

Interchangeability of two diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus, *Haemophilus influenzae* type b conjugate vaccines as a fourth dose in 15–20-month-old toddlers[☆]

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Abstract

Background: Since 1998, all children in Canada have been immunized with a pentavalent diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus, *Haemophilus influenzae* type b conjugate vaccine (DTaP-IPV-Hib) produced by one manufacturer (Pentacel™). Recently, another DTaP-IPV-Hib (Infanrix™-IPV-Hib) became available. Data on the interchangeability of these products was lacking.

Methods: In this multicentered, observer-blind study, healthy 15–20-month-old children previously immunized with three doses of Pentacel™ were randomly allocated to receive a single dose of Pentacel™ or Infanrix™-IPV-Hib. Adverse events were documented by diary for 7 days post-immunization and unsolicited adverse events were documented for 30 days.

Results: 433 participants were enrolled (mean age 17.1 months). Rates of fever, anorexia and irritability were similar in both groups. Injection-site redness >20 mm (11.5% versus 5.6%; $p=0.038$), injection-site pain (52.1% versus 39.4%; $p=0.009$) and moderate or greater drowsiness (13.8% versus 7.4%; $p=0.042$) were more common after Pentacel™ than Infanrix™-IPV-Hib. The proportions of participants who were seroprotected or who seroresponded were similar for all antigens. Geometric mean titers or concentrations were similar for antibodies against diphtheria toxoid and poliovirus type 3. Geometric mean concentrations or titers were higher in the Infanrix™-IPV-Hib group against pertussis toxin (88.5 EU/mL versus 65.6 EU/mL), filamentous hemagglutinin (207.3 EU/mL versus 132.1 EU/mL), pertactin (251.9 EU/mL versus 166.9 EU/mL) and poliovirus type 1 (1293.7 versus 976.2 reciprocal dilution). Geometric mean titers or concentrations were higher in the Pentacel™ group against *H. influenzae* type b (29 µg/mL versus 19 µg/mL), tetanus toxoid (5.6 IU/mL versus 4.7 IU/mL) and poliovirus type 2 (1437.3 versus 1134.2 reciprocal dilution).

Conclusions: A booster dose of Infanrix™-IPV-Hib after three priming doses of Pentacel™ is well-tolerated and immunogenic in 15–20-month-old toddlers and can be used interchangeably.

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1. Introduction

Since 1998, all Canadian children have been immunized with diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus, *Haemophilus influenzae* type b conjugate combination vaccine (DTaP-IPV-Hib) produced by a single manufacturer (Pentacel™, Sanofi Pasteur, Toronto, ON). In 2004, a second pentavalent DTaP-IPV-Hib was licensed (Infanrix™-IPV-Hib, GlaxoSmithKline Biologicals, Rixensart, Belgium). The interchangeability of the two products was an important issue facing advisory committees and vaccine providers because of movement of children between vaccine providers and interruptions in vaccine supply. The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention and the National Advisory Committee on Immunization of the Public Health Agency of Canada recommend that in view of the lack of interchangeability data, whenever possible, the same acellular pertussis-containing vaccines should be used to complete the first three doses [1,2]. Although data are similarly lacking for the fourth (18 months) and fifth (4–6 years) doses, vaccines were considered interchangeable for these doses.

There are good data to support the interchangeability of some vaccines, particularly where serological correlates of immunity have been established (diphtheria, tetanus, *H. influenzae* type b, poliovirus, hepatitis B) [3]. Although there is a relationship between antibody levels and protection against *Bordetella pertussis* infection, protective levels have not been established [4]. We studied the interchangeability of two pentavalent DTaP-IPV-Hib vaccines (Pentacel™ and Infanrix™-IPV-Hib) given as a fourth dose in 15–20-month-old toddlers previously immunized with three doses of Pentacel™. We hypothesized that the immune response to Infanrix™-IPV-Hib would be non-inferior to the response to Pentacel™ and that the two vaccines would have similar adverse event profiles. Because the data are specific to these two products, trade names rather than generic names are used throughout the article.

2. Methods

2.1. Vaccines

Two licensed vaccines were used in the study. Pentacel™ (Sanofi Pasteur, Toronto, ON) and Infanrix™-IPV-Hib (GlaxoSmithKline Biologicals, Rixensart, Belgium) are pentavalent vaccines containing diphtheria and tetanus toxoids, acellular pertussis, inactivated poliovirus and *H. influenzae* type b-conjugate vaccines (Table 1).

2.2. Study population

Healthy toddlers between 15 and 20 months of age were recruited into the study. All infants needed documented evidence of receiving three doses of Pentacel™ at 2, 4 and 6

Table 1
Vaccine composition

Vaccine composition	Pentacel™	Infanrix™-IPV-Hib
Diphtheria toxoid	15 Lf	25 LF
Tetanus toxoid	5 Lf	10 Lf
Pertussis toxoid	20 µg	25 µg
Filamentous hemagglutinin	20 µg	25 µg
Pertactin	3 µg	8 µg
Fimbriae 2 and 3	5 µg	0
Inactivated poliovirus type 1	40 D antigen unit	40 D antigen unit
Inactivated poliovirus type 2	8 D antigen unit	8 D antigen unit
Inactivated poliovirus type 3	32 D antigen unit	32 D antigen unit
Polyribosylribitolphosphate (Hib-PRP)	10 µg	10 µg
Alum	1.5 mg (phosphate)	0.5 mg (as hydroxide)
2-Phenoxyethanol	3 mg	2.5 mg

months of age (defined as starting after 6 weeks of age, separated by at least 6 weeks and completed by 9 months of age). Toddlers were excluded from participation if they had already received their fourth dose of DTaP-IPV-Hib, if there was a plan to administer another vaccine within 30 days before or after the study vaccine, receipt of immunosuppressive medication or immunoglobulin, or a history of seizures, allergic disease, history of diphtheria, tetanus, pertussis or invasive *H. influenzae* disease, or personal or family history of immunodeficiency.

2.3. Study design and procedures

The study was an observer-blinded, randomized, controlled, five-center study. Participants provided written informed consent prior to any study procedure; the study was approved by the Research Ethics Board of each participating center. Participants were randomly allocated to receive Pentacel™ or Infanrix™-IPV-Hib by a center-stratified, centralized computer-generated list accessed via the internet. The randomization list was produced by the study statistician who had no interaction with study participants. Randomization was in a 1:1 ratio with a block size of 4.

Parents of study participants and study personnel who had ongoing contact with participants remained blinded to the treatment assignment. One nurse at each site was assigned to prepare and administer the vaccines. This unblinded nurse had no other contact with participants and was required to maintain confidentiality of treatment assignment.

Vaccines were given as intramuscular injections into the deltoid muscle with a 25 gauge, 1 in. needle. Participants were monitored by study staff for 15 min after the injection for immediate reactions and by their parents for 8 days (day 0–7) post-immunization by completing a standardized symptom diary. Temperature was measured daily with a supplied digital thermometer and injection-site reactions (erythema, swelling) and systemic adverse events (drowsiness, irritability or fussiness, loss of appetite) were assessed daily; all unsolicited adverse events were collected and tabulated by

body system. Solicited adverse events were either measured (fever, erythema, swelling) or categorized as mild (awareness of symptom but easily tolerated), moderate (discomfort sufficient to cause interference with usual activity) or severe (incapacitating with inability to do usual activity). Blood was collected by venipuncture before and one month post-immunization. Anti-diphtheria, anti-tetanus, anti-pertussis toxoid, anti-filamentous hemagglutinin, anti-pertactin and anti-PRP were measured by enzyme immunoassay; anti-poliovirus types 1, 2 and 3 were measured by microneutralization. All testing was done in a blinded fashion on sera in the laboratories of GlaxoSmithKline Biologicals in Rixensart, Belgium, for poliovirus neutralization assays and at the laboratory of Dr. M. Pichichero, University of Rochester, NY, for all other antibodies.

2.4. Data analysis and statistical considerations

Adverse events were tabulated and the maximum severity reported was used for each time period. Grade 2 reactions were defined as measured reactions >20 mm and ≤ 50 mm, fever $>38.5^{\circ}\text{C}$ and $\leq 39.5^{\circ}\text{C}$ and severity of moderate (sufficiently discomforting to interfere with normal activities) for other symptoms. Grade 3 reactions were defined as measured reactions >50 mm, temperature $>39.5^{\circ}\text{C}$ and events assessed as severe (prevented normal, everyday activities) for all other adverse events. The proportion of participants having an adverse event by vaccine group and severity was calculated with exact 95% confidence intervals and compared by Fisher's exact test; $p < 0.05$ was considered statistically significant. No adjustments were made for multiple comparisons.

Geometric mean antibody titers or concentrations (GMT, GMC) and 95% confidence intervals were calculated pre- and post-immunization and the proportion of each vaccine group achieving seroprotective antibody concentrations or titers was calculated (≥ 1.0 $\mu\text{g/mL}$ for anti-PRP antibodies, ≥ 0.1 IU/mL for anti-diphtheria and anti-tetanus antibodies and ≥ 8 reciprocal dilution for anti-poliovirus 1, 2 and 3 antibodies). Seroresponse rates (and 95% confidence intervals), defined as appearance of antibodies in participants initially seronegative or a twofold increase in antibodies in participants initially seropositive, were calculated for antibodies against PT, FHA and PRN. Antibody concentrations below the assay cut-off were given an arbitrary value of half the cut-off. Non-inferiority of the two groups was declared if the upper limit of the 95% confidence interval for the difference in seroprotection rates between the two groups was $<10\%$. Since seroprotective levels are not established for pertussis antigens, non-inferiority was declared if the lower limit of the 95% confidence intervals for the ratio of the geometric mean antibody levels was $>67\%$. A sample size of 220 was selected to account for an estimated 15% participant drop-out and provide 87% power for the total 9 immunogenicity outcomes; the powers for each of the individual immunogenicity outcomes were 95%–99%.

3. Results

3.1. Demographics and participant disposition

A total of 433 participants enrolled in the study; 216 were randomly allocated to receive InfanrixTM-IPV-Hib and 217 to receive PentacelTM. All but 1 (99.8%) InfanrixTM-IPV-Hib participant, who was lost to follow-up, completed the study. Two participants were excluded from the safety analysis because they received an additional non-study vaccine (both in the PentacelTM group). An additional 41 participants were excluded from the per protocol immunogenicity analysis: 31 because they lacked a serum sample (12 in the InfanrixTM-IPV-Hib group and 19 in the PentacelTM group) and 10 for protocol violation or non-compliance with the blood sampling schedule (6 in the InfanrixTM-IPV-Hib group and 4 in the PentacelTM group).

Participant characteristics did not differ by study group. In the according to protocol immunogenicity cohort, the mean age (range) of the InfanrixTM group was 16.9 months (15–20 months) and the PentacelTM group was 17.1 months (15–20 months). The proportion of female participants was 49.5% and 46.9%, respectively; Caucasians comprised 92.9% and 93.8% of the groups, respectively. Mean body mass index (weight/height²) was 18.8 and 17.6 kg/m².

3.2. Adverse events

Both vaccines were well tolerated by participants and in general had similar adverse event profiles. There were no statistically significant differences between the two groups in injection-site swelling (Fig. 1A). PentacelTM recipients more frequently reported redness >20 mm (11.5%, 95% confidence interval 7.6–16.5%, versus 5.6%, 2.9–9.5%, $p = 0.038$) and injection-site pain (any pain 52.1%, 95% confidence interval 45.2–58.9%, versus 39.4%, 32.8–46.2%, $p = 0.009$; moderate or greater pain 19.4%, 95% confidence interval 14.3–25.2%, versus 9.7%, 6.1–14.5%, $p = 0.006$; severe pain 6.9%, 95% confidence interval 3.9–11.1%, versus 1.4%, 0.3–4.0%, $p = 0.006$). Rates of systemic adverse events were very similar (Fig. 1B) with only moderate or greater drowsiness reported more frequently by PentacelTM recipients (13.8%, 95% confidence interval 9.5–19.1%, versus 7.4%, 4.3–11.8%, $p = 0.042$). There were no statistically significant differences between the groups in reports of fever (Fig. 1C).

There were three serious adverse events reported during the study. Two toddlers in the InfanrixTM-IPV-Hib group were hospitalized, one for Kawasaki's Disease 21 days after immunization and one for Respiratory Syncytial Virus bronchiolitis 25 days after immunization. One PentacelTM recipient was hospitalized 23 days post-immunization for a lower respiratory tract infection associated with wheezing. All participants recovered from these illnesses; none of the illnesses was assessed as related to immunization.

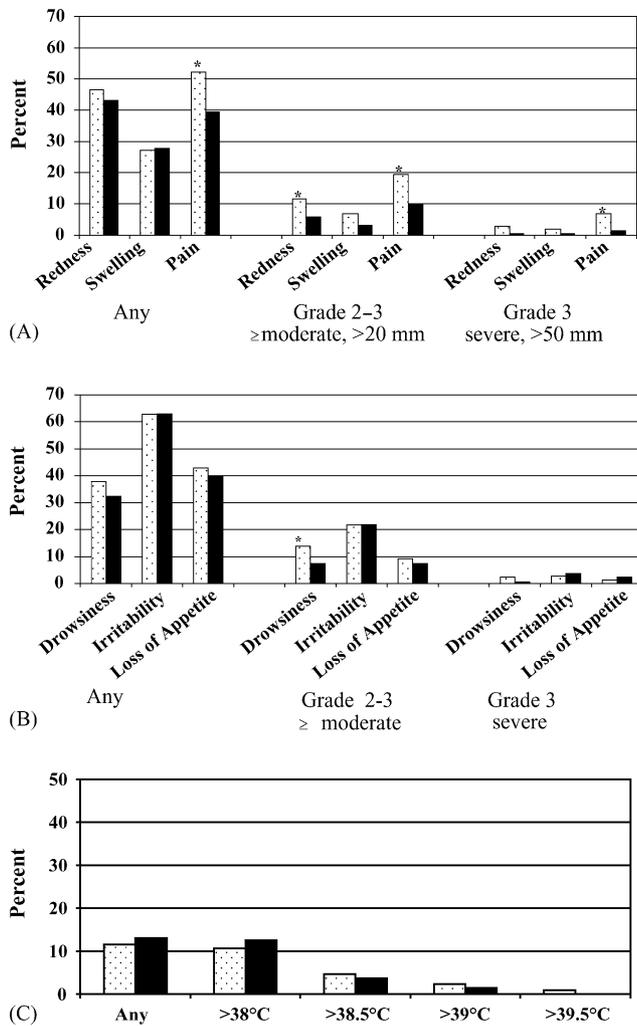


Fig. 1. Proportion of participants reporting an adverse event on days 0–7 post-immunization with Infanrix™-IPV-Hib or Pentacel™. Panel A depicts injection-site reactions, panel B depicts systemic adverse events and panel C, fever. Stippled bars represent the Pentacel™ group; solid bars, the Infanrix™-IPV-Hib group; (*) indicates $p < 0.05$ by two-sided Fisher’s exact test.

3.3. Antibody response

Pre-immunization antibody levels were similar between the groups for all antigens; both vaccines elicited vigorous antibody responses (Table 2). There were no statistically significant differences between the groups for post-immunization antibody levels against diphtheria toxoid or poliovirus type 3. Infanrix™-IPV-Hib recipients achieved higher antibody levels against PT (88.5, 95% confidence interval 79.3–98.7, versus 65.6, 58.8–73.2; 95% CI on the ratio 1.16–1.57), FHA (207.3, 95% confidence interval 188.8–227.6, versus 132.1, 121.2–144.0; 95% CI on the ratio 1.35–1.72), PRN (251.9, 95% confidence interval 217.2–292.3, versus 166.9, 145.5–191.4; 95% CI on the ratio 1.20–1.63) and poliovirus type 1 (1293.7, 95% confidence interval 1061.1–1577.4, versus 976.2, 782.7–1217.6; 95% CI on the ratio 1.04–1.76) and lower antibody concentra-

tions against *H. influenzae* type b PRP (19.1, 95% confidence interval 16.4–22.1, versus 29.0, 24.4–34.5; 95% CI on the ratio 0.49–0.76), tetanus toxoid (4.7, 95% confidence interval 4.2–5.1, versus 5.6, 5.1–6.2; 95% CI on the ratio 0.73–0.93) and poliovirus type 2 (1134.2, 95% confidence interval 964.3–1334.0, versus 1437.3, 1224.2–1687.6; 95% CI on the ratio 0.66–0.99). The proportion of participants seroprotected after immunization for diphtheria, tetanus, *H.*

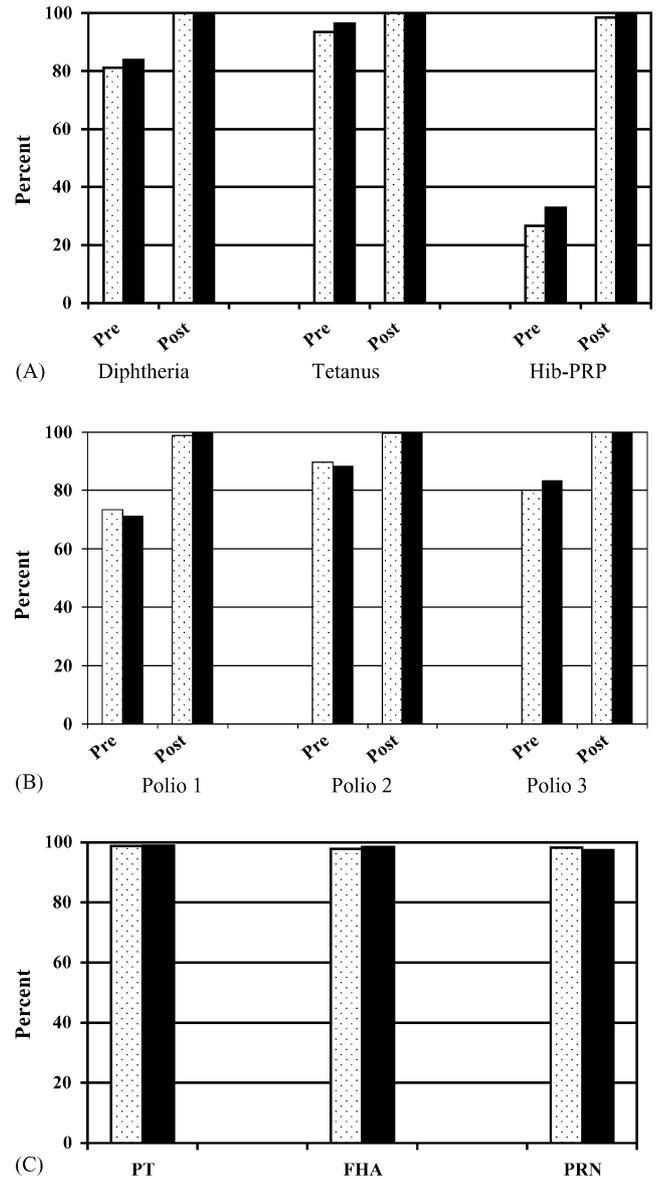


Fig. 2. Proportion of participants seroprotected against diphtheria, tetanus and *Haemophilus influenzae* type b (panel A), poliovirus (panel B) pre- and post-immunization and the proportion of participants who seroresponded to pertussis toxin, filamentous hemagglutinin and pertactin (panel C). Seroprotection was defined as antibody level ≥ 0.1 IU/mL for diphtheria and tetanus, ≥ 1.0 $\mu\text{g/mL}$ for Hib and eight reciprocal dilution for poliovirus 1, 2 and 3. Seroresponse to pertussis toxin, filamentous hemagglutinin and pertactin was defined as appearance of antibodies in a participant previously seronegative or a twofold increase in a participant seropositive before immunization. Stippled bars depict the Pentacel™ group; solid bars, the Infanrix™-IPV-Hib group.

Table 2

Geometric mean antibody levels after immunization with Infanrix™-IPV-Hib or Pentacel™ in 15–20-month-old infants (according to protocol immunogenicity cohort)

Antigen	Sample	Infanrix™-IPV-Hib	Pentacel™
Pertussis toxoid	Pre-immunization	4.5 (4.0–5.1)	5.0 (4.4–5.6)
	Post-immunization	88.5 (79.3–98.7)	65.6 (58.8–73.2) ^a
Filamentous hemagglutinin	Pre-immunization	14.3 (12.5–16.3)	12.5 (11.0–14.2)
	Post-immunization	207.3 (188.8–227.6)	132.1 (121.2–144.0) ^b
Pertactin	Pre-immunization	14.4 (12.3–16.7)	12.9 (11.1–14.9)
	Post-immunization	251.9 (217.2–292.3)	166.9 (145.5–191.4) ^c
Diphtheria toxoid	Pre-immunization	0.44 (0.36–0.53)	0.37 (0.30–0.45)
	Post-immunization	5.75 (5.06–6.53)	5.86 (5.13–6.69)
Tetanus toxoid	Pre-immunization	0.36 (0.32–0.41)	0.37 (0.32–0.42)
	Post-immunization	4.66 (4.24–5.11)	5.64 (5.11–6.23) ^d
Hib-PRP	Pre-immunization	0.69 (0.60–0.79)	0.66 (0.57–0.76)
	Post-immunization	19.1 (16.4–22.1)	29.0 (24.4–34.5) ^e
Poliovirus 1	Pre-immunization	23.2 (18.6–28.8)	22.9 (18.5–28.3)
	Post-immunization	1293.7 (1061.1–1577.4)	976.2 (782.7–1217.6) ^f
Poliovirus 2	Pre-immunization	44.3 (36.4–53.8)	46.6 (37.5–58.0)
	Post-immunization	1134.2 (964.3–1334.0)	1437.3 (1224.2–1687.6) ^g
Poliovirus 3	Pre-immunization	47.8 (37.5–61.0)	44.2 (34.3–56.9)
	Post-immunization	2118.0 (1777.9–2523.1)	2150.2 (1766.7–2616.9)

^a Ratio 1.35; 95% confidence interval 1.16–1.57.

^b Ratio 1.52; 1.35–1.72.

^c Ratio 1.40; 1.20–1.63.

^d Ratio 0.83; 0.73–0.93.

^e Ratio 0.61; 0.49–0.76.

^f Ratio 1.35; 1.04–1.76.

^g Ratio 0.81; 0.66–0.99.

influenzae type b PRP and polioviruses 1, 2 and 3 were similar and exceeded 98.4% for both groups and all antigens (Fig. 2A and B). For pertussis antigens where seroprotective levels have not been established, rates of seroresponse were similar between the two vaccines and exceeded 97.4% for the three pertussis antigens. In a post-hoc analysis, the proportion of participants with fourfold antibody response post-immunization was 97.2% (95% confidence interval 93.6–99.1), 91.5% (86.6–95.1) and 94.8% (90.6–97.5) for PT, FHA and PRN, respectively in the Infanrix™-IPV-Hib group and 91.1% (85.8–94.9), 89.5% (84.1–93.6) and 95.0% (90.8–97.7), respectively in the Pentacel™ group; the difference in response rates was significantly different for anti-PT antibody (difference 6.08%; 95% confidence interval 1.28–11.66).

Post-immunization, the pre-set non-inferiority criteria for Infanrix™-IPV-Hib compared to Pentacel™ were met for the nine vaccine antigens.

4. Discussion

This study demonstrates that Pentacel™ and Infanrix™-IPV-Hib are “interchangeable” (Infanrix™-IPV-Hib can be substituted for Pentacel™) for the fourth dose of DTaP-IPV-Hib in toddlers. Although some differences were identified

in rates of adverse reactions (less drowsiness and injection-site redness and pain after Infanrix™-IPV-Hib) and antibody responses (lower geometric mean antibody titers against PT, FHA, PRN and poliovirus type 1 and higher antibody concentrations against *H. influenzae* type b PRP, tetanus toxoid and poliovirus type 2 after Pentacel™), these differences are not clinically important and supported the non-inferiority hypothesis of Infanrix™-IPV-Hib compared to Pentacel™. The lower rates of adverse events after Infanrix™-IPV-Hib may be due to it being the first exposure of these toddlers to this product compared to the fourth exposure to Pentacel™ rather than an inherent decreased reactogenicity of the product. As with Pentacel™ [5,6], increased adverse events (particularly injection-site reactions) have been reported with increasing number of doses of Infanrix™-containing vaccines [7–9]. It is possible that a group of toddlers primed with three doses of Infanrix™-IPV-Hib given Pentacel™ as the fourth dose would likewise have fewer adverse events than a group immunized with all four doses of Infanrix™-IPV-Hib; the lack of that comparison group precludes conclusions of relative reactogenicity of the two products. The reason for the lower responses to *H. influenzae* type b PRP is not known but has been suggested previously [9,10]. The differences observed in the pertussis antibody responses may be the result of the higher pertussis antigen content of Infanrix™-IPV-Hib, or may be related to differences in the adsorption of per-

tussis antigens to the different adjuvants used in each product. Of note, we did not measure levels of anti-fimbriae antibodies elicited by the booster dose; however, one can assume that the increase in anti-fimbriae antibodies was inferior in the recipients of Infanrix™-IPV-Hib since the vaccine does not contain this antigen. The significance of these differences in antibody levels is unclear since the relative importance of the antigens contained in acellular pertussis vaccines has not been established. The level of antibodies achieved in both groups far exceeded those levels achieved after three doses of both related DTaP vaccines in the pre-licensure infant efficacy studies [11,12]. High levels of antibodies against pertactin, fimbriae and pertussis toxin have been correlated with increased protection against pertussis [13,14], although a vaccine containing only pertussis toxin was also efficacious [15].

Although data are available concerning the interchangeability of hepatitis A [16] and B [17,18] vaccines and *H. influenzae* type b conjugate vaccines [19–23], interchangeability studies for pediatric combination vaccines are not common (reviewed in [3,24,25]). Two studies have evaluated the interchangeability of DTaP vaccines for the first three primary doses with similar findings of comparable adverse events and variable differences in antibody response [26,27]. Studies comparing the interchangeability of the fifth doses between acellular and whole-cell vaccines have also been reported [28,29]; these studies also showed no increase in adverse events with the mixed schedule. Antibody responses after mixed acellular pertussis vaccine products were similar, although responses to the whole cell vaccine were somewhat diminished. This current study is the first to look at the interchangeability of a pentavalent combination vaccine for immunization against diphtheria, tetanus, poliovirus, pertussis and *H. influenzae* type b and the first to address the issue for the fourth dose.

As these multivalent combination vaccines are introduced in multiple countries around the world, information about the ability to change from one product to another will become increasingly important for the individual who moves between jurisdictions and programmatically in response to changes in contracts or product availability. This study provides supporting data for existing recommendations that products can be used interchangeably for the fourth dose given during the second year of life. However, given the differences that were observed in antibody response and the lack of established serological correlates of immunity for the pertussis vaccine, these data cannot be extrapolated to the first three doses of the primary series. Additional studies would be required to assess the interchangeability of the vaccines for the primary series.

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Conflict of interest: Drs. Elrick and Jacquet are employees of GlaxoSmithKline. Drs. Halperin, Tapiero, Law, Duval, Diaz-Mitoma and Langley had no financial interest in the vaccine or its manufacturer but received research funding to undertake the study.

References

- [1] National Advisory Committee on Immunization (NACI). Interchangeability of diphtheria, tetanus, acellular pertussis, polio, *Haemophilus influenzae* type B combination vaccines presently approved for use in Canada for children <7 years of age. *Can Commun Dis Rep* 2005;31(ACS-1):1–10.
- [2] Centers for Disease Control and Prevention. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1994;43(RR-1):1–38.
- [3] Feldman S. Interchangeability of vaccines. *Pediatr Infect Dis J* 2001;20(Suppl.):S23–9.
- [4] Hewlett EL, Halperin SA. Serological correlates of immunity to *Bordetella pertussis*. *Vaccine* 1998;16:1899–900.
- [5] Halperin SA, Mills E, Barreto L, Pim C, Eastwood BJ. Acellular pertussis vaccine as a booster dose for seventeen- to nineteen-month-old children immunized with either whole cell or acellular pertussis vaccine at two, four and six months of age. *Pediatr Infect Dis J* 1995;14:792–7.
- [6] Halperin SA, Scheifele D, Mills E, Guasparini R, Humphreys G, Barreto L, et al. Nature, evolution, and appraisal of adverse events and antibody response associated with the fifth consecutive dose of a five-component acellular pertussis-based combination vaccine. *Vaccine* 2003;21:2298–306.
- [7] Schmitt HJ, Zepp F, Muschenborn S, Sumenicht G, Schuind A, Beutel K, et al. Immunogenicity and reactogenicity of a *Haemophilus influenzae* type b tetanus conjugate vaccine when administered separately or mixed with concomitant diphtheria-tetanus-toxoid and acellular pertussis vaccine for primary and for booster immunizations. *Eur J Pediatr* 1998;157:208–14.
- [8] Rennels MB. Extensive swelling reactions occurring after booster doses of diphtheria-tetanus-acellular pertussis vaccines. *Semin Pediatr Infect Dis* 2003;14:196–8.
- [9] Halperin SA, King J, Law B, Mills E, Willems P. Safety and immunogenicity of *Haemophilus influenzae*-tetanus toxoid conjugate vaccine given separately or in combination with a three-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids and inactivated poliovirus vaccine for the first four doses. *Clin Infect Dis* 1999;28:995–1001.
- [10] Goldblatt D, Richmond P, Millard E, Thornton C, Miller E. The induction of immunologic memory after vaccination with *Haemophilus influenzae* type b conjugate and acellular pertussis-containing diphtheria, tetanus, and pertussis vaccine combination. *J Infect Dis* 1999;180:538–41.
- [11] Olin P, Rasmussen F, Gustafsson L, Hallander HO, Heijbel H. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. *Ad Hoc Group for the Study of Pertussis Vaccines. Lancet* 1997;350:1569–77.

- [12] Greco D, Salmaso S, Mastrantonio P, Giuliano M, Tozzi AE, Anemona A, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group. *N Engl J Med* 1996;334:341–8.
- [13] Cherry JD, Gornbein J, Heininger U, Stehr K. A search for serologic correlates of immunity to *Bordetella pertussis* cough illnesses. *Vaccine* 1998;16:1901–6.
- [14] Storsaeter J, Hallander HO, Gustafsson L, Olin P. Levels of anti-pertussis antibodies related to protection after household exposure to *Bordetella pertussis*. *Vaccine* 1998;16:1907–16.
- [15] Trollfors B, Taranger J, Lagergard T, Lind L, Sundh V, Zackrisson G, et al. A placebo-controlled trial of a pertussis-toxoid vaccine. *N Engl J Med* 1995;333:1045–50.
- [16] Bryan JP, Henry CH, Hoffman AG, South-Paul JE, Smith JA, Cruess D, et al. Randomized, cross-over, controlled comparison of two inactivated hepatitis A vaccines. *Vaccine* 2000;19:743–50.
- [17] Seto D, West DJ, Gilliam RR, Ioli VA, Ferrara DK, Rich B. Antibody responses of healthy neonates of two mixed regimens of hepatitis B vaccine. *Pediatr Infect Dis J* 1999;18:840–2.
- [18] Bush LM, Moonsammy GI, Boscia JA. Evaluation of initiating a hepatitis B vaccination schedule with one vaccine and completing it with another. *Vaccine* 1991;9:807–9.
- [19] Bewley KM, Schwab JG, Ballanco GA, Daum RS. Interchangeability of *Haemophilus influenzae* type b vaccines in the primary series: evaluation of a two-dose mixed regimen. *Pediatrics* 1996;98:898–904.
- [20] Scheifele D, Law B, Mitchell L, Ochnio J. Study of booster doses of two *Haemophilus influenzae* type b conjugate vaccines including their interchangeability. *Vaccine* 1996;14:1399–406.
- [21] Goldblatt D, Fairley CK, Cartwright K, Miller E. Interchangeability of conjugated *Haemophilus influenzae* type b vaccines during primary immunisation of infants. *BMJ* 1996;312:817–8.
- [22] Anderson EL, Decker MD, Englund JA, Edwards KM, Anderson P, McInnes P, et al. Interchangeability of conjugated *Haemophilus influenzae* type b vaccines in infants. *JAMA* 1995;273:849–53.
- [23] Greenberg DP, Lieberman JM, Marcy SM, Wong VK, Partridge S, Chang SJ, et al. Enhanced antibody responses in infants given different sequences of heterogeneous *Haemophilus influenzae* type b conjugate vaccines. *J Pediatr* 1995;126:206–11.
- [24] Greenberg DP, Feldman S. Vaccine interchangeability. *Clin Pediatr (Phila)* 2003;42:93–9.
- [25] Decker MD. Principles of pediatric combination vaccines and practical issues related to use in clinical practice. *Pediatr Infect Dis J* 2001;20(Suppl.):S10–8.
- [26] Greenberg DP, Pickering LK, Senders SD, Bissey JD, Howard RA, Blatter MM, et al. Interchangeability of 2 diphtheria-tetanus-acellular pertussis vaccines in infancy. *Pediatrics* 2002;109:666–72.
- [27] von König CH, Herden P, Palitzsch D, Schneeweiss B, Bier N. Immunogenicity of acellular pertussis vaccines using two vaccines for primary immunization. *Pediatr Infect Dis J* 2000;19:757–9.
- [28] Halperin SA, Scheifele D, Barreto L, Pim C, Guasparini R, Medd L, et al. Comparison of a fifth dose of a five-component acellular or a whole cell pertussis vaccine in children four to six years of age. *Pediatr Infect Dis J* 1999;18:772–9.
- [29] Pichichero ME, Edwards KM, Anderson EL, Rennels MB, Englund JA, Yerg DE, et al. Safety and immunogenicity of six acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fifth dose in four- to six-year-old children. *Pediatrics* 2000;105:e11.