Summary of the 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

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Abstract

Background: Age and certain medical/social conditions are risk factors for invasive pneumococcal disease (IPD). For prevention of IPD, the National Advisory Committee on Immunization (NACI) has recommended the 23-valent polysaccharide pneumococcal vaccine, PNEU-P-23, for adults 65 years of age and older and adults over 18 years of age living with certain underlying conditions. NACI has also recommended 13-valent conjugate pneumococcal vaccine, PNEU-C-13, for adults; however, in publicly funded programs, this recommendation is limited to individuals with risk factors for IPD. Two new conjugate vaccines, PNEU-C-15 and PNEU-C-20, have been authorized by Health Canada for prevention of IPD in adults. This article summarizes NACI public health recommendations for pneumococcal vaccines in adults given these new conjugate vaccines that provide additional serotype coverage over PNEU-C-13.

Methods: Key studies evaluating the immunogenicity and safety of PNEU-C-15 and PNEU-C-20 were reviewed. The Grading of Recommendations, Assessment, Development and Evaluations framework methodology was used to assess the certainty of evidence.

Results: The PNEU-C-15 and PNEU-C-20 vaccines showed comparable immune responses, and safety profiles for all mild, moderate, and severe adverse events, to the currently used vaccines. No data were available on the efficacy or effectiveness of PNEU-C-15 or PNEU-C-20. Economic evidence and feasibility assessments supported the use of the PNEU-C-20 vaccine.

Conclusion: NACI recommends PNEU-C-20 for adults 65 years of age and older, 50–64 years of age and living with factors placing them at higher risk of pneumococcal disease, and 18–49 years of age with immunocompromising conditions, with PNEU-C-15+PNEU-P-23 an alternative.

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Introduction

Pneumococcal disease (PD) includes both invasive pneumococcal diseases (IPD), such as meningitis, bacteremia, bacteremic pneumonia and empyema, and non-invasive pneumococcal disease, such as community-acquired pneumonia, sinusitis, and acute otitis media. The burden of disease is predominately attributable to a small number of the more than 100 identified

serotypes of a *Streptococcus pneumoniae* bacteria. Invasive pneumococcal disease is most common in the very young, the elderly and individuals living with medical conditions and/or other risk factors that place them at higher risk of IPD.

The incidence of IPD in adults in Canada increased from 2001 to 2004, followed by relatively stable incidence in the subsequent 15 years. It was highest in adults 65 years of age and older, with incidence proportional to age starting at 50 years of age, and higher in Northern Canada compared to the rest of the country. Furthermore, the proportion of IPD caused by vaccine targeted serotypes have remained relatively stable since 2016 (1,2). Current National Advisory Committee on Immunization (NACI) recommendations for the prevention of IPD in adults include two vaccines: a 23-valent polysaccharide pneumococcal vaccine, PNEU-P-23 (Pneumovax®); and a 13-valent conjugate pneumococcal vaccine, PNEU-C-13 (Prevnar 13®). The PNEU-P-23 vaccine is recommended for routine immunization against IPD for all adults 65 years of age and older and adults 18–64 years of age with underlying medical conditions or social factors that put them at higher risk of IPD. The PNEU-C-13 vaccine, in series with PNEU-P-23, is recommended for adults 18 years of age and older and living with immunocompromising conditions resulting in high risk of IPD. A complete list of conditions that increase the risk of IPD along with dose and schedule of recommended vaccinations is available in the Pneumococcal Vaccine Chapter of the *Canadian Immunization Guide* (3).

Two new conjugate pneumococcal vaccines for adults, PNEU-C-15 (Vaxneuvance™) and PNEU-C-20 (Prevnar 20®) were authorized by Health Canada on November 16, 2021, and May 9, 2022, respectively. The PNEU-C-15 vaccine was first authorized for adults 18 years of age and older with an indication for prevention of IPD caused by 15 serotypes of *S. pneumoniae* (PNEU-C-13 plus serotypes 22F and 33F) (4). The PNEU-C-20 vaccine is authorized for adults 18 years of age and older with an indication for prevention of pneumonia and IPD caused by 20 serotypes of *S. pneumoniae* (PNEU-C-13 plus serotypes 8, 10A, 11A, 12F, 15B, 22F and 33F) (5). Complete details can be found in the NACI statement, *Public health level recommendations on the use of pneumococcal vaccines in adults, including the use of 15-valent and 20-valent conjugate vaccines*. PNEU-C-15 (Vaxneuvance™) has also recently been authorized for use in infants, children and adolescents from six weeks through 17 years of age and is under review by NACI for use in paediatric programs.

The objective of this article is to summarize the NACI recommendations (6) on the use of PNEU-C-15 and PNEU-C-20 vaccines in adults.

Methods

The NACI reviewed evidence pertaining to the burden of IPD in the adult population, along with the safety, immunogenicity, efficacy, and effectiveness of the vaccines, along with an economic analysis and application of the Ethics, Equity, Feasibility and Acceptability (known as EEFA) framework. Clinical trials were assessed via a targeted review, and a health economic model was created by the Public Health Agency of Canada (PHAC) to assess cost-effectiveness in the Canadian population and was used in a multi-model comparison in combination with other cost effectiveness models. The knowledge synthesis was performed by the NACI Secretariat and reviewed by the Pneumococcal Working Group. The Grading of Recommendations, Assessment, Development and Evaluations framework methodology was used to assess certainty of the evidence and arrive at recommendations. For complete details of the methods refer to the NACI statement (6).

Results

The burden of IPD in the adult population since the introduction of paediatric pneumococcal vaccination programs in 2002 has been relatively stable; however, despite being strongly recommended for vaccination, the oldest adults (65 years of age and older) continue to have consistently higher incidence rates than younger cohorts with the exception of infants and children under five years of age.

There are currently no efficacy or effectiveness data available for PNEU-C-15 or PNEU-C-20 for any adult indication. Authorization was based on an assessment of the immune responses using opsonophagocytic activity assays of both vaccines compared to currently recommended vaccines.

For PNEU-C-15, in immunocompetent pneumococcal vaccine-naïve adults 65 years of age and older and for shared serotypes, PNEU-C-15 demonstrated overall similar immune responses, including for serotype 3, compared to PNEU-C-13, although seroresponses varied (7–11). Studies comparing PNEU-C-15 to PNEU-P-23 showed similar results, although seroresponse was higher with serotype 3 with PNEU-C-15 (7).

For PNEU-C-20, non-inferiority criteria were met in vaccine-naïve populations over 60 years of age; however, there was an observed lower proportion of seroresponders compared to PNEU-C-13 for shared serotypes (12,13).

Persistence of immune responses over a 12-month period for both PNEU-C-15 and PNEU-C-20 were comparable to PNEU-C-13.

Data on local and systemic adverse events (AE), both solicited and unsolicited, were collected in similar fashion for both vaccines, with shorter follow-up periods for solicited events after each dose and follow-up for up to six months for serious adverse events (SAE).

There was little to no difference reported in clinical trials between PNEU-C-15 and PNEU-P-23 or PNEU-C-13 for all mild/moderate and severe systemic AEs occurring within 14 days of vaccination as well as reported SAEs up to six months after vaccination in all evaluated populations, including in adults 65 years of age and older with an immunocompromising condition (7–11). There was also little to no difference in AEs for PNEU-C-15 administered concomitantly with quadrivalent influenza vaccine in vaccine-naïve adults (11).

There was little to no difference between PNEU-C-20 and PNEU-C-13 in all mild/moderate and severe systemic AEs up to seven days post vaccination and SAEs up to one month post vaccination for vaccine-naïve adults aged 60 years or older (12,13). For adults 65 years of age and older who have previously been vaccinated with PNEU-P-23 (one to five years prior), SAE up to six months and systemic AEs seven days after vaccination were similar between PNEU-C-20 and PNEU-C-13 (14).

A systematic review of economic analyses conducted in the United States found that PNEU-C-20 use in older adults was generally associated with increased quality-adjusted life years, with lower incremental cost-effectiveness ratios when the vaccine was used in those 65 years of age and older compared to programs in those 50 years of age and older. Incremental cost-effectiveness ratio estimates for PNEU-C-15 use in series with PNEU-P-23 at those six years of age showed variability across studies (16).

A cost-utility model developed by PHAC was used to evaluate the cost-effectiveness of different age-based recommendations. The analysis indicated that PNEU-C-20 used alone is likely a cost-effective strategy for those 65 years of age and older. Compared to PNEU-C-20, PNEU-C-15 is unlikely to be a cost-effective option. Results of the multi-model comparison were consistent with the PHAC economic evaluation.

The PNEU-C-20 vaccine covers more than 90% of serotypes included in PNEU-P-23 and could be offered in immunization programs as a single dose. A single dose vaccine schedule minimizes complexity and cost in a vaccine program and can facilitate vaccination of populations that are otherwise difficult to reach to complete a series requiring multiple doses. To optimize the protection of PNEU-C-15, PNEU-P-23 would also need to be offered in a multi-product, two-dose series.

Recommendations

Following the review of available evidence, NACI made the following recommendations for public health level decision-making. 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.

The full statement contains a more detailed explanation of the recommendations and a management options table (6). This information should be reviewed in order to inform decision-making; in particular for individuals who have not been included in their respective provincial or territorial publicly funded program. In considering NACI recommendations for publicly funded immunization programs and for the purposes of publicly funded program implementation, provinces and territories may take into account other local operational factors.

For adults not previously vaccinated with a pneumococcal vaccine, or adults whose vaccination status is unknown

1. **The NACI recommends that the pneumococcal conjugate vaccine PNEU-C-20 should be offered to pneumococcal vaccine naïve adults or adults whose vaccination status is unknown and who are ≥65 years of age and, or 50–64 years of age living with risk factors placing them at higher risk of pneumococcal disease, or who are 18–49 years of age living with immunocompromising conditions. *(Strong NACI recommendation)***
   Individuals at increasing age and/or with certain underlying medical conditions (both non-immunocompromising and immunocompromising) and other factors, including community-level risk, are at higher risk of IPD. Adults 65 years of age and older have the highest incidence rate of IPD compared to other adult age groups, and the current uptake of pneumococcal vaccines in this age group is well below national goals. Age-based recommendations may need to be modified for communities with younger age distributions, such as First Nations, Métis, or Inuit communities, where autonomous decisions should be made by Indigenous Peoples with the support of healthcare and public health partners in accordance with the *United Nations Declaration on the Rights of Indigenous Peoples.*

2. **The NACI recommends that PNEU-C-15 followed by PNEU-P-23 may be offered as an alternative to PNEU-C-20 to pneumococcal vaccine naïve adults or adults whose vaccination status is unknown and who are ≥65 years of age, 50–64 years of age living with risk factors placing them at higher risk of pneumococcal disease, or who are 18–64 years of age living with immunocompromising conditions. *(Discretionary NACI recommendation)***

Although PNEU-C-15 is not expected to yield the same population-level epidemiological benefits as PNEU-C-20 and requires a second dose with PNEU-P-23, it is anticipated that it will improve disease outcomes compared to offering PNEU-P-23 alone. As to timing of the doses, an interval of one year is recommended for adults 65 years of age and older and adults 50–64 years of age who are living with risk factors for pneumococcal disease. An interval of eight weeks is recommended for adults who are 18–64 years of age and living with immunocompromising conditions to allow for quicker completion of the series, however a longer interval may result in less blunting of immune responses and could be considered if risk of pneumococcal infection is low.

For adults previously vaccinated with a pneumococcal vaccine

3. **The NACI recommends that the pneumococcal conjugate vaccine PNEU-C-20, should be offered to adults ≥65 years of age who have been previously immunized with PNEU-P-23 alone, or PNEU-C-13 and PNEU-P-23 in series, if it has been at least 5 years from the last dose of a previous pneumococcal vaccine (PNEU-P-23 or PNEU-C-13). *(Strong NACI recommendation)***
   If PNEU-C-20 is not available there may be a benefit to offering PNEU-C-15 to adults 65 years of age and older who have received PNEU-P-23 alone. There is limited benefit to giving PNEU-C-15 to individuals who received PNEU-C-13 as it will only offer protection against two additional serotypes. In addition, for those adults 65 years of age and older who are also at the highest risk of IPD, an additional dose of PNEU-P-23 may be offered one year following PNEU-C-15 (or PNEU-C-13 had they received it prior to availability of PNEU-C-15).

4. **The NACI recommends that the pneumococcal conjugate vaccine PNEU-C-20 may be offered to adults 65 years of age and older who have been previously immunized with PNEU-C-13 alone, if it has been 1 year from the last dose of PNEU-C-13. *(Discretionary NACI recommendation)***
   Offering PNEU-C 20 is intended to expand serotype coverage offered by PNEU-C-13. A shorter interval of eight weeks may be considered to align with operational considerations for immunization clinics and/or programs. The additional benefit of offering PNEU-C-15 is limited; however, PNEU-C-15 in series with PNEUP-23 or PNEU-P-23 alone can be considered if PNEU-C-20 is unavailable or inaccessible.

For hematopoietic stem cell transplant (HSCT) recipients

5. **NACI recommends pneumococcal conjugate vaccine PNEU-C-20 should be offered to adults 18 years old or older who received a hematopoietic stem cell transplant (HSCT) after consultation with transplant specialist. A primary series of 3 doses of PNEU-C-20 starting 3–9 months after transplant should be administered at least 4 weeks apart, followed by a booster dose of PNEU-C-20 12–18 months post-transplant (6–12 months after the last dose of PNEU-C-20). *(Strong NACI recommendation)***
   The recommended timing of PNEU-C-20 for hematopoietic stem cell transplant recipients should be determined in consultation with the recipient's transplant specialist. The PNEU-C-15 vaccine may be considered if PNEU-C-20 is unavailable or inaccessible, to ensure the needed protection.

Conclusion

Prior to the authorization by Health Canada of PNEU-C-15 and PNEU-C-20 for adults, NACI's recommendation for adults 65 years of age and older was for the use of PNEU-P-23, with PNEU-C-13 only recommended for individuals at highest risk of IPD, such as those with immunocompromising conditions. Conjugate vaccines induce immunological memory and provide longer duration of protection in part due to the ability for boosting by involving T lymphocytes in a way that polysaccharide vaccines cannot. For this reason, conjugate vaccines may provide more durable protection and may result in fewer cases of pneumococcal disease. The new vaccines offer an opportunity to protect adults and further reduce the burden of disease; therefore, NACI is recommending their use more widely in the publicly funded immunization programs.

Both PNEU-C-20 and PNEU-C-15 have shown robust immune responses in adults previously vaccinated with pneumococcal vaccines and have demonstrated a comparable safety profile to PNEU-C-13 in all adult population studied. However, PNEU-C-20 is anticipated to yield greater population-level epidemiological benefits over the use of PNEU-C-15.

It should be further noted that, at this time, no PNEU-C-20 studies in immunocompromised adults have been conducted but PNEU-C-20 is expected to be similarly efficacious as PNEU-C-13 against disease attributable to the 13 matched serotypes, including in hematopoietic stem cell transplant recipients.

NACI only supports the continued use of PNEU-C-13 and PNEU-P-23 in adults when PNEU-C-15 and/or PNEU-C-20 are unavailable or inaccessible.

At this time, there are no public health level recommendations on the use of PNEU-C-15 or PNEU-C-20 for adults 18–49 years of age with non-immunocompromising risk factors that place them at high risk of IPD, as additional analyses on the cost-effectiveness of conjugate PNEU-C-15 and PNEU-C-20 in this population are needed. The PNEU-C-15 or PNEU-C-20 vaccines may be considered at clinical discretion for these individuals. While PNEU-P-23 and PNEU-C-13 continue to be available and jurisdictions continue providing these vaccines for this group, previous NACI recommendations remain for this group.

Authors' statement

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Competing interests

None.

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