LITERATURE REVIEW ON DTaP BASED PENTA- AND HEXAVALENT VACCINES APPROVED FOR CLINICAL USE IN CANADA

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INTRODUCTION

In Canada, there are two manufacturers, Sanofi Pasteur and GlaxoSmithKline (GSK), that supply three combined *pentavalent* vaccines against diphtheria, tetanus, acellular pertussis (*DTaP*), polio and *Haemophilus influenzae* type b (Hib), and one manufacturer (GSK) that supplies a *hexavalent* vaccine against the above mentioned infections plus hepatitis B.

Given the specific goal of this report, data on combined *DTaP* based vaccines approved for use in infants in Canada were analysed. Trade names of vaccines are used to minimize product confusion : *Pentacel®* (Sanofi Pasteur); *Pediacel®* (Sanofi Pasteur); *Infanrix™-IPV/Hib* (GSK); and *Infanrix™-hexa* (GSK).

A modified version of the analytical framework for immunization programs in Canada (Erickson L and De Wals P, 2005)[1], section “Vaccine characteristics” was used for the purpose of this report. Issues including the burden of disease, ethical, legal and political considerations, as well as eventual immunization programs in Canada go beyond the objectives of this report. On several occasions, comparisons with similar vaccines not used in Canada, but used in other countries, were done. Data are presented for each antigen of each vaccine.

This report is based on scientific peer-reviewed published data.

METHODS

Literature Search

A systematic search of MEDLINE (January 1966 - August 2006) and EMBASE (January 1966 - August 2006) was conducted.

Explored keywords in MEDLINE "*Quadracel*", "*Pentacel*", "*Pediacel*" and "*Infanrix*". The latter keyword was explored with limits "Infant: 1-23 months, Clinical trial, Humans".

Explored keywords in EMBASE "*Pentacel* AND clinical AND trial", "*Pediacel* AND clinical AND trial", "*Quadracel* AND clinical AND trial", and "*Infanrix* AND clinical AND trial".

To avoid the exclusion of studies which did not contain the trade names of vaccines, an additional search by using keywords "*DTaP-Hib-IPV* OR *DTaP-HBV-IPV-Hib* OR *DTaP-IPV-Hib* OR *DTaP-IPV-HBV-Hib*" was done.

Literature Search Results

A total of 69 publications were identified in MEDLINE and 81 in EMBASE by using vaccines trade names, and respectively 38 and 18 by using vaccines abbreviations. After the exclusion of publications cited repeatedly in the same or different databases, and those which reported results obtained with other than Sanofi Pasteur or GSK vaccines of interest, 82 full text articles were reviewed. Articles containing both primary series vaccination and/or first booster dose results were selected for detailed data extraction. Studies in which antigens used in combined vaccines were produced by different manufacturers were excluded from the main analysis.

All 20 publications reporting 22 clinical trials' results on immunogenicity and/or reactogenicity of *Pentacel®* (Sanofi Pasteur), *Pediacel®* (Sanofi Pasteur), *Infanrix™-IPV/Hib* (GSK), and *Infanrix™-hexa* (GSK) were retained for the purpose of this report.

Citations and full-text published articles were screened independently by two reviewers (VG and BD).

RESULTS

1. Nature and characteristics of immunizing agent

Pentacel® (Sanofi Pasteur)

Since 1997, *Pentacel®* has been used for the 3-dose primary series and 18-month booster dose in Canada[2] [3]. *Pentacel ®*is reconstituted immediately prior to administration by combining a lyophilized powder containing polyribosyl ribitol phosphate conjugated to tetanus protein (PRP-T) vaccine (*Act-Hib®*) with *Quadracel®*, a liquid product containing acellular pertussis (aP) vaccine, adsorbed diphtheria and tetanus toxoids and inactivated polio vaccine. The *pertussis* vaccine has five antigens*: pertussis* toxoid (PT), filamentous *hemagglutinin* (FHA), *pertactin* (PRN) and *fimbrial* proteins 2 and 3 (FIM2 and FIM 3). The diphtheria and tetanus toxoids are denaturated with formaldehyde. The three poliovirus types are propagated in human diploid cells and formalin inactivated (Table 1).

Pediacel® (Sanofi Pasteur)

Pediacel® was approved for use in Canada in 2000 for the primary series and 18-month booster dose. It differs from *Pentacel®* in that the *Hib* component comes pre-mixed in a liquid formulation with the other components in an ampoule.

While the concentrations and types of the three poliovirus strains in *Pediacel®* are identical to those in *Pentacel®*, they are grown in Vero monkey kidney cell lines. The *pertussis* vaccine contains the five component antigens at the same concentrations as *Pentacel®*, the amounts of tetanus and diphtheria toxoids are also the same (Table 1).

Infanrix™-IPV/Hib [GlaxoSmithKline]

Infanrix™-IPV/Hib was approved for use in Canada in 2004. It is a five-component vaccine that requires reconstitution prior to administration. This is done by combining PRP-T Hib vaccine (*Hiberix®*) with the *Infanrix™-IPV*, a product composed of acellular pertussis, adsorbed diphtheria and tetanus toxoids and inactivated polio vaccines. This vaccine differs from the *Pediacel®* vaccines in that the pertussis portion is derived from three antigens: PT, PRN, and FHA. The concentrations of each of these antigens are 5 µg greater than in the five-component pertussis vaccines. The tetanus and diphtheria concentrations are 5 Lf and 10 Lf greater per dose, respectively, than in *Pediacel®*. The poliovirus strains, as in *Pediacel®*, are grown in Vero monkey kidney cell lines (Table 1).

Infanrix™-hexa [GlaxoSmithKline]

Combined diphtheria and tetanus toxoid, *acellular pertussis*, hepatitis B (recombinant), inactivated poliomyelitis and PRP-T Hib vaccine requires reconstitution prior to administration. This is done by combining single dose pre-filled syringe *Pediarix™* (*DTaP-HBV-IPV* suspension for injection) and single dose vial (regular or Bioset) adsorbed Hib (lyophilized powder injection) (Table 1). This vaccine has been used in European Union countries since 2000, and more recently has been in use in Australia and other countries[4].

2. Characteristics of the commercial products

Table 1*. Composition: Pentacel®, Pediacel®, Infanrix™-IPV/Hib, and Infanrix™-hexa

Contents (for each 0.5 mL dose)	**Pentacel® (Sanofi Pasteur)**	**Pediacel® (Sanofi Pasteur)**	**Infanrix™-IPV/Hib (GlaxoSmithKline)**	**Infanrix™-hexa (GlaxoSmithKline)**
Diphtheria toxoid	15 Lf	15 Lf	25 Lf (30 IU)	25 Lf (30 IU)
Tetanus toxoid	5 Lf	5 Lf	10 Lf (40 IU)	10 Lf (40 IU)
Pertussis:				
Pertussis toxoid (PT)	20 µg	20 µg	25 µg	25 µg
Filamentous haemagglutinin (FHA)	20 µg	20 µg	25 µg	25 µg
Pertactin (PRN)	3 µg	3 µg	8 µg	8 µg
Fimbriae (agglutinogens 2&3)	5 µg	5 µg	none	none
Polio:				
Type 1	40 DU	40 DU	40 DU	40 DU
Type 2	8 DU	8 DU	8 DU	8 DU
Type 3	32 DU	32 DU	32 DU	32 DU
Hepatitis B				
AgHBs recombinant	none	none	none	10 µg
Hib:				
PRP	10 µg	10 µg	10 µg	10 µg
Binding protein	20 µg tetanus toxoid	20 µg tetanus toxoid	30 µg tetanus toxoid	30 µg tetanus toxoid
Format	Lyophilized powder	Pre-mixed in ampoule with other components	Lyophilized powder	Lyophilized powder
Other contents				
Aluminium	1.5 mg Al_3PO_4	1.5 mg Al_3PO_4	0.5 mg $Al(OH)_3$	0.7 mg Aluminum salts
2-phenoxyethanol	0.6% v/v	0.6% v/v	2.5 mg	2.5 mg
Tween 80	10 ppm (by calculation)	Less than 0.1% (by calculation)		
Other	Bovine serum:≤ 50ng; Trace amounts of formaldehyde; Trace amounts of polymixin B and neomycin may be present from the cell growth medium	Bovine serum:≤ 50ng; Trace amounts of formaldehyde; Trace amounts of neomycin, streptomycin and polymyxin B may be present in the	Lactose (as stabilizer): 12.6 mg Sodium chloride: 4.5 mg Residual formaldehyde, polysorbate 80, M199 (as stabilizer), potassium	Lactose (as stabilizer): 12.6 mg Sodium chloride: 4.5 mg Residual formaldehyde, polysorbate 80, M199 (as stabilizer), potassium

Contents (for each 0.5 mL dose)	**Pentacel® (Sanofi Pasteur)**	**Pediacel® (Sanofi Pasteur)**	**Infanrix™-IPV/Hib (GlaxoSmithKline)**	**Infanrix™-hexa (GlaxoSmithKline)**
		final product.	chloride, disodium phosphate, monopotassium phosphate, glycine, and trace amounts of neomycin sulfate and polymyxin sulfate	chloride, disodium phosphate, monopotassium phosphate, glycine, and trace amounts of neomycin sulfate and polymyxin sulfate.
Note: The Hib component of Pentacel® and Infanrix-IPV/HIB are also marketed separately as Act-Hib® and Hiberix® respectively. When used separately, a diluent is provided. When used as part of the pentavalent product, Act-HIB® is reconstituted with Quadracel® to make Pentacel®, and Hiberix® is reconstituted with Infanrix™-IPV to make Infanrix™-IPV /Hib. When used as part of the hexavalent product, Hiberix® is reconstituted with Pediarix™ (DTaP-HBV-IPV).				

*adapted from CCDR, 1 February 2005, Volume 1, ACS-1

All four vaccines have to be stored at between +2 C to +8 C. The vaccines have to be discarded if frozen.

3. Production capacity and supply issues

In Canada, two manufacturers, Sanofi Pasteur and GSK, supply three combined *pentavalent* vaccines against diphtheria, tetanus, pertussis, polio and Hib, and one manufacturer (GSK) supplies a *hexavalent* vaccine against the above mentioned infections plus hepatitis B.

Both companies are international long-term vaccine manufacturers with important production capacity in many countries. In 2004, serious supply difficulties were reported in Canadian provinces and territories because of production problems experienced by Sanofi Pasteur. At that time Sanofi Pasteur was the only manufacturer with approved and actively-marketed *pentavalent* vaccines in Canada.

According to recent information (July 2006) received from Sanofi Pasteur and GSK, both companies are ready to supply the needed quantity of *pentavalent* vaccines approved in Canada. In 2005, GSK was able to supply most of the European markets with *Infanrix™-hexa,* when Sanofi Pasteurs' *Hexavac®* vaccine was pulled from the market. Also, *Infanrix™-hexa* was almost immediately shipped to Australia when a new program was launched. Meanwhile, consistent with the Vaccine Industry Committee recommendations, both companies continue to ask Canadian provinces and territories for at least a 6-9 month lead time on new vaccines programs.

Pentacel® and *Pediacel®* currently have a limited international market[5]. The vaccine *Pentacel®* has been used for a relatively long term only in Canada. In anticipation of a potential switch to the use of IPV and aP in the United Kingdom (UK) immunization programme, a clinical trial with *Pediacel®* was recently reported in this country[6].

Infanrix™-IPV-Hib has been available for almost one decade and *Infanrix™-hexa* for more than four years on most European Union countries' market, and recently in Australian as well. The main components of *Infanrix™-hexa*, the *pentavalent* (*DTaP-HBV-IPV*) *Pediarix™,* are also available on the USA market [7].

4. Administration schedule, number of doses, association with other vaccines

There were 4 different vaccination schedules in peer reviewed published studies: 2, 3, and 4 months of age; 3, 4, and 5 months of age; 2, 4, and 6 months of age; and 3, 5, and 11 months of age. The results obtained with 3, 5, and 11 months primary series schedule will be analysed separately because of important differences in timetable and results interpretation. Results obtained in clinical studies for each of the vaccine and for each of the vaccines' components are summarized below (Tables 2, 2a, 3, and 4).

Table 2. Summary of Immunogenicity Data With Pentacel® (Sanofi Pasteur); Pediacel® (Sanofi Pasteur); Infanrix™-IPV/Hib (GSK); and Infanrix™-hexa (GSK)

Vaccine/ Reference	Vaccine schedule	N	Diphtheria		Tetanus		Polio 1		Polio 2		Polio 3	
			% SP* (≥ 0.01 IU/mL)	GMC (IU/mL)	% SP (≥ 0.1 IU/mL)	GMC (IU/mL)	% SP (≥ 1:8)	GMT	% SP (≥ 1:8)	GMT	% SP (≥ 1:8)	GMT
Pentacel; Scheifele D, 2006, Canada[8]	2, 4, 6 months of age	122-124	100	5.6	99.2	0.9	85.0	40.8	92.5	54.9	91.7	77.4
Pentacel; Halperin S, 2002, Canada[9]	2, 4, 6 months of age	168	100	1.9	100	2.5	95	N/A	100	N/A	98	N/A
Pediacel; Kitchin N, 2006, UK[10]	2, 3, 4 months of age	96-105	99	0.1	100	1.6	100	372	100	735	97.9	1077
Pediacel Lin TY, 2005, Taiwan[11]	2, 4, 6 months of age	100	100	2.4	100	5.66	100	1082	100	2504	100	1607
Infanrix-IPV/Hib; Schmitt HJ, 2003, Germany [12]	2, 3, 4 months of age	75	97	0.6	100	4.4	N/A	289	N/A	282	N/A	682
Infanrix-IPV/Hib; Aristegui J, 2003, Spain [13]	2, 4, 6 months of age	31	100	3.5	100	3.4	100	612	100	468	100	850
Infanrix-IPV/Hib; Dagan R, 1997, Israel [14]	2, 4, 6 months	101	99	1.2	99	2.1	100	24-248 times the cutoff	100	24-248 times the cutoff	100	24-248 times the cutoff

Vaccine/ Reference	Vaccine schedule	N	Diphtheria		Tetanus		Polio 1		Polio 2		Polio 3	
			% SP* (≥ 0.01 IU/mL)	GMC (IU/mL)	% SP (≥ 0.1 IU/mL)	GMC (IU/mL)	% SP (≥ 1:8)	GMT	% SP (≥ 1:8)	GMT	% SP (≥ 1:8)	GMT
Infanrix-hexa; Schmitt HJ, 2000, Germany[15]	2, 3, 4 months of age	145	100	1.7	100	1.5	100	331	99	161	100	684
Infanrix-hexa; Knuf M, 2006, Germany [16]	2, 3, 4 months of age	111	99.1	0.09	100	3.6	98	299	100	325	100	927
Infanrix-hexa; Tichmann-Schuman, 2005, Germany [17]	2, 3, 4 months of age	138	100	1.4	100	1.7	100	262	98.4	165	99.2	580
Infanrix-hexa; Aristegui J, 2003, Spain [13]	2, 4, 6 months of age	32-40	100	4.0	100	2.9	100	482	96.9	351	100	1152
Infanrix-hexa; Zepp F, 2004, Germany [18]	3, 4, 5 months of age	419-472	99.8	1.7	100	1.6	99.8	315	99.0	181	100	725
Infanrix-hexa; Tejedor JC, 2006, Spain[19]	2, 4, 6 months of age	41-114	100	3.6	100	2.7	100	714	98.9	524	100	1340
Infanrix-hexa; Tejedor JC, 2004, Spain[20]	2, 4, 6 months of age	195-224	100	9.6	100	2.0	100	732	99.5	530	99.5	1172

Vaccine/ Reference	Vaccine schedule	N	Diphtheria		Tetanus		Polio 1		Polio 2		Polio 3	
			% SP* (≥ 0.01 IU/mL)	GMC (IU/mL)	% SP (≥ 0.1 IU/mL)	GMC (IU/mL)	% SP (≥ 1:8)	GMT	% SP (≥ 1:8)	GMT	% SP (≥ 1:8)	GMT
Infanrix-hexa; Omenaca F, 2005, Spain [21]	2, 4, 6 months of age	68-89	100	5.4	100	2.3	100	774	100	614	100	1208
Infanrix-hexa; Tichmann I, 2005, Germany [22]	2, 4, 6 months of age	214	100	1.5	100	2.4	99.5	284	98.4	272	99.5	911
Infanrix-hexa; Gabutti G, 2004, Italy and Germany [23]	3, 5, 11 months of age	177	100	3.9	100	4.9	100	1371	100	1341	100	2298
Infanrix-hexa; Avdicova M, 2002, Slovakia [24]	3, 5, 11 months of age	141	100	3.7	100	4.3	100	1479	100	1775	100	1776
Booster												
Pentacel; Halperin SA, 2006, Canada [25]	15-20 months of age	204	100	5.9	100	5.6	99	976	100	1437	100	2150
Infanrix-IPV/Hib; Halperin SA, 2006, Canada [25]	15-20 months of age	198	100	5.8	100	4.7	100	1294	100	1134	100	2118
Infanrix-IPV/Hib; Schmitt HJ, 2003, Germany [12]	Booster 11-15 months of age	48	100	3.4	100	9.7	N/A	N/A	N/A	N/A	N/A	N/A

Vaccine/ Reference	Vaccine schedule	N	Diphtheria		Tetanus		Polio 1		Polio 2		Polio 3	
			% SP* (≥ 0.01 IU/mL)	GMC (IU/mL)	% SP (≥ 0.1 IU/mL)	GMC (IU/mL)	% SP (≥ 1:8)	GMT	% SP (≥ 1:8)	GMT	% SP (≥ 1:8)	GMT
Infanrix-IPV/Hib; Dagan R, 1997, Israel [14]	Booster at 12 months	92	100	4.3	100	6.1	100	80-511 times the cutoff	100	80-511 times the cutoff	100	80-511 times the cutoff
Infanrix-hexa; Knuf M, 2006, Germany [16]	12-15 months of age	106	100	5.8	100	8.9	100	1153	100	1783	100	2276
Infanrix-hexa; Tichmann-Schuman, 2005, Germany [17]	11-14 months of age	114	100	6.9	100	6.8	100	1977	100	2135	100	3697

*SP – seroprotection; GMC – geometrical mean concentration; GMT – geometrical mean titres.

Table 2a (continuation of Table 2)

Vaccine/ Reference	Vaccine schedule	Hib			PT		PRN		FHA		FIM 2&3		Hepatitis B	
		% ≥0.15 µg/ml	% ≥1.0 µg/ml	GMC (µg/ml)	%VR	GMC (EU/mL)	%VR	GMC (EU/mL)	%VR	GMC (EU/ mL)	%VR	GMC (EU/ mL)	%SP* (≥10m IU/ml)	GMC (mIU/mL)
Pentacel; Scheifele D, 2006, Canada	2, 4, 6 months of age	77.7	43	0.6	80.2	26.0	77.7	23.3	57.0	40.9	N/A	N/A	96.7‡	169‡
Pentacel; Halperin S, 2002, Canada	2, 4, 6 months of age	83	N/A	3.7	N/A	25	N/A	36	N/A	31	N/A	N/A	N/A	N/A
Pediacel; Kitchin N, 2006,	2, 3, 4 months of age	93	73	2.2	N/A	78.7	N/A	32.7	N/A	51.9	N/A	279	N/A	N/A
Pediacel Lin TY, 2005, Taiwan	2, 4, 6 months of age	100	97	11.4	100	221	98	82.3	94	117.0	100	823	N/A	N/A
Infanrix-IPV/Hib; Schmitt HJ, 2003, Germany	2, 3, 4 months of age	96	67	1.9	92	44.3	96	236.3	77	67.5	N/A	N/A	N/A	N/A
Infanrix-IPV/Hib; Aristegui J, 2003, Spain	2, 4, 6 months of age	100	93.5	5.0	90.3	52.8	96.8	259.2	96.8	191.5	N/A	N/A	100†	1827†

Vaccine/ Reference	Vaccine schedule	Hib			PT		PRN		FHA		FIM 2&3		Hepatitis B	
		% ≥0.15 µg/ml	% ≥1.0 µg/ml	GMC (µg/ml)	%VR	GMC (EU/mL)	%VR	GMC (EU/mL)	%VR	GMC (EU/ mL)	%VR	GMC (EU/ mL)	%SP* (≥10m IU/ml)	GMC (mIU/mL)
Infanrix-IPV/Hib; Dagan R, 1997, Israel	2, 4, 6 months	98	89	5.1	99	57.4	100	156.8	100	148.5	N/A	N/A	N/A	N/A
Infanrix-hexa; Knuf M, 2006, Germany	2, 3, 4 months of age	91	60	1.2	92	52.9	95	244.6	89	86.6	N/A	N/A	99	439
Infanrix-hexa; Tichman n-Schuman, 2005, Germany	2, 3, 4 months of age	95.7	75.4	2.3	98.2	51.7	97.8	150.1	97.8	141.8	N/A	N/A	97.8	462
Infanrix-hexa; Schmitt HJ, 2000, Germany	2, 3, 4 months of age	99	77	2.6	99	53	99	161.7	99	151.4	N/A	N/A	99	393
Infanrix-hexa; Zepp F, 2004, Germany	3, 4, 5 months of age	96	67	2.0	98.5	57.0	97.4	131	98.8	170.5	N/A	N/A	98.5	567

Vaccine/ Reference	Vaccine schedule	Hib			PT		PRN		FHA		FIM 2&3		Hepatitis B	
		% ≥0.15 µg/ml	% ≥1.0 µg/ml	GMC (µg/ml)	%VR	GMC (EU/mL)	%VR	GMC (EU/mL)	%VR	GMC (EU/ mL)	%VR	GMC (EU/ mL)	%SP* (≥10m IU/ml)	GMC (mIU/mL)
Infanrix-hexa; Tichman n I, 2006, Germany	2, 4, 6 months of age	94.9	N/A	2.7	98.1	65	97.6	167.4	99.1	302.8	N/A	N/A	98.6	906
Infanrix-hexa; Tejedor JC, 2006, Spain	2, 4, 6 months of age	99.1	81.6	3.8	99.0	60	100	188.7	100	329.0	N/A	N/A	96.5	622.5
Infanrix-hexa; Omenaca F, 2005, Spain	2, 4, 6 months of age	97.8	86.5	4.2	98.9	60.4	98.9	200.3	100	253	N/A	N/A	95.2	867
Infanrix-hexa; Tejador JC, 2004, Spain	2, 4, 6 months of age	99	82	4.4	99	52.2	100	160.7	99.5	245.1	N/A	N/A	99	1108
Infanrix-hexa; Aristegui J, 2003, Spain	2, 4, 6 months of age	100	85	4.7	100	73.6	97.5	177.4	100	307.3	N/A	N/A	97.5	970
Infanrix-hexa; Poolman J, 2001, USA[26]	2, 4, 6 months of age	100	86.3	2.8	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Vaccine/ Reference	Vaccine schedule	Hib			PT		PRN		FHA		FIM 2&3		Hepatitis B	
		% ≥0.15 µg/ml	% ≥1.0 µg/ml	GMC (µg/ml)	%VR	GMC (EU/mL)	%VR	GMC (EU/mL)	%VR	GMC (EU/ mL)	%VR	GMC (EU/ mL)	%SP* (≥10m IU/ml)	GMC (mIU/mL)
Infanrix-hexa; Gabutti G, 2004, Italy and Germany	3, 5, 11 months of age	100	99.4	37.7	100	132	100	392	100	445	N/A	N/A	98.9	6695
Infanrix-hexa; Avdicova M, 2002, Slovakia	3, 5, 11 months of age	100	98.6	19.1	100	90.8	99.3	247.2	100	421.4	N/A	N/A	98.6	4301
Booster														
Pentacel; Halperin SA, 2006, Canada	15-20 months of age	99	98.4	29	91.1	65.6	95.0	167	89.5	132	N/A	N/A	N/A	N/A
Infanrix-IPV/Hib; Halperin SA, 2006, Canada	15-20 months of age	100	N/A	19	97.2	88.5	94.8	252	91.5	207	N/A	N/A	N/A	N/A

Vaccine/ Reference	Vaccine schedule	Hib			PT		PRN		FHA		FIM 2&3		Hepatitis B	
		% ≥0.15 µg/ml	% ≥1.0 µg/ml	GMC (µg/ml)	%VR	GMC (EU/mL)	%VR	GMC (EU/mL)	%VR	GMC (EU/ mL)	%VR	GMC (EU/ mL)	%SP* (≥10m IU/ml)	GMC (mIU/mL)
Infanrix-IPV/Hib; Schmitt HJ, 2003, Germany	11-15 months of age	N/A	N/A	18.2	N/A	68.7	N/A	526.1	N/A	256.3	N/A	N/A	N/A	N/A
Infanrix-IPV/Hib; Dagan R, 1997, Israel	Booster at 12 months	100	100	23.1	100	11.5	100	524.5	100	373.9	N/A	N/A	N/A	N/A
Infanrix-hexa; Knuf M, 2006, Germany	12-15 months of age	100	94	13.2	N/A	77.9	N/A	663.8	N/A	171.4	N/A	N/A	100	6539
Infanrix-hexa; Tichman n-Schuman, 2005, Germany	11-14 months of age	100	99.1	47.7	98.2	100.1	99.1	504.2	98.2	520.5	N/A	N/A	99.1	5754

*SP – seroprotection; GMC – geometrical mean concentration; GMT – geometrical mean titres.

† Engerix™-B 10µg vaccine was given simultaneously in different thighs

‡ Recombivax®-HB 5 µg vaccine was given simultaneously in different thighs

5. Nature and characteristics of immune response

5.1 Primary series

Response to Diphtheria

One month after completion of the three-dose primary vaccination series, 97%-100% of vaccinees achieved ≥0.01IU/mL of antibodies against diphtheria regardless of the type of vaccine used. There were five studies where less than 100% of vaccinees were reported as protected. In these studies different approaches to data presentation and interpretation were used. In Schmitt et al. and Dagan et al. studies with *Infantrix™-IPV/Hib* and the Zepp et al. study with *Infanrix™-Hexa* only the proportions of those who had titres ≥0.1 IU/ml are presented, respectively 97%, 99% and 99.8%. Therefore, it is not known the proportion of vaccinees who had ≥0.01 IU/ml. In the study with *Infanrix™-Hexa* performed by Knuf et al. both results for ≥0.01 IU/ml and ≥0.1 IU/ml are presented, respectively 99.1% and 39.6%. In Kitchen et al. study with *Pediacel®* only the proportion of those who achieved ≥0.01 IU/ml is presented (99%). To be noted that in Kitchen (*Pediacel®*), Knuf (*Infanrix™-Hexa)* and Schmitt *(Infantrix™-IPV/Hib)* studies first three doses of vaccine were given at the age of 2, 3, and 4 months.

Antibody geometrical mean concentration (GMC) varied from 0.09IU/mL to 9.6 IU/mL. GMC <1IU/mL were observed in only three studies[6 12 16] with three different vaccines (*Pediacel®*, *Infantrix™-IPV/Hib*, and *Infanrix™-Hexa*). In these three studies, the vaccines were administered in a 2, 3, and 4 months schedule. The highest antibody titres (9.6 IU/mL) were observed in a study with *Infanrix™-hexa*[20], when the vaccine was administered in a 2, 4, and 6 months schedule.

Response to Tetanus

One month after completion of the three-dose primary series, at least 99% of vaccinees had an antibody titre of ≥0.1IU/mL, regardless of the type of vaccine used.

Only in one study[8] with *Pentacel®* vaccine given at 2, 4, and 6 months of age was the GMC <1 IU/mL (0.9 IU/mL). In this study *Pentacel®* was administered concurrently with the *HBV* vaccine, given in different limbs (thighs), and blood tests were performed 8 weeks after the third dose.
The vaccinees in this group also received a 7-valent *pneumococcal* conjugate vaccine at 3, 5, and 7 months of age. Because of these study peculiarities, the obtained results will be treated separately in section 11.

In all the other studies antibody titres varied from 1.5 IU/mL to 5.7 IU/mL. Antibody titres did not appear to depend on the primary series schedule or type of vaccine used.

Response to Poliovirus

One month after completion of the three-dose primary series, at least 95% of vaccinees had a seroprotective level of antibodies against all three types of polioviruses. The results were lower in a Canadian study where antibodies were measured 8 weeks after three dose primary series[8].

Variations of GMT were observed among different studies and for different poliovirus types. These variations may be due to different vaccination schedules, study populations, different laboratory techniques or differences in interpretation of results. However, despite important variation, high neutralizing antibody GMTs against all three types of polioviruses were observed in all studies.

Response to Haemophilus influenzae type b

One month after the third dose of vaccine, the response rates to PRP (≥0.15 µg/ml) varied between 91% and 100% regardless of the type of vaccine used, in all but two studies with *Pentacel*® [8 9] given at 2, 4 and 6 months of age. Only 78-83% of subjects achieved above mentioned level of antibodies in these two studies with *Pentacel*®.

In general, higher vaccine response rates, of 95-100%, were observed in other studies with a 2, 4, 6 month schedule compared to compressed schedules (2, 3, and 4 months or 3, 4, and 5 months).

Anti-PRP level of ≥1 µg/ml was achieved by 43-97% vaccinees. In general, lower proportion of children vaccinated according to the compressed schedules achieved the above mentioned antibody level (60-77%) compared to those vaccinated using a 2, 4, and 6 months schedule (82-97%).

The anti-PRP GMT ranged from 0.6 µg/ml to 11.4 µg/ml depending on the schedule and the population. When results from studies using a 2, 4, and 6 month schedule were analyzed, only one Taiwanese study with *Pediacel*® [11] showed anti-PRP two to four fold higher (11.4 µg/mL) compared to other studies. However, the higher antibody titres observed in Taiwanese children may have been due to a different probability of natural exposure to Hib during the first months of life. Importantly, in this study higher antibody titres were also obtained against tetanus and all three types of polio.

Response to Pertussis

There is no agreement on correlations of protection for pertussis. Different approaches to the response interpretation to pertussis antigens were used in analyzed studies. The vaccine response (VR) was determined as appearance of antibodies in subjects seronegative before vaccination, or at a minimum, maintenance of pre-vaccination antibody concentrations in subjects who were initially seropositive, or a four-fold rise in antibody titres.

One month after the third dose, the *VRs* in all studies were greater than 90% and 95%, respectively to PT and PRN. The VR to FHA varied from 77% to 100%. The VR to FHA was 94% or higher in all studies where a 2, 4, and 6 month schedule was used. The results were lower in a Canadian study where antibodies were measured 8 weeks after three dose primary series[8].

To date, there are no head-to-head studies available for primary vaccination at 2, 4 and 6 months of age; two head-to-head studies are in development in Finland, Poland, Sweden and France. However, no data will be available until the end of 2006. Published results seem to indicate a higher GMC to PT in those vaccinated with *Pediacel®* (in Taiwanese study only), and higher GMC to PRN and FHA in those vaccinated with *Infanrix™-IPV-Hib* and *Infanrix™-hexa* (Table 2a).
The *anti-pertussis* FIM 2&3 were reported in two studies with Sanofi Pasteur *Pediacel®* [10] [11]. A 4-fold increase of FIM 2&3 antibody level was observed in 100% of subjects. The GMC varied from 279 EU/ml to 823 EU/ml. No differences in FIM 2&3 antibody GMCs were observed when Hib was administered as a *Pediacel®* component or in a separate syringe [11]. However, FIM2&3 GMC after *Pediacel®* was two times lower when compared to DTwP/Hib results, 279EU/ml and 591EU/ml, respectively[10]. The GSK vaccines do not contain FIM2&3 antigens, and no study with *Infanrix™* vaccines reported the *anti-pertussis* FIM2&3 results.

Response to Hepatitis B

Seroprotection rates against hepatitis B were measured in several studies with *pentavalent* vaccines[8] [12] (*Pentacel®* and *Infanrix™ IPV/Hib*) where hepatitis B vaccine (*Recombivax® -HB or Engerix™-B*) was administered concurrently in different limbs (thighs) and in studies with *Infanrix™-hexa*. Seroprotection rates in all studies varied between 95% and 100% regardless of the type of vaccine used.

The GMC varied from 169 mIU/mL to 439 mIU/mL when *Recombivax®-HB* 5 µg vaccine was used concurrently with *pentavalent* vaccine[8] or when vaccines were administered according to the compressed schedule (2, 3 and 4 months)[15] [16]. In studies where a 2, 4, and 6 month schedule was used, the GMC varied between 867 mIU/mL and 1827 mIU/mL. In these latter studies *Engerix™-B* 10µg vaccine was used concurrently with *Infanrix™-IPV/Hib* or as a component part of *Infanrix™-hexa*.

Comparable seroprotection rates and GMCs were observed in many other studies with hepatitis B vaccines administered separately[27-31]. Higher GMCs were observed after *Engerix™–B* vaccine when compared to *Recombivax®-HB*.

5.2 Booster vaccination

Several immunogenicity studies have been performed with *penta-* and *hexavalent DTaP* based vaccines. The age for booster dose administration varied from 11 to 20 months.

Response to Diphtheria

One month after the booster dose 100% of vaccinees in all studies had an antibody titre superior to 0.1 IU/mL, regardless of the type of vaccine used. There was very little variation in the GMC (3.4 - 6.9 IU/mL) observed in the published studies (Table 2).

Response to Tetanus

Observed seroprotection rates were 100% in all studies, regardless of the primary vaccination schedule or type of vaccine used. A strong consistent antibody response was observed in all studies. Antibodies GMCs one month after the booster dose varied between 4.7 IU/mL and 9.7 IU/mL. It seems higher GMCs are obtained when booster dose is given at the age of 11-15 months when compared to the age 15-20 months (6.1- 9.7IU/mL vs. 4.7-5.6IU/mL).

Response to Poliovirus

Seroprotection rates to the three polioviruses one month after the booster dose were 99-100% regardless of the type of vaccine used. Antibody GMTs were in the high ranges (976 NA/mL to 3697 NA/mL). No important difference in antibody titres between polioviruses type 1 and 2 was observed. In comparison, in all studies the titres were higher to type 3 poliovirus.

Response to Haemophilus influenzae type b

The anti-PRP antibody level of ≥0.15 µg/ml was observed in 99-100% of vaccinees independently of the vaccine used in the primary series or as booster dose.

The proportion of vaccinees with an anti-PRP level ≥1.0 µg/ml was reported in four booster studies. The proportion of those who achieved these anti-PRP levels varied from 94% to 100%. In studies with Infanrix administered in a 2, 4, and 6 months primary series schedule, 99-100% of vaccinees achieved an anti-PRP level of ≥1.0 µg/ml after a booster dose. In a Canadian study on interchangeability of two vaccines, 98.4% and 100% (P>0.05) in the *Pentacel®* and *Infanrix™-IP-Hib* group, respectively, had a titer of anti-PRP ≥1µg/ml[25].

The anti-PRP GMCs observed in different studies varied from 13 µg/ml to 48 µg/ml. Higher GMCs (23-48 µg/ml) were reported in booster studies where primary series schedule was 2, 4 and 6 months[14 17] compared to 2, 3, and 4 months[16].

Response to Pertussis

Booster response rates varied from 91% to 100%, 90% to 100%, and 95% to 100%, for PT, FHA, and PRN, respectively. No tests for FIM 2 and 3 were performed in booster studies[25] .

Important variation in GMCs were observed among different studies and among different antigens. The antibodies GMC to PT, FHA and PRN varied from 12 EU/mL to 100 EU/mL, 132 EU/mL to 521 EU/mL, and 167 EU/mL to 664 EU/mL, respectively. No important differences between the vaccines from the two manufacturers were observed when PT post-booster antibody levels were compared. However, anti-PRN and anti-FHA in booster studies with *Infanrix™* were higher when compared to *Pentacel®* booster-study, respectively 252-663.8 EU/mL vs 167 EU/mL and 171-520 EU/mL vs132 EU/mL.

Response to Hepatitis B

Seroprotection rates and anti-HBs titres after the fourth booster dose of hepatitis B vaccine given as a component of *Infanrix™-hexa* were measured in two studies [16 17]. The seroprotection rates were 99-100% and a high anti-HBs GMC (5754-6539 mIU/mL) was observed. These GMCs were in the range of that observed after three doses of *Engerix™-B* or two doses of *Twinrix*™ vaccine in adolescents and young adults[27-31].

5.3 Mixed schedule: 3, 5, and 11 months vaccination

Two studies measured the immnunogenicity of *Infanrix™-hexa* in a 3, 5, and 11 months schedule[24] [23]. Both studies were *Infanrix™-hexa* head-to-head with *Infanrix™-IPV//Hib + HBV*; Hib and HBV vaccines were administered concurrently in comparator groups. Non-inferiority criteria of *Infanrix™-hexa* for all vaccine components were met in both studies. Results obtained in the two studies with *Infanrix™-hexa* are presented in Table 5.

Table 5. Immunogenicity of Infanrix™-hexa given at age of 3, 5, and 11 months

Antibody	SP/ VR rates (%) N=318*		GMCs/ GMTs n=318*	
	Post - II	Post - III	Post - II	Post - III
Anti-diphtheria ≥0.1 IU/mL	97.1-100	98.9-100	1.6-1.8	3.7-3.9
Anti-tetanus ≥0.1 IU/mL	100	100	1.5-2.4	4.3-4.9
Anti-polio 1	98.8-100	100	201-259	1372-1479
Anti-polio 2	95.0-97.6	100	119-204	1341-1775
Anti-polio 3	99.2-99.4	100	302-468	1776-2298
Ant-PRP			2.6-3.5	19.1-37.7
≥0.15 µg/ml	93.5-93.7	100		
≥1.0 µg/ml	62.9-77.7	98.6-99.4		
Anti-PT	99.2-100	100	58-66	91-132
Anti-FHA	98.7-99.3	100	149-157	421-445
Anti-PRN	95.7-100	99.3-100	79-157	247-392
Ant-HBs	96.4-98.3	98.6-98.9	593-623	4301-5199

*N for two studies together; variation between studies' results are presented

Both studies reported very similar results. Response rates obtained after the first two doses given at 3 and 5 months of age were in the range of those obtained with the three doses schedule. Antibody GMCs/GMTs to PRP after two doses given at 3 and 5 months of age varied between 2.6-3.5 µg/ml, while in five studies with three doses given at 2, 3, and 4 months of age it varied from 1.2 µg/ml to 2.6 µg/ml. No other important differences in results obtained with two and three doses primary vaccination schedule were observed when comparing GMCs/GMTs.

Excellent response rates (>98.5%) to all antigens were obtained after the third dose given at 11 months of age. GMCs/GMTs were comparable to those obtained in other booster studies with a three doses primary vaccine series.

6. Immunogenicity in different population groups

Hib and Pertussis immunogenicity in pre-term newborns
(search keywords: Hib vaccination, Preterm Newvborns; and Pertussis vaccination, Preterm Newborns)
A lower response to *Hib* vaccine has been reported in pre-term and low birth weight (LBW) newborns since the middle 90's [21] [32]. In the study conducted by Munoz et al (1995) the GMT increased significantly, however, were still markedly lower than values reported in full-term infants. After the second immunization, only 24 infants (67%) attained antibody concentrations of > 0.25 µg/mL; defined in that study as seropositivity. Also, only 53% of infants achieved antibody concentrations of > 1.0 µg/mL compared with 92% of term infants. Logistic regression identified gestational age of 27 weeks or less and the amount of intravenous immunoglobulin received as the significant variables influencing the antibody response after the first immunization. The incidence of side effects was negligible. Authors concluded that LBW infants, and especially those born at 27 or less weeks' gestation, do not respond as effectively to the Hib vaccine.

In another study, both pre-term (50) and full-term (50) infants showed an increase in antibody GMTs to pertussis antigens. However, similar to Hib, a significantly lower immune response was reported in pre-term infants compared with full-term infants[33]. The GMT for PT antibody of pre-term infants was 64.2 U/L, compared to 99 U/L in full-term infants. The GMT for FHA was 51 U/L in pre-term versus 86 U/L in full term infants.

A more recent study (Sikora JP, 2003) determined the levels of antibodies against *Bordetella pertussis*, Hib and Poliovirus type 1 in pre-term infants after immunization with acellular pertussis (*Infanrix™-DTPa*) and Hib conjugate (*Hiberix®)* vaccines, as well as inactivated vaccine against poliomyelitis (*Imovax Polio*).
Thirty-two children were given 3 doses of *Infanrix™-DTPa* and *Hiberix®* vaccines concurrently with *Imovax* Polio vaccine. Samples of blood were taken from children 4 weeks after application of the 3rd dose of vaccines and compared with the initial levels of antibodies. Seroconversion was evaluated in 32 children immunized with both *Infanrix™-DTPa* and *Hiberix®* and in the 20 immunized with *Imovax* Polio. All the children (100%) demonstrated protective levels of antibodies after immunization with the 3-rd dose of *Infanrix™-DTPa* and *Hiberix®*. Only one child (5%) did not respond when *Imovax* Polio was administered. The observed increase in antibody titers post-vaccination to all studies antigens was statistically significant ($p<0.05$). No significant correlations between birth weight, gestational age and the levels of post-vaccination antibody titres were noticed. The author concluded that the results prove that nearly all

pre-term infants achieve the protective levels of antibodies against pertussis, Hib and poliomyelitis.

A 2005 study with *Infanrix™-hexa* in pre-term newborns (Table 6) in which 94 pre-term infants between 24 and 36 weeks gestation (mean +/- SD gestational age: 31.05 +/- 3.45 weeks; mean birth weight: 1420 +/- 600 g) and a control group of 92 full-term infants were enrolled to receive 3 doses of a *DTPa-HBV-IPV/Hib* vaccine at 2, 4, and 6 months of age. Immunogenicity was assessed in serum samples that were taken before and 4 weeks after completion of the primary series. All pre-term (n = 93) and full-term (n = 89) infants who were included in the immunogenicity analysis had seroprotective titers to diphtheria, tetanus, and polio virus types 1, 2, and 3. The immune response to Hib was lower in pre-term than in full-term infants: 92.5% versus 97.8%. Noninferiority of the anti-Hib seroprotection rate in pre-term versus full-term infants could not be concluded 1 month after the third dose. Nonetheless, authors concluded that responses to Hib vaccine was satisfactory; only 4 premature infants who were <27 weeks of gestation had titers below the cut-off. Moreover, GMCs in the group of pre-term infants was similar to those found in full-term children who were immunized with the same vaccine at 2, 3, and 4 months[15]. In this study, although anti-HBs GMCs were slightly lower in pre-term infants (634IU/mL versus 867IU/mL; p>0.05), seroprotection rates to HBV were similar between the 2 groups (93.4% versus 95.2%). Intrauterine growth retardation and poor weight gain in the first 6 months of life seem to diminish the probability of an adequate response to HBV vaccine.

Vaccine response rates for pertussis antigens were $\geq$98.9% in both study groups. Although most GMT were lower in pre-term infants, anti-PT and anti-FHA titers were similar. Anti-PRN titers were lower in pre-term infants (155EU/mL versus 200 EU/mL; P<0.05). The vaccine was well tolerated, and there were no differences in reactogenicity between the two groups. Some extremely premature infants experienced transient cardiorespiratory events within the 72 hours after the first dose of vaccine with no clinical repercussions.

The authors concluded that pre-term infants who were immunized with the *hexavalent DTPa-HBV-IPV/Hib* vaccine at 2, 4, and 6 months displayed good immune response to all antigens and that the availability of this vaccine greatly facilitates the vaccination of premature infants.

Table 6. Immunogenicity of Infanrix™-hexa given at age of 2, 4, and 6 months to full-term and pre-term infants, one month after the third dose

Antibody	SP/ VR rates (%)		GMCs/ GMTs	
	Full-term n=62-89	Preterm n=65-93	Full-term n=62-89	Preterm n=65-93
Anti-diphtheria ≥0.1 IU/mL	100	100	5.4*	3.7
Anti-tetanus ≥0.1 IU/mL	100	100	2.3	2.5
Anti-polio 1	100	100	774*	424
Anti-polio 2	100	100	614	450
Anti-polio 3	100	100	1208*	468
Ant-PRP			4.2*	2.2
≥0.15 µg/ml	97.8	92.5		
≥1.0 µg/ml	86.5*	76.3		
Anti-PT	98.9	98.9	60	61
Anti-FHA	100	100	253	240
Anti-PRN	98.9	100	200*	155
Ant-HBs	95.2	93.4	867	634

*significant differences between results in full-term and pre-term infants; P<0.05

Aboriginal population

(keywords search : Hib vaccination, aboriginal population; Pertussis vaccination, aboriginal population)

Prospective surveillance of Hib disease in Aboriginal North American population in pre-vaccination era showed the attack rate in children < 5 years of age was 5-10 times higher than in the general population (Sanstosham M, 1992). Between 1981-1984, a community-based surveillance study in Manitoba and Keewatin District, NWT, revealed earlier onset of Hib infection in Aboriginal children compared to non-Aboriginal children (Hammond GW, CMAJ, 1988). Authors concluded that prevention of Hib meningitis through vaccination would likely be more difficult in Aboriginal children. At least four different Hib vaccines have been used in Aboriginal children since the early 90's. Different immunogenicity and reactogenicity depending on the type of vaccine and schedule used were reported (Bulkow LR,1993).

Although sharp decline in invasive Hib disease rate in Alaska Natives were observed after Hib vaccination program implementation [34] [35], the switch from outer membrane protein conjugate vaccine (PRP-OMP) to DTP- *Haemophilus b* oligosaccaride conjugate vaccine (DTP-HbOC) in 1996 was followed by an increase in invasive Hib disease, suggesting ongoing Hib transmission despite widespread vaccination[35]. It should be mentioned that PRP-OMP provides the earliest antibody levels thought to be protective against invasive disease. However, PRP-OMP vaccination does not achieve as high a peak antibody

concentration after a full course as is seen after vaccination with either HbOC or PRP-T vaccines (Bulkow LR, 2003; Decker MD, 1992; Granoff DM, 1992).

No recent clinical trials in Aboriginal infants with vaccines of interest were found.

7. Short and long-term vaccine efficacy including reduction of disease and death risks.

The efficacy of combination vaccines in reduction of disease incidence and mortality from diphtheria, tetanus, polio 1, 2 and 3 is commonly recognized. A large number of clinical trials and long-term field epidemiological data has demonstrated high efficacy/effectiveness of different *DTaP* based vaccines[36 37].

The efficacy of three other components (HBV, Hib, and Pertussis) when given in combined vaccines continues to be a subject of scientific discussion and clinical trials [35 38-41].

HBV

Monovalent and bivalent (HBV combined with hepatitis A virus [HAV]) vaccines are performing very well. Surveillance data from all countries which have implemented programs are showing incontestable data on vaccine effectiveness [42 43]. Canadian data have also confirmed the effectiveness of HBV vaccines [44 45].

Since the implementation of universal vaccination of 8-10 year-old children in the province of Quebec in 1994, the incidence has decreased by 79% in the general population and by 91% in 10- to 19-year-olds[44]. The incidence decrease reported a few years ago in British Columbia was in the same range as occurred in Quebec[45].

HBV vaccine as a component of *Pediarix™*, *Hexavac®*, and *Infanrix™-hexa* has been tested and has been incorporated in universal infant programs in many countries since the late 1990's [5 22 46]. In general, the combination vaccine retains the immunogenicity profile of the separate components and stimulates antibody concentrations associated with protection using a variety of schedules.

A comparison of combined vaccine given in a 2, 4, and 6 months schedule versus a currently recommended schedule in the USA – HBV at birth, 1 and 6 months of age and DT3aP at 2, 4, and 6 months of age – found significantly higher antibody responses for combined vaccine for every component except hepatitis B, which was significantly lower[47]. However, the HBV antibody with combined vaccine was nonetheless high (1280 mIU/mL), and 98% of subjects had levels > 10 mIU/mL, the level considered protective.

Slightly lower anti-HBs GMTs were reported when HBV vaccine was given as a component of *Hexavac®* compared to *Infanrix™-hexa*[22] or separate HBV vaccine administration. Although no increase in HBV incidence was reported in any country after the shift to any of combined vaccines containing HBV, in December 2004, the *Hexavac®* vaccine was pulled off the market by the manufacturer because of lower immunogenicity of HBV component compared to concurrent *Infanrix™-hexa* and *monovalent* hepatitis B vaccines.

Because of the relatively recent HBV component addition to different *DTaP* based vaccines, no long-term efficacy data are available.

Hib

Several different protein carriers have been used in the conjugate process for Hib vaccines. In the Canadian context, all of the currently approved combined vaccines use Hib conjugated to tetanus toxoid (PRP-T). PRP-T has been shown to cause fewer local reactions than many of the other protein carriers used [3].

Several studies have demonstrated lower immunogenicity to the Hib component of combination whole-cell pertussis vaccine products that include Hib antigens when compared with individually administered Hib conjugate vaccine. Several studies evaluating acellular pertussis combination products containing Hib have also demonstrated decreased titres when compared with individually administered Hib vaccine[48 49]. This appear to be particularly evident with the combination vaccines containing fewer pertussis antigens, including *Infanrix™* [48 50]. However, given that the anti-Hib titres of the acellular pertussis combination vaccines are in the range of what is believed to be protective, the functional activity of antibodies remains unchanged and immune memory is not decreased by the combined products, there has been an acceptance of their use as a combination vaccine.

In Germany, the first country to introduce *Infanrix™/Hib* on a national scale, there was a continued decline in invasive disease with vaccine effectiveness estimated at 98.8% following completion of the primary series[52]. To note, the *Infanrix™-Hib* introduced in 1996 in Germany gained rapid acceptance (65% market share in 1997). *Infanrix™-Hib* was itself gradually supplanted by an *Infanrix™-IPV-Hib* combination. This vaccine was joined by another *DTaP-IPV-Hib* combination, *Pentavac®* (Sanofi Pasteur), in 1998. During 1998-1999, there were five deaths linked with an episode of invasive *H. influenzae* disease reported by two independent surveillance systems in Germany. None of those five children had received Hib vaccination, although with the exception of one neonate all were 15 months of age or older.

The above mentioned results are similar to those reported for monovalent Hib conjugate vaccines in several other countries.

Although Hib conjugate vaccines have been used since the late eighties and new formulations are now recommended for use throughout the world, the duration of protective immunity afforded by them is not well known. The immunogenity of PRP-D conjugate vaccine (to be noted that PRP-D is a weak immunogen) given in infancy was assessed in one study in 74 nine to ten year-old children by giving them a dose of Hib polysaccharide (PS) vaccine as a test. The anti-Hib PS antibodies were measured before and after this test vaccination, and the values compared to those in 37 control children who had not previously received any Hib vaccine. Prior to the test vaccination, the anti-Hib concentrations in the Hib conjugate group were 3.6-fold higher than in the control group. After the test vaccination, the Hib-conjugate group had higher total anti-Hib concentrations, a higher proportion of IgG and higher avidity of anti-Hib than the control group, suggesting persistent immunological memory in a Hib conjugate group[53].

In Canada, invasive Hib infections remain rare, with most cases occurring in unimmunized children or children too young to have completed the primary series. Protection after vaccination appears to extend into later childhood and does not appear to be diminished by co-administration of newer infant vaccines[54]. The following can be concluded from this experience: Hib disease although uncommon, remain dangerous, so children should complete the vaccination series in a timely manner. Among children vaccinated with the current Hib vaccine, breakthrough infections are rare. Surveillance should continue to confirm long-term protection [41] and to assess the effectiveness of concurrent vaccination with other conjugate vaccines as new provincial/territorial programs are implemented[54].

Based on antibody levels among study children who did not develop invasive Hib disease, it was estimated that it was necessary to have 0.10 µg/ml or 0.15 µg/ml of antibodies at the time of Hib exposure in order to be protected from invasive disease[55]. Given the demonstrated waning of antibody levels over time, it was suggested that a post-immunization level of 1 µg/ml was required for long-term protection, to ensure a minimal level of 0.10 µg/ml during the second year of life. It is increasingly questioned, however, whether these benchmark levels, derived from studies of unconjugated PRP vaccines, are equally applicable to antibody responses produced by conjugated vaccines. Not only do the conjugated vaccines stimulate higher antibody responses, but there is an associated maturation of the immune response (i.e. increased functional capacity of the antibodies) that results in increased avidity of the antibodies prior to and after the booster challenge. Moreover, the levels obtained with the *DTaP*-based Hib combinations are still within the broad range of antibody titers achieved with other licensed Hib conjugates administered separately[55] .

Perhaps most importantly, the conjugated vaccines induce B-cell memory that leads to a rapid anamnestic response after Hib exposure,[55] and consequently protection may not depend solely on pre-infection levels of circulating antibody.

Combination vaccines that manifest reduced Hib antibody have been approved by European, Australian and other authorities. Hospital and laboratory-based surveillance of Hib disease in Germany, where combination vaccines were progressively introduced starting in 1996, has not detected any increase thus far in invasive Hib disease, and incidence rates continue to fall [52 56].

However, surveillance of Hib disease in the UK has detected an increase in invasive Hib disease that appears to be associated with a recent reduction in population immunity to Hib[57]. The UK report documents a seven- to eight-fold higher risk of invasive Hib disease among recipients of the *DT3aP/Hib* combination vaccine introduced in January 1999[57]. Even if this report is substantiated, however, the issue may be of relevance only in the context of the immunization schedule which was used in the UK, which was administration of Hib-containing vaccine at 2, 3, and 4 months with no subsequent booster[5]. In Canada this schedule is not recommended.

No *DTaP/Hib* combination vaccine is licensed for primary immunization in the USA[7].

Pertussis

Despite the dramatic pertussis decrease since the licensure of whole-cell pertussis vaccines in the middle 1940s, the disease remains endemic in many countries[58], including Canada[59]. The incidence of pertussis has increased during the past 25 years, with a notable shift in incidence from young children to adolescents and young adults[60]. It is unclear whether the recent rise in the incidence of pertussis is real or a reflection of improved diagnosis[61]. In recent years, there has been a renewed emphasis on the occurrence of pertussis in adolescent and young adult populations. Recent publications have alerted providers to consider pertussis when evaluating patients with prolonged cough. Additionally, technological advances in the diagnosis of pertussis, such as polymerase chain reaction assay, have improved the likelihood of a pertussis diagnosis. However, in the USA, since the 1980s, there has been an 11% increase in the incidence of pertussis among infants too young to receive three doses of vaccine containing pertussis[60].

In countries where a resurgence of pertussis has been validated, three reasons have been proposed: vaccine failure, changes in the organism, and the effect of the vaccination program on dynamics of infection. Increases in Canada have been linked to these factors and potentially to the use of a poorly effective

vaccine[62]. The Netherlands had a large resurgence of pertussis in 1996, which has been attributed to a change in the circulating organism. Microbiologists in other countries have attempted to replicate the studies undertaken in the Netherlands and have also found evidence of emergence of non-vaccine variants of *pertactin* and *pertussis* toxin[63], but not accompanied by any changes in vaccine effectiveness[64-66]. The Netherlands has now switched from using a domestically produced whole-cell vaccine to an *acellular* vaccine.

Studies confirm high rates of susceptibility with severity of infection correlating with time since vaccination[67 68]. Thus, Brisgard et al.[58] reported that, under field conditions, receipt of ≥3 pertussis vaccine doses among children 6 to 59 months of age was highly protective against pertussis, regardless of vaccine type or manufacturer. In the meantime, using information from the National Immunization Survey and surveillance data from 1998 to 1999, the Centers for Disease Control and Prevention (CDC) in the United States calculated that ***DTaP*** vaccines and *DTwP* vaccines administered during childhood are at least 88% effective[60 69]. However, the immunity induced by childhood vaccination or natural infection wanes after 5 to 13 years[70].

In a recent Austrian study[71] authors undertake an analysis of the epidemiology of pertussis disease among hospitalized children during the transition period from whole-cell to *acellular pertussis* vaccine (1996-2003) in order to compare the respective estimates of vaccine effectiveness. The mean annual hospitalization incidence decreased over time, from 27.9 per 100 000 population in 1996 to 6.8 cases per 100 000 population in 2003. Estimated vaccine effectiveness was 79% for the whole-cell versus 92% for the *acellular pertussis* vaccine. During 1996-1997 only whole-cell vaccines were used, in 1998 and 1999 both whole-cell and *acellular* vaccines were used, and from 2000 to 2003 only *acellular* vaccines were used (2P or 3P components containing vaccines were used in this country.
Study results suggest that the effectiveness for hospitalization of the currently used *acellular pertussis* vaccines (*Tetravac®*, *Infanrix™*, *Infanrix™-hexa*) was higher in children up to the age of 24 months.

Sweden, a country where the withdrawal of whole-cell pertussis vaccine from the childhood immunization schedule took place in 1980, and *DTaP* vaccines were introduced in 1996, reported an important decrease in pertussis incidence during the last decade. Several studies with pertussis vaccines were conducted since 1986 in Sweden. Cohorts of infants (from 6442 to 20240 infants per vaccine-cohort) were vaccinated with different acellular vaccines. Results showed that *acellular pertussis* vaccines are effective from the second dose (if administered at 3 and 5 months of age) and the third dose of vaccine was associated with a significant reduction in disease incidence. The effect was more pronounced during the first year following vaccination, but seemed to remain fairly stable for 4-5 years following the completion of the full vaccination schedule. These

findings are in accord with the Italian and German experiences [56]. Interestingly, there was a non-significant trend of more vaccine failures among DT5aP recipients than among *DTPw* and *DT3aP* recipients. This early observation warrants further follow-up to detect potential differences in long-term protection that may be at variance with the results of the observed short-term efficacy. However, obtained results partially confirm the non-correlation between the number of pertussis antigens in the vaccine and protection against disease.

In general, *B. pertussis* infections in adolescents and adults are of concern as they are the most important source of transmission of *B. pertussis* infections to young, unprotected infants. Many studies with diphtheria and tetanus toxoid, *acellular pertussis* component combination vaccines, specifically designed for use in adolescents and adults, have been performed and excellent tolerability and immunogenicity have been demonstrated.

With the availability of two such products, booster doses in adolescents have been introduced in Canada, Austria, Australia, France, Germany and the US, and many other countries are considering a similar expansion of their immunization programmes at present. NACI recommends that every Canadian adult receive a dose of acellular pertussis vaccine. In addition, universal immunization of adults (Austria, every 10 years) or targeting high risk groups (e.g., parents of newborns and other care-givers to children; Germany) have been recommended in various countries. If lifelong regular booster doses against pertussis were to be recommended and universal implementation would be obtained, it is believed that the morbidity of pertussis and its spread to infants can be dramatically reduced, and it is possible that the circulation of *B. pertussis* could be eliminated [40]. However, no scientific reliable data exist concerning the frequency and the number of booster doses needed for *B. pertussis* elimination.

The incidence of pertussis declined to low levels in Canada after the introduction of *dTap* (*Adacel®),* which was approved for use in Canada in 1999. As of September 2004 all Canadian jurisdictions had implemented universal adolescent acellular pertussis programs. Introducing routine childhood immunization with *acellular pertussis* vaccines, *Pentacel®* and *Quadracel®,* in 1998 and adding *Adacel®* for individuals aged 14 to 16 years, likely contributed to this outcome. Although pertussis outbreaks have occurred, they primarily involved adolescents and adults who had not yet received a booster with d*Tap* and who would have received only whole-cell pertussis vaccine during childhood. The cumulative benefits of *acellular pertussis* combination vaccination programs in children and routine adolescent/adult immunization with d*Tap* may become more evident as additional age cohorts are immunized. However, using *dTap* in adults might achieve broader population immunity more rapidly[72 73].

8. Effect of the vaccine on transmission of specific and related organisms (i.e. reduction in carriage rate, replacement)

In numerous studies, diphtheria, tetanus, poliomyelitis 1, 2 and 3 serotypes, as well as hepatitis B vaccine components have been demonstrated to have a dramatic influence on the disease's transmission and ultimately on carriage rates independently of the vaccine used.

Pertussis

For pertussis vaccines, the number of components in the vaccine does not necessarily affect efficacy against disease transmission[5]. However, historically important differences in vaccine effectiveness have been reported. In Canada, the recently implemented *dTap* immunization program for adolescents is expected to curb the increasing pertussis incidence[61] and to diminish the transmission risk for non-immunized or partially immunized infants.

Genetic and antigenic analysis of *B. pertussis* isolates recovered from clinical cases in Ontario, before and after the introduction of the *acellular pertussis* vaccines showed a temporal genetic variation among isolates, which is consistent with the current view that *B. pertussis* evolves over time. However, no specific antigenic or genetic type was detected in isolates collected after the introduction of the *acellular pertussis* vaccines[5 66 59]. Several other studies were conducted to verify the possible replacement of circulating *B. pertussis* and all but one have concluded that no evidence exists concerning such a replacement.

Hib

Vaccination against Hib is a major contributor to the reduction of nasopharyngeal carriage[74]. Widespread vaccination against type b has not yet caused problems with serotype replacement. Strains recovered from vaccinated children are indistinguishable from those recovered from unvaccinated children (Landarverde M et al, 1999).

As discussed previously, an increase in Hib in British children has been linked to the widespread use of a *DTaP-Hib* combination vaccine[35] without a booster. Anti-polyribosyl-ribitol phosphate antibody concentration and avidity before and after a Hib booster in children 2-4 years of age who had received 3 doses of DTP-*Hib* (either *DTwP-Hib* or *DTaP-Hib*) combination vaccine in infancy and pharyngeal carriage of Hib was measured in a recent UK study (Johnson NG et al, 2006). Antibody concentrations before and avidity indices after vaccination were low (GMC 0.46 mug/mL, 95% confidence interval [CI] 0.36-0.58; geometric mean avidity index 0.16, 95% CI 0.14-0.18) and inversely related to the number of previous doses of *DTaP-Hib* ($p = 0.02$ and $p<0.001$, respectively). Hib carriage was found in 2.1% (95% CI 0.7%-6.0%) of study participants. According to authors' opinion, these data support an association between *DTaP-Hib* vaccine

combinations and clinical Hib disease through an effect on antibody concentration and avidity (Johnson NG et al, 2006). It should be noted that the vaccination schedule in the UK was 2, 3, and 4 months without a booster dose during the second year of life. In most reviewed studies the use of a 2, 4, and 6 months schedule produced higher anti-PRP antibody GMCs compared to compressed schedule, independently of the vaccine used. Thus, the UK experience should not be extrapolated to other countries.

9. Short and long-term population effectiveness (i.e. impact on reduction of burden of disease, including herd immunity).

Important short and medium-term effectiveness of at least 3 out of 4 vaccines of interest, except the new *Pediacel®*, were reported[54 75] . Taking into consideration the very close similarity of *Pediacel®* and *Pentacel®*, one can expect the same effectiveness.

It is likely that reported lower effectiveness of combined vaccines in some countries was mostly related to the schedule and not to the type of vaccine used. Also, the clinical importance of lower immunogenicity of Hib component when given in combination with a *DTaP*-based vaccine is a subject of scientific discussion. The existing field data have shown no increase in the incidence when vaccines are given according to the package insert. A recent study, from UK, (Berrington JE, 2006) shows that the receipt of 1 or more *acellular* vaccine doses was associated with lower anti-PRP antibody and a dose response effect was observed. However, an adequate response to fourth dose (>93%) was achieved independently of the nature of the pertussis component of the priming *DTPHib*. Observed decrease in the incidence of Hib in UK after the reintroduction of a fourth dose of vaccine and catch-up campaign demonstrate that the main cause of the previous resurgence of Hib in this country was the inadequate schedule used.

Implementation of *Pentacel®* in Canada and *Infanrix™-IPV/Hib* and *Infanrix™-hexa* in Europe has not been related to an increased incidence of any disease compared to use of a single vaccine. Waning immunity and importance of titers of different types of antigens to pertussis and Hib is likely to continue to be a subject of scientific and public health discussions for several more years, until long term effectiveness data will be available. However, the clinical importance of this finding continues to be unknown.

10. Safety: rates and severity of adverse events, contraindications, precautions

Safety of *DTaP* based *penta*- and *hexavlent* vaccines approved for use in Canada has been studied in several studies. Incidence of solicited reports of systemic reactions following any dose of *Pentacel®*; *Pediacel®*; *Infanrix™-IPV/Hib* ; and *Infanrix™-hexa* published in peer reviewed journals are presented in table 7.

Incidence of solicited reports of local reactions following any dose of *Pediacel®*; *Infanrix™-IPV/Hib* ; and *Infanrix™-hexa* are presented in Table 8 .

For summary results/comparisons by vaccine manufacturer P*entacel®/Pediacel®* versus *Infanrix™* see tables 9 and 10.

Table 7. Incidence of Solicited Reports of Systemic Reactions Following Any Dose of Pentacel® (Sanofi Pasteur); Pediacel® (Sanofi Pasteur); Infanrix™-IPV/Hib (GSK); and Infanrix™-hexa (GSK)

Vaccine/ Reference	Vaccine schedule	Vaccine Doses	Fever (%)		Restlessness/ Unusual crying	Decreased appetite	Drowsiness	Fussiness
			≥ 38°C	≥ 39.5°C	(%)	(%)	(%)	(%)
Primary vaccination								
Pentacel; Halperin S, 2002, Canada	2, 4, 6 months of age	527	9.7	N/A	39.0	16.3	N/A	N/A
Pediacel; Kitchin N, 2006, UK	2, 3, 4 months of age	361	0.6 *(11.6% >37.5C)*	0.0	48.5	25.8	22.7	N/A
Pediacel Lin TY, 2005, Taiwan	2, 4, 6 months of age	300	7	0.0	18.7	23.3	12.3	14.3
Infanrix-IPV/*Hib*; Schmitt HJ, 2003, Germany	2, 3, 4 months of age	324	27.0	2.5*	N/A	9.3	22.5	23.5
Infanrix-IPV/*Hib*; Dagan R, 1997, Israel	2, 4, 6 months of age	286	22	1.4	28	15	N/A	N/A
Infanrix-IPV/*Hib*; Aristegui J, 2003, Spain	2, 4, 6 months of age	345	12.2	0.3	32.8	21.4	29.0	N/A
Infanrix-hexa; Knuf M, 2006, Germany	2, 3, 4 months of age	359-368	22	2.5*	N/A	13	22.7	27.1
Infanrix-hexa; Tichmann-Schuman, 2005,	2, 3, 4 months of age	494	23.4	0.2	N/A	17.6	34.1	28.8

Vaccine/ Reference	Vaccine schedule	Vaccine Doses	Fever (%)		Restlessness/ Unusual crying	Decreased appetite	Drowsiness	Fussiness
			≥ 38°C	≥ 39.5°C	(%)	(%)	(%)	(%)
Germany								
Infanrix-hexa; Schmitt HJ, 2000, Germany	2, 3, 4 months of age	537	17.7	0.4	22.8	N/A	22.8	19.2
Infanrix-hexa; Zepp F, 2004, Germany	3, 4, 5 months of age	1665	23	0.5	31	19	39	N/A
Infanrix-hexa; Aristegui J, 2003, Spain	2, 4, 6 months of age	360	21.1	0.0	39.7	25.3	27.5	N/A
Infanrix-hexa; Tejedor JC, 2004, Spain	2, 4, 6 months of age	705	16.2	0.3	N/A	20.6	24.1	31.6
Infanrix-hexa; Omenaca F, 2005, Spain	2, 4, 6 months of age	828	12.0	0.0	17.4	14.5	19.2	N/A
Infanrix-hexa; Tichmann I, 2006, Germany	2, 4, 6 months of age	673	4.8 (>38.5C)	0.0	N/A	0.6	0.9	N/A
Infanrix-hexa; Gabutti G, 2004, Italy and Germany	3, 5, 11 months of age	531	29.3	0.9	N/A	18.1	25.8	29.8
Infanrix-hexa; Avdicova M, 2002, Slovakia	3, 5, 11 months of age	464	11.0	0.2	14.4	N/A	N/A	17.5
Booster								
Pentacel; Halperin	15-20 months of	642	11.0	1.0	63	43	13.8	N/A

Vaccine/ Reference	Vaccine schedule	Vaccine Doses	Fever (%)		Restlessness/ Unusual crying	Decreased appetite	Drowsiness	Fussiness
			≥ 38°C	≥ 39.5°C	(%)	(%)	(%)	(%)
SA, 2006, Canada	age							
Infanrix-IPV/*Hib*; Halperin SA, 2006, Canada	15-20 months of age	648	12.0	0.0	63	40	7.4	N/A
Infanrix-IPV/*Hib*; Schmitt HJ, 2003, Germany	Booster 11-15 months of age	81	46.9	8.9*	N/A	13.6	19.8	29.6
Infanrix-IPV/*Hib*; Dagan R, 1997, Israel	Booster 12 months of age	92	16	2.2	25	15	N/A	N/A
Infanrix-hexa; Tichmann-Schuman, 2005, Germany	11-14 months of age	121	38.8	1.7	24.8	N/A	31.4	31.4
Infanrix-hexa; Saenger R, 2005, Germany[76]	12-24 months of age	221	40.7	5.4	39.8	26.7	33.0	N/A
Infanrix-hexa; Knuf M, 2006, Germany	12-15	108-110	33.6	2.7	N/A	16.7	10.5	19.1
Infanrix-hexa; Saenger R, 2005, Germany[76]	12-24 months of age	685	42.2	3.6	34.7	28.5	33.7	N/A

*39.1C

Table 8. Incidence of Solicited Reports of Local Reactions Following Any dose of Pentacel® (Sanofi Pasteur); Pediacel® (Sanofi Pasteur); Infanrix™-IPV/Hib (GSK); and Infanrix™-hexa (GSK)

Vaccine/ Reference	Vaccine schedule	Vaccine Doses	Pain/ Tenderness (%)		Redness (%)		Swelling(%)	
			Any	Severe	Any	Severe	Any	Severe
Pentacel; Scheifele D, 2006, Canada	2, 4, 6 months of age	369	23.7	N/A	23.8	0.5	28.3	0.3
Pentacel; Halperin S, 2002, Canada	2, 4, 6 months of age	527	8.3	0.0	16.3	1.0	18.0	0.7
Pediacel; Kitchin N, 2006, UK	2, 3, 4 months of age	361	18.0	1.4	37.9	4.4	24.7	4.4
Pediacel Lin TY, 2005, Taiwan	2, 4, 6 months of age	300	6.7	0.3	14.7	0.3	10.7	0.0
Infanrix-IPV/*Hib*; Schmitt HJ, 2003, Germany	2, 3, 4 months of age	324	7.3	2.2	14.0	0.3	5.7	0.3
Infanrix-IPV/*Hib*; Aristegui J, 2003, Spain	2, 4, 6 months of age	345	16.8	1.2	20.9	0.3	15.1	0.9
Infanrix-IPV/*Hib*; Dagan R, 1997, Israel	2, 4, 6 months of age	286	15	0	9	1.7	9	2.4
Infanrix-hexa; Knuf M, 2006, Germany	2, 3, 4 months of age	359-368	16.5	1.4	27.8	2.2	10.3	2.2
Infanrix-hexa; Tichmann-Schuman, 2005, Germany	2, 3, 4 months of age	494	14.3	0.6	33.2	1.8	18.0	2.6

Vaccine/ Reference	Vaccine schedule	Vaccine Doses	Pain/ Tenderness (%)		Redness (%)		Swelling(%)	
			Any	Severe	Any	Severe	Any	Severe
Infanrix-hexa; Schmitt HJ, 2000, Germany	2, 3, 4 months of age	537	24	1.1	43	3.9	36.9	5.6
Infanrix-hexa; Zepp F, 2004, Germany	3, 4, 5 months of age	1665	19	1.0	43	2.0	26	2.6
Infanrix-hexa; Tichmann I, 2006, Germany	2, 4, 6 months of age	647	N/A	0.9	N/A	3.9	N/A	6.1
Infanrix-hexa; Omenaca F, 2005, Spain	2, 4, 6 months of age	828	17.8	0.0	13.0	0.0	12.7	1.4
Infanrix-hexa; Tejedor JC, 2004, Spain	2, 4, 6 months of age	705	19.4	0.9	33	4.0	23.4	4.3
Infanrix-hexa; Aristegui J, 2003, Spain	2, 4, 6 months of age	359	22.6	2.5	30.4	1.1	22.6	1.4
Infanrix-hexa; Gabutti G, 2004, Italy and Germany	3, 5, 11 months of age	531	18.7	1.6	26.4	3.8	22.4	4.1
Infanrix-hexa; Avdicova M, 2002, Slovakia	3, 5, 11 months of age	464	19.2	0.4	31.9	3.0	17.5	3.2

Vaccine/ Reference	Vaccine schedule	Vaccine Doses	Pain/ Tenderness (%)		Redness (%)		Swelling(%)	
			Any	Severe	Any	Severe	Any	Severe
Booster								
Pentacel; Halperin SA, 2006, Canada	15-20 months of age	642	52.1	6.9	11.5	3.0	27	2.0
Infanrix-IPV/*Hib*; Halperin SA, 2006, Canada	15-20 months of age	648	39.4	1.4	5.6	1.0	28	1.0
Infanrix-IPV/*Hib*; Saenger R, 2005, Germany	12-24 months of age	221	29.4	4.5	43.4	10.9	27.1	11.8*
Infanrix-IPV/*Hib*; Schmitt HJ, 2003, Germany	11-15 months of age	91	21.1	8.9	28.6	5.5	12.1	4.4*
Infanrix-IPV/*Hib*; Dagan R, 1997, Israel	12 months of age	92	9	1.1	15	5.4	15	1.1
Infanrix-hexa; Knuf M, 2006, Germany	12-15 months of age	108-110	23.9	1.1	37.6	10.1	17.6	3.7
Infanrix-hexa; Tichmann-Schuman, 2005, Germany	11-14 months of age	121	22.3	1.7	38.0	2.5	29.8	2.5
Infanrix-hexa; Saenger R, 2005, Germany	12-24 months of age	685	31.2	6.4	48.2	8.8	30.7	8.6*

* >2 0 mm

Table 9. Incidence of systemic and local reactions by vaccine manufacturer/primary vaccination series:

	Pentacel-Pediacel	**Infanrix**
	3 studies[8 9 11]	**13 studies**[12-24]
Fever >38ºC	0.6%-10.3%	11.0%-29.3%
Fever >39ºC or >39.5ºC	0.0%-1.2%	0.0%-1.4%
	18.7%-48.5%	14.4%-39.7%
Restlessness/Unusual crying		
	16.3%-25.8%	0.6%-25.3%
Decreased appetite	12.3%-22.7%	0.9%-39%
Drowsiness	14.3%	17.5%-31.6%
Fussiness		
Incidence of local reactions	**4 studies**[6 8 9 11]	**13 studies**[12-24]
Pain		
- Any	8.3%-23.7%	7.3%-24.0%
- Severe	0.0%-1.4%	0.0%-2.5%
Redness		
- Any	14.7%-37.9%	9.0%-43.0%
- Severe	0.3%-4.4%	0.0%-4.0%
Swelling		
- Any	10.7%-28.3%	5.7%-36.9%
- Severe	0.0%-4.4%	0.3%-6.1%

Pentacel® -Pediacel® Vaccines

Lower incidence of fever but higher incidence of unusual crying was observed in the study using a 2, 3, and 4 months schedule compared to a 2, 4, and 6 months schedule.

Higher incidence of severe local reactions was reported in the study with a 2, 3, and 4 months schedule compared to studies using a 2, 4, and 6 months schedule.

Infanrix™ Vaccines

Higher incidence of fever was observed in studies where either a 2, 3, and 4 months or a 3, 5, and 11 months schedule was used, compared to a 2, 4, and 6 months schedule.

Pentacel® and Pediacel® versus Infanrix™-IPV-HIB and Infanrix™-hexa

No head-to-head studies are available. Only three studies have been conducted with the *Pentacel®-Pediacel®* family. The only potential difference between the two vaccine families was the higher incidence of fever >=38C reported with *Infanrix*™ vaccines. However, this higher incidence was due to studies conducted with a 2, 3, and 4 months or 3, 5, and 11 months schedule.

Booster vaccination:

Table 10. Incidence of systemic and local reactions by vaccine manufacturer/booster vaccination:

Incidence of systemic reactions:	**Pentacel®**	**Infanrix™**
	1 study[25]	**7 studies**[12 14 16 22-25]
Fever >38 C	11%	12%-46.9%
Fever >39.5 C	1.0%	0.0%-5.4%
Restlessness/Unusual crying	63%	24.8%-63.0%
Decreased appetite	43%	13.6%-40.0%
Drowsiness	13.8%	7.4%-33.7%
Fussiness	N/A	19.1%-31.4%
Incidence of local reactions	1 study[25]	7 studies[12 14 16 22-25]
Pain		
- Any	52.1%	9.0%-39.4%
- Severe	6.9%	1.1%-8.9%
Redness		
- Any	11.5%	5.6%-48.2%
- Severe	3.0%	1.0%-10.9%
Swelling		
- Any	27.0%	12.1%-30.7%
- Severe	2.0%	1.0%-3.7%

A tendency to higher incidence of systemic and local reactions was observed after booster doses compared to primary vaccination series.

Higher incidence of fever >=38 C was observed in *Infanrix™* studies compared to *Pentacel®* study and, vice versa, the incidence of pain was higher in those receiving *Pentacel®* compared with those receiving *Infanrix™*.
It should be mentioned that only one booster study with *Pentacel®* was retrieved versus seven with *Infanrix™* and no conclusions may be driven from these comparisons.

11 Potential interaction with other vaccines

In many countries *DTaP* combined vaccines are given concurrently with pneumococcal conjugate and/or meningococcal conjugate, and /or hepatitis B vaccine. Potential interaction of *DTaP* based *penta*- and *hexavalent* vaccine with three above mentioned vaccines has been studied in several clinical trials (Table 11).

Table 11. Immunogenicity of penta- and hexavalent vaccines when <u>coadministrated</u> with pneumococcal or pneumococcal and hepatitis B vaccines, or administered separately

Antibody	SP/ VR rates (%)		GMCs/ GMTs	
	Co-administered	Separate administration	Co-administered	Separate administration
Schmitt H.J, 2003, Germany, Infanrix-IPV/*Hib* coadministered at 2, 3, 4, and 11-15 months with Prevnar; or Prevnar given separately at 6, 7, 8, and 11-15 months of age	N=83	N=75	N=83/61*	N=75/48*
Anti-diphtheria ≥0.1 IU/mL	99	97	1.15/3.95¶	0.61/3.35
Anti-tetanus ≥0.1 IU/mL	100	100	3.79/8.11	4.44/9.69
Anti-polio 1	100	100	242/N/A	289/N/A
Anti-polio 2	100	100	234/N/A	282/N/A
Anti-polio 3	100	100	558/N/A	682/N/A
Ant-PRP			1.68/16.2	1.94/18.2
≥0.15 µg/ml	99	96		
≥1.0 µg/ml	66	67		
Anti-PT	84	92	37.8/57.4	44.3/68.7
Anti-FHA	69	77	60.6/219	67.5/256
Anti-PRN	80	96	139/387	236/526¶
Tichmann-Schumann I, 2004, Germany, Infanrix-hexa coadministered at 2, 3, 4, and 12-23 months with Prevnar; or Infanrix-hexa alone	N=141/128*	N=138/114*	N=141/128*	N=138/114*
Anti-diphtheria ≥0.1 IU/mL	100/100	100/100	2.34*/8.46	1.43/6.91
Anti-tetanus ≥0.1 IU/mL	100/100	100/100	1.39/4.80	1.71/6.81
Anti-polio 1	100/100	100/100	255/1371	262/1977
Anti-polio 2	99.3/100	98.4/100	141/1430	165/2136
Anti-polio 3	100/100	99.2/100	561/2427	581/3697
Ant-PRP			1.59/35.6	2.27/47.66
≥0.15 µg/ml	93.6/100	95.7/100		
≥1.0 µg/ml	57.4/96.8	75.4/99.1		
Anti-PT	98.6/100	98.2/98.2	44.3/73.4	51.7/100
Anti-FHA	94.8/96.8	97.8/98.2	141/459	142/521
Anti-PRN	95.0/98.4	97.8/99.1	119/344	150/504
Anti-HBs	97.9/96.8	97.8-99.1	378/3809	462/5754

Antibody	SP/ VR rates (%)		GMCs/ GMTs	
	Co-administered	Separate administration	Co-administered	Separate administration
Knuf M, 2006, Germany, Infanrix-hexa coadministered at 2, 3, 4, and 12-15 months with Prevnar; or Infanrix-hexa alone + Prevnar at 5, 6, 7, and 12-16 months	N=115/106*	N=111/106*	N=115/106*	N=111/106*
Anti-diphtheria ≥0.1 IU/mL	100/100	99.1/100	0.15/7.41	0.09/5.78
Anti-tetanus ≥0.1 IU/mL	100/100	100/100	2.70/8.09	3.57/8.97
Anti-polio 1	100/100	100/100	198/870	299/1153
Anti-polio 2	99.3/100	98.4/100	207/1439	325/1783
Anti-polio 3	100/100	99.2/100	782/2201	927/2276
Ant-PRP			1.16/11.4	1.16/13.2
≥0.15 µg/ml	93.9/100	91.0/100		
≥1.0 µg/ml	58.3/95.2	60.4/94.3		
Anti-PT†	92.1/78.6	89.2/78.9	46.5/71.3	52.9/77.9
Anti-FHA†	71.9/84.8	74.8/77.9	75.6/165.6	86.6/171
Anti-PRN†	86.7/94.3	91.8/95.2	193.8/542	244/664
Anti-HBs	96.4/99.0	99.1/100	405/4523	439/6539
Scheifele W.D, 2006, Canada, Pentacel and Recombivax-HB (5µg) coadministered with Prevnar at 2, 4, 6 months or Prevnar given sequentially at 3, 5, and 7 months‡	For all groups N=124-126			
Anti-diphtheria ≥0.1 IU/mL	100	100	2.55	5.64*
Anti-tetanus ≥0.1 IU/mL	100	100	1.3	0.94
Anti-polio 1	83.8	85.0	35.8	40.8
Anti-polio 2	87.4	92.5	62.4	54.9
Anti-polio 3	85.6	91.7	61.3	77.4
Ant-PRP			1.11	0.64*
≥0.15 µg/ml	84.3	77.7		
≥1.0 µg/ml	59.5*	43.0		
Anti-PT†	74.2	80.2	29.5	26.0
Anti-FHA†	64.2	57.0	39.3	40.9
Anti-PRN†	77.5	77.7	28.3	23.3
Anti-HBs	87.2	91.7	75.3	169*

* after the third dose/after the fourth dose; ¶ $p<0.05$; † >4 fold rise; ‡ in this study some blood samples were drawn 8 weeks after the third dose administration, that may explain observed lower seroprotection rates and GMCs compared to other studies.

Schmitt et al.[12] compared concurrent administration of *Infanrix™-IPV-Hib* and *Prevnar®* vaccines at age of 2, 3, 4 and 11-15 months with *Infanrix™-IPV-Hib* vaccine at the same age plus *Prevnar®* "catch-up vaccination" at age 6, 7, 8 and 11-15 months (control group). Authors found that a significant immunological response to all pneumococcal serotypes was elicited by the conjugate vaccine when given concurrently and in isolation *(it should be noted that no consensus on seroprotection to pneumococcal serotypes exists)*. However, a comparison between the two groups is not appropriate since they received primary immunization at different ages. For the *DTaP-IPV-Hib* components GMCs were comparable between two groups, except for diphtheria and PRN. Diphtheria antibody concentrations were higher in the group with concurrent vaccines administration; PRN antibody concentrations were higher in the control group.

A higher percentage of infants experienced increased drowsiness, fever and used antipyretic medication after dose one in the group with concurrent administration of two vaccines compared to the control group. The frequency of all other systematic reactions after each dose of the primary immunization series was similar in both groups. After the booster dose children experienced fever >39 C more frequently (concurrent administration 8.3%, control group: 8.9%) compared to doses 2 and 3. The author's main conclusion is that the *Prevnar ®* vaccine was safe, well tolerated and highly immunogenic when concomitantly administered with a five component *Infanrix™* vaccine and there were no clinically relevant interactions.

In Tichmann-Schumann et al. study[17] the immunogenicity and safety of *Infanrix™-hexa* and *Prevnar®*® when coadministered at 2, 3 and 4 months and 12-23 months of age compared with the administration of the *Infanrix™-hexa* given alone were compared. Immunogenicity analysis yielded similar results in two groups. Pre-established criteria for non-inferiority were met for all antigens.
All vaccinees in both groups who were seronegative for pertussis antibodies before vaccination responded to vaccination. The concurrent administration of *Prevnar®* vaccine resulted in higher *antidiphtheria* antibody GMC compared to *Infanrix™* given alone (2.34 vs. 1.42 IU/mL, P<0.05). Post-primary GMCs/GMTs for antibodies against all other common antigens were similar in the two groups. In the concomitant vaccination group, 97.2%-100% of vaccinees exhibited a post-dose 3 IgG antibody concentration ≥0.05 µg/ml against each of the 7 pneumococcal serotypes. Antibodies before the *Prevnar®* booster dose were similar in both groups.

The fourth dose induced a vigorous booster response with seroprotection/seropositivity rates to all antigens ranging from 96.8% to 100% in the 2 groups. All subjects in both groups exhibited anti-PRP antibody concentrations ≥0.15µg/ml and at least 96.8% had anti-PRP antibody concentrations ≥1.0 µg/ml. The co-administered *Prevnar®* vaccine booster

elicited at least a 5-fold increase in GMC of antibodies against the 7 pneumococcal serotypes.

Higher local reactogenicity was observed for all doses after concomitant administration of the *Infanrix™-hexa* and *Prevnar®* as compared with the administration of the *Infanrix™-hexa* alone. However, these differences reached statistical significance only for swelling after the first dose and injection site pain or any local redness and redness >20 mm after the booster dose (P<0.05). Authors mention that *Prevnar*® injection site reactions were as frequent as the *Infanrix™-hexa* injection site reactions and present only the cumulative incidence of local reaction for *Infanrix™-hexa + Prevnar*®. The number of primary doses followed by local symptoms with grade 3 intensity remained low (0.6-11.6%). In general, solicited local symptoms were reported more frequently after the booster dose.
The co-administration of the vaccines resulted in overall increased incidence of solicited general symptoms compared with the *hexavalent* vaccine alone. The most important increase was observed for fever (P<0.05). The increase in fever of >39 C was not statistically significant. The unsolicited symptoms reported during the 31-day follow-up period after each dose were those usually seen in paediatric population with similar frequencies reported in the 2 study groups. None of the 8 serious adverse events were determined by investigator to be related to vaccination. The author's main conclusion was that the effectiveness and safety of the concomitant administration of the *Infanrix™-hexa* and the *Prevnar®* vaccines enables vaccination against 7 significant childhood diseases without increasing the number of clinic visits.

Knuf et al. [16], reported no statistical differences between treatment groups regarding the percentage of subjects achieving predefined post-dose 3 antibody levels for all vaccine antigens, with the exception of diphtheria. The percentage of subjects in the concomitant administration group having achieved a diphtheria antibody level of ≥0.1 IU/mL was significantly higher compared to the control group (59% vs. 40%, p=0.004). A statistically significant increase in GMCs was seen for all seven serotypes of antigens included in *Prevnar®*. After dose three, 98.3% (serotypes 9V and 23F) to 100% (serotypes 4, 6B, 14, 18C and 19F) of subjects achieved pneumococcal antibody concentration ≥0.15 µg/mL, and 92.1% to 99.1% of subjects achieved concentrations ≥0.5 µg/mL after the booster dose. There were no statistically significant differences between the two groups regarding local reactions. The percentage of infants with any systematic reaction after dose 1 was significantly higher in the group with concurrent administration of the *Prevnar®* (64%) than in the control group (48%), mainly due to a higher rate of sleepiness.

No statistically significant difference was seen after doses 2 and 3, except decreased appetite after dose 3, which was significantly higher in the group with

concurrent administration of two vaccines. After dose 4, the presence of any event occurred more frequently in the group with concurrent administration of two vaccines. Intake of antipyretic medication was reported with a frequency between 6.0% and 18.9% and was significantly higher in the group with concurrent administration of two vaccines after dose 2 and dose 4. The overall frequency of subjects with adverse events was similar between vaccination groups during primary immunization. The author's main conclusion is that overall both study vaccines were highly immunogenic, well tolerated and safe when concurrently administered. *Prevnar®* did not show any clinically relevant influence on the immunogenicity and safety of the concurrently administered *Infanrix™-hexa*.

Scheifele et al.[8] phase 4 study was a randomized, controlled trial with evaluator blinding, to compare concurrent versus non-concurrent vaccination of infants. There were no statistically significant differences in antibody responses between groups for any of the seven pneumococcal serotypes. Eight weeks following series completion, GMCs were comparable between groups for all four (FIM2&3 are presented together in all retrieved studies) pertussis antigens, poliovirus types 1-3 and tetanus antitoxin.

Sequentially vaccinated subjects had significantly higher antibody levels to diphtheria toxin (P<0.001) and hepatitis B surface antigen (P=0.006) compared with concurrently vaccinated subjects. Conversely, in sequentially vaccinated subjects a significantly lower anti-PRP GMC was observed when compared to concurrently vaccinated subjects (P=0.008). Significantly fewer subjects in concurrently vaccinated group had antibody levels to HBsAg $\geq$10 mIU/mL whereas significantly fewer subjects in sequential group had anti-PRP levels $\geq$1.0 µg/mL. The proportions with anti-PRP levels $\geq$0.15 µg/mL did not differ significantly between groups. Lower general responses in this study compared to many other studies seem to be related to longer intervals between vaccination and blood sampling (8 weeks versus 4 weeks in other studies). Subjects given all three vaccines concurrently did not have higher rates of significant adverse events during 3 days after vaccination compared to those given only *Pentacel®* and HBV vaccines for any of the three vaccination visits. Giving *Pentacel®* and HBV vaccines in the same thigh but in different sites resulted in higher rates of local reactions than giving either vaccine alone. The authors concluded that *Prevnar®* and *DTaP-IPV/Hib* vaccines were mutually comparable, causing no diminution of responses with concurrent administration. Adjacent administration of HBV and *Pentacelr®* in the same thigh is the likely explanation for reduced responses to HBV, pointing to the uncertainties introduced with adjacent injections and the desirability of avoiding them through the use of combination vaccines that include hepatitis B. It should be noted that in studies with *Hexavac®*, but not with *Infanrix™-hexa*, the same tendency to lower immungenicity for hepatitis B vaccine was observed.

In summary, no clinically important interactions were observed when *DTaP-IPV/Hib* or *Infanrix™-hexa* were administered concurrently with *Prevnar®*. The administration of *Pentacel®* and hepatitis B vaccine in the same thigh might result in higher rates of local reactions and lower immunogenicty of HBV vaccine compared to vaccines given alone.

Table 12. Immunogenicity of penta- and hexavalent vaccines when <u>coadministrated</u> with meningococcal vaccines, or administered separately

Antibody	**SP/ VR rates (%)**		**GMCs/ GMTs**	
Halperin S.A, 2002, Canada, Pentacel given at 2, 4, 6 and 15-18 either with Engerix-B or Menjugate vaccine;	Pentacel + Menjugate N= 157-170	Pentacel + Engerix-B N=168-174	Pentacel + Menjugate N= 157-170	Pentacel + Engerix-B N=168-174
Anti-diphtheria ≥0.1 IU/mL	100	100	4.7*	1.9
Anti-tetanus ≥0.1 IU/mL	100	100	2.4	2.5
Anti-polio 1	N/A	N/A	97	95
Anti-polio 2	N/A	N/A	98	100
Anti-polio 3	N/A	N/A	98	98
Ant-PRP	81	83	3.1	3.7
Anti-PT	N/A	N/A	23	25
Anti-FHA	N/A	N/A	26	31
Anti-PRN	N/A	N/A	31	36
Anti Men C bactericidal	N/A	N/A	232/1344[†]	2/2.1
Meningococcal C by ELISA	N/A	N/A	10/34	0.21/0.21
Tejador J.C, 2004, Spain, Infanrix-hexa and meningococcal C conjugate vaccines (Meningitec) given during the same visit at 2, 4, and 6 months with Prevnar; or meningococcal C conjugate vaccine given separately at 3, 5, and 7 months	Infanrix-hexa + Men C N=192-228	Separate administration of Men C conjugate vaccine N=195-224	Infanrix-hexa + Men C N=192-228	Separate administration of Men C conjugate vaccine N=195-224
Anti-diphtheria ≥0.1 IU/mL	100	100	3.67	9.62*
Anti-tetanus ≥0.1 IU/mL	100	100	2.41	1.97
Anti-polio 1	100	100	870	732
Anti-polio 2	100	99.5	635	530
Anti-polio 3	99.5	99.5	1487	1172
Ant-PRP			4.70	4.38
≥0.15 µg/ml	99.1	99.1		
≥1.0 µg/ml	85.1	81.7		
Anti-PT	100	99.1	58.8	52.2
Anti-FHA	99.1	99.5	295	245
Anti-PRN	100	100	162	161

Antibody	**SP/ VR rates (%)**		**GMCs/ GMTs**	
Anti-HBs	97.8	99.1	1013	1108
Anti Men C			1373	2257*
>=1/8	99.5	100		
>=1/128	99.1	99.5		
Anti-PSC			25.3	55.5*
0.3 µg/mL	100	100		
2 µg/mL	100	100		
Kitchin N, 2006, UK, Pediacel coadministered at 2, 3, 4, months with MCC-TT (NeisVac-C) or MCC-CRM (Menjugate)	Pediacel + MCC-TT N=51-53	Pediacel + MCC-CRM N=49-50	Pediacel + MCC-TT N=51-53	Pediacel +MCC-CRM N=49-50
Anti-diphtheria ≥0.1 IU/mL	98.1	100	0.04	0.10*
Anti-tetanus ≥0.1 IU/mL	100	100	1.96	1.3
Anti-polio 1[¶]	100		372	
Anti-polio 2[¶]	100		735	
Anti-polio 3[¶]	97.9		1077	
Ant-PRP (ELISA)			5.17*	2.17
≥0.15 µg/ml	94.2	87.8		
≥1.0 µg/ml	90.4	69.4		
Anti-PT[¶]	N/A		78.7	
Anti-FHA[¶]	N/A		51.9	
Anti-PRN[¶]	N/A		32.7	
FIM[¶]	N/A		279	
Anti-Men C (% >=1:8)	98	100	690	2165*

[†] results after the third dose/results after the fourth dose; [*] $p<0.005$; [¶] results by subgroup are not available

Halperin et al.[9] demonstrated that a protective (>=1:8) bactericidal antibody level was achieved in 99% of the meningococcal C conjugate (MenC) recipients after the first 2 doses and 100% after 3-dose primary series. Before the booster injection, 74% had maintained protective levels; all achieved a protective titer after the booster. In this study, Men C or HBV were administered as an intramuscular injection of 0.5 mL into the right thigh (2, 4, 6 months) or deltoid (15-18 months). No differences in GMTs or the proportion achieving protective levels were found for tetanus toxoid, pertussis antigens, Hib, or polioviruses 1, 2, and 3. Recipients of MenC had a higher GMC diphtheria antibody titer (4.7 IU/mL) than HBV recipients (1.9 IU/mL), likely the result of the diphtheria toxoid carrier used in the MenC vaccine. In all study participants, vaccines were well tolerated. Only persistent crying was reported more frequently with the booster dose of MenC (3%) than HBV (0%) (P=0.026). The author's main conclusion is

that the administration of the MenC vaccine at the same time as the first 4 doses of the *Pentacel®* vaccine does not adversely affect the antibody response to the antigens contained in either vaccine.

Tejador et al.[20] reported that the immune response elicited by the PRP antigen was similar in both groups. The upper limit of the 95% CI for the difference in seroprotection rates between both groups was below the predefined 10% limit for noninferiority for diphtheria, tetanus, hepatitis and polioviruses 1, 2, and 3. The vaccine response to pertussis antigens, 1 month after the third dose of the *Infanrix™-hexa* vaccine, was at least 99.1% in both groups. The GMCs for PT and PRN antibodies were similar in both groups, whereas the FHA antibody GMC was 1.2-fold higher in the coadministration group than in the group that received the vaccines separately. Two months after the second dose of the MenC vaccine, almost all subjects in both groups had seroprotective SBA MenC titres ($\geq$1/8) and were seropositvie for anti-PSC antibodies. One month after the third MenC vaccine dose, at least 99.5% of subjects in both groups achieved a SBA MenC titer $\geq$1/8, and at least 99.1% of subjects in both groups achieved a SBA MenC titer $\geq$1/128. Coadministration of vaccines did not result in increased reactogenicity. The authors' main conclusion was that coadministration of *Infanrix™-hexa* vaccine and the meningococcal C conjugate vaccine is well-tolerated and safe and does not impair the immunogenicity of either vaccine.

Kitchin et al.[10] reported a study with *Pediacel®* and *DTwP/Hib* when administered each with one of two different meningococcal group C conjugate vaccines at 2, 3, and 4 months of age. Post-vaccination the proportion of subjects with anti-PRP ≥0.15 µg/mL was 93.2% (95% CI 86.6-96.7) in the *Pediacel®* group compared to 100% (95% CI 96.4-100) in the *DTwP/Hib* group. The anti-PRP response was lower in subjects receiving either *Pediacel®* or *DTwP/Hib* when these vaccines were given concomitantly with meningococcal serogroup C conjugate vaccine, employing diphtheria-derived protein as conjugate (MCC-CRM) compared with the same vaccine employing tetanus toxoid as the conjugate (MCC-TT). The Men C SBA GMT was lower in those receiving *Pediacel®* with MCC-TT compared to those receiving *DTwP/Hib* and MCC-CRM. Responses to all other vaccine components were equivalent in the two groups. It is not clear whether these differences have any clinical significance. The authors' main conclusion was that *Pediacel®* is immunogenic when administered at 2, 3, and 4 months of age. Co-administration with MCC-CRM negatively influenced the Hib response and *Pediacel®* co-administration with MCC-TT vaccine negatively influenced the MCC responses.

12 Potential impact of immunization program on resistance to antibiotics and antivirals

Due to the relatively common characteristics of the immune response to the *DTaP* based vaccines approved for use in Canada, no differences on potential impact on resistance to antibiotics and antivirals are likely to be seen from moving from one vaccine to another one. Existing clinical trial and field studies did not show any clinically important impact of immunization programs with the four vaccines of interest on resistance to antibiotics or antivirals.

SUMMARY

The systematic search of MEDLINE and EMBASE permitted to detect an important number of publications containing key words of interest. However, no head-to-head studies with *Pentacel®/Pediacel®* versus Infanrix™ primary series and no head to head booster studies in children who had received all their doses with the same vaccine are available. The number of reported studies with *Pentacel®/Pediacel®* vaccines was relatively small compared to *Infanrix™* vaccines.

The nature and characteristics of immunizing agents in *Pentacel®/Pediacel®* and *Infanrix™* vaccines, although different, have many common qualitative and quantitative components and characteristics. Both companies, Sanofi Pasteur and GSK, are international long term vaccine manufacturers with important production capacity. However, because of production problems experienced with some vaccines (e.g. *Pentacel®, Prevnar®, Influenza*), currently many countries (e.g. EU countries, USA, Australia) have two or more suppliers for the same vaccine (see same infections).

Two vaccines, *Pediacel®* and *Infanrix™-hexa*, have logistical and operational advantages compared to the other two vaccines. *Pediacel®* is pre-mixed by manufacturer vaccine and from operational perspectives will exclude any error during vaccine mixing and will save some vaccine administration related time. *Infanrix™-hexa* contains *HBV* antigen and, if used in infants, would reduce by 3 the number of injections related to immunization in provinces and territories with an infant hepatitis B program, with the potential to abolish school-based *HBV* vaccination program several years later.

Several different schedules of *penta-* and *hexavalent* vaccines were tested in clinical trials. Taking into consideration current epidemiology of these infections in Canada and safety and immunogenicity clinical trials' data, the schedule in use with the vaccine given at the age of 2, 4, 6 months, with a booster dose at 12-23 months appears to be the most appropriate. The 3, 5, 11 months schedule is very attractive. However, additional epidemiological data analyses are needed before making conclusions about its acceptability in the Canadian context.

No important differences in immune response to diphtheria, tetanus, poliovirus 1, 2 and 3, were observed between *Pentacel®/Pediacel®* and *Infanrix™* vaccines. The anti-PRP response seems to be associated more with age and schedule of vaccine administration than with the type of vaccine. Some short time increase in Hib disease incidence was reported in some regions and populations when switching from one Hib vaccine to another one or from *DTwP* to *DTaP* coadministered with Hib vaccine. No different effectiveness against Hib infection

when comparing *Pentacel®* versus *Infanrix™* or switching from one to another was reported by any country using four-dose schedules. Existing epidemiological data do not confirm a lower protection against Hib infection with a combined vaccine given in four-dose schedule compared to separately administered Hib vaccine or higher effectiveness of Hib vaccine when administered with a five- or three-component *acellular pertussis* vaccine, despite differences in reported immunogenicity.

The immune response (GMTs) to hepatitis B vaccine component was higher after *Infanrix™-hexa* when compared to separate administration of *Pentacel®* and *Recombivax®-HB* vaccine. Higher anti-HBs GMTs with *Engerix™-B* (component part of *Infanrix™-hexa*) compared to *Recombivax®-HB* vaccine is reported in numerous other studies with monovalent *HBV* vaccine.

The response to pertussis remains difficult for interpretation because no consensus on the protective antibodies level and the role of different types of antibodies in protection against disease exists. The response to pertussis in clinical trials is differently interpreted, the number of antigens varies depending on vaccine manufacturer, and the response to PT, FHA and PRN has different amplitudes depending on vaccine used. Thus, existing epidemiological data do not permit conclusions to be made about the higher effectiveness of one or another vaccine of interest. Nevertheless, consistently high response to all pertussis vaccine antigens was observed after the booster vaccination during the second year of life independently of the vaccine used during primary series or booster administration.

Penta- and *hexa-* vaccines can be administered to pre-term children without impairing their immune response. Conflicting results were found for Hib response in premature infants, the clinical significance of which is unclear.

No changes in currently recommended schedule or vaccine seem to be needed for aboriginal infants. Nevertheless, the need of timely vaccination and high immunization coverage should be continually addressed for preventing invasive Hib infection.

Both vaccines families *Pentacel®/Pediacel®* and *Infanrix™* have been used since the mid nineties in different countries and have demonstrated a good effectiveness in the reduction of diseases and death risk.

More long-term effectiveness data are needed to make conclusions concerning possible differences between *Pentacel®/Pediacel®* and *Infanrix™* vaccines. Both manufacturer's vaccines, *Pentacel®/Pediacel®* and *Infanrix™* , have shown an important impact on the transmission of related organisms and reduction of Hib carriage without clinically important organisms' replacement.

With respect to vaccine safety, to date, no clinical trials demonstrating lower safety profile of one vaccine when compared to another one exists.

DTaP based vaccines might be concurrently administered with other vaccines used in infancy without important interaction when administered in different sites.

There is no evidence of impact of any of the analysed vaccines on resistance to antibiotics or antivirals.

CONCLUSIONS

1) All four *penta* - and *hexavalent DTaP* based vaccines approved for use in Canada were reported as well-tolerated and immunogenic in numerous clinical trials conducted in different countries since the mid-nineties.
2) Currently available data do not confirm any clinically important differences between *Pentacel®/Pediacel®* and *Infanrix™-IPV-Hib/Infanrix™-hexa* effectiveness if vaccines are administered at the age of 2, 4, 6 months with a booster between 11-23 months. The effectiveness against invasive Hib infection may be lower after the *DTaP* vaccines compared to *DTwP* when given in an accelerated 3 dose schedule at the age of 2, 3, 4 months without a booster dose during the second year of life.
3) The use of a *hexavalent* vaccine should be considered if *HBV* vaccine is given during infancy.
4) Having more than one vaccine manufacturer that supplies *DTaP* based vaccines in Canada would diminish the risk of inadequate supply in situations of production problems encountered by a manufacturer.

REFERENCES

1. Erickson LJ, De Wals P, Farand L. An analytical framework for immunization programs in Canada. *Vaccine* 2005;23(19):2470-6.
2. CCNI, editor. *Guide canadien d'immunisation*. Sixième ed. Ottawa, Ontario: Association médicale canadienne, 2002.
3. 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.
4. Nolan T, Altmann A, Skeljo M, Streeton C, Schuerman L. Antibody persistence, PRP-specific immune memory, and booster responses in infants immunised with a combination DTPa-HBV-IPV/Hib vaccine. *Vaccine* 2004;23(1):14-20.
5. *Vaccines*. Fourth Edition ed. Philadelphia: Saunders, 2004.
6. Kitchin N, Southern J, Morris R, Hemme F, Cartwright K, Watson M, et al. A randomised controlled study of the reactogenicity of an acellular pertussis-containing pentavalent infant vaccine compared to a quadrivalent whole cell pertussis-containing vaccine and oral poliomyelitis vaccine, when given concurrently with meningococcal group C conjugate vaccine to healthy UK infants at 2, 3 and 4 months of age. *Vaccine* 2006;24(18):3964-70.
7. FDA licensure of diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant), and poliovirus vaccine combined, (PEDIARIX) for use in infants. *MMWR Morb Mortal Wkly Rep*, 2003:203-4.
8. Scheifele DW, Halperin SA, Smith B, Ochnio J, Meloff K, Duarte-Monteiro D. Assessment of the compatibility of co-administered 7-valent pneumococcal conjugate, DTaP.IPV/PRP-T Hib and hepatitis B vaccines in infants 2-7 months of age. *Vaccine* 2006;24(12):2057-64.
9. Halperin SA, McDonald J, Samson L, Danzig L, Santos G, Izu A, et al. Simultaneous administration of meningococcal C conjugate vaccine and diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine in children: a randomized double-blind study. *Clin Invest Med* 2002;25(6):243-51.
10. Kitchin N, Southern J, Morris R, Hemme F, Thomas S, Watson M, et al. Evaluation of a diphtheria-tetanus-acellular pertussis- inactivated poliovirus-Hib vaccine given concurrently with meningococcal group C conjugate vaccine at 2, 3 and 4 months of age. *Arch Dis Child* 2006 May 2 online.
11. Lin TY, Wang YH, Chang LY, Huang YC, Kao HT, Lin PY, et al. A fully liquid diphtheria-tetanus-five component acellular pertussis-inactivated poliomyelitis-Haemophilus influenzae type b conjugate vaccine: immunogenicity and safety of primary vaccination in Taiwanese infants. *Int J Infect Dis* 2006, June 9 (in press).
12. Schmitt HJ, Faber J, Lorenz I, Schmole-Thoma B, Ahlers N. The safety, reactogenicity and immunogenicity of a 7-valent pneumococcal conjugate

vaccine (7VPnC) concurrently administered with a combination DTaP-IPV-Hib vaccine. *Vaccine* 2003;21(25-26):3653-62.

13. Aristegui J, Dal-Re R, Diez-Delgado J, Mares J, Casanovas JM, Garcia-Corbeira P, et al. Comparison of the reactogenicity and immunogenicity of a combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio (DTPa-HBV-IPV) vaccine, mixed with the Haemophilus influenzae type b (Hib) conjugate vaccine and administered as a single injection, with the DTPa-IPV/Hib and hepatitis B vaccines administered in two simultaneous injections to infants at 2, 4 and 6 months of age. *Vaccine* 2003;21(25-26):3593-600.
14. Dagan R, Igbaria K, Piglansky L, Melamed R, Willems P, Grossi A, et al. Safety and immunogenicity of a combined pentavalent diphtheria, tetanus, acellular pertussis, inactivated poliovirus and *Haemophilus infuenzae* type b-tetanus conjugate vaccine in infants, compared with a whole cell pertussis pentavalent vaccine. *Pediatr Infect Dis J* 1997;16(12):1113-1121.
15. Schmitt HJ, Knuff M, Ortiz E, Sänger R, Uwamwezi MC, Kaufhold A. Primary vaccination of infants with diphtheria-tetanus-acellular pertussis-hepatitis B virus-inactivated polio virus and *Haemophilus influenzae* type b vaccines given as either separate or mixed injections. *J Pediatr* 2000;137(3):304-312.
16. Knuf M, Habermehl P, Cimino C, Petersen G, Schmitt HJ. Immunogenicity, reactogenicity and safety of a 7-valent pneumococcal conjugate vaccine (PCV7) concurrently administered with a DTPa-HBV-IPV/Hib combination vaccine in healthy infants. *Vaccine* 2006;24(22):4727-36.
17. Tichmann-Schumann I, Soemantri P, Behre U, Disselhoff J, Mahler H, Maechler G, et al. Immunogenicity and reactogenicity of four doses of diphtheria-tetanus-three-component acellular pertussis-hepatitis B-inactivated polio virus-Haemophilus influenzae type b vaccine coadministered with 7-valent pneumococcal conjugate Vaccine. *Pediatr Infect Dis J* 2005;24(1):70-7.
18. Zepp F, Knuf M, Heininger U, Jahn K, Collard A, Habermehl P, et al. Safety, reactogenicity and immunogenicity of a combined hexavalent tetanus, diphtheria, acellular pertussis, hepatitis B, inactivated poliovirus vaccine and Haemophilus influenzae type b conjugate vaccine, for primary immunization of infants. *Vaccine* 2004;22(17-18):2226-33.
19. Tejedor JC, Moro M, Ruiz-Contreras J, Castro J, Gomez-Campedera JA, Navarro ML, et al. Immunogenicity and Reactogenicity of Primary Immunization with a Hexavalent Diphteria-Tetanus-Acellular Pertussis-Hepatitis B-Inactivated Polio-Haemophilus Influenzae Type B Vaccine Coadministred with two Doses of a Meningococcal C-Tetanus Toxoid Conjugate Vaccine. *The Pediatric Infectious Disease Journal* 2006;25(8):713-20.

20. Tejedor JC, Omenaca F, Garcia-Sicilia J, Verdaguer J, Van Esso D, Esporrin C, et al. Immunogenicity and reactogenicity of a three-dose primary vaccination course with a combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-haemophilus influenzae type b vaccine coadministered with a meningococcal C conjugate vaccine. *Pediatr Infect Dis J* 2004;23(12):1109-15.
21. Omenaca F, Garcia-Sicilia J, Garcia-Corbeira P, Boceta R, Romero A, Lopez G, et al. Response of preterm newborns to immunization with a hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B virus-inactivated polio and Haemophilus influenzae type b vaccine: first experiences and solutions to a serious and sensitive issue. *Pediatrics* 2005;116(6):1292-8.
22. Tichmann I, Preidel H, Grunert D, Habash S, Schult R, Maier R, et al. Comparison of the immunogenicity and reactogenicity of two commercially available hexavalent vaccines administered as a primary vaccination course at 2, 4 and 6 months of age. *Vaccine* 2005;23(25):3272-9.
23. Gabutti G, Zepp F, Schuerman L, Dentico P, Bamfi F, Soncini R, et al. Evaluation of the immunogenicity and reactogenicity of a DTPa-HBV-IPV Combination vaccine co-administered with a Hib conjugate vaccine either as a single injection of a hexavalent combination or as two separate injections at 3, 5 and 11 months of age. *Scand J Infect Dis* 2004;36(8):585-92.
24. Avdicova M, Prikazsky V, Hudeckova H, Schuerman L, Willems P. Immunogenicity and reactogenicity of a novel hexavalent DTPa-HBV-IPV/Hib vaccine compared to separate concomitant injections of DTPa-IPV/Hib and HBV vaccines, when administered according to a 3, 5 and 11 month vaccination schedule. *Eur J Pediatr* 2002;161(11):581-7.
25. Halperin SA, Tapiero B, Law B, Diaz-Mitoma F, Duval B, Langley JM, et al. 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. *Vaccine* 2006;24(18):4017-23.
26. Poolman J, Kaufhold A, De Grave D, Goldblatt D. Clinical relevance of lower Hib response in DTPa-based combination vaccines. *Vaccine* 2001;19:2280-2285.
27. Duval B, Gilca V, Boulianne N, De Wals P, Masse R, Trudeau G, et al. Comparative long term immunogenicity of two recombinant hepatitis B vaccines and the effect of a booster dose given after five years in a low endemicity country. *Pediatr Infect Dis J* 2005;24(3):213-8.
28. Cassidy WM, Watson B, Ioli VA, Williams K, Bird S, West DJ. A randomized trial of alternative two- and three-dose hepatitis B vaccination regimens in adolescents: antibody responses, safety, and immunologic memory. *Pediatrics* 2001;107(4):626-631.
29. Duval B, Gilca V, Boulianne N, Deceuninck G, Rochette L, De Serres G. Immunogenicity of two paediatric doses of monovalent hepatitis B or

combined hepatitis A and B vaccine in 8-10 year old children. *Vaccine* 2005;23:4082-4087.

30. Duval B, Boulianne N, De Serres G, Laflamme N, De Wals P, Massé R, et al. Comparative immunogenicity under field conditions of two recombinant hepatitis B vaccines in 8-10-year-old children. *Vaccine* 2000;18:1467-1472.
31. Levie K, Beran J, Collard F, Nguyen C. Long term (24 months) follow-up of a hepatitis A and B vaccine, comparing a two and three dose schedule in adolescents aged 12-15 years. *Vaccine* 2002;20:2579-2584.
32. Slack MH, Cade S, Schapira D, Thwaites RJ, Crowley-Luke A, Southern J, et al. DT5aP-Hib-IPV and MCC vaccines: preterm infants' response to accelerated immunisation. *Arch Dis Child* 2005;90(4):338-41.
33. Schloesser RL, Fischer D, Otto W, Rettwitz-Volk W, Herden P, Zielen S. Safety and immunogenicity of an acellular pertussis vaccine in premature infants. *Pediatrics* 1999;103(5):e60.
34. Singleton R, Bulkow LR, Levine OS, Butler JC, Hennessy TW, Parkinson A. Experience with the prevention of invasive Haemophilus influenzae type b disease by vaccination in Alaska: the impact of persistent oropharyngeal carriage. *J Pediatr* 2000;137(3):313-20.
35. Galil K, Singleton R, Levine OS, Fitzgerald MA, Bulkow L, Getty M, et al. Reemergence of invasive *Haemophilus influenzae* type b disease in a well-vaccinated population in remote Alaska. *J Infect Dis* 1999;179:101-106.
36. Vaugelade J, Pinchinat S, Guiella G, Elguero E, Simondon F. Non-specific effects of vaccination on child survival: prospective cohort study in Burkina Faso. *Bmj* 2004;329(7478):1309.
37. Strine TW, Luman ET, Okoro CA, McCauley MM, Barker LE. Predictors of age-appropriate receipt of DTaP dose 4. *Am J Prev Med* 2003;25(1):45-9.
38. Daum RS, Zenko CE, Given GZ, Ballanco GA, Parikh H, Vidor E, et al. Absence of a significant interaction between a Haemophilus influenzae conjugate vaccine combined with a diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine in the same syringe and inactivated polio vaccine. *Pediatr Infect Dis J* 2000;19(8):710-7.
39. Rennels MB, Englund JA, Bernstein DI, Losonsky GA, Anderson EL, Pichichero ME, et al. Diminution of the anti-polyribosylribitol phosphate response to a combined diphtheria-tetanus-acellular pertussis/*Haemophilus influenzae* type b vaccine by concurrent inactivated poliovirus vaccination. *Pediatr Infect Dis J* 2000;19(5):417-423.
40. Heininger U, Cherry J. Pertussis immunization in adolescents and adults-Bordetella pertussis epidemiology should guide vaccination recommandations. *Expert Opin Biol Ther* 2006;7:685-697.
41. Makela PH, Kayhty H, Leino T, Auranen K, Peltola H, Ekstrom N, et al. Long-term persistence of immunity after immunisation with *Haemophilus influenzae* type b conjugate vaccine. *Vaccine* 2003;22(2):287-92.

42. Wang LY, Hu CT, Ho TY, Lin HH. Geographic and ethnic variations of long-term efficacy and immunogenicity of hepatitis B vaccination in Hualien, a HBV hyperendemic area. *Vaccine* 2006;24(20):4427-32.
43. Tawk HM, Vickery K, Bisset L, Selby W, Cossart YE. The impact of hepatitis B vaccination in a Western country: recall of vaccination and serological status in Australian adults. *Vaccine* 2006;24(8):1095-106.
44. Gilca V, Duval B, Boulianne N, Dion R, De Serres G. Impact of the quebec school-based hepatitis B immunization program and potential benefit of the addition of an infant immunization program. *Pediatr Infect Dis J* 2006;25(4):372-4.
45. Patrick DM, Bigham M, Ng H, White R, Tweed A, Skowronski DM. Elimination of acute hepatitis B among adolescents after one decade of an immunization program targeting Grade 6 students. *Pediatr Infect Dis J* 2003;22(10):874-7.
46. Mallet E, Fabre P, Pines E, Salomon H, Staub T, Schödel F, et al. Immunogenicity and safety of an new liquid hexavalent combined vaccine compared with separate administration of reference licensed vaccines in infants. *Pediatr Infect Dis J* 2000;19(12):1119-1127.
47. Greenberg DP, Wong VK, Partridge S, Howe BJ, Ward JI. Safety and immunogenicity of a combination diphtheria-tetanus toxoids-acellular pertussis-hepatitis B vaccine administered at two, four and six months of age compared with monovalent hepatitis B vaccine administered at birth, one month and six months of age. *Pediatr Infect Dis J* 2002;21(8):769-776.
48. Greenberg DP, Wong VK, Partridge S, Chang S-J, Jing J, Howe BJ, et al. Immunogenicity of a *Haemophilus influenzae* type b-tetanus toxoid conjugate vaccine when mixed with a diphtheria-tetanus-acelluar pertussis-hepatitis B combination vaccine. *Pediatr Infect Dis J* 2000;19(12):1135-1140.
49. Gylca R, Gylca V, Benes O, Melnic A, Chicu V, Weisbecker C, et al. A new DTPa-HBV-IPV vaccine co-adminstered with Hib, compared to a commercially available DTPw-IPV/Hib vaccine co-administered with HBV, given at 6, 10 and 14 weeks following HBV at birth. *Vaccine* 2001;19:825-833.
50. Eskola J, Ölander R-M, Hovi T, Litmanen L, Peltola S, Käyhty H. Randomised trial of the effect of co-administration with acellular pertussis DTP vaccine on immunogenicity of *Haemophilus influenzae* type b conjugate vaccine. *Lancet* 1996;348:1688-1692.
51. Scheifele D, Halperin S, Vaudry W, Jadavji T, Law B, MacDonald N, et al. Lutte contre l'infection à *Haemophilus influenzae* de type B à l'aide de Pentacel, Canada, 1998-1999. *RMTC* 2000;26(11):93-96.
52. Schmitt HJ, von Kries R, Hassenpflug B, Hermann M, Siedler A, Niessing W, et al. Haemophilus influenzae type b disease: impact and effectiveness of diphtheria-tetanus toxoids-acellular pertussis (-inactivated poliovirus)/H.

influenzae type b combination vaccines. *Pediatr Infect Dis J* 2001;20(8):767-74.
53. 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;180:538-541.
54. Scheifele D, Halperin S, Law B, King A, Morris R, Janeway CA, et al. Invasive Haemophilus influenzae type b infections in vaccinated and unvaccinated children in Canada, 2001-2003. *Cmaj* 2005;172(1):53-6.
55. Eskola J, Ward J, Dagan R, Goldblatt D, Zepp F, Siegrist C-A. Combined vaccination of *Haemophilus influenzae* type b conjugate and diphtheria-tetanus-pertussis containing acellular pertussis. *Lancet* 1999;354:2063-2068.
56. Salmaso S, Mastrantonio P, Tozzi AE, Stefanelli P, Anemona A, Ciofi degli Atti ML, et al. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: the Italian experience. *Pediatrics* 2001;108(5):www.pediatrics.org/cgi/content/full/108/5/e81.
57. McVernon J, Andrews N, Slack MP, Ramsay ME. Risk of vaccine failure after Haemophilus influenzae type b (Hib) combination vaccines with acellular pertussis. *Lancet* 2003;361(9368):1521-3.
58. Bisgard KM, Rhodes P, Connelly BL, Bi D, Hahn C, Patrick S, et al. Pertussis vaccine effectiveness among children 6 to 59 months of age in the United States, 1998-2001. *Pediatrics* 2005;116(2):e285-94.
59. Tsang RS, Sill ML, Martin IE, Jamieson F. Genetic and antigenic analysis of Bordetella pertussis isolates recovered from clinical cases in Ontario, Canada, before and after the introduction of the acellular pertussis vaccine. *Can J Microbiol* 2005;51(10):887-92.
60. Wilson TR. Update on adolescent immunization: review of pertussis and the efficacy, safety, and clinical use of vaccines that contain tetanus-diphtheria-acellular pertussis. *J Pediatr Health Care* 2006;20(4):229-37.
61. Galanis E, King AS, Varughese P, Halperin SA. Changing epidemiology and emerging risk groups for pertussis. *Cmaj* 2006;174(4):451-2.
62. Ntezayabo B, De Serres G, Duval B. Pertussis resurgence in Canada largely caused by a cohort effect. *Pediatr Infect Dis J* 2003;22(1):22-27.
63. Mastrantonio P, Spigaglia P, van Oirscho H, van der Heide HGJ, Heuvelman K, Stefanelli P, et al. Antigenic variants in *Bordetella pertussis* strains isolated from vaccinated and unvaccinated children. *Microbiology* 1999;145:2069-2075.
64. Njamkepo E, Rimlinger F, Thiberge S, Guiso N. Thirty-five years' experience with the whole-cell pertussis vaccine in France: vaccine strains analysis and immunogenicity. *Vaccine* 2002;20(9-10):1290-4.
65. Peppler MS, Kuny S, Nevesinjac A, Rogers C, de Moissac YR, Knowles K, et al. Strain variation among *Bordetella pertussis* isolates from Québec and

Alberta provinces of Canada from 1985 to 1994. *J Clin Microbiol* 2003;41(7):3344-7.
66. Hallander HO, Gustafsson L, Ljungman M, Storsaeter J. Pertussis antitoxin decay after vaccination with DTPa. Response to a first booster dose 3 1/2-6 1/2 years after the third vaccine dose. *Vaccine* 2005;23(46-47):5359-64.
67. Ward JI, Cherry JD, Chang SJ, Partridge S, Keitel W, Edwards K, et al. Bordetella Pertussis infections in vaccinated and unvaccinated adolescents and adults, as assessed in a national prospective randomized Acellular Pertussis Vaccine Trial (APERT). *Clin Infect Dis* 2006;43(2):151-7.
68. Crowcroft NS, Pebody RG. Recent developments in pertussis. *Lancet* 2006;367(9526):1926-36.
69. CDC. General recommendations on immunization - Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR* 2002;51(RR-2):1-35.
70. Anonymous. Pertussis Vaccination: Use of Acellular Pertussis Vaccines Among Infants and Young Children. *MMWR* 1997;46(RR-7):1-25.
71. Rendi-Wagner P, Kundi M, Mikolasek A, Vecsei A, Fruhwirth M, Kollaritsch H. Hospital-based active surveillance of childhood pertussis in Austria from 1996 to 2003: Estimates of incidence and vaccine effectiveness of whole-cell and acellular vaccine. *Vaccine* 2006;24(33-34):5960-5.
72. Pertussis in Newfoundland and Labrador: 1991-2004. *Can Commun Dis Rep* 2005;31(22):235-7.
73. Capiau C, Poolman J, Hoet B, Bogaerts H, Andre F. Development and clinical testing of multivalent vaccines based on a diphtheria-tetanus-acellular pertussis vaccine: difficulties encountered and lessons learned. *Vaccine* 2003;21(19-20):2273-87.
74. Murphy TV, White KE, Pastor P, Gabriel L, Medley F, Granoff DM, et al. Declining incidence of haemophilus influenzae type b disease since introduction of vaccination. *Journal of the American Medical Association* 1993;269(2):246-248.
75. Partridge S, Yeh SH. Clinical evaluation of a DTaP-HepB-IPV combined vaccine. *Am J Manag Care* 2003;9(1 Suppl):S13-22.
76. Saenger R, Maechler G, Potreck M, Zepp F, Knuf M, Habermehl P, et al. Booster vaccination with hexavalent DTPa-HBV-IPV/Hib vaccine in the second year of life is as safe as concomitant DTPa-IPV/Hib + HBV administered separately. *Vaccine* 2005;23(9):1135-43.