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

Re-Immunization with Polysaccharide 23-Valent Pneumococcal Vaccine (Pneu-P-23)

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

Également disponible en français sous le titre :
Revaccination avec le vaccin polysaccharidique 23-valent contre le pneumocoque (Pneu-P-23)

This publication can be made available in alternative formats upon request.

Publication date: April 2015

Cat.: HP40-135/2015E-PDF
ISBN: 978-1-100-25790-7
Pub.: 140493

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.

TABLE OF CONTENTS

SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

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

	Age 2 years and over with Risk factors for invasive pneumococcal disease (IPD).	Age 65 years and over
1. What	One lifetime booster dose is recommended 5 years after the initial dose for those at highest risk of IPD. This is a change in the interval for re-vaccination for children initially vaccinated at 10 years of age and younger, where re-vaccination was previously recommended 3 years after the initial dose.	Regardless of other risk factors, those 65 years and over should receive one dose of Pneu-P-23 as long as 5 years has passed since the previous Pneu-P-23 dose.
2. Who	For individuals aged 2 years with a condition that places them at highest risk of IPD (functional or anatomic asplenia or sickle cell disease; hepatic cirrhosis; chronic renal failure or nephrotic syndrome; HIV infection; and immunosuppression related to disease or therapy).	All individuals at the age of 65 years, regardless of risk factors.
3. How	For highest risk individuals, provide one booster dose of Pneu-P-23 5 years after the initial dose of Pneu-P-23.	For individuals aged 65 years and over, one dose of Pneu-P-23 should be given. For those who have received a previous dose of Pneu-P-23 because of a medical condition that places them at highest risk of IPD (functional or anatomic asplenia or sickle cell disease; hepatic cirrhosis; chronic renal failure or nephrotic syndrome; HIV infection; and immunosuppression related to disease or therapy), a dose of Pneu-P-23 should be administered, as long as 5 years has passed since the previous Pneu-P-23 dose.
4. Why	Over time immunity wanes, providing one booster 5 years after the first dose will provide a boost to the immune system as these individuals continue to be at risk for IPD. A single re-vaccination at 5 years after the initial vaccination harmonizes the pediatric and adult schedules.	Individuals over the age of 65 are at a higher risk of IPD; therefore a dose of Pneu-P-23 will provide protection against IPD.

I. INTRODUCTION

This statement will supplement previous pneumococcal statements[1][2] and provide the evidence used to determine the optimal time between initial vaccination with polysaccharide 23-valent pneumococcal vaccine (Pneu-P-23) and subsequent booster doses to protect against IPD in those at highest risk for IPD.

Individuals who are 2 years of age and over and at high risk for IPD, as defined in the *Canadian Immunization Guide (CIG)* (http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pneu-eng.php), are recommended to receive Pneu-P-23 vaccine, in addition to age and risk-specific recommendations for the conjugate 13-valent pneumococcal vaccine (Pneu-C-13). Age and risk-specific recommendations and schedules for these vaccines are outlined in the *CIG*.

NACI currently recommends re-immunization with one life-time booster dose of Pneu-P-23 for those 2 years of age and older at highest risk of IPD. Individuals included in the group at highest risk of IPD are those with functional or anatomic asplenia or sickle cell disease; hepatic cirrhosis; chronic renal failure or nephrotic syndrome; HIV infection; and immunosuppression related to disease or therapy. Currently, for these groups, a single re-immunization after 5 years is recommended in persons who were 11 years of age or over at the time of initial immunization with Pneu-P-23 vaccine. A single re-immunization after 3 years is recommended for those who were 10 years of age or younger at the time of initial immunization with Pneu-P-23 vaccine. Because there are insufficient data to recommend repeated administration of Pneu-P-23 vaccine, re-vaccination following a second dose is not routinely recommended.

This update will:

- Provide a systematic review of the literature on booster doses of pneumococcal vaccine for individuals at high risk of IPD disease.
- Make recommendations for booster doses of pneumococcal vaccine.

II. METHODS

NACI reviewed such considerations as the target population, safety, immunogenicity, efficacy, effectiveness of the vaccines, vaccine schedules, and other aspects of the overall immunization strategy when available. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence were prepared using NACI's methodological hierarchy (Tables 2 and 3), and proposed recommendations for vaccine use were developed. Ms. Chelsea Caya (M.Sc. PH candidate at McGill University) and Ms. Constantina Boikos (M.Sc.PH and Ph.D. (epidemiology) at McGill University) performed the systematic review.[3] Ms. Caya and the Working Group chair presented the evidence and proposed recommendations to NACI. Following thorough review of the evidence and consultation at NACI meeting (February 5, 2013), 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 update. The Agency maintains documentation of these processes throughout knowledge synthesis and recommendation development.

III. EPIDEMIOLOGY OF PNEUMOCOCCAL DISEASE

Please refer to the *CIG* (http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php) for recent epidemiology data.

In summary, since the sequential NACI recommendations to introduce conjugate pneumococcal vaccines to the routine childhood immunization programs (Pneu-C-7[4], Pneu-C-10[5] and most recently Pneu-C-13[2]), the incidence of IPD has decreased. The change has been most notable among children, but the incidence of disease among adults has also decreased, due to the herd effect. IPD due to serotypes included in conjugate vaccines has seen a sharp decline. There has been a concurrent increase in serotypes not included in the conjugate vaccines, but the overall incidence remains below the incidence observed prior to the introduction of conjugate vaccines. Based on national data, the 0-4-year-old group continues to be most affected, as well as those over the age of 60 years. National epidemiological level data does not provide information that would allow analysis specifically for those at high risk for IPD or those over the age of 65 years.

IV. VACCINES

There is no change in vaccines currently available in Canada. Please refer to previously updated NACI Statement including the recent statement regarding the use of conjugate pneumococcal vaccine for adults[1] and the *CIG* (http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-pneu-eng.php) that synthesizes NACI recommendations.

IV.1 Efficacy – Direct and Indirect

No study found

IV.2 Effectiveness

No study found

IV.3 Immunogenicity

A total of 10 studies were reviewed: one focused on pediatric participants only, 8 looked at adults and one included pediatric and adult participants. It should be noted that there was heterogeneity in the assays used for immunologic evaluations, as well as in the threshold used to determine immune response, the age cut-offs used, and the underlying illnesses that constituted risk. A full review of all of the studies, their methodologies and outcome measures can be found in Table 1. An overview of the studies is provided below.

Pediatric Studies

Only one study (Smets)[6] was specific to the pediatric population. This prospective randomized controlled trial included 8 patients who had received an initial dose of Pneu-P-23, 3 to 5 years prior to enrollment. Participants were revaccinated and *S. pneumoniae* antibody levels were

measured at the time of immunization, and 1 month and 6 months post vaccination. One month after re-vaccination, depending on the serotype, 75-100% of participants were considered vaccine responders and 62-100% maintained adequate antibody levels to meet the study-defined threshold at 6 months post-vaccination.

Adult Studies

Seven cohort studies provided data on booster dose(s) of Pneu-P-23 in adults over the age of 18 years with risk factors for IPD. Davidson[7] recruited 52 adults, half of whom had previously received Pneu-P-23 on average 7.4 years prior to enrollment and half of whom were unvaccinated age-matched controls. All participants were vaccinated with Pneu-P-23; antibody levels were measured prior to vaccination and approximately one month after vaccination. Prior to immunization, both groups had similar geometric mean titers (GMTs). At baseline, individuals aged less than 65 years of age had a higher serotype specific antibodies compared to those over the age of 65 years. After vaccination, 82% of previously naïve participants and 83% of boosted participants had GMTs that were considered protective. After revaccination, there was no difference in response based on age.

A second cohort study (Hammitt et al)[8] looked at Pneu-P-23 response in three groups: naïve participants, a group who had received one previous dose of Pneu-P-23 and a group that had received 2 or 3 previous doses of Pneu-P-23. Previously vaccinated participants were eligible if a minimum of 6 years had passed since their last Pneu-P-23 vaccine. Blood samples were collected at baseline and one month after immunization. At baseline, pneumococcal IgG levels were higher in participants who had previously received Pneu-P-23 compared to the naïve group. After immunization, absolute IgG levels were similar in all three groups but the fold-increase in antibody titers was lower in previously vaccinated individuals ($p<0.001$); the lower fold increase in the previously vaccinated group is likely because this group had higher antibodies before re-vaccination. The fold increase in serotype-specific functional antibody measured using opsonophagocytic killing (OPK) was not different between the naïve and previously vaccinated group.

Lackner et al[9] conducted a cohort study with frail nursing home residents. All participants had received vaccine at least 5 years prior to enrolment. Again, younger age was associated with higher baseline antibody titers. One month after Pneu-P-23, depending on the serotype, 45-61% of participants had an adequate immune response, while only 17% met the criteria for all 7 serotypes tested. One year following vaccination, depending on the serotype only 23-44% of participants displayed an adequate immune response, with only 7% meeting criteria for all 7 tested serotypes.

Manoff[10] conducted a single blinded prospective cohort of a group of adults aged 65 years and older in which approximately half of the group was naïve, while the other half had received Pneu-P-23 three to five years earlier. At baseline, antibody levels as well as functional antibody (as measured by OPK) were higher in the previously immunized group. Mean-fold rise in antibody levels was greater in those who had not been vaccinated previously. Five years after vaccination, both groups had similar antibody levels as well as functional antibody levels.

One other cohort study also reported on both antibody levels and functional antibodies.[11] In this prospective cohort study, previously immunized Pneu-P-23 recipients received one additional dose of Pneu-P-23 five years after their previous dose. When stratified by serotype, antibody levels 1 and 12 months after revaccination were significantly greater for all serotypes tested

compared to baseline except for serotype 19F, which had not significantly increased 12 months after revaccination ($p = 0.08$). Furthermore, antibody levels peaked 1 month after revaccination. Twelve months post-revaccination, antibody levels had declined yet remained higher than baseline levels for all serotypes tested.

Musher et al.[12] studied a cohort of ambulatory older adults who had received either one or two doses of Pneu-P-23 10 years earlier. After revaccination, statistically significant increases in antibody levels were observed from baseline to day 30 post-revaccination for second-dose recipients ($p<0.05$) for all serotypes tested. Among third-dose recipients, statistically significant increases in antibody levels were found for all serotypes except for serotypes 6B and 12F. Age was inversely proportional to antibody response.

Torling et al.[13] conducted a prospective cohort study in which participants who had been part of a previous study and previously vaccinated with Pneu-P-23 on average 5.3 years earlier (range 4-7 years) were offered revaccination with Pneu-P-23. Antibody levels 4 weeks post-revaccination significantly increased relative to baseline levels ($p = 0.0004$). However, in this study, response to Pneu-P-23 revaccination was "significantly lower than after the primary vaccination, with a combined GMC of 7.47 µg/mL versus 19.06 µg/mL ($p<0.001$)". This was the only study where some hyporesponsiveness was identified.

Adults Post-Transplant

Tobudic et al[14] randomized renal transplant recipients who had undergone transplant at least 6 months earlier who had not had Pneu-P-23 in the past 5 years to either a 7-valent conjugated pneumococcal vaccine or Pneu-P-23, followed in both cases one year later by Pneu-P-23. Given the question asked as part of this review, we will focus on participants ($n = 26$) who received 2 doses of Pneu-P-23. Eight weeks after the second dose of Pneu-P-23, antibody levels were significantly higher for serotypes 9F and 19F in the Pneu-P-23/Pneu-P-23 group relative to those in the Pneu-C/Pneu-P-23 group. Serotype-specific antibody levels declined during the 12 months between vaccinations, "but antibody levels persisted well for the majority of serotypes" in the group who received their first dose as Pneu-P-23.

Combined Studies

Fuchshuber[15] conducted a prospective cohort study that included children and young adults with chronic renal disease aged 3-27 years. One year after primary immunization, a subgroup was re-immunized with Pneu-P-23 because their antibody levels had fallen below pre-vaccination levels. Antibody levels rapidly declined after re-vaccination, in particular in participants who had lost their antibodies rapidly following primary vaccination: 6 months following revaccination only 2 participants (9%) were still considered responders. Although this study seems to show hyporesponsiveness in participants vaccinated with a second dose of Pneu-P-23 one year after the previous dose, one should note that revaccinated participants represent a sub-group with a sub-optimal response to the first dose of Pneu-P-23. It is therefore possible that participants who did not maintain an adequate response to Pneu-P-23 at one year were different immunologically from the other study participants. As not all participants were revaccinated, it is difficult to draw any firm conclusion on the antibody response when a second dose of Pneu-P-23 is administered one year after the first one.

IV.4 Safety

Safety of re-vaccination with Pneu-P-23 was assessed in eight of the studies reviewed. In the one study that enrolled only pediatric patients, only mild adverse reactions to Pneu-P-23 were observed (Smets).[6] In the adult studies, mild reactions, such as arthralgias, fatigue, headache, swelling at the site of injection and limitation in arm movement, were reported adverse events (range 11%-63%).[8][9][11][13]-[15] Systemic reactions (i.e. fever) were also reported in 11% of adults in one study.[9] When comparing those receiving third dose versus second dose, there was a statistically significant increase in the proportion of individuals with mild adverse events but not with systemic reactions (Musher).[12]

V. RECOMMENDATIONS

In summary, based on all the studies reviewed, immunity following Pneu-P-23 declines rapidly and re-vaccination of those at highest risk of IPD disease provides a boost in immune response, suggesting an improved ability to prevent IPD related illnesses. Individuals, who had received one or two doses of Pneu-P-23 before age 65 years, demonstrated a good immune response and an acceptable safety profile to a repeated dose of Pneu-P-23 when administered at age 65 years or over. There is little evidence to suggest that hyporesponsiveness occurs with one additional booster of Pneu-P-23, nor is there evidence to suggest safety is a concern. To guide recommendations for additional doses (i.e. more than one booster dose), further studies are needed to understand how the immune system responds to additional doses of Pneu-P-23.

Recommendation #1:

For all individuals aged 2 years and over who are at highest risk of IPD (functional or anatomic asplenia or sickle cell disease; hepatic cirrhosis; chronic renal failure or nephrotic syndrome; HIV infection; and immunosuppression related to disease or therapy) and who have received age-appropriate doses of 13-valent conjugate pneumococcal vaccine followed 8 weeks later by Pneu-P-23, revaccination with a second dose of Pneu-P-23 should be provided 5 years after the initial dose of Pneu-P-23. This is a change from the previous recommendation that recommended that children aged 10 years or younger at their first dose of Pneu-P-23 should receive the second dose 3 years later. This change is based on the absence of evidence to support the 3-year timing of the booster dose in children and on the universal use of Pneu-C-13 in children that has contributed to the marked decrease in the incidence of IPD. The single re-vaccination at 5 years after the initial vaccination harmonizes the pediatric and adult schedules for those at highest risk of IPD. (*NACI recommendation Grade B*)

Recommendation #2:

There is currently insufficient evidence to determine the optimal timing and number of Pneu-P-23 boosters in high-risk adults (i.e. functional or anatomic asplenia or sickle cell disease; hepatic cirrhosis; chronic renal failure or nephrotic syndrome; HIV infection; and immunosuppression related to disease or therapy). One lifetime booster of Pneu-P-23 is currently recommended for individuals at highest risk for IPD, 5 years after the previous dose. (*NACI recommendation Grade I*)

Recommendation #3:

Given the increased risk of IPD in adults aged 65 years and older and the rapid decline in antibodies following Pneu-P-23, all individuals should receive one dose of Pneu-P-23 at age 65 years – as long as 5 years have passed since a previous Pneu-P-23 dose. Studies reviewed for this updated statement have all administered a dose of Pneu-P-23 to individuals aged 65 years and over, regardless of their prior vaccination history. No additional booster dose is currently recommended for those over the age of 65 years who do not have other underlying medical conditions that would put them at higher risk for IPD. (*NACI recommendation Grade B*)

VI. SURVEILLANCE AND RESEARCH PRIORITIES

- Enhanced surveillance that includes high risk individuals and can provide incidence of IPD stratified by risk factors and serotypes for individuals in the greater than 65-year age group.
- Vaccine effectiveness of Pneu-P-23 programs (first and second dose) in high risk patients and in those over 65 years of age.
- Duration of vaccine effectiveness after first and second dose of Pneu-P-23 in those at high risk of IPD.
- Further studies to determine if hyporesponsiveness occurs.
- Studies investigating vaccine failures.
- Data on vaccine coverage for first and second doses in at-risk populations and those aged 65 years and over.
- Understanding barriers to accessing vaccination appropriately within high risk groups.
- Further studies with standardized cut offs on antibody response to additional doses of Pneu-P-23.
- Epidemiological studies of non-invasive disease such as community acquired pneumonia or acute otitis media in children caused by *S. pneumoniae.*

TABLES

Table 1. Summary of Vaccines Studies

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
Davidson et al[7]	1994	USA	Radioimmuno assay GMT: response if increase by 40% or more; Inadequate if level <500 ng/mL	Previously immunized vs. 1st dose of Pneu-P-23	Prospective cohort study (intervention study) • Previously administered vaccines (14- or 23-valent) were identified from PH nursing records and computerized Indian Health Service immunization files • Participants matched on age, number of chronic diseases, ethnicity and gender	Pnu-Immune **Dose**: 0.5mL **Route**: Intramuscular **Schedule**: One dose **Time since last dose**: On average 7.4 years (btw 67-109 months) **Serotypes tested:** 1, 3, 4, 6B, 7F, 8, 9V, 12F, 14, 18C, 19F, 23F.	Adult residents of northwest Alaska (n=52) =26 booster arm: 9 previously received Pneu-P-23 others PPV14, 67-109 months previously =26 unimmunized previously	Following Pneu-P-23 revaccination: • The majority of cases had a 1.4-fold increase in antibody levels. • 82% of controls had protective antibody levels. • 83% of Pneu-P-23 revaccinees had protective antibody levels. • In patients with chronic conditions (not only immunosuppre-ssion), revaccination was associated with a trend toward lower non-response: 33% in primary vaccinees vs. 13% in boosted (p=.17)	**Good**	**II-1**

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
Fuchshuber et al[15]	1996	Germany	ELISA serum obtained before and 4 weeks, 6 months, and 12 months after 1st vaccination in all participants. 22 participants were revaccinated and serum was collected 4 weeks and 6 months after this booster. Response: at least 2-fold increase in Ab titer AND titer >200	Primary vs. revaccination with a 2nd dose of Pneu-P-23	Prospective cohort study (no control); (intervention study)	Pneumovax®23 **Dose**: 0.5mL **Route**: Subcutaneous (upper extremities) **Schedule**: 0 and 12 months later for 22 of the 40 participants **Time since last dose**: 1 year **Serotypes tested:** 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F	Both children and young adults aged 2.9-27 years old, with chronic renal diseases (including idiopathic nephrotic syndrome, chronic renal failure, patients undergoing dialysis and after transplantation) • n=40 Of which, 22, whose ab titers decreased to prevaccination levels, were revaccinated 1-year after initial vaccination)	Post dose 1: % responders: • 4 weeks: 88% • 6 months: 68% • 12 months: 48% Post dose 2 (n=22): % responders: • 4 weeks: 45% • 6 months: 9%	**Good**	**II-2**

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
Hammitt et al[8]	2011	USA	ELISA and OPK assay serum obtained at baseline and 30 days after vaccination Response: examined fold-rise	Primary dose vs. revaccination with a 2nd or 3rd or 4th dose of Pneu-P-23	Prospective cohort study between December 2004 and April 2006 (intervention study)	Pneumovax®23 **Dose**: 0.5mL **Route**: Intramuscular (deltoid) **Schedule**: 1 vaccination **Time since last dose**: On average 7.4 years (6-22 years) **Serotypes tested:** 1, 4, 6B, 14 and 19F	Adults (aged 55-74 year old) considered to be at high risk for IPD based on local guidelines, who were either previously unvaccinated or were previously vaccinated with Pneu-P-23 at least 6 years prior to the study period • group 1 = first Pneu-P-23 vaccination, • group 2 = second Pneu-P-23 vaccination, • group 3 = 3rd or 4th Pneu-P-23 vaccination Group 3 was older and had more Alaskan natives	• Baseline IgG levels higher in revaccinated compared to never-before vaccinated ($p<.05$) • Absolute IgG levels achieved post-vaccination similar for all 3 groups • Fold-increases in antibody levels were lower in revaccinees compared to first-time vaccines for all serotypes tested ($p<0.001$); inverse correlation between fold-rise and baseline Ab levels. • At 30 days: fold-rises in revaccinated similar regardless of time since last vaccine.	**Good**	**II-2**

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
								• Similar results to IgG for OPK GMTs. Similar response for 1st time and revaccinated except stronger response for 6B. • Re-vaccinees reported more mild adverse reactions than primary vaccines. No difference in reported adverse experiences between persons receiving a 2nd dose of Pneu-P-23 compared to those receiving a 3rd or 4th dose.		

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
Lackner et al[9]	2003	USA	ELISA serum obtained at baseline (1 week before revaccination) and 1 and 12 months after revaccination GMT: response if increase by 40% or more	Previously immunized vs. 2nd dose of Pneu-P-23	Prospective cohort study (December 1998 and July 2000); (intervention study)	Pnu-Immune 23 **Dose**: 0.5 mL **Route**: Intramuscular (deltoid) **Schedule**: 1 vaccination **Time since last dose**: On average 7.2 years (±2.4 years) **Serotypes tested:** 4, 6B, 9V, 14, 18C, 19F, 23F.	Frail adult residing in nursing facility (aged >=65 y.o.) in the Minneapolis, St. Paul, Minnesota, metropolitan area having received primary Pneu-P-23 vaccination at least 5 years before study enrollment n=43	• One month and 1 year after revaccination, lower baseline antibody levels were significantly correlated with magnitude of fold-increase of antibody levels. • Fold-increase of at least 40%: 1. At 1 month: 45.6-61.4% depending on serotype 2. At 1 year: 23.3-44.2% depending on serotypes 3. When requiring a 40% increase for all 7 serotypes tested: only 17.5% at 1 month and 7% at 1 year reached the target	**Good**	**II-2**

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
								• Mild adverse events during the 3 days after revaccination were noted in 14/62 (22.6%) subjects and all were resolved within 3 days.		
Manoff et al[10]	2010	USA	EIA and OPK assay Serum analyzed at: day 0 (baseline), 30 days after vaccination and 5 years after vaccination Response: reference level for OPK titers was ≥ 8 for EIA concentration the reference levels were ≥0.5, ≥1.0, ≥1.5 µg/mL	Previously immunized vs. revaccina-tion with a 2nd dose of Pneu-P-23	Prospective cohort study (1997-1998) • This is a sub-study of a larger study (n=1008) with analysis of available serum to evaluate opsonic antibody responses to serotypes 4, 14 and 23F • Single blinded	Pneumovax®23 **Dose**: - **Route**: - **Schedule**: Only got one vaccination in this study (either 1st Pneu-P-23 vaccine – primary vaccination group - or had received first vaccine 3-5 years prior and were revaccinated with Pneu-P-23 – revaccination group.)	Ambulatory adults aged ≥ 65 years old with stable underlying chronic illnesses (if any). Exclusion: Immunosuppre-ssion or history of IPD N=120; 60 from each vaccination group (primary and revaccination)	• At baseline, revaccinated group had higher OPK and EIA titers compared to primary (persistence of Ab 3-5 years post) • Antibody levels significantly (p<.05) increased from day 0 to day 30. • Five years after revaccination there were no differences between the revaccination and primary vaccination groups in either OPK or EIA levels.	**Good**	**II-2**

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
						Time since last dose: 3-5 years for revaccination group **Serotypes tested:** 4, 14, 23F (most common at causing IPD).				
Musher et al[12]	2011	USA	ELISA serum obtained at baseline (10 years after last injection) and 30 days after injection Response GMC: Reference levels of ≥ 1.0 or ≥5.0 µg/mL	Second dose of Pneu-P-23 vs. third dose of Pneu-P-23	Prospective cohort study (2007; extension of larger study) Multicenter (5 out of 7 participated in the extension study)	Pneumovax®23 **Dose:** 0.5mL **Route:** Intramuscular (deltoid) **Schedule:** One dose of vaccine administered in this study **Time since last dose:** 10 years after first or second Pneu-P-23 vaccination **Serotypes tested:** 3, 4, 6B, 8, 9V, 12F, 14, 23F.	Ambulatory older adults from 5 of 7 original study sites "with the usual range of comorbid conditions associated with aging" N=134 subjects completed the extension study per protocol (n= 67 in dose 2 group - n= 66 in dose 3 group exclusion: immunosuppre-ssion due to treatment or disease; history of IPD; received	• 30 days after second or third Pneu-P-23 dose at year 10, mean IgG levels increased for all 8 serotypes. • 30 days after second or a third Pneu-P-23 dose at year 10, among second dose recipients, IgG levels increased stat sig ($p<.05$) for all 8 serotypes. • Among third-dose recipients, IgG increases were stat sig for 6 serotypes (all except 6B and 12F).	**Good**	**II-2**

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
							additional doses of Pneu-P-23 outside the study. Mean age: 75 y (60-93) in dose 2 group vs. 77 y (60-88) in dose 3	• For all 8 serotypes, IgG responses declined with advancing age. • Injection-site adverse events were reported more frequently among third-dose than second-dose recipients (83% vs. 62%, respectively, p<0.05)		
Smets et al[6]	2007	Belgium	Anti-*S.pneumoniae* ELISA sera obtained at baseline, 1 month and 6 months after revaccination Titers were considered protective if at least 0.2 µg/mL (PCV) and at least 1 µg/mL (PPV) OR 4-fold increase from baseline	Previously immunized vs. revaccination with 2nd dose of Pneu-P-23	Prospective, randomized single-center intervention study (March 2002 and February 2003) Participants included in the study were enrolled during March 2002-August 2002	Pneumo®23 vs. Prevnar-7® **Dose:** 1 dose **Route:** 0.5 mL IM **Schedule:** Once **Time since last dose:** Participants received vaccination with Pneu-P-23 at least 3 years	Children aged >5 years with anatomic or functional asplenia from Brussels, Belgium. • N=21; 11 in the PCV7 group and 8 in the Pneu-P-23 group • In the Pneu-P-23 group all were male (aged 11.7 ±3.4 years	• Time since last vaccine (Pneu-P-23 group): 6.2 y (SD 1.5) – n=8 • Following Pneu-P-23 revaccination, there were no statistically significant increases in the GMC values for any serotypes from baseline to 1 month after revaccination. • Based on the 1-µg/mL threshold, after	**Fair** (small sample size)	**I**

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
						before the study **Serotypes tested:** 4, 6B. 9V, 14, 18C, 19F, 23F.		PSV23 revaccination, 75-100% responded at 1 month (looking at each serotype separately), and 62-100% at 6 months.		
Tobudic et al[14]	2012	Austria	ELISA serotypes were measured at baseline, 8 weeks after 1st vaccination, before 2nd vaccination and 8 weeks after 2nd vaccination ELISA: 2-fold increase in antibody concentration from baseline and an absolute post-vaccination value of at least 1 µg/mL.	Primary dose vs. revaccina-tion with 2nd dose of Pneu-P-23	Randomized, single blind controlled trial (recruitment period: November 2008-October 2009)	Pneumo®23 **Dose:** 0.5 mL **Route: -** **Schedule:** 0 and 12 months **Time since last dose:** 1 year (initially randomized to receive either to 7vPnC or PPV; all received PPV 1 year later) **Serotypes tested:** 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F.	Adult renal-transplant recipients at the general hospital of Vienna who had undergone renal transplantation at least 6 months earlier N=80 recruited – 40 received PPV/PPV only **29** completed the study in the Pneu-P-23 group	• Eight weeks after revaccination, a significantly better response to serotypes 19F and 9F in the Pneu-P-23/Pneu-P-23 group relative to the PCV/Pneu-P-23 group: 3.4 (95% CI 1.7-5.1) vs. 1.5 (96% 0.9-2.2), P=0.049, and 5.6 (95% CI 3.5-7.7) vs. 3.0 (95% CI 1.5-4.4)" • Decline in serotype-specific IgG GMCs was observed during the interval to	**Good** (could have small sample size)	**I**

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
								revaccination, but antibody levels persisted well for the majority of serotypes in the Pneu-P-23/Pneu-P-23 group. • Pneu-P-23 revaccination was tolerated; only mild adverse events reported.		
Torling et al (13)	2003	Sweden	ELISA Sera was obtained before, 4 weeks and 1 year after primary vaccination and again before and 4 weeks after revaccination. Response: GMFI of ≥2 for ≥2 of the 6 serotypes tested was considered protective	Previously immunized vs. revaccina-tion with 2nd dose of Pneu-P-23	Prospective cohort study (Recruited: 23 November 1998-15 February 1999)	Pneu-P-23 **Dose:** 0.5 mL **Route:** intramuscular **Schedule:** **Time since last dose:** revaccination with Pneu-P-23 done on average 5.3 (4-7 years) years after primary vaccination	Elderly patients living in Stockholm county with a history of hospital treatment for community-acquired pneumonia and previously got one dose of Pneu-P-23 (aged 56-88; mean 75 years) • n=61 • sera collected from all patients immediately before and 4 weeks after revaccination	• Antibody levels significantly increased 4 weeks after Pneu-P-23 revaccination relative to baseline (P=0.0004). • The response to revaccination was significantly lower than after the primary vaccination, with a combined GMC of 7.47μg/ml versus 19.06μg/ml (P<0.001).	**Good**	**II-2**

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
						Serotypes tested: 1, 4, 7F, 14, 18C, 19F.		• The difference in geometric mean fold increase following primary vaccination and revaccination, respectively, was also significant, 2.73 versus 1.84 (P=0.001).		
Waites et al[11]	2008	USA	ELISA and OPK assay Sera collected just prior to, 1 month and 1 year after revaccination ELISA and OPA. Ab titers of at least 0.35 µg/mL were considered protective	Previously immunized vs. revaccination with 2nd dose of Pneu-P-23	Prospective cohort study	Pneumovax®23 **Dose:** 0.5 mL **Route:** Deltoid or lateral mid-thigh **Schedule:** **Time since last dose:** A minimum of 5 years (5 years ±1 month) **Serotypes tested:** 3, 4, 14, 19F, 23F.	Community residing adults in the U.S. with spinal cord injury (tetraplegic or paraplegic) who received primary pneumococcal vaccination between 1993 and 1998 that are <65 years old (aged 25-56; mean 41) Exclusion: significant chronic underlying condition or immunosuppressive illness. • n=23	• Antibody levels were significantly higher for all serotypes relative to baseline. • Antibody levels were significantly higher for all serotypes except for serotype 19F 1 year after revaccination relative to baseline. (P = 0.08). • Antibody levels peaked 1 month following revaccination.	**Fair** (small sample size)	**II-2**

STUDY DETAILS									SUMMARY	
Authors	***Year***	***Country***	***Measure Method***	***Comparison***	***Study Design***	***Vaccine Schedule***	***Study Population***	***Outcome Measures***	***Quality***	***Level of Evidence***
								• One year after revaccination, antibody levels had declines yet were still greater than baseline values for all 5 serotypes. • 13% of revaccinees reported mild local adverse events.		

Table 2. 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 3. 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 4. 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.

LIST OF ABBREVIATIONS

Abbreviation	***Term***
Ab	antibodies
CIG	Canadian Immunization Guide
GMC	Geometric mean antibody concentration
GMT	Geometric mean titers
IPD	Invasive pneumococcal disease
NACI	National Advisory Committee on Immunization
OPK	Opsonophagocity killing
Pneu-P-23	Pneumococcal polysaccharide vaccine-23-valent
Pneu-C-7	Pneumococcal conjugate vaccine-7-valent
Pneu-C-10	Pneumococcal conjugate vaccine-10-valent
Pneu-C-13	Pneumococcal conjugate vaccine-13-valent
SD	Standard Deviation
The Agency	Public Health Agency of Canada

ACKNOWLEDGMENTS

†**NACI Members:** Dr. I. Gemmill (Chair), Dr. C. Quach-Thanh (Vice-Chair), Dr. S. Deeks, Dr. B. Henry, Dr. D. Kumar, Dr. M. Salvadori, Dr. B. Seifert, Dr. N. Sicard, Dr. W. Vaudry, Dr. R. Warrington.

Former NACI Members: Dr. B. Warshawsky (Chair).

Liaison Representatives: Dr. J. Blake (Society of Obstetricians and Gynaecologists of Canada), Dr. J. Brophy (Canadian Association for Immunization Research and Evaluation), Dr. J. Emili (College of Family Physicians of Canada), Dr. M. Lavoie (Council of Chief Medical Officers of Health), Dr. C. Mah (Canadian Public Health Association), Dr. D. Moore (Canadian Paediatric Society), Dr. A. Pham-Huy (Association of Medical Microbiology and Infectious Disease Canada), Ms. E. Sartison (Canadian Immunization Committee).

Former Liaison Representative: Dr. A. Mawle (Centers for Disease Control and Prevention, United States)

Ex-Officio Representatives: Ms. G. Charos (Centre for Immunization and Respiratory Infectious Diseases [CIRID], Public Health Agency of Canada [PHAC], Dr. G. Coleman (Biologics and Genetic Therapies Directorate, Health Canada [HC]), Dr. (LCol) P. Eagan (National Defence and the Canadian Armed Forces), Dr. J. Gallivan (Marketed Health Products Directorate [MHPD], HC), Dr. B. Law (CIRID, PHAC), Ms. M. St-Laurent (CIRID, PHAC), Dr. T. Wong (First Nations and Inuit Health Branch [FNIHB], HC).

Former Ex-Officio Representatives: Dr. D. Garcia (FNIHB, HC), Dr. B. Raymond (CIRID, PHAC), Dr. E. Taylor (MHPD, HC).

†This statement was prepared by Dr. S. Desai, Dr. C. Quach-Thanh, Ms. C. Caya and Ms. C. Boikos, and approved by NACI.

NACI gratefully acknowledges the contribution of Dr. P. De Wals, Dr. D. Fisman, Dr. J. Johnstone, Dr. J. Kellner, Dr. M. Landry, Dr. S. McNeil, Dr. S. Rechner, Ms. L. Sherrard, Dr. G. Tyrrell and Dr. P. Van Buynder.

REFERENCES

(1) The National Advisory Committee on Immunization (NACI). An Advisory Committe Statement (ACS). Statement on the Use of Conjugate Pneumococcal Vaccine-13 Valent in Adults (Pneu-C-13). Canada Communicable Disease Report. October 2013;Volume 39, ACS-5:1-52.

(2) The National Advisory Committee on Immunization (NACI). An Advisory Committee Statement (ACS). Update on the Use of Conjugate Pneumococcal Vaccines in Childhood. Canada Communicable Disease Report. November 2010;Volume 36, ACS-12:1-21.

(3) C. Boikos CC. Dosing Regimen of the 23-Valent Pneumococcal Vaccination: A Systematic Review. Manuscript submitted. 2014.

(4) The National Advisory Committee on Immunization (NACI). An Advisory Committee Statement (ACS). Statement on Recommended Use of Pneumococcal Conjugate Vaccine. Canada Communicable Disease Report. 15 January 2002;Volume 28, ACS-2:1-32.

(5) The National Advisory Committee on Immunization (NACI). An Advisory Committee Statement (ACS). Update on Pediatric Invasive Pneumococcal Disease and Recommended Use of Conjugate Pneumococcal Vaccines. Canada Communicable Disease Report. April 2010;Volume 36, ACS-3:1-30.

(6) Smets F, Bourgois A, Vermylen C, et al. Randomised revaccination with pneumococcal polysaccharide or conjugate vaccine in asplenic children previously vaccinated with polysaccharide vaccine. Vaccine. 2007;25(29):5278-82.

(7) Davidson M, Bulkow LR, Grabman J, et al. Immunogenicity of pneumococcal revaccination in patients with chronic disease. Arch Intern Med. 1994;154(19):2209-14.

(8) Hammitt LL, Bulkow LR, Singleton RJ, et al. Repeat revaccination with 23-valent pneumococcal polysaccharide vaccine among adults aged 55-74 years living in Alaska: No evidence of hyporesponsiveness. Vaccine. 2011;29(12):2287-95.

(9) Lackner TE, Hamilton RG, Hill JJ, et al. Pneumococcal polysaccharide revaccination: Immunoglobulin G seroconversion, persistence, and safety in frail, chronically ill older subjects. J Am Geriatr Soc. 2003;51(2):240-5.

(10) Manoff SB, Liss C, Caulfield MJ, et al. Revaccination with a 23-valent pneumococcal polysaccharide vaccine induces elevated and persistent functional antibody responses in adults aged = 65 years. J Infect Dis. 2010;201(4):525-33.

(11) Waites KB, Canupp KC, Chen Y-, et al. Revaccination of adults with spinal cord injury using the 23-valent pneumococcal polysaccharide vaccine. J Spinal Cord Med. 2008;31(1):53-9.

(12) Musher DM, Manoff SB, McFetridge RD, et al. Antibody persistence ten years after first and second doses of 23-valent pneumococcal polysaccharide vaccine, and immunogenicity and safety of second and third doses in older adults. Human Vaccines. 2011;7(9):919-28.

(13) Törling J, Hedlund J, Konradsen HB, et al. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. Vaccine. 2003;22(1):96-103.

(14) Tobudic S, Plunger V, Sunder-Plassmann G, et al. Randomized, Single Blind, Controlled Trial to Evaluate the Prime-Boost Strategy for Pneumococcal Vaccination in Renal Transplant Recipients. PLoS ONE. 2012;7(9).

(15) Fuchshuber A, Kühnemund O, Keuth B, et al. Pneumococcal vaccine in children and young adults with chronic renal disease. Nephrology Dialysis Transplantation. 1996;11(3):468-73.