Immunogenicity and Safety of 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants and Toddlers Given With Routine Pediatric Vaccinations in Canada

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BACKGROUND

- *Streptococcus pneumoniae* infections are a major cause of morbidity and mortality worldwide.
- 7-valent pneumococcal conjugate vaccine (PCV7; serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) has decreased the incidence of invasive pneumococcal disease (IPD).
- A 13-valent pneumococcal conjugate vaccine (PCV13; PCV7 serotypes plus serotypes 1, 3, 5, 6A, 7F, and 19A) was approved in Canada in December 2009 to extend serotype coverage.

OBJECTIVES AND METHODS

- To demonstrate that following administration of combination DTaP-IPV-Hib vaccine (Pentacel®, Sanofi Pasteur) and meningococcal C conjugate vaccine (NeisVac-C™, GlaxoSmithKline) concomitantly with PCV13, immune responses to *Haemophilus influenzae* type b (Hib), 5-component pertussis, and conjugated meningococcal C antigens were noninferior to those when administered with PCV7
  - Serum concentrations of immunoglobulin G (IgG) antibodies to Hib (antipolyribosylribitol phosphate) and pertussis antigens (pertussis toxoid, filamentous hemagglutinin, pertactin, and fimbrial agglutinogens), and serum bactericidal assay responses to meningococcal C antigen were measured 1 month after both the infant series and toddler dose.
- To assess the immune response to PCV13, serum concentrations of serotype-specific pneumococcal anticapsular IgG–binding antibodies were measured 1 month after both the infant series and toddler dose.
- To assess the safety of PCV13

Study Design and Subjects

- This was a Phase III, double-blind, multicenter trial in 12 centers across Canada.
- Healthy infants were randomly assigned 1:1 to receive PCV13 plus routine pediatric vaccines or PCV7 plus routine pediatric vaccines per national guidelines (Table 1).

Table 1. Study Design

Visit	2 Months	4 Months	6 Months	7 Months	12 Months	13 Months	18 Months
PCV13 or PCV7	x	x	x		x		
Tetanus-conjugated meningococcal C vaccine	x		x		x		
DTaP-IPV-Hib	x	x	x				
MMR					x		
Varicella					x		
Blood draw	x			x		x	
Access adverse events	x	x	x	x	x	x	x

Endpoints and Statistical Analysis

- Analysis populations
  - Immunogenicity analyses were performed on all subjects who received all study vaccinations and had at least 1 valid and determinate assay result after the third vaccination.
  - Safety analyses were performed on all subjects who received at least 1 dose of study vaccine.
- Immunogenicity end points for all subjects:
  - Primary immunologic end points were concomitant antigen immune responses in subjects receiving PCV13 relative to PCV7 subjects. For each antigen, the proportion of subjects in each vaccine group achieving serum antibody concentration greater than or equal to a prespecified concentration were compared. In addition, for pertussis antigens, the proportion of PCV13 subjects achieving serum antibody concentration greater than or equal to the level achieved by 95% of the subjects in the PCV7 group for pertussis antigens, was determined.
  - For each comparison, noninferiority was demonstrated if the lower limit of the 95% confidence interval (CI) for the difference between groups was >–0.10 for each antigen.
- Immunogenicity end points for pneumococcal serotypes in PCV13 subjects only:
  - The proportion of subjects achieving a serotype-specific IgG antibody concentration ≥0.35 µg/mL, which is defined by the World Health Organization (WHO) as a reference concentration for assessment of vaccine efficacy against invasive pneumococcal disease[1]
  - IgG antibody geometric mean concentrations (GMCs)
- Parent(s)/legal guardian(s) were required to monitor and record in an electronic diary the subject's local reactions, systemic events, and use of antipyretic medication to treat and prevent symptoms for 4 days after each vaccination.

RESULTS

Subjects

- A total of 300 subjects were randomly assigned to receive PCV13 and 303 received PCV7; 293 and 291 subjects, respectively, completed the infant series.
- A total of 569 subjects (287 in the PCV13 group and 282 in the PCV7 group) were vaccinated with the toddler dose, and 565 subjects completed the toddler dose portion of the study.
- There was no difference between treatment groups with respect to sex, race, age, and weight.

Response to Concomitant Vaccines

- Comparisons of the proportions of subjects with predefined levels of antibodies to concomitant vaccine antigens met the noninferiority criteria for each antigen in both infant and toddler populations (Tables 2a and 2b).

RESULTS (cont'd)

Table 2a. Proportion of Subjects With Predefined Levels of Antibodies to Concomitant Vaccine Antigens: Infant Population

Vaccine Antigen	Comparison Level	PCV13 % (n=272–284)	PCV13 95% CI	PCV7 % (n=266–278)	PCV7 95% CI	Difference[a] %	95% CI
Meningococcal C	≥1:8[b]	96.8	94.1, 98.5	99.3	97.4, 99.9	–2.4	–5.3, –0.1
Pertussis							
PT	≥12.00 EU/mL[c]	98.6	96.4, 99.6	96.0	93.0, 98.0	2.6	–0.2, 5.7
FHA	≥20.00 EU/mL[c]	99.3	97.5, 99.9	95.7	92.6, 97.7	3.6	1.1, 6.8
PRN	≥7.00 EU/mL[c]	96.8	94.0, 98.5	96.0	93.0, 98.0	0.8	–2.5, 4.2
FIM	≥4.00 EU/mL[c]	93.6	90.1, 96.2	95.3	92.1, 97.5	–1.7	– 5.7, 2.3
Hib (PRP)	≥0.15 µg/mL	97.8	95.3, 99.2	99.6	97.9, 100.0	–1.8	– 4.4, 0.1
	≥1.0 µg/mL	81.6	76.5, 86.0	84.6	79.7, 88.7	–3.0	– 9.4, 3.4

CI=confidence interval; FHA=filamentous hemagglutinin; FIM=fimbrial agglutinogens; Hib (PRP)=*H influenzae* type b polyribophosphate; PRN=pertactin; PT=pertussis toxoid.
[a]Difference in proportions, PCV13–PCV7.
[b]Serum bactericidal assay.
[c]The level achieved by 95% of subjects in the PCV7 group.

Table 2b. Proportion of Subjects With Predefined Levels of Antibodies to Concomitant Vaccine Antigens: Toddler Population

Vaccine Antigen	Comparison Level	PCV13 % (n=265)	PCV13 95% CI	PCV7 % (n=268)	PCV7 95% CI	Difference[a] %	95% CI
Meningococcal C	≥1:8[b]	100	98.6, 100.0	100.0	98.6, 100.0	0.0	–1.4, 1.4

CI=confidence interval.
[a]Difference in proportions, PCV13–PCV7.
[b]Serum bactericidal assay.

- Comparisons of GMCs/titers of antibodies to concomitant vaccine antigens met the noninferiority criteria for each antigen in both infant and toddler populations (Tables 3a and 3b).

Table 3a. Concomitant Vaccine Antibody Geometric Mean Concentrations: Infant Population

Vaccine Antigen	Units	PCV13 (n=272–284) GM	PCV7 (n=266–278) GM	Ratio[a]	95% CI
Meningococcal C	titer	361.16	302.55	1.19	0.96, 1.48
Pertussis					
PT	EU/mL	46.06	40.37	1.14	1.02, 1.27
FHA	EU/m	78.08 L	69.52	1.12	1.01, 1.25
PRN	EU/mL	42.90	40.69	1.05	0.89, 1.24
FIM	EU/mL	11.54	12.98	0.89	0.78, 1.02
Hib (PRP)	µg/mL	2.87	3.14	0.91	0.75, 1.12

CI=confidence interval; FHA=filamentous hemagglutinin; FIM=fimbrial agglutinogens; GM=geometric mean; Hib (PRP)=*H influenzae* type b polyribophosphate; PRN=pertactin; PT=pertussis toxoid.
[a]Ratio of geometric means, PCV13:PCV7.

Table 3b. Concomitant Vaccine Antibody Geometric Mean Concentrations: Toddler Population

Vaccine Antigen	Units	PCV13 (n=265) GM		PCV7 (n=268) GM		Ratio[a]	95% CI
Meningococcal C	titer	1379.75	1235.06, 1541.39	1083.96	962.54, 1220.69	1.27	1.08, 1.50

GM=geometric mean.
[a]Ratio of geometric means, PCV13:PCV7.

Antipneumococcal Immunogenicity

- The percentage of responders among infants receiving PCV13 was >90% for all serotypes except serotypes 3 and 5 (Table 4).
- Antipneumococcal IgG antibody concentrations were ≥1.00 µg/mL for all serotypes except serotypes 3 and 5 in the infant population (Table 5a) and ≥2.00 µg/mL for all serotypes except serotype 3 in the toddler population (Table 5b).

Table 4. Percentage of PCV13 Subjects With Pneumococcal IgG Antibody Concentrations ≥0.35 µg/mL[a]

Serotype	% (n=272–277)	95% CI
Included in PCV7		
4	97.1	94.4, 98.7
6B	93.1	89.5, 95.8
9V	95.3	92.1, 97.5
14	98.2	95.8, 99.4
18C	96.4	93.5, 98.3
19F	98.5	96.3, 99.6
23F	90.2	86.0, 93.4
Additional		
1	95.7	92.6, 97.7
3	79.6	74.4, 84.2
5	87.0	82.4, 90.7
6A	96.4	93.4, 98.2
7F	98.6	96.3, 99.6
19A	97.8	95.3, 99.2

CI=confidence interval; IgG=immunoglobulin G.
[a]Defined by the World Health Organization as a reference concentration for assessment of vaccine efficacy against invasive pneumococcal disease.

Table 5a. Antipneumococcal IgG Antibody Concentrations in PCV13 Subjects: Infant Population

Serotype	GMC µg/mL (n=272–277)	95% CI
Included in PCV7		
4	1.46	1.33, 1.60
6B	2.16	1.87, 2.49
9V	1.12	1.03, 1.22
14	5.43	4.86, 6.06
18C	1.37	1.23, 1.52
19F	2.18	1.99, 2.39
23F	1.15	1.03, 1.30
Additional		
1	1.82	1.63, 2.04
3	0.63	0.58, 0.70
5	0.90	0.81, 0.99
6A	1.92	1.73, 2.12
7F	2.26	2.09, 2.45
19A	2.00	1.82, 2.19

CI=confidence interval; GMC=geometric mean concentration; IgG=immunoglobulin G.

Table 5b. Antipneumococcal IgG Antibody Concentrations in PCV13 Subjects: Toddler Population

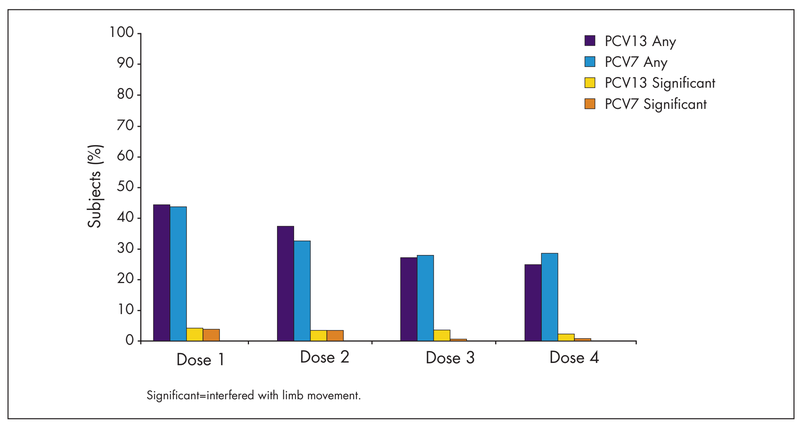
Serotype	GMC µg/mL (n=262–264)	95% CI
Included in PCV7		
4	2.67	2.43, 2.92
6B	0.83	8.83, 10.94
9V	2.04	1.87, 2.23
14	7.58	6.86, 8.37
18C	2.00	1.80, 2.21
19F	5.70	5.06, 6.42
23F	3.59	3.21, 4.01
Additional		
1	3.45	3.11, 3.82
3	0.74	0.67, 0.81
5	2.38	2.15, 2.62
6A	6.47	5.87, 7.12
7F	3.88	3.59, 4.21
19A	8.36	7.61, 9.19

CI=confidence interval; GMC=geometric mean concentration; IgG=immunoglobulin G.

Safety

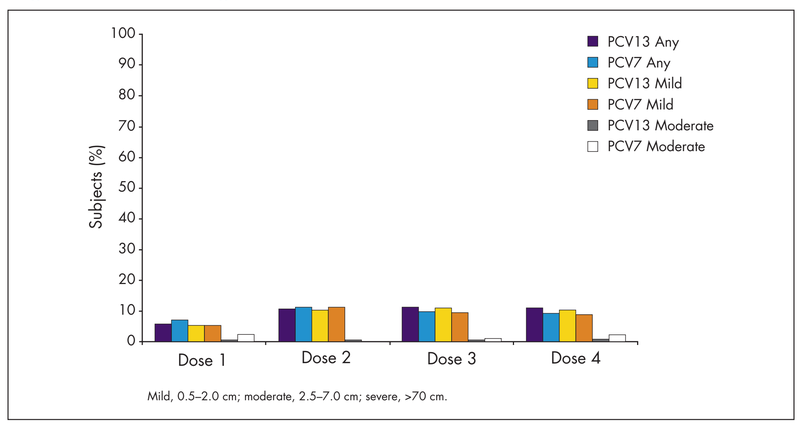
- There were no severe local reactions after any dose.
- Most local reactions were mild or moderate in severity and the incidence was similar between treatment groups for all doses (Figures 1–3).
- The incidence of fever (Figure 4) and other systemic adverse events was similar between treatment groups for all doses (Table 6).
- Most unsolicited adverse events were diseases/conditions expected in infants and toddlers. Infections were most common.
- There were no differences between treatment groups in incidence of adverse events related to study vaccine.
- One subject in the PCV13 group reported a related adverse event of severe pyrexia. In addition, 5 subjects were withdrawn after the infant series because of adverse events (mild urticaria that started during the infant series, febrile neutropenia, convulsion, febrile convulsion, and movement disorder)
- No serious adverse events related to study vaccine were noted.

Figure 1. Tenderness



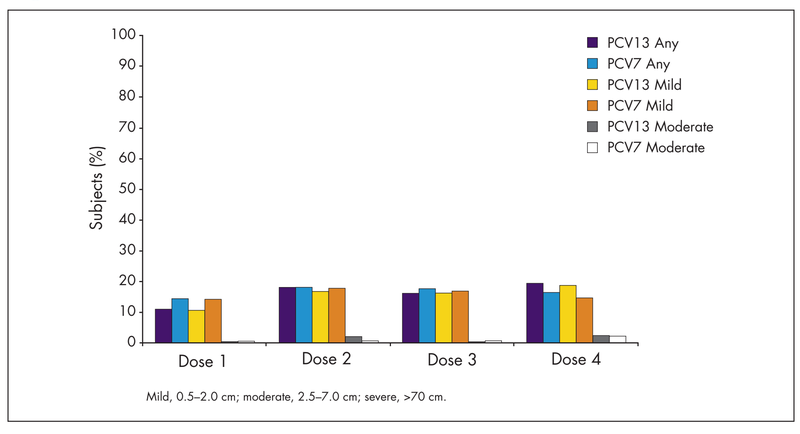
Significant=interfered with limb movement.

Figure 2. Swelling



Mild, 0.5–2.0 cm; moderate, 2.5–7.0 cm; severe, >70 cm.

Figure 3. Redness



Mild, 0.5–2.0 cm; moderate, 2.5–7.0 cm; severe, >70 cm.

Figure 4. Fever

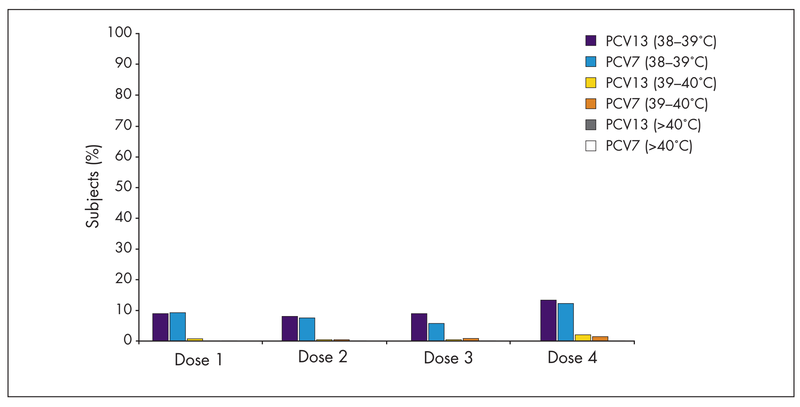


Table 6. Systemic Events

	% Subjects							
	Dose 1		Dose 2		Dose 3		Dose 4	
	PCV13	PCV7	PCV13	PCV7	PCV13	PCV7	PCV13	PCV7
Decreased appetite	43	36	29	31	33	31	37	34
Irritability	81	83	71	70	68	66	69	58
Increased sleep	63	65	54	52	36	40	34	33
Decreased sleep	30	28	26	31	30	28	34	34
Antipyretic treatment	43	46	41	42	36	30	33	28
Antipyretic preventive	38	41	39	41	35	39	37	42

CONCLUSIONS

- **Immune responses to selected concomitantly administered vaccine antigens were comparable between groups.**
- **PCV13 is immunogenic and well tolerated when administered in healthy infants and toddlers.**

REFERENCE

1. World Health Organization. WHO Technical Report Series, No. 927, 2005 for the 0.35 cutoff.

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