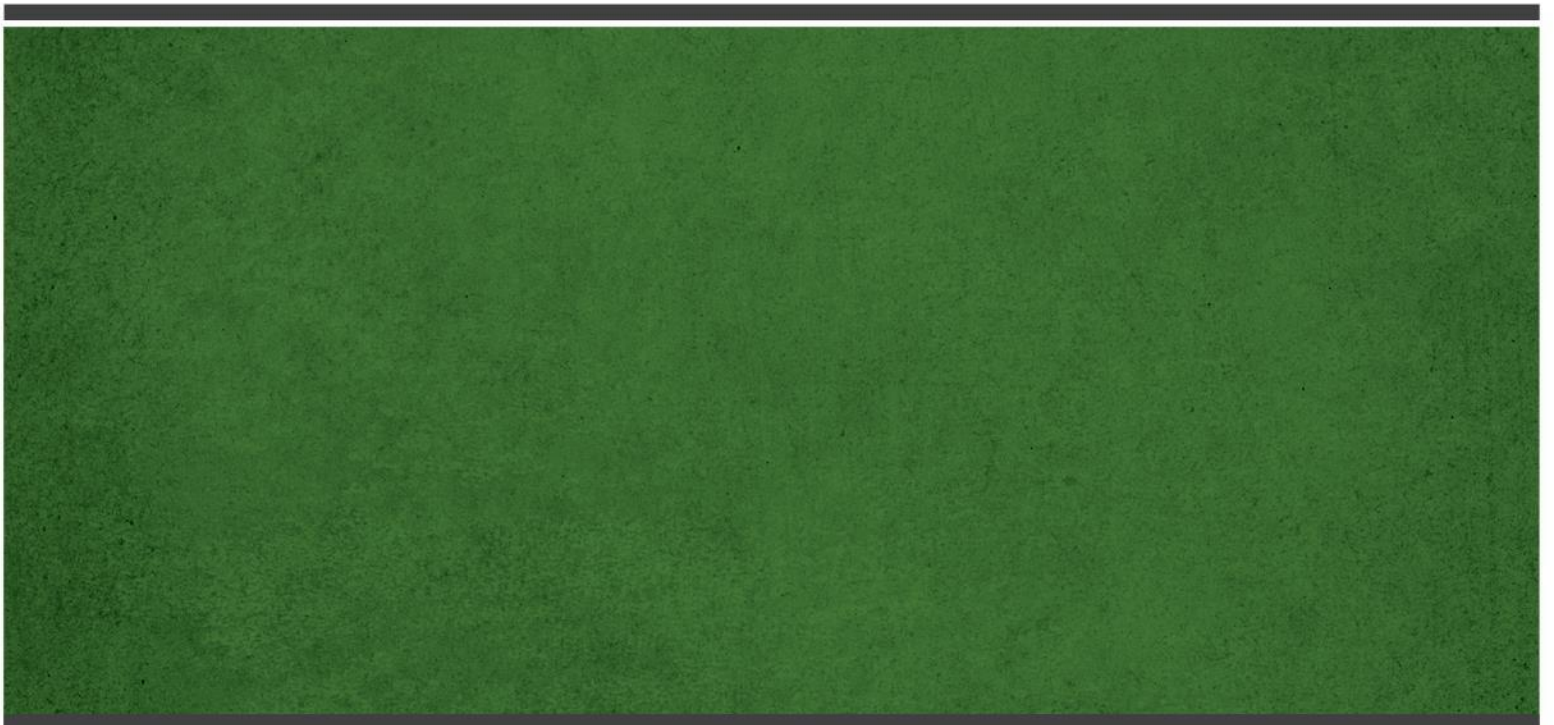
An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)

Recommendations on the use of pneumococcal vaccines in adults, including PNEU-C-21



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—Public Health Agency of Canada

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Recommandations sur l'utilisation des vaccins contre le pneumocoque chez les adultes, y compris le PNEU-C-21

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PREAMBLE

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines 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 PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

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

1. What

Pneumococcal disease in adults includes invasive pneumococcal disease (IPD), an acute and serious communicable disease with manifestations such as meningitis, bacteremia and bacteremic pneumonia and empyema. Bacteremic pneumococcal pneumonia is the most common presentation of IPD among adults. In addition, non-invasive pneumococcal disease such as community acquired pneumonia and acute otitis media (typically in children) can occur. These conditions are caused by the *Streptococcus pneumoniae* bacterium. Of the more than 100 serotypes of this bacterium, a small number cause the majority of disease.

On July 15, 2024, Health Canada authorized a new pneumococcal conjugate (PNEU-C) vaccine:

- Pneu-C-21 is authorized for adults 18 years of age and older with an indication for prevention of IPD caused by 21 serotypes of *S. pneumoniae* (3, 6A/6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B/15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B).
- Pneu-C-21 contains 10 unique, non-cross-reactive serotypes (9N, 15A, 16F, 17F, 20A, 23A, 23B, 24F, 31 and 35B) compared to Pneu-C-20, and Pneu-C-20 contains 9 unique serotypes not included in Pneu-C-21 (1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F).

2. Who

IPD is most common in the very young, older adults, and groups with medical conditions and/or other risk factors that place them at high risk of IPD (see Table 1). Young children and adults over 65 years of age are at highest risk of non-invasive pneumococcal disease.

NACI recommends the use of a higher valency pneumococcal vaccine (i.e., Pneu-C-20 or Pneu-C-21) in adult pneumococcal immunization programs. All adults 65 years of age and older and adults under 65 years of age at increased risk of IPD (see Table 1) should receive 1 dose of either Pneu-C-20 or Pneu-C-21, regardless of pneumococcal vaccination history with Pneu-C-13, Pneu-C-15 or Pneu-P-23.

Additional details, including immunization of adults who received a hematopoietic stem cell transplant, as well as intervals between previous pneumococcal vaccination, are discussed in Section VIII.

Table 1: Adult risk factors for IPD

It should be noted that some conditions listed below carry higher risk than others. In adults, risk increases at a population level with advancing age (beginning at age 50). In addition, having multiple risk factors at once may also increase risk for an individual.

Program level recommendations may focus on the populations particularly at risk.

Medical conditions:

- Hematopoietic stem cell transplant recipients
- Chronic cerebrospinal fluid (CSF) leak
- Cochlear implants, including those who are to receive implants
- 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
- Immunocompromising conditions or immunosuppressive therapy within the past 2 years, including use of long-term corticosteroids, chemotherapy, radiation therapy, and immunosuppressive biologics
- Active malignant neoplasms[a], including leukemia and lymphoma
- Candidates and recipients of solid organ or islet transplants
- Chronic kidney disease, particularly those individuals with stage 4 and 5 chronic kidney disease, and those with nephrotic syndrome, on dialysis or renal transplant recipients
- Chronic liver disease including cirrhosis, biliary atresia and chronic hepatitis
- HIV infection
- Functional or anatomic asplenia (congenital or acquired) or splenic dysfunction, including sickle cell disease and other hemoglobinopathies
- Chronic neurologic conditions that may impair clearance of oral secretions
- Chronic heart disease requiring regular medication and follow up for ischemic heart disease, congenital heart disease, chronic heart failure, or hypertension with cardiac complications
- Diabetes mellitus, particularly in those over 50 years of age
- Chronic lung disease (particularly chronic obstructive pulmonary disease, emphysema, bronchiectasis, interstitial lung fibrosis, and cystic fibrosis), including asthma that required medical care in the preceding 12 months

Social, behavioural, and environmental factors:

- Individuals who are unhoused
- Individuals living in communities or settings experiencing sustained high IPD rates, including those who are in residential care [b,c]
- Smoking, particularly in those over 50 years of age
- Substance use (i.e., alcohol misuse, cocaine use and injection drug use)
- Occupational risk with long-term continuous exposure to metal fumes (i.e., welders)

[a] Immune compromised status can vary over time depending upon the disease state, which may or may not involve immunosuppressive medication.
[b] Including long-term care homes.
[c] Individuals should be vaccinated with a vaccine that covers serotypes circulating in the community.

3. How

Pneu-C-15, Pneu-C-20, and Pneu-C-21 are supplied in a single-dose, prefilled syringe, and are to be administered intramuscularly. A standard schedule for immunization is one 0.5ml dose. Contraindications to administration of Pneu-C-15, Pneu-C-20, or Pneu-C-21 include hypersensitivity (e.g., anaphylaxis) to the vaccine or any of its components. Pneumococcal vaccines may be administered concurrently with other vaccines, except for a different formulation of pneumococcal vaccine (e.g., concurrent use of conjugate and polysaccharide).

4. Why

Pneumococcal infection can cause severe infections and can lead to significant mortality and morbidity with lifelong complications. The most effective way to prevent these infections is through immunization.

I. INTRODUCTION

The need for updated NACI guidance on adult pneumococcal vaccine programs arose from the authorization of a new product. On July 15, 2024, Health Canada authorized the use of Pneu-C-21 (CAPVAXIVE™, Merck), a 21-valent pneumococcal conjugate vaccine. This follows the relatively recent authorization of Pneu-C-15 and Pneu-C-20, for which a NACI statement was published on February 2023, to provide guidance on their use in public health programs.

Guidance Objective:

The objective of this statement is to review evidence on Pneu-C-21 and provide guidance on the recommended use of pneumococcal vaccines, within the existing adult pneumococcal vaccination program recommendations, given the disease burden of pneumococcal disease in Canada among adults at increased risk for invasive pneumococcal disease (IPD), including adults aged 65 and older and adults under 65 years with risk factors (Table 1).

Background on adult pneumococcal immunization programs in Canada:

All provinces, territories and federal jurisdictions have publicly funded adult pneumococcal vaccination programs, although there is some variation in the eligible populations in each jurisdiction. In 2023, NACI provided updated guidance recommending the use of Pneu-C-20 in adult immunization programs, with Pneu-C-15 and Pneu-P-23 in series as an alternative (at the time the advice was issued, Pneu-P-23 was still available for use). Prior to the availability of Pneu-C-20 and Pneu-C-15 vaccines, Pneu-P-23 and Pneu-C-13 were incorporated in programs based on age and additional risk factors.

A national coverage goal of 80% in adults 65 years of age and older, by the year 2025, has been established for the receipt of one dose of a pneumococcal vaccine to protect people in Canada at high risk for infection and medical complications [1]. However, recent estimates of vaccine coverage in adults have shown that this coverage goal has not been reached [2].

II. METHODS

In brief, the broad stages in the preparation of this NACI advisory committee statement were:

1. Analysis of the burden of IPD in Canada.
2. Knowledge synthesis (retrieve and summarize individual studies, rank the level [i.e., study design] and quality of the evidence from individual studies) – summarized in Section XI. Evidence Tables.
3. Synthesis of the body of evidence of benefits and harms, considering the quality of the evidence and magnitude of effects observed across the studies.
4. Use of a published, peer-reviewed framework and evidence-informed tools [3], to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into the guidance.

5. Use of systematic reviews and a model-based cost-utility analysis of higher valency pneumococcal conjugate vaccines in adults to generate economic evidence.
6. Translation of evidence and programmatic considerations into recommendations, leveraging a GRADE-informed Evidence-to-Decision framework.

Further information on NACI's evidence-based methods is available elsewhere [4,5].

For this advisory committee statement, NACI reviewed the key questions for the literature review as proposed by the Pneumococcal Working Group, including considerations such as the burden of illness to be prevented among the target population(s), safety, immunogenicity, efficacy/effectiveness of the vaccine, economic evaluation of the immunization product(s), immunization schedules, and other aspects of the overall immunization strategy. The knowledge synthesis was performed by the NACI Secretariat and supervised by the Working Group.

The evidence and proposed recommendations were presented to NACI on June 12, 2024 and September 18 and 19, 2024. Following a thorough review of the evidence and consultation at the NACI meetings, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in this statement.

The policy questions addressed in this statement are:

1. Should Pneu-C-21 be recommended for use in immunization programs for adults currently recommended to receive pneumococcal vaccine, and who have never received pneumococcal vaccination or whose vaccination status is unknown?
2. Should Pneu-C-21 be recommended for use in immunization programs for adults currently recommended to receive pneumococcal vaccine, and who have previously received pneumococcal vaccination?
3. Are there other adults at risk of IPD who should be recommended to receive a higher valency pneumococcal vaccination (i.e., Pneu-C-20 or Pneu-C-21)?

II.2 Literature review of Pneu-C-21 studies

A systematic review of the efficacy, effectiveness, immunogenicity, and safety of Pneu-C-21 for preventing IPD was conducted, including evidence from key clinical trials, published studies, and supplementary data obtained from manufacturers. The components of the research question are summarized as:

Population: Adults 18 years of age and older with or without risk factors for IPD (Table 1)

Intervention: Pneu-C-21

Comparator: Pneu-C-20

Outcomes: Death due to vaccine preventable *S. pneumoniae* serotypes, IPD due to vaccine preventable pneumococcal serotypes, IPD due to any pneumococcal serotype (vaccine preventable and not vaccine preventable), pneumococcal community-acquired pneumonia (pCAP) due to a vaccine-preventable serotype, serious adverse events (SAEs), severe systemic adverse events (AEs), and mild/moderate systemic AEs following vaccination.

In the absence of disease endpoint and mortality data, immunogenicity (opsonophagocytic assay [OPA] geometric mean titre [GMT] ratios and percentage of seroresponders defined as greater or equal to a 4-fold increase in OPA GMT ratio from before vaccination to after vaccination) was evaluated.

The methodology for reviewing pneumococcal vaccine studies has been previously documented [6]. Following critical appraisal of individual studies, summary tables with ratings of the certainty of the evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology were prepared. Studies in which Pneu-C-20 was not the comparator vaccine were reviewed as supporting evidence on the efficacy, effectiveness, immunogenicity and safety of Pneu-C-21, and were not assessed using GRADE.

III. EPIDEMIOLOGY

III.1 Disease burden of IPD in Canada

A detailed summary of the epidemiology of pneumococcal disease in Canada is available in the 2023 NACI statement on public health level recommendations on the use of pneumococcal vaccines in adults. The summary below includes information that became available after the review of the evidence for the 2023 NACI adult pneumococcal statement.

III.2 Distribution of IPD Serotypes in adults in Canada, 2019 to 2023

From 2019 to 2023, a combined 14,563 isolates of *S. pneumoniae* causing invasive disease in adults were characterized by the NML, with 39% of these being identified from adults 65 years of age and older. The majority of IPD cases were caused by vaccine-contained serotypes (Figure 1). Based on NML data, serotypes 4, 3 and 22F were the most common causes of IPD overall in adults during this time period. The most common serotypes for adults 18 to 49 years were 4 and 12F; serotypes 3 and 4 for adults 50 to 64 years; and serotypes 3 and 22F for adults 65 years of age and older (Figure 1).

See Table 2 for a description of vaccine categorization for IPD serotype distribution in Canada. Further breakdowns by age are available in the Appendix.

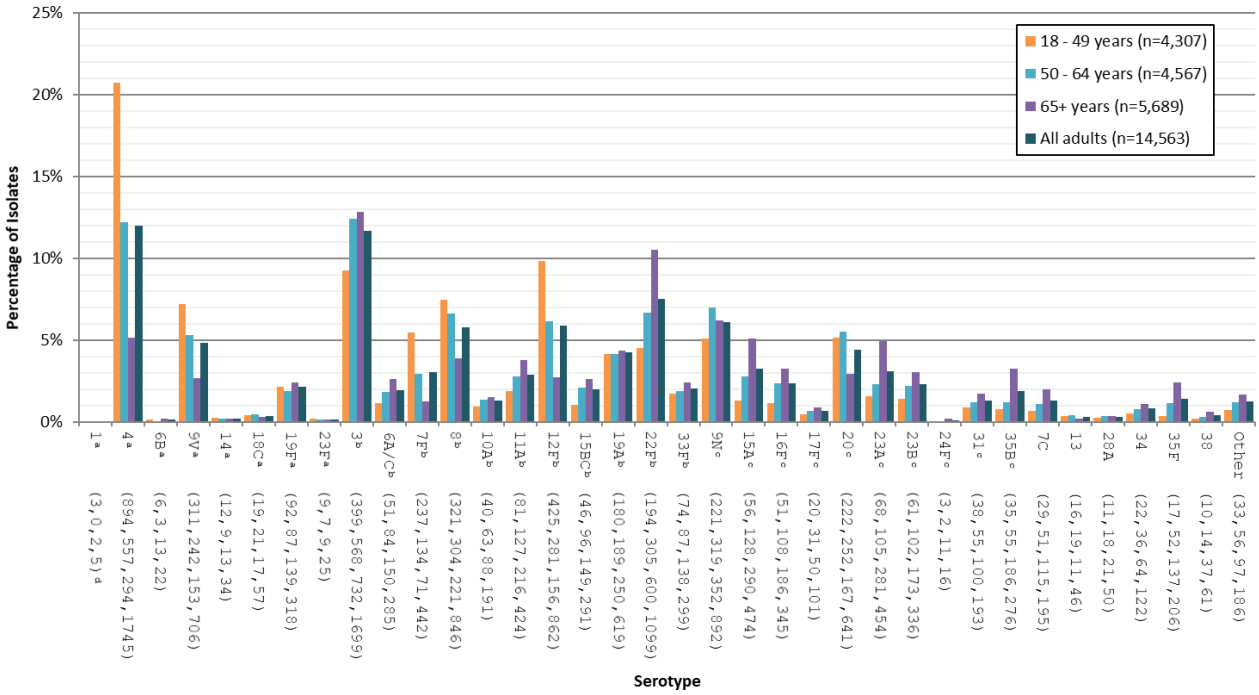
Table 2. Vaccine categorization for descriptions for IPD serotype distribution in Canada

Vaccine Categorization	Serotypes

Pneu-C-20/non-Pneu-C-21	1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F
Pneu-C-20 and Pneu-C-21 shared	3, 6A, 6C*, 7F, 8, 10A, 11A, 12F, 15B/C**, 19A, 22F, 33F
Pneu-C-21/non-Pneu-C-20	9N, 15A, 16F, 17F, 20A, 23A, 23B, 24F, 31, 35B
NVT	all serotypes not included in Pneu-C-20 and Pneu-C-21

*Serotype 6C included in PNEU-C-20/PNEU-C-21 shared serotypes due to cross protection with 6A.
**Serotypes 15B and 15C were grouped together as 15B/C because of reported reversible switching between them *in vivo* during infection, making it difficult to precisely differentiate between the two types.

Figure 1. Proportion of isolates of invasive *S. pneumoniae* for adults 18 to 49 years, 50 to 64 years, 65 years of age and older, and all ages in Canada, by serotype (2019 to 2023, combined total)

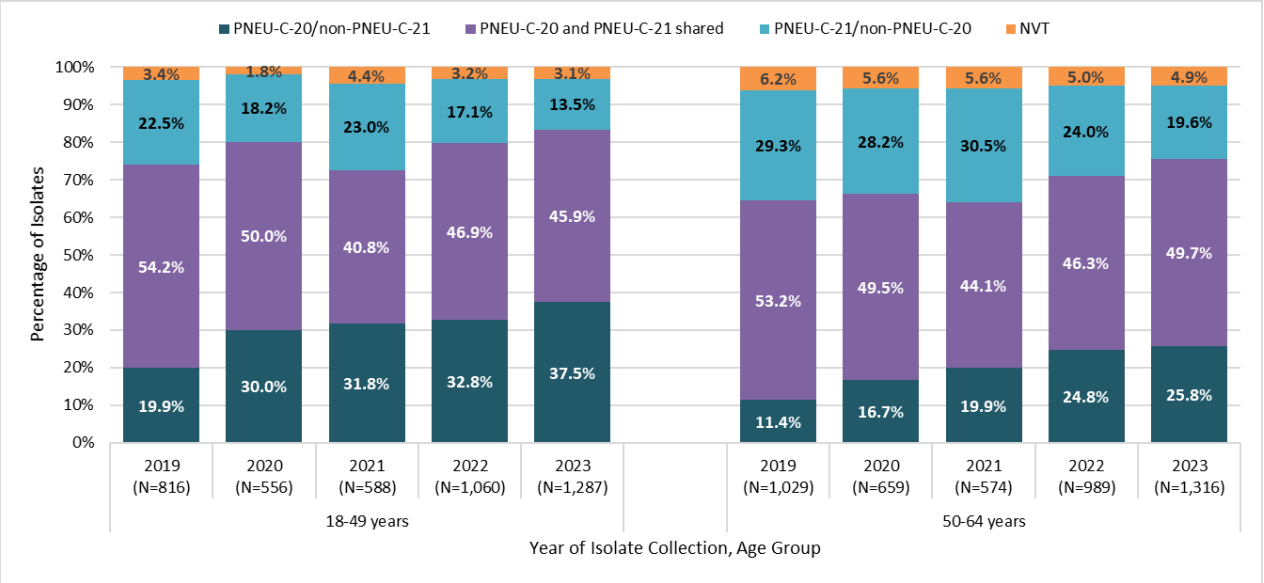


[a] Pneu-C-20/non-Pneu-C-21 serotype; [b] Pneu-C-20 and Pneu-C-21 shared serotype; [c] Pneu-C-21/non-Pneu-C-20 serotype; [d] Number of isolates for adults 18 to 49 years, 50 to 64 years, ≥65 years and all ages all ages, respectively (2019-2023, combined total).

Among adults 18 to 49 years of age, the majority (approximately 97%) of isolates collected between 2019 and 2023 were caused by Pneu-C-20/Pneu-C-21 vaccine-containing serotypes. Overall, there has been an increasing trend in the proportion of Pneu-C-20/non-Pneu-C-21 isolates, ranging between 20 and 38% of all isolates in this age group between 2019 and 2023 (Figure 2). In comparison, the proportion of Pneu-C-21/non-Pneu-C-20 isolates has been decreasing, ranging between 23 and 13% of all isolates during the same time period. Similar trends were noted in the 50 to 64 year age group (Figure 2). Between 2019 and 2023, the

proportion of Pneu-C-20/non-Pneu-C-21 isolates increased from 11 to 26%, while the proportion of Pneu-C-21/non-Pneu-C-20 serotypes decreased from 30 to 20%.

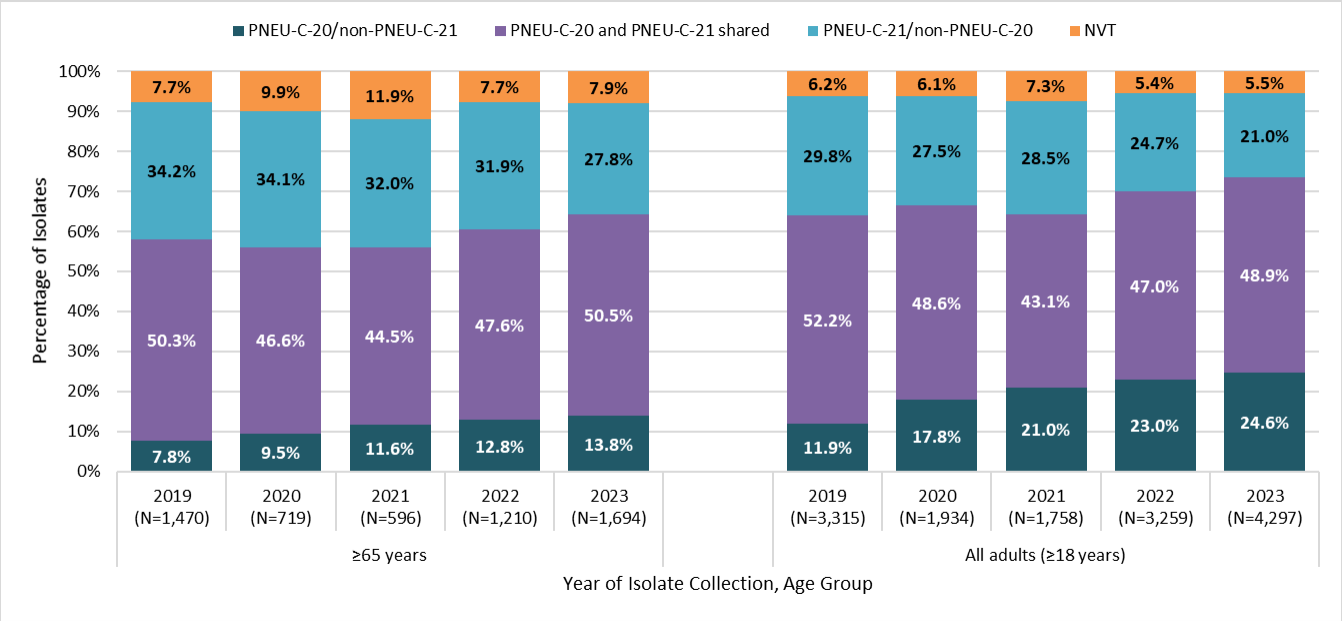
Figure 2. Proportion of IPD isolates from 2019 to 2023 by vaccine, for the 18 to 49 year and 50 to 64 year age groups



*Pneu-C-20/non-Pneu-C-21 serotypes include 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F; Pneu-C-20/Pneu-C-21 shared serotypes include 3, 6AC, 7F, 8, 10A, 11A, 12F, 15BC, 19A, 22F, 33F; Pneu-C-21/non- Pneu-C-20 serotypes include 9N, 15A, 16F, 17F, 20, 23A, 23B, 24F, 31, 35B; NVT = all serotypes not included in Pneu-C-20 and Pneu-C-21. Serotype 6C included in Pneu-C-20/ Pneu-C-21 shared serotypes due to cross protection with 6A. Serotypes 15B and 15C were grouped together as 15B/C because of reported reversible switching between them *in vivo* during infection, making it difficult to precisely differentiate between the two types.

In contrast to adults less than 65 years of age, among those 65 years of age and older, the proportion of Pneu-C-21/non-Pneu-C-20 serotypes was higher and remained more stable between 2019 and 2023, ranging between 28 and 34% of isolates (Figure 3). Similarly to other adult age groups, there was an overall increasing trend observed in the proportion of Pneu-C-20/non-Pneu-C-21 serotypes, though it was not as pronounced (8 to 14%). Though the majority of isolates collected between 2019 and 2023 were caused by Pneu-C-20/Pneu-C-21 vaccine-containing serotypes, there was a higher proportion of non-vaccine serotypes in this age group (ranging between 8 and 12%).

Figure 3. Proportion of IPD isolates from 2019 to 2023 by vaccine, for adults ≥65 years of age and all adults



*Pneu-C-20/non-Pneu-C-21 serotypes include 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F; Pneu-C-20/Pneu-C-21 shared serotypes include 3, 6AC, 7F, 8, 10A, 11A, 12F, 15BC, 19A, 22F, 33F; Pneu-C-21/non-Pneu-C-20 serotypes include 9N, 15A, 16F, 17F, 20, 23A, 23B, 24F, 31, 35B; NVT = all serotypes not included in Pneu-C-20 and Pneu-C-21. Serotype 6C included in Pneu-C-20/Pneu-C-21 shared serotypes due to cross protection with 6A. Serotypes 15B and 15C were grouped together as 15B/C because of reported reversible switching between them *in vivo* during infection, making it difficult to precisely differentiate between the two types.

The trend of increased prevalence of Pneu-C-20/non-Pneu-C-21 serotypes in the 18 to 49 and 50 to 64 year age groups between 2019 and 2023 is partially due to the resurgence of Pneu-C-13/Pneu-C-20 vaccine-contained serotypes 4 and 9V (that Pneu-C-21 does not cover).These serotypes also increased in adults over 65 years of age, but to a much lesser extent (see Appendix).

Further details are available in the annual report for invasive pneumococcal disease in Canada [7].

III.3 Distribution of IPD serotypes in Northern Canada, 2019 to 2023

IPD distribution in Northern Canada was assessed using data from the 5 Arctic regions captured by the International Circumpolar Surveillance (ICS) program, including Yukon, Nunavut, northern Québec, northern Labrador, and the Northwest Territories. Overall, 222 isolates of invasive *S. pneumoniae* were reported to ICS between 2019 and 2023: 29% of *S. pneumoniae* isolates were Pneu-C-20/non- Pneu-C-21 serotypes, 28% were Pneu-C-20/Pneu-C-21 shared serotypes, 27% were Pneu-C-21/non-Pneu-C-20 serotypes, and 4% were NVT serotypes. Additionally, 12% of isolates were an unknown serotype. Trends are difficult to ascertain due to the small number of cases and relatively smaller population in the North.

III.4 IPD in groups at increased risk of IPD

The risk of IPD in adults generally increases with factors including age, the number of risk factors, and with the degree of organ impairment for certain chronic medical conditions. However, the data to assess absolute and relative risk of IPD for a number of conditions are limited, making it challenging to inform a clear assessment of risk stratification.

The Toronto Invasive Bacterial Diseases Network (TIBDN), an active surveillance program in Metropolitan Toronto and the Peel region, found that between 2014 to 2023 (excluding 2020 to 2021), overall IPD incidence was 2.5 cases per 100,000 for adults 18 to 49 years old. Specifically, incidence was 1.6 per 100,000 for those without underlying illness, and 5.2 per 100,000 for those with at least one underlying illness (incidence rate ratio [IRR]=3.3; 95% confidence interval [CI]: 2.7-4.0). Among adults 50 to 64 years old, IPD incidence was 8.7 per 100,000 with an incidence of 3.8 per 100,000 for those without underlying illness, and 15.3 per 100,000 for those with at least one underlying illness (IRR=4; 95%CI: 3.3-4.8) [8].

Evidence on burden of IPD in people who are unhoused and individuals with occupational risk for IPD was also reviewed.

Among people who are unhoused, IPD incidence is disproportionately higher than the general population. A literature review of studies published up to 2021 found that medical and social factors such as alcohol use and smoking can contribute to increased IPD risk, with serotype 4 being the most predominant serotype among people experiencing homelessness [9]. This review included studies describing an outbreak of IPD in Victoria, BC, attributed to an increase in serotype 4 (of which approximately half occurred in the unhoused or unstably housed populations) [10], and an analysis of data from The Calgary Area *Streptococcus pneumoniae* Epidemiology Research team in AB, where 321/1,729 (18.8%) of all adult IPD cases between 2000 and 2016 occurred among individuals who were unhoused, of which 54.4% were associated with pneumococcal serotypes 4, 5 and 8 [11].

More recent information includes data from TIBDN, where between 2014 and 2023 (excluding 2020 to 2021), an elevated risk of IPD was shown in unhoused individuals, with an overall IPD incidence of 66 cases per 100,000 adults 18 to 49 years old, and 151 cases per 100,000 adults 50 to 64 years old [8]. In Anchorage, Alaska, a surveillance study reported IPD incidence being 72 times higher among people who are unhoused compared to the general adult population, with a rise in cases in recent years driven by serotypes 4 and 12F [12]. In Marseille, France, pneumococcal carriage rate was higher among males who are unhoused (13.0%) compared to controls (3.7%). Vaccination rates among people who are unhoused were also low (3.1%) despite around 25% having IPD medical risk factors [13].

Additionally, an occupational risk for IPD exists among welders. A recent systematic review and meta-analysis of observational studies and case series (outbreak) reports investigated IPD outcomes in industrial workers exposed to metal and welding fumes compared to the general population [14]. From a meta-analysis of three observational studies, welders were found to have increased odds of developing IPD compared to non-welders (odds ratio [OR]: 2.59; 95% CI:

2.00-3.35) and of dying from IPD (standardized mortality ratio: 2.42; 95% CI: 1.96-2.99). Out of six occupational pneumococcal outbreak reports where serotype information was available, serotype 4 was the most commonly reported serotype, followed by 12F, 8, 3, and 9N.

III.5 Summary of adult pneumococcal vaccine coverage in Canada

The adult National Immunization Coverage Survey (aNICS) is a national survey conducted by PHAC to measure routine immunization coverage in Canada. Respondents to the survey were health care providers, 18 to 64 years of age with at least one chronic health condition, or 65 years of age and older (or 50 years and older in Nunavut), at the time of the survey.

In the 2023 aNICS survey, routine immunization coverage for one dose of pneumococcal vaccine was estimated to be 38.5% among adults aged 18 and older. Among adults aged 65 and older, 54.7% had received a recommended pneumococcal vaccine, while this estimate was higher for adults aged 80 and older (62.8%) [2]. However, Canadian pneumococcal vaccination coverage for adults 65 years of age and older remains suboptimal compared to the 80% coverage goal.

Adults between the ages of 18 and 64 years with chronic health conditions were less likely than the people without chronic health conditions to have received the pneumococcal vaccine as an adult (29.3% versus 35.8%). However, among adults 50 years of age and older, coverage for individuals with chronic health conditions is higher than those without (40.3% versus 35.8%, respectively). Among provinces and territories, NL experiences the lowest coverage (26.3%), while YK has the highest coverage (54.2%). All other provinces and territories have a coverage between 27.7% and 43.5%: NB (27.7%), SK (31.6%), QC (34.8%), NS (35.5%), BC (36.5%), PE (38.8%), NT (41.3%), ON (42.1%), AB (42.3%), and MB (43.5%). Data is not reported for NU due to high sampling variability and/or small sample size.

Additional information on adult pneumococcal vaccine coverage is available on the Adult National Immunization Coverage Survey (aNICS): 2023 results webpage.

IV. Vaccine

This section focuses primarily on evidence available for Pneu-C-21. Information on other pneumococcal vaccines is available in past NACI statements, including the 2023 NACI statement on Public health level recommendations on the use of pneumococcal vaccines in adults, including the use of 15-valent and 20-valent conjugate vaccines.

IV.1 Preparation(s) authorized for use in Canada

Characteristics of the five preparations of pneumococcal vaccine currently authorized for use in adults in Canada are summarized in Table 3.

Table 3. Comparison of vaccines authorized for use in Canada

	PREVNAR® 13 (Pneu-C-13) [15]	**VAXNEUVANCE®** (Pneu-C-15) [16]	**PREVNAR20™** (Pneu-C-20) [17]	**CAPVAXIVE™** (Pneu-C-21) [18]	**PNEUMOVAX 23®** (Pneu-P-23) [19]
Manufacturer	Pfizer	Merck	Pfizer	Merck	Merck
Date of authorization in Canada	December 21, 2009	November 16, 2021	May 9, 2022	July 15, 2024	December 23, 1983
Type of vaccine	Conjugate vaccine	Conjugate vaccine	Conjugate vaccine	Conjugate vaccine	Polysaccharide vaccine
Composition	2.2 mcg of each saccharide for *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F, 4.4 mcg of saccharide for serotype 6B, 34 mcg of CRM197 carrier protein, 4.25 mg of sodium chloride, 100 mcg of polysorbate 80, 295 mcg of succinic acid and 125 mcg of aluminum as aluminum phosphate adjuvant and water for injection	32 mcg of total pneumococcal polysaccharide (2.0 mcg each of polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F and 4.0 mcg of polysaccharide serotype 6B) conjugated to 30 mcg of CRM197 carrier protein, 125 mcg of aluminum as aluminum phosphate adjuvant, 1.55 mg L-histidine, 1 mg of polysorbate 20, 4.50 mg sodium chloride and water for injection	2.2 mcg of each of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F saccharides, 4.4 mcg of 6B saccharide, 51 mcg CRM197 carrier protein, 100 mcg polysorbate 80, 295 mcg succinic acid, 4.4 mg sodium chloride, and 125 mcg aluminum as aluminum phosphate adjuvant and water for injection	84 mcg of pneumococcal polysaccharide antigen (4 mcg each of polysaccharide serotypes 3, 6A, 6C 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) conjugated to approximately 65 mcg of CRM197 carrier protein	25 mcg of capsular polysaccharides from each of *S. pneumoniae* serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F, sodium chloride 0.9 % w/w, phenol 0.25% w/w and water for injection

Schedule	1-dose schedule	1-dose schedule	1-dose schedule	1-dose schedule	1-dose schedule
Route of administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular or subcutaneous injection
Adult Indications	Indicated for active immunization of adults 18 years of age and older for prevention of pneumonia and invasive pneumococcal disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F	Indicated for active immunization of adults 18 years of age and older for the prevention of invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F	Indicated for active immunization of adults 18 years of age and older for the prevention of pneumonia and invasive pneumococcal disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F	Indicated for active immunization of adults 18 years of age and older for the prevention of invasive pneumococcal disease caused by *S. pneumoniae* serotypes 3, 6A, 6C, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B	Indicated for active immunization of adults 50 years of age and older, and individuals 2 years of age and older who are at increased risk for pneumococcal disease, for prevention of pneumococcal disease caused by pneumococcal types included in the vaccine (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F)
Contraindications	Known hypersensitivity to any component of the vaccine, including diphtheria toxoid	History of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or any diphtheria toxoid-containing vaccine	Known hypersensitivity to the active substance or to any component of the vaccine, including diphtheria toxoid	History of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine including diphtheria toxoid	Known hypersensitivity (e.g., anaphylaxis) to any component of the vaccine
Precautions	-Individuals with	-Individuals with immunocompro	-Individuals with	-Individuals with	-Pregnancy (no data)

	immunocompromising conditions (limited data; may have reduced immune response) -Pregnancy (limited data) -Breastfeeding (limited data)	mising conditions (may have reduced immune response) -Pregnancy (limited data) -Breastfeeding (no data)	immunocompromising conditions (no data) -Pregnancy (limited data) -Breastfeeding (limited data)	immunocompromising conditions (no data) -Pregnancy (limited data) -Breastfeeding (no data) -Pediatrics (no data)	-Breastfeeding (no data)
Storage Requirements	Single-dose prefilled syringe. Refrigerate at 2°C to 8°C. Do not freeze. Store in original package.	Single-dose prefilled syringe. Refrigerate at 2°C to 8°C. Do not freeze. Protect from light. Administer as soon as possible after being removed from the refrigerator.	Single-dose prefilled syringe. Refrigerate at 2°C to 8°C. Store syringes horizontally in the refrigerator. Do not freeze. Administer as soon as possible after being removed from the refrigerator.	Single-dose prefilled syringe. Refrigerate at 2°C to 8°C. Do not freeze. Protect from light. Administer as soon as possible after being removed from the refrigerator.	Single-dose prefilled syringe. Refrigerate at 2°C to 8°C. Discard opened vial after 48 hours. Administer as soon as possible after being removed from the refrigerator.

For complete prescribing information, please consult the product leaflet or information contained within Health Canada's authorized product monographs available through the Drug Product Database (DPD).

IV.2 Efficacy/Effectiveness

There are currently no randomized controlled trials evaluating efficacy, or effectiveness data available for high-valency pneumococcal conjugate vaccines (Pneu-C-15, Pneu-C-20, or Pneu-C-21) for any adult indication.

IV.3 Immunogenicity

NACI reviewed the available evidence on the immunogenicity of Pneu-C-21 in the context of routine adult immunization programs, as well as catch-up and re-immunization schedules (see Table 5 for a summary of evidence comparing Pneu-C-21 and Pneu-C-20). Immunogenicity

following immunization with Pneu-C-21 was available for NACI review from five Phase 2/3 clinical trials (V116-003, V116-004, V116-005, V116-006, V116-007) [20] and two phase 1/2 clinical trials (V116-001, Haranaka et al.) [20, 21]. See Table 6 for a summary of the clinical trials.

These studies enrolled over 7,600 adults who were vaccine-naive or had previously received Pneu-C-13, Pneu-P-23, and/or Pneu-C-15. Approximately one third of these adults were 65 years of age and older, and/or had one or more chronic conditions predisposing them for IPD (including diabetes; chronic kidney, lung, heart or liver disease; smoking or alcohol use disorder).

IV.3.1 Measures of immunogenicity

OPA assays were used to assess immune response for Pneu-C-21. While no specific threshold of OPA titre has been identified that correlates with protection against IPD or pneumonia in adults, OPA responses have been used as a surrogate of protection to infer efficacy when comparing to a vaccine with established efficacy. Previously, OPA responses were used as a surrogate marker of vaccine efficacy for IPD and pneumonia in the approval of Pneu-C-13 in adults.

Immunogenicity measured as GMTs of serotype-specific OPA titres pre-and post-vaccination and percentage of participants with a greater than 4-fold rise in OPA titres pre- and post-vaccination were reviewed. For all studies, immunogenicity outcomes were measured one month following dose administration.

IV.3.2 Immunogenicity in immunocompetent, vaccine-naïve, adults

Immunogenicity data from immunocompetent, vaccine-naïve adults were available from three studies (V116-003, V116-004 and V116-005) [20]. In the pivotal double-blind clinical trial V116-003, adults aged 18 years and older were vaccinated with either Pneu-C-20 (N=1,379) or Pneu-C-21 (N=1,277). Pneu-C-21 elicited comparable immune responses to Pneu-C-20 for shared serotypes and higher responses for unique serotypes across age subgroups (18 to 49 years, 65-74 years, and 75 years and older). The proportion of responders was higher for all unique serotypes.

Generally, higher immune responses were observed for most serotypes in participants 18 to 49 years of age compared to those 65 years of age and older. Similar immunogenicity was observed between study participants with and without risk factors for IPD. In the lot-consistency study (V116-004) [20], participants (N=2,157) received either Pneu-C-21 or Pneu-P-23. Immunogenicity of Pneu-C-21 (combined lots) for serotypes shared with Pneu-P-23 was found to be comparable between the intervention groups. Pneu-C-21 was also found to be immunogenic for all vaccine-contained serotypes in the study where it was administered sequentially with QIV (V116-005) [20].

A GRADE assessment was conducted for one study comparing Pneu-C-21 and Pneu-C-20 (V116-003) [20]. The certainty of immunogenicity evidence was rated as moderate because of downrating for indirectness (immunogenicity was used in absence of disease endpoints) and uncertainty as to how these findings will translate to vaccine effectiveness against clinical outcomes over the long term. Overall evidence was assessed as being of moderate certainty for adults over 65 years of age and adults over 50 years of age with IPD risk factors.

IV.3.3 Immunogenicity in immunocompetent, vaccine-experienced adults

One study (V116-006) [20] assessed immunity in vaccine-experienced adults aged 50 years and older who had been previously vaccinated with Pneu-C-13 (n=348), Pneu-P-23 (N=259), or Pneu-C-13/Pneu-C-15 and Pneu-P-23 (N=105). In all study cohorts, Pneu-C-21 was found to be immunogenic, with immune responses for common serotypes generally being reported as comparable between intervention groups (adults who received Pneu-C-15 or Pneu-P-23). The majority of individuals in the study were 65 years of age and older. In adults who previously received Pneu-P-23, OPA GMT titres and seroresponse rates were generally lower compared to vaccine-naïve adults and those who were vaccinated with Pneu-C-13 (OPA GMT titres 30 to 50% lower).

IV.3.4 Immunogenicity in special populations

One study assessed immunogenicity in adults 18 years of age and older with HIV (25% with CD4+ T-cell count ≥50 to <500 cells/μL, and 75% with CD4+ T-cell count ≥500 cells/μL) who were vaccine-naive or had previously received Pneu-C-13, Pneu-P-23, or both (V116-007) [22]. Pneu-C-21 was found to be immunogenic for all 21 serotypes, with comparable immune responses for common serotypes to those reported following the sequential administration of Pneu-C-15 and Pneu-P-23.

IV.4 Vaccine administration and schedule

Pneu-C-21 is supplied in a single-dose, prefilled syringe. The standard schedule for immunization is one dose.

A single 0.5ml dose of Pneu-C-21 should be administered to adults by intramuscular injection. A single dose of Pneu-C-21 can be given to adults who have been previously vaccinated with another pneumococcal vaccine at least one year prior. Please see the product monograph for additional details [18].

When rapid immunization is required (e.g., for immunocompromised individuals), the minimum interval between two different Pneu-C vaccines is 8 weeks.

IV.5 Serological testing

Serological testing is not recommended before or after receiving pneumococcal vaccine.

IV.6 Storage requirements

Pneu-C-21 should be refrigerated at 2°C to 8°C. The vaccine should not be frozen. Protect the vaccine from light. The prefilled syringes should be administered as soon as possible after being removed from the refrigerator. In the event of temporary temperature excursions, stability data indicate that Pneu-C-21 is stable at temperatures up to 25°C for 96 hours.

IV.7 Concurrent administration with other vaccines

Pneumococcal vaccines may be administered concurrently with other vaccines, with the exception of a different formulation of pneumococcal vaccine (i.e., there should be no concurrent use of pneumococcal conjugate and pneumococcal polysaccharide vaccines).

One study (V116-P005) [20] evaluated the immunogenicity and safety of Pneu-C-21 when administered concurrently with QIV in healthy adults over 50 years of age (N=1,072). The results showed numerically lower, but non-inferior, immune responses to most pneumococcal serotypes (20 out of 21) and influenza strains (3 out of 4) after concurrent administration compared to sequential administration. However, all OPA GMT titres were numerically lower after concurrent administration. There was also an observed trend towards lower GMT OPA titres in adults over 65 years of age compared to adults 50 to 64 years of age, similar to Pneu-C-20. The safety profile was comparable between those who received concurrent administration and those who received sequential administration, with no vaccine-related deaths reported. One vaccine-related SAE of bronchospasm was reported in the sequential administration group. It occurred 30 minutes after vaccination, required medical intervention, and resolved after approximately 24 hours.

No data are available on co-administration of Pneu-C-21 with other adult vaccines.

IV.8 Vaccine safety

Over the past 20 years, pneumococcal conjugate vaccines (namely Pneu-C-7, Pneu-C-10, and Pneu-C-13) have had a good safety profile, with hundreds of millions of doses administered. While post-market safety data on the higher valency conjugate vaccines continue to accrue, they are also expected to have a similar safety profile.

Evidence on the safety of Pneu-C-21 administration was available from all reported clinical trials and included vaccine-naive and vaccine-experienced adults. The rate of vaccine related and non-related AEs, including death and SAEs was found to be comparable between intervention groups.

An integrated safety analysis combined data from multiple trials (V116-003, V116-004, V116-005 and V116-006) [20] with a total population of over 6,000 individuals, of whom 4,000 received Pneu-C-21. The analysis showed that Pneu-C-21 was well-tolerated in adults 18 years of age

and older, with similar frequencies of SAEs, vaccine-related SAEs, and deaths compared to the comparator vaccines (Pneu-C-20, Pneu-C-15, and Pneu-P-23).

IV.9.1 Local and systemic adverse events following immunization

Across the trials, the most commonly reported solicited adverse reactions following Pneu-C-21 administration in individuals 18 to 49 years were: injection site pain (approximately 75%), fatigue (approximately 35%), headache (approximately 30%), and myalgia, injection site erythema and injection site swelling (approximately 15%). In adults 50 years of age and older, the most common AEs were injection site pain (approximately 40%), fatigue (approximately 20%), and headache (approximately 10%).

The majority of local and systemic solicited adverse reactions were mild and of short duration (≤3 days), with severe events occurring in less than 1% of study participants.

IV.9.2 Serious adverse events following immunization

The available evidence suggests there are no meaningful differences in SAEs in individuals who received Pneu-C-21 compared to individuals who received Pneu-C-15, Pneu-C-20, or Pneu-P-23.

IV.10 Contraindications and precautions

Pneu-C-21 is contraindicated in individuals with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or any diphtheria toxoid-containing vaccine. Administration of vaccine should be postponed in persons suffering from acute severe febrile illness.

V. VACCINATION OF SPECIFIC POPULATIONS

V.1 Immunization of Immunocompromised Persons

In general, immunocompromised people are more susceptible to vaccine-preventable infections and may have more severe infections. The effectiveness of vaccines in immunocompromised people is determined by the type of immunodeficiency and degree of immunosuppression. Each immunocompromised person is different and presents unique considerations regarding immunization. The relative degree of immunodeficiency is variable depending on the underlying condition, the progression of disease, and use of immunosuppressive agents [23].

Individuals with immunocompromising conditions, including those receiving immunosuppressive therapy, may have a reduced immune response to the vaccine.

V.2 Immunization in Pregnancy and Breastfeeding

There are no adequate and well-controlled studies of Pneu-C-20 or Pneu-C-21 in women and individuals who are pregnant or breastfeeding.

VI. ECONOMICS

Systematic reviews of economic evaluations and a de novo model-based economic evaluation were used to support decision-making for the use of higher valency pneumococcal vaccines in adults.

VI.1 Systematic Reviews

Two systematic reviews were conducted to identify economic evidence for the use of pneumococcal conjugate vaccines in adult populations. All costs are presented in 2023 Canadian dollars. A systematic review was conducted by the Canada's Drug Agency to assess the cost-effectiveness of pneumococcal conjugate vaccines in adults less than 65 years of age at higher risk of IPD. This review was not restricted to higher valency conjugate vaccines and had a search completion date of Feb 22, 2024 (and regular alerts updating the search until May 13, 2024). It found that conjugate vaccines (Pneu-C-13, alone or in combination with Pneu-P-23, or Pneu-C-20) may be cost-effective compared to no vaccination at a threshold of $50,000 per quality-adjusted life year (QALY) gained [24]. However, no studies in this systematic review included Pneu-C-21.

An additional systematic review of the peer-reviewed and grey literature that was not restricted to adults aged less than 65 years of age was conducted, with a search end date of July 3, 2024 [25]. This review identified five economic evaluations assessing the cost-effectiveness of Pneu-C-21 in adults. Three economic evaluations were included from the peer-reviewed literature [26-28]. Results from two additional economic evaluations were summarised and presented to the Advisory Committee on Immunization Practices [29]. For clarity, the models summarised to ACIP are referred to by the names of the model authors (Owusu-Edusei et al., 2024; Stoecker, 2024). Four evaluations were conducted in the United States (Altawalbeh et al., 2024; Owusu-Edusei et al., 2024; Stoecker, 2024; Wateska et al., 2023) and one was conducted in the Netherlands (de Boer et al., 2024). The evaluation by Owusu-Edusei et al., 2024 was sponsored by Merck.

Four economic evaluations included a strategy of vaccinating adults aged 65 years with Pneu-C-21 compared to Pneu-C-20 (de Boer et al., 2024; Owusu-Edusei et al., 2024; Stoecker, 2024; Wateska et al., 2023). Compared to Pneu-C-20, Pneu-C-21 ranged from dominant (i.e., less costly and more effective) (de Boer et al., 2024) to having an incremental cost-effectiveness ratio (ICER) of $52,000 per QALY gained (Wateska et al., 2023).

In the three economic evaluations which included a strategy of vaccinating adults at age 50 with Pneu-C-21 compared to no vaccination (Altawalbeh et al., 2024; Owusu-Edusei et al., 2024;

Stoecker, 2024), Pneu-C-21 was never the optimal strategy at a $50,000 per QALY gained threshold. Among adults who are immunocompromised or living with chronic medical conditions aged younger than 50 years, Pneu-C-21 dominated Pneu-C-20 in two economic evaluations (Owusu-Edusei et al., 2024; Stoecker, 2024). A catch-up dose of Pneu-C-21 following a dose of Pneu-C-20 was not cost-effective in any age group considered (Owusu-Edusei et al., 2024; Stoecker, 2024).

Overall conclusions were not impacted by analytical perspective (i.e., societal or health system perspective) or the inclusion of indirect effects or serotype replacement from vaccination in pediatric populations with a pneumococcal conjugate vaccine. The applicability of these evaluations to the Canadian context is limited, as findings are sensitive to the region- and time-specific serotype distribution of pneumococcal disease cases and vaccine price.

VI.2 Economic model description

A static Markov cohort model was used to estimate ICERs in 2023 Canadian dollars per QALY for the use of Pneu-C-21 in population cohorts of adults aged 33 (midpoint of 18 to 49 age group), 50, and 65 years [30]. This model is an update of a model previously used to assess the cost-effectiveness of Pneu-C-15 and Pneu-C-20 in Canadian adults [31]. For each age group, the vaccine comparators and risk groups modelled were based on the policy questions under consideration and vaccine recommendations at the time of the analysis. For adults aged 18 to 49 years at high risk for pneumococcal disease, two population groups were modelled: one representing people who are unhoused and the other representing people with chronic medical conditions (CMC). For these population groups, different relative risks of pneumococcal disease were also compared to the population average, to determine how this influenced estimated cost-effectiveness.

Results were calculated for the health system and societal perspectives and discounted to present value at 1.5%. For population groups not currently recommended a pneumococcal conjugate vaccine, Pneu-C-21 was compared to Pneu-C-20 and no vaccination, and sequential ICERs were calculated. For the primary analysis, pneumococcal serotype distribution data for the year 2022 were used, as the data for 2023 were still preliminary at the time of the analysis. No indirect effects or serotype replacement were included, and list prices for Pneu-C-20 ($109.91 per dose) and Pneu-C-21 ($129.90 per dose) were used. Additional analyses included indirect effects from pediatric vaccination with Pneu-C-15 or Pneu-C-20 with serotype replacement, and use of pneumococcal serotype distribution data for the years 2015 to 2019. Results are summarized below for the health system perspective and full results are available in a separate publication [30].

VI.3 Results

Cost-effectiveness of Pneu-C-21 in population groups recommended a conjugate vaccine at the time of the economic evaluation

For population groups recommended a conjugate vaccine at the time of the economic analysis, i.e., adults aged 65 and older, adults aged 50 to 64 years living with factors that place them at higher risk of pneumococcal disease, and adults aged 18 to 49 years with immunocompromising conditions, Pneu-C-21 was compared to Pneu-C-20. In these groups, the cost-effectiveness of Pneu-C-21 was dependent on the prevalence of IPD due to serotypes covered by Pneu-C-21 compared to Pneu-C-20. When Pneu-C-21 serotype coverage was higher than Pneu-C-20 coverage, the use of Pneu-C-21 was always cost-effective, using a $50,000 per QALY cost-effectiveness threshold, and frequently dominated Pneu-C-20 (i.e., Pneu-C-21 was less costly and more effective). These results were observed even with the conservative assumption of no indirect effects and no serotype replacement following introduction of Pneu-C-15 or Pneu-C-20 pediatric vaccination. When Pneu-C-20 serotypes were more prevalent than or as prevalent as Pneu-C-21 serotypes, as was observed for some age groups, results were more sensitive to assumptions about serotype replacement. Additional details for the different population groups are provided below.

In the population aged 65 years and older, 2022 Canadian serotyping data show that IPD attributable to Pneu-C-21 serotypes was more prevalent than for Pneu-C-20 serotypes. Consequently, use of Pneu-C-21 at age 65 years was projected to prevent more cases of pneumococcal disease compared to Pneu-C-20. Use of Pneu-C-21 dominated Pneu-C-20 (i.e., Pneu-C-21 was less costly and more effective) in the primary analysis. The inclusion of indirect effects and serotype replacement following the introduction of Pneu-C-15 or Pneu-20 in the pediatric population resulted in greater cost-savings per QALY gained with the use of Pneu-C-21 compared to Pneu-C-20. When Pneu-P-23 was included as a comparator, it was also dominated by Pneu-C-21. Results did not change when using serotype distribution data for the years 2015-2019, where there was a larger difference between the burden of disease caused by unique serotypes contained Pneu-C-21 versus Pneu-C-20 compared to the 2022 data.

For adults aged 50 to 64 years living with risk factors that place them at higher risk of pneumococcal disease, vaccination with Pneu-C-21 may be cost-effective compared to Pneu-C-20, depending on the distribution of serotypes covered by the two conjugate vaccines. Using 2022 serotyping data, for which there was an equal proportion of IPD attributable to the serotypes contained in both vaccines, Pneu-C-20 was optimal for a $50,000 per QALY threshold in the primary analysis. In the presence of indirect effects and serotype replacement following pediatric program introduction, Pneu-C-21 was often the optimal choice. When IPD attributable to Pneu-C-21 serotypes was more common, as was observed for the 2015-2019 serotyping data for this age group, Pneu-C-21 dominated Pneu-C-20, even without serotype replacement.

For adults aged 18 to 49 years living with immunocompromising conditions, the optimal vaccine choice depended on serotype coverage data. When IPD due to Pneu-C-20 serotypes was more common (2022 data), Pneu-C-20 dominated Pneu-C-21, whereas when IPD due to Pneu-C-21 serotypes was more common (2015-2019 data), Pneu-C-21 dominated Pneu-C-20.

Cost-effectiveness of Pneu-C-21 in population groups not recommended a conjugate vaccine at the time of the economic evaluation

For population groups not recommended a conjugate vaccine at the time the economic evaluation was conducted, i.e., adults aged 50 to 64 years at average risk of pneumococcal

disease and adults aged 18 to 49 living with chronic medical conditions or who are unhoused, a strategy of vaccination using a conjugate vaccine (either Pneu-C-20 or Pneu-C-21) was expected to be cost-effective compared to no vaccination. The optimal vaccine was dependent on the proportion of IPD attributable to Pneu-C-20 as compared to Pneu-C-21 serotypes, which has changed over time. Additional details for the different population groups are provided below.

For adults aged 50 to 64 years without risk factors for IPD, a strategy of vaccination with either Pneu-C-20 or Pneu-C-21 was expected to be cost-effective compared to no vaccination. In the primary analysis, using 2022 serotyping data where the proportion of IPD attributable to the serotypes in either vaccine was equal, Pneu-C-20 was optimal for a $50,000 per QALY threshold, with an ICER of $15,800 per QALY compared to no vaccination. The assumption of serotype replacement due to pediatric vaccination programs resulted in Pneu-C-21 being the optimal vaccine choice. Using 2015-2019 serotyping data, where IPD attributable to Pneu-C-21 serotypes was more common, Pneu-C-21 was optimal, with ICERs of $13,700 to $15,040 per QALY compared to no vaccination, depending on serotype replacement assumptions.

For the population who are unhoused and aged 18 to 49 years, vaccination was always cost-effective compared to no vaccination, regardless of the magnitude of elevated pneumococcal disease risk. The optimal vaccine depended on the epidemiologic context, with Pneu-C-20 preferred when Pneu-C-20 serotypes were more common (2022 data) and Pneu-C-21 preferred when Pneu-C-21 serotypes were more common (2015-2019 data).

For people with CMCs aged 18 to 49 years, using a $50,000 per QALY cost-effectiveness threshold, vaccination with a conjugate vaccine (either Pneu-C-20 or Pneu-C-21) was always cost-effective compared to no vaccination when relative risk of pneumococcal disease was assumed to be four times that of the population average. The optimal vaccine depended on the time period for serotyping data used, with similar results as for the people who are unhoused. When relative risk of pneumococcal disease was lowered to 2, vaccination with Pneu-C-20 was optimal only when using the 2022 serotyping data and there was no or limited serotype replacement assumed (i.e., due to use of Pneu-C-15 in infants). For all other scenarios assessed for a relative risk of 2 (2015-2019 serotyping data and/or serotype replacement due to use of Pneu-C-20 in infants) or when relative risk was less than 2, a no vaccination strategy was optimal.

Summary

This analysis is subject to limitations associated with simplifying assumptions and data uncertainty, including the assumption of equivalent vaccine effectiveness for both vaccines. Vaccination with Pneu-C-21 for people previously vaccinated with Pneu-C20 was not evaluated but, as described in the systematic review, is not expected to be cost-effective in the population groups considered: adults aged 65 years and older, adults aged 50 years and older, and adults younger than 50 years who are immunocompromised or have CMCs. Transmission was not modelled, and although scenario analyses explored indirect effects and serotype replacement due to pediatric vaccination programs, it is not possible to fully capture dynamic changes in disease epidemiology and vaccine impact over time. The analysis did not consider the budget impact of the modelled vaccination programs.

In summary, use of a conjugate vaccine (specifically Pneu-C-20 or Pneu-C-21) is expected to be a cost-effective strategy in all population groups evaluated. The choice of vaccine is dependent on the prevalence of IPD due to the serotypes covered by Pneu-C-20 and Pneu-C-21, which has changed in recent years for some age groups. Aside from the dependence on assumed serotype coverage, the findings of this economic analysis were robust in probabilistic and deterministic sensitivity analyses. For adults aged 18 to 49 years with CMCs, the magnitude of increased risk of pneumococcal disease compared to the general population influenced the estimated cost-effectiveness of vaccination with a higher valency pneumococcal conjugate vaccine. Overall, these findings support the cost-effectiveness of Pneu-C-20 or Pneu-C-21 in the modelled populations, with the choice of vaccine dependent on epidemiology.

VII. ETHICS, EQUITY, FEASIBILITY AND ACCEPTABILITY CONSIDERATIONS

NACI uses a published, peer-reviewed framework and evidence-informed tools [3] to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into its guidance.

A number of EEFA considerations for adult pneumococcal immunization programs have been discussed in the recent NACI Statement on Public health level recommendations on the use of pneumococcal vaccines in adults, including the use of 15-valent and 20-valent conjugate vaccines. The EEFA considerations below will provide additional focus on introducing Pneu-C-21 into pneumococcal immunization programs given the current (and future) vaccine product landscape.

VII.1 Ethics

NACI evaluated the following ethical considerations when making its recommendations: promoting well-being and minimizing risk of harm; maintaining trust; respect for people and fostering autonomy; and promoting justice and equity. In developing these recommendations, no significant ethical issues were identified by NACI other than the equity considerations discussed below.

VII.2 Equity

It has been established that pre-existing disease, social factors, place of residence, and age are important to consider with pneumococcal recommendations. Pneumococcal disease burden increases with age, and certain medical, social and/or environmental conditions can also increase the risk of IPD in adults. Therefore, both age-based and risk-based vaccine program recommendations can contribute to reducing inequity. Publicly funded programs help ensure higher coverage and thus increased individual immunity and reduction of bacterial transmission.

Programs should ideally be aligned/equitable across the country when and where burden of illness is comparable.

Pneu-C-20 and Pneu-C-21 both broaden the range of protection, but provide different serotype coverage. Some groups develop IPD caused by serotypes that may not be included in both Pneu-C-20 and Pneu-C-21 vaccines, so the benefit of each vaccine can differ in different age groups and populations due to varying serotype distribution. However, the addition of Pneu-C-21 provides the opportunity of broadening the range of protection given the different serotype coverage compared to Pneu-C-20, with the additional immune benefits of conjugate vaccines compared to polysaccharide vaccines.

Individuals in or from First Nations, Inuit or Métis communities in Canada have a younger age distribution compared to the general Canadian population but have also been observed to have increased risk for severe PD due to a variety of intersecting factors including medical conditions resulting from intersecting health determinants. These intersecting health determinants include social, environmental, and economic factors, rooted in historic and ongoing colonization and systemic racism (i.e., structural inequity). Therefore, age-based recommendations may need to be modified to offer effective protection to individuals in or from these communities. Autonomous decisions should be made by Indigenous Peoples with the support of culturally safe healthcare and public health partners in accordance with the United Nations Declaration on the Rights of Indigenous Peoples (UNDRIP).

VII.3 Feasibility

NACI consulted with the Canadian Immunization Committee (CIC) regarding the feasibility of administering Pneu-C-21 in provincial/territorial/federal adult pneumococcal vaccine programs. Given that jurisdictions are in the process of transitioning to using Pneu-C-15 and Pneu-C-20 in their pediatric and adult programs, incorporating Pneu-C-21 would add program complexity to inventory management, communications and training, and other operational/administrative activities. Having multiple products can also increase the risk of administration errors. For smaller jurisdictions, procurement and vaccine management can be particularly challenging if the program included limited numbers of vaccine doses that are to be used in select ways for specific populations in a multi-product environment. While regional epidemiology can better inform the choice of product(s) to use in adult programs, jurisdictions do not collect and/or have equal access to detailed data, therefore there may be variability in how or when each jurisdiction is able to adopt any new recommendations on the use of the Pneu-C-21.

Pre-pandemic and post-pandemic differences in IPD serotype epidemiology have been noted earlier in the statement. The COVID-19 pandemic has broadly impacted the uptake of routine vaccines, particularly among children. Because pediatric pneumococcal immunization offers indirect protection to adults, it is uncertain how IPD serotype epidemiology will evolve with improved pediatric vaccination and the use of higher valency pneumococcal vaccines in both children and adults. However, recognizing that indirect protection does occur, the choice of

product(s) for the adult immunization program can also take into consideration the vaccines being used in the pediatric program.

The impact of the recent changes to Canadian pneumococcal vaccine programs may not be evident in the short-term as it can take several years to observe notable changes to IPD serotype epidemiology. In the meantime, other higher valency pneumococcal vaccines are under development and could potentially become available in the Canadian market in the coming years, adding further complexity.

VII.4 Acceptability

Pneumococcal vaccine recommendations have historically been challenging to develop, due to factors such as disease epidemiology, serotype replacement, and differences in direct and indirect vaccine protection and vaccine coverage in pediatric and adult populations. While adult pneumococcal vaccine programs have been in place for many years, vaccine uptake continues to be lower than the national vaccine coverage goal, and the choice of vaccine product is unlikely to be a significant barrier to vaccination. It is anticipated that program and individual level acceptability of Pneu-C-21 will depend on the complexity of the recommendations and will need to be clearly communicated if programs are recommended to use multiple products, given that Pneu-C-15 and Pneu-C-20 have been recently recommended for use in pediatric and adult immunization programs.

VIII. RECOMMENDATIONS

Following the review of available evidence summarized above (and in Table 4 below), NACI makes the following recommendations for public health level decision-making.

Please note:

- A *strong recommendation* applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.
- A *discretionary recommendation* may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Please see Table 7 for a more detailed explanation of strength of NACI recommendations and see Table 8 for the GRADE certainty of evidence.

NACI will continue to carefully monitor the scientific developments related to adult pneumococcal vaccines and will update recommendations as evidence evolves.

Recommendations for public health program level decision-making

(i.e., Provinces/Territories making decisions for publicly funded immunization programs)

In considering these recommendations and for the purposes of publicly funded program implementation, provinces and territories are anticipated to take into account local programmatic factors (e.g., current immunization programs, resources). Recognizing that there are differences in operational contexts across Canada, jurisdictions may wish to refer to Product Considerations below (Table 4) for a summary of the relative merits of the different vaccines.

1. NACI recommends that adult pneumococcal immunization programs in Canada should include at least one of Pneu-C-20 or Pneu-C-21.

(*Strong NACI Recommendation*)

Considerations:

- The aim of the pneumococcal vaccine program is to protect adults at high risk for infection and medical complications. With the uncertainty around ongoing IPD epidemiology and as vaccine effectiveness data accrues, simplicity and flexibility in the recommendations are needed to allow jurisdictions the ability to consider how to best achieve the highest possible benefit in the targeted populations.
- The choice of the vaccine used will depend on determining the most suitable vaccine(s) based on regional epidemiology, vaccine eligibility (including prior immunization with a pneumococcal vaccine), and programmatic considerations.
- See the Management Options Table (Table 4) for considerations to assess the product of choice.

Summary of evidence and rationale:

- Pneu-C-20 and Pneu-C-21 each contain a number of unique serotypes. Both vaccines are immunogenic and have a good safety profile, based on available clinical data.
- Post-pandemic changes in circulating pneumococcal serotypes make it difficult to determine the relative benefit of Pneu-C-20 and Pneu-C-21 at this time, and there may be interjurisdictional variability in serotype circulation. Regional epidemiology should be considered when data are available and when deciding which vaccine to use with the selection guided by the largest proportion of serotypes covered in the populations recommended for vaccination.
- The choice of vaccine for adult immunization programs will also depend on programmatic considerations in the context of the existing pneumococcal immunization programs, such as cost-effectiveness, feasibility, acceptability to providers and patients, and product(s) being used in the pediatric programs (see Table 4).
- Use of either Pneu-C-20 or Pneu-C-21 is expected to be a cost-effective intervention for adults at increased risk of IPD, based on commonly used cost-effectiveness thresholds.
- With the increased availability of pneumococcal vaccines with higher valency (Pneu-C-20 and Pneu-C-21), Pneu-C-15 should be used only when these vaccines are unavailable or inaccessible.

2. NACI recommends that one dose of either Pneu-C-20 or Pneu-C-21, regardless of pneumococcal vaccination history with Pneu-C-13, Pneu-C-15 or Pneu-P-23, should be given to:

(*Strong NACI Recommendation*)

- **Adults 65 years of age and older**
- **Adults under 65 years of age at increased risk of IPD (see Table 1)**

Considerations:

- The risk of IPD increases with age, with the number of risk factors, and with the degree of organ impairment. Table 1 presents a list of conditions that increase the risk of IPD, and the use of Pneu-C-20 or Pneu-C-21 is likely a cost-effective strategy in most population groups evaluated. However, there is a broader range of risk for some conditions among adults under 65 years of age, compared to adults 65 years of age and older, and additional considerations that further increase the risk have been noted in the table to assist with program decision-making.
- **It should also be noted that individuals 18 years of age and older who are not included for higher valency pneumococcal vaccine in publicly funded programs may opt to receive higher valency pneumococcal vaccination in consultation with their health care provider. Healthcare providers can use the information presented in Table 1 as a guide when considering individual patient risk(s), and when counselling patients.**
- For adults who have previously received pneumococcal vaccination:
    - The choice of vaccine and interval from the last dose will depend on the type of vaccine previously received and time since vaccination.
    - Based on expert opinion, the recommended interval between Pneu-P-23 and either of Pneu-C-20 or Pneu-C-21 conjugate vaccine is now 1 year; however, an interval as short as 8 weeks may be considered in those who might be anticipating initiation of immunosuppressive treatments or who have diseases that might lead to immunodeficiency.
    - When rapid immunization is required (e.g., for immunocompromised individuals), the minimum interval between two different Pneu-C vaccines is 8 weeks.
- See the Management Options Table (Table 4) for considerations around recommended populations.

Summary of evidence and rationale:

- Both Pneu-C-20 and Pneu-C-21 are immunogenic in vaccine naïve and previously vaccinated adult age groups and have a comparable safety profile, based on available clinical data.
- Use of either Pneu-C-20 or Pneu-C-21 may be a cost-effective intervention in vaccine-naive adults, based on commonly used cost-effectiveness thresholds. The optimal vaccine to use is dependent on the amount of pneumococcal disease attributable to the serotypes covered by Pneu-C-20 and Pneu-C-21, which may vary by population group or regional

epidemiology. Pneumococcal vaccination may be cost-effective for all individuals 50 years of

age and older without additional risk factors, however the cost impact of potentially needing a booster dose at a later date has not been evaluated.
- Notably in adults 18 to 49 years of age with chronic medical conditions, cost-effectiveness is expected to vary with the magnitude of increased risk of pneumococcal disease compared to the general population, such that vaccinating individuals at higher risk of IPD in this age group is more likely to be cost-effective at lower thresholds compared to individuals at lower relative risk.
- The data to assess the relative benefit of vaccination for different conditions that increase the risk of IPD are limited.
- Age-based recommendations may need to be modified for communities with younger age distributions such as those in or from Indigenous populations. However, in First Nations, Inuit or Métis communities, autonomous decisions should be made by Indigenous Peoples with the support of culturally safe healthcare and public health partners in accordance with UNDRIP.

For hematopoietic stem cell transplant recipients

3. NACI recommends that both Pneu-C-20 and Pneu-C-21 should be offered to adults 18 years of age or older who received a hematopoietic stem cell transplant (HSCT) after consultation with the transplant specialist.

(*Strong NACI recommendation)*

Considerations:

- A primary series of 3 doses starting 3 to 9 months after transplant should be administered at least 4 weeks apart, followed by a booster dose 12 to 18 months post-transplant (6 to 12 months after the last dose). The recommended timing of pneumococcal vaccination for HSCT recipients should be determined in consultation with the recipient's transplant specialist.
- HSCT recipients will benefit from broader serotype coverage, therefore, the higher valency vaccine that was not given as part of the primary series can be offered as the booster dose at 12 to 18 months post-transplant (i.e., 3 doses of Pneu-C-20 + 1 dose of Pneu-C-21, or 3 doses of Pneu-C-21 + 1 dose of Pneu-C-20).
- See the Management Options Table (Table 4) for considerations around age and regional epidemiology if additional information is needed to assess whether there is a preferred product for the individual.

Summary of evidence and rationale:

- No studies assessing immunogenicity and safety of Pneu-C-21, or Pneu-C-21 in a mixed series with Pneu-C-20 in HSCT recipients were available; however, Pneu-C-21 is expected to have similar immunogenicity and safety profiles to other conjugate vaccines in this population.

There are other individuals at very high risk of IPD that could benefit from receiving both Pneu-C-20 and Pneu-C-21. NACI is reviewing these risk groups and will provide recommendations at a later date.

Product considerations

Various considerations for the vaccine type based upon age cohort and/or risk group are available, and the decision on which option is preferable will depend on the considerations listed below.

Table 4. Management options table for choice of Pneu-C-20 or Pneu-C-21 conjugate pneumococcal products for use in adults*

Factors for consideration	PCV20 considerations	PCV21 considerations
Epidemiology		
• Age is a major risk factor for IPD. Incidence begins to increase at 50 years old, and sharply increases among persons 65 years of age and older. • There are also medical, social, behavioural, and/or environmental factors that increase the risk of IPD, some of which are independent of the effects of age/duration of exposure. • The serotype distribution of IPD cases varies by age group, risk factor, and/or geographic region. • Where data are available, an assessment of local/regional epidemiology can inform which vaccine to offer in the local adult immunization programs in the short-term. For jurisdictions where data are limited or not available, either vaccine will provide better protection compared to the previously available pneumococcal vaccines. • Pneumococcal disease and serotype epidemiology will also evolve over time, and while	• IPD caused by Pneu-C-20-containing serotypes have been increasing between 2020 and 2023 in adults, but was least pronounced in adults 65 years of age and older. This increase is in part due to resurgence of serotypes 4 in younger adults (and particularly among individuals who are unhoused), and serotype 9V, which are not included in Pneu-C-21 but are included in Pneu-C-20. • Serotype 4 is the most reported serotype in Northern Canada, and is driven by increased incidence in the 18 to 49 year old age group.	• There has been a higher proportion of IPD cases in adults 65 years of age and older attributed to Pneu-C-21-containing serotypes, which has remained relatively stable between 2020 and 2023. However, the proportion of Pneu-C-21-containing serotypes causing IPD in adults under 65 years of age has been decreasing over the same period.

serotype replacement is expected, the speed and extent of replacement is uncertain. • Time is needed to assess how pneumococcal disease epidemiology is impacted with the implementation of higher valency vaccines in the adult and pediatric immunization programs. • Pneu-C-21 and Pneu-C-20 contain different serotypes and may have differing impacts on IPD rates.		
Vaccine characteristics (Efficacy/ effectiveness, immunogenicity and safety)		
• All pneumococcal conjugate vaccines have similar safety profiles and are well-tolerated. • Efficacy/effectiveness data are not yet available for the new pneumococcal conjugate vaccines. The vaccines were approved based on immunogenicity, and have been shown to be immunogenic in adults with and without a history of previous pneumococcal vaccination. • The clinical significance of any differences in immune responses between the higher valency conjugate vaccines are currently unknown. • Lower immunogenic responses have been observed with higher valency vaccines. There are no correlates of protection for pneumococcal vaccination to assess the potential clinical impact of these reduced responses.	• Pneu-C-20 contains 9 unique serotypes not included in Pneu-C-21. • Pneu-C-20 generated similar immune responses as other pneumococcal vaccines for shared serotypes. The immune responses to Pneu-C-20 unique serotypes were not reported in the clinical trial comparing Pneu-C-20 and Pneu-C-21.	• Pneu-C-21 contains 10 unique, non-cross-reactive serotypes compared to Pneu-C-20. • Pneu-C-21 generated similar immune responses as other conjugate vaccines for shared serotypes, and greater immune responses against all Pneu-C-21-unique serotypes (however, serotype 15C did not meet criteria for statistical superiority).
Economics		
• Based on a cost-utility analysis, the choice between the higher valency vaccines is dependent on serotype epidemiology and the amount of pneumococcal disease	• Pneu-C-20 may be cost-effective when the proportion of IPD attributed to Pneu-C-20 serotypes is greater than	• Pneu-C-21 may be cost-effective when the proportion of IPD attributed to Pneu-C-21 serotypes is greater than

potentially prevented by each vaccine. • All provinces and territories will have to explore affordability of the vaccines and the publicly funded immunization programs.	or equal to the proportion attributed to Pneu-C-21 serotypes.	the proportion attributed to Pneu-C-20 serotypes. • When Pneu-C-20 serotypes are more common or equally as common, Pneu-C-21 may still be a cost-effective option in some populations, if indirect effects and serotype replacement are observed following the use of Pneu-C-15 or Pneu-C-20 in infants.
Ethics, equity, feasibility, acceptability (EEFA)		
• Equitable access to pneumococcal vaccines should be available to populations who need them most. • Uptake of pneumococcal vaccines in adults, including amongst those at highest risk for IPD is below target. A simple and streamlined program may improve uptake and prevention of disease. • Program feasibility is a vital consideration in determining the choice of vaccine(s) used in the immunization program given the uncertainty around future epidemiologic trends and clinical benefit of the higher valency vaccines relative to each other. • The choice of vaccine in a jurisdiction may also change over time, depending on factors including the local serotype and age-specific epidemiology of IPD. • The choice between the higher valency vaccines in the adult program should also consider the product(s) used in the pediatric program, given that some degree of indirect protection in adults	• In 2023, prior to the authorization of Pneu-C-21, Pneu-C-20 was recommended as the preferred product in adults and high-risk children. Changes to immunization programs are underway to incorporate this advice, and some jurisdictions may find it challenging to incorporate Pneu-C-21 soon after implementing Pneu-C-20 recommendations.	• Pneu-C-21 provides additional serotype coverage, which could offer better protection to adults 65 years of age and older, based on current epidemiology. However, adding Pneu-C-21 on top of the existing adult immunization program could be challenging to manage as well as communicate to patients, which could be a barrier to vaccine uptake.

occur can be expected from routine pediatric vaccination.		
* Pneu-C-15 can be used if Pneu-C-20 or Pneu-C-21 are unavailable or inaccessible. In adults, it has been recommended that Pneu-C-15 be offered in series with Pneu-P-23. Pneu-P-23 may no longer be available as immunizations programs incorporate the use of higher valency conjugate vaccines.		

IX. RESEARCH PRIORITIES

Research to address the following outstanding issues is encouraged:

- Estimates/assessments of vaccine effectiveness of higher valency vaccines in the general population of individuals 65 years of age and older and in the additional populations at high risk for IPD.
- Identification of individuals who would benefit from receiving both Pneu-C-20 and Pneu-C-21 and estimates/assessments of vaccine effectiveness and duration of vaccine protection.
- Assessment of the effects of community immunity and serotype replacement of Pneu-C-15 and Pneu-C-20 childhood programs over time on the incidence of IPD, vaccine type IPD, CAP, and vaccine type CAP and on carriage within the Canadian population of individuals 65 years of age and older and in additional populations (e.g., Indigenous, people living with chronic medical, social, and immunocompromising conditions).
- Estimates of efficacy and effectiveness of Pneu-C-20 and/or Pneu-C-21 booster doses in adults who have previously received pneumococcal vaccination.
- Evolution of the level of functional antibodies over time following a dose of Pneu-C-20 or Pneu-C-21 in adults to inform the need for booster vaccination.
- Assessment of pneumococcal vaccination programs on the reduction of myocardial infarction and stroke.
- Determining the immunological correlates of protection against various disease outcomes (severity and disease manifestations).
- The relative importance of multi-drug resistant *S. pneumoniae* serotypes and how immunization could favourably impact the ecology.

X. SURVEILLANCE ISSUES

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

- Conducting national enhanced surveillance that will allow the analysis of severity, risk factors, demographics, and regional variation by serotype.

- Enhancing ongoing pneumococcal disease surveillance including non-IPD pneumococcal diseases and *S. pneumoniae* carriage.
- Ensure reliable estimates of vaccine uptake amongst populations at heightened risk for IPD.
- Determining any rare and very rare AEs that may not have been reported due to limited sample size in clinical trials.

XI. EVIDENCE TABLES

Additional tables are available in a supplement to this statement.

Table 5. Summary of evidence comparing Pneu-C-21 and Pneu-C-20

Measured outcome (Certainty of evidence)	Adults 18-64 years of age with no additional risk factors	Adults ≥50 years of age with one or more medical risk factors for IPD	Adults ≥65 years of age
Immunogenicity			
OPA GMTs (Moderate certainty of evidence)	Distribution of serotype-specific OPA titres was generally comparable between groups for common serotypes. Serotype-specific OPA titres were significantly higher for Pneu-C-21 unique serotypes.	Distribution of serotype-specific OPA titres was generally comparable between groups for common serotypes. Serotype-specific OPA titres were significantly higher for nearly all Pneu-C-21 unique serotypes.	Distribution of serotype-specific OPA titres was generally comparable between groups for common serotypes, and numerically higher for most Pneu-C-21 unique serotypes.
% with ≥4 fold rise in OPA responses (Moderate certainty of evidence)	The proportion of seroresponders was numerically higher against all unique serotypes for Pneu-C-21 compared to Pneu-C-20.	Proportion of seroresponders was numerically higher against all unique serotypes for Pneu-C-21 compared to Pneu-C-20.	The proportion of seroresponders was numerically higher against all unique serotypes for Pneu-C-21 compared to Pneu-C-20. The difference was lowest for serotype 15C.
IgG geometric mean concentrations (GMCs) (Moderate certainty of evidence)	Not assessed	For the common serotypes shared between Pneu-C-21 and Pneu-C-20, serotype-specific IgG GMCs were comparable between the two vaccines. For the serotypes unique to Pneu-C-21, serotype-specific IgG GMCs were higher in the Pneu-C-21 group compared to Pneu-C-20.	Not assessed
Safety			
Vaccine-related SAEs (Moderate certainty of evidence)	No vaccine-related SAEs were observed in either group.	No vaccine-related SAEs were observed	No vaccine-related SAEs were observed in either group.

Total SAEs (Moderate certainty of evidence)	Pneu-C-21: 9/787 Pneu-C-20: 11/685 • Relative effects: Peto OR 0.68 (95% CI: 0.32 to 1.47) • Absolute effects: 9 fewer per 1,000 (from 18 fewer to 12 more)	<u>Single risk factor</u>: Pneu-C-21: 3/347 Pneu-C-20: 8/328 • Relative effects: Peto OR 0.38 (95% CI: 0.11 to 1.23) • Absolute effects: 15 fewer per 1,000 (22 fewer to 5 more) <u>2 or more risk factors</u> Pneu-C-21: 6/100 Pneu-C-20: 3/81 • Relative effects: Peto OR 1.62 (95% CI: 0.42 to 6.22) • Absolute effects: 22 more per 1,000 (21 fewer to 156 more)	Pneu-C-21: 11/590 Pneu-C-20: 16/590 • Relative effects: Peto OR 0.68 (95% CI: 0.32 to 1.47) • Absolute effects: 9 fewer per 1,000 (from 18 fewer to 12 more)
Death (Moderate certainty of evidence)	No vaccine-related deaths were observed.	No vaccine-related deaths were observed.	No vaccine-related deaths were observed.

Table 6. Summary of Pneu-C-21 (V116) clinical trials

Study	Comparisons	Study design	Participants
V116-001: A Phase 1/Phase 2, Randomized, Double-blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Polyvalent Pneumococcal Conjugate Vaccine in Adults [20]	Phase 1 : V116-1 (2 µg per pneumococcal polysaccharide per 0.5 ml) vs V116-2 (4 µg per pneumococcal polysaccharide per 1 ml) vs Pneu-P-23 Phase 2: V116 vs Pneu-P-23	Phase 1, randomized to V116-1 (N=30) or V116-2 (N=30) or Pneu-P-23 (N=30) Total randomized: 90 Phase 2, randomized to single dose of V116 (N=254) or Pneu-P-23 (N=256)	Phase 1: Healthy, pneumococcal vaccine-naïve adults aged 18–49 years with or without stable chronic medical conditions Gender (total study; phase 1): 66% female Phase 2: Healthy adults ≥50 years of age who are vaccine-naïve Gender (total study; phase 2): 55.3% female Ethnicity (total study): 57.7% non-Hispanic or Latino, 41.9% Hispanic or Latino, 0.2% not reported, 0.2% unknown

		Total randomized = 510	Race (total study): 87.0% White, 10.8% Black or African American, 1.0% Asian, 0.6% American Indian or Alaska Native, 0.4% multiple, 0.2% Native Hawaiian or other Pacific Islander Age (total study): 50 to 64 years: 71.1% 65 to 74 years: 23.4% ≥75 years: 5.5%
Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in Japanese healthy adults: A Phase I study [21]	V116 vs Pneu-P-23	Phase I, randomized to V116 (N=51) or Pneu-P-23 (N=51)	Healthy, pneumococcal vaccine-naïve adults aged ≥20 years with or without stable chronic medical conditions Gender (total study): 51% female Age (total study): 20 to 49 years: 15.7% 50 to 64 years: 17.6% ≥65 years: 66.7%
Safety, tolerability, and immunogenicity of an adult pneumococcal conjugate vaccine, V116 (STRIDE-3): a randomised, double-blind, active comparator controlled, international phase 3 trial [20,32]	Cohort 1 and 2: V116 vs Pneu-C-20	Cohort 1: Phase 3, randomized to single dose of V116 (N=1,179) or Pneu-C-20 (N=1,177) at Day 1 Total randomized = 2,356 Cohort 2: Phase 3, randomized to single dose of V116 (N=200) or Pneu-C-20 (N=100) at Day 1 Total randomized = 300	Cohort 1: Adults aged ≥50 years who are vaccine- naïve Cohort 2: Adults 18 to 49 years who are vaccine-naïve Gender (total study): 58.7% female Ethnicity (total study): 77.1% non-Hispanic or Latino, 22.0% Hispanic or Latino, 0.7% not reported, 0.3% unknown Race (total study): 72.0% White, 13.9% Asian, 9.7% Black or African American, 2.7% multiple, 1.4% Native Hawaiian or other Pacific Islander, 0.3% American Indian or Alaska Native Age (cohort 1): 50 to 64 years: 50.0% 65 to 74 years: 39.3% 75 to 84 years: 9.5% ≥85 years: 1.2% Demographics and baseline characteristics were generally comparable between intervention groups.
V116-004: A Phase 3 Randomized, Double-blind, Active Comparator-controlled, Lot-to-Lot	V116 vs Pneu-P-23	Phase 3, randomized to single dose of V116 Lot 1 (N=541), Lot 2 (N=540), Lot 3 (N=541),	Adults 18 to 49 years who are vaccine-naïve Gender (total study): 57.7% female Ethnicity (total study): 79.7% non-Hispanic or Latino, 19.5% Hispanic or Latino, 0.7% unknown

Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults 18 to 49 Years of Age [20]		or Pneu-P-23 (N=540) on Day 1 Total randomized = 2,162	Race (total study): 84.5% White, 9.0% Black or African American, 3.8% multiple, 1.6% Asian, 0.7% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 0.1% unknown Clinical study report states that demographics and baseline characteristics were generally comparable between intervention groups.
V116-005: A Phase 3 Randomized, Double-blind, Placebo-Controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 When Administered Concomitantly with Influenza Vaccine in Adults 50 Years of Age and Older [20]	V116 concomitantly with QIV vs V116 sequentially with QIV	Phase 3, randomized to concomitant group (N=540) or sequential group (N=540) Total randomized = 1,080	Adults aged ≥50 years with or without a history of previous vaccination with Pneu-C-13 and/or Pneu-P-23 Gender (total study): 54.5% female Ethnicity (total study): 75.7% non-Hispanic or Latino, 23.5% Hispanic or Latino, 0.6% not reported, 0.2% unknown Race (total study): 76.7% White, 19.4% Black or African American, 2.0% multiple, 1.2% Asian, 0.5% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 0.1% missing Age (total study): 50 to 64 years: 50.0% 65 to 74 years: 38.8% 75 to 84 years: 10.0% ≥85 years: 1.2% Clinical study report states that demographics and baseline characteristics were generally comparable between intervention groups.
V116-006: A Phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age and Older [20,33]	Cohort 1: V116 vs Pneu-C-15 Cohort 2: V116 vs Pneu-P-23 Cohort 3: V116 only	Cohort 1: Participants who received Pneu-P-23 prior to enrolment randomized to single dose of V116 (N=231) or Pneu-C-15 (N=119) on Day 1 Cohort 2: Participants who received Pneu-C-13 prior to enrolment	Adults aged ≥50 years who are vaccine-experienced Gender (total study): 53.4% female Ethnicity (total study): 85.4% non-Hispanic or Latino, 14.4% Hispanic or Latino, 0.3% unknown Race (total study): 64.0% White, 32.9% Asian, 2.6% Black or African American, 0.4% multiple Clinical study report states that within cohorts 1 and 2, demographics and baseline characteristics were generally

		randomized to single dose of V116 (N=176) or Pneu-P-23 (N=85) on Day 1 Cohort 3: Participants who received Pneu-C-15 or Pneu-C-13 + Pneu-P-23 or Pneu-C-15 + Pneu-P-23 or Pneu-P-23 + Pneu-C-13 prior to enrolment received single dose of V116 (N=106). Total randomized = 717	comparable between intervention groups.
V116-007: A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults Living With HIV [22]	V116 + Placebo vs Pneu-C-15 + Pneu-P-23	Randomized to receive V116 + Placebo (N=156) or Pneu-C-15 + Pneu-P-23 (N=157) Total randomized = 313	Adults ≥18 years of age living with HIV who are vaccine-naïve or vaccine-experienced Gender (total study): 70.8% male Ethnicity (total study): 75.3% non-Hispanic or Latino, 24.4% Hispanic or Latino, 0.3% unknown Race (total study): 47.8% White, 39.7% Black or African American, 10.6% Asian, 1.0% multiple, 0.6% American Indian or Alaska Native, 0.3% missing Clinical trial summary reports demographic and baseline characteristics were generally comparable between intervention groups.

Table 7. NACI recommendations: Strength of recommendation

Strength of Recommendation	STRONG	DISCRETIONARY
Wording	"should/should not be offered"	"may/may not be offered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Table 8. GRADE certainty of evidence for NACI recommendations

GRADE certainty of evidence rating	Description
High	Very confident that the true effect lies close to that of the effect estimate.
Moderate	Moderately confident: the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different.
Low	Limited confidence in the effect estimate: the true effect may be substantially different from the effect estimate.
Very low	Very little confidence in the effect estimate: true effect likely to be substantially different from the effect estimate.

LIST OF ABBREVIATIONS

AB	Alberta
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
aNICS	Adult National Immunization Coverage Survey
BC	British Columbia
CAP	Community acquired pneumonia
CI	Confidence interval
CIC	Canadian Immunization Committee
CMC	Chronic medical conditions
CSF	Cerebrospinal fluid
DPD	Drug Product Database
EEFA	Ethics, equity, feasibility and acceptability
GMT	Geometric mean titre
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
ICER	Incremental cost-effectiveness ratio
ICS	International Circumpolar Surveillance
IgG	Immunoglobulin G
IPD	Invasive pneumococcal disease
MB	Manitoba
NACI	National Advisory Committee on Immunization

NB	New Brunswick
NL	Newfoundland and Labrador
NML	National Microbiology Laboratory
NS	Nova Scotia
NT	Northwest Territories
NU	Nunavut
NVT	Non-vaccine type
ON	Ontario
OPA	Opsonophagocytic assay
OR	Odds ratio
pCAP	Pneumococcal community-acquired pneumonia
PD	Pneumococcal disease
PE	Prince Edward Island
PHAC	Public Health Agency of Canada
PNEU-C	Pneumococcal conjugate vaccine
PNEU-C-13	13-valent pneumococcal conjugate vaccine
PNEU-C-15	15-valent pneumococcal conjugate vaccine
PNEU-C-20	20-valent pneumococcal conjugate vaccine
PNEU-C-21	21-valent pneumococcal conjugate vaccine
PNEU-P	Pneumococcal polysaccharide vaccine
PNEU-C-23	23-valent pneumococcal polysaccharide vaccine
QALY	Quality-adjusted life year
QC	Quebec
QIV	Quadrivalent inactivated influenza vaccine

SAE	Serious adverse effect
SK	Saskatchewan
TIBDN	Toronto Invasive Bacterial Diseases Network
UNDRIP	United Nations Declaration on the Rights of Indigenous Peoples
YK	Yukon

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APPENDIX

Epidemiology Tables

Table A-1: Distribution of serotypes among IPD isolates submitted to Canada's National Microbiology Laboratory for all adults ≥18 years, 2019-2023

	Serotype	2019	2020	2021	2022	2023	Total
PNEU-C-20/ PNEU-C-21 Shared	Shared Total	52.2% (1729)	48.6% (939)	43.1% (758)	47.0% (1531)	48.9% (2100)	7057
	3	11.9% (395)	10.7% (206)	9.3% (163)	12.3% (400)	12.5% (535)	1699
	6A/C*	2.3% (76)	1.8% (34)	2.0% (36)	1.5% (49)	2.1% (90)	285
	7F	3.4% (113)	2.8% (54)	2.7% (48)	2.5% (82)	3.4% (145)	442
	8	6.4% (213)	7.4% (143)	5.4% (95)	5.3% (174)	5.1% (221)	846
	10A	1.9% (62)	1.9% (36)	1.0% (18)	1.0% (33)	1.0% (42)	191
	11A	2.7% (88)	3.1% (60)	2.7% (48)	3.1% (101)	3.0% (127)	424
	12F	4.3% (141)	6.2% (119)	6.9% (121)	6.1% (200)	6.5% (281)	862
	15B/C	2.1% (69)	1.9% (36)	1.8% (31)	1.9% (62)	2.2% (93)	291
	19A	4.0% (134)	3.7% (71)	4.3% (75)	5.2% (170)	3.9% (169)	619
	22F	9.7% (322)	6.9% (134)	4.8% (84)	6.6% (215)	8.0% (344)	1099
	33F	3.5% (116)	2.4% (46)	2.2% (39)	1.4% (45)	1.2% (53)	299
PNEU-C-20 Unique	Pneu-C-20 all Total	64.0% (2122)	66.4% (1284)	64.2% (1128)	69.9% (2279)	73.4% (3156)	9969
	Pneu-C-20 unique Total	11.9% (393)	17.8% (345)	21.0% (370)	23.0% (748)	24.6% (1056)	2912
	1	0.0% (0)	0.1% (1)	0.0% (0)	0.1% (3)	0.0% (1)	5
	4	7.8% (257)	11.9% (230)	13.8 % (242)	13.8% (449)	13.2% (567)	1745
	5	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0
	6B	0.2% (8)	0.1% (1)	0.1% (2)	0.2% (8)	0.1% (3)	22
	9V	1.4% (45)	2.9% (57)	4.8% (84)	5.7% (187)	7.7% (333)	706
	14	0.3% (9)	0.3% (5)	0.1% (2)	0.3% (9)	0.2% (9)	34
	18C	0.4% (14)	0.5% (9)	0.2% (3)	0.3% (11)	0.5% (20)	57
	19F	1.8% (59)	2.1% (40)	2.0% (36)	2.2% (72)	2.6% (111)	318

	23F	0.0% (1)	0.1% (2)	0.1% (1)	0.3% (9)	0.3% (12)	25
PNEU-C-21 Unique	Pneu-C-21 all Total	82.0% (2717)	76.1% (1471)	71.6% (1259)	71.6% (2335)	69.9% (3003)	10785
	Pneu-C-24 unique Total	29.8% (988)	27.5% (532)	28.5% (501)	24.7% (804)	21.0% (903)	3728
	9N	7.3% (243)	6.9% (133)	7.6% (134)	5.5% (180)	4.7% (202)	892
	15A	4.3% (142)	3.4% (66)	3.1% (55)	2.9% (94)	2.7% (117)	474
	16F	2.9% (96)	2.6% (51)	2.8% (49)	2.2% (71)	1.8% (78)	345
	17F	1.0% (34)	0.9% (17)	0.7% (13)	0.6% (19)	0.4% (18)	101
	20	4.0% (131)	4.1% (79)	6.3% (110)	4.8% (158)	3.8% (163)	6414
	23A	3.7% (121)	3.3% (63)	2.4% (43)	2.9% (96)	3.0% (131)	454
	23B	3.0% (99)	2.1% (41)	2.0% (36)	2.4% (79)	1.9% (81)	336
	24F	0.3% (9)	0.1% (2)	0.1% (2)	0.1% (2)	0.0% (1)	16
	31	1.2% (39)	1.8% (35)	1.5% (26)	1.6% (53)	0.9% (40)	193
	35B	2.2% (74)	2.3% (45)	1.9% (33)	1.6% (52)	1.7% (72)	276
NVT	NVT all	6.2% (205)	6.1% (118)	7.3% (129)	5.4% (176)	5.5% (238)	866
	35F	1.4% (48)	1.8% (34)	1.7% (30)	1.5% (48)	1.1% (46)	206
	7C	1.3% (42)	1.1% (22)	1.4% (24)	1.5% (48)	1.4 % (59)	195
	34	1.0% (33)	0.8% (16)	1.2% (21)	0.9% (28)	0.6% (24)	122
	38	0.7% (24)	0.7% (13)	0.1% (1)	0.1% (3)	0.5% (20)	61
	28A	0.2% (8)	0.4% (7)	0.6% (11)	0.3% (9)	0.3% (15)	50
	13	0.3% (9)	0.2% (4)	0.7% (12)	0.4% (12)	0.2% (9)	46
	6D	0.3% (9)	0.2% (4)	0.3% (5)	0.2% (6)	0.2% (8)	32
	21	0.1% (4)	0.2% (3)	0.2% (4)	0.1% (3)	0.4% (17)	31
	Other	0.8% (28)	0.8% (15)	1.2% (21)	0.6% (19)	0.9% (40)	123
	Total	3315	1934	1758	3259	4297	14563

Table A-2. Distribution of serotypes among IPD isolates submitted to Canada's National Microbiology Laboratory for adults 18 to 49 years of age, 2019-2023

	Serotype	2019	2020	2021	2022	2023	Total
PNEU-C-20/ PNEU-C-21 Shared	Shared Total	54.2% (442)	50.0% (278)	40.8% (240)	46.9% (497)	45.9% (591)	2048
	3	10.0% (82)	8.8% (49)	7.5% (44)	9.2% (97)	9.9% (127)	399
	6A/C*	0.5% (4)	0.7% (4)	1.0% (6)	1.5% (16)	1.6% (21)	51
	7F	7.4% (60)	4.9% (27)	5.1% (30)	4.2% (45)	5.8% (75)	237
	8	9.3% (76)	11.0% (61)	6.6% (39)	6.0% (64)	6.3% (81)	321
	10A	1.2% (10)	1.1% (6)	1.2% (7)	0.8% (9)	0.6% (8)	40
	11A	1.3% (11)	2.0% (11)	0.3% (2)	2.1% (22)	2.7% (35)	81
	12F	8.2% (67)	11.2% (62)	9.0% (53)	10.8% (114)	10.0% (129)	425
	15B/C	1.3% (11)	0.9% (5)	1.0% (6)	1.2% (13)	0.9% (11)	46
	19A	4.3% (35)	2.9% (16)	4.4% (26)	5.7% (60)	3.3% (43)	180
	22F	6.9% (56)	4.5% (25)	2.9% (17)	4.6% (49)	3.7% (47)	194
	33F	3.7% (30)	2.2% (12)	1.7% (10)	0.8% (8)	1.1% (14)	74
PNEU-C-20 Unique	Pneu-C-20 all Total	74.0% (604)	80.0% (445)	72.6% (427)	79.7% (845)	83.4% (1073)	3394
	Pneu-C-20 unique Total	19.9% (162)	30.0% (167)	31.8% (187)	32.8% (348)	37.5% (482)	1346
	1	0.0% (0)	0.2% (1)	0.0% (0)	0.2% (2)	0.0% (0)	3
	4	14.5% (118)	20.9% (116)	23.0% (135)	21.8% (231)	22.8% (294)	894
	5	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0
	6B	0.2% (2)	0.0% (0)	0.0% (0)	0.4% (4)	0.0% (0)	6
	9V	2.1% (17)	5.8% (32)	6.6% (39)	7.9% (84)	10.8% (139)	311
	14	0.2% (2)	0.5% (3)	0.2% (1)	0.2% (2)	0.3% (4)	12
	18C	0.5% (4)	0.4% (2)	0.2% (1)	0.1% (1)	0.9% (11)	19
	19F	2.2% (18)	2.2% (12)	1.9% (11)	2.2% (23)	2.2% (28)	92
	23F	0.1% (1)	0.2% (1)	0.0% (0)	0.1% (1)	0.5% (6)	9
PNEU-C-21 Unique	Pneu-C-21 all Total	76.7% (626)	68.2% (379)	63.8% (375)	64.0% (678)	59.4% (765)	2823
	Pneu-C-21 unique Total	22.5% (184)	18.2% (101)	23.0% (135)	17.1% (181)	13.5% (174)	775
	9N	7.1% (58)	5.9% (33)	6.6% (39)	4.7% (50)	3.2% (41)	221

	15A	1.8% (15)	1.4% (8)	1.5% (9)	1.3% (14)	0.8% (10)	56
	16F	2.0% (16)	0.7% (4)	1.2% (7)	0.8% (9)	1.2% (15)	51
	17F	0.6% (5)	0.2% (1)	1.0% (6)	0.3% (3)	0.4% (5)	20
	20	4.2% (34)	4.0% (22)	7.7% (45)	6.1% (65)	4.4% (56)	222
	23A	2.6% (21)	1.8% (10)	2.0% (12)	0.8% (8)	1.3% (17)	68
	23B	2.1% (17)	1.4% (8)	1.0% (6)	1.6% (17)	1.0% (13)	61
	24F	0.2% (2)	0.0% (0)	0.0% (0)	0.1% (1)	0.0% (0)	3
	31	0.9% (7)	1.4% (8)	1.0% (6)	0.8% (9)	0.6% (8)	38
	35B	1.1% (9)	1.3% (7)	0.9% (5)	0.5% (5)	0.7% (9)	35
NVT	NVT all	3.4% (28)	1.8% (10)	4.4% (26)	3.2% (34)	3.1% (40)	138
	7C	0.9% (7)	0.5% (3)	1.0% (6)	0.6% (6)	0.5% (7)	29
	34	0.6% (5)	0.2% (1)	0.5% (3)	0.7% (7)	0.5% (6)	22
	35F	0.5% (4)	0.2% (1)	0.5% (3)	0.6% (6)	0.2% (3)	17
	13	0.1% (1)	0.2% (1)	0.7% (4)	0.7% (7)	0.2% (3)	16
	28A	0.0% (0)	0.2% (1)	0.7% (4)	0.3% (3)	0.2% (3)	11
	38	0.6% (5)	0.2% (1)	0.0% (0)	0.0% (0)	0.3% (4)	10
	Other	0.7% (6)	0.4% (2)	1.0% (6)	0.5% (5)	1.1% (14)	28
	Total	816	556	588	1060	1287	4307

Table A-3: Percentage (number) of IPD isolates by serotype for adults 50 to 64 years of age, 2019-2023

	Serotype	2019	2020	2021	2022	2023	Total
PNEU-C-20/ PNEU-C-21 Shared	Shared Total	53.2% (547)	49.5% (326)	44.1% (253)	46.3% (458)	49.7% (654)	2238
	3	11.5% (118)	12.4% (82)	9.9% (57)	14.4% (142)	12.8% (169)	568
	6A/C*	2.6% (27)	2.0% (13)	2.3% (13)	0.9% (9)	1.7% (22)	84
	7F	3.6% (37)	2.9% (19)	1.9% (11)	2.7% (27)	3.0% (40)	134
	8	7.7% (79)	8.6% (57)	4.7% (27)	6.5% (64)	5.9% (77)	304
	10A	1.9% (20)	1.8% (12)	0.9% (5)	1.2% (12)	1.1% (14)	63
	11A	2.9% (30)	2.7% (18)	3.3% (19)	2.7% (27)	2.5% (33)	127
	12F	4.6% (47)	5.8% (38)	8.2% (47)	5.7% (56)	7.1% (93)	281
	15B/C	2.3% (24)	2.3% (15)	1.7% (10)	1.7% (17)	2.3% (30)	96
	19A	3.8% (39)	3.8% (25)	3.8% (22)	4.7% (46)	4.3% (57)	189
	22F	9.4% (97)	5.2% (34)	5.1% (29)	4.7% (46)	7.5% (99)	305
	33F	2.8% (29)	2.0% (13)	2.3% (13)	1.2% (12)	1.5% (20)	87
PNEU-C-20 Unique	Pneu-C-20 all Total	64.5% (664)	66.2% (436)	63.9% (367)	71.1% (703)	75.5% (994)	3164
	Pneu-C-20 unique Total	11.4% (117)	16.7% (110)	19.9% (114)	24.8% (245)	25.8% (340)	926
	1	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0
	4	8.4% (86)	11.4% (75)	12.7% (73)	15.0% (148)	13.3% (175)	557
	5	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0
	6B	0.0% (0)	0.0% (0)	0.0% (0)	0.2% (2)	0.1% (1)	3
	9V	1.6% (16)	2.3% (15)	5.1% (29)	6.7% (66)	8.8% (116)	242
	14	0.2% (2)	0.2% (1)	0.2% (1)	0.2% (2)	0.2% (3)	9
	18C	0.3% (3)	0.9% (6)	0.2% (1)	0.5% (5)	0.5% (6)	21
	19F	1.0% (10)	1.8% (12)	1.7% (10)	1.9% (19)	2.7% (36)	87
	23F	0.0% (0)	0.2% (1)	0.0% (0)	0.3% (3)	0.2% (3)	7
PNEU-C-21 Unique	Pneu-C-21 all Total	82.4% (848)	77.7% (512)	74.6% (428)	70.3% (695)	69.3% (912)	3395
	Pneu-C-21 unique Total	29.3% (301)	28.2% (186)	30.5% (175)	24.0% (237)	19.6% (258)	1157
	9N	8.9% (92)	7.0% (46)	9.6% (55)	5.3% (52)	5.6% (74)	319
	15A	2.6% (27)	3.6% (24)	3.0% (17)	2.7% (27)	2.5% (33)	128

	16F	3.1% (32)	2.6% (17)	3.5% (20)	2.0% (20)	1.4% (19)	108
	17F	0.9% (9)	0.8% (5)	0.7% (4)	0.8% (8)	0.4% (5)	31
	20	5.9% (61)	6.4% (42)	7.7% (44)	5.3% (52)	4.0% (53)	252
	23A	2.5% (26)	2.9% (19)	1.4% (8)	2.9% (29)	1.7% (23)	105
	23B	3.1% (32)	1.8% (12)	2.1% (12)	2.0% (20)	2.0% (26)	102
	24F	0.1% (1)	0.0% (0)	0.2% (1)	0.0% (0)	0.0% (0)	2
	31	0.7% (7)	1.5% (10)	1.2% (7)	2.0% (20)	0.8% (11)	55
	35B	1.4% (14)	1.7% (11)	1.2% (7)	0.9% (9)	1.1% (14)	55
NVT	NVT all	6.2% (64)	5.6% (37)	5.6% (32)	5.0% (49)	4.9% (64)	246
	35F	1.3% (13)	1.5% (10)	1.2% (7)	1.2% (12)	0.8% (10)	52
	7C	1.3% (13)	0.8% (5)	1.0% (6)	1.1% (11)	1.2% (16)	51
	34	1.1% (11)	1.1% (7)	0.9% (5)	0.6% (6)	0.5% (7)	36
	13	0.4% (4)	0.3% (2)	0.7% (4)	0.5% (5)	0.3% (4)	19
	28A	0.4% (4)	0.6% (4)	0.5% (3)	0.4% (4)	0.2% (3)	18
	6D	0.5% (5)	0.3% (2)	0.5% (3)	0.3% (3)	0.3% (4)	17
	38	0.3% (3)	0.6% (4)	0.0% (0)	0.2% (2)	0.4% (5)	14
	Other	1.1% (11)	0.5% (3)	0.7% (4)	0.6% (6)	1.1% (15)	39
	Total	1029	659	574	989	1316	4567

Table A-4. Percentage (number) of IPD isolates by serotype for adults 65 years of age and older, 2019-2023

	Serotype	2019	2020	2021	2022	2023	Total
table	Shared Total	50.3% (740)	46.6% (335)	44.5% (265)	47.6% (576)	50.5% (855)	2771
	3	13.3% (195)	10.4% (75)	10.4% (62)	13.3% (161)	14.1% (239)	732
	6A/C*	3.1% (45)	2.4% (17)	2.9% (17)	2.0% (24)	2.8% (47)	150
	7F	1.1% (16)	1.1% (8)	1.2% (7)	0.8% (10)	1.8% (30)	71
	8	3.9% (58)	3.5% (25)	4.9% (29)	3.8% (46)	3.7% (63)	221
	10A	2.2% (32)	2.5% (18)	1.0% (6)	1.0% (12)	1.2% (20)	88
	11A	3.2% (47)	4.3% (31)	4.5% (27)	4.3% (52)	3.5% (59)	216
	12F	1.8% (27)	2.6% (19)	3.5% (21)	2.5% (30)	3.5% (59)	156
	15B/C	2.3% (34)	2.2% (16)	2.5% (15)	2.6% (32)	3.1% (52)	149
	19A	4.1% (60)	4.2% (30)	4.5% (27)	5.3% (64)	4.1% (69)	250
	22F	11.5% (169)	10.4% (75)	6.4% (38)	9.9% (120)	11.7% (198)	600
	33F	3.9% (57)	2.9% (21)	2.7% (16)	2.1% (25)	1.1% (19)	138
PNEU-C-20 Unique	Pneu-C-20 all Total	58.1% (854)	56.1% (403)	56.0% (334)	60.4% (731)	64.3% (1089)	3411
	Pneu-C-20 unique Total	7.8% (114)	9.5% (68)	11.6% (69)	12.8% (155)	13.8% (234)	640
	1	0.0% (0)	0.0% (0)	0.0% (0)	0.1% (1)	0.1% (1)	2
	4	3.6% (53)	5.4% (39)	5.7% (34)	5.8% (70)	5.8% (98)	294
	5	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0
	6B	0.4% (6)	0.1% (1)	0.3% (2)	0.2% (2)	0.1% (2)	13
	9V	0.8% (12)	1.4% (10)	2.7% (16)	3.1% (37)	4.6% (78)	153
	14	0.3% (5)	0.1% (1)	0.0% (0)	0.4% (5)	0.1% (2)	13
	18C	0.5% (7)	0.1% (1)	0.2% (1)	0.4% (5)	0.2% (3)	17
	19F	2.1% (31)	2.2% (16)	2.5% (15)	2.5% (30)	2.8% (47)	139
	23F	0.0% (0)	0.0% (0)	0.2% (1)	0.4% (5)	0.2% (3)	9
PNEU-C-21 Unique	Pneu-C-21 all Total	84.6% (1243)	80.7% (580)	76.5% (456)	79.5% (962)	78.3% (1326)	4567
	Pneu-C-21 unique Total	34.2% (503)	34.1% (245)	32.0% (191)	31.9% (386)	27.8% (471)	1796
	9N	6.3% (93)	7.5% (54)	6.7% (40)	6.4% (78)	5.1% (87)	352
	15A	6.8% (100)	4.7% (34)	4.9% (29)	4.4% (53)	4.4% (74)	290

	16F	3.3% (48)	4.2% (30)	3.7% (22)	3.5% (42)	2.6% (44)	186
	17F	1.4% (20)	1.5% (11)	0.5% (3)	0.7% (8)	0.5% (8)	50
	20	2.4% (36)	2.1% (15)	3.5% (21)	3.4% (41)	3.2% (54)	167
	23A	5.0% (74)	4.7% (34)	3.9% (23)	4.9% (59)	5.4% (91)	281
	23B	3.4% (50)	2.9% (21)	3.0% (18)	3.5% (42)	2.5% (42)	173
	24F	0.4% (6)	0.3% (2)	0.2% (1)	0.1% (1)	0.1% (1)	11
	31	1.7% (25)	2.4% (17)	2.2% (13)	2.0% (24)	1.2% (21)	100
	35B	3.5% (51)	3.8% (27)	3.5% (21)	3.1% (38)	2.9% (49)	186
NVT	NVT all	7.7% (113)	9.9% (71)	11.9% (71)	7.7% (93)	7.9% (134)	482
	35F	2.1% (31)	3.2% (23)	3.4% (20)	2.5% (30)	2.0% (33)	137
	7C	1.5% (22)	1.9% (14)	2.0% (12)	2.6% (31)	2.1% (36)	115
	34	1.2% (17)	1.1% (8)	2.2% (13)	1.2% (15)	0.7% (11)	64
	38	1.1% (16)	1.1% (8)	0.2% (1)	0.1% (1)	0.7% (11)	37
	21	0.2% (3)	0.3% (2)	0.3% (2)	0.2% (3)	0.7% (11)	21
	28A	0.3% (4)	0.3% (2)	0.7% (4)	0.2% (2)	0.5% (9)	21
	13	0.3% (4)	0.1% (1)	0.7% (4)	0.0% (0)	0.1% (2)	11
	35D	0.1% (1)	0.1% (1)	0.5% (3)	0.1% (1)	0.2% (4)	10
	Other	1.0% (15)	1.7% (12)	2.0% (12)	0.8% (10)	1.0% (17)	35
	Total	1470	719	596	1210	1694	5689