intramuscular injection in the right anterolateral thigh. The injections were given to the study participants at 2, 4, and 6 months of age.

Safety/reactogenicity data

Vaccine-associated solicited adverse events were monitored by parental observation on the day of and for 3 subsequent days following each dose and were recorded on a diary card. Research personnel collected the completed diary cards from the parents during the next visit. Solicited adverse reactions included local reactions at the injection site (pain, redness, and swelling) and systemic reactions (rectal

temperature, irritability/fussiness, drowsiness, and loss of appetite). Unsolicited reactions were also tabulated during the 30-day follow-up period after each vaccine dose. For local swelling and redness, the largest diameter was measured and categorized as grade 1 (≤ 5 mm), grade 2 (> 5 mm to ≤ 20 mm), or grade 3/severe (> 20 mm). Fever (rectal temperature) was categorized as grade 1 (≥ 38 to ≤ 38.5 °C), grade 2 (> 38.5 to ≤ 39.5 °C), or grade 3/severe (> 39.5 °C).

Immunogenicity data

Blood samples were collected before the first vaccine dose and 1 month after the third vaccine dose. Levels of serum antibodies to diphtheria and tetanus toxoids, *B. pertussis* antigens (PT, FHA, and PRN), and Hib PRP were measured by an in-house enzyme-linked immunosorbent assay (ELISA). The lower limits of the assay for PT, FHA, and PRN were set at 5 EU/ml; those for tetanus and diphtheria antitoxins were set at 0.1 IU/ml; and that for Hib PRP was set at 0.15 μg/ml. Levels of neutralizing antibodies to the 3 poliovirus types were determined by an in-house microneutralization assay; titers were expressed as the reciprocal of the highest dilutions showing 50% neutralization, and a titer of ≥ 8 indicated seropositivity.

Statistical analysis

The analysis was based on data for the evaluable subjects who completed the study procedures in compliance with the protocol. The seropositivity/seroprotection rate (percentage of subjects with antibody titers ≥ assay cut-off) and a geometric mean titer (GMT) with 95% confidence intervals (95% CIs) for antibodies to all vaccine antigens was calculated at each blood sampling time point. Vaccine response rates (defined as the appearance of antibody titers ≥ assay cut-off in subjects who were seronegative before vaccination and post-vaccination antibody titers ≥ pre-vaccination titers in subjects who were seropositive before vaccination) to the 3 pertussis antigens with 95% CIs were calculated 1 month after the third dose. The incidences of local and systemic adverse events (solicited/unsolicited after each vaccine dose) were calculated with exact 95% CIs, in addition to tabulating the intensity and relationship. Serious adverse events and discontinuation due to adverse events were described. Chi-square test was used to measure differences of incidences of adverse events and seropositivity/seroprotection rates between the 2 groups. The antibody titers were not normally distributed, and data were thus logarithmically transformed before statistical analysis. Thereafter, Student's t-test was applied to measure differences in antibody titers between groups. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Demographics

In total, 60 infants were enrolled in the study and were equally allocated into the combined- or

Table 1. Adverse Events Occurring after Immunization of Infants with DTaP-IPV Given Separately or Combined with the Hib-Tetanus Toxoid Conjugate Vaccine

	Combined group (N = 30) % (95% CI)	Separate group (N = 30) % (95% CI)
Local symptoms		
All	33.3 (23.7, 44.1)	40.0 (29.8, 50.9)
Pain		
All	22.2 (14.1, 32.2)	34.4 (24.7, 45.2)
Grade 3	1.1 (0.0, 6.0)	2.2 (0.3, 7.8)
Redness		
All	20.0 (12.3, 29.8)	25.6 (16.9, 35.8)
Grade 3 (> 20 mm)	0.0 (0.0, 4.0)	2.2 (0.3, 7.8)
Swelling		
All	11.1 (5.5, 19.5)	23.3 (15.1, 33.4)
Grade 3 (> 20 mm)	0.0 (0.0, 4.0)	1.1 (0.0, 6.0)
Systemic symptoms		
All	65.6 (54.8, 75.3)	63.3 (52.5, 73.2)
Drowsiness		
All	36.7 (26.8, 47.5)	36.7 (26.8, 47.5)
Grade 3	0.0 (0.0, 4.0)	1.1 (0.0, 6.0)
Irritability		
All	38.9 (28.8, 49.7)	46.7 (36.1, 57.5)
Grade 3	1.1 (0.0, 6.0)	3.3 (0.7, 9.4)
Loss of appetite		
All	31.1 (21.8, 41.7)	43.3 (32.9, 54.2)
Grade 3	0.0 (0.0, 4.0)	2.2 (0.3, 7.8)
Fever		
All	6.7 (2.5, 13.9)	10.0 (4.7, 18.1)
Grade 3	0.0 (0.0, 4.0)	0.0 (0.0, 4.0)

Abbreviations: N, number of symptom sheets completed and returned after each vaccine dose; 95% CI, 95% confidence interval, lower and upper limits.

All p values were > 0.05 according to the X^2 test.

separate-injection groups. The mean age of the participants at study enrollment was 8.8 weeks in both groups; there was an equal distribution of males and females between the groups. All 60 subjects enrolled completed the study. Two subjects (3.3%) were eliminated from the immunogenicity analysis due to protocol violations.

Reactogenicity

Adverse reactions were commonly reported after all vaccine doses, whether the Hib-tetanus toxoid conjugate vaccine was given separately or as a combined injection (Table 1). There was no increase in reactogenicity in the combined-injection group ($p > 0.05$). Furthermore, there was no increase in reactogenicity with subsequent doses of either regimen. Pain at the injection site was the most frequent solicited local symptom reported. The vaccinees in the combined-injection group tended to have a lower incidence of pain (22.2% vs. 34.4%) and swelling (11.1% vs. 23.3%). Irritability was the most frequently solicited systemic symptom reported. Few of the solicited local and systemic adverse reactions were categorized as grade 3. No serious adverse events were reported during the study.

Antibody response

One month after the third vaccine dose, seropositivity/seroprotection rates and geometric mean titers of antibodies to all antigens were comparable between the 2 groups (Table 2). The antibody responses to *B. pertussis* antigens, diphtheria, and tetanus toxoids, and the 3 poliovirus types were similar in both groups whether the DTaP-IPV vaccine was given as a separate injection or as a single injection combined with the Hib-tetanus conjugate vaccine ($p > 0.05$). One month after the third vaccine dose, the vaccine response to the 3 pertussis antigens (anti-PT, anti-FHA, and anti-PRN) ranged between 96.2% and 100% in both groups ($p > 0.05$). Recipients of the combined injection had lower levels of antibody to PRP after the third dose (8.45 μg/ml) than those who were given the Hib-tetanus toxoid conjugate vaccine as a separate injection (20.61 μg/ml) ($p > 0.05$). However, the percentage of subjects achieving protective levels of antibodies to PRP (≥ 0.15 μg/ml or ≥ 1.0 μg/ml) after the 3-dose vaccination course was similar in both groups ($p > 0.05$) (Table 3). The percentage of subjects achieving protective levels of diphtheria and tetanus antitoxins (≥ 0.1 IU/ml) after the 3-dose vaccination course was similar whether they had received the combined vaccine or separate vaccine injections ($p > 0.05$) (Table 3). Results of analysis of safety and immunogenicity for all antibodies were similar when the total cohort was analyzed (intention-to-treat analysis).

Table 2. Geometric Mean Titers of Antibodies in Infants Immunized with DTaP-IPV Given Separately or Combined with the Hib-Tetanus Toxoid Conjugate Vaccine

	Geometric mean titer of antibody (95% CI)				
	Before dose 1		After dose 3		
Antigen	Combined group	Separate group	Combined group	Separate group	*p
PT (EU/ml)	3.1 (2.5, 3.7)	3.2 (2.5, 4.0)	85.0 (65.5, 110.3)	85.0 (68.1, 106.2)	1.000
FHA (EU/ml)	5.7 (4.1, 7.8)	7.2 (5.0, 10.3)	363.5 (299.8, 440.7)	344.0 (277.3, 426.8)	0.736
PRN (EU/ml)	2.9 (2.5, 3.3)	3.3 (2.6, 4.2)	252.6 (198.9, 320.8)	282.2 (241.3, 330.1)	0.404
Diphtheria toxoid (IU/ml)	0.052 (0.048,0.055)	0.050 (0.050, 0.050)	3.075 (2.363, 4.002)	3.367 (2.668, 4.248)	0.592
Tetanus toxoid (IU/ml)	0.109 (0.071, 0.166)	0.096 (0.066, 0.138)	4.465 (3.605, 5.531)	4.763 (3.497, 6.486)	0.695
Polio 1 (reciprocal dilution)	12.6 (7.9, 20.0)	12.0 (7.0, 20.5)	663.6 (435.7, 1010.7)	565.2 (406.1, 786.7)	0.539
Polio 2 (reciprocal dilution)	9.1 (6.1, 13.5)	9.1 (6.8, 12.3)	524.9 (311.0, 885.9)	558.5 (396.7, 786.3)	0.839
Polio 3 (reciprocal dilution)	5.5 (4.1, 7.4)	5.2 (3.8, 7.0)	1132.5 (694.5, 1846.8)	1482.6 (1030.9, 2132.2)	0.362
Hib PRP (μg/ml)	0.097 (0.074, 0.127)	0.113 (0.077, 0.167)	8.445 (5.320, 13.405)	20.611 (13.362, 31.790)	0.004

Abbreviations: DTaP-IPV, 3-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids and inactivated poliovirus vaccine; PT, pertussis toxin; FHA, filamentous hemagglutinin; PRN, pertactin; EU, ELISA unit; PRP, polyribose ribitol phosphate; 95% CI, 95% confidence interval, lower and upper limits.

All p values before dose 1 were > 0.05.

*p values were calculated by comparing the combined-injection group with the separate-injection group after dose 3 by Student's t-test.

Table 3. Proportion of Infants Who Had Specified Antibody Levels after Immunization with DTaP-IPV Given Separately or Combined with the Hib-Tetanus Toxoid Conjugate Vaccine

	Percent of participants achieving specified antibody level (95% CI)			
	Before dose 1		After dose 3	
Antigen	Combined group	Separate group	Combined group	Separate group
PT ≥ 5 EU/ml			100.0 (87.7, 100.0)	96.2 (80.4, 99.9)
FHA ≥ 5 EU/ml			100.0 (88.4, 100.0)	100.0 (87.7, 100.0)
PRN ≥ 5 EU/ml			100.0 (88.4, 100.0)	100.0 (87.7, 100.0)
Diphtheria toxoid ≥ 0.1 IU/ml	3.3 (0.1, 17.2)	0.0 (0.0, 12.3)	100.0 (88.4, 100.0)	100.0 (87.7, 100.0)
Tetanus toxoid ≥ 0.1 IU/ml	40.0 (22.7, 59.4)	39.3 (21.5, 59.4)	100.0 (88.4, 100.0)	100.0 (87.7, 100.0)
Polio 1 ≥ 1:8	64.3 (44.1, 81.4)	57.7 (36.9, 76.6)	100.0 (87.7, 100.0)	100.0 (87.7, 100.0)
Polio 2 ≥ 1:8	48.3 (29.4, 67.5)	63.0 (42.4, 80.6)	96.4 (81.7, 99.9)	100.0 (87.7, 100.0)
Polio 3 ≥ 1:8	20.7 (8.0, 39.7)	11.1 (2.4, 29.2)	100.0 (87.2, 100.0)	100.0 (87.7, 100.0)
Hib PRP ≥ 0.15 μg/ml	13.3 (3.8, 30.7)	17.9 (6.1, 36.9)	100.0 (88.4, 100.0)	100.0 (87.7, 100.0)
Hib PRP ≥ 1.0 μg/ml	6.7 (0.8, 22.1)	3.6 (0.1, 18.3)	93.3 (77.9, 99.2)	96.4 (81.7, 99.9)

Abbreviations: DTaP-IPV, 3-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids and inactivated poliovirus vaccine; PT, pertussis toxin; FHA, filamentous hemagglutinin; PRN, pertactin; Hib: Haemophilus influenzae type b; PRP, polyribose ribitol phosphate; 95% CI: 95% confidence interval, lower and upper limits.
All p values were > 0.05 according to X^2 test.

DISCUSSION

The extensive use of diphtheria, tetanus, and whole-cell pertussis vaccines has brought about a dramatic reduction in these diseases. The whole-cell pertussis vaccine is the most reactogenic among the currently used routine childhood vaccines.[6] The acellular pertussis vaccine was developed and proven to be immunogenic, efficacious, and safe.[7,8] The acellular pertussis vaccine is universally used in Japan, North America, and some European countries. In Taiwan, this vaccine has been licensed and used on an optional basis since 1993.

Although the annual prevalence rate of invasive Hib infections was only 1.9 per 100,000 children under 5 years of age in Taiwan,[9] Hib is the most common pathogen of childhood purulent meningitis in Taiwan. The conjugated Hib vaccine has routinely been used in the US since 1990, and has dramatically reduced invasive Hib infections.[10] The conjugate Hib vaccine was introduced in Taiwan in 1994 for optional use and is expected to become a routine childhood vaccine in the future.

The oral polio vaccine (OPV) has been used successfully to reduce the incidence of paralytic poliomyelitis in many parts of the world. In recent years, concern over vaccine-associated paralytic poliomyelitis coupled with the development of a newer enhanced-potency inactivated polio vaccine (IPV), has led to the reconsideration of IPV in poliomyelitis vaccine policies.[11,12] A switch from OPV to IPV has been recommended in North America and some European countries. In Taiwan, the last case of wild-type paralytic poliomyelitis occurred in 1983. Eradication of poliomyelitis in the Western Pacific region, including Taiwan, was declared on October 29, 2000. But the first confirmed case of vaccine-associated paralytic poliomyelitis was diagnosed on April 2001, in an 8-year-old boy with common variable immunodeficiency. IPV is also a future candidate for routine vaccination in Taiwan.

There is concern that additional antigens in any combination vaccine might affect their reactogenicity profiles. However, Eskola et al. and Lagos et al. did not find the combination of DTaP and IPV to be more reactogenic than DTaP and IPV administered separately.[13-16] In our study, the total incidence of systemic and local reactions was similar whether the DTaP-IPV vaccine was administered as a single injection mixed with Hib vaccine or administered separately in concomitant injections. There was a tendency for those who received the combined injection to have lower reaction rates, in particular for pain and swelling. The incidence of systemic symptoms in the combined-injection group was similar to

that of the separate-injection group, showing that the additional Hib component did not increase the reactogenicity. Grade 3 (severe) reactions were few and were associated to the same extent between the combined and separate administrations. The findings substantiate the results of Lee et al. that the combined DTaP and Hib vaccine is well tolerated by Taiwanese infants.[17]

The DTaP-IPV vaccine mixed with the Hib vaccine induced protective antibody titers against diphtheria, tetanus, poliomyelitis, *H. influenzae*, and marked anti-pertussis titers. The anti-PRP GMTs were lower in the combined group. This is consistent with the reduction in anti-PRP levels seen with other DTaP vaccines.[18] The lower anti-PRP titers in the combined group do not have clinical relevance since all subjects reached the cut-off level of 0.15 μg/ml, a level traditionally thought to be associated with short-term protection. Poolman et al. showed that although the levels of antibodies in the combined DTaP-HBV-IPV/Hib group were lower than those of subjects receiving a separate Hib conjugate, the nature (isotype and IgG subclass) and function (avidity and opsonic activity) of the antibodies were the same, and immunologic memory was induced.[19] Furthermore, recent epidemiological data from Germany, where DTaP-based Hib combination vaccines have been in widespread use since 1996, show that the annual number of reported cases is on the decline, demonstrating that such combinations are effective in reducing the incidence of invasive Hib disease.[20] This field effectiveness data further support the use of Hib in such combinations to facilitate and maintain vaccine coverage.

In conclusion, this study suggests that the DTaP-IPV vaccine may be safely and effectively administered to children, with a lyophilized PRP-T vaccine as a combined vaccine in a single injection, using a 2-, 4-, and 6-month vaccination schedule. The DTaP-IPV/Hib combined vaccine described in this study affords a convenient means of providing recommended pediatric immunization against 5 diseases in a single injection per health visit, without compromising the effectiveness of the individual components. The fewer injections involved in such vaccines are likely to greatly improve vaccine acceptability and perform a key role in increasing national vaccination coverage rates.

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對台灣嬰兒於2、4、6個月大時接種白喉、破傷風、三成份非細胞性百日咳疫苗、非活性小兒麻痺疫苗(DTaP-IPV)和b型嗜血桿菌疫苗(Hib)混合疫苗的安全性及免疫反應評估

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背 景： 隨著建議接種的疫苗日益增加，更凸顯出兒童對混合疫苗的迫切需要。本研究是針對台灣嬰兒施予白喉、破傷風、三成份非細胞性百日咳疫苗、非活性小兒麻痺疫苗(DTaP-IPV)，和b型嗜血桿菌疫苗 (Hib) 一起或分開接種的安全性及抗體反應，作評估比較。

方 法： 共有60位6週至12週大的健康嬰兒參加。一組接受DTaP-IPV和Hib疫苗混合同一針筒內接種，而另一組則 DTaP-IPV和Hib疫苗分開於不同部位接種。接種後由父母觀察副作用並詳實記錄於日記本中。於第一劑疫苗接種前及第三劑疫苗接種後一個月，分別收集血清，以評估免疫抗體變化。

結 果： 相較於分開接種組，DTaP-IPV和Hib疫苗混合接種的副作用並無增加，局部副作用反而減少。接種第三劑後一個月，除了在混合接種組抗小兒麻痺第2型抗體陽轉率(96.4%)較低外，對所有抗原的血清陽轉率皆高達100%。研究亦發現，混合接種組的PRP抗體 (8.45 μg/ml) 比分開接種組來得低 (20.61 μg/ml)，但PRP抗體達到保護效果的比率 (≥0.15 μg/ml 或 ≤1.0 μg/ml)，兩組則無差異。

結 論： 本研究說明利用2、4、6個月時程，DTaP-IPV 可以很安全而且有效地和Hib疫苗混合接種，這種混合疫苗是 cost-effective，容易被家長及醫師接受，同時可減少兒童接種的痛苦。

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關鍵字： 白喉，破傷風，非細胞性百日咳疫苗，非活性小兒麻痺疫苗，b型嗜血桿菌疫苗，副作用，免疫反應。

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