An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)

Recommendations for Public Health Programs on the Use of Pneumococcal Vaccines in Children, Including the Use of 15-Valent and 20-Valent Conjugate Vaccines: Economic Evidence Supplementary Appendix

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

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Recommandations sur l'utilisation du vaccin contre le pneumocoque conjugué - 15 valent (Pneu-C-15) et 20 valent (Pneu-C-20) chez les enfants du Comité consultatif national de l'immunisation (CCNI) : Annexe supplémentaire sur les données économiques

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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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A systematic review and *de novo* model-based economic evaluation were used as economic evidence to support decision-making for the use of 15-valent (Pneu-C-15) and 20-valent (Pneu-C-20) pneumococcal conjugate vaccines in the pediatric population. Each component is described below.

I. SYSTEMATIC REVIEW

A systematic review of economic evaluations of Pneu-C-15 and Pneu-C-20 vaccines for preventing pneumococcal disease (PD) was conducted. The review included economic evaluations that compared Pneu-C-15 or Pneu-C-20 to currently used vaccines to prevent PD in the pediatric population aged less than 18 years. The research question components included:

- Population: Individuals less than 18 years of age
- Intervention: Pneu-C-15 or Pneu-C-20 (alone or in series with other pneumococcal vaccines)
- Comparator: Current vaccines for PD (10-valent conjugate vaccine (Pneu-C-10), 13-valent conjugate vaccine (Pneu-C-13), 23-valent polysaccharide (Pneu-P-23))
- Outcomes: Measures of economic outcomes (incremental cost per quality-adjusted life year (QALY), incremental cost per life year, etc.)

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [(1)]. A systematic literature search for English- and French-language studies was conducted in six electronic databases: Embase, Ovid Medline, International Pharmaceutical Abstracts, EBM Reviews, SCOPUS, and Econlit. A comprehensive search strategy was developed in consultation with and validated by a Librarian. The search was limited to records published between January 1, 2018 to March 7, 2023. Search terms included pneumococcal vaccine, conjugate vaccine, pneumococcal infection, PCV15 (Pneu-C-15), PCV20 (Pneu-C-20), cost, cost-effectiveness, cost-utility, economic evaluation, economic impact, and financial effect. A search of grey literature was also conducted following the Canadian Agency for Drugs and Technologies in Health Grey Matters tool [(2)]. References of the included studies were also manually searched to identify any additional relevant studies.

All levels of screening including title, abstract, and full text, were completed in duplicate using predetermined eligibility criteria. Any discrepancies during the study selection process were resolved through consensus. A standardized data extraction tool developed based on the Consolidated Health Economics Evaluation and Reporting Standards statement [(3)] was used to collect study characteristics, methods and findings of included studies. The overall quality of included studies was assessed using Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Economic Evaluations [(4)]. The applicability or transferability of included studies was assessed using Heyland's Generalizability Criteria [(5)]. No studies were excluded based on these appraisals.

Study and population characteristics were summarized qualitatively. Incremental cost-effectiveness ratios (ICERs) were adjusted to 2022 Canadian dollars (C$) using the purchasing power parity rates from the Organization for Economic Co-operation and Development (OECD)[(6)]

and inflation rates from the Bank of Canada [7]. For the remainder of this review, results are reported as adjusted ICERs (2022 C$).

I.1. Description of Included Studies

The systematic literature search identified two model-based studies that met the eligibility criteria, both conducted in the United States (US) [8, 9]. The study characteristics are summarized in Table 1. Each of the studies included both a cost-utility analysis and a cost-effectiveness analysis [8, 9]. Cost-utility analyses and cost-effectiveness analyses differ in how they measure the effectiveness of an intervention. Cost-utility analysis uses QALYs as the metric for effectiveness, which combines both quality and quantity of life, whereas cost-effectiveness analysis uses natural units such as life-years saved, or PD cases or deaths prevented. The findings of the two US studies included in this review [8, 9] were also reported by the Advisory Committee on Immunization Practices [10]. One of the two included studies was industry sponsored [9]. Both studies used a societal perspective and the US-recommended 3% discount rate for costs and outcomes [8, 9]. One study used a lifetime time horizon [9], while the other used a 17-year time horizon to track disease incidence, but included lifetime costs and effects of long-term sequelae and premature mortality due to PD during the model time horizon [8]. Economic outcomes were reported as ICERs, expressed as the incremental cost per QALY gained, incremental cost per LY saved, and/or incremental cost per PD cases averted.

One study used a cohort Markov model that followed a single age cohort over time [8] and the other study used a multi-cohort Markov model that followed the entire US population from birth up to age of 100 years and allowed new birth cohorts to enter the population each year over 100 years of model duration [9]. Both models employed a similar approach to model the risk of PD, including invasive pneumococcal disease (IPD), non-bacteremic pneumococcal pneumonia, pneumococcal acute otitis media (AOM) and long-term post-meningitis sequelae as health outcomes. Deterministic sensitivity analysis and scenario analyses were reported for both studies [8, 9].

Both reviewed studies compared the cost and health impacts of using Pneu-C-15 to current recommendations. No eligible studies were identified that included Pneu-C-20. At the time the studies were conducted, the US recommended 3 + 1 dosing schedules of Pneu-C-13 for all children younger than two years of age. Vaccination coverage was estimated as 92% for all 3-doses in the primary series and 82% for the booster dose [8, 9]. In an additional analysis examining the impact of a supplementary dose of Pneu-C-15 for children aged two to five years who were fully vaccinated with Pneu-C-13 (as a catch-up campaign), 50% vaccination coverage was assumed [8]. The price of Pneu-C-15 was unknown at the time the studies were conducted. Both studies assumed price parity with Pneu-C-13 for the base case analysis, using a weighted average price estimated based on public (61-65%) and private (35-39%) purchase shares for Pneu-C-13 [8, 9]. One study carried out a threshold analysis to establish the maximum price at which Pneu-C-15 is cost-saving [9].

Both studies assumed that Pneu-C-15 had the same vaccine effectiveness (VE) as Pneu-C-13 for serotypes included in Pneu-C-13, but included protection against two additional serotypes (i.e.,

22F and 33F). One study assumed that Pneu-C-15 and Pneu-C-13 vaccines also offer protection against serotype 6C, due to assumed cross-protection by serotype 6A (which is included in both vaccines) [8]. All studies assumed 15 years of vaccine protection, with full protection for the first 5 years after complete vaccination and a linear waning to 0% effectiveness over the next 10 years [8, 9]. Both models were static and did not simulate transmission dynamics. The models assessed the potential indirect effects of childhood Pneu-C-15 vaccination by incorporating a relative reduction in the incidence of IPD or PD caused by serotypes 22F and 33F [8, 9]. One study included the indirect effect as yearly reduction of 7.8% in PD incidence associated with serotypes 22F and 33F [8] while the other assumed a 7.8% reduction of IPD incidence during the first year that gradually increased to a maximum reduction of 33.4% per year in year 5 and subsequent years [9].

Table 1. Study and population characteristics of economic evaluations comparing Pneu-C-15 to Pneu-C-13

Author, year, country	Analytic technique, Perspective	Model type (cohort)	Indirect effects included	Outcome measure	Time horizon, discount rate	Dosing schedule	Vaccination coverage	Duration of vaccine protection
Prasad *et al.,* 2023, United States [8]	CUA, Societal	Markov (single cohort, 3.9 million infants	Yes, included as a relative reduction in the incidence rate of PD	Cost per QALY; Cost per LY	17 years to track disease incidence and lifetime for long-term outcomes, 3%	3 + 1 (3-dose primary series and a booster dose)	92.4% for the primary series; and 82.3% for the booster dose	Full protection for first 5 years and linear waning to 0% effectiveness over next 10 years
Huang *et. al.,* 2023, United States [9]	CUA, Societal	Markov (multi-cohort, 345 million infants over 100 year model duration	Yes, included as a relative reduction in the incidence rate of IPD	Cost per QALY; Cost per LY	100 years to track disease incidence and lifetime for long-term outcomes, 3%	3 + 1 (3-dose primary series and a booster dose)	91.9% for the primary series and 82.4% for the booster dose	Full protection for first 5 years and linear waning to 0% effectiveness over next 10 years

I.2. Main Results

Both model-based economic evaluations reported the incremental cost-effectiveness of replacing Pneu-C-13 with Pneu-C-15 in the pediatric population, and the results are summarized in Table 2. The use of Pneu-C-15 within the routine immunization program was found to be the dominant strategy in these studies, resulting in lower costs and improved health outcomes compared to Pneu-C-13 when vaccine price equivalence was assumed.

For the societal perspective, medical cost savings accounted for 47% of the total cost savings in the single cohort model [8] and 63% in the multicohort model analyses [9]. About 47% of the total cost savings and 67% of total QALY gains in the multicohort study were attributed to indirect effects of the vaccine among the unvaccinated population [9].

The study that evaluated the impact of a supplemental Pneu-C-15 dose among children aged two to five years who were fully vaccinated with Pneu-C-13 found that a catch-up campaign was unlikely to be cost-effective under commonly used thresholds, with ICERs ranging from C$3,594,936 to C$7,592,987 per QALY gained [8].

Table 2. Main results by study

Author, Year	Strategy	Original currency, year	Incremental cost (adjusted, C$2022)	Incremental Effects	ICER
Prasad *et. al.,* 2023 [8]	Pneu-C-15 vs. Pneu-C-13	US$2021	-202,279,620 (total cost-saving). C$94,947,577 medical cost savings; C$68,802,592 vaccine cost savings; and C$37,153,400 nonmedical cost savings	759 QALYs gained; 664 LYs saved; prevented 92,290 additional PD events and 22 associated deaths	Pneu-C-15 Dominant
Huang *et. al.,* 2023 [9]	Pneu-C-15 vs. Pneu-C-13	US$2021	-14,885,513,811 (total cost-saving). C$9.7 billion medical cost savings; $5.7 billion non-medical cost savings; and C$34,996 additional vaccine costs	96,056 QALYs gained; 90,026 LYs saved; prevented 12,328,503 PD cases and 20,238 associated deaths	Pneu-C-15 Dominant

I.3. Influential Parameters and Assumptions

Several scenario and sensitivity analyses were reported for both studies [8, 9] and with the exception of the vaccine price threshold analysis [9], all results showed that Pneu-C-15 was a dominant vaccination strategy compared to Pneu-C-13 (Table 3), consistent with the base case conclusions. The most influential parameters for the single cohort model were QALY decrements for AOM and QALY decrements for tympanostomy tube insertions [8]. Results of the multicohort model were most sensitive to changes in VE against all-cause inpatient pneumonia, vaccination coverage, indirect effects of vaccination (modelled as a relative reduction of IPD incidence), and incidence and fatality rates of bacteremic pneumonia in older adults [9]. In both models, exclusion of indirect effects associated with use of Pneu-C-15 reduced the cost savings and QALYs gained, but Pneu-C-15 remained the dominant strategy, when the vaccine was assumed to be priced the same as Pneu-C-13 [8, 9]. Use of a health care payer perspective scenario that included only vaccination and direct medical costs resulted in continued dominance of Pneu-C-15 over Pneu-C-13, assuming both were priced equally [9].

Although both economic evaluations assumed an equivalent price for Pneu-C-15 and Pneu-C-13 in the base case analyses, increased vaccine prices for Pneu-C-15 were explored in scenario analyses. When the public price of Pneu-C-15 in the single cohort model was assumed to be 5% higher than Pneu-C-13 (C$219.94 vs. C$209.46), Pneu-C-15 led to $123 million cost savings and 759 more QALYs compared to Pneu-C-13 [8]. Threshold analysis in the multicohort model indicated that Pneu-C-15 would remain the dominant vaccination strategy with a maximum price per dose 18% higher than Pneu-C-13 [9].

Sensitivity analyses of the catch-up campaign of Pneu-C-15 for children under five assuming a higher proportion of pneumococcal AOM (19% among children aged less than 2 years and 23% among children aged 2 years and older) and a higher proportion of sequalae after meningitis (20% among children aged less than 5 years and 30% among children aged ≥5 years) resulted in ICERs of more than $3.5 million per QALY and $3.6 million per QALY, respectively.

Table 3. Scenario analysis assumptions and results

(A) Single birth cohort model (3.9 million infants) [a] [8]

Base case assumptions	Scenario analysis assumptions	Incremental cost ($ millions, adjusted)	Incremental effects (QALYs gained)	ICER
Assumed equal price of Pneu-C-15 and Pneu-C-13	5% higher public price for Pneu-C-15	-123.60	759	Pneu-C-15 dominant
Included indirect effects	Excluded indirect effects	-184.71	622	Pneu-C-15 dominant

[a]In base case analysis, Pneu-C-15 was dominant, with an incremental cost of -$202 million and 759 QALYs gained.

(B) Multiple birth cohort model (345 million infants) [a] [9]

Base case assumptions	Scenario analysis assumptions	Incremental cost ($ millions, adjusted)	Incremental effects (QALYs gained)	ICER
Multiple birth cohort, and full vaccine protection for first 5 years and decreased linearly to 0 over the next 10 years	Single birth cohort and full vaccine protection for first 10 years after vaccination and no vaccine protection thereafter	-296.22	1,329	Pneu-C-15 dominant
Societal perspective	Health care system perspective	-9443.42	96,056	Pneu-C-15 dominant
100 year model duration for disease incidence and lifetime time horizon for long-term outcomes	10 year model duration for disease incidence and lifetime time horizon for long-term outcomes	-2,979.67	10,696	Pneu-C-15 dominant
VE of Pneu-C-15 against IPD and AOM was same as Pneu-C-13, but included additional protection for serotypes 22F and 33F	VE against IPD and AOM derived from post-primary series immunogenicity of Pneu-C-15 [11], with higher VE for serotype 3 and lower VE for 6A. Additionally, higher VE against IPD for serotypes 4, 19F, and 23F; and lower VE against IPD for serotypes 1, 5, 6B, 7F, 9V, 14, 18C, and 19A were assumed.	-15,440.55	98,501	Pneu-C-15 dominant
QALY decrements for each PD event based on Rubin *et al.*, 2010 [12] and Mangen *et al*., 2015 [13]	Applied lower QALY decrement than the base case for all PD events, except: inpatient pneumonia in less than 18 years of age and outpatient pneumonia in 18+ years of age, which had higher QALY decrements [14]	-15,022.82	85,926	Pneu-C-15 dominant
Included indirect effects	Excluded indirect effects	-7,915.25	28,050	Pneu-C-15 dominant
Multiple birth cohort and included indirect effects	Single birth cohort and excluded indirect effects	-243.03	916	Pneu-C-15 dominant
Multiple birth cohort, QALY decrements for each PD event based on Rubin *et al*., 2010 [12] and Mangen *et al*., 2015 [13]	Single birth cohort; applied lower QALY decrement than the base case for all PD events, except for: inpatient pneumonia in less than 18 years of age and outpatient pneumonia in 18+ years of age, which had higher QALY decrements [14]	-292.47	958	Pneu-C-15 dominant

[a]In base case analysis, Pneu-C-15 was dominant, with an incremental cost of -$14,885 million and 96,056 QALYs gained.

I.4. Quality of Studies

Both studies met 100% of the JBI quality appraisal checklist criteria [8, 9] (Table 4).

Table 4. Quality appraisal results

	Critical appraisal: Joanna Briggs Institute checklist*										
Author; year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Huang *et. al.*, 2023	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Prasad *et. al.,* 2023	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y= Yes, N= No, U= Unclear

***Questions:** 1. Is there a well-defined question? 2. Is there comprehensive description of alternatives? 3. Are all important and relevant costs and outcomes for each alternative identified? 4. Has clinical effectiveness been established? 5. Are costs and outcomes measured accurately? 6. Are costs and outcomes valued credibly? 7. Are costs and outcomes adjusted for differential timing? 8. Is there an incremental analysis of costs and consequences? 9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences? 10. Do study results include all issues of concern to users? 11. Are the results generalizable to the setting of interest in the review?

I.5. Generalizability

Given that neither of the studies were conducted in Canada, the transferability of the cost-effectiveness estimates was assessed. Both studies are generally applicable to the Canadian health system because they were conducted in OECD country. The methods used for costing and outcome measurement, and analytic techniques used in the US studies were consistent with NACI guidelines [15], but the 3% discount rate was higher than recommended in Canada (1.5%). Higher healthcare costs in the United States compared to Canada may limit generalizability to the Canadian context [16]. It is also important to note that the studies from the US used a 4-dose schedule, but Canada's routine vaccination program recommends either a 3-dose or a 4-dose schedule, potentially influencing cost-effectiveness estimates. The applicability of the base case assumption of an equivalent price per dose for Pneu-C-13 and Pneu-C-15 [8, 9] to the Canadian context is uncertain because Pneu-C-15 was not publicly procured in Canada at the time of the review.

I.6. Conclusions

A review of the peer-reviewed and grey literature identified two model-based economic evaluations comparing Pneu-C-15 to Pneu-C-13 and no evaluations comparing Pneu-C-20 to other vaccines in the pediatric population. Both studies included in this review were considered high-quality**.** The studies generally indicated that Pneu-C-15 was a dominant vaccination strategy at price parity between Pneu-C-15 and Pneu-C-13, resulting in substantial cost savings as well as gains in health. The most influential parameters identified in the studies included indirect effects, VE against all-cause inpatient pneumonia, QALY decrements for AOM, QALY decrements for tympanostomy tube insertions, vaccination coverage, and incidence and fatality rates of bacteremic pneumonia in older adults. Vaccine price was also identified as influential though limited sensitivity analyses on its impact were reported.

II. COST-UTILITY ANALYSIS

II.1 Economic Model Description

A model-based cost-utility analysis was conducted to assess the cost-effectiveness of Pneu-C-15 and Pneu-C-20 vaccines compared to Pneu-C-13 in previously unvaccinated infants eligible for routine pneumococcal vaccination, using health system and societal perspectives. An impact inventory table summarizing the impacts that were included and excluded in the economic evaluation for each of the two reference cases is provided in Appendix A. A static Markov cohort model was used to explore the impact of alternate pediatric vaccination policies on *S. pneumoniae*-associated health outcomes in the Canadian population. Incidence of IPD, non-invasive pneumococcal community acquired pneumonia (pCAP), and AOM were used to inform the cost-utility analysis. Outcomes included PD cases and deaths averted, QALYs lost, costs, and ICERs. Scenario and sensitivity analyses were conducted to examine the impact of uncertainty on the results.

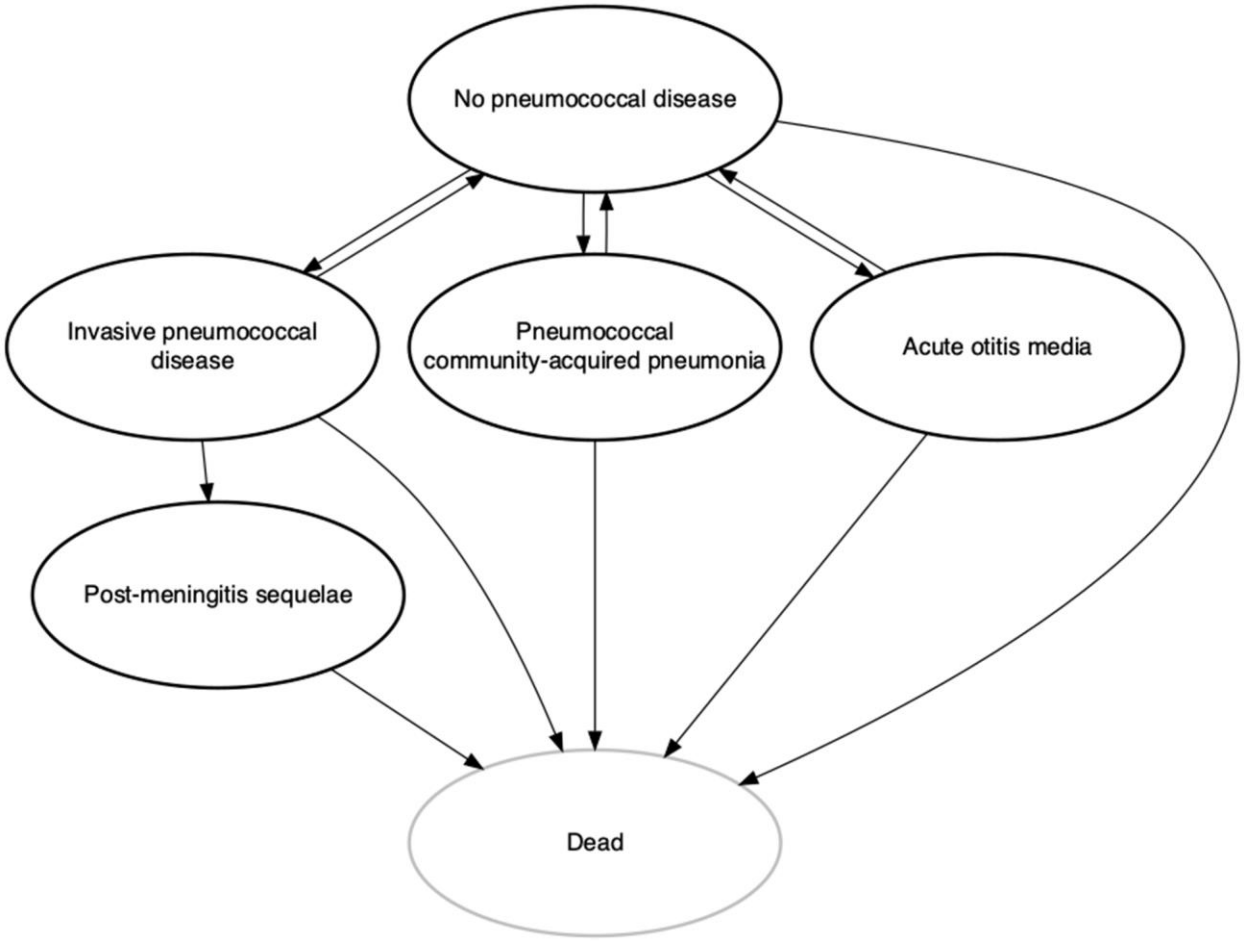
The model follows a multi-age population cohort over a 10-year period, with births and deaths occurring (i.e., an open population model) according to Canadian population projections [17-19]. Upon model entry, a proportion of each birth cohort was vaccinated, based on estimated Canadian pediatric vaccination coverage, assuming a 2+1 schedule (at 2, 4, and 12 months of age). People did not have pneumococcal disease (PD) on model entry but could develop IPD, pCAP, and AOM over their lifetime (Figure 1). There was a risk of death associated with PD. A proportion of people with IPD developed meningitis and could experience major long-term sequelae (post-meningitis sequelae). IPD was assumed to be treated in hospital, while non-invasive pCAP could be treated in an inpatient or outpatient setting. AOM was treated in an outpatient setting. Incidence, costs, and health consequences of AOM were restricted to people aged less than 10 years [20]. Vaccination was assumed to reduce the risk of PD due to the serotypes included in the vaccine.

The model was static and did not incorporate dynamic feedbacks (i.e., community immunity effects). Indirect effects of vaccination in older age groups and unvaccinated pediatric population groups due to vaccination of the pediatric population were approximated and assessed in a scenario analysis. A 10-year period was used at the program level to assess the cost-effectiveness of vaccination programs over a policy-relevant time horizon, and a lifetime time horizon was used at the individual level (i.e., all long-term consequences of PD accrued over an individual's lifetime were included). Costs and QALYs were used to calculate ICERs. Costs are in 2022 Canadian dollars and, where necessary, were converted using the Canadian Consumer Price Index [21]. A discount rate of 1.5% was used for costs and outcomes and cost-effectiveness was assessed from both the health system and societal perspectives, consistent with NACI guidelines [15]. The model was constructed and analyzed using R [22].

Probabilistic model estimates were based on 10,000 simulations; for each model simulation, parameters were drawn from distributions, results were calculated for each scenario and summary results across the 10,000 simulations were calculated. A sequential analysis was conducted to compare multiple vaccination strategies. Sequential ICERs were calculated by ordering the strategies from lowest to highest cost and comparing incremental costs and QALYs gained for a given strategy to the next less costly strategy. In the sequential analysis, a strategy is eliminated if there are other strategies that are projected to result in more QALYs gained at lower costs (i.e., the strategy is dominated) or there is a combination of other strategies that would result in more QALYs gained at lower costs, such that the excluded strategy would never be the optimal intervention, regardless of the cost-effectiveness threshold used (i.e., the strategy is subject to extended dominance). Cost-effectiveness acceptability curves were derived from the probabilistic

outputs.

Figure 1. Overview of health states included in the model and possible transitions between health states.



II.2 Model Parameters

Model parameters describing PD epidemiology (Table 5), vaccine characteristics (Table 6), costs (Table 7 and Table 8), and health utilities (Table 9) were obtained from available data and published studies, wherever possible, and by assumption otherwise. Canadian data were used preferentially. Where ranges are specified, model parameters were drawn from distributions for the analysis. Beta distributions were used for probabilities and utilities, and gamma distributions were used for costs.

Data on annual incidence of IPD by age were obtained from the International Circumpolar Surveillance (ICS) program and the Canadian Notifiable Disease System (CNDSS), using rates for the year 2019. Data on annual incidence of CAP and AOM were based on an analysis for the provinces of Ontario and British Columbia [23]. Literature-derived estimates of the proportion of disease attributable to *S. pneumoniae* were used to estimate pneumococcal-attributable disease burden for CAP and AOM [24-27]. The proportion of CAP treated in the outpatient setting was estimated from published studies [28]. The proportion of PD cases attributable to serotypes contained in the vaccines was obtained from Canadian IPD surveillance data; in the base case analysis, this proportion was assumed to be the same for all disease manifestations. Estimates

of case-fatality and risk of long-term sequelae were obtained from the literature [20, 26, 29, 30]. Post-meningitis sequelae were conceptualized as auditory or neurologic sequelae in survivors of meningitis. Post-meningitis sequelae were assumed to be permanent.

A 2+1 immunization schedule was assumed, with coverage of the full series estimated from the childhood National Immunization Coverage Survey [31]. National coverage data for first and second doses were not available; coverage for the first two doses was assumed to be 2.5 percentage points higher than the third, as was observed for the dTaP vaccine [31]. Adverse events following immunization were not included in the model.

Immune responses are lower for Pneu-C-15 and Pneu-C-20 compared to Pneu-C-13 for a number of shared serotypes, but it is not known how this may impact VE; consequently, VE was assumed to be equal to that reported for Pneu-C-13 but extended to include the additional serotypes included in these vaccines. VE for preventing PD due to serotype 3 (ST3) was lower than for other serotypes [8, 32]. VE for IPD was higher than for pCAP and AOM [8, 33, 34]. Full VE was assumed to be reached after completion of the full three dose series, with lower VE achieved after two doses [35]. Vaccine protection was assumed to start after the second dose (at 4 months), resulting in 8 months of protection in the first year of life in vaccinated infants. VE following immunization was assumed to remain constant for 5 years after the last dose, followed by a linear decline to 0 over the subsequent 10 years [36].

Age-specific utilities for the general population aged 18 years and older were based on EQ-5D-5L index scores for the Canadian population [37]. Utilities for the Canadian population aged 6 to 17 were based on the Health Utilities Mark 3 [38]. Utilities for the population aged less than 6 years were assumed equivalent to those for the population aged 6 years. Utility decrements associated with PD were based on a recent review [14].

Hospitalization costs of IPD were estimated using Resource Intensity Weights obtained from the Discharge Abstract Database (DAD, 2015-2019) [39-42] and the cost of a standard hospital stay [43]. IPD cases were defined using ICD-10-CA diagnostic codes from the National Case Definition [44]. Costs of inpatient and outpatient pneumonia were based on attributable costs derived from a retrospective population-based cohort study in Ontario, Canada [28]. Costs of AOM were based on a Canadian randomized controlled trial and administrative data [45, 46]. Costs of long-term post-meningitis sequelae were based on costs of auditory or neurologic complications of bacterial meningitis [47]. Vaccination costs included administration costs [48] and vaccine price. Vaccine prices were estimated from publicly-available US data [49] and an unpublished comparative analysis conducted by the Public Health Agency of Canada of Canadian negotiated vaccine prices to US published contract prices, which suggests that Canadian negotiated vaccine prices are typically 30 to 50% of US contract prices; the base case analysis used a 40% discount rate compared to US contract prices for adults.

For the societal perspective, costs included productivity loss due to illness, long-term disability, and death, caregiver costs, and out-of-pocket medical costs. Productivity loss was estimated using the human capital method [15]. Age-specific labour force participation rates [50] and average employment income were obtained from Statistics Canada [51]. Caregiver wages were estimated based on the average employment income and labour force participation of the population aged 25 to 54 years [51]. For hospitalized pediatric cases, the number of caregivers missed workdays was assumed to be equivalent to length of hospital stay. Additional details about caregiver time are provided in Table 8.

Table 5. Epidemiological parameters

Parameter	Base	Range	Reference
IPD incidence (per 100,000)			
Less than 2 years	14.5		CNDSS 2019; ICS 2019 [52]
2 to 4 years	10.2		
5 to 17 years	2.1		
18 to 49 years	5.2		
50 to 64 years	13.6		
65+ years	23.8		
CAP incidence (per 100,000)			
Less than 5 years	4,991.1		Nasreen et al. 2022 [23]
5 to 17 years	1,249.0		
18 to 39 years	815.9		
40 to 64 years	1,529.9		
65 to 74 years	3,095.7		
75 to 84 years	5,398.1		
85+ years	10,122.7		
AOM incidence (per 100,000)			
Less than 5 years	25,467.6		Nasreen et al. 2022 [23]
5 to 17 years	7,225.9		
18 to 39 years	2,204.4		
40 to 64 years	2,058.6		
65 to 74 years	1,954.7		
75 to 84 years	1,857.4		
85+ years	1,621.4		
Proportion of patients with CAP attributed to *S. pneumoniae* (%)			
Less than 1 year	6.0	5.1-9.1	King 2023; LeBlanc et al. 2022; Pneumonia Etiology Research for Child Health (PERCH) Study Group 2019 [24-26]
1 to 15 years	12.0	10.1-18.2	
16 to 49 years	19.5	17.3-21.7	
50 to 64 years	19.0	17.3-20.7	
65+ years	11.2	10.4-12.1	
Proportion of patients with AOM attributed to *S. pneumoniae* (%)			
Less than 18 years	17	14-22	Kim et al. 2017; King 2023 [24, 27]
Proportion of patients with CAP managed in inpatient setting (%)			
Less than 65 years	4.6	2.2-9.3	O'Reilly et al. 2023 [28]
65+ years	12.3	7.9-18.6	
Proportion of patients with IPD with meningitis (%)			
Less than 1 year	16.9	13.3-21.1	Morrow et al. 2007 [20]
1 to 4 years	4.6	3.0-6.8	
5 to 9 years	8.7	4.1-15.9	
10 to 19 years	8.5	5.1-13.3	
20 to 64 years	5.1	3.9-6.4	
65+ years	3.1	2.2-4.1	
Proportion of patients with meningitis with long-term post-meningitis sequelae (%)			
Neurologic sequelae	12.2	5.3-19.1	Jit 2010 [29]
Hearing loss	8.2	4.5-11.9	
Proportion of patients with AOM with ear tube placement (%)			
Less than 10 years	6	4-12	Canadian Institute for Health Information 2020; Chuck et al. 2010; Nasreen et al 2022; Assumption [23, 45, 53]
Case fatality (%)			
IPD			Wijayasri et al. 2019 [30]
Less than 1 year	11.8	11.2-12.3	
1 to 4 years	1.6	0.8 – 2.7	

5 to 49 years	5.7	4.9 – 6.7	
50 to 64 years	10.9	9.9-12	
65+ years	17.2	16.2-18.3	
pCAP (inpatient)			LeBlanc et al. 2022; Morrow et al. 2007; Assumption [20, 26]
Less than 10 years	1.0	0.3-3.1	
10 to 15 years	1.6	0.6-4.3	
16 to 49 years	3.8	1.7-7.0	
50 to 64 years	4.8	2.7-7.1	
65+ years	9.9	7.7-12.3	
Vaccine-type serotype distribution (%)			
less than 2 years			National Microbiology Laboratory 2019 [52]
ST3	8		
Pneu-C-13/non-ST3	9		
Pneu-C-15/non-Pneu-C-13	21		
Pneu-C-20/non-Pneu-C-15	19		
NVT	43		
2 to 4 years			
ST3	11		
Pneu-C-13/non-ST3	16		
Pneu-C-15/non-Pneu-C-13	16		
Pneu-C-20/non-Pneu-C-15	23		
NVT	33		
5 to 17 years			
ST3	8		
Pneu-C-13/non-ST3	23		
Pneu-C-15/non-Pneu-C-13	20		
Pneu-C-20/non-Pneu-C-15	14		
NVT	35		
18 to 49 years			
ST3	10		
Pneu-C-13/non-ST3	32		
Pneu-C-15/non-Pneu-C-13	11		
Pneu-C-20/non-Pneu-C-15	21		
NVT	26		
50 to 64 years			
ST3	12		
Pneu-C-13/non-ST3	32		
Pneu-C-15/non-Pneu-C-13	11		
Pneu-C-20/non-Pneu-C-15	21		
NVT	26		
65+ years			
ST3	13		
Pneu-C-13/non-ST3	16		
Pneu-C-15/non-Pneu-C-13	15		
Pneu-C-20/non-Pneu-C-15	14		
NVT	42		

Table 6. Vaccine characteristics

Parameter	Base	Range	Reference
Vaccination coverage (%)			
2 doses	87.0		Assumption
2+1 doses	84.5		Childhood National Immunization Coverage Survey (cNICS) 2022 [31]
Pneu-C effectiveness (%)*			
2+1 doses			
VT-IPD	85	67-96	Farrar et al 2022; Prasad et al 2023; Assumption [8, 32]
ST3-IPD	33	10-66	Farrar et al 2022; Prasad et al 2023; Assumption [8, 32]
VT-CAP	64	50-72	Prasad et al 2023; Stoecker 2023; Assumption (based on adult data for relative VE for IPD vs CAP) [8, 34]
ST3-CAP	25	19-28	Assumption (based on IPD)
VT-AOM	54	40-64	Eskola 2001 [33]
ST3-AOM	21	15-25	Assumption (based on IPD)
2 doses			
% of VE achieved with first 2 doses of series	75	60-90	Andrews et al 2014; Assumption [54]
Duration of protection			
Pneu-C	15 years: stable for 5 years, linear decline to 0 over 10 years		Prasad et al. 2023 [8]

*VT refers to VE for preventing vaccine-type disease, excluding serotype 3 (ST3). Lower VE estimates were assumed for prevention of ST3 disease, as indicated.

Table 7. Direct cost parameters

Parameter	Base ($)	Range ($)	Reference
Cost of vaccine administration	16.77	12.58-20.96	O'Reilly et al. 2017 [55]
Cost per dose of vaccine			
Pneu-C-13	71.50		Centers for Disease Control and Prevention; Assumption [49]
Pneu-C-15	78.10 (9.2% higher than Pneu-C-13)	72.2-87.9 (1-23% higher than Pneu-C-13)	
Pneu-C-20	90.10 (26.1% higher than Pneu-C-13)	78.6-107.2 (10-50% higher than Pneu-C-13)	
Cost per patient with IPD			
Less than 5 years	20,468	17,422-23,755	DAD 2015-2019 [39-42]
5 to 17 years	14,717	12,510-17,100	
18 to 49 years	28,812	26,559- 31,155	
50 to 64 years	29,146	27,363- 30,984	
65 to 74 years	28,955	26,727- 31,271	
75+ years	21,501	20,001-23,054	
Cost per patient with CAP managed in inpatient setting			
Less than 18 years	7,345	7,189-7,545	O'Reilly et al. 2023 [28]
18 to 64 years	14,185	13,708-14,686	
65+	14,179	13,931-14,433	
Cost per patient with CAP managed in outpatient setting			
Less than 18 years	450	438–461	O'Reilly et al. 2023 [28]
18 to 64 years	1,187	1,154–1,221	
65+	3,343	3,283–3,400	
Cost per AOM case, excluding ear tube placement			
Less than 2 years	260	258-301	Gaboury et al. 2010; Assumption [46]
2 to 9 years	178	148-207	
Cost of surgery for ear tube placement	1,790	1,340-2,240*	Canadian Institute for Health Information 2020 [45]
Cost of care for patients with post-meningitis sequelae (per year)			
Annual cost of care for those with auditory sequelae	2,783	2,087-3,479*	Christensen et al. 2014 [47]
Annual cost of care for those with neurologic sequelae	9,262	6,947-11,578*	Christensen et al. 2014 [47]
Out-of-pocket costs			
Medication, less than 65 years	18.10	13.06-22.60	American Academy of Pediatrics 2021; Metlay et al. 2019; Ontario Ministry of Health 2022; Patented Medicine Prices Review Board Canada 2019-2020 [56-59]
Transportation to inpatient care	139	29 – 333	Canada Revenue Agency 2022; Colbert 2020; DAD 2015-2019 [39-42, 60, 61]
Transportation to outpatient care	3.70	2.80 – 4.60*	Canada Revenue Agency 2022; Pong and Pitblado 2005 [61, 62]

*Range defined as defined as ±25% of the base value

Table 8. Indirect cost parameters

Parameter	Base	Range	Reference
Workdays lost (16+ years)			
Inpatient IPD or CAP	15	9-29	Pasquale et al. 2019 [63]
Outpatient CAP	5.4	1.8-6.3	
Reduction in employment in patients with post-meningitis sequelae (%)			
Auditory sequelae	25	15-35	Bizier et al. 2016; Jiang et al. 2012 [64, 65]
Neurologic sequelae	98	75-100	Jiang et al. 2012; Assumption [65]
Caregiver workdays lost			
IPD			
Less than 5 years	11.2	9.4-13.0	DAD 2015-2019 [39-42]
5 to 15 years	9.9	7.8-12.0	
16+ years	5.4	1.5-10.8	Wyrwich et al. 2015 [66]
Inpatient CAP			
Less than 5 years	4.2	4.2-4.3	DAD 2015-2019 [39-42]
5 to 15 years	5.0	7.8-12.0	
16+ years	5.4	1.5-10.8	Wyrwich et al. 2015 [66]
Outpatient CAP			
Less than 16 years	5.4	1.8-6.3	Pasquale et al. 2019; Assumption [63]
16+ years	1.1	1.0-1.2	Dubé et al. 2011 [67]
AOM			
AOM	1.3	0.8-1.7	Barber et al. 2014; Dubé et al. 2011 [67, 68]
Ear tube placement	2.1		Petit et al. 2003 [69]
Sequelae			
Auditory sequelae (annual)	0		Assumption
Neurologic sequelae (annual)	190	146-240*	Ganapathy et al. 2015 [70]
Vaccination			
Visit healthcare provider for vaccination	0.5		Assumption
Average employment income ($)			
Age 16+	Age-specific values		Statistics Canada [51]
Caregiver	58,811		Statistics Canada [51]
Labour force participation (%)			
Age 16+	Age-specific values		Statistics Canada [50]
Caregiver (age 25 to 54)	87		Statistics Canada [50]

*Range defined as ±25% of the base value

Table 9. Health utilities and decrements

Parameter	Base	Range	Reference
Background health utility			
Less than 6 years	0.970	0.960-0.980	Molina et al. 2023; Assumption [38]
6 to 11 years	0.950	0.940-0.960	Molina et al. 2023 [38]
12 to 17 years	0.890	0.870-0.910	Yan et al. 2023 [37]
18 to 24 years	0.879	0.863-0.895	Yan et al. 2023 [37]
25 to 34 years	0.881	0.864-0.898	Yan et al. 2023 [37]
35 to 44 years	0.878	0.863-0.893	Yan et al. 2023 [37]
45 to 54 years	0.855	0.838-0.872	Yan et al. 2023 [37]
55 to 64 years	0.839	0.822-0.856	Yan et al. 2023 [37]
65 to 74 years	0.867	0.849-0.885	Yan et al. 2023 [37]
75+ years	0.861	0.835-0.887	Yan et al. 2023 [37]
IPD utility decrement			
Less than 19 years	0.028	0.0165-0.0308	Tang et al. 2022; Assumption [14]
19 to 64 years	0.0533	0.0425-0.0547	
65+ years	0.0745	0.0001-0.0745	
Outpatient CAP utility decrement			
Less than 19 years	0.0004	0.0001-0.0329	Tang et al. 2022 [14]
19 to 64 years	0.0094	0.0001-0.0205	
65+ years	0.0586	0.0271-0.0659	
Inpatient CAP utility decrement			
Less than 19 years	0.0105	0.001-0.0155	Tang et al. 2022; Assumption [14]
19 to 64 years	0.0396	0.0001-0.168	
65+ years	0.1154	0.0068-0.290	
AOM utility decrement			
Less than 10 years	0.0016	0-0.146	Tang et al 2022 [14]
Auditory sequelae utility decrement (per year)			
Less than 19 years	0.214	0.070-0.720	Tang et al. 2022 [14]
19+ years	0.365	0.273-0.418	Tang et al. 2022; Assumption [14]
Neurologic sequelae utility decrement (per year)			
Less than 19 years	0.246	0.160-0.490	Tang et al. 2022 [14]
19+ years	0.528	0.220-0.783	Tang et al. 2022; Assumption [14]

II.3 Sensitivity and Scenario Analyses

Sensitivity of the results to individual model parameters was examined in a one-way sensitivity analysis, which was conducted by applying a polynomial regression metamodel to the model probabilistic outputs [71]. Briefly, for each parameter, a regression model was fit by treating costs and QALYs as dependent variables and the parameter of interest as the independent variable, allowing for the estimation of outcome values across a range of values for each parameter, conditional on the average value for all other parameters. This analysis was conducted for all relevant parameters. To allow for a comparison of results for all three vaccines simultaneously, the optimal strategy across parameter ranges was evaluated at cost-effectiveness thresholds of $30,000 and $60,000 per QALY. Results for this analysis were restricted to the most influential parameters for each vaccine comparison.

Given uncertainty in vaccine price, a two-way sensitivity analysis of vaccine price was conducted by varying the incremental increases in price for Pneu-C-15 and Pneu-C-20 compared to Pneu-C-13. The incremental prices for Pneu-C-15 and Pneu-C-20 were varied as percent increases (ranging from 0 to 50% in 5% increments) relative to the assumed Pneu-C-13 price. The price per dose of Pneu-C-15 or Pneu-C-20 was calculated as: Pneu-C-13 price x (1 + incremental increase). For instance, for a price per dose of Pneu-C-13 of $71.50 and incremental increase for Pneu-C-15 of 10%, the price of Pneu-C-15 would be $78.65 per dose.

The impact of lower VE for Pneu-C-15 and Pneu-C-20 relative to Pneu-C-13 was also explored in a two-way sensitivity analysis; for this analysis, VE for all outcomes was varied from 80 to 100% of the assumed VE for Pneu-C-13. Data on PD burden used in the model represent observed cases in the presence of a mature Pneu-C-13 pediatric vaccination program. To enable an exploration of differential VE for Pneu-C-15 and Pneu-C-20 in sensitivity analysis, the incidence of PD outcomes in the absence of vaccination in the pediatric population was estimated. These calculations only considered the direct effects of vaccination and did not account for replacement with serotypes not contained in Pneu-C-13. The adjusted incidence for PD due to serotypes contained in Pneu-C-13 was calculated as:

> Annual incidence without vaccination = reported annual incidence with vaccination / (1- coverage_full * VE_full – coverage_partial * VE_partial),

where coverage_full and coverage_partial represent population coverage of the full or partial vaccine series, and VE_full and VE_partial represent VE after completion of the full or partial series, respectively. This adjustment was only applied to age groups eligible to receive the new conjugate vaccines (i.e., Pneu-C-15 and Pneu-C-20). For all other age groups, unadjusted estimates of PD incidence were used.

The following scenario analyses were conducted, with associated parameters, where relevant, provided in Table 10:

i. Inclusion of indirect effects

Incidence of PD associated with serotypes unique to Pneu-C-15 or Pneu-C-20 were decreased for all ages to approximate indirect effects of a pediatric vaccination program, as has been previously observed with introduction of pneumococcal conjugate vaccines. Following the introduction of Pneu-C-13, one multi-country study that included Canada reported a 60 to 90% decrease in IPD incidence due to the additional serotypes contained in Pneu-C-13 vs. Pneu-C-7 in the population aged less than 5 years, with incidence stabilizing after 3 to 4 years [72]. In adults aged 65 and older, a corresponding 60-80% decrease in IPD attributable to the extra Pneu-C-13 serotypes was observed, with the reduction reaching a steady state after 4 to 5 years [72]. Indirect

effects were conservatively modelled as an exponential decline in PD incidence from unique Pneu-C-15 or Pneu-C-20 serotypes by up to 50% over 5 to 10 years, starting one year after initiation of the Pneu-C-15 or Pneu-C-20 pediatric program. Potential serotype replacement was not modelled**.**

ii. Higher PD incidence and higher direct costs

A scenario analysis was conducted to evaluate the impact of alternate pediatric vaccination strategies in a setting of higher pneumococcal disease incidence and higher costs associated with medical care, which could better reflect realities for some communities, particularly in Northern Canada. To develop a realistic high-incidence, high-cost scenario analysis, relative rates of IPD in the North compared to all of Canada were estimated from ICS and CNDS surveillance data. These relative rates were applied to the base case estimates of IPD, pCAP, and AOM incidence. The relative increase in costs for inpatient and outpatient medical care in the North compared to all of Canada were based on data for adults [(73)] and applied to the base case costs. Note that the higher rates and costs were applied to the base case model population (reflective of the entire Canadian population) to provide a generalized comparison of differences in cost-effectiveness relative to the base case results that could be applicable to jurisdictions across Canada experiencing higher PD burden and direct costs.

iii. Lower incidence of CAP and AOM

Annual CAP and AOM incidence was based on data from Ontario and British Columbia [(23)]. Estimates of CAP and AOM were generally higher for Ontario than British Columbia, which may have been partially due to non-availability of data on emergency department visits in British Columbia. The base case analysis used Ontario estimates and the lower estimates for British Columbia were used in a scenario analysis.

iv. Alternate serotype distribution for AOM cases

Due to limited availability of Canadian data for non-invasive PD outcomes, the base case analysis assumed the same serotype distributions for non-invasive outcomes as for IPD. This assumption was tested using serotype distribution data from AOM cases obtained from a US pediatric population where Pneu-C-13 had been routinely used [(74)]. The AOM-specific data had lower estimates of disease attributable to the unique serotypes contained in Pneu-C-13 and Pneu-C-15, such that the conjugate vaccines would be projected to prevent fewer AOM cases than in the base case analysis.

v. More rapid waning of VE

The impact of faster waning of VE was modelled by assuming that after 1 year at maximum vaccine protection following receipt of the vaccine dose, VE waned linearly to 0 over a 10-year period. By contrast, the base case assumed that maximum VE was sustained for 5 years before declining linearly to 0 over a 10-year period.

Results for all sensitivity and scenario analyses are presented for the health system perspective but key results for the societal perspective are also provided, where relevant.

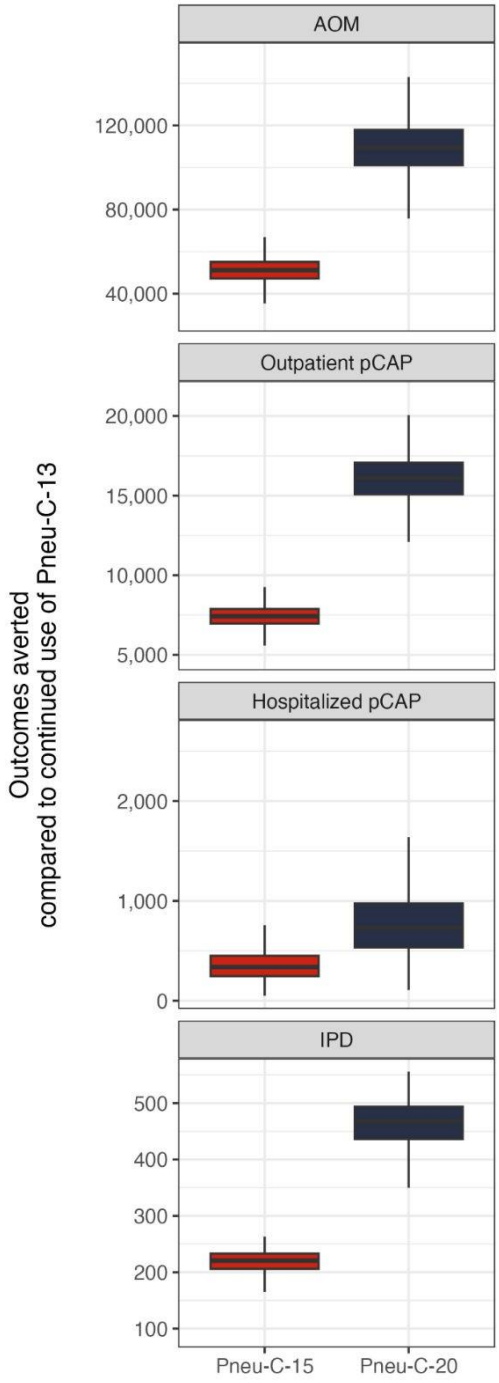
Table 10. Parameters for scenario analyses

Parameter	Base	Reference
CAP incidence (per 100,000)		
Less than 5 years	2464.1	Nasreen et al. 2022 [23]
5 to 17 years	945.2	
18 to 39 years	634.8	
40 to 64 years	1183.8	
65 to 74 years	2543.7	
75 to 84 years	4800.3	
85+ years	10174.5	
AOM incidence (per 100,000)		
Less than 5 years	13603.8	Nasreen et al. 2022 [23]
5 to 17 years	6205.7	
18 to 39 years	1734.8	
40 to 64 years	1654.7	
65 to 74 years	1686.7	
75 to 84 years	1649.8	
85+ years	1504.6	
Vaccine-type serotype distribution for AOM (%)		
ST3	6.0	Kaur et al. 2022 [74]
Pneu-C-13/non-ST3	3.0	
Pneu-C-15/non-Pneu-C-13	8.2	
Pneu-C-20/non-Pneu-C-15	23.5	
NVT	59.3	
Relative risk of PD in Northern Canada compared to all of Canada		
Less than 2 years	6.8	CNDSS 2019; ICS 2015-2019 [52]
2 to 4 years	0.9	
5 to 17 years	3.9	
18 to 49 years	2.1	
50 to 64 years	2.1	
65+ years	2.4	
Relative cost increase in Northern Canada compared to all of Canada		
Inpatient case	1.8	NACI [73]
Outpatient case	1.2	NACI [73]
Travel for outpatient case	33	NACI [73]

II.4 Base Case Results

Health outcomes averted compared to continued use of Pneu-C-13 in the pediatric population are displayed graphically in Figure 2. Both Pneu-C-15 and Pneu-C-20 prevented more cases of IPD, pCAP, and AOM than Pneu-C-13. Use of Pneu-C-20 was projected to avert more cases of IPD, pCAP, and AOM than Pneu-C-15. For instance, compared to Pneu-C-13, use of Pneu-C-20 was estimated to avert a median of 470 additional cases of IPD compared to 220 cases averted with Pneu-C-15 over the 10-year study period.

Figure 2. Health outcomes averted outcomes with the use of Pneu-C-15 or Pneu-C-20 compared to Pneu-C-13



Outcomes are summed over a 10-year period and are compared to expected incidence in pediatric cohorts vaccinated with Pneu-C-13. Results are shown for 10,000 model simulations. The lower, middle, and upper hinges of the box indicate the 25th, 50th, and 75th percentiles, respectively, with the whiskers extending to the smallest and largest values up to 1.5 times the interquartile range. Note that y-axes vary across graphs. For reference, the median total number of outcomes projected in the entire population (all ages, not just the pediatric cohort) over the 10-year period with continued use of Pneu-C-13 was: 1,008,780; 1,039,280; 82,910; and 39,970 for AOM, outpatient pCAP, hospitalized pCAP, and IPD, respectively. AOM, acute otitis media; pCAP, pneumococcal community acquired pneumonia; IPD, invasive pneumococcal disease.

Mean costs, QALYs, and ICERs from the base case for the health system and societal perspective are presented in Table 11. ICERs are presented as sequential ICERs, which compare all possible vaccination strategies. For reference, a direct estimate of the costs per QALY gained when each vaccination strategy is directly compared to current recommendations (Pneu-C-13) is also provided. In the sequential analysis, strategies with ICERs considered cost-effective by commonly used thresholds when compared to the current recommendation are excluded if there are other strategies that represent better value for money, regardless of the cost-effectiveness threshold used.

Figure 3 shows the proportion of model simulations for which each strategy was the optimal strategy over a range of cost-effectiveness threshold values. For the health system perspective, Pneu-C-15 was the optimal strategy at threshold ranges of $43,000 to $127,000. Above $127,000, Pneu-C-20 was the optimal strategy. For the societal perspective, Pneu-C-15 was the optimal strategy at threshold ranges of $3,000 to $86,000, with Pneu-C-20 the optimal strategy at thresholds above $86,000.

Table 11. Base case: discounted quality-adjusted life years lost, mean discounted costs, and incremental cost-effectiveness ratios for the different vaccination strategies

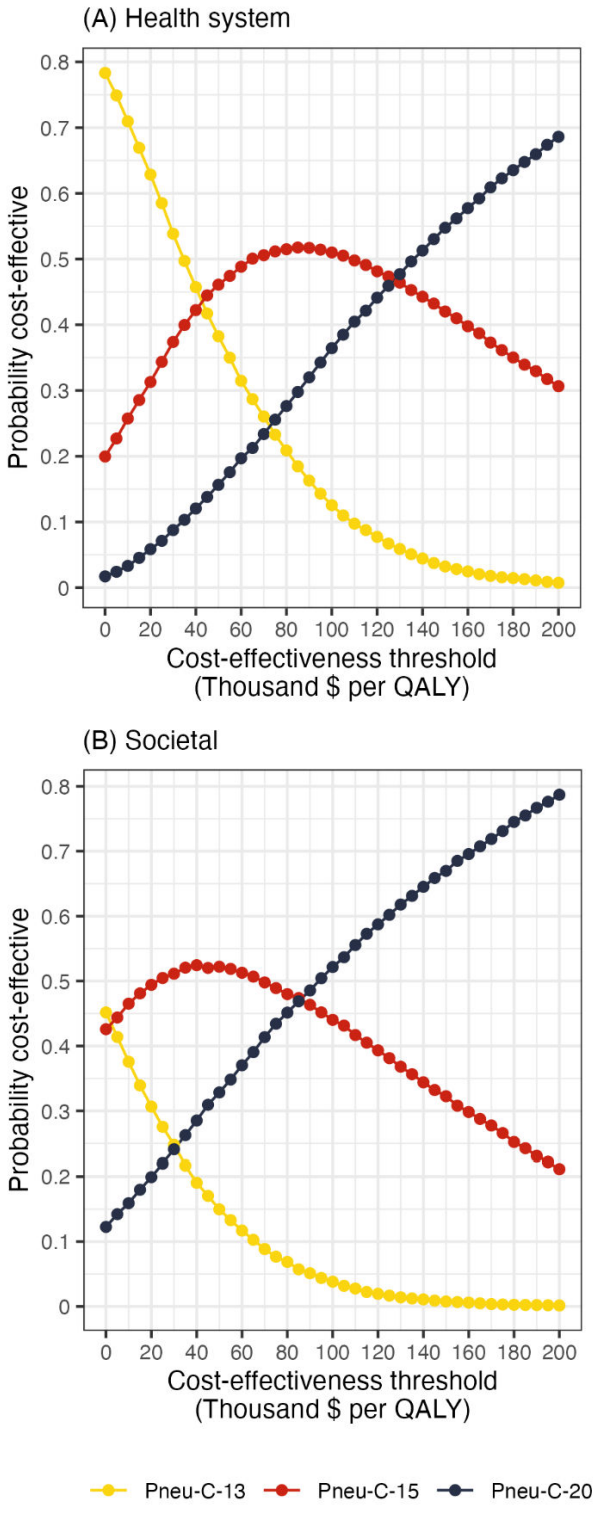
(A) Health system perspective

Strategy	Effect (Discounted QALYs lost)	Cost (Discounted $, millions)	Sequential ICER ($/QALY)	ICER (vs. Pneu-C-13) ($/QALY)
Pneu-C-13	229,769	4,945	--	--
Pneu-C-15	229,272	4,975	58,823	58,823
Pneu-C-20	228,730	5,048	135,289	98,707

(B) Societal perspective

Strategy	Effect (Discounted QALYs lost)	Cost (Discounted $, millions)	Sequential ICER ($/QALY)	ICER (vs. Pneu-C-13) ($/QALY)
Pneu-C-13	229,769	432,243	--	--
Pneu-C-15	229,272	432,252	18,272	18,272
Pneu-C-20	228,730	432,303	93,416	57,466

Figure 3. Percent of simulations for which each strategy was the optimal strategy for a given cost- effectiveness threshold, for the (A) health system and (B) societal perspectives

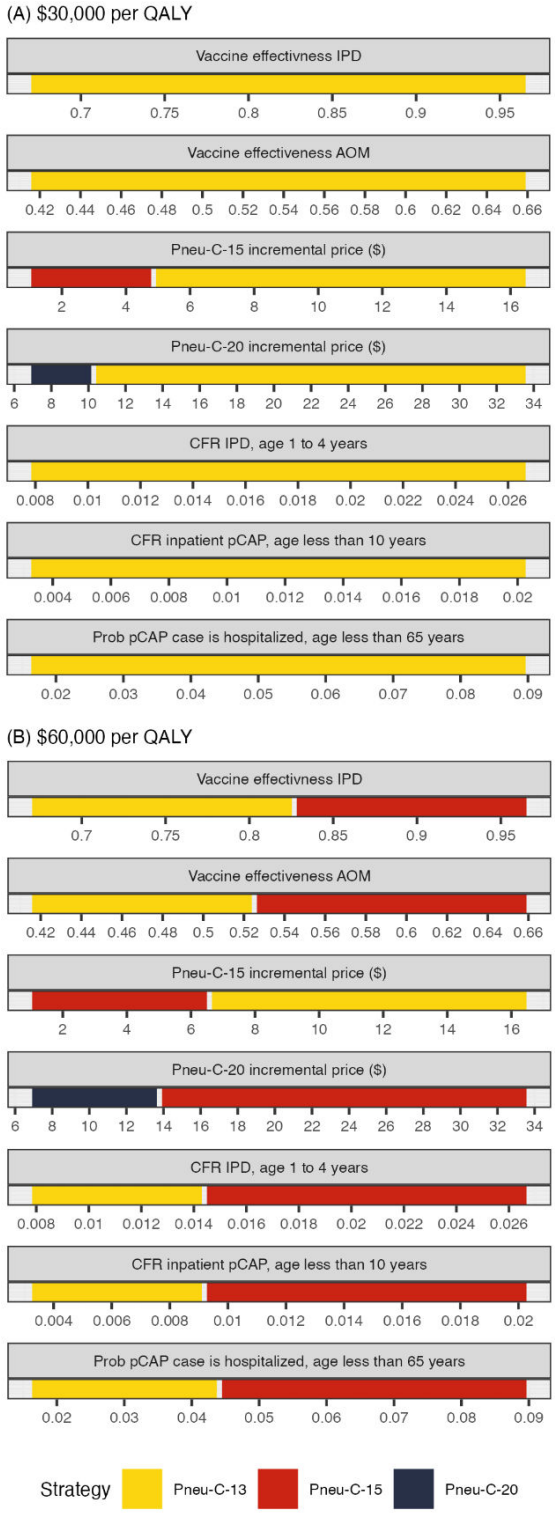


II.5 Sensitivity and Scenario Analyses Results

Unless otherwise indicated, results for sensitivity and scenario analyses are presented for the health system perspective. The impact of varying key model parameters one at a time over the ranges listed in Table 5 to Table 9 was evaluated in a one-way sensitivity analysis to identify the parameters that were most influential on estimated ICERs. For these most influential parameters, the vaccination strategy that would be most cost-effective at thresholds of $30,000 or $60,000 per QALY was identified across each parameter range (Figure 4). At $30,000 per QALY, the most cost-effective strategy was Pneu-C-13, except when the incremental price of a dose of Pneu-C-15 or Pneu-C-20 was relatively low. When the price of Pneu-C-15 was less than $5 (7%) more than Pneu-C-13 per dose, it was the most cost-effective option. When the price of Pneu-C-20 was less than $10 (14%) more than Pneu-C-13, it was the most cost-effective option. The optimal strategy was more variable when a $60,000 per QALY threshold was used, with Pneu-C-15 more frequently identified as the most cost-effective strategy. At the $60,000 per QALY threshold, Pneu-C-15 was the preferred strategy when VE for preventing IPD or AOM was higher, when the CFR for patients with IPD or pCAP was higher, or when the probability a patient with pCAP requiring hospitalization was higher. At the $60,000 per QALY threshold, the preferred strategy remained sensitive to the incremental price per dose of Pneu-C-15 or Pneu-C-20.

For the societal perspective (results not shown), at $30,000 per QALY, Pneu-C-15 was generally the most cost-effective strategy, with the following exceptions: price per dose of Pneu-C-20 less than $14 (20%) more than Pneu-C-13 (Pneu-C-20 was the most cost-effective option); price per dose of Pneu-C-15 was more than $7 (10%) more than the price of Pneu-C-13 (Pneu-C-13 was the most cost-effective option); or VE for preventing AOM was less than 44% (Pneu-C-13 was the most cost-effective option). Pneu-C-15 was the most cost-effective option at $60,000 per QALY using the societal perspective, unless the incremental cost of Pneu-C-20 was less than $16 per dose (23%) more than Pneu-C-13 or the incremental price per dose of Pneu-C-15 was more than $9 (12%) more than Pneu-C-13; in both of these cases, Pneu-C-20 was the most cost- effective strategy.

Figure 4. One-way sensitivity analysis comparing Pneu-C-13, Pneu-C-15, and Pneu-C-20 at cost-effectiveness thresholds of (A) $30,000 and (B) $60,000 per QALY



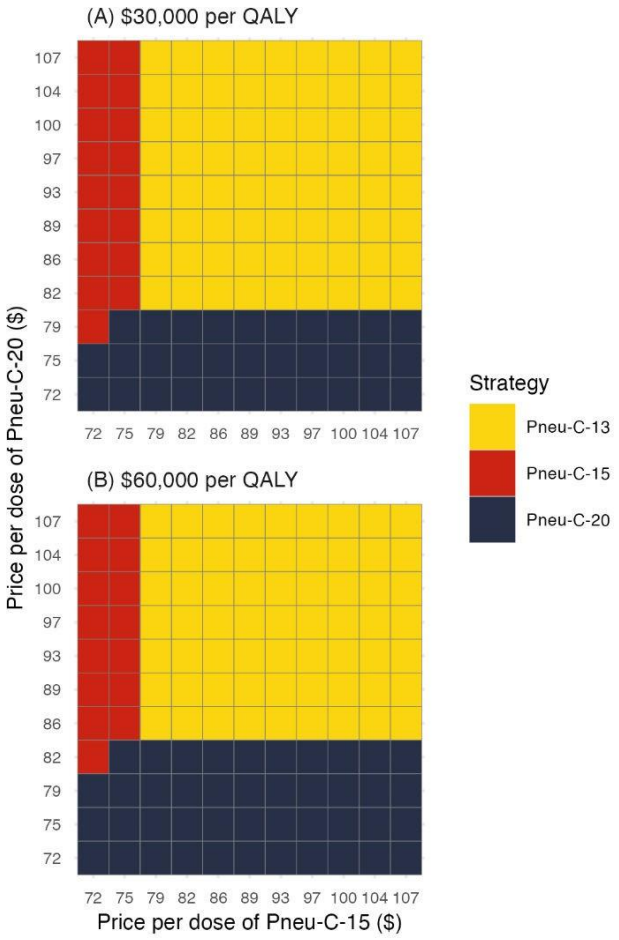
Each parameter was varied across the indicated range. The most cost-effective vaccination strategy for the indicated cost-effectiveness threshold and parameter value is represented by the color of the bar. Results are shown for the health system perspective. Prob=probability.

The influence of vaccine prices on results was further examined in a two-way sensitivity analysis, with prices per dose of Pneu-C-15 and Pneu-C-20 varied while keeping the price of Pneu-C-13 constant at $71.50 per dose (Figure 5, health system perspective). For a $30,000 per QALY cost-effectiveness threshold, when the prices of Pneu-C-15 and Pneu-C-20 were greater than approximately $75 and $79 (5% and 10% higher than Pneu-C-13), respectively, Pneu-C-13 was the optimal strategy. For lower vaccine prices, when Pneu-C-15 and Pneu-C-20 were priced equivalently, Pneu-C-20 was the optimal strategy. Pneu-C-15 was the optimal strategy if the price per dose was up to $75 (5% higher than Pneu-C-13) and Pneu-C-20 was priced at $79-82 (10-15% higher than Pneu-C-13). Pneu-C-20 was the optimal strategy when priced at up to $79 (10% higher than Pneu-C-13) per dose and the price of Pneu-C-15 was $75 (5% higher than Pneu-C-13) or less.

Using a $60,000 per QALY cost-effectiveness threshold, Pneu-C-13 was the optimal strategy when the prices of Pneu-C-15 and Pneu-C-20 were greater than approximately $75 and $82 (5% and 15% higher than Pneu-C-13), respectively. When the prices for Pneu-C-15 and Pneu-C-20 were $75 or $82 (5% or 15% higher than Pneu-C-13) or less, respectively, the optimal strategy was either Pneu-C-15 or Pneu-C-20, with the optimal strategy depending on the difference in price between the two vaccines.

For the societal perspective, Pneu-C-15 or Pneu-C-20 could be the optimal strategy at a price of up to $79 or $86 (10% or 20% higher than Pneu-C-13), respectively, using a $30,000 per QALY threshold. For a $60,000 threshold and societal perspective, Pneu-C-15 and Pneu-C-20 could be the optimal strategy at prices of up to $79 and $89 (10% and 25% higher than Pneu-C-13), respectively (data not shown). As with the health system perspective, at lower vaccine prices, when Pneu-C-15 and Pneu-C-20 were priced equivalently, Pneu-C-20 was the optimal strategy.

Figure 5. Sensitivity analysis of vaccine costs. ICERs were calculated for a range of prices per dose for Pneu-C-15 and Pneu-C-20 ($71.50-107.25 or 0-150% of the price of Pneu-C-13) and the optimal strategy was identified for cost-effectiveness thresholds of (A) $30,000 and (B) $60,000 per QALY

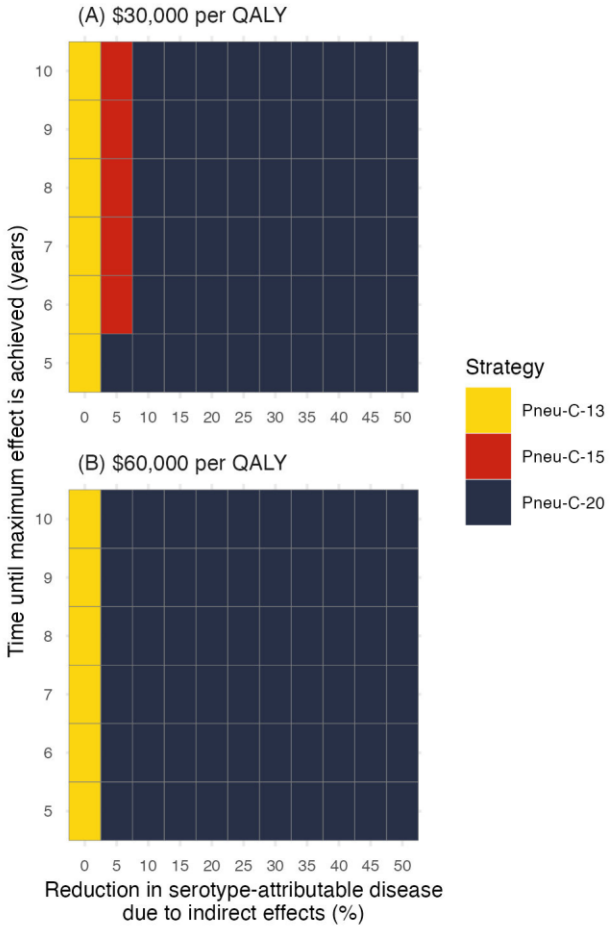


Results are based on a deterministic analysis and are shown for the health system perspective. The base case analysis assumed prices of $78.10 for Pneu-C-15 and $90.10 for Pneu-C-20.

A sensitivity analysis on VE demonstrated that ICERs would increase if VE is lower for Pneu-C-15 or Pneu-C-20 than Pneu-C-13, compared to the base case estimates of equal VE for all vaccines (results not shown). As an example, for Pneu-C-15, the ICER increased from approximately $60,000 per QALY if VE was equal to approximately $90,000 per QALY if Pneu-C-15 was 80% as effective at preventing PD outcomes attributable to the serotypes contained in the vaccines as Pneu-C-13.

Compared to results in the absence of indirect effects, a reduction in PD in the population (all ages) not receiving the vaccine resulted in a substantial reduction in ICERs (Figure 6). For instance, a 5% reduction in PD caused by the additional serotypes contained in Pneu-C-15 over a 6-year period would result in Pneu-C-15 being the optimal strategy at a cost-effectiveness threshold of $30,000 per QALY. Assuming a 10% or more reduction over 5 years would result in Pneu-C-20 being the preferred strategy at a $30,000 per QALY threshold. For the societal perspective, even smaller indirect effects would result in Pneu-C-15 or Pneu-C-20 being the optimal strategy (not shown).

Figure 6. Impact of indirect effects from a pediatric vaccination program. A two-way sensitivity analysis evaluated the cost-effectiveness of Pneu-C-13, Pneu-C-15, and Pneu-C-20 for a range of population-wide reductions in pneumococcal disease due to the additional vaccine-containing serotypes (x-axis) and times for the maximum reduction in pneumococcal disease to occur (y-axis)



The base case results, which assume no indirect effects, are represented by a 0% reduction. Results are based on a deterministic analysis and are shown for the health system perspective. The most cost-effective vaccination strategy for cost-effectiveness thresholds of (A) $30,000 and (B) $60,000 per QALY for each combination of parameter values is represented by the color of the square. Results are shown for the health system perspective.

Results for the additional scenario analyses are summarized in Table 12 for the health system perspective. Compared to the base case analysis, the assumption of lower incidence of CAP and AOM, an alternate serotype distribution for AOM resulting in reduced proportion of cases attributable to serotypes contained in the vaccines, or more rapid waning of VE resulted in increased ICERs. The assumption of higher PD incidence and higher medical costs resulted in Pneu-C-20 dominating (less costly and fewer QALYs lost) the other vaccines.

Similar trends were observed for the societal perspective, with Pneu-C-20 dominating other strategies in a higher burden and higher medical cost scenario and higher ICERs than the base case when there was lower incidence of CAP and AOM, an alternate serotype distribution for patients with AOM, or more rapid waning of VE (results not shown).

Table 12. Scenario analyses: discounted quality-adjust life years lost, mean discounted costs, and incremental cost-effectiveness ratios (health system perspective)

(A) Higher pneumococcal disease incidence and higher direct costs

Strategy	Effect (Discounted QALYs lost)	Cost (Discounted $, millions)	Sequential ICER ($/QALY)	ICER (vs. Pneu-C-13) ($/QALY)
Pneu-C-20	15,794	541,539	--	Dominates Pneu-C-13
Pneu-C-15	15,819	543,513	Dominated by Pneu-C-20	Dominates Pneu-C-13
Pneu-C-13	15,897	545,613	Dominated by Pneu-C-20	--

(B) Lower incidence of CAP and AOM

Strategy	Effect (Discounted QALYs lost)	Cost (Discounted $, millions)	Sequential ICER ($/QALY)	ICER (vs. Pneu-C-13) ($/QALY)
Pneu-C-13	4,386	208,709	--	--
Pneu-C-15	4,425	208,319	100,060	100,060
Pneu-C-20	4,508	207,904	200,691	151,949

(C) Alternate serotype distribution for patients with AOM

Strategy	Effect (Discounted QALYs lost)	Cost (Discounted $, millions)	Sequential ICER ($/QALY)	ICER (vs. Pneu-C-13) ($/QALY)
Pneu-C-13	4,506	209,577	--	--
Pneu-C-15	4,548	209,195	107,944	107,944
Pneu-C-20	4,621	208,732	157,982	135,372

(D) More rapid waning of VE

Strategy	Effect (Discounted QALYs lost)	Cost (Discounted $, millions)	Sequential ICER ($/QALY)	ICER (vs. Pneu-C-13) ($/QALY)
Pneu-C-13	4,944	229,952	--	--
Pneu-C-15	4,977	229,511	75,577	75,577
Pneu-C-20	5,053	229,033	157,972	118,493

II.6 Limitations

The current economic evaluation focused on children who were receiving pneumococcal vaccination for the first time. Estimates of PD burden included children with IPD risk factors but vaccination recommendations specifically for children with IPD risk factors were not considered in this evaluation. Vaccination of children who had initiated their vaccination with a lower valency vaccine or use of higher valency vaccines to complement protection achieved with lower valence vaccines was also not evaluated. The 10-year time horizon of the model may also have underestimated the full impact of vaccination, since vaccine protection would not have waned completely in vaccinated individuals at the end of the analytic time period.

Population-wide reductions in PD due to indirect effects associated with pediatric use of Pneu-C-15 and Pneu-C-20 are uncertain and were explored in a scenario analysis. This analysis did not include serotype replacement, which has been observed with the introduction of other pneumococcal conjugate vaccines in Canada [30, 75] and may be expected to counteract potential

herd effects. The magnitude of the indirect effects considered was conservative compared to reported effects following the introduction of Pneu-C-13 [72].

As with all model-based analyses, simplifying assumptions were made. Not all health outcomes associated with pneumococcal disease were included, such as sinusitis and empyema. There was substantial uncertainty related to some key input parameters, including incidence of non-hospitalized pCAP and AOM, the proportion of CAP and AOM caused by *S. pneumoniae*, the serotype distributions for non-invasive disease, VE for non-invasive disease, and durability of vaccine protection. Sensitivity analyses were used to evaluate the impact of these uncertain parameters and were not found to impact the overall findings. Attributable cost data were not available for IPD, AOM, and post-meningitis sequelae, which may result in an overestimate of medical costs in patients experiencing these outcomes.

Although the evaluation included both a health system and societal perspective, societal costs may have been underestimated due to an exclusion of non-medical consumption and education impacts. For example, the impact of hearing loss caused by otitis media on development of communication disorders and educational performance is not well characterized [76]. Data related to long-term costs associated with post-meningitis sequelae were limited.

II.7 Conclusions

Use of Pneu-C-20, and to a lesser extent, Pneu-C-15, in the pediatric population starting their primary series is projected to reduce pneumococcal disease burden, compared to continued use of Pneu-C-13. Base case sequential ICERs for Pneu-C-15 and Pneu-C-20 were $58,800 and $135,200 per QALY gained, respectively, using the health system perspective. Although Canada does not have a cost-effectiveness threshold, Pneu-C-15 may be considered cost-effective based on some commonly used thresholds [77, 78]. The base case ICER for Pneu-C-20 is above commonly used cost-effectiveness thresholds. Results were sensitive to vaccine price, with lower vaccine prices increasing the cost-effectiveness of both novel vaccines. If use of Pneu-C-15 or Pneu-C-20 in the pediatric population results in a reduction in pneumococcal disease in the rest of the population via indirect effects, ICERs would be substantially reduced. In settings with higher burden and higher medical costs, Pneu-C-20 was projected to dominate the other vaccines. Lower incidence of CAP and AOM in the population, an alternate serotype distribution for AOM resulting in a smaller proportion of patients with AOM due to serotypes contained in the vaccines, or more rapid waning of VE resulted in reduced cost-effectiveness of both Pneu-C-15 and Pneu- C-20.

APPENDIX A.

Table 13. Impact inventory table

Area of Impact	Definitions/Examples	Included in Reference Case?		Comments
		Publicly funded health system perspective	Societal perspective	
Health				
Health outcomes	Individual health outcomes for persons intended for vaccination			
	Mortality	☑	☑	
	Health-related quality of life	☑	☑	
	Safety (i.e., adverse events)	☒	☒	
	Health impacts not captured by QALYs	☒	☒	
	Individual health outcomes for informal caregivers			
	Health-related quality of life	☒	☒	
	Population health outcomes			
	Incidence of infection and disease in vaccinated and unvaccinated individuals	☒	☒	Impact of vaccination on incidence in unvaccinated people not included in reference case but considered in scenario analysis
	Changes in age distribution of individuals who develop infection and disease	☒	☒	
	Emergence of new diseases related to variations of the pathogen (i.e., serotypes, serogroups, strains) or unrelated pathogens that may replace the one(s) targeted by the vaccine	☒	☒	
	Disease eradication	☒	☒	
Publicly funded health system costs	Healthcare costs			
	Publicly funded healthcare services (e.g., physician visits, diagnostic tests, drug treatment where applicable, hospitalization, formal caregiving,[a] rehabilitation in a facility or at home,[a] home care,[a] long-term care in nursing homes[a])	☑	☑	
	Future related and unrelated healthcare costs	☑	☑	Included future healthcare costs for individuals with post-meningitis sequelae

Area of Impact	Definitions/Examples	Included in Reference Case?		Comments
		Publicly funded health system perspective	Societal perspective	
	Public Health costs			
	Program-related costs (e.g., implementation, delivery and recurrent costs including Public Health campaigns and health promotion activities; transaction costs related to introduction of new vaccines or switching between vaccines; costs related to screening, diagnosis, and treatment of disease; epidemiological surveillance, contact tracing, investigation and management of outbreaks)	☒	☒	
	Intervention-related costs (e.g., cost of vaccine doses, distribution such as transportation and cold storage, administration including personnel, wastage and ancillary supplies)	☑	☑	Included cost of vaccine doses and vaccine administration
Healthcare costs NOT funded by the health system	Prescription medications (in some cases)	N/A	☑	
	Formal caregiver services,[a] rehabilitation in a facility or at home,[a] home care,[a] long-term care in nursing homes[a] (in some cases)	N/A	☒	
	Miscellaneous out-of-pocket costs (e.g., non-prescription medications)	N/A	☒	
	Ancillary costs (e.g., private insurance copayments, dental care, vision care, assistive devices, physiotherapy, etc.)	N/A	☒	
Non-Health				
Direct out-of-pocket costs	Transportation costs	N/A	☑	
	Accommodation costs	N/A	☒	
Losses in productivity	Paid work			
	Time off work resulting from vaccine administration, treatment, illness, disability, or death	N/A	☑	
	Presenteeism	N/A	☒	
	Lifetime productivity consequences of childhood disease	N/A	☑	

Area of Impact	Definitions/Examples	Included in Reference Case?		Comments
		Publicly funded health system perspective	Societal perspective	
	Unpaid work			
	Time off work in informal labour market (e.g., volunteering, helping, mentoring) resulting from vaccine administration, treatment, illness, disability, or death	N/A	☒	
	Uncompensated household production (e.g., cooking, cleaning, shopping, raising children, other tasks related to household management)	N/A	☒	
	Informal caregiver productivity			
	Time off work resulting from caring for sick individuals, accompanying individuals to vaccine appointments	N/A	☑	
	Caregiver presenteeism	N/A	☒	
	Macroeconomic consequences			
	Labour supply shocks, widespread business closures	N/A	☒	
Consumption	Future individual non-medical consumption	N/A	☒	
	Changes in household consumption	N/A	☒	
	Health impacts of consumption (e.g., associated with job loss)	N/A	☒	
Education	Level of educational achievement as a result of physical health, mental health, and cognition	N/A	☒	
	Costs of special education needs as a result of illness/disability	N/A	☒	
	Disruptions to learning outcomes (e.g., as a result of school-based vaccine delivery, pediatric disease and disability, or death/disability of a close family member)	N/A	☒	
Social services and community services	Social services and community services (e.g., disability support, programs to improve access to vaccination programs for adults)	N/A	☒	

Area of Impact	Definitions/Examples	Included in Reference Case?		Comments
		Publicly funded health system perspective	Societal perspective	
	Child and Youth Services (e.g., awareness programs, family respite, programs to improve access to vaccination programs for children and youth)	N/A	☒	
Environment	Environmental impact of vaccination programs and comparators from manufacturing, distribution, and implementation (e.g., antibiotic use)	N/A	☒	
	Food and non-food waste	N/A	☒	
	Carbon consumption	N/A	☒	
Other Areas	Consider areas such as housing when applicable	N/A	☒	

[a] Some of these costs may or may not be incurred by the publicly funded health system, depending on the precise nature of these costs and the relevant jurisdiction
Abbreviation: QALY, quality-adjusted life-year

LIST OF ABBREVIATIONS

AOM	Acute otitis media
CAP	Community-acquired pneumonia
CEA	Cost-effectiveness analysis
CFR	Case fatality ratio
CNDSS	Canadian Notifiable Disease Surveillance System
CUE	Cost-utility analysis
DAD	Discharge Abstract Database
IC	Immunocompromising conditions
ICER	Incremental cost-effectiveness ratio
ICS	International Circumpolar Surveillance
IPD	Invasive pneumococcal disease
LY	Life year
NVT	Non-vaccine type
pCAP	Pneumococcal community-acquired pneumonia
PD	Pneumococcal disease
Pneu-C-13	13-valent pneumococcal conjugate vaccine
Pneu-C-15	15-valent conjugate pneumococcal vaccine
Pneu-C-20	20-valent conjugate pneumococcal vaccine
Pneu-P-23	23-valent pneumococcal polysaccharide vaccine
QALY	Quality-adjusted life year
ROC	Rest of Canada
ST3	Serotype 3
US	United States
VE	VE
VT	Vaccine-type

REFERENCES

1. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
2. CADTH. Grey Matters: a practical tool for searching health-related grey literature [Internet]. Ottawa (ON): CADTH Research Information Services; 2019 Apr [cited 2023 Mar 16]. Available from: https://www.cadth.ca/grey-matters-practical-tool-searching-health-related-grey-literature.
3. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. BMC Med. 2022;20(1):23.
4. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews: Checklist for Economic Evaluations [Internet]. Adelaide (SA): The Joanna Briggs Institute; 2017 [cited 2023 Mar 16]. Available from: https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Economic_Evaluations2017_0.pdf.
5. Heyland DK, Kernerman P, Gafni A, Cook DJ. Economic evaluations in the critical care literature: do they help us improve the efficiency of our unit? Crit Care Med. 1996;24(9):1591-8.
6. Purchasing power parities (PPP) (Indicator) [Internet]. OECD Library; 2023 [cited 2023 Mar 31]. Available from: https://www.oecd-ilibrary.org/content/data/1290ee5a-en. .
7. Inflation calculator [Internet]. 2023 [cited 2023 Apr 1]. Available from: https://www.bankofcanada.ca/rates/related/inflation-calculator/.
8. Prasad N, Stoecker C, Xing W, Cho B-H, Leidner AJ, Kobayashi M. Public health impact and cost-effectiveness of 15-valent pneumococcal conjugate vaccine use among the pediatric population of the United States. Vaccine. 2023.
9. Huang M, Hu T, Weaver J, Owusu-Edusei K, Elbasha E. Cost-Effectiveness Analysis of Routine Use of 15-Valent Pneumococcal Conjugate Vaccine in the US Pediatric Population. Vaccines. 2023;11(1).
10. Leidner AJ. Economic analysis and public health impact of PCV15 use among children in the US [slides presented at Advisory Committee on Immunization Practices (ACIP) meeting June 22, 2022] [Internet]. Atlanta (GA): Center for Disease Control and Prevention; 2022 Jun 22 [cited 2023 Mar 14]. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-06-22-23/03-pneumo-leidner-508.pdf.
11. Ryman J, Weaver J, Yee KL, Sachs JR. Predicting effectiveness of the V114 vaccine against invasive pneumococcal disease in children. Expert Rev Vaccines. 2022;21(10):1515-21.
12. Rubin JL, McGarry LJ, Strutton DR, Klugman KP, Pelton SI, Gilmore KE, et al. Public health and economic impact of the 13-valent pneumococcal conjugate vaccine (PCV13) in the United States. Vaccine. 2010;28(48):7634-43.

13. Mangen M-JJ, Rozenbaum MH, Huijts SM, van Werkhoven CH, Postma DF, Atwood M, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J. 2015;46(5):1407-16.

14. Tang Z, Matanock A, Jeon S, Leidner AJ. A review of health-related quality of life associated with pneumococcal disease: pooled estimates by age and type of disease. J Public Health (Oxf). 2022;44(2):e234-e40.

15. National Advisory Committee on Immunization. Guidelines for the economic evaluation of vaccination programs in Canada [Internet]. Ottawa (ON): Public Health Agency of Canada; 2023 [cited 2023 Mar 31]. Available from: https://www.canada.ca/en/public-health/programs/guidelines-economic-evaluation-vaccine-programs-canada-stakeholder-consultation/guidelines-document.html.

16. OECD. Health at a Glance 2023. Paris: OECD Publishing; 2023.

17. Statistics Canada. Table 98-10-0027-01. Age (in single years), average age and median age and gender: Canada and forward sortation areas [Internet]. Ottawa (ON): Statistics Canada; 2021 Sep 21 [cited 2023 Mar 31]. Available from: https://doi.org/10.25318/9810002701-eng.

18. Statistics Canada. Table 13-10-0837-01. Life expectancy and other elements of the complete life table, single-year estimates, Canada, all provinces except Prince Edward Island [Internet]. Ottawa (ON): Statistics Canada; 2022 Jan 24 [cited 2023 Mar 31]. Available from: https://doi.org/10.25318/1310083701-eng.

19. Statistics Canada. Table 17-10-0057-01. Projected population, by projection scenario, age and sex, as of July 1 (x 1,000) [Internet]. Ottawa (ON): Statistics Canada; 2022 Aug 22 [cited 2023 Mar 31]. Available from: https://doi.org/10.25318/1710005701-eng.

20. Morrow A, De Wals P, Petit G, Guay M, Erickson LJ. The burden of pneumococcal disease in the Canadian population before routine use of the seven-valent pneumococcal conjugate vaccine. Can J Infect Dis Med Microbiol. 2007;18(2):121-7.

21. Statistics Canada. Table 18-10-0005-01. Consumer Price Index, annual average, not seasonally adjusted [Internet]. Ottawa (ON): Government of Canada; 2023 Jan 17 [cited 2023 Mar 31]. Avalible from: https://doi.org/10.25318/1810000501-eng.

22. R Core Team. R: A language and environment for statistical computing [Software]. 4.0 ed. Vienna (AT): R Foundation for Statistical Computing; 2020 [cited 2023 Mar 31]. Available from: https://www.r-project.org/.

23. Nasreen S, Wang J, Sadarangani M, Kwong JC, Quach C, Crowcroft NS, et al. Estimating population-based incidence of community-acquired pneumonia and acute otitis media in children and adults in Ontario and British Columbia using health administrative data, 2005–2018: a Canadian Immunisation Research Network (CIRN) study. BMJ Open Respiratory Research. 2022;9(1):e001218.

24. King L. Pediatric outpatient ARI visits and antibiotic use attributable to serotypes in higher valency PCVs. [slides presented at Advisory Committee on Immunization Practices (ACIP) meeting February 22, 2023][Internet]. Atlanta (GA): Center for Disease Control and Prevention; 2023 Feb 22 [cited 2023 Mar 14]. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-22/Pneumococcal-03-King-508.pdf.

25. Pneumonia Etiology Research for Child Health Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet. 2019;394(10200):757-79.

26. LeBlanc JJ, ElSherif M, Ye L, MacKinnon-Cameron D, Ambrose A, Hatchette TF, et al. Recalibrated estimates of non-bacteremic and bacteremic pneumococcal community acquired pneumonia in hospitalized Canadian adults from 2010 to 2017 with addition of an extended spectrum serotype-specific urine antigen detection assay. Vaccine. 2022.

27. Kim SH, Jeon E-J, Hong SM, Bae CH, Lee HY, Park MK, et al. Bacterial species and antibiotic sensitivity in Korean patients diagnosed with acute otitis media and otitis media with effusion. J Korean Med Sci. 2017;32(4):672-8.

28. O'Reilly R, Lu H, Kwong JC, McGeer A, To T, Sander B. The epidemiology and healthcare costs of community-acquired pneumonia in Ontario, Canada: a population-based cohort study. J Med Econ. 2023;26(1):293-302.

29. Jit M. The risk of sequelae due to pneumococcal meningitis in high-income countries: A systematic review and meta-analysis. Journal of Infection. 2010;61(2):114-24.

30. Wijayasri S, Hillier K, Lim GH, Harris TM, Wilson SE, Deeks SL. The shifting epidemiology and serotype distribution of invasive pneumococcal disease in Ontario, Canada, 2007-2017. PLoS One. 2019;14(12):e0226353.

31. Public Health Agency of Canada. Vaccine coverage in Canadian children: Results from the 2019 childhood National Immunization Coverage Survey (cNICS). Ottawa (ON): Government of Canada; 2020 Dec 22 [cited 2023 Mar 31]. Available from: https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/2019-childhood-national-immunization-coverage-survey-results.html.

32. Farrar J, Nsofor C, Childs L, Kobayashi M, Pilishvili T, editors. Systematic Review of 13-Valent Pneumooccal Conjugate Vaccine Effectiveness Against Pneumonia Among Children. 12th International Symposium on Pneumococci and Pneumococcal Diseases; 2022; Toronto (ON).

33. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med. 2001;344(6):403-9.

34. Stoecker C. Economic assessment of routine PCV20 for children [slides presented at Advisory Committee on Immunization Practices (ACIP) meeting June 22, 2023][Internet]. Atlanta (GA): Center for Disease Control and Prevention; 2023 Jun 22 [cited 2023 Jun 24]. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-06-21-23/02-Pneumococcal-Stoecker-508.pdf.

35. Lewnard JA, Givon-Lavi N, Dagan R. Dose-specific effectiveness of 7- and 13-valent pneumococcal conjugate vaccines against vaccine-serotype Streptococcus pneumoniae colonization in children. Clin Infect Dis. 2020;71(8):e289-e300.

36. Choi YH, Andrews N, Miller E. Estimated impact of revising the 13-valent pneumococcal conjugate vaccine schedule from 2+1 to 1+1 in England and Wales: A modelling study. PLOS Medicine. 2019;16(7):e1002845.

37. Yan J, Xie S, Johnson JA, Pullenayegum E, Ohinmaa A, Bryan S, et al. Canada population norms for the EQ-5D-5L. Eur J Health Econ. 2023.

38. Molina M, Humphries B, Guertin JR, Feeny D, Tarride JE. Health Utilities Index Mark 3 scores for children and youth: Population norms for Canada based on cycles 5 (2016 and 2017) and 6 (2018 and 2019) of the Canadian Health Measures Survey. Health Rep. 2023;34(2):29-39.

39. Canadian Institute for Health Information (CIHI). Data Quality Documentation, Discharge Abstract Database — Current-Year Information, 2015–2016 [Internet]. Ottawa (ON): CIHI; 2016 [cited 2023 Mar 31]. Available from: https://www.cihi.ca/sites/default/files/document/dad-data-quality_15-16_en.pdf.

40. Canadian Institute for Health Information (CIHI). Data Quality Documentation Discharge Abstract Database - Current-Year Information 2018–2019 [Internet]. Ottawa (ON): CIHI; 2019 [cited 2023 Mar 31]. Available from: https://www.cihi.ca/sites/default/files/document/current-year-information-dad-2018-2019-en-web.pdf.

41. Canadian Institute for Health Information (CIHI). Data Quality Documentation, Discharge Abstract Database - Current-Year Information, 2016–2017 [Internet]. Ottawa (ON): CIHI; 2017 [cited 2023 Mar 31]. Available from: https://www.cihi.ca/sites/default/files/document/current-year_information_dad_2016-2017-en-web.pdf.

42. Canadian Institute for Health Information (CIHI). Data Quality Documentation, Discharge Abstract Database - Current-Year Information, 2017–2018 [Internet]. Ottawa (ON): CIHI; 2018 [cited 2023 Mar 31]. Available from: https://www.cihi.ca/sites/default/files/document/current-year-information-dad-2017-2018-en-web.pdf.

43. Canadian Institute for Health Information (CIHI). Cost of a Standard Hospital Stay [Internet]. Ottawa (ON): CIHI; 2023 [cited 2023 Mar 31]. Available from: https://yourhealthsystem.cihi.ca/hsp/inbrief?lang=en#!/indicators/015/cost-of-a-standard-hospital-stay-cshs/;mapC1;mapLevel2;provinceC9001;/.

44. Public Health Agency of Canada. National case definition: Invasive Pneumococcal Disease [Internet]. Ottawa (ON): Government of Canada; 2008 May [cited 2023 Mar 31]. Available from: https://www.canada.ca/en/public-health/services/immunization/vaccine-preventable-diseases/invasive-pneumococcal-disease/health-professionals/national-case-definition.html.

45. Canadian Institute for Health Information. Implantable medical devices in Canada: Insights into high-volume procedures and associated costs [Internet]. Ottawa (ON): CIHI; 2020 [cited 2023 Mar 31]. Available from: https://secure.cihi.ca/free_products/implantable-medical-devices-report-en.pdf.

46. Gaboury I, Coyle K, Coyle D, Le Saux N. Treatment cost effectiveness in acute otitis media: A watch-and-wait approach versus amoxicillin. Paediatr Child Health. 2010;15(7):e14-8.

47. Christensen H, Trotter CL, Hickman M, Edmunds WJ. Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study. BMJ. 2014;349:g5725.

48. National Advisory Committee on Immunization. Update on the use of pneumococcal vaccines in adults 65 years of age and older – A Public Health Perspective [Internet]. Ottawa (ON): Public Health Agency of Canada; 2018 Nov [cited 2023 Mar 31]. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/update-on-the-use-of-pneumococcal-vaccines-in-adult.html.

49. Centers for Disease Control and Prevention (CDC). Archived CDC Vaccine Price List as of April 1, 2022 [Internet]. Atlanta (GA): CDC; 2022 Apr 01 [cited 2023 Mar 31]. Available from: https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/2022/2022-04-01.html.

50. Statistics Canada. Table 14-10-0327-02. Unemployment rate, participate rate and employment rate by sex, annual [Internet]. Ottawa (ON); Statistics Canada; 2023 Jan 06 [cited 2023 Mar 31]. Available from: https://doi.org/10.25318/1410032701-eng.

51. Statistics Canada. Table 11-10-0239-01. Income of individuals by age group, sex and income source, Canada, provinces and selected census metropolitan areas [Internet]. Ottawa (ON): Statistics Canada; 2023 May 02 [cited 2023 May 31]. Available from: https://doi.org/10.25318/1110023901-eng.

52. IPD in Canada, 2011-2020. Ottawa (ON): Public Health Agency of Canada; 2022.

53. Chuck AW, Jacobs P, Tyrrell G, Kellner JD. Pharmacoeconomic evaluation of 10- and 13-valent pneumococcal conjugate vaccines. Vaccine. 2010;28(33):5485-90.

54. Andrews NJ, Waight PA, Burbidge P, Pearce E, Roalfe L, Zancolli M, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. Lancet Infect Dis. 2014;14(9):839-46.

55. O'Reilly R, Kwong JC, McGeer A, To T, Sander B. The cost-effectiveness of a pneumococcal conjugate vaccine (PCV13) program for older adults (65+) in Ontario, Canada in the context of infant immunization and changing serotype distributions. Society for Medical Decision Making 39th Annual North American Meeting; 22-25 October 2017; Pittsburgh, PA.

56. Ontario Ministry of Health. Ontario Drug Benefit Formulary/Comparative Drug Index [Internet]. 43rd ed. Toronto (ON): Ontario Ministry of Health; 2022 May 31 [cited 2023 Mar 31]. Available from: https://www.health.gov.on.ca/en/pro/programs/drugs/formulary43/edition_43.pdf.

57. Committee on Infectious Diseases AAoP, Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH. Red Book: 2021–2024 Report of the Committee on Infectious Diseases: American Academy of Pediatrics; 2021.

58. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45-e67.

59. Patented Medicine Prices Review Board Canada. Dispensing fee policies in public drug plans, 2019/20 [Internet]. Ottawa (ON): Government of Canada; 2020 [cited 2023 Mar 24]. Available from: http://www.pmprb-cepmb.gc.ca/CMFiles/NPDUIS/refdocs/ReferenceDoc_Dispensing_Fees_2019-20_EN.pdf.

60. Colbert Y. 'My jaw dropped,' says Ontario woman of $12K air ambulance bill in Nova Scotia [Internet]. CBC News; 2020 November 27 [cited 2023 Mar 31]. Available from: https://www.cbc.ca/news/canada/nova-scotia/ground-and-air-ambulance-fees-health-care-universal-health-care-1.5817284. 2020.

61. Canada Revenue Agency. Reasonable per-kilometre allowance 2022 [Internet]. Ottawa (ON): Government of Canada; 2023 Jan 27 [cited 2023 Mar 31]. Available from: https://www.canada.ca/en/revenue-agency/services/tax/businesses/topics/payroll/benefits-allowances/automobile/automobile-motor-vehicle-allowances/reasonable-kilometre-allowance.html.

62. Pong RW, Pitblado JR. Geographic distribution of physicians in Canada: beyond how many and where [Internet]. Ottawa (ON): Canadian Institute for Health Information; 2006 [cited 2023 Mar 31]: Available from: https://secure.cihi.ca/estore/productFamily.htm?locale=en&pf=PFC609. 200.

63. Pasquale CB, Vietri J, Choate R, McDaniel A, Sato R, Ford KD, et al. Patient-reported consequences of community-acquired pneumonia in patients with chronic obstructive pulmonary disease. Chronic Obstr Pulm Dis. 2019;6(2):132-44.

64. Bizier C, Contreras R, Walpole A. Hearing disabilities among Canadians aged 15 years and older, 2012 [Internet]. Ottawa (ON): Statistics Canada; 2016 Feb 29 [cited 2023 Mar 31]. Available from: https://www150.statcan.gc.ca/n1/pub/89-654-x/89-654-x2016002-eng.htm. 2016.

65. Jiang Y, Gauthier A, Annemans L, van der Linden M, Nicolas-Spony L, Bresse X. Cost–effectiveness of vaccinating adults with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in Germany. Expert Review of Pharmacoeconomics & Outcomes Research. 2012;12(5):645-60.

66. Wyrwich KW, Yu H, Sato R, Powers JH. Observational longitudinal study of symptom burden and time for recovery from community-acquired pneumonia reported by older adults surveyed nationwide using the CAP Burden of Illness Questionnaire. Patient Relat Outcome Meas. 2015;6:215-23.

67. Dubé E, De Wals P, Gilca V, Boulianne N, Ouakki M, Lavoie F, et al. Burden of acute otitis media on Canadian families. Can Fam Physician. 2011;57(1):60-5.

68. Barber C, Ille S, Vergison A, Coates H. Acute otitis media in young children - what do parents say? Int J Pediatr Otorhinolaryngol. 2014;78(2):300-6.

69. Petit G, De Wals P, Law B, Tam T, Erickson LJ, Guay M, et al. Epidemiological and economic burden of pneumococcal diseases in Canadian children. Can J Infect Dis. 2003;14(4):215-20.

70. Ganapathy V, Graham GD, DiBonaventura MD, Gillard PJ, Goren A, Zorowitz RD. Caregiver burden, productivity loss, and indirect costs associated with caring for patients with poststroke spasticity. Clin Interv Aging. 2015;10:1793-802.

71. Alarid-Escudero F, Knowlton G, Easterly C, Enns EA. Decision Analytic Modeling Package (dampack). R package version 1.0.0. 2021. Available from: https://github.com/DARTH-git/dampack.

72. Perdrizet J, Horn EK, Hayford K, Grant L, Barry R, Huang L, et al. Historical population-level impact of infant 13-valent pneumococcal conjugate vaccine (PCV13) national immunization programs on invasive pneumococcal disease in Australia, Canada, England and Wales, Israel, and the United States. Infect Dis Ther. 2023;12(5):1351-64.

73. National Advisory Committee on Immunization. Recommendations on the use of conjugate pneumococcal vaccine - 15 valent (PNEU-C-15) and 20 valent (PNEU-C-20) in adults: Economic evidence supplementary appendix [Internet]. Ottawa (ON): Public Health Agency of Canada; 2023 Feb 24 [cited 2023 Apr 27]. Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/public-health-level-recommendations-use-pneumococcal-vaccines-adults-including-use-15-valent-20-valent-conjugate-vaccines/economic-evidence-supplementary-appendix.html.

74. Kaur R, Fuji N, Pichichero ME. Dynamic changes in otopathogens colonizing the nasopharynx and causing acute otitis media in children after 13-valent (PCV13) pneumococcal conjugate vaccination during 2015-2019. Eur J Clin Microbiol Infect Dis. 2022;41(1):37-44.

75. Mahmud SM, Sinnock H, Mostaco-Guidolin LC, Pabla G, Wierzbowski AK, Bozat-Emre S. Long-term trends in invasive pneumococcal disease in Manitoba, Canada. Hum Vaccin Immunother. 2017;13(8):1884-91.

76. Homoe P, Heidemann CH, Damoiseaux RA, Lailach S, Lieu JEC, Phillips JS, et al. Panel 5: Impact of otitis media on quality of life and development. Int J Pediatr Otorhinolaryngol. 2020;130 Suppl 1(Suppl 1):109837.

77. Pichon-Riviere A, Drummond M, Palacios A, Garcia-Marti S, Augustovski F. Determining the efficiency path to universal health coverage: cost-effectiveness thresholds for 174 countries based on growth in life expectancy and health expenditures. Lancet Glob Health. 2023;11(6):e833-e42.

78. Ochalek J, Lomas J, Claxton K. Assessing health opportunity costs for the Canadian health care systems. Accessed 5 Dec 2022: http://www.pmprb-cepmb.gc.ca/CMFiles/Consultations/new_guidelines/Canada_report_2018-03-14_Final.pdf. 2018.