An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)†

Statement on the Booster for 4-6 Year-Olds for Protection Against Pertussis

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

— Public Health Agency of Canada

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

Table 1. The following table highlights key information for immunization providers. Please refer to the remainder of the Statement for details

1. What	Children in Canada receive a booster dose of diphtheria (d or D), tetanus (T), acellular pertussis (ap or aP) and inactivated polio vaccine (IPV) - at 4-6 years of age through vaccines that contain combinations of these antigens. There are products with a lower concentration of pertussis antigen (ap) and others with a higher concentration of pertussis antigen (aP). Fewer adverse events (local immunization site reactions) are reported with Tdap-IPV. DTaP-IPV elicits a greater immune response to pertussis, however, the clinical significance of this is not known. Either DTaP-IPV or Tdap-IPV vaccines may be used for the 4- to 6-year-old booster in children. NACI does not preferentially recommend one vaccine over the other.
2. Who	Children 4-6 years of age who are scheduled to receive booster vaccines.
3. How	One dose of combined diphtheria, tetanus, acellular pertussis and inactivated polio vaccine product should be administered intramuscularly.
4. Why	Pertussis continues to occur in a cyclic pattern every 2-5 years, therefore ongoing protection is needed.

I. INTRODUCTION

The purpose of this statement is to review the literature relevant to the 4- to 6-year-old preschool booster immunization and provide updated recommendations as required. Current recommendations for the 4- to 6-year-old preschool booster include additional doses of diphtheria, tetanus, acellular pertussis and polio containing vaccine (DTaP-IPV or Tdap-IPV). These four components are usually given as a single injection. In Canada there are products approved for use that contain either a lower concentration of pertussis and diphtheria [Tdap-IPV (Adacel®-Polio, Boostrix®-Polio)] or higher concentration of pertussis and diphtheria [DTaP-IPV (Quadracel®, Infanrix™-IPV)]. According to the Canadian Immunization Guide (CIG), products with either higher or lower concentration of can be used between 4 and 6 years old. (http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pert-coqu-eng.php)

In January 2012, there was an impending shortage of Quadracel® which prompted a review of other currently available vaccines that could serve as alternatives to Quadracel®.

The question NACI investigated and answers in this statement is:

- Should there be a preferential recommendation for either low or high concentration pertussis product for children at 4-6 years of age?

II. METHODS

NACI reviewed the key questions and literature review proposed by the Tetanus, Diphtheria, Pertussis and Polio Working Group including such considerations as the burden of illness of the disease to be prevented and the target population(s), safety, immunogenicity, efficacy, effectiveness of the vaccine(s), vaccine schedules, and other aspects of the overall immunization strategy. The knowledge synthesis was performed by two medical specialists and a research coordinator and supervised by the Tetanus, Diphtheria, Pertussis and Polio Working Group.

In conjunction with Library Services at Public Health Ontario (PHO), a literature search was designed to address the questions tasked to the NACI Tetanus, Diphtheria, Pertussis and Polio Working Group. Results of the literature search were assessed for inclusion by a single reviewer and studies included were limited to immunization of pre-school/early school-age children who had been primed with acellular pertussis products. Nineteen studies were relevant.

Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy (Tables 5 and 6) were prepared, and proposed recommendations for vaccine use developed. The Working Group chair and PHAC medical specialist presented the evidence and draft statement to NACI on February 7th, 2012. Following further review of the evidence and statement by NACI, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

For further information, NACI methodology has been summarized in Evidence-Based Recommendations for Immunization: Methods of the NACI, January 2009, CCDR. (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php)

What follows is information on 4- to 6-year-old diphtheria, tetanus, pertussis and polio boosters in Canada and vaccines approved for this use; vaccine product options framed based on the question presented to NACI (including relevant epidemiology, efficacy, effectiveness, immunogenicity and safety/adverse event information) along with further information regarding research priorities and surveillance issues.

III. CANADIAN 4- TO 6-YEAR-OLD BOOSTER PROGRAMS

There is some variability in diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type B (Hib) schedules in Canada (see Table 2), for the most part with respect to the inclusion of hepatitis B immunization in infancy and the timing of the adolescent tetanus-diphtheria-acellular pertussis (Tdap) booster. As of 2011, all provinces and territories, with the exception of Québec, gave diphtheria, tetanus, acellular pertussis and polio containing vaccine to 4- to 6-year-olds which contained the same concentrations of these antigens as is included in the infant doses (DTaP-IPV). In April 2011, Québec changed to Tdap-IPV, a product with a lower concentration of diphtheria and pertussis antigens, for the 4- to 6-year-old tetanus-diphtheria-acellular pertussis-polio booster.[1] See Table 2 for further details.

Table 2: Routine schedules for publicly-funded infant to adolescent pertussis-containing vaccine immunization programs in Canada (2011).[a]

Province/ Territory	DTaP-HB-IPV-Hib	DTaP-IPV-Hib	DTaP-IPV	Tdap-IPV	Tdap
NACI recommendation		2, 4, 6, 18 months	4-6 years (either product may be used)		10 years after the previous booster (14-16 years in general)
BC	2, 4, 6 months	18 months	4-6 years		Grade 9, Jan 2004
AB		2, 4, 6, 18 months	4-6 years		Grade 9, Sep 2004
SK		2, 4, 6, 18 months	4-6 years		Grade 8, Sep 2003
MB		2, 4, 6, 18 months	4-6 years		14-16 years, Aug 2003
ON		2, 4, 6, 18 months	4-6 years		14-16 years, Dec 2003
QC		2, 4,6, 18 months		4-6 years[b]	Grade 9, Sep 2004
NL		2, 4, 6, 18 months	4-6 years		Grade 9, Sep 1999
NB		2, 4, 6, 18 months	4 years		Grade 9 (Sep 2004) changed to Grade 7 in (Sep 2012)
NS		2, 4, 6, 18 months	4-6 years		Grade 7, Sep 2007

Province/ Territory	DTaP-HB-IPV-Hib	DTaP-IPV-Hib	DTaP-IPV	Tdap-IPV	Tdap
PE		2, 4, 6, 18 months	4-6 years		Grade 9, Fall 2003
YK	2, 4, 6 months	18 months	4-6 years		Grade 9, Spring 2004
NT		2, 4, 6, 18 months	4-6 years		Grade 9, Oct 2000
NU		2, 4, 6, 18 months	4-6 years		Grade 9 (14-16 years), Sep 2002

Notes:
Personal Communication, Julie Laroche, Manager, Immunization Assessment and Information, Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada

a) Changed from DTaP-IPV in 2011.
b) Dates when the adolescent pertussis dose was introduced are provided.

Following the Quadracel® shortage, which began in the winter of 2012, all Canadian provinces and territories, except for Saskatchewan and the Northwest Territories, changed to Tdap-IPV for the 4- to 6-year-old tetanus, diphtheria, acellular pertussis and polio booster. See Table 3.

Table 3: Post Quadracel® Shortage (as of June 2013) routine schedules for publicly-funded infant to adolescent pertussis-containing vaccine immunization programs in Canada[a,b]

Province/ Territory	DTaP-HB-IPV-Hib	DTaP-IPV-Hib	DTaP-IPV	Tdap-IPV	Tdap
NACI recommendation		2, 4, 6, 18 months	4-6 years (either product may be used)		10 years after the previous booster (14-16 years in general)
BC	2, 4, 6 months	18 months	4-6 years		Grade 9
AB		2, 4, 6, 18 months	4-6 years		Grade 9
SK		2, 4, 6, 18 months	4-6 years		Grade 8
MB		2, 4, 6, 18 months	4-6 years		14-16 years
ON		2, 4, 6, 18 months		4-6 years	14-16 years
QC	2, 4, 18 months	6 months		4-6 years	Third year of high school
NL		2, 4, 6, 18 months	4-6 years		Grade 9
NB		2, 4, 6, 18 months	4 years		Grade 7

NS		2, 4, 6, 18 months		4-6 years	Grade 7
PE		2, 4, 6, 18 months	4-6 years		Grade 9
YK	2, 4, 6 months	18 months	either 4-6 years		Grade 9
NT		2, 4, 6, 18 months,	4-6 years		Grade 9
NU		2, 4, 6, 18 months	4-6 years		Grade 9 (14-16 years)

Notes:

a) Personal Communication, Julie Laroche, Manager, Immunization Assessment and Information, Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada

b) For more recent information on publically funded immunization programs in Canada, please refer to the *Publicly funded Immunization Programs in Canada – Routine Schedule for Infants and Children in cluding special programs and catch-up programs* (http://www.phac-aspc.gc.ca/im/ptimprog-progimpt/table-1-eng.php) or *Programmes d'immunisation subventionnés par l'État au Canada – Calendrier d'immunisation systématique des nourrissons et des enfants incluant les programmes de rappel (en date de septembre 2013)* (http://www.phac-aspc.gc.ca/im/ptimprog-progimpt/table-1-fra.php)

IV. VACCINES

Characteristics of vaccines approved for use in Canada for the 4-6 year old diphtheria, tetanus, acellular pertussis and polio booster are shown in Table 4 below. Note that Boostrix®-Polio and Adacel®-Polio received notice of compliance in the 4 to 6 year age group in 2008 and 2010, respectively.[2, 3]

Table 4: Preparation(s) authorized for use in Canada (e.g. description, composition)*

Brand name	Quadracel®	Adacel® -Polio	Boostrix® -Polio	I Infanrix™ –IPV
Antigens	DTaP-IPV	Tdap-IPV	Tdap-IPV	DTaP-IPV
Manufacturer	Sanofi	Sanofi	GSK	GSK
Authorization	-primary and booster immunization 2 months up to 6 years of age (prior to 7th birthday)	-booster dose 4 years of age and above -in children 4 to 6 years of age, may be considered as an alternative for the 5th dose of DTaP-IPV	-booster dose 4 years of age and above -not intended for primary immunization	- booster dose up to and including 6 years of age, who have previously been immunized with three or four doses of DTaP vaccine or DTwP vaccine
PT (µg)	20	2.5	8	25
FHA (µg)	20	5	8	25
PRN (µg)	3	3	2.5	8

FIM 2/3 (µg)	5	5	-	-
Diphtheria Antigen (Lf)	15	2	2.5	25
Tetanus (Lf)	5	5	5	10
Polio 1/2/3 Antigens (DU)	40/8/32	40/8/32	40/8/32	40/8/32

Legend: Diphtheria tetanus, acellular pertussis (DTaP), Diphtheria, tetanus, whole cell pertussis (DTwP), Pertussis Toxin (PT), micrograms(µg) Filamentous Hemagglutinin (FHA), Pertactin (PRN), Fimbriae Antigen (FIM), Limit of flocculation (Lf), D-antigen units (DU).

Further information on the antigens can be found in section V.3 (page 9) of this statement.

*****Please see Canadian Immunization Guide (http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php) or relevant product monographs for other ingredients.

V. SHOULD THERE BE A PREFERENTIAL RECOMMENDATION FOR EITHER LOWER OR HIGHER CONCENTRATION OF ANTIGEN PRODUCTS FOR CHILDREN AT 4 TO 6 YEARS OF AGE?

V.1 Epidemiology of Pertussis in Canada

Pertussis is a cyclical disease, which peaks at two to five year intervals. With the introduction of the whole-cell pertussis vaccine in 1943, the incidence of pertussis decreased significantly in Canada, from an average of 165 cases per 100,000 population from 1933 to 1943 to a low annual average of 6.7 cases per 100,000 from 2001 to 2011.[4] A resurgence of pertussis was observed beginning in 1990. This was likely due to a combination of factors, including the low effectiveness of the combined adsorbed diphtheria-tetanus-pertussis whole-cell vaccine given to children in Canada between 1981 and 1998, waning immunity from the previous vaccine among adolescents and adults, as well as increased physician awareness and improved diagnosis and reporting of pertussis infection.[5] The whole cell vaccines were replaced with acellular vaccines made from purified antigens of *B. pertussis* in 1997/98 in Canada.

The incidence of pertussis is highest in infants and children, and decreases sharply among those older than 14 years. Average incidence rates from 2007 to 2011 were highest among infants less than 1 year of age at 64.0 cases per 100,000 population, followed by 1- to 4 year olds (20.5 cases per 100,000), and 10- to 14-year-olds (11.6 cases per 100,000).[4] In the 1990's, an increase in incidence was observed in adolescents and adults due to low vaccine effectiveness in the population cohort that was immunized with the vaccine available between 1981 and 1999.[5] Adolescents constituted a major reservoir for the disease and were an important source of transmission to infants. As such, in 2003 the NACI recommended a single dose of the adolescent/adult formulation of the combined diphtheria-tetanus-acellular pertussis vaccine (Tdap). This was incorporated into vaccine programs across Canada by the end of

2004. The incidence of pertussis has decreased in the 15 to 19 year age group from 18.7 cases per 100,000 population in 2003 to 1.7 cases per 100,000 population in 2011.[4] NACI has also recommended all adults receive one dose of Tdap if not previously immunized in adulthood.

Since the last major peak in 1998, pertussis incidence in Canada had been on a steady decline. However, in 2012, all Canadian provinces and territories reported an increase in pertussis activity with the exception of Saskatchewan, Prince Edward Island, Newfoundland and Labrador and Nunavut. New Brunswick in particular experienced a significant increase in activity following a province-wide outbreak that began in early 2012. Based on preliminary data, 4845 cases were reported in 2012 in Canada, corresponding to a national incidence of 14.1 cases per 100,000 population. Three deaths were reported, all in previously well infants less than seven months of age. The increased incidence occurring across the country is not limited to one specific age group or to those who are unimmunized but instead varies by jurisdiction.[4]

V.2 Effectiveness of 4-6 year-old Pertussis Booster Vaccines

Literature regarding the effectiveness of pertussis-containing pre-school booster vaccines is summarized in Table 8. Two recent studies have suggested a waning of immunity over the five years after the fifth dose of DTaP.[6, 7] In Klein and co-authors' study, after the 5th dose of DTaP, the odds of acquiring pertussis increased by an average of 42% per year in those vaccinated more than five years before.[6] Misegades and colleagues investigated the vaccine effectiveness in children after receipt of five doses of pertussis containing vaccine.[7] Using a case-control design, they showed that vaccine effectiveness declined each year after the 5th dose of DTaP. Their estimates of VE based on time since the 5th dose were for those within one year of receipt 98.1% (95% CI 96.1 – 99.1), 12-23 months since last dose 95.3% (95% CI 91.2-97.5), 24-35 months since last dose 92.3% (95% CI 86.6%-95.5%), 36-47 months since last dose 87.3% (95% CI 76.2-93.2), 48-59 months since last dose 82.8% (95% CI 68.7-90.6) and in those greater than 60 months from last dose of DTaP 71.2% (95% CI 45.8 – 84.8).[7]

Comparative effectiveness of high versus low potency pertussis formulations as a 4- to 6-year-old booster dose has not been studied, and it is not known whether higher antigenic content of the pertussis vaccine is associated with higher levels of protection.

V.3 Immunogenicity of 4- to 6-year old Pertussis Booster Vaccines (including Evidence for Adequacy of Correlates of Immunity)

To provide an understanding of the different antigens and their functions we have included a short primer on humoral antibodies used by the regulator, Health Canada, to assess immune response to pertussis vaccines (in the absence of defined correlates of protection for pertussis). Pertussis toxin (PT) has a few activities including binding to the host cells, induction of lymphocytosis and modifying the immune response. Antibodies to PT develop after natural infection as well as vaccination. Filamentous hemagglutinin (FHA) is a protein that is secreted by *B pertussis*. It plays a major role in the adhesion to epithelium cells in a host. Pertactin (PRN) is a highly immunogenic surface protein that promotes binding to host cells. Fimbriae types 2 and 3 (FIM 2/3) are surface components of *B. pertussis* and are involved in colonization of the nasopharynx. Some or all of these components are included in various vaccines that are currently used in Canada (please refer to Table 4). Antibodies against each of these

components are measured and compared to the immune responses from historical efficacy trials. Protection is likely conferred by the interplay of the above antibodies in conjunction with cell mediated immunity.[8]

Serological correlates of protection have been defined for diphtheria and tetanus.

A number of studies have shown that both higher and lower concentration acellular pertussis products are able to elicit immune responses. Publications obtained with respect to 4- to 6-year-old pertussis booster immunogenicity are shown in Table 8. There are a total of four studies that have investigated the use of ap after priming with aP in the childhood immunization schedule [9-11]. Of these, only two were randomized controlled trials of ap versus aP. In the Ferrara et al. study (2012),[9] Boostrix®-Polio (GSK) (Tdap-IPV) was compared head to head with Tetravac® (Sanofi), a two-pertussis-component aP product not available in Canada. It should be noted that these children received only three doses of priming, as compared to the Canadian schedule that recommends a three dose primary series and one booster (at 18 months) prior to the 4- to 6-year-old booster dose. The reduced content product provided a non-inferior immune response to the full strength product when immunogenicity was measured to the two common components one month after immunization.[9] One other study (Langley et al. 2006)[10] investigated the immunogenicity of lower content pertussis and diphtheria containing vaccine Adacel® (Sanofi) (Tdap) with a higher content pertussis and diphtheria content vaccine Quadracel® (DTap-IPV).[10] This was a Canadian study; therefore children received three primary doses and 18 month booster prior to immunization at 4-6 years of age. The majority of children in both arms of this study had a four-fold rise in their pertussis antibodies approximately one month after immunization.[10] The study by Scheifele et al.[27] used the same two products as the Langley et al.[10] study and was also done in Canadian children. The study primary objectives related to safety but the investigators also reported on serum antibody concentrations before and 4 weeks after booster immunization. GMC values for PT were significantly higher in the DTaP-IPV group than in the Tdap group while the GMC values for FIM 2/3 were significantly higher in the Tdap group. The clinical significance of this finding is unknown.

Children in the Langley et al.[10] study were followed for five years after the 4-to 6-year-old booster and PT responses were lower in the ap group versus the aP group at that time (data on file, Sanofi). The responses to other antigens were similar between the two groups, five years after immunization. The clinical significance of these findings are unknown. One other study provided information on long term durability of immune response (Meyer, 2008).[12] In a subset analysis of about 120 subjects, anti-PT, anti-FHA and anti-PRN antibodies were similar between both Boostrix® (GSK) (Tdap) and Infanrix™ (GSK) (DTaP) at 3.5 years after the 4-to 6-year-old booster.[12]

V.4 Adverse Events Associated with 4- to 6-year-old Pertussis Booster Vaccines

All products approved for use in Canada for the diphtheria, tetanus, pertussis and polio booster dose at 4-6 years of age are safe. Below is a brief summary of the safety data from studies of these vaccines, as well as available Canadian safety data (see Table 8 for details of the studies).

Large local reactions are the primary safety concern with DTaP-containing vaccines[13-17, 27] although the frequency with which they occur is variable, depending on the study. The highest rate of large local reaction seen in studies of DTaP-IPV was reported by Nilsson.[14] In this study

of 416 Italian and Swedish 4-6 year olds, “any large swelling reaction” (at least one of: > 50mm, diffuse swelling, or swelling to ≥ 1 adjacent joint) occurred in 13.5% of DTaP-IPV recipients and 17.4% of DTaP recipients.[14] Four studies compared the safety of aP versus ap products (Ferrera, Meyer, Langley, Scheifele)[9, 10, 12, 27] and in all of these, the proportion of children who experienced signs and symptoms of local reaction was smaller in the ap groups. Overall frequency of local reactions and differences between aP and ap groups varied across studies.[9, 10, 12, 27]

Systemic reactogenicity was similar among children who received DTaP-IPV and those who received Tdap+/-IPV in the four trials comparing aP to ap products.[9, 10, 12, 27] Fever was generally the most common systemic reaction and frequency of its occurrence ranged from < 10% to > 20%. There were no vaccine-attributable serious adverse events in these four studies.

The Québec provincial Adverse Events Following Immunization Surveillance System detected an increased frequency of large local reactions with the 4-6 year DTaP-IPV booster. This was consistent with clinical trials that had shown greater reactogenicity with the higher antigen product. Due to increasing reports of large local reactions when children who received primary immunization with exclusively acellular pertussis-containing vaccine were given the 4-6 year booster, that province decided to change to Tdap-IPV for the 4-6 year booster in 2011, prior to the Quadracel® shortage.[1] Since then, as expected, there has been a decrease in the number of reports of immunization site reactions experienced after the 4-6-year booster dose (personal communication, Eveline Toth, ministère de la Santé et des services Sociaux du Québec).
Data from the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) is consistent with pre- and post-marketing studies that show that DTaP-IPV is very safe. Looking at reporting trends over time in CAEFISS it is clear that adverse events are much less frequently reported following acellular pertussis products than they were when whole cell pertussis products were used. Hospitalizations for large local reactions, which may be diagnosed as cellulitis, are not frequently reported to CAEFISS.[18]

Based on review of the available literature, there appears to be waning immunity after the 4-to 6-year-old DTaP booster, as demonstrated by recent studies of vaccine effectiveness. In trials comparing ap versus aP boosting among children primed with aP vaccines, the high concentration product produces a greater antibody response. The clinical significance of this is unknown given the lack of correlates of protection. Local reactogenicity is less common with ap versus aP.

VI. RECOMMENDATIONS

Please note that provinces and territories must consider economic factors and other local programmatic/operational factors, as well as local epidemiology when considering inclusion of the following recommendations in publicly funded immunization programs.

“Should there be a preferential recommendation for either low or high dose pertussis product for children at 4-6 years of age?”

Recommendation: Either DTaP-IPV or Tdap-IPV vaccines may be used for the 4- to 6-year-old booster in children. NACI does not preferentially recommend one vaccine over the other.

As outlined in this statement, NACI did a thorough review of issues related to safety, effectiveness and immunogenicity. Adverse events are less common with Tdap-IPV than with DTaP-IPV, however DTaP-IPV may elicit a higher and more durable immune response although

the correlates of protection for pertussis are not definitive. Based on this level of uncertainty, it would be important to consider the epidemiology in a province/territory and the public's response to local reactions following vaccination when determining which product to choose.

NACI recommendation Grade C

VII. RESEARCH PRIORITIES

Research to address the following outstanding questions is encouraged:

- Establishment and better understanding of pertussis correlates of protection;
- Further investigation into longevity of protection provided by pertussis containing vaccines and whether the adolescent dose should be given sooner;
- Comparison of various pertussis-containing products (i.e. ap vs. aP) with respect to vaccine effectiveness, duration of protection, immunogenicity and safety, including the impact of using different products for both priming and boosting on duration of protection;
- Better understanding of pertussis immunity through serosurveys or studies of infected and uninfected household contacts of cases of pertussis;
- Improved understanding of the natural history of pertussis immunity; and
- Development of vaccines with greater effectiveness.

VIII. SURVEILLANCE ISSUES

Ongoing and systematic data collection, analysis, interpretation and timely dissemination are fundamental to planning, implementation, evaluation, and evidence-based decision-making. Tetanus, diphtheria, pertussis and polio are nationally notifiable. To support such efforts, NACI encourages surveillance improvements in the following areas:

1. Epidemiology
   - Further investigation into the role of waning immunity in the epidemiology of pertussis.

2. Laboratory
   - Improved laboratory methods for pertussis detection including the use of serology and oral fluid diagnosis;
   - Contribution of non-*Bordetella* pertussis species (e.g. *Bordetella holmesii).*

3. Vaccine
   - Immunization registry to improve accuracy of coverage reporting;
   - Vaccine effectiveness;
   - Ongoing, timely vaccine safety surveillance.

Table 5. Levels of Evidence Based on Research Design

I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 6. Quality (internal validity) Rating of Evidence

Good	A study (including meta-analyses or systematic reviews) that meets all design specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21-35.

Table 7. NACI Recommendation for Immunization -- Grades

A	NACI concludes that there is **good** evidence to recommend immunization.
B	NACI concludes that there is **fair** evidence to recommend immunization.
C	NACI concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against immunization; however other factors may influence decision-making.
D	NACI concludes that there is **fair** evidence to recommend against immunization.
E	NACI concludes that there is **good** evidence to recommend against immunization.
F	NACI concludes that there is **insufficient** evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

LIST OF ABBREVIATIONS

Abbreviation	***Term***
ap	Acellular pertussis (low concentration pertussis)
aP	Acellular pertussis (high concentration pertussis)
CIG	Canadian Immunization Guide
DTaP	Diphtheria, tetanus, acellular pertussis vaccine (high concentration diphtheria and pertussis)
DTaP-IPV	Diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (high concentration diphtheria and pertussis)
DTaP-IPV-Hib	Diphtheria, tetanus, acellular pertussis, inactivated polio, *Haemophilus influenza* type b vaccine (high concentration diphtheria and pertussis)
GPEI	Global Polio Eradication Initiative
IPV	Inactivated polio vaccine
OPV	Oral poliovirus vaccine
Tdap	Tetanus, diphtheria, acellular pertussis vaccine (low concentration diphtheria and pertussis)
VAPP	Vaccine associated paralytic poliomyelitis
WPV	Wild poliovirus

Table 8. Summary of Evidence for NACI Recommendations

Evidence for Efficacy						
STUDY DETAILS					**SUMMARY**	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
No efficacy or effectiveness studies found in literature search.						
Evidence for Effectiveness						
STUDY DETAILS					**SUMMARY**	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Study Vaccine: DTaP-IPV (Infanrix™-IPV, GSK) or DTaP (Infanrix™, GSK)+IPV						
Torvaldsen S et al. Pediatr Infect Dis J 2003[19]	DTaP (may be DTaP-IPV or DTaP + IPV, not stated in paper) Infanrix™-IPV or Infanrix™+IPV	Cohort (nationally notifiable diseases surveillance system) Pertussis case definition: lab-confirmed, or epi-linked to lab-confirmed, or fulfilled clinical case definition without laboratory tests	All residents of Australia, 1993-2001	Fifth dose of pertussis-containing vaccine introduced 1994 (initially 4-5 years of age, from 1996 4 years of age). In 1999, all doses changed from wP to aP Findings: "from the time that 5- to 9-year-olds have been eligible to receive the 5th dose, their notification rates have become progressively lower" Comparing 1997 and 2001 epidemic years: - ≥ 100/100 000 notifications per year among all of 5-7 years of age in 1997 (only 5 & 6 years of age eligible for 5th dose) whereas < 50/100 000 notifications per year among same age groups (all eligible for 5th dose) in 2001	II-2	n/a (surveillance study)

STUDY DETAILS					SUMMARY	
Vaccine	***Study Design***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Study Vaccines: DTaP-IPV (Infanrix™-IPV, GSK *and* Quadracel®, Sanofi Pasteur) or DTaP (Infanrix™, GSK *and* Daptacel®, Sanofi Pasteur)+IPV						
Klein et al., New England J Med Sept 2012[6]	DTaP with and without combined IPV. Both GSK and Sanofi products used (confirmed with study authors).	Retrospective Case-control, single health maintenance organization (HMO)* Cases: pertussis PCR+ Jan 2006-June 2011; had received DTaP between 47-84 months of age; aP primed Controls: 1) PCR – and had 5th dose DTaP 2) Matched controls (sex, age, race, clinic), had 5th dose DTaP	n=277 cases age 4-12 years, 2006-2011 n=3318 PCR- controls n=6086 matched controls	Objective: examination of DTaP waning immunity in highly-vaccinated school-aged population who had only received aP products; in setting of 2010 California pertussis outbreak Key Findings: Pertussis incidence 2006-2011: < 1 year: 115/100 000/ year 5 year: 29/100 000 / year 10 &11 years of age: 226/100 000/year Time since fifth DTaP (cases versus PCR- controls): 1699 days (95% CI: 1627, 1772) vs 1028 days (95% CI: 1003, 1053) p < 0.001 Odds of pertussis per year after fifth DTaP: Cases vs. PCR- controls: OR 1.42 (95% CI: 1.21, 1.66) Cases vs. Matched controls: OR 1.50 (95% CI: 1.13, 2.00)	II-2	Good

STUDY DETAILS					SUMMARY	
Vaccine	***Study Design***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		*Also used entire HMO cohort to calculate incidence				
Misegades et al. J Amer Med Assoc 2012[7]	DTaP with and without combined IPV. Assumed both GSK and Sanofi products as both licensed in USA.	Case-control (retrospective and prospective), 15 California counties Jan 1st to Dec 14th, 2010. Cases: suspected, probable, and confirmed pertussis cases among 4-10 year olds Controls: 4-10 year olds who received care from same clinicians as cases	n=682 cases, 4-10 years, 2010 n=2016 controls, 4-10 years, 2010	Objective: assess association between pertussis disease and receipt of 5 doses of aP-containing vaccine by time since 5th dose Key findings: Estimated VE ([1-OR] x 100%) for 5 doses aP = 88.7% (95% CI: 79.4, 93.8) < 12 months from receipt of 5th dose, estimated VE 98.1% (95% CI: 96.1, 99.1) ≥60 months from receipt of 5th dose, estimated VE = 71.2% (95% CI: 45.8, 85.4) Estimated decline in VE from < 12 months to ≥60 months since 5th aP was 27.4%	II-2	Good

Evidence for Immunogenicity						
STUDY DETAILS					**SUMMARY**	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Study Vaccine: DTaP-IPV (Infanrix™-IPV, GSK)						
Nilsson et al. Scand J Infect Dis 2005[14]	DTaP-IPV (Infanrix™-IPV) vs DTaP (Infanrix™+ IPV)	Open, randomized -7 sites in Italy and Sweden	n =416 - 4-6 years (previously received 3 dose primary series)	Outcomes: Evaluation of immunogenicity of DTaP-IPV vs. DTaP + IPV prior to and one month post-immunization Seroprotection defined as: Diphtheria and tetanus ≥0.1 IU/ml Poliovirus ≥1:8 Seropositivity defined as: Pertussis (PT, FHA, PRN) ≥5EL.U/ml Vaccine response to pertussis (PT, FHA, PRN) defined as: seropositivity in those seronegative at baseline or 2-fold increase in antibody concentrations in those seropositive at baseline Key findings: Seroprotection/positivity one month after vaccine, DTaP-IPV vs. DTaP+IPV, % (95% CI) Anti-diphtheria: 99 (96.6-99.9) vs. 100 (98.1-100) Anti-tetanus: 100 (98.2-100) vs. 100 (98.1-100) Anti-PT: 100 (98.2-100) vs. 99.5 (97.1-100)	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Marshall et al. Vaccine Aug 2006[20]	DTaP-IPV (Infanrix™-IPV) vs DTaP (Infanrix™) + IPV	Open-label, randomized, non-inferiority, Phase IIIb - 3 Australian Centres	n=366 (362 vaccinated) -4-6 years	Outcomes: Evaluation of immunogenicity of DTaP-IPV+MMR vs. DTaP +IPV+MMR, pre- and 21 to 48 days post immunization; also examined MMR immunogenicity Seroprotection defined as: Diphtheria and tetanus ≥0.1 IU/ml Poliovirus ≥1:8 Seropositivity defined as: Pertussis (PT, FHA, PRN) ≥5EL.U/ml Measles >150mIU/ml Mumps ≥231 U/mL Rubella ≥4 and ≥10 IU/ml Key findings: Seroprotection/positivity 21-48 days after vaccine, DTaP-IPV+MMR vs. DTaP+IPV+MMR, % (95% CI) Anti-diphtheria: 100 (97.8-100) vs. 100 (97.7-100) Anti-tetanus: 100 (97.8-100) vs. 100 (97.7-100) Anti-PT: 99.4 (96.7-100) vs. 100 (97.7-100) Anti-FHA: 100 (97.9-100) vs. 100 (98-100) Anti-PRN: 100 (97.8-100) vs. 100 (97.7-100) Anti-polio1:	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				100 (97.7-100) vs. 100 (97.6-100) Anti-polio2: 100 (97.6-100) vs. 100 (97.6-100) Anti-polio3: 100 (97.6-100) vs. 100 (97.5 -100) Anti-measles: 100 (97.8-100) vs. 99.4 (96.6-100) Anti-mumps: 100 (97.6-100) vs. 100 (97.7-100) Anti-Rubella ≥ 4 IU/mL: 100 (97.8-100) vs. 100 (97.7-100) Anti-Rubella ≥ 10 IU/mL: 100 (97.8-100) vs. 100 (97.7-100)		
Black et al. Pediatr Infect Dis J April 2008[17]	DTaP-IPV (Infanrix™-IPV) vs. DTaP (Infanrix™) +IPV	Open randomized Phase III randomized study -24 US centers	N=4209	Outcomes: DTaP-IPV vs. DTaP+IPV post booster subjects seroprotected Seroprotection defined as: Diphtheria and tetanus ≥0.1 IU/ml Poliovirus ≥1:8 Pertussis ≥5EL.U/ml Measles ≥150mIU/ml Mumps ≥1:28 Rubella ≥10 IU/ml Booster – 4X pre-vaccination Ab level Key Findings: seroprotection one month after vaccine, DTaP-IPV vs. DTaP+IPV, % (95% CI) Anti-diphtheria: 100 (99.6-100) vs. 100 (98.6-100) Anti-tetanus:	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				100 (99.6-100) vs. 100 (98.6-100) Anti-PT: 99.8 (99.2-100) vs. 100 (98.6-100) Anti-FHA: 100 (99.6-100) vs. 100 (98.6-100) Anti-PRN: 100 (99.6-100) vs. 100 (98.6-100) Anti-polio1: 99.9 (99.3-100) vs. 100 (98.5-100) Anti-polio2: 100 (99.6-100) vs. 100 (98.5-100) Anti-polio3: 100 (99.5-100) vs. 100 (98.5-100)		
Klein et al. Vaccine Jan 2012[21]	DTaP-IPV (Infanrix™-IPV)	Open-label, randomized, non-inferiority, Phase IIIb - 11 US Centres	n =478 (461 completed active phase) - 4-6 years	Outcomes: Evaluation of immunogenicity of DTaP-IPV+ MMR + V vs. DTaP-IPV + MMR, pre and one month post; did not study immunogenicity of MMR or V Seroprotection defined as: Diphtheria and tetanus $\geq$0.1 IU/ml Poliovirus $\geq$1:8 Pertussis (PT, FHA, PRN) $\geq$5EL.U/ml Booster response defined as: Diphtheria and tetanus ≥0.4 IU/ml in those seronegative at baseline and ≥ 4 times pre-vaccination anti-body in those seropositive at baseline	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				Poliovirus presence of antibodies in those seronegative at baseline or ≥ 4 times baseline antibody in those with pre-booster antibodies ≥1:8 Pertussis (PT, FHA, PRN) ≥ 20EL.U/ml in those seronegative at baseline; ≥ 4 times baseline antibody in those with baseline antibodies between ≥5 EL.U/mL and < 20 EL.U/mL; ≥ 2 times baseline in those with baseline antibodies ≥ 20 EL.U/mL Key Findings: Seroprotection one month after immunization, DTaP-IPV + MMR + V and DTaP-IPV + MMR groups combined % (95% CI) Anti-diphtheria: 100 (98.3-100) Anti-tetanus: 100 (98.3-100) Anti-PT: 100 (98.3-100) Anti-FHA: 100 (98.3-100) Anti-PRN: 100 (98.3-100) Anti-polio1: 100 (98.3-100) Anti-polio2: 100 (98.3-100) Anti-polio3: 100 (98.3-100) Key Findings: Booster response one month after immunization, DTaP-IPV + MMR + V vs. DTaP-IPV + MMR % (95% CI) Anti-diphtheria: 99.1 (96.6-99.9) vs. 99.0 (96.6-99.9)		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				Anti-tetanus: 98.6 (95.9-99.7) vs. 97.6 (94.5-99.2) Anti-PT: 95.0 (91.2-97.5) vs. 95.7 (92.0-98.0) Anti-FHA: 98.6 (96.0-99.7) vs. 99.5 (97.4-100) Anti-PRN: 100 (98.3-100) vs. 98.6 (96.0-99.7) Anti-polio1: 98.1 (95.3-99.5) vs. 96.7 (93.2-99.6) Anti-polio2: 95.3 (91.6-97.7) vs. 98.1 (95.2-99.5) Anti-polio3: 99.1 (96.7-99.9) vs. (95.2-99.5)		
Study Vaccine: Tdap-IPV (Boostrix®-Polio, GSK)						
Sanger et al. Eur J Pediatr Dec 2007[11]	Tdap-IPV (Boostrix®-Polio) vs. Tdap (Boostrix®) +IPV	Partially blinded, randomized controlled trial (one injection vs. two injections not blinded) -59 centers in Germany	n=959 4-8 years subset n=566 for one year follow up	Outcomes: Evaluation of immunogenicity of Tdap-IPV vs. Tdap+IPV pre and one month post, subset with 1 year follow-up Seroprotection defined as: Diphtheria and tetanus ≥ 0.1IU/ml Poliovirus ≥1:8 Pertussis (PT, FHA, PRN) 2 fold rise in Ab titres in initially seropositive subjects and appearance of antibodies (cut-off	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				5EL.U/mL) in initially seronegative subjects Key Findings: Seroprotection one year post immunization, Tdap-IPV vs. Tdap+IPV, % (95% CI) Anti-diphtheria: 100 (99-100) vs. 100 (94.4-100) Anti-tetanus: 99.8 (98.8-100) vs. 98.8 (93.3-100) Anti-PT : 81.2 (77.4-84.6) vs. 75.3 (64.5-84.2) Anti-FHA: 100 (99.2-100) vs. 98.8 (93.3-100) Anti-PRN: 98.1 (96.4-99.1) vs. 97.5 (91.4-99.7) Anti-polio1: 100 (99.2-100) vs. 100 (95.4-100) Anti-polio2: 100 (99.2-100) vs. 100 (95.4-100) Anti-polio3: 99.8 (98.8-100) vs. 98.6 (92.4-100)		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Ferrera et al. Hum Vaccin Immuno-ther March 2012[9]	Tdap-IPV (Boostrix®-Polio) Vs. DTaP-IPV [Tetravac] (PT &FHA containing Sanofi product, not available in Canada) both co-adminstered with MMRV	Randomized controlled trial -multicentered Italy	n=305 5-6 year olds	Outcomes: Evaluation of immunogenicity of Tdap-IPV vs. TDaP-IPV pre and one month post booster Seroprotection defined as: Diphtheria and tetanus ≥ 0.1IU/ml Poliovirus ≥1:8 Pertussis (PT, FHA, PRN) 2 fold rise in Ab titres in initially seropositive subjects and appearance of antibodies (cut-off 5EL.U/mL) in initially seronegative subjects. Non-inferior seroprotection defined as: upper limit of standardized asymptotic 95% CI on group difference ≤ 10% (diphtheria, tetanus, polio) Key Findings: Tdap-IPV vs. DTaP-IPV, seroprotection one month post booster Seroprotection with anti-diphtheria, anti-tetanus, anti-polio(1,2,3), anti-PT and anti-FHA in all subjects (anti-FHA in 99.3% of Tdap-IPV group) Diphtheria, tetanus, polio (1,2,3) all non-inferior Key Findings: Tdap-IPV vs. DTaP-IPV, pertussis, one month post-	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				booster GMC/T (95%CI) Anti-PT: 59.8 (52.2-68.5) vs. 75.9 (65.7-87.7 Anti-FHA: 556.2 (491.4-629.5) vs. 613.5 (547-688.2) Anti-PRN: 354.8 (280.2-449.4) vs. 7.8 (6.5-9.2)		
Study Vaccine: Tdap-IPV (Adacel®-Polio, Sanofi Pasteur)						
Hendrikx, LH et al. Vaccine Nov 2009[22]	Tdap-IPV (Adacel®-Polio) vs DTaP-IPV (Infanrix™-IPV)	Convenience sample	n=69 (aP primed) and received 4 year olds booster	Outcomes: IgG levels (pooled) 28 days post booster Key Findings: Tdap-IPV vs. DTaP-IPV, IgG level (95%) Anti-PT: 44.7 (31-64.5) vs. 192.3 (144-256.7) Anti-FHA: 182.3 (99.0-335.7) vs. 518 (429.4-624.9) Anti-PRN: 629.1 (264.5-1496) vs. 1273.5 (932.5-1739) Anti-Fim2/3: 2.7 (1.3-5.5) vs. 1.2 (1.0-1.4)	Level II-3	Fair
Kitchin N et al. Vaccine Aug 2009[23]	Adacel®-Polio (Tdap-IPV)	Randomized controlled trial but presenting only one arm	n=77 3.5-4.5 year olds (primed with DTaP-IPV-Hib)	Outcomes: Evaluation of immunogenicity of Tdap-IPV pre and one month post booster (GMC/GMT)	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				Key Findings: GMC/GMT pre vs. post booster, GMC/GMT (95% CI) Diphtheria GMC: 0.041(0.029 – 0.057) vs. 7.95 (4.97-12.73) Tetanus GMC: 0.43 (0.3-0.61) vs. 7.26 (5.69-9.26) Pertussis: Anti-PT: 3.71 (2.89-4.75) vs. 94.84 (71.89-125.11) Anti-FHA: 7.05 (4.91-10.12) vs. 103.14 (78.03-136.33) Anti-PRN: 3.93 (3.07-5.02) vs. 127.42 (96.31-168.58) Anti-FIM: 9.66 (7.13-13.10) vs. 671.33 (499.6-902.1) Anti-polio1: 37 (25.16 – 54.41) vs. 10173.24 (6887.35-15026.79) Anti-polio2: 51.75 (32.18-83.21) vs. 5272.46 (3856.83- 7215.89) Anti-polio3: 47.18 (33.16-67.13) vs. 11221.8 (7755.59 – 16237.18)		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Study Vaccine: Tdap (Boostrix®, GSK)						
Meyer CU et al. Hum Vaccin May-Jun 2008[12]	Tdap (Boostrix®) vs. DTaP (Infanrix™) vs. Td (Novartis product)	Randomized single blind trial	n=422 4-6 year olds	Outcomes: Evaluation of immunogenicity of Tdap vs. DTaP vs. Td pre, one month and 3.5 years post booster. (Also subset with cell-mediated immunity testing, not shown) Seroprotection defined as: Diphtheria ≥ 0.016 IU/ml or ≥ 0.1IU/ml Pertussis (PT, FHA, PRN) ≥ 5 El.U/mL in initially seronegative (< 5 El.U/mL) and two-fold increase in initially seropositive Key Findings: Tdap vs DTaP, seroprotection 3.5 years after booster, % Anti Diphtheria: 100 vs. 100 Anti tetanus: 100 vs.100 Anti-PT: 58.7 vs. 60.6 Anti-FHA: 100 vs. 100 Anti-PRN: 99.2 vs. 100	Level I	Fair
Study Vaccine: Tdap (Adacel®, Sanofi Pasteur)						
Scheifele et al. 2005[27]	Tdap-IPV (Quadracel®) vs. Tdap (Adacel®)	Randomized controlled trial 2 Canadian centers	N=290 N=145 Tdap	Outcome measures: Evaluation of immunogenicity of Tdap vs. DTaP-IPV, pre and 4 weeks after immunization. Seroprotection defined as: Diphtheria and tetanus ≥ 0.1IU/ml	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				Pertussis PT %≥10EU/ml, FHA %>10EU/ml, FIM 2/3 %≥16EU/ml, PRN %≥7EU/ml Key findings: Tdap vs. DTaP-IPV post booster GMC (95% CI) Tetanus 9.8 (8.5-11.3) vs. 8.0 (6.9-9.2) Diphtheria 3.8 (3.2-4.4) vs. 6.4 (5.3-7.7) PT 61.7 (54.3-70) vs. 118.8 (105-135) FHA133 (116-152) vs. 167.6 (147-191) Fim2/3 982.7 (843-1145) vs. 640.6 (542-757) PRN 187.3 (152-230) vs. 162.8 (135-196)		
Langley et al. Vaccine Jan 2007[10]	Tdap (Adacel®) + IPV(4-6wk later) vs DTaP-IPV (Quadracel®)	Single blinded randomized controlled trial 8 Canadian centers	n=593 children between 4-7 years of age who completed primary series with fourth dose of pentacel	Outcome measures: Evaluation of immunogenicity of Tdap vs. DTaP-IPV, pre and 4-6 weeks after immunization. Seroprotection defined as: Diphtheria and tetanus ≥ 0.1IU/ml, four-fold rise also used Pertussis (PT, FHA, FIM, PRN), four-fold rise over pre-vaccination titres Key Findings: Non-inferiority between vaccines -diphtheria and tetanus antibody	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				level >0.10IU/ml ->1.0IU/ml to diphtheria and tetanus similar between two groups -majority of participants achieved four-fold rise Proportion with four-fold rise Tdap vs. DTaP-IPV, % (95% CI) Anti diphtheria: 89.8 (85.5-93.2) vs. 93.7 (89.9-96.3) Anti tetanus: 94.3 (90.8-96.8) vs. 93.7 (89.9-96.3) Anti-PT: 91.9 (87.8-94.9) vs. 96.8 (93.8-98.6) Anti-FHA: 88.1 (83.6-91.8) vs. 92.8 (88.9-95.7) Anti-FIM: 94.6 (91.2-97.0) vs. 87.6 (82.9-91.5 Anti-PRN: 94.3 (90.7-96.7) vs. 92.0 (88.0-95.1)		

Evidence for Safety						
STUDY DETAILS					**SUMMARY**	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Study vaccine: DTaP-IPV (Infanrix™-IPV, GSK)						
Gold MS et al. Med J Australia Aug 2003[13]	Infanrix™ (DTaP) (nb: Australia changed from DTwP to DTaP between Aug 1997 and Dec 1998)	Passive, population-based AEFI surveillance Retrospective review of AEFIs reported	Children given immunizations by practitioners who report to Southern Australia Immunisation Coordination Unit between 1997 and 2000	Not a study of 4-6 years but illustrates increased risk of local reactogenicity with more DTaP doses. 166 380 DTaP/DTaP-HepB vaccines given; 41 459 were 4th dose 581 AEFI reports during the time period; 138 (23.4%) were local reactions after pertussis-containing vaccines Jan 1998-Dec 2000: Median age of those with local reaction 19.5 months; relative risk local reaction at fourth dose versus first dose = 36 (95% CI: 8.78, 146). Rate of local reaction at fourth dose 171/100 000. Risk of local reaction greater in those primed with DTaP vs. DTwP	II-2	n/a (surveillance study)

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Nilsson et al. Scand J Infect Dis 2005[14]	DTaP-IPV (Infanrix™-IPV) vs DTaP (Infanrix™) + IPV	Open, randomized - 7 sites in Italy and Sweden	n =416 - 4-6 years (previously received 3 dose* primary series) *nb: Canadian children receive a 4-dose primary series whereas children in this study received only 3 priming doses	Outcomes: Evaluation of safety of DTaP-IPV vs. DTaP +IPV. Solicited local and systemic adverse events day 0 to day 3. Any other AE up to day 30. Key Findings: No statistically significant differences between groups. Local (DTaP-IPV vs. DTaP)*, % : -pain: 71% vs. 69% -redness: 50% vs. 49% -swelling: 55% vs. 56% -any large swelling reaction (any of > 50mm, diffuse swelling, or swelling to ≥ 1 adjacent joint: 13.5% vs. 17.4% -swelling involving ≥ 1 adjacent joint(s): 0% vs. 1.5% Systemic (DTaP-IPV vs. DTaP+IPV)*, %: -fever (axillary T > 38.0 ^{0}C): 21% vs. 17% -drowsiness: 25% vs. 25% -loss of appetite: 20% vs. 18% -irritability: 18% vs. 20% *proportions extrapolated from figure, did not extrapolate 95% CIs	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Black et al. Vaccine Aug 2006[16]	DTaP-IPV (Infanrix™-IPV) vs. DTaP (Infanrix™ + IPV)	Open randomized phase II non-inferiority trial 14 US centers	N=400	Outcomes: -local solicited adverse events (15 days post vaccination) -general adverse events (15 day post vaccination) -MMR specific general symptoms (43 days post vaccination) -unsolicited events (31 days post vaccination) -serious adverse events within 6 months of vaccination Key Findings: DTaP-IPV vs. DTaP, % (95% CI) Local -pain: 60.2% (53-67.1) vs. 57.4 % (50.2-64.5) -redness: 57.1% (49.9-64.2) vs. 50.8% (43.5-58.0) -swelling: 39.8% (32.9-47) vs. 41% (34-48.3) Systemic: -fever: 18.9% (13.7-25.1) vs. 21.6% (16.1-28.1) -drowsiness: 24.5% (18.6-31.3) vs. 22.2% (16.5-28.7) -loss of appetite: 20.9% (15.4-27.3) vs. 17.5% (12.5-23.6)	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Marshall et al. Vaccine Aug 2006[20]	DTaP-IPV (Infanrix™-IPV) vs DTaP (Infanrix™) + IPV	Open-label, randomized, non-inferiority, Phase IIIb - 3 Australian Centres	n=366 - 4-6 years	Outcomes: Evaluation of safety of DTaP-IPV (left deltoid) vs. DTaP (left deltoid) +IPV (right arm), both with concomitant MMR (right arm). Specific local and systemic adverse events (day 0 to day 3); MMR-specific symptoms (day 0 to day 14); unsolicited and serious adverse events up to day 30. Key Findings: Local (DTaP-IPV vs. DTaP), % (95% CI) -pain: 80.1% (73.3-85.8) vs. 64.1% (56.3-71.3) -redness: 77.8% (70.8-80.3) vs. 77.25 (70.1-83.4) -swelling: 60.2% (52.5-67.6) vs. 65.3% (57.5-72.5) -swelling involving ≥ 1 adjacent joint(s): 6.4% vs. 6.0% Systemic (DTaP- IPV+MMR vs. DTaP+IPV+MMR), up to 15 days, %, 95% CI -fever (axillary T > 39.0 ^{0}C): 4.1% (1.7-8.3) vs. 5.4% (2.5-10) -drowsiness: 23.4% (29.2-44.3) vs. 24% (17.7-31.2) -loss of appetite: 20.5% (14.7-25.3) vs. 24% (17.7-31.2)	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				-vaccine-related rash: 2.9% (1.0-6.7) vs. 3.6% (1.3-7.7)		
Black et al. Pediatr Infect Dis J April 2008[17]	DTaP-IPV (Infanrix™-IPV) vs. DTaP (Infanrix™ + IPV)	Open randomized Phase III randomized study - 24 US centers	N=4209	Outcomes: -local solicited adverse events (4 days post vaccination) -general adverse events (4 days post vaccination) -MMR specific general symptoms (15 days post vaccination) -unsolicited and serious adverse events (6 months post vaccination) Key findings: DTaP-IPV vs. DTaP+IPV, % (95% CI) Local -pain: 57% (55.2-58.7) vs. 53.3% (50.2-56.4) -redness: 36.6 (34.9-38.3) vs. 36.6% (33.6-39.6) -swelling: 26% (24.5-27.6) vs. 27% (24.3-29.8) -increase in limb circumference: 36% (34.3-37.7) vs. 37.8% (34.9-40.9) General -fever: 16% (14.7-17.4) vs. 14.8 % (12.7-17.2) -drowsiness: 19.1% (17.7-20.5) vs. 17.5% (15.2-19.9) -loss of appetite: 15.5% (14.3-16.8) vs. 16 %(13.8-18.4)	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Kemmerenet al. Vaccine June 2011[24]	DTaP-IPV (Infanrix™-IPV)	Cross-sectional study - Netherlands	n=849 (group who were aP primed)	Outcome measures: local and systemic reactions to DTaP-IPV in wP vs. aP primed 4 year olds children reported in survey returned one week after immunization. (Results shown below are only for aP primed group.) Local (n=824) % (95% CI) -pain: 45.5% (42.2-49) -redness: 30.5% (27.5-33.7) -swelling: 23.1% (20.3-26.1) -reduced use of arm: 20.4% (17.8-23.3) -swelling in axilla: 1.5% (0.8-2.5) Systemic (n=824) % (95% CI) -fever: 10.4% (8.5-12.7) -headache 5.6% (4.2-7.4) -pallor 3.5% (2.5-5.0) -nausea 5.2% (3.9-7.0) -vomiting 3.3% (2.3-4.7) -dizziness 1.1% (0.6-2.1) -abnormal perspiration 6.6% (5.1- 8.5) -syncope 0.4% (0.1-1.1)	Level III	Not possible to rate quality using Harris criteria

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Klein et al. Vaccine Jan 2012[21]	DTaP-IPV (Infanrix™ IPV)	Open-label, randomized, non-inferiority, Phase IIIb - 11 US Centres	n =478	Outcomes: Evaluation of safety of DTaP-IPV comparing Group 1 (DTaP-IPV + MMR + V simultaneously) and Group 2 (DTaP-IPV + MMR simultaneously and V one month later). All vaccines given in left arm. Specific local and systemic adverse events (4-day period following immunization) and unsolicited AEs (day 0-30) and serious AEs (up to 6 months). Key Findings (Group 1 vs. Group 2) Local* % -pain: 66% vs. 70% -redness: 50% vs. 49% -swelling: 41% vs. 38% -diffuse swelling: 1/239 (0.4%) in Group 1 and 6/237 (2.5%) in Group 2 -swelling involving one adjacent joint: 0/239 (0%) in Group 1 and 1/237 (0.4%) in Group 2. Systemic* -fever (axillary T > 39.0 ^{0}C): 26% vs. 27% -drowsiness: 25% vs. 26% -loss of appetite: 25% vs. 24% Unsolicited AEs (event types and	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				relationship to immunization not noted by authors): Group 1: 31.4 (95% CI: 25.6, 37.7%) Group 2: 30.4% (95% CI: 24.6, 36.7%) *proportions extrapolated from figure, did not extrapolate 95% CIs		
Study Vaccine: DTaP (Infanrix™, GSK *and* Daptacel®, Sanofi Pasteur)						
Study Vaccine: Tdap-IPV (Boostrix®-Polio, GSK)						
Jackson LA et al. Pediatrics Mar 2011[25]	DTaP (did not identify formulations/ brands)	Retrospective cohort study	n=233 616 4-6 year olds children who were enrolled in 1 of 7 managed care organizations (MCOs) participating in Vaccine Safety Datalink (VSD) collaborative project received DTaP between 2002 and 2006	1270 presumptive reactions (based on relevant ICD codes, ex. cellulitis) in first four days after vaccination (0.5% of 233 616 doses) Chart review completed for 1221/1270 (96%) and 1017/1221 confirmed (83%) 75% of all DTaP given in arm Higher BMI independently associated with risk of medically-attended local reaction (inadequate IM injection) Adjusting for age, gender, MCO site, RR medically-attended local reaction 1.78 (95% CI: 1.43, 2.21) for arm injection vs. thigh	II-2	Fair (retrospec-tive review of MD notes, did not have record of which DTaP product, not all presump-tive visits confirmed to be local reactions)

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				injection. When also adjusted for BMI (among subgroup with valid BMI)		
Sanger et al. Eur J Pediatr Dec 2007[11]	Tdap-IPV (Boostrix®-Polio) vs. Tdap (Boostrix®) +IPV	Partially blinded, randomized controlled trial (one injection vs. two injections not blinded) - 59 centers in Germany	N=959 - 4-8 years	-Endpoints/Outcomes -assessed through diary card 15 post vaccination -local symptoms (redness, pain, swelling, drowsiness, fever, irritability, loss of appetite) -serious adverse events – 30 days post immunization -Outcome measures: Tdap-IPV vs. Tdap+IPV Local reactions: -pain grade III 2.8% vs. 6.6% (p=0.035) -swelling 44.8% vs. 54.4%) (p=0.041) -fever >39C 6.0% vs. 1.5% (p=0.036) -no serious adverse outcomes reported	Level I	Fair
Ferrera et al. Hum Vaccin Immuno-ther March 2012[9]	Tdap-IPV (Boostrix®-Polio) vs DTaP-IPV [Tetravac] (PT &FHA containing Sanofi product, not available in	Randomized controlled trial - multicentered Italy	N=305 5-6 year olds	Endpoints/Outcomes: - 4d symptom diary for - solicited, unsolicited localized and general adverse events Outcomes: DTap-IPV vs. TdaP-IPV Pain (58.9% vs. 61.2%) Grade III swelling (5.3% – 3.3%) Fatigue (26.5%-23.7%)		

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
	Canada) both co-adminstered with MMRV			Fever (21.2%-19.7%) No serious adverse events		
Study Vaccine: Tdap (Boostrix®, GSK)						
Meyer CU et al. Hum Vaccin May-June 2008[12]	Tdap (Boostrix®) vs DTaP (Infanrix™) vs Td (Novartis product)	Randomized single blind trial	N=422	Outcome measures: -local solicited adverse events (15 days post vaccination) -general adverse events (15 day post vaccination) -unsolicited/serious adverse events within 31 days of vaccination Key findings: Local Tdap vs. DTaP -pain 47.8% vs. 63.3% -redness 33.9% vs 48.9% -swelling 32.2% vs 43.3% General Tdap vs DTaP -diarrhea 10% vs. 8.9% -irritability 16.1% vs. 21.1% -loss of appetite 17.8% vs. 17.8% -fever 20% vs. 22% -vomiting 7.8% vs. 4.4%	Level I	Fair
Study Vaccine: Tdap (Adacel®, Sanofi Pasteur)						
Scheifele et al. 2005 [27]	Tdap-IPV (Quadracel) vs. Tdap (Adacel)	Randomized controlled trial 2 Canadian centers	N=290 N=145 Tdap	Outcome measures: -30 minutes post immunization -2 weeks post immunization – SE diary -home visit at approximately 48 hour post immunization, if reaction	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				noted then telephone interview at 7days post immunization Key findings: Tdap vs. DTaP-IPV group -erythema ≥50mm 6.3% vs. 17.2% -swelling ≥25mm 23.1% vs. 35.9% -pain (mod/severe) 6.7% vs. 13.1% -fever 1.4% vs. 6.3% Rates of erythema >25mm, swelling statistically significant between groups, fever, pain (moderate/severe) not significant between groups		
Langley et al. Vaccine Jan 2007[10]	Tdap (Adacel®) + IPV(4-6 week later) vs. DTaP-IPV (Quadracel®)	Single blinded randomized controlled trial 8 Canadian centers	N=593 n=299 DTaP-IPV n=294 Tdap -children between 4-7 years of age who completed primary series with 4th dose of pentacel	Outcome measures: -30 minutes post immunization -2 weeks post immunization – SE diary -phone contact day 4 and 15 post immunization -unsolicited AE up to 6 weeks post immunization -Key findings: -localized findings less common in Tdap group vs. DTaP-IPV group -erythema 34.6% vs. 51.7% -swelling 24.2% vs. 33.8% -pain 39.6% vs. 67.2%	Level I	Fair

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
				-fever 8.72% vs. 16.9% -rates of any or moderate and severe erythema, swelling, pain and fever - non-inferior b/w vaccines		

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