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An Advisory Committee Statement (ACS)
National Advisory Committee on Immunization (NACI)†
Update on the Use of Conjugate Pneumococcal Vaccines in Childhood

Preamble

The National Advisory Committee on Immunization (NACI)† provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. PHAC 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 PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

Introduction

This statement will supplement previous conjugate pneumococcal statements[1-3] and provide information regarding a newly authorized conjugate vaccine against pneumococcal disease, Prevnar® 13 (PNEU-C-13). It is anticipated that adult pneumococcal immunization programs will be changing over the next few years, as other vaccines are in development and as new data on Synflorix™ (PNEU-C-10) and PNEU-C-13 is published. These vaccines and new indications for already authorized products will be reviewed in one or more additional statements once they are authorized or further indications are authorized for use in Canada. The 23-valent polysaccharide vaccine will not be discussed in this statement. Recommendations for its use remain unchanged.

This statement will:

- review existing NACI recommendations on the use of conjugate pneumococcal vaccines;
- update the epidemiology of pneumococcal disease in Canada relevant to the introduction of PNEU-C-13;
- provide an update on the conjugate pneumococcal vaccination schedules used in Canada;
- provide a literature review on the use of 3 doses (2 infant doses +1 booster) versus 4 doses (3 infant doses +1 booster) of conjugate pneumococcal vaccines;
- provide information on a newly licensed 13-valent vaccine against pneumococcal disease; and
- provide recommendations for the use of the 13-valent conjugate vaccine (PNEU-C-13).

Overview of past NACI recommendations for conjugate pneumococcal vaccine

A conjugate seven-valent formulation, Prevnar™, (Pneu-C-7) was authorized for use in Canada in infants in 2002. NACI issued a statement[1] recommending the addition of this vaccine to the routine infant immunization schedule. Addenda to this

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statement were published in 2003, with recommendations for children in whom pneumococcal vaccine schedule had been interrupted[2], in 2006 with evidence for an alternate PNEU-C-7 three-dose schedule,[3] and in 2009, with recommendations on a newly authorized product, PNEU-C-10.[4]

Currently, vaccination with a 7- or 10- valent pneumococcal conjugate vaccine is recommended for all Canadian children <59 months of age. In addition, vaccination with a 10-valent conjugate vaccine is recommended for children who have not previously received adequate vaccination with a 10-valent vaccine when protection is needed during outbreaks of pneumococcal infection due to serotypes 1, 5 or 7F.

Methods

NACI reviewed such considerations as the burden of disease and the target population, safety, immunogenicity, efficacy, effectiveness of the vaccine(s), vaccine schedules, and other aspects of the overall immunization strategy. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence were prepared using NACI's methodological hierarchy (Tables 4 and 5), and proposed recommendations for vaccine use were developed. The Working Group chair and a PHAC medical specialist presented the evidence and proposed recommendations to NACI. Following thorough review of the evidence and consultation at NACI meetings, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text of this statement. PHAC maintains documentation of these processes throughout knowledge synthesis and recommendation development.

Epidemiological data were collected from five sources of Canadian pneumococcal surveillance data: the provinces of Alberta, British Columbia, and Quebec, the Toronto Invasive Bacterial Diseases Network (TIBDN) and the International Circumpolar Surveillance (ICS) project. A literature search was conducted for data comparing 3- dose and 4-dose vaccine series for immunization with pneumococcal conjugate vaccine.

Epidemiology of Pneumococcal Disease in Canada

Epidemiologic data on the burden of disease in Canadian children was reviewed in a recent NACI statement.[4] That review also summarized all currently available sources of surveillance data on invasive pneumococcal disease in Canada, and is not repeated here. Additional epidemiologic data and analysis specifically relevant to PNEU-C-13 are provided in this statement.

The introduction of pediatric PNEU-C-7 programs in Canada has been associated with a greater than 80% decline in the incidence of pediatric invasive pneumococcal disease (IPD, defined as infection associated with a sterile site culture positive for *S. pneumoniae*) caused by serotypes contained in PNEU-C-7.[5-9] However, the incidence of IPD caused by non-vaccine serotypes has increased, resulting in a somewhat lesser reduction in the overall incidence of IPD.[5-9] Between 2004 and 2009, a widespread community-based outbreak of serotype 5 disease occurred, principally in adults in western Canada.[10] Across Canada, and in other countries, the incidence of disease due to strains of serotype 19A, including multidrug resistant 19A has also increased.[11-15] The proportion of IPD caused by serotype 19A has been increasing steadily from 2000 to 2007 in children admitted to IMPACT centers. In 2000-2001, 19A caused 2% of all IPD but increased to 14% by 2006-2007. Amongst non-PNEU-C-7 cases, 19A rose from 8% of all such cases in 2000-2001 to 19% in 2006-2007. Of all IPD caused by vaccine-preventable serotypes, the proportion of IPD caused by serotype 19A rose from 25 to 39% of the additional serotypes in PNEU-C-13 over PNEU-C-7 but represented 62% of cases caused by additional serotypes in PNEU-C-13 over PNEU-C-10.[5]

Table 1 provides data on the incidence of IPD in various regions of Canada in 2007 and 2008 (after implementation of routine PNEU-C-7 vaccination programs). Table 2 provides information from the same regions on the number of cases in infants less than 5 months of age. These cases are less likely to be directly vaccine preventable, although they may be prevented indirectly by herd immunity. Figure 1 shows, for 2007 and 2008 (that is, 2 or more years after the implementation of routine PNEU-C-7 vaccination programs in all provinces), the proportion of cases in children aged 6 months to 5 years due to serotypes included in different conjugate vaccines authorized for use in Canada. These relative proportions are similar for children aged 6 to 12 months, and children aged 1 to 4 years.

Table 1. Incidence (per 100 000) and number of cases of IPD by serotype categories among children aged less than 5 years, 2007 and 2008

Region‡	Serotypes in PNEU-C-7 (4, 6B, 9V, 14, 18C, 19F, 23F)		Additional serotypes in PNEU-C-10 over PNEU-C-7 (serotypes 1, 5, 7F)		Additional serotypes in PNEU-C-13 over PNEU-C-7 (serotypes 1,5,7F, 3, 6A, 19A)		Other (serotypes not included in any conjugated vaccine formulation)	
	2007 Rate (n)	2008 Rate (n)	2007 Rate (n)	2008 Rate (n)	2007 Rate (n)	2008 Rate (n)	2007 Rate (n)	2008 Rate (n)
BC*	3.3 (7)	2.3 (5)	1.9 (4)	0.0 (0)	6.2 (13)	3.7 (8)	5.7 (12)	6.0 (13)
Quebec*	3.1 (12)	1.0 (4)	2.8 (11)	1.5 (6)	13.2 (51)	17.8 (71)	12.7 (49)	11.5 (46)
Toronto/Peel*	6.2 (13)	0.0 (0)	0.5 (1)	2.1 (4)	5.7 (12)	11.0 (21)	4.3 (9)	3.2 (6)
Alberta[1]	1.8 (4)	2.6 (6)	3.7 (8)	0.0 (0)	6.4 (14)	7.5 (17)	7.3 (16)	9.2 (21)
Northern Canada*	7.8 (1)	7.8 (1)	0.0 (0)	0.0 (0)	7.8 (1)	31.2 (4)	7.8 (1)	54.5 (7)

‡ Data from passive, population-based surveillance for invasive pneumococcal disease are available for the provinces of British Columbia, Alberta and Quebec, and in Northern Canada (northern Labrador, northern Quebec, Nunavut, the Yukon and the Northwest Territories) as part of International Circumpolar Surveillance (ICS); active population-based surveillance is conducted in metropolitan Toronto and Peel Region (labeled as Toronto). Details of these surveillance systems can be found in reference 4.

* Number of cases with unknown serotypes in children less than 5 years of age were: BC 2 in 2007 and 4 in 2008;
Quebec, 8 in 2007 and 7 in 2008, Toronto/Peel, 2 in 2007 and 5 in 2008; Northern Canada (ICS), none.

[1] Based on number of case-isolates received for typing at the National Centre for Streptococcus

Table 2. Cases of IPD by serotype categories among infants ages 0 to 5 months (2007 and 2008)

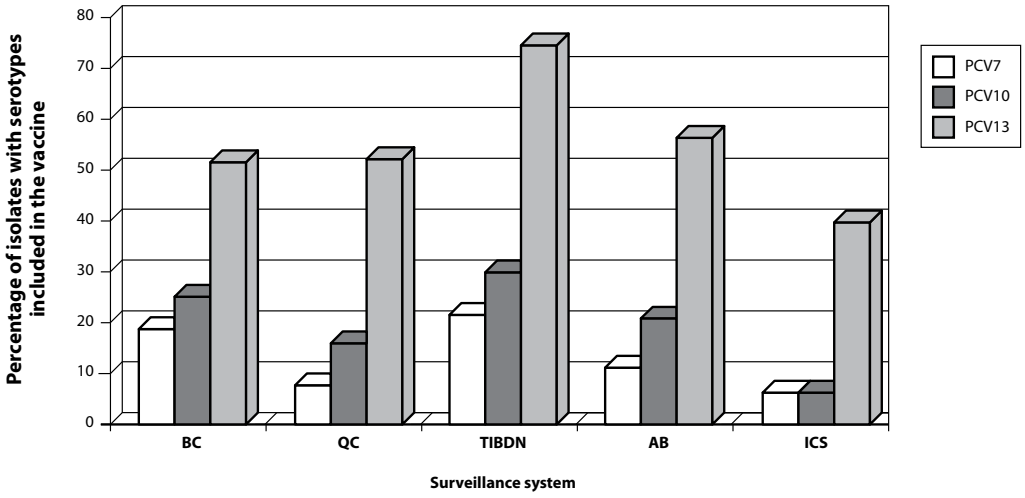
Region‡	Serotypes in PNEU-C-7 (4, 6B, 9V, 14, 18C, 19F, 23F)	Additional in PNEU-C-10 over PNEU-C-7 (serotypes 1, 5, 7F)	Additional in PNEU-C-13 over PNEU-C-7 (serotypes 1,5,7F, 3, 6A,19A)	Other serotypes (not included in any infant formulation)
	2007 and 2008	2007 and 2008	2007 and 2008	2007 and 2008
BC*	5	1	2	2
Quebec*	2	2	10	12
Toronto/Peel*	3	0	1	1
Alberta[1]	2	1	4	7
Northern Canada*	1	0	1	0

‡ Data from passive, population-based surveillance for invasive pneumococcal disease are available for the provinces of British Columbia, Alberta and Quebec, and in Northern Canada (northern Labrador, northern Quebec, Nunavut, the Yukon and the Northwest Territories) as part of International Circumpolar Surveillance; active population-based surveillance is conducted in metropolitan Toronto and Peel Region (labeled as Toronto/Peel),. For details of these surveillance systems, see reference 4

* Number of cases with unknown serotypes in children less than 6 months of age: BC no cases; Quebec, 1 case; Toronto/Peel, 1 case; Northern Canada (ICS), no cases.

[1] Based on number of case-isolates received for typing at the National Centre for Streptococcus

Figure 1. Percentage of isolates causing IPD in children aged 6 months to 5 years of age during 2007 and 2008 with serotypes included in different conjugate vaccines



Pneumococcal conjugate immunization schedules used in Canada, January, 2010

With the authorization for use of PNEU-C-10 in December 2008, a number of provinces and territories have changed their product of choice for pneumococcal conjugate vaccination. Please refer to the PHAC website (www.phac-aspc.gc.ca/im/ptimprog-progimpt/table-1-eng.php), for updated information on schedule and product used by jurisdiction.

Recent Literature Regarding Vaccination Schedules

Three-dose versus four-dose schedule using PNEU-C-7

At the time of publication of the May 2006 NACI statement, two published studies[16, 17] reported on immunogenicity associated with three-dose immunization schedules (2+1) for PNEU-C-7(Table 5). Both reports suggested that two doses of PNEU-C-7 given at 3 and 5 months of age provided satisfactory immune responses for serotypes other than 6B and 23F, and a third dose given after 12 months of age evoked a strong response for all serotypes. Since that time, Goldblatt *et al.* have confirmed these findings for two doses of PNEU-C-7 at 2 and 4 months of age, and identified that two doses given at 2 and 3 months of age resulted in significantly reduced immunogenicity for serotypes 6B and 23F, and lower 12 month EIA titers for serotypes 4 and 9V, when compared to two doses given at 2 and 4 months of age.[18]

Since that time, four publications have assessed the clinical efficacy of three-dose schedules of PNEU-C-7 for routine infant immunization (Table 5). Whitney et al.[19] used a case control study to determine PNEU-C-7 vaccine effectiveness during the US vaccine shortage (2001-2004). From this data, two doses given prior to 7 months of age with an additional booster at 12 to 16 months provided 96% (95% CI 75-100%) vaccine effectiveness against IPD. Vestrheim et al.[20] described the effectiveness of a three-dose schedule using PNEU-C-7 in Norwegian children. The program was introduced into the routine infant schedule in July 2006 with doses at 3, 5 and 12 months of age. National surveillance data was used to determine the incidence of IPD and the causative serotypes in children less than 2 years of age. In the two years prior to the introduction of PNEU-C-7, the incidence of vaccine serotype IPD was 47.1 per 100 000 population. One year after the introduction of PNEU-C-7, the incidence of vaccine serotype IPD decreased to 13.7 per 100 000, a reduction in IPD incidence of 74% (95% CI 57-85%), similar to reductions achieved in jurisdictions with four-dose schedules. Canadian data are provided by a Quebec case control study using PNEU-C-7.[21] Cases were children between the ages of 2 months and 59 months who had an episode of IPD between 2005 and 2007. Controls were identified from the provincial health registry to include five randomly selected controls per case. In children who received two doses prior to 7 months of age with an additional booster at 12-16 months of age, the estimated vaccine effectiveness was 100% (95% CI 15-100%). Similarly, a study from the Netherlands, presented in abstract form, reported a 98% reduction in the incidence of IPD caused by PNEU-C-7 serotypes in vaccine eligible children two years after implementation of routine infant vaccination with a three-dose schedule.[22] Despite inferior immunogenicity of serotype 6B after two (at 2, 4 months) as compared to three (at 2, 4, 6 months) infant doses, the estimated efficacy of three doses of vaccine against serotype 6B was 94% (95% CI 77-98%) in the US case-control study[19], and, in the Quebec study, the efficacy of one or more doses of PNEU-C-7 against serotype 6B IPD was 90% (95% CI 49-98%).[21]

Two studies have reported data on nasopharyngeal (NP) colonization with the use of a three-dose infant immunization schedule. A study from Israel documented no difference in the rate of nasopharyngeal colonization with PNEU-C-7 serotypes in children vaccinated with three-dose versus four-dose schedules.[23] In a study from the Netherlands, children were randomized to receive no vaccine (controls), two infant doses (2 and 4 months) or two infant doses with one booster dose (2, 4 months and 11 months of age). Children and their parents were tested for NP carriage of *S. pneumoniae* at 12 months, 18 months and 24 months of age. In the two vaccinated groups, fewer children and their parents were colonized with *S. pneumoniae*[24] compared to controls suggesting that herd immunity can be maintained with two or three doses of PNEU-C-7.

Two jurisdictions in Canada currently recommend a three-dose schedule for PNEU-C-7 in healthy children. (http://www.phac-aspc.gc.ca/im/ptimprog-progimpt/table-1-eng.php) During a shortage of PNEU-C-7 between August 2001 and September 2004, the Advisory Committee on Immunization Practices (ACIP) approved a three-dose schedule in the US; however, in October 2004, the ACIP once again recommended a four-dose routine infant schedule.[25] Within the European Union, in 2009, 11 of 24 countries reporting PNEU-C-7 programs used a three-dose schedule for all children, and a twelfth (Switzerland) recommended a three-dose schedule for healthy children but a four-dose schedule for children with chronic conditions increasing their risk of IPD.[26]

Three-dose versus four-dose schedule using PNEU-C-13

One study done in Italy investigated a three-dose schedule where infants were vaccinated with either PNEU-C-13 or PNEU-C-7 at 3 months, 5 months and 11 months of age.[27] Most PNEU-C-13 recipients had ELISA titres >0.35mcg/mL after two infant doses of vaccine for all serotypes except 6A, 6B and 23F. After a toddler booster dose, >90% of vaccine recipients in the PNEU-C-13 group achieved ELISA titers >0.35mcg/mL for all serotypes. The safety profile of recipients of PNEU-C-13 or PNEU-C-7 series was similar. More patients in the PNEU-C-13 arm reported irritability after one dose

(P<0.05) than in the PNEU-C-7 group. Otherwise, there were no statistically significant differences in the percentage of patients in either group experiencing local reactions or unsolicited adverse events. One serious adverse event was noted in the PNEU-C-7 group (infantile spasms). At the time of writing of this statement, study results were available only as a poster presentation; therefore further information is not available.[27]

Prevnar® 13

Vaccine composition

PNEUMOCOCCAL - CONJUGATE - VALENT 13 is a sterile solution of polysaccharide capsular antigen of 13 serotypes of Streptococcus pneumoniae (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F). The polysaccharides are conjugated individually to a diphtheria CRM_{197} protein carrier prior to compounding to a multivalent vaccine. The CRM_{197} protein carrier is adsorbed on aluminum phosphate as an adjuvant. Each 0.5mL dose of vaccine contains 4.4mcg of the 6B polysaccharide, and 2.2 mcg each of the remaining polysaccharides.

PNEU-C-13 is the same as PNEU-C-7 with the exception of the additional six serotypes, a modification of the conjugation for serotype 19F to improve stability, the addition of 0.02% polysorbate (Tween) 80 as emulsifier, and succinate buffer. The syringe stopper is latex free.

PNEU-C-13 is marketed in a single dose, prefilled syringe containing 0.5mL of vaccine.

Efficacy

There are currently no efficacy data available for PNEU-C-13 for any indication. It is anticipated that the licensing of future pneumococcal conjugate vaccines for protection against IPD in children will require only immunogenicity data rather than efficacy data because placebo-controlled trials are not possible and very large studies would need to be done to show differences in the incidence of IPD between vaccines differing by only a few serotypes.[28, 29]

Immunogenicity

A review of the serologic correlates of protection from IPD that are used to assist in the interpretation of immunogenicity studies is provided in a recent NACI statement.[4]

More than 3000 children have received PNEU-C-13 in trials comparing PNEU-C-7 to PNEU-C-13, and assessing the immune response to concurrently administered vaccines in routine childhood vaccination schedules. No studies have compared PNEU-C-13 and PNEU-C-10.

In the two pivotal studies comparing PNEU-C-13 and PNEU-C-7, non-inferiority criteria for the defined primary outcome - the percent of infants with enzyme-linked immunosorbent assay (ELISA)>0.35mcg/ml after primary series - were met for 5 and 6 of the 7 serotypes included in PNEU-C-7, respectively.[30-33] In both pivotal studies, the ELISA response to 6B was inferior in PNEU-C-13 as compared to PNEU-C-7 (87.3% vs. 92.4% in the US study after three doses of vaccine administered at 2, 4, 6 months) and (77.5% vs. 87.1% in the German study after three doses of vaccine at 2, 3, 4 months). Non-inferiority criteria for all secondary outcomes for response to serotype 6B were met, including non-inferiority as assessed by opsonophagocytic assay (OPA). It is, however, important to recognize that the power to detect non-inferiority for some outcomes was limited. Responses to serotype 6B were significantly lower in primary series with vaccination at 2, 3 and 4 months (77.5%), than in those with vaccination at 2, 4, 6 months (87.3%). In the German, but not the US, pivotal study, serotype 23F also failed to meet the primary non-inferiority criteria (88.7% vs 89.5% of infants with IgG by ELISA of >0.35mcg/ml). All secondary criteria were met. When comparing geometric mean concentration (GMC) by ELISA, titres achieved after PNEU-C-13 were lower than those achieved after PNEU-C-7 for all serotypes other than 19F; however, there were no apparent differences in titers assessed by OPA. When compared to ELISA GMC measured after two doses of PNEU-C-7, ELISA GMC after two doses of PNEU-C-13 were significantly lower for 4 of 7 serotypes included in PNEU-C-7; but these differences were not present when OPA geometric mean titres (GMT) were compared. The clinical significance of these differences is not clear.

In these studies, non-inferiority for the 6 additional serotypes in PNEU-C-13 was assessed by comparing the titers achieved after PNEU-C-13 for each serotype to the titers achieved against the serotype with the lowest response after vaccination with PNEU-C-7. By this criterion, non-inferiority was met for all 6 additional serotypes in the German trial, and 5 of the 6 additional serotypes (all serotypes other than serotype 3) in the US trial. This difference may be related to geographic differences in the epidemiology and immune response to serotype 3 *S.* pneumoniae. In trials conducted to date, responses to serotype 3 appeared to be similar to other serotypes in European trials, but lower than responses to other serotypes in North American trials. In North American trials completed to date, after a three-dose series at 2, 4, and 6 months, the percent of children with ELISA IgG of>0.35 mcg/mL to serotype 3 ranged from 63.5% to 79.6%. In comparison, in a European trial, after a three-dose series at 2, 4, and 6 months, the percent of children with EIA IgG of >0.35 mcg/mL to serotype 3 was 90.3% (95% CI 86.1-93.5%). Neither the reason for, nor the clinical implications of, these differences is known.

Three studies have examined the immunogenicity of toddler doses of PNEU-C-13 in children who have not received doses of PNEU-C-13 as infants. Wysocki et al. administered two doses of PNEU-C-13 to 112 children aged 12-23 months at first dose, and a single dose to 152 children aged 24 to 72 months of age.[53] More than 95% of children had ELISA

GMC of >0.35mcg/ml post-vaccination for all 13 serotypes included in the vaccine, and the GMCs were comparable to or greater then those achieved after a routine 3-dose infant series. Grimprel et al. compared the effect of administering a single dose of PNEU-C-13 at 12 months in children who had previously been immunized with three infant doses of either PNEU-C-7 (N=137) or PNEU-C-13 (N=273).[34] At one month after the toddler dose, GMC by EIA and OPA to the 6 serotypes in PNEU-C-13 but not PNEU-C-7 were higher in the children who had received PNEU-C-13 as infants. However, 89.9% (serotype 6A), 90.1 %(serotype 5), 93.8% (serotype 3), 95.5% (serotype 1) and 100% (serotypes 7F and 19A) of children who had received only a single dose of PNEU-C-13 had EIA GMC titers of >0.35mcg/ml, and more than 97.5% of such children had OPA titers of >1:8 to all six serotypes. Silfverdal et al., in an open label study, administered a single dose of PNEU-C-13 to 116 12-month old children. Post-vaccination, all children had ELISA GMC of >0.35mcg/mL for all 13 serotypes included in the vaccine.[36] Thus, one dose of PNEU-C-13 administered at 12 months of age or later offers adequate immunogenicity, regardless of the pneumococcal infant series used.

Very few studies have looked at the immunogenicity of PNEUMOCOCCAL - CONJUGATE - VALENT doses in immunocompromised patients. Vieira et al[37] determined antibody response following the administration of 2 doses of PNEU-C-7 to 48 children between 1 and 9 years of age with chronic renal failure (both on conservative treatment and dialyzed). None of these children had been previously vaccinated with any pneumococcal vaccine. Sixty days after the second PNEU-C-7 dose, 100% of children on conservative treatment and 95.8% of dialyzed children had GMC titers ≥ 0.35 mcg/mL. Meerveld-Eggink et al[38] determined the antibody response after 2 doses of PNEU-C-7 administered with a 6-week interval one year following reduced-intensity conditioning regimens for allogeneic stem cell transplants in 26 patients aged 44 to 67 years. Except for serotype 6B, more than 73% of the patients developed antibody levels ≥ 0.35 mcg/mL.

Schedule and Dosage

The dose for infants and children less than five years of age is 0.5 mL. The product monograph recommends that the primary immunization series consist of three doses at approximately 2-month intervals beginning at 2 months of age, followed by a fourth dose at 12-15 months of age (3+1 schedule), but adds that a 2+1 schedule may be considered, with doses given at 2 months, 4 months, and 11-12 months of age.

Children between 12 and 23 months vaccinated for the first time with a conjugate pneumococcal vaccine should receive two doses of PNEU-C-13, with at least 8 weeks between each dose. Children between 24 and 59 months vaccinated for the first time with a conjugate pneumococcal vaccine only require one dose of PNEU-C-13.

Route of Administration

Administer PNEU-C-13 by intramuscular injection. Shake the syringe well to create a homogenous white suspension, then expel air from the syringe before vaccine administration.

Booster Doses and Re-Immunization

There are no data regarding booster doses or re-immunization after completion of the routine pediatric schedule.

Serological Testing

There is no indication for routine pre- or post-immunization serology.

Storage Requirements

The vaccine should be refrigerated, with the temperature maintained between 2ºC to 8ºC. Vaccine which has been frozen should be discarded. In cases of temporary breaks in the cold chain, PNEU-C-13 has been shown to be stable at temperatures up to 40oC for up to 4 days.[39] However, practitioners should adhere to usual provincial procedures for deciding on vaccine viability following breaks in the cold chain.

Simultaneous Administration with Other Vaccines

PNEU-C-13 has been studied when given concomitantly with a number of vaccine antigens used in a childhood schedule in Canada with no adverse effect on immunogenicity or safety profile. These antigens include: diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, inactivated poliomyelitis, rotavirus, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella.[40] As with general guidance given for all vaccines, PNEU-C-13 should be administered at a different site than concomitantly administered vaccines, using a different needle and syringe.

Vaccine Safety and Adverse Events

According to data provided by the manufacturer, a total of 14 studies with a safety review component have been conducted. Presented below are data in the public domain as of September 2009.

PNEU-C-13 has the same formulation as PNEU-C-7, with the exception of a modification in the conjugation for serotype 19F, and the presence of 0.02% polysorbate (Tween) 80, and succinate buffer, both of which are excipients present in other vaccines. The pivotal trials in Germany and the US used a formulation of PNEU-C-13 without Tween 80. A trial in Poland compared the reactogenicity of formulations with and without Tween 80. There was a small but statistically significantly increase in mild induration and erythema in the Tween 80 arm of the study with the first and second doses, but no differences in moderate or severe local adverse events, and statistically fewer infants that reported systemic adverse events after dose two ($p<0.05$).[41]

A total of 2116[30, 33, 40, 42, 43] children received PNEU-C-13 as compared to PNEU-C-7 as a primary series. In one study, there were significant differences between groups in the incidence of induration (28.2% PNEU-C-13 vs. 20.5% PNEU-C-7, P= 0.04) and erythema (27.2% PNEU-C-13 vs. 36.4% PNEU-C-7, P=0.04) after any dose.[32] In the same study, more children receiving PNEU-C-7 reported increased sleep after the second vaccine dose (53.9% PNEU-C-13 vs. 66.8% PNEU-C-7, p= 0.003).[32] In other studies[41, 44-47] there were no statistically significant differences in local or systemic adverse events. No differences in rates of severe adverse events, and no unanticipated adverse events were identified.

Three studies, including 844 children who received PNEU-C-13, have compared PNEU-C-13 versus PNEU-C-7 initial doses or boosters at 12 to 15 months of age. No significant differences in local or systemic adverse events were identified. Only one serious adverse event was reported - status asthmaticus in a child who had received PNEU-C-13, which was deemed unrelated to the vaccine.[32, 48]

Contraindications and Precautions

PNEU-C-13 is contraindicated in any individual with a history of anaphylaxis to any component of the vaccine, including diphtheria toxoid.

Interchangeability

A single study reported that, in children who received a primary series of immunization with PNEU-C-7, a single dose of PNEU-C-13 at 12 to 15 months of age was non-inferior to a PNEU-C-7 dose for the seven serotypes in the PNEU-C-7 vaccine, and induced an antibody response >0.35mcg/mL by ELISA for the additional 6 serotypes included in PNEU-C-13 in over 90% of children.[31] There were no significant differences in rates of adverse events associated with the 12-15 month dose of PNEU-C-7 compared to PNEU-C-13 after primary immunization with PNEU-C-7. There are no other available data on the interchangeability of PNEU-C-7 and PNEU-C-13, or PNEU-C-10 and PNEU-C-13.

Summary

PNEU-C-13 use is supported by immunogenicity data suggesting protection against 6 additional serotypes, (including 19A), and by similarity in formulation to PNEU-C-7, a vaccine which has proven efficacy. However, no clinical efficacy or effectiveness data are yet available, and there is no direct evidence that correlates of immunity developed for the seven serotypes in PNEU-C-7 also apply to the six additional serotypes included in the PNEU-C-13. In addition, using the World Health Organization's agreed upon primary criterion for assessment of immunogenicity (non-inferior to PNEU-C-7 when the percentage of children with IgG >0.35 mcg/mL measured by ELISA[31], immunogenicity to serotypes 6B and 23F are inferior to PNEU-C-7 with the currently formulated PNEUMOCOCCAL - CONJUGATE - VALENT-13 vaccine. However, reduced titers to serotypes 6B and 23F are not observed when antibody titers are measured by opsonophagocytic assays, and most experts believe that the differences are unlikely to affect direct protection against invasive pneumococcal disease. Some experts note that reduced ELISA titres might correlate with reduced protection against pneumonia, otitis media and nasopharyngeal colonization (and thus herd immunity).[47] There are no studies comparing the immunogenicity of PNEU-C-10 and PNEU-C-13. However, in studies comparing PNEU-C-10 and PNEU-C-7, there is a similar trend to that seen in studies comparing PNEU-C-13 and PNEU-C-7; that is, antibody concentrations to serotypes 6B and 23F measured by EIA after vaccination with PNEU-C-10 are somewhat lower than those achieved after vaccination with PNEU-C-7. PNEU-C-10 does not contain antigens for serotypes 3, 6A or 19A; however, it may provide some protection against otitis media due to non-typeable *H. influenzae*.[4]

Initially, North American expert recommendations were that infant conjugate pneumococcal immunization programs provide vaccination at 2, 4, and 6 months, with a booster dose at 12 to 18 months. Although immunogenicity after two doses of vaccine (at 2 and 4 months of age) is lower than that thought to be required for direct protection of individuals for some serotypes, it is clear that infant immunization schedules with three doses of PNEU-C-7 (at 2, 4 and 11 to 15 months) result in reductions in invasive pneumococcal infections that are indistinguishable from programs using four doses of PNEU-C-7. It is not clear whether the reduced immunogenicity of PNEU-C-10 and PNEU-C-13 to serotypes 6B and 23F compared to PNEU-C-7 would reduce the effectiveness of a three-dose versus four-dose schedule of PNEU-C-10 or PNEU-C-13. It is, however, anticipated that the indirect protection against PNEU-C-7 serotypes observed with the introduction of routine heptavalent pneumococcal conjugate vaccine programs will also be observed for the additional 6 serotypes in PNEU-C-13 when PNEU-C-13 programs are introduced. In other words, it is expected that, when routine PNEU-C-13 vaccination programs are introduced, a reduction in IPD due to the 6 additional serotypes in PNEU-C-13 will be seen not only in vaccinated children, but also in unvaccinated persons (herd immunity). For instance, if PNEU-C-13 were given only to children over the age of 12 months, protection against serotype 19A in children less than 12 months of age would be expected to arise from indirect protection from older children who have received the 13-valent vaccine. How effective this indirect protection might be, what proportion of older children need to be vaccinated to achieve protection of younger children, and how long it would take after the vaccination program starts to see reductions in disease in unvaccinated younger children are all unknown.

There is evidence that a single dose of 13-valent conjugate vaccine is cost-effective for healthy children aged 24-59 months who have received complete age-appropriate vaccination with PNEU-C-7.[48]

Recommendations

For the purposes of these recommendations, we consider as high risk of IPD, children with either immunocompromise or chronic conditions that put them at increased or presumed increased risk of IPD but who are expected to mount an antibody response to conjugate pneumococcal vaccines that is close to that of healthy children. These children include those who have:

- Chronic CSF leak
- Chronic neurologic condition that may impair clearance of oral secretions[49]
- Cochlear implants (including those children who are to receive implants)
- Chronic cardiac or pulmonary disease (excluding asthma)
- Poorly controlled diabetes mellitus
- Asplenia (functional or anatomic)
- Sickle cell disease or other hemoglobinopathies
- Congenital immunodeficiencies involving any part of the immune system, including B-lymphocyte (humoral) immunity, T-lymphocyte (cell) mediated immunity, complement system (properdin, or factor D deficiencies), or phagocytic functions
- Hematopoietic stem cell transplant (candidate or recipient)
- Human immunodeficiency virus (HIV) infection
- Immunosuppressive therapy including use of long term corticosteroids, chemotherapy, radiation therapy, post-organ-transplant therapy, and certain anti-rheumatic drugs
- Chronic kidney disease, including nephrotic syndrome
- Chronic liver disease (including hepatitis B and C, and hepatic cirrhosis due to any cause)
- Malignant neoplasms including leukemia and lymphoma
- Solid organ or islet cell transplant (candidate or recipient).

Table 3 (age < 24 months) and Table 4 (age 24-59 months) provide detailed schedules for PNEU-C-13 for Canadian children that incorporate routine schedule recommendations and the specific recommendations provided below.

Routine Infant Immunization Schedules

1. NACI concludes that there is **good** evidence to recommend that all **routine infant immunization schedules** for children in Canada include a conjugate pneumococcal vaccine (**NACI Recommendation A**);
2. Given the current epidemiology of IPD in Canada with increased burden of illness due to serotypes contained in PNEU-C-13 but not in the other PNEU-C-valent , in particular 19A, NACI concludes that there is **good** evidence to recommend that PNEU-C-13 vaccine be the current product of choice for routine infant immunization schedule (**NACI Recommendation A**);
3. Taking into account herd immunity (indirect protection), serotypes replacement, and the relative cost of vaccines, the choice of pneumococcal vaccine for the primary infant series in a jurisdiction may change over time and will depend on the local serotype and age-specific epidemiology of IPD. NACI therefore concludes that in the future there is **good** evidence to recommend that a pneumococcal conjugate vaccine be part of the infant immunization schedule, in accordance with circulating serotypes. (**NACI Recommendation A**);
4. In regards to 3-dose schedules (2. 4, and 12 to 15 months), NACI concludes that there is **good** evidence that, in the context of a population-based program, PNEU-C-7 used as a three-dose schedule for healthy infants is non-inferior to a four-dose schedule (2, 4, 6 and 12 to 18 months) (**NACI Recommendation A**). Of note, programs using a 3-dose schedule should offer the 3rd dose early in the 2nd year of life (at 12 months of age) to allow for early complete protection. For PNEU-C-10 and PNEU-C-13, NACI concludes that there is **insufficient** evidence to determine whether three-dose schedules are non-inferior to four-dose schedules for healthy children (NACI Recommendation I). Provinces and territories electing to implement a PNEU-C-10 or 13 3-dose program should continue ongoing surveillance of vaccine program effectiveness. For infants at high risk for IPD, NACI concludes that there is **fair** evidence to recommend a four-dose schedule (**NACI Recommendation B**);
5. For infants who have started an immunization schedule with one conjugate vaccine, NACI concludes that there is **fair** evidence to recommend that they may continue their immunization schedule with a different conjugated vaccine (**NACI Recommendation B**)

PNEUMOCOCCAL - CONJUGATE - VALENT Dose between 12 – 23 months of age

For children aged 12-23 months of age who have not previously received a conjugate pneumococcal vaccine, two doses of PNEU-C-13 are recommended, with at least 8 weeks between each dose. **Children in this age group who are at high risk of IPD** should also receive a dose of Pneu-P-23 once they turn 24 months of age with an interval between the PNEU-C-13 and PNEU-P-23 dose of at least 8 weeks (**NACI Recommendation A**). Moreover, it should be noted that immunocompromised children will benefit from herd immunity (indirect protection).

For children aged 12-23 months who have had complete, age-appropriate pneumococcal vaccination but who have not previously received a PNEU-C-13 vaccine, NACI concludes that:

1. There is **good** evidence to recommend that **healthy (not high risk) children** receive one dose of PNEU-C-13 (**NACI Recommendation A**);
2. Based on a small number of studies and expert opinions, there is **fair** evidence to recommend that **children who are at high risk of IPD** receive one dose of PNEU-C-13 at or after 12 months of age and a dose of PNEU-P-23 once they turn 24 months of age with an interval between the PNEU-C-13 and PNEU-P-23 dose of at least 8 weeks (**NACI Recommendation B**). According to experts' opinion, immunocompromised children are expected to benefit from herd immunity against serotypes included in the vaccine.

Catch-up Dose (24 – 35 months of age)

For children aged 24-35 months of age who have not previously received a pneumococcal vaccine or completed a series, one doses of PNEU-C-13 is recommended. **Children in this age group who are at high risk of IPD** should also receive a dose of PNEU-P-23 with an interval between the PNEU-C-13 and PNEU-P-23 dose of at least 8 weeks (**NACI Recommendation A**). Moreover, it should be noted that immunocompromised children will benefit from herd immunity (indirect protection).

For children aged 24-35 months who have had complete, age-appropriate pneumococcal vaccination but who have not previously received a PNEU-C-13 vaccine, NACI concludes that:

1. There is **good** evidence to recommend that **healthy (not high risk) children** receive one dose of PNEU-C-13 (**NACI Recommendation A**);
2. There is fair evidence to recommend that children **at high risk of IPD** receive one dose of a PNEU-C-13. This dose should be given whether or not the child has already received PNEU-P-23. If the child has not previously received PNEU-P-23, a dose should be administered with an interval of at least 8 weeks between the PNEU-C-13 and PNEU-P-23 dose (**NACI Recommendation B**). According to experts' opinion, immunocompromised children are expected to benefit from herd immunity against serotypes included in the vaccine.

Catch-up Dose (36 – 59 months of age)

For children aged 36 - 59 months of age who have not previously received a pneumococcal vaccine or completed a series, one doses of PNEU-C-13 is recommended. **Children in this age group who are at high risk of IPD** should also receive a dose of PNEU-P-23 with an interval between the PNEU-C-13 and PNEU-P-23 dose of at least 8 weeks (**NACI Recommendation A**). Moreover, it should be noted that immunocompromised children will benefit from herd immunity (indirect protection).

For children aged 36-59 months who have had complete, age-appropriate pneumococcal vaccination but who have not previously received PNEU-C-13, NACI concludes that:

1. There is **good** evidence to recommend that **for healthy (not high risk) children who are of aboriginal origin or who attend group child care**, a single dose of PNEU-C-13 be given (**NACI Recommendation A**);
2. There is **fair** evidence to recommend that for **healthy (not high risk) children**, a single dose of PNEU-C-13 be considered, taking into account the age of the child (the incidence of IPD declines from age 24 to age 59 months), the degree of exposure to other young children, and the local epidemiology of IPD (**NACI Recommendation B**). The benefit of vaccinating such children is expected to be greater in the next 1-3 years, as it is expected that the incidence of disease due to serotypes in PNEU-C-13 will decline due to herd immunity associated with increasing use of PNEU-C-13 in routine programs. Vaccinating children in this age group with PNEU-C-13 may result in the more rapid onset of herd immunity and protection in unvaccinated cohorts for the specific serogroups in the PNEU-C-13. Healthy children, previously unvaccinated or vaccinated with an incomplete age-appropriate vaccination schedule with PNEU-C-7 or 10, should receive one dose of PNEU-C-13;
3. There is **fair** evidence to recommend that **children at high risk for IPD** receive one dose of PNEU-C-13. This dose should be given whether or not the child has already received PNEU-P-23. If the child has not previously received PNEU-P-23, one dose should be given with an interval of at least 8 weeks following the dose of PNEU-C-13 (**NACI Recommendation B**). According to experts' opinion, immunocompromised children are expected to benefit from herd immunity against serotypes included in the vaccine.

Children at high risk for IPD aged 60 months and older

1. There is **fair** evidence to recommend that **children at high risk for IPD** receive one dose of PNEU-C-13. This dose should be given whether or not the child has already received PNEU-P-23. If the child has not previously received PNEU-P-23, one dose should be given with an interval of at least 8 weeks following the dose of PNEU-C-13 (**NACI Recommendation B**).

Table 3. Recommended schedules for conjugate pneumococcal vaccine for children under 24 months of age in Canada, by Pneumococcal - Conjugate - valent vaccination history*

Age at examination	Number of previous doses of PNEU-C-7, PNEU-C-10 or PNEU-C-13 received	Recommended regimen if using a schedule with PNEU-C-13 only
2-6 months*	0 doses 1 dose 2 doses	• 2 or 3 doses† (8 weeks apart) and a booster at age 12-15 months • 1 or 2 doses† (8 weeks apart) and a booster age 12-15 months • 0 or 1 dose† (≥8 weeks after second dose) and a booster at age 12-15 months
7-11 months*	0 doses 1 dose 2 doses	• 2 doses (8 weeks apart) and a booster at age 12-15 months • 1 doses at 7-11 months, and 1 dose of 12-15 months (≥8 weeks later) • 0 or 1 dose† (≥8 weeks after second dose) and a booster at age 12-15 months
12-23 months healthy	0 doses, **or** 1 dose at <12 months; 2 or more doses at <12 months, **or** 1 dose at ≥12 months, **or** complete age-appropriate vaccination with PNEU-C-7 or PNEU-C-10 (no PNEU-C-13)	• 2 doses ≥8 weeks apart • 1 doses ≥8 weeks after most recent dose
12-23 months, high risk for IPD*	0 doses, **or** 1 dose at <12 months; 2 or more doses at <12 months, **or** 1 dose at ≥12 months, **or** complete age-appropriate vaccination with PNEU-C-7 or PNEU-C-10 (no PNEU-C-13)	• 2 doses ≥8 weeks apart • 1 dose ≥8 weeks after most recent dose; Followed by one dose of PNEU-P-23 when child turns 2 years of age, at least 8 weeks after previous PNEUMOCOCCAL - CONJUGATE - VALENT dose

* Children who are at high risk of IPD should receive a dose of PNEU-P-23. Because young children do not respond to polysaccharide vaccines, the youngest age at which this dose should be given is 24 months of age.

† Provincial schedules vary as to whether 3 doses (2, 4 and booster), or 4 doses (2, 4, 6, and booster) are recommended for healthy children. Prescribers should follow their relevant provincial schedule.

Children at high risk of IPD

include children who have:

- Chronic CSF leak
- Chronic neurologic condition that may impair clearance of oral secretions[49]
- Cochlear implants (including those children who are to receive implants)
- Chronic cardiac or pulmonary disease (excluding asthma)
- Poorly controlled diabetes mellitus
- Asplenia (functional or anatomic)
- Sickle cell disease or other hemoglobinopathies
- Congenital immunodeficiencies involving any part of the immune system, including B-lymphocyte (humoral) immunity, T-lymphocyte (cell) mediated immunity, complement system (properdin, or factor D deficiencies), or phagocytic functions
- Hematopoietic stem cell transplant (candidate or recipient)
- Human immunodeficiency virus (HIV) infection
- Immunosuppressive therapy including use of long term corticosteroids, chemotherapy, radiation therapy, post-organ-transplant therapy, and certain anti-rheumatic drugs
- Chronic kidney disease, including nephrotic syndrome
- Chronic liver disease (including hepatitis B and C, and hepatic cirrhosis due to any cause)
- Malignant neoplasms including leukemia and lymphoma
- Solid organ or islet cell transplant (candidate or recipient).

Table 4. Recommended schedules for conjugate pneumococcal vaccine for Canadian children aged 24-59, by Pneumococcal - Conjugate - valent vaccination history

Age at examination	Number of previous doses of PNEU-C-7, PNEU-C-10 or PNEU-C-13 received	Recommended regimen if using a combination of PNEU-C-7, PNEU-C-10, PNEU-C-13
24-35 months healthy	Any incomplete age-appropriate vaccination schedule with any product **or** complete schedule with PNEU-C-7 or PNEU-C-10 (no PNEU-C-13)	• 1 dose of PNEU-C-13, ≥8 weeks after most recent dose
24-35 months, high risk of IPD	Any incomplete age-appropriate vaccination schedule with any product **or** complete schedule with PNEU-C-7 or PNEU-C-10 (no PNEU-C-13)	• 1 dose of PNEU-C-13, ≥8 weeks after most recent dose; Followed by one dose of PPV 23 8 weeks after previous PNEUMOCOCCAL - CONJUGATE - VALENT dose
36-59 months healthy	Complete schedule with PNEU-C-7 or PNEU-C-10 (no PNEU-C-13)	• If of aboriginal origin or attend group child care, 1 dose of PNEU-C-13, ≥8 weeks after most recent dose • All other children, consider a single dose of PNEU-C-13‡
	Any incomplete age-appropriate vaccination schedule with any product	• 1 dose of PNEU-C-13 should be administered
36-59 months, high risk of IPD*	Any incomplete age-appropriate vaccination schedule with any product, or complete schedule with PNEU-C-7 or PNEU-C-10 (no PNEU-C-13)	• 1 dose of PNEU-C-13, ≥8 weeks after most recent dose; Followed by one dose of PNEU-P-23 8 weeks after previous PNEUMOCOCCAL - CONJUGATE - VALENT dose

* Children who are at high risk of IPD should also receive a dose of PNEU-P-23 at 24 months of age. This dose should be given whether or not the child has already received PNEU-P-23. If the child has not previously received PNEU-P-23, it should be given at least 8 weeks after the last dose of PNEU-C-13.

‡ The decision to vaccinate healthy children age 36-59 months of age should be make taking into account the age of the child (the incidence of IPD declines from age 24 to age 59 months), the degree of exposure to other young children, and the local epidemiology of invasive pneumococcal disease (NACI recommendation B). The benefit of vaccinating such children is expected to be greater in the next 1-3 years than in subsequent years, as it is expected that the incidence of disease due to serotypes in the 13-valent vaccine will decline due to herd immunity associated with increasing use of 13-valent pneumococcal conjugate vaccines in routine programs

Children at high risk of IPD

include children who have:

- Chronic CSF leak
- Chronic neurologic condition that may impair clearance of oral secretions[49]
- Cochlear implants (including those children who are to receive implants)
- Chronic cardiac or pulmonary disease (excluding asthma)
- Poorly controlled diabetes mellitus
- Asplenia (functional or anatomic)
- Sickle cell disease or other hemoglobinopathies
- Congenital immunodeficiencies involving any part of the immune system, including B-lymphocyte (humoral) immunity, T-lymphocyte (cell) mediated immunity, complement system (properdin, or factor D deficiencies), or phagocytic functions
- Hematopoietic stem cell transplant (candidate or recipient)
- Human immunodeficiency virus (HIV) infection
- Immunosuppressive therapy including use of long term corticosteroids, chemotherapy, radiation therapy, post-organ-transplant therapy, and certain anti-rheumatic drugs
- Chronic kidney disease, including nephrotic syndrome
- Chronic liver disease (including hepatitis B and C, and hepatic cirrhosis due to any cause)
- Malignant neoplasms including leukemia and lymphoma
- Solid organ or islet cell transplant (candidate or recipient)

Surveillance and Research Priorities

The epidemiology of invasive pneumococcal disease is changing in Canada and elsewhere, both due to and independent of the use of pneumococcal vaccines. Ongoing changes are expected as PNEU-C-10 and PNEU-C-13 vaccines are used. Surveillance systems to detect these changes over time are essential. Optimal decisions about the use of pneumococcal vaccines in children requires on-going surveillance for serotype-specific rates of invasive pneumococcal disease, and other disease syndromes (e.g. frequency of empyema associated with streptococcal pneumonia), serotype-specific estimates of the efficacy of different vaccines, and continuing assessment of the effectiveness and cost-effectiveness of different vaccination schedules over time.

Surveillance and research which addresses the following outstanding questions is particularly encouraged:

- Which conjugate vaccine schedule is the most effective and cost-effective for Canadian children?

- What is the impact of conjugate pneumococcal vaccines on rates of pneumococcal pneumonia and acute otitis media?
- What is the serotype-specific efficacy and effectiveness of PNEU-C-10 and PNEU-C-13?
- What antibody concentrations, or other immunologic markers, correlate best with protection against invasive pneumococcal disease, pneumococcal pneumonia, acute otitis media and nasopharyngeal carriage?
- Do three-dose schedules of PNEU-C-10 and PNEU-C-13 offer direct protection and herd immunity comparable to PNEU-C-7 for relevant pneumococcal serotypes?
- Will serotype replacement offset the benefits of pneumococcal conjugate vaccine use in children?
- What population vaccination coverage is needed to provide indirect protection (herd immunity) in children?
- What are the determinants of indirect protection of adults from pediatric vaccines?
- Are current 10- and 13-valent conjugate pneumococcal vaccines interchangeable?
- What factors other than immunization influence changes in the incidence of disease due to different serotypes over time?
- Will vaccination against pneumococcal disease increase the risk of infection due to *S. aureus*?

Evidence Tables

Table 5. Summary of Evidence for NACI Recommendation(s):

Evidence for 2+1 schedule						
Study	***Vaccine***	***Study Design***	***Participants***	***Outcomes***	***Level of Evidence***	***Quality***
Kayhty et al, 2005[17]	PNEU-C-7, Wyeth	Open non-randomized trial 4 Centers in Sweden	N=99 -3 month old children -relevant details	- serotype specific IgG titres - GMT (using both 0.2mcg/mL and 0.35mcg/mL)	Level I	Good
Esposito et al, 2005[16]	PNEU-C-7, Wyeth	Open non-randomized trial One center	N=92 46 pre term, 46 term Age 75-105 days	GMT by serotype ELISA (anti IgG)	Level I	Fair No description of study recruitment
Whitney et al., 2006[19]	PNEU-C-7, Wyeth	Case-control	1.7 million children <5yrs part of ABC Surveillance program	- laboratory confirmed IPD	Level II-2	Good
Vestrheim et al, 2008[20]	PNEU-C-7, Wyeth	Retrospective Cohort	Total population of children <5yrs in 2002-07 in Norway	-laboratory confirmed IPD	Level II-2	Good
Deceuninck et al. 2010[21]	PNEU-C-7, Wyeth	Case –Control	N=180 cases, 897 controls	-laboratory confirmed IPD	Level II-2	Good
Esposito et al.[27]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized controlled Trial -Italy	N=303 3 months of age 3,5 and 11 mos schedule Concomitant DtaP-IPV-HBV-Hib	ELISA >0.35mcg/mL for PNEU-C-13 group one month after 2nd dose, prior to booster and one month after booster. PNEU-C-7 group, one month after booster. OPA >1:8, in a subset of patients GMT	Level 1	Good -using 2+1 schedule and PNEU-C-13 -poster
Klinger et al.[50]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized Controlled Trial -UK	N=278 2 months of age -immunized at 2, 4 mos of age -concomitant DTaP-IPV-Hib, MenC	Data not available as yet	Level 1	Good -2 dose infant series, no toddler dose in data set -poster

Evidence for Safety (Infant Series) PNEU-C-13						
Study	***Vaccine***	***Study Design***	***Participants***	***Outcomes***	***Level of Evidence***	***Quality***
Bryant et al.[30, 31]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized controlled trial US (18 sites)	N=249 2 months of age -immunized at 2, 4, 6 mos -concomitant DTaP-IPV-HepB and Hib	Parent reported diary of safety 5 days after each dose Response to concomitant vaccines	Level I	Good -abstract (oral presentation)
Kieninger et al[32, 33]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized Controlled Trial Germany	N=603 2 months of age -immunized at 2,3,4 and 11-12 mos -concomitant DTaP-IPV-Hib-HepB	Parent reported electronic diary for 4 days after each vaccine dose	Level 1	Good -includes infant and toddler doses -poster
Esposito et al.[27]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized controlled Trial -Italy	N=303 3 months of age 3,5 and 11 mos schedule Concomitant DtaP-IPV-HBV-Hib	Parent reported electronic diary for 4 days after each vaccine dose	Level 1	Good -using 2+1 schedule and PNEU-C-13 -poster
Klinger et al.[50]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized Controlled Trial -UK	N=278 2 months of age -immunized at 2, 4 mos of age -concomitant DTaP-IPV-Hib, MenC	Parent reported electronic diary for 4 days after each vaccine dose	Level 1	Good -2 dose infant series -poster
Grimpel et al.[45]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized Controlled Trial -France	N=613 2 months of age -concomitant DTaP-IPV-Hib	Parent reported electronic diary for 4 days after each vaccine dose	Level 1	Good -poster
Gadzinowski et al.[41]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized Controlled Trial -Poland -with and without polysorbate 80	N=250 2 months of age -2,3,4 and 12 mos Concomitant DTaP-IPV-Hib, HepB, MMR	Parent reported electronic diary for 4 days after each vaccine dose	Level 1	Good -poster
Amdekar et al.[42]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized controlled Trial -India	N=355 6wks of age 6wks, 10wks, 14 wks Concomitant DTP-Hib-HBV, OPV	Parent reported electronic diary for 4 days after each vaccine dose	Level 1	Fair -concomitant vaccines different than Canadian schedule (ie DTP, OPV) -poster
Diez-Domingo et al.[43]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized controlled Trial -Spain (35 sites)	N=621 2 months of age -2,4,6 and 15 mos Concomitant DTaP-HBV-IPV-Hib, MenC-CRM	Parent reported electronic diary for 4 days after each vaccine dose -unsolicited adverse events for duration of study	Level 1	Good -poster

Gadzinowski et al.[51]	PNEU-C-13 -compared vaccine from pilot scale production and manufacturer scale Wyeth	Randomized controlled trial -Poland	N=269 2 months of age 2,3,4 mos vaccine schedule Concomitant DTaP-IPV-Hib-HBV	Parent reported electronic diary for 4 days after each vaccine dose -unsolicited adverse events for duration of study	Level 1	Good -poster
Payton et al.[35, 52]	PNEU-C-13 (3 separate lots), PNEU-C-7	Randomized Controlled Trial -USA (80 sites)	N=1712 -2,4,6 months schedule -Concomitant DTap-IPV-HiB	Parent reported electronic diary for 7 days after each vaccine dose -unsolicited adverse events for duration of study	Level 1	Good -poster
Martinon-Torres et al.[44]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized Controlled Trial -Spain	N=449 2 months of age -2,4,6 mons schedule Concomitant DTaP-IPV-HepB-Hib, MenC(TT)	Parent reported electronic diary for 4 days after each vaccine dose -unsolicited adverse events for duration of study	Level 1	Good -poster
Kellner et al.[32]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized Controlled Trial -Canada (11 sites)	N=603 2 months of age 2,4,6,12-18 mos schedule Concomitant DTaP-IPV-Hib, MenC, MMR	Parent reported diary for 4 days after each vaccine dose -unsolicited adverse events for duration of study	Level 1	Good -poster
Evidence for Safety (Toddler dose) for PNEU-C-13						
Study	***Vaccine***	***Study Design***	***Participants***	***Outcomes***	***Level of Evidence***	***Quality***
Bryant et al.[31]	PNEU-C-13, PNEU-C-7, Wyeth	Continuation of infant study. See above for more details	N=189 Toddler dose at 12-15 months of age	Parent reported diary of safety 5 days after each dose Phone call 6 months after series for unexpected physician visits, ED visits, hospitalizations or SAEs	Level 1	Good -abstract (poster)
Hughes et al.[46]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized double blind trial Continuation of infant study In UK (9 sites)	N=250 12 months of age -concomitant Hib/Men-TT Previously received 2 doses of infant series	Parent reported diary of safety 4 days after booster dose	Level 1	Good -poster

Evidence for Safety for PNEUMOCOCCAL - CONJUGATE - VALENT-7 to PNEUMOCOCCAL - CONJUGATE - VALENT-13 Cross-over						
Study	***Vaccine***	***Study Design***	***Participants***	***Outcomes***	***Level of Evidence***	***Quality***
Grimpel et al.[34]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized Controlled Trial 4 doses PNEU-C-13 at 2,3,4 and 12 mos OR PNEU-C-7 at 2,3,4 and 12 mos OR 3 doses PNEU-C-7 and one dose PNEU-C-13 at 12 mos	N=582 2 months of age, then doses at 3,4, and 12 mos France (39 sites	Parent reported electronic diary 4 days after 12 months dose Adverse events were collected up to one mos after toddler dose	Level 1	Good -poster
Evidence for Safety (Catch up Schedule) PNEU-C-13						
Study	***Vaccine***	***Study Design***	***Participants***	***Outcomes***	***Level of Evidence***	***Quality***
Wysocki et al.[53]	PNEU-C-13, Wyeth	Randomized controlled trial	N=355 Previously naive to pneumococcal vaccine -if 7 mos to <12mos (2 doses) -if 12 mos to <24 mos (2 doses) -if 24 mos to <72 mos (1dose)	Parent reported electronic diary for 4 days after each vaccine dose -unsolicited adverse events for duration of study	Level 1	Good -poster
Evidence for Immunogenicity (for Infant Doses) PNEU-C-13						
Study	***Vaccine***	***Study Design***	***Participants***	***Outcomes***	***Level of Evidence***	***Quality***
Bryant et al.[30, 31]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=202	Serum IgG>0.35mcg/mL OPA>1:8 One month post third dose,	Level 1	Good (oral presentation)
Kieninger et al.[32, 33]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=564	Serum IgG>0.35mcg/mL – percent responders OPA>1:8 (subset n=100) Reverse distribution curves Anti-PRP, Dip, HepB IgG ELISA		
Klinger et al.[50]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=278	Serum IgG>0.35mcg/mL – percent responders Anti-PRP, rSBA, PT, FHA, Pertactin, FIM	Level 1	Good -2 dose infant series -no OPA measurements -poster
Grimpel et al.[45]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=613	Serum IgG>0.35mcg/ mL – percent responders Anti-PRP, Dip (IgG), TT (IgG), PT, FHA, Polio (1,2,3) antibodies Assessed one mos after dose 3	Level 1	Good -no OPA measurements -poster

Gadzinowski et al.[41]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=250	Serum IgG>0.35mcg/ mL – percent responders, GMC, Antibody reverse distribution curves, OPA>1:8 Assessed one month after last dose	Level 1	Good -no data on concomitant vaccines -poster
Amdekar et al.[42]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=355	Serum IgG>0.35mcg/ mL – percent responders PT, FHA, PRN	Level 1	Fair -no OPA data -different vaccines than Canadian routine schedule (DTP, OPV)
Esposito et al.[27]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=303	Serum IgG>0.35mcg/ mL – percent responders, GMC, Antibody reverse distribution curves, OPA>1:8, OPA GMTs HepB Ab, Anti-PRP, PT, FHA, Pertactin, Anti-Dip, Anti-TT, Polio (1,2,3) antibodies Assessed 1 mos after 3rd dose, before 4th dose and 1 mos after 4th dose	Level 1	Good -poster
Diez-Domingo et al.[43]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=621	Serum IgG>0.35mcg/ml – percent responders SBA, IgG TT, PT, FHA, PRN, IgG Dip, Poliovirus (1,2,3) antibody Assessed one month after 2nd dose, 3rd dose and 4th dose	Level 1	Good -no OPA data
Gadzinowski et al.[41]	PNEU-C-13 compared pilot scale vaccine to production scale Wyeth	See above	N=269	Serum IgG>0.35mcg/ mL (percent responders), GMC, OPA>1:8 (subset n=100), GMT Assessed one month after infant series	Level 1	Good production -Poster
Payton et al.[35]		See above	N=1712	Serum IgG>0.35mcg/ml Anti TT, HepB antibodies, Polio (1,2,3) antibodies Assessed one month after 3rd dose	Level 1	Good -no OPA data -poster
Martinon-Torres et al.[44]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=449	Serum IgG>0.35mcg/ mL (percent responders), GMC sBSA, anti-TT, anti-Dip by antibody level, GMC, GMT assessed one month after 2nd dose (sBSA), and one month after 3rd dose (TT, Dip)	Level 1	Good -no OPA data -poster
Kellner et al.[40]	PNEU-C-13, PNEU-C-7, Wyeth	Randomized Controlled Trial -Canada	N=603 2 months of age 2,4,6,12-18 mos schedule Concomitant DTaP-IPV-Hib, MenC, MMR	Serum IgG>0.35mcg/ mL (percent responders), GMC Anti-PRP, PT, FHA, PRN, FA, sBSA Assessed one month after 3rd dose	Level 1	Good -no OPA data -poster

Evidence for Immunogenicity for Toddler dose for PNEU-C-13						
Study	***Vaccine***	***Study Design***	***Participants***	***Outcomes***	***Level of Evidence***	***Quality***
Bryant et al.[31]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=187	Serum IgG>0.35mcg/ mL OPA>1:8 Assessed one month before and after dose	Level 1	Good (poster)
Hughes et al.[46]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=250	Serum IgG>0.35mcg/ mL Assessed before and one month after toddler dose -IgG anti-PRP. MenC SBA titre	Level 1	Good -no OPA measure-ments -poster
Evidence for Immunogenicity for PNEUMOCOCCAL - CONJUGATE - VALENT-7 to PNEUMOCOCCAL - CONJUGATE - VALENT-13 Cross-over						
Study	***Vaccine***	***Study Design***	***Participants***	***Outcomes***	***Level of Evidence***	***Quality***
Grimpel et al.[34]	PNEU-C-13, PNEU-C-7, Wyeth	See above	N=582	Serum IgG>0.35mcg/ mL (percent responders) OPA>1:8 (subset n=100) Assessed one month before and after dose	Level 1	Good -poster
Evidence for Immunogenicity of catch up program						
Study	***Vaccine***	***Study Design***	***Participants***	***Outcomes***	***Level of Evidence***	***Quality***
Wysocki et al.[53]	PNEU-C-13, Wyeth	See above	N=355	GMC Assessed one month after final dose of vaccine	Level 1	Fair -no OPA data -no data on percent of participants responding to WHO standard of IgG -poster
Evidence for Immunogenicity of catch up program						
Study	***Vaccine***	***Study Design***	***Participants***	***Outcomes***	***Level of Evidence***	***Quality***
Vieira et al.[37]	PNEU-C-7, Wyeth	Prospective cohort	N = 48;children aged 1-9 years with chronic renal failure 24 on conservative treatment 24 dialyzed (peritoneal and hemodialysis)	GMC Assessed 60 days after the 2nd PNEU-C-7 dose	Level II-2	Fair
Meerveld-Eggink et al.[38]	PNEU-C-7, Wyeth	Prospective cohort	N = 26 adults post allogeneic BMT	GMT Assessed 3 weeks after vaccination dose	Level II-2	Fair

† PCV7 is no longer available for purchase.

Table 6. 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 7. Levels of Evidence Based on Research Design

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 et al., 2001.[54]

Table 8. 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.
I	NACI concludes that there is **insufficient** evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

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