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# Cost-Effectiveness of Conjugate Pneumococcal Vaccines in At-Risk Adults Aged 18 to 64 Years

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## Abbreviations

<b>CDC</b>	US Centers for Disease Control and Prevention
<b>CKD</b>	chronic kidney disease
<b>COPD</b>	chronic obstructive pulmonary disease
<b>CSF</b>	cerebrospinal fluid
<b>ICER</b>	incremental cost-effectiveness ratio
<b>IPD</b>	invasive pneumococcal disease
<b>JBI</b>	Joanna Briggs Institute
<b>NBP</b>	nonbacteremic pneumonia
<b>NPP</b>	nonbacteremic pneumococcal pneumonia
<b>OECD</b>	Organisation for Economic Co-operation and Development
<b>PCV9</b>	pneumococcal 9-valent conjugate vaccine
<b>PCV13</b>	pneumococcal 13-valent conjugate vaccine
<b>PCV15</b>	pneumococcal 15-valent conjugate vaccine
<b>PCV20</b>	pneumococcal 20-valent conjugate vaccine
<b>PCV21</b>	pneumococcal 21-valent conjugate vaccine
<b>PPSV23</b>	pneumococcal polysaccharide 23-valent vaccine
<b>QALY</b>	quality-adjusted life-year
<b>WTP</b>	willingness to pay

## Key Messages

- Eight economic evaluations (6 peer-reviewed, 2 summarized in a single grey literature source) assessing the cost-effectiveness of pneumococcal conjugate vaccines in adults aged 18 to 64 years at high risk of invasive pneumococcal disease (IPD) in high-income countries were identified.
  - The 2 economic evaluations summarized in the single grey literature source were industry-sponsored analyses. A version of the results was previously summarized by the Public Health Agency of Canada. As such, the methods and results of the industry-funded models are only summarized in [Appendix 3](#) for this review.
  - None of the peer-reviewed studies identified assessed the cost-effectiveness of pneumococcal 15-valent conjugate vaccine (PCV15), pneumococcal 20-valent conjugate vaccine (PCV20), or pneumococcal 21-valent conjugate vaccine (PCV21).
  - Of the peer-reviewed studies, 2 were conducted in the US, 2 in South Korea, 1 in Spain, and 1 in Hong Kong. All results were presented in terms of incremental cost-effectiveness ratios (ICERs) (i.e., incremental cost per quality-adjusted life-years gained).
    - Four studies concluded that 1 dose of pneumococcal 13-valent conjugate vaccine (PCV13) was cost-effective relative to either no vaccination, 2 doses of PCV13, PCV13 plus 2 doses of pneumococcal polysaccharide 23-valent vaccine (PPSV23), or 2 doses of PPSV23.
    - Two studies concluded that PCV13 plus PPSV23 was cost-effective relative to either no vaccination or 1 dose of PPSV23, but the studies did not evaluate the cost-effectiveness of PCV13 alone.
    - The studies did not all consider the same vaccination strategies.
  - The sources used to parameterize vaccine effectiveness in the peer-reviewed studies are highly uncertain, as the clinical evidence was either not representative of the target population or heavily reliant on expert input and assumptions.
- The generalizability of the economic evaluations may be limited because the study settings were notably different from Canada. To estimate the potential cost-effectiveness of pneumococcal conjugate vaccines in Canada, a de novo economic evaluation conducted from a setting in Canada is required.

## Introduction and Rationale

### Background and Rationale

Pneumococcal conjugate vaccines are used to prevent complications from infection with the bacterium *Streptococcus pneumoniae*, which occurs most frequently among young children aged younger than 5 years, particularly those younger than 2, adults aged 65 years and older, and others who are considered to be at high risk of IPD.<sup>1,2</sup> Individuals at high risk of IPD, as defined by the Public Health Agency of Canada in

[Appendix 1, Table 2](#), include those with certain nonimmunocompromising conditions, immunocompromising conditions, and/or other risk factors.<sup>1</sup> Pneumococcal infections most commonly occur in the spring and winter and are a large contributor to morbidity and mortality, as infections can lead to pneumonia, meningitis, and bloodstream infections.<sup>3,4</sup> Infections with antibiotic-resistant *Streptococcus pneumoniae* can increase the complexity and costs of treatment compared with infections caused by nonresistant pneumococcus, and pneumococcal vaccination is an effective tool for slowing the development of pneumococcal resistance.<sup>5</sup> Therefore, using vaccines as a preventive measure is important not only from a public health perspective, but also from a health system perspective, as the use of the vaccines may aid in reducing future use of health care resources.

Currently, 3 pneumococcal conjugate vaccines and 1 pneumococcal polysaccharide vaccine available in Canada are indicated for use in adults:

- pneumococcal 13-valent conjugate vaccine (PCV13) (Pevnar 13)
- pneumococcal 15-valent conjugate vaccine (PCV15) (Vaxneuvance)
- pneumococcal 20-valent conjugate vaccine (PCV20) (Pevnar 20)
- pneumococcal polysaccharide 23-valent vaccine (PPSV23) (Pneumovax 23).

[Appendix 1, Table 3](#) and [Table 4](#) provide a comparison of the respective vaccine manufacturers, dates of initial authorization in Canada, vaccine type, adult dosage, indicated age, Health Canada indication, price per dose, and serotypes included in the respective vaccines. At the time of this review, a new pneumococcal conjugate vaccine, PCV21, is under review by Health Canada.<sup>6</sup>

At the time of this review, the National Advisory Committee on Immunization recommended adults at higher risk of IPD receive a single dose of PCV20, or, if PCV20 is unavailable, a single dose of PCV15 followed by a single dose of PPSV23.<sup>7</sup>

This review of literature was requested by the Public Health Agency of Canada to support a National Advisory Committee on Immunization statement on the use of pneumococcal vaccines in adults.

## Research Question

1. What is the cost-effectiveness of pneumococcal conjugate vaccination in adults aged 18 to 64 years at high risk of IPD?

## Methods

A review of the economic literature was undertaken to identify published economic evidence on the cost-effectiveness of the use of pneumococcal conjugate vaccination (i.e., PCV13, PCV15, PCV20, and PCV21) relative to no vaccination or other pneumococcal vaccination in adults aged 18 to 64 years at high-risk of IPD in high-income countries.

## Literature Search Methods

An information specialist conducted a literature search on key databases, including MEDLINE, Embase, and the Cochrane Database of Systematic Reviews. Grey literature was also searched, including the International HTA Database, the websites of Canadian and major international health technology agencies, websites from the health economics section of CADTH’s Grey Matters: A Practical Tool for Searching Health-Related Grey Literature, as well as a focused internet search, including the websites of National Immunization Technical Advisory Groups. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevance. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were pneumococcal vaccines, adults, and high-income countries. CADTH-developed search filters were applied to limit retrieval to economic studies and, for background, health technology assessments, systematic reviews, meta-analyses, and indirect treatment comparisons. The search was completed on February 22, 2024, and limited to English- or French-language documents published since January 1, 2011. Retrieval was limited to the human population. Regular alerts updated the search until May 13, 2024.

## Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

**Table 1: Inclusion Criteria**

Criteria	Description
Population	Adults aged 18 to 64 years at high risk <sup>a</sup> of invasive pneumococcal disease
Intervention	Pneumococcal conjugate vaccination (i.e., PCV13, PCV15, PCV20, and PCV21) or a pneumococcal conjugate vaccine plus a pneumococcal polysaccharide vaccination (i.e., PPSV23)
Comparators	No vaccination (i.e., placebo, no intervention) or other pneumococcal vaccination
Outcomes	QALYs, disability-adjusted life-years, incremental costs and incremental cost-effectiveness ratio (e.g., cost per QALY gained or incremental cost per event or event avoided), net monetary benefit, net health benefit
Study designs	Full economic evaluations (e.g., cost-minimization analysis, cost-consequence analyses, cost-effectiveness analyses, cost-utility analyses), health technology assessments, and systematic reviews

PCV13 = pneumococcal conjugate 13-valent; PCV15 = pneumococcal 15-valent conjugate vaccine; PCV20 = pneumococcal 20-valent conjugate vaccine; PCV21 = 21-valent pneumococcal conjugate vaccine; PPSV23 = pneumococcal polysaccharide 23-valent; QALY = quality-adjusted life-year.

<sup>a</sup>Refer to [Appendix 1, Table 2](#), for a list of high-risk factors, as defined by the Public Health Agency of Canada.

## Exclusion Criteria

Studies were excluded if they:

- did not meet the inclusion criteria outlined in [Table 1](#)
- were duplicate publications
- were published in languages other than English or French

- were not conducted in countries identified as high income by the World Bank<sup>8</sup>
- were systematic reviews whose primary cost-effectiveness studies were otherwise captured or excluded
- were published before 2011
- had insufficient information to include and did not have full-text available.

### Data Extraction and Critical Appraisal

During data extraction, the following were collected: author, publication year, country, currency, source of funding, study design, modelling approach, study perspective, discounting, time horizon, outcomes, source of clinical efficacy, study population characteristics, and results. The quality of the included studies was critically appraised by 1 reviewer using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Economic Evaluations. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Cost-effectiveness outcomes were reported as unadjusted and adjusted. Where adjusted, outcomes were adjusted to 2024 Canadian dollars using Organisation for Economic Co-operation and Development (OECD)<sup>9</sup> purchasing power parity rates and inflation rates from the Bank of Canada.<sup>10</sup> [Appendix 1, Table 5](#) details the purchasing power parity rates and inflation rates used to adjust monetary amounts to 2024 Canadian dollars.

## Summary of Evidence

### Quantity of Research Available

A total of 1,917 citations were identified in the literature search. Following the screening of titles and abstracts, 1,794 citations were excluded and 123 potentially relevant publications from the electronic search were retrieved for full-text review. In addition, 10 potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant publications, 126 were excluded for various reasons, leading to 7 publications that met the inclusion criteria and were included in this review. Eight economic evaluations that met the inclusion criteria were identified: 6 were original peer-reviewed economic evaluations,<sup>11-16</sup> and 2 were summarized in a single grey literature source.<sup>17</sup> [Appendix 4, \(Figure 1\)](#) presents the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart of the publication selection and reasons for exclusions.

The grey literature source (Kobayashi et al.) was a report published by the US Centers for Disease Control and Prevention (CDC), which included a summary of 3 economic models.<sup>17</sup> The report compared 2 industry-funded models (1 produced by Merck and 1 produced by Pfizer) and a third economic model, termed the Tulane-CDC model.<sup>17</sup> The Tulane-CDC model did not meet the inclusion criteria for this review and was thus not summarized.<sup>17</sup> The 2 industry-funded economic evaluations described in Kobayashi et al.<sup>17</sup> met the inclusion criteria and are only summarized in [Appendix 3](#) of this review, as a version of the aforementioned



economic evaluations were summarized previously by the Public Health Agency of Canada.<sup>7,18</sup> Therefore, only the 6 peer-reviewed studies are summarized in the main text of this review.<sup>11-16</sup>

Of the modeling types used in the 6 peer-reviewed studies summarized in this review, there were 5 Markov models<sup>11-14,16</sup> and 1 did not state the model structure, only that a sequential deterministic model was used.<sup>15</sup> Two studies were conducted in the US,<sup>13,16</sup> 2 in South Korea,<sup>11,12</sup> 1 in Spain,<sup>14</sup> and 1 in Hong Kong.<sup>15</sup> All of the peer-reviewed studies included either PCV13 alone or 1 dose of PCV13 used in series with PPSV23 (i.e., PCV13 plus PPSV23) as the intervention.<sup>11-16</sup> None of the peer-reviewed studies included PCV15, PCV20, or PCV21 as an intervention or comparator. [Table 6](#) in [Appendix 2](#) provides an overview of the characteristics of the 6 peer-reviewed studies.

### Summary of Critical Appraisal

The 6 peer-reviewed studies included in this review ranged from meeting 3 to 6 out of 11 of the JBI Critical Appraisal Checklist criteria ([Appendix 2, Table 7](#)) regarding study quality and applicability to adults aged 18 to 64 years at high-risk of IPD. None of the publications included all issues of concern to users (e.g., none considered the cost-effectiveness of all the interventions of interest). It was unclear whether the economic evaluations were generalizable to the population in Canada because they were conducted in health care settings or countries dissimilar from Canada. Moreover, in 4 studies,<sup>12-15</sup> PCV13 efficacy was primarily informed by the CAPiTA trial for the populations relevant to this review. Notably, the CAPiTA trial was restricted to adults aged 65 years and older who did not have an immune deficiency or suppression at time of enrolment.<sup>19</sup> As the clinical evidence was not representative of the target population, clinical effectiveness in the population of interest for this review was not established. There is also uncertainty as to whether outcomes were measured accurately and valued credibly. No studies were excluded on the basis of these appraisals.

### Funding Sources of Examined Literature

Among the 6 peer-reviewed studies, 3 did not receive any industry funding<sup>12,13,16</sup> and the remaining 3 studies reported receiving funding from Pfizer.<sup>11,14,15</sup> Notably, 2 authors from 1 study<sup>14</sup> were employees of Pfizer, and authors from 2 studies<sup>15,16</sup> reported previously receiving research funding for work unrelated to the published study.

### Summary of Findings

As stated previously, as the results included in Kobayashi et al.<sup>17</sup> were previously summarized,<sup>7,18</sup> this section describes only the 6 peer-reviewed studies.<sup>11-16</sup> The inputs for the peer-reviewed studies discussed in this section are also summarized in a series of tables in [Appendix 2](#).<sup>11-16</sup> Study characteristics and results for the 2 economic evaluations included in Kobayashi et al. are summarized in [Appendix 3, Table 14](#) and [Table 15](#).<sup>17</sup>

## Methods

### *Population*

The population risk factors included across the studies varied widely and are summarized in [Appendix 2, Table 6](#). As studies may have included multiple target populations, only those relevant to this review are summarized.

Four studies had broader risk definitions and included multiple risk factors.<sup>11,12,15,16</sup> Shami et al. included individuals with a history of IPD, which was not identified as a risk factor by the Public Health Agency of Canada ([Table 2](#)).<sup>7</sup> This study was not excluded on this basis, as a history of IPD was not deemed to represent a significant source of heterogeneity in the target population.<sup>7,15</sup> Two studies were specific to single chronic conditions (i.e., chronic kidney disease [CKD]<sup>13</sup> and chronic obstructive pulmonary disease [COPD]).<sup>14</sup> Smith et al. included a secondary analysis that was specific to individuals living with HIV.<sup>16</sup>

The age of the target population differed across studies. Four studies (Heo et al., Ishigami et al., Rodriguez Gonzalez-Moro et al., and Shami et al.) reported results for adults aged 50 to 64 years.<sup>12-15</sup> Choi et al. reported results for adults aged 18 to 64 years,<sup>11</sup> Smith et al. reported results for adults aged 19 to 64 years,<sup>16</sup> and Shami et al. also reported results for a broader age range, consisting of adults aged 20 to 64 years.<sup>15</sup>

### *Perspective, Time Horizon, Discounting, and Reported Outcomes*

Perspective, time horizon, and discounting inputs are summarized in [Appendix 2, Table 6](#). Three studies (Choi et al., Ishigami et al., and Rodriguez Gonzalez-Moro et al.) were conducted from a health care payer perspective,<sup>11,13,14</sup> and 3 studies (Heo et al., Shami et al., Smith et al.) were conducted from a societal perspective.<sup>12,15,16</sup> Heo et al. and Smith et al. considered a 15-year time horizon,<sup>12,16</sup> while the remaining studies considered a lifetime horizon (reported as 82 years in Rodriguez Gonzalez-Moro et al.;<sup>14</sup> unreported by all other studies).<sup>11,13-15</sup> There were slight differences in choice of discount rates: 5% in Heo et al.,<sup>12</sup> 4% in Shami et al.,<sup>15</sup> and 3% in the remaining studies.<sup>11,13,14,16</sup> All studies reported cost-effectiveness as ICERs using cost per quality-adjusted life-year (QALY) gained.<sup>11-16</sup>

### *Vaccination Strategies*

While all of the peer-reviewed studies included either 1 dose of PCV13 or 1 dose of PCV13 sequentially with 1 dose of PPSV23 (PCV13 plus PPSV23) as the intervention of interest, the vaccination strategies that were compared varied across studies, and some studies compared multiple vaccination strategies. Unless otherwise stated, vaccination strategies assume 1 dose per vaccine. Strategies that were reported by multiple studies included:

- PCV13 relative to no vaccination (Heo et al., Ishigami et al., and Smith et al.)<sup>12,13,16</sup>
- PCV13 relative to PPSV23 (Heo et al. and Rodriguez Gonzalez-Moro et al.).<sup>12,14</sup>

Strategies that were reported only by 1 study included:

- PCV13 plus PPSV23 relative to no vaccination (Choi et al.)<sup>11</sup>
- PCV13 plus PPSV23 relative to PPSV23 (Shami et al.)<sup>15</sup>
- PCV13 plus 2 doses of PPSV23 relative to PCV13 (Smith et al.)<sup>16</sup>

- 2 doses of PCV13 relative to PCV13 plus 2 doses of PPSV23 (Smith et al.).<sup>16</sup>

None of the peer-reviewed studies included PCV15, PCV20, or PCV21 as an intervention or comparator.

### **Vaccine Effectiveness**

The sources for information on vaccine effectiveness were similar across studies. [Appendix 2, Table 8](#) and [Table 9](#) summarize the key clinical parameters of the peer-reviewed studies. With the exception of Choi et al.<sup>11</sup> and Smith et al.,<sup>16</sup> studies drew vaccine effectiveness for PCV13 from the CAPIA clinical trial for the relevant populations included in this review.<sup>20</sup>

Estimates from an expert panel informed PCV13 vaccine effectiveness in Smith et al. and vaccine effectiveness in the moderate-risk population in Choi et al.<sup>11,16</sup> Vaccine effectiveness estimates for PCV13 in Choi et al.<sup>11</sup> and Heo et al.<sup>12</sup> were also informed by a randomized controlled trial investigating the effectiveness of pneumococcal 9-valent conjugate vaccine (PCV9) in infants.<sup>21</sup> Point estimates for initial PCV13 effectiveness against IPD and pneumonia ranged from 50% to 82% and 3.5% to 52.0%, respectively.<sup>11-16</sup> A wider range was reported for vaccine effectiveness against pneumonia, as 1 study reported vaccine effectiveness against all-cause pneumonia,<sup>11</sup> 1 study reported vaccine effectiveness against all-cause nonbacteremic pneumonia (NBP),<sup>14</sup> 1 study reported vaccine effectiveness against all-cause NBP for PPSV23 but against NBP for PCV13,<sup>15</sup> 1 study reported vaccine effectiveness against noninvasive pneumococcal pneumonia,<sup>13</sup> and 2 studies reported vaccine effectiveness against nonbacteremic pneumococcal pneumonia (NPP).<sup>12,16</sup>

Vaccine effectiveness for PPSV23 was informed by a Cochrane meta-analysis<sup>22</sup> for the relevant populations included in this review in 2 studies (Heo et al. and Rodriguez Gonzalez-Moro et al.).<sup>12,14</sup> The efficacy of PPSV23 in 1 study (Rodriguez Gonzalez-Moro et al.) was also informed by an observational study conducted in adults aged 65 years and older in addition to the Cochrane meta-analysis.<sup>23</sup> All 5 studies (Choi et al., Heo et al., Rodriguez Gonzalez-Moro et al., Shami et al., and Smith et al.) that modelled PPSV23 relied on at least 1 assumption,<sup>11,12,14-16</sup> but 2 of the studies (Choi et al. and Heo et al.) also relied on input from an expert panel to inform PPSV23 vaccine effectiveness.<sup>11,12</sup> Point estimates for initial PPSV23 effectiveness against IPD ranged from 25% to 95.3%.<sup>11,12,14-16</sup> In base-case analyses, Smith et al., assumed that vaccine effectiveness for PPSV23 was 50% of the base efficacy value for PCV13 against IPD.<sup>16</sup> The 5 studies that considered PPSV23 in their economic evaluation assumed that PPSV23 did not protect against pneumonia.<sup>11,12,14-16</sup>

### **Vaccine Serotype Coverage**

Apart from Ishigami et al., all studies reported vaccine serotype coverage (i.e., the proportion of disease due to the serotypes covered by the vaccine) ([Appendix 2, Table 8](#)).<sup>11,12,14-16</sup> Three studies (Choi et al., Heo et al., and Rodriguez Gonzalez-Moro et al.) reported values specific to IPD and pneumonia,<sup>11,12,14</sup> and 2 studies (Shami et al. and Smith et al.) reported age-specific values.<sup>15,16</sup>

Choi et al. and Heo et al. reported the same serotype coverage for PCV13 (IPD = 35.1% and NPP = 35.2%) and PPSV23 (IPD = 59.5% and NPP = 49.8%).<sup>11,12</sup> Heo et al. was the only study that reported serotype coverage for PCV13 plus PPSV23 (IPD = 60.8% and NPP = 53.4%).<sup>12</sup> Rodriguez Gonzalez-Moro et al. reported PCV13 and PPSV23 coverage for IPD serotypes as 70.0% and 76.5%, respectively.<sup>14</sup> Additionally, Rodriguez

Gonzalez-Moro et al. reported PCV13 coverage for any-cause NBP serotypes as 19.4% but did not report the coverage for PPSV23.<sup>14</sup> Shami et al. reported PCV13 and PPSV23 serotype coverage as 65% and 76%, respectively.<sup>15</sup> Smith et al. reported PCV13 and PPSV23 serotype coverage for adults aged 19 to 49 years as 51.9% and 78.0%, respectively.<sup>16</sup>

### ***Vaccination Uptake and Indirect Effects***

Vaccination uptake ranged from 0% to 100% across the 6 peer-reviewed studies ([Appendix 2, Table 8](#)).<sup>11-16</sup> Shami et al. assumed 0% uptake of PPSV23 in adults 20 to 64 years, as PPSV23 is not indicated for this age cohort.<sup>15</sup> Indirect effects of vaccination were considered in 4 studies.<sup>11,12,14,16</sup>

### ***Utility Values***

Utility values were reported by 5 studies.<sup>11-14,16</sup> Shami et al. did not report the sources or utility values utilized in their economic evaluation.<sup>15</sup>

Choi et al.<sup>11</sup> and Heo et al.<sup>12</sup> derived their utility values from the same source.<sup>24</sup> For moderate- and high-risk adults, Choi et al. reported utility values of 0.843 and 0.792 for adults aged 18 to 49 years and adults aged 50 to 64 years, respectively.<sup>11</sup> For moderate-risk adults, Heo et al. reported utility values of 0.972 and 0.948 for adults aged 18 to 49 years and adults aged 50 to 64, respectively.<sup>12</sup> Similarly, for high-risk adults, Heo et al. reported utility values of 0.843 and 0.792 for adults aged 18 to 19 years and adults aged 50 to 64 years, respectively.<sup>12</sup> Heo et al. also applied utility values, stratified by age and risk, for acute events of IPD and NPP.<sup>12</sup>

Smith et al.<sup>16</sup> used utility values from published literature and applied age-specific utility values for individuals with immunocompromising conditions ranging from 0.51 to 0.72.<sup>25,26</sup> Smith et al.<sup>16</sup> applied a utility value of 0.4 for individuals who developed a disability and 0.9 for vaccine adverse events.<sup>26</sup> No details were provided for how adverse event utility values were applied in Smith et al.<sup>16</sup>

Three studies (Choi et al., Ishigami et al., and Smith et al.)<sup>11,13,16</sup> used a utility weight of 0.2 for IPD and for NBP requiring hospitalization.<sup>24,25</sup> It is unclear whether these values were applied as disutilities or health state utility values in the 3 studies.<sup>11,13,16</sup>

Health state utility values for studies focusing on a population with a specific health condition (i.e., CKD and COPD) in Rodriguez Gonzalez-Moro et al.<sup>14</sup> and Ishigami et al.<sup>13</sup> ranged from 0.53 to 0.83 and were drawn from published literature.<sup>25,27,28</sup> Rodriguez Gonzalez-Moro et al. applied a disutility value of 0.1 for IPD and NBP in inpatients.<sup>29,30</sup>

### ***Cost Inputs***

All monetary amounts are reported in 2024 Canadian dollars in this review, unless stated otherwise. Vaccine costs were reported by all studies, apart from Shami et al.<sup>15</sup> Five studies (Choi et al., Heo et al., Ishigami et al., Rodriguez Gonzalez-Moro et al., and Smith et al.) reported a cost for PCV13 that ranged from \$80 to \$227 per dose.<sup>11-14,16</sup> Four studies (Choi et al., Heo et al., Rodriguez Gonzalez-Moro et al., and Smith et al.) reported PPSV23 costs that ranged from \$21 to \$76 per dose.<sup>11,12,14,16</sup> The costs per dose from 2 studies (Smith et al. and Ishigami et al.) included administration costs.<sup>13,16</sup>

Three studies were conducted from a health care payer perspective.<sup>11,13,14</sup> Choi et al. included direct health care costs associated with managing IPD, all-cause pneumonia, as well as vaccination costs associated with drug management, injection, and diagnoses.<sup>11</sup> Ishigami et al. included acute hospitalization costs, baseline medical costs associated with the management of different stages of CKD, and vaccination costs.<sup>13</sup> Rodriguez Gonzalez-Moro et al. included management costs for IPD and inpatient and outpatient management costs for all-cause NBP.<sup>14</sup> This study also assumed vaccine administration costs were \$0 under the assumption that because pneumococcal vaccinations would be administered alongside the influenza vaccine.<sup>14</sup>

The remaining 3 studies were conducted from a societal perspective.<sup>12,15,16</sup> Heo et al. included hospitalization costs for NPP and IPD, vaccine administration costs, and societal costs such as transportation costs and caregiver time.<sup>12</sup> Shami et al. included direct costs for hospitalization, inpatient care, outpatient consultation, and vaccination administration costs as well as indirect costs associated with productivity losses attributed to all-cause pneumonia and IPD.<sup>15</sup> Smith et al. included hospitalization costs for IPD and NBP, stratified by whether a patient was discharged alive or died, and vaccine administration costs.<sup>16</sup> Limited details were provided by Smith et al. regarding the methodology used to obtain costs from the Healthcare Cost and Utilization Project.<sup>16</sup> While Smith et al. stated that the analysis was conducted from a societal perspective, the authors did not report on the indirect costs considered in their economic evaluation.<sup>16</sup>

## Results

### *Population Intended for Vaccination: At-Risk Adults Aged 18 to 64 Years*

Three studies (Choi et al., Shami et al., and Smith et al.) reported results for adults at least 18 years to 64 years.<sup>11,15,16</sup> Unadjusted and adjusted results are reported in [Appendix 2, Table 10](#) and [Table 12](#), respectively.

Choi et al. reported the results of 2 vaccination strategies for at-risk adults aged 18 to 64.<sup>11</sup> For this population, Choi et al. reported an ICER of \$10,499 per QALY gained for PCV13 plus PPSV23 relative to no vaccination and \$5,735 per QALY gained for PCV13 plus PPSV23 relative to PPSV23.<sup>11</sup>

Shami et al. also reported the results for PCV13 plus PPSV23 relative to PPSV23, but in adults aged 20 to 49 years (results were also presented for adults aged 50 to 64 years, discussed in the subsequent section).<sup>15</sup> While Shami et al. assert that the sequential strategy was being compared with PPSV23, since uptake of PPSV23 is 0% among adults aged younger than 65 years, it is likely more appropriate to state that the sequential strategy was being compared with no vaccination in adults aged 20 to 49 years.<sup>15</sup> However, this report maintains the author's description, as it was unclear whether the sequential strategy was being compared with no vaccination. Shami et al. reported ICERs of \$39,597 per QALY gained and \$24,788 per QALY gained for PCV13 plus PPSV23 relative to PPSV23, respectively, for adults aged 20 to 49 years with selected chronic conditions (chronic cardiac, pulmonary, liver or renal disease; diabetes mellitus; or cerebrospinal fluid [CSF] leakage) and are at high risk (defined as having a history of IPDs, immunocompromising conditions [asplenia, HIV/AIDS, primary immunodeficiency, immunodeficiencies related to malignancy and transplant, immunodeficiencies related to use of immunosuppressive drugs/systemic steroids], chronic conditions, or cochlear implants).<sup>15</sup> PCV13 plus PPSV23 was dominant (i.e., less

costly and more effective) compared with PPSV23 in adults aged 20 to 49 years with immunocompromising conditions.<sup>15</sup>

Smith et al. reported ICERs for 3 vaccination strategies that were not reported by the other studies assessing pneumococcal vaccines in adults aged at least 18 years to 64 years: PCV13 relative to no vaccination, PCV13 plus 2 doses of PPSV23 relative to PCV13, and 2 doses of PCV13 relative to PCV13 plus 2 doses of PPSV23.<sup>16</sup> The results for each vaccination strategy were reported separately for adults aged 19 to 64 years with immunocompromising conditions (defined as “HIV infection, Hodgkin disease, leukemia, lymphoma, myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, solid organ or bone marrow transplant, immunoglobulin deficiency, asplenia, sickle cell disease, or current immunosuppressive therapy [including radiation, systemic steroids, or chemotherapy]”) and those with HIV infection only.<sup>16</sup> Smith et al. estimated ICERs of \$125,724 per QALY gained and \$78,543 per QALY gained for people who are immunocompromised and HIV-positive, respectively, for PCV13 relative to no vaccination.<sup>16</sup> For PCV13 plus 2 doses of PPSV23 relative to PCV13, Smith et al. reported ICERs of \$242,320 per QALY gained and \$158,431 per QALY gained for people who are immunocompromised and HIV-positive, respectively.<sup>16</sup> Last, in both people who are immunocompromised and HIV-positive, 2 doses of PCV13 was dominated by PCV13 plus 2 doses of PPSV23.<sup>16</sup> Additionally, both 1 dose of PPSV23 and 2 doses of PPSV23 were subject to extended dominance through no vaccination and PCV13.<sup>16</sup>

Results of sensitivity analyses were reported by all 3 studies.<sup>11,15,16</sup> However, 1 study (Choi et al.) conducted a sensitivity analysis only for adults aged 65 years and older; thus, this report does not discuss the results, as the population is not relevant to this review.<sup>11</sup>

One-way sensitivity analyses were conducted by Shami et al. and Smith et al.<sup>15,16</sup> The studies identified vaccine effectiveness,<sup>15,16</sup> incidence of inpatient pneumonia,<sup>15</sup> and life expectancy<sup>16</sup> as influential parameters. Shami et al. found that PCV13 plus PPSV23 was still considered cost-effective relative to PPSV23 at the regional willingness-to-pay (WTP) threshold of \$68,564 (US\$46,193) per QALY gained.<sup>15</sup> Smith et al. found that PCV13 and PCV13 plus 2 doses of PPSV23 exceeded the regional WTP threshold of \$177,233 (US\$100,000) per QALY gained when life expectancy was 8 years or less and were less than the WTP threshold when life expectancy exceeded 19 years.<sup>16</sup> The average life expectancy in the base case for people who are immunocompromised was 11.7 years.<sup>16</sup>

In 2-way sensitivity analyses, Smith et al. found that, when varying parameters associated with greater uncertainty, such as PPSV23 effectiveness against IPD relative to PCV13 and PCV13 effectiveness against NPP relative to effectiveness against IPD, PPSV23 was favoured for people who are immunocompromised at a WTP of \$177,233 (US\$100,000) per QALY gained.<sup>16</sup> This finding assumed that the relative effectiveness of PPSV23 was high and PCV13 effectiveness against NPP was low.<sup>16</sup> Smith et al. also found that, when vaccine effectiveness against NPP was high for PCV13 and PPSV23 vaccine effectiveness was low, a single dose of PCV13 was favoured for people who are immunocompromised.<sup>16</sup> Among people who are in the immunocompromised population, PCV13 plus 2 doses of PPSV23 was favoured only if vaccine effectiveness was high for both vaccines.<sup>16</sup> Similar results were presented for people who are HIV-positive, such that PCV13 plus 2 doses of PPSV23 was the preferred vaccination strategy if the relative vaccine effectiveness

of PCV13 against NPP was more than 52% and the effectiveness of PPSV23 relative to PCV13 was greater than 49%.<sup>16</sup>

In probabilistic sensitivity analyses, Smith et al. found that no vaccination was likely to be considered the optimal strategy among the immunocompromised population if the WTP threshold was \$177,233 (US\$100,000).<sup>16</sup> If the WTP threshold was increased to \$119,072 (US\$110,000), PCV13 was likely the optimal strategy among people who are immunocompromised.<sup>16</sup> If the WTP threshold was increased to \$248,127 (US\$140,000), PCV13 plus 2 doses of PPSV23 was likely the optimal strategy among people who are immunocompromised.<sup>16</sup> Among those who are HIV-positive, PCV13 plus 2 doses of PPSV23 was considered the optimal strategy if the WTP threshold was \$177,233 (US\$100,000) or greater.<sup>16</sup>

Choi et al. concluded that, at a regional WTP threshold of \$43,673 (US\$27,633), PCV13 plus PPSV23 was cost-effective relative to no vaccination and PPSV23 among at-risk individuals aged 18 to 64 years.<sup>11</sup> Shami et al. concluded that PCV13 plus PPSV23 is dominant compared with PPSV23 among individuals with immunocompromising and chronic conditions aged 20 to 64 years.<sup>15</sup> Smith et al. concluded that, among people who are immunocompromised aged 18 to 64 years, PCV13 is more cost-effective than 2 doses of PPSV23 and may be more cost-effective than PCV13 plus 2 doses of PPSV23 (the recommendation at the time of the analysis), depending on the cohort life expectancy. As well, the efficacy of PPSV23 was higher than predicted by the expert panel consulted for the study.<sup>16</sup>

#### ***Population Intended for Vaccination: At-Risk Adults Aged 50 to 64 Years***

Four studies (Heo et al., Ishigami et al., Rodriguez Gonzalez-Moro et al., and Shami et al.) presented results for adults aged 50 to 64 years.<sup>12-15</sup> Two studies (Heo et al. and Shami et al.) reported the results for a broader population in which multiple risk factors were considered.<sup>12,15</sup> Unadjusted and adjusted results are reported in [Appendix 2, Table 11](#) and [Table 13](#), respectively.

Heo et al. reported the results for PCV13 relative to no vaccination and for PCV13 relative to PPSV23.<sup>12</sup> In the moderate-risk population (individuals must have at least 1 of the following: diabetes mellitus, chronic liver disease, chronic pulmonary disease, or chronic cardiovascular or other chronic conditions affecting cardiac function), Heo et al. reported that, relative to no vaccination, PCV13 was associated with an ICER of \$26,523 per QALY gained. In the high-risk population (individuals must have at least 1 of the following: splenic dysfunction including postsplenectomy status, hematologic malignancy, a condition affecting the bone marrow or lymphatic system, solid organ or stem cell transplant, CKD, HIV infection, high-dose corticosteroid use lasting 2 or more weeks, or treatment with a recombinant human immunomodulator), PCV13 was associated with an ICER of \$11,360 per QALY gained relative to no vaccination.<sup>12</sup> Relative to PPSV23, Heo et al. reported that PCV13 was associated with ICERs of \$16,666 and \$5,944 per QALY gained among the moderate-risk population and high-risk population, respectively.<sup>12</sup>

Shami et al. reported the results for PCV13 plus PPSV23 relative to PPSV23.<sup>15</sup> However, as stated previously, as uptake of 1 dose of PPSV23 was 0% among adults aged younger than 65 years, it appears that the sequential strategy was compared with no vaccination in adults aged 20 to 49 years.<sup>15</sup> Shami et al. reported

that PCV13 plus PPSV23 was dominant relative to PPSV23 in all risk populations examined (chronic conditions, immunocompromised, and high-risk).<sup>15</sup>

Two studies presented the results for populations in which only 1 health condition was considered.<sup>13,14</sup> Ishigami et al. reported ICERs of \$36,150, \$24,582, and \$1,446 per QALY gained for people with moderate-risk CKD, high-risk CKD, and kidney failure or the nephrotic range of the urinary albumin-creatinine ratio, respectively, for PCV13 relative to no vaccination.<sup>13</sup> Rodriguez Gonzalez-Moro et al. reported an ICER of \$23,300 per QALY gained for PCV13 relative to PPSV23 among adults aged 50 to 64 years with COPD.<sup>14</sup>

Sensitivity analysis results were reported by all 4 studies.<sup>12-15</sup> However, Heo et al. conducted sensitivity analyses only for adults aged 65 years and older; thus, this report does not discuss the results, as the population is not relevant to this review.<sup>12</sup> Additionally, the sensitivity analyses and conclusions by Shami et al. are summarized in the previous section of the report (At-Risk Adults Aged 18 to 64 Years) and thus are not discussed further in this section.<sup>15</sup>

In sensitivity analyses, vaccine effectiveness,<sup>13,14</sup> price per dose,<sup>13,14</sup> and time horizon<sup>14</sup> were identified as influential parameters. Although the analyses were sensitive to selected parameters, Ishigami et al. and Rodriguez Gonzalez-Moro et al. concluded that PCV13 is cost-effective relative to either no vaccination<sup>13</sup> or a single dose of PPSV23,<sup>14</sup> with all reported ICERs being less than the specified regional WTP thresholds.<sup>13,14</sup>

## Discussion

The review identified 8 economic evaluations conducted in high-income countries that assessed the cost-effectiveness of pneumococcal conjugate vaccines in adults aged 18 to 64 years at high-risk of IPD. Six of the economic evaluations<sup>11-16</sup> were peer reviewed and summarized in-depth in this review, and 2 economic evaluations<sup>17</sup> were retrieved from a single grey literature source and are summarized in [Appendix 3](#). Of the 6 peer-reviewed studies, 3 studies presented findings spanning from individuals aged at least 18 years to 64 years.<sup>11,15,16</sup> Four studies reported results specific to adults aged 50 to 64 years.<sup>12-15</sup> All 6 peer-reviewed studies assessed and reported the cost-effectiveness associated with PCV13, either alone or sequentially with PPSV23, in terms of an ICER.<sup>11-16</sup>

Four studies concluded that PCV13 was cost-effective relative to no vaccination;<sup>12,13,16</sup> PPSV23;<sup>12,14,16</sup> 2 doses of PCV13;<sup>16</sup> PCV13 plus 2 doses of PPSV23;<sup>16</sup> or 2 doses of PPSV23.<sup>16</sup> Two studies concluded that PCV13 plus PPSV23 was cost-effective relative to either no vaccination<sup>11</sup> or PPSV23,<sup>11,15</sup> but the studies did not evaluate the cost-effectiveness of PCV13 alone.<sup>11,15</sup> The studies did not all consider the same vaccination strategies. Reported ICERs were not significantly influenced in scenario analyses, apart from the analyses conducted by Smith et al., which found that values for vaccine effectiveness and life expectancy influenced which vaccine strategy was considered optimal.<sup>16</sup>



## Limitations

None of the 6 peer-reviewed studies included in this review assessed the cost-effectiveness of PCV15, PCV20, or PCV21 or included individuals who use illicit drugs, who are experiencing homelessness, or who live in communities or settings experiencing sustained high IPD rates. Based on the critical appraisal using the JBI criteria, the studies are of poor quality, as pertinent details (e.g., cost per dose, costs considered, utility values or utility value sources, and epidemiologic and incidence rates) were frequently lacking and methods were often vague and unclear. One study (Shami et al.) reported that results were presented for PCV13 plus PPSV23 relative to PPSV23.<sup>15</sup> However, as uptake of PPSV23 was assumed to be 0% among adults aged younger than 65 years, it is likely more appropriate to state that the sequential strategy was being compared with no vaccination in adults aged 20 to 49 years.<sup>15</sup> As stated previously, this report maintains the author's description, as it was unclear whether the sequential strategy was being compared with no vaccination. Additionally, 2 studies did not conduct sensitivity analyses on the population of interest for this review (i.e., sensitivity analyses were conducted only on adults aged 65 years and older).<sup>11,12</sup>

Importantly, the sources used to parameterize vaccine effectiveness in all studies were highly uncertain, as the clinical evidence was either not representative of the target population or heavily reliant on expert input and assumption. Four studies relied on the CAPiTA trial to inform PCV13's efficacy for the relevant populations included in this review.<sup>12-15</sup> The CAPiTA trial was conducted in the Netherlands and assessed the efficacy of PCV13 relative to placebo in adults aged 65 years and older who did not have an immune deficiency or suppression at time of enrolment.<sup>19</sup> The trial was also restricted to individuals who had not previously received a pneumococcal vaccination and did not reside in a nursing home, long-term care home, or similar facility.<sup>19</sup> Hence, the CAPiTA trial failed to establish clinical efficacy in the target population of the economic evaluations because it excluded the population of interest. Results from the CAPiTA trial had not yet been published at the time of Smith et al.'s study, and efficacy estimates informing that evaluation are, in general, considerably lower than those reported by the other peer-reviewed studies that relied on the CAPiTA trial to inform PCV13 efficacy.<sup>16</sup> Thus, it follows that the estimated ICERs from Smith et al. were higher than those from the other studies included in this review. Additionally, while several studies compared PCV13 or PCV13 plus PPSV23 to PPSV23, neither direct nor indirect evidence assessing the relative treatment effect among the interventions informed the analyses. As a result, a direct comparison of the cost-effectiveness of these vaccines should not be made.

The price per dose for PCV13 and PPSV23 varied widely across studies, with costs ranging from \$80 to \$227 per dose for PCV13<sup>11-14,16</sup> and \$21 to \$76 per dose for PPSV23.<sup>11,12,14,16</sup> Based on wholesale prices obtained from IQVIA DeltaPA, the cost per dose for PCV13 and PPSV23 is \$99.91 and \$35.24, respectively, in Canada ([Appendix 1, Table 3](#)).<sup>31</sup> Thus, the range of vaccine prices considered by the peer-reviewed studies may not reflect Canadian prices. However, the price per dose, while identified as an influential parameter by 2 studies,<sup>13,14</sup> did not result in the ICERs exceeding the regional WTP thresholds used in the studies. Additionally, 2 studies did not conduct a sensitivity analysis on adults aged younger than 65 years. Thus, it is unclear whether the conclusions drawn apply to adults aged younger than 65 years.<sup>11,12</sup>

Three studies reported receiving funding from industry, which should be considered when assessing the results.<sup>11,14,15</sup>

### Generalizability

None of the included economic evaluations are broadly applicable to the health care systems in Canada, despite being conducted in high-income countries, as defined by the World Bank.<sup>8</sup> The review did not identify any economic evaluations from a setting in Canada. Two peer-reviewed studies were set in the US,<sup>13,16</sup> 2 in South Korea,<sup>11,12</sup> 1 in Spain,<sup>14</sup> and 1 in Hong Kong.<sup>15</sup> These studies may not be generalizable to the health care setting in Canada, given differences in the structure of the health care systems, culture, access to health care services, mortality rates, and health care costs.<sup>32-34</sup> Specifically, unit cost parameters for health care resource use were specific to the study settings and may not reflect clinical practice or health care costs in Canada. As a result, the model structures may be adaptable to the context in Canada, but the results reported by the publications may not be generalizable to the setting in Canada.

## Conclusions

Eight economic evaluations (6 peer-reviewed, 2 from grey literature) assessing the cost-effectiveness of pneumococcal conjugate vaccines in adults aged 18 to 64 years at high-risk of IPD were identified. The 2 economic evaluations summarized in a single grey literature source were industry-sponsored analyses and have been summarized previously by the Public Health Agency of Canada. The methods and results of the industry-funded models are summarized in [Appendix 3](#) for this review.

Of the 6 peer-reviewed studies summarized in this report, 4 concluded that PCV13 was cost-effective relative to no vaccination, 2 doses of PCV13, PCV13 plus 2 doses of PPSV23, or 2 doses of PPSV23. Two studies concluded that PCV13 plus PPSV23 was cost-effective relative to either no vaccination or PPSV23, but the studies did not evaluate the cost-effectiveness of PCV13 alone. Vaccination strategies considered in the included studies varied. After adjusting for currency and inflation, more than 75% of the reported ICERs were cost-saving or less than \$50,000 per QALY. Smith et al. was the only study that reported ICERs exceeding \$50,000 per QALY.<sup>16</sup> The Smith et al. study based PCV13 efficacy on estimates sourced from an expert panel.<sup>16</sup> By contrast, the other studies relied on the CAPiTA trial results, which were not yet available at the time of the Smith et al. study. Furthermore, the CAPiTA trial excluded high-risk adults aged younger than 65 years. Therefore, clinical efficacy in the population of interest for this review was not established in any of the peer-reviewed studies.

Clinical efficacy in the target population and the generalizability of the economic evaluations to the health care setting in Canada are unknown. To understand the potential cost-effectiveness of pneumococcal conjugate vaccination, a de novo economic evaluation conducted from a setting in Canada is required.

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## Appendix 1: Background Information

Note that this appendix has not been copy-edited.

**Table 2: High-Risk Factors for IPD**

Nonimmunocompromising conditions	Immunocompromising conditions <sup>a</sup>	Other risk factors
<ul style="list-style-type: none"> <li>Chronic cerebrospinal fluid (CSF) leak</li> <li>Chronic neurologic condition that may impair clearance of oral secretions</li> <li>Cochlear implants, including children and adults who are to receive implants</li> <li>Chronic heart disease</li> <li>Diabetes mellitus</li> <li>Chronic kidney disease<sup>a</sup></li> <li>Chronic liver disease, including hepatic cirrhosis due to any cause<sup>a</sup></li> <li>Chronic lung disease, including asthma requiring medical care in the preceding 12 months</li> </ul>	<ul style="list-style-type: none"> <li>Sickle cell disease, congenital or acquired asplenia, or splenic dysfunction<sup>b</sup></li> <li>Congenital immunodeficiencies involving any part of the immune system, including B-lymphocyte (humoral) immunity, T-lymphocyte (cell) mediated immunity, complement system (properdin, or factor D deficiencies), or phagocytic functions</li> <li>Immunocompromising therapy, including use of long-term corticosteroids, chemotherapy, radiation therapy, and postorgan transplant therapy</li> <li>HIV infection</li> <li>Hematopoietic stem cell transplant (recipient)<sup>c</sup></li> <li>Malignant neoplasms, including leukemia and lymphoma</li> <li>Nephrotic syndrome</li> <li>Solid organ or islet transplant (candidate or recipient)</li> </ul>	Individuals <ul style="list-style-type: none"> <li>who smoke</li> <li>who use illicit drugs</li> <li>with alcohol use disorder</li> <li>who are experiencing homelessness</li> <li>who live in communities or settings<sup>d</sup> experiencing sustained high IPD rates.</li> </ul>

<sup>a</sup>Conditions considered to result in the highest risk of IPD.

<sup>b</sup>Generally, asplenia (functional or anatomic), sickle cell disease, and other hemoglobinopathies are not considered immunocompromising conditions, but for the purposes of pneumococcal vaccine recommendations, they are included in this category.

<sup>c</sup>Hematopoietic stem cell transplant recipients have specific pneumococcal vaccination recommendations.

<sup>d</sup>Can include long-term care facilities.

Source: Public Health Agency of Canada.<sup>7</sup>

**Table 3: Comparison of Pneumococcal Vaccines Authorized for Use in Adults in Canada**

Vaccine	PCV13 (PREVNAR 13) <sup>35</sup>	PCV15 (VAXNEUVANCE) <sup>36</sup>	PCV20 (PREVNAR 20) <sup>37</sup>	PPSV23 (PNEUMOVAX 23) <sup>38</sup>
Manufacturer	Pfizer	Merck	Pfizer	Merck
Date of initial authorization in Canada	December 21, 2009	November 16, 2021	May 9, 2022	December 23, 1983
Type of vaccine	Conjugate vaccine	Conjugate vaccine	Conjugate vaccine	Polysaccharide vaccine

Vaccine	PCV13 (PREVNAR 13) <sup>35</sup>	PCV15 (VAXNEUVANCE) <sup>36</sup>	PCV20 (PREVNAR 20) <sup>37</sup>	PPSV23 (PNEUMOVAX 23) <sup>38</sup>
Adult dosage	Single 0.5 mL injection given intramuscularly	Single 0.5 mL injection given intramuscularly	Single 0.5 mL injection given intramuscularly	Single 0.5 mL injection given subcutaneously or intramuscularly
Indicated age	Adults 18 years of age and older	Individuals 6 weeks of age and older	Adults 18 years of age and older	Individuals 2 years of age and older with IPD risk factors and all individuals 50 years of age and older.
Health Canada indication	For the prevention of pneumonia and invasive pneumococcal disease (including sepsis, meningitis, bacteremic pneumonia, pleural empyema and bacteremia) caused by <i>Streptococcus pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.	For the prevention of invasive disease (including sepsis, meningitis, bacteremic pneumonia, pleural empyema and bacteremia) caused by <i>Streptococcus pneumoniae</i> serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F).	For the prevention of pneumonia and invasive pneumococcal disease (including sepsis, meningitis, bacteremic pneumonia, pleural empyema and bacteremia) caused by <i>Streptococcus pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F.	For pneumococcal disease caused by those pneumococcal types included in the vaccine (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F).
Price per dose (\$) <sup>a</sup>	99.91	99.90	109.90	35.24

Note: at the time of this review, the Health Canada product monograph for PCV21 is not publicly available.

<sup>a</sup>All prices are wholesale prices retrieved from IQVIA DeltaPA (accessed May 2024) and do not include dispensing fees.<sup>31</sup>

**Table 4: Comparison of Serotypes Included In Pneumococcal Vaccines Authorized for Use in Canada**

Serotype	PCV13	PCV15	PCV20	PPSV23
1	Yes	Yes	Yes	Yes
2	No	No	No	Yes
3	Yes	Yes	Yes	Yes
4	Yes	Yes	Yes	Yes
5	Yes	Yes	Yes	Yes
6A	Yes	Yes	Yes	No
6B	Yes	Yes	Yes	Yes
7F	Yes	Yes	Yes	Yes
8	No	No	Yes	Yes
9N	No	No	No	Yes
9V	Yes	Yes	Yes	Yes
10A	No	No	Yes	Yes

Serotype	PCV13	PCV15	PCV20	PPSV23
11A	No	No	Yes	Yes
12F	No	No	Yes	Yes
14	Yes	Yes	Yes	Yes
15B	No	No	Yes	Yes
17F	No	No	No	Yes
18C	Yes	Yes	Yes	Yes
19A	Yes	Yes	Yes	Yes
19F	Yes	Yes	Yes	Yes
20	No	No	No	Yes
22F	No	Yes	Yes	Yes
23F	Yes	Yes	Yes	Yes
33F	No	Yes	Yes	Yes

Note: vaccine serotypes were sourced from the respective product monographs.<sup>35-38</sup>

**Table 5: Currency Conversion Rates**

Author, year	Country, currency	PPP rate	Inflation rate
Choi et al., 2018 <sup>11</sup>	South Korea, 2015 USD	1.248042	1.2663477
Heo et al., 2017 <sup>12</sup>	South Korea, 2015 USD	1.248042	1.2663477
Ishigami et al., 2019 <sup>13</sup>	US, 2018 USD	1.206524	1.1984906
Rodriguez Gonzalez-Moro et al., 2016 <sup>14</sup>	Spain, 2015 Euros	1.877489 <sup>a</sup>	1.2663477
Shami et al., 2020 <sup>15</sup>	Hong Kong, 2017 USD	1.212304	1.2243639
Smith et al., 2013 <sup>16</sup>	US, 2006 USD	1.205365	1.4703704

CAD = Canadian dollar; PPP = purchasing power parity; USD = US dollar.

Note: Monetary amounts were first converted to CAD using OECD PPP rates<sup>9</sup> for the respective currency year and then inflated to 2024 CAD using the Bank of Canada inflation calculator (accessed April 3, 2024).<sup>10</sup>

<sup>a</sup>Rate obtained by dividing the Canadian 2015 PPP rate for CAD per USD (1.248042) by the Spanish 2015 PPP rate for Euro per USD (0.664740).<sup>9</sup>



## Appendix 2: Included Peer-Reviewed Study Results

**Table 6: Characteristics of Included Peer-Reviewed Studies**

Author, Year	Choi et al., 2018 <sup>11</sup>	Heo et al., 2017 <sup>12</sup>	Ishigami et al., 2019 <sup>13</sup>	Rodriguez Gonzalez-Moro et al., 2016 <sup>14</sup>	Shami et al., 2020 <sup>15</sup>	Smith et al., 2013 <sup>16</sup>
Country	South Korea	South Korea	US	Spain	Hong Kong	US
Perspective	Health care payer	Societal	Health care payer	Health care payer	Societal	Societal
Modelling approach	Markov model	Markov model	Markov model	Markov model	Sequential deterministic model (model structure not specified)	Markov model
Time horizon	Lifetime	15-years	Lifetime	Lifetime	Lifetime	15-years
Discount rate	3%	5%	3%	3%	4%	3%
Study population	<b>Primary analysis:</b> Adults aged ≥ 65 years and at-risk <sup>a</sup> adults aged ≥ 65 years <b>Secondary analysis:</b> At-risk <sup>a</sup> adults aged 18 to 64 years	<b>Primary analysis:</b> Adults aged ≥ 65 years <b>Secondary analysis:</b> Low-, moderate-, and high-risk <sup>b</sup> adults aged 50 to 64 years	Adults with CKD aged 50 to 64 and 65 to 79 years	Adults with COPD aged ≥ 50 years	Adults aged 20 to 64 years with high-risk conditions <sup>d</sup> and adults ≥ 65 years	Immunocompromised <sup>e</sup> adults aged 19 to 64 years
Relevant population	At-risk <sup>a</sup> adults aged 18 to 64 years	Moderate- and high-risk <sup>b</sup> adults aged 50 to 64 years	Adults with CKD aged 50 to 64 years	Adults with COPD aged 50 to 64 years	Adults aged 20 to 64 years with high-risk <sup>d</sup> conditions	Aligned with study population
Relevant intervention(s)	PCV13 + PPSV23	PCV13	PCV13	PCV13	PCV13 + PPSV23	PCV13 2 doses of PCV13 PCV13 + 2 doses of PPSV23
Comparator(s)	PPSV23	No vaccination PPSV23	No vaccination	PPSV23	PPSV23	No vaccination PPSV23 2 doses of PPSV23

Author, Year	Choi et al., 2018 <sup>11</sup>	Heo et al., 2017 <sup>12</sup>	Ishigami et al., 2019 <sup>13</sup>	Rodriguez Gonzalez-Moro et al., 2016 <sup>14</sup>	Shami et al., 2020 <sup>15</sup>	Smith et al., 2013 <sup>16</sup>
<b>Cost per dose (original currency)</b>	PCV13 = US\$50.48 PPSV23 = US\$16.74	PCV13 = US\$50.31 PPSV23 = US\$14.13	PCV13 = US\$132 <sup>c</sup>	PCV13 = €47.04 PPSV23 = €8.70	NR	PCV13 = US\$128 <sup>c</sup> PPSV23 = US\$43 <sup>c</sup>
<b>Cost per dose (CA\$ 2024)<sup>f</sup></b>	PCV13 = \$79.78 PPSV23 = \$26.46	PCV13 = \$79.51 PPSV23 = \$22.33	PCV13 = \$191 <sup>c</sup>	PCV13 = \$111.84 PPSV23 = \$20.68	NA	PCV13 = \$226.86 <sup>c</sup> PPSV23 = \$76.21 <sup>c</sup>
<b>Industry funding</b>	Pfizer	None	None	Pfizer	Pfizer	None

CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; NA = not applicable; NR = not reported; PCV13 = pneumococcal conjugate 13-valent; PPSV23 = pneumococcal polysaccharide 23-valent.

Notes: All studies were cost-utility analyses. Relevant interventions and comparators assume 1 dose per vaccine unless otherwise specified.

Note: This table has not been copy-edited.

<sup>a</sup>At-risk conditions, as defined by the authors, include any of the following: chronic heart disease, chronic liver disease, chronic respiratory disease, diabetes, asthma, alcohol abuse and smoking, chronic renal disease, nephrotic syndrome, malignant tumour (hematologic malignancy, solid tumour), and immune deficiency (HIV, organ or bone marrow transplant, low immunoglobulin, asplenia, sickle cell disease, or immunosuppressive therapy).<sup>11</sup>

<sup>b</sup>As defined by the authors, individuals are considered low-risk if they do not satisfy the criteria for high- or moderate-risk. Individuals are considered moderate-risk if they have any of the following: diabetes mellitus, chronic liver disease, chronic pulmonary disease, such as asthma or chronic obstructive lung disease, or chronic cardiovascular disease, such as heart failure, cardiomyopathy, or other chronic conditions affecting cardiac function. Individuals are considered high-risk if they have any of the following: splenic dysfunction including postsplenectomy status, hematologic malignancy such as multiple myeloma, leukemia, or lymphoma, a condition affecting the bone marrow or lymphatic system, such as chemotherapy with alkylating drugs or antimetabolites, or radiation within the previous 3 months, solid organ or stem cell transplant, chronic renal disease such as nephrotic syndrome or chronic renal failure, HIV infection, high-dose corticosteroid use ( $\geq 20$  mg/day of prednisone or an equivalent) lasting 2 or more weeks, or treatment with a recombinant human immunomodulator.<sup>12</sup>

<sup>c</sup>Cost is inclusive of administration costs. Vaccine costs are not presented separately.

<sup>d</sup>As defined by the authors, individuals are considered high-risk if they have any of the following: history of invasive pneumococcal disease, immunocompromised states (asplenia, HIV/AIDS, primary immunodeficiency, immunodeficiencies related to malignancy and transplant, immunodeficiencies related to use of immunosuppressive drugs/systemic steroid), chronic disease (chronic cardiac, pulmonary, liver, or renal disease), diabetes mellitus, or CSF leakage, with cochlear implants.<sup>39</sup>

<sup>e</sup>As defined by the authors, immunocompromising conditions include any of the following: HIV infection, Hodgkin disease, leukemia, lymphoma, myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, solid organ or bone marrow transplant, immunoglobulin deficiency, asplenia, sickle cell disease, or current immunosuppressive therapy (including radiation, systemic steroids, or chemotherapy).<sup>16</sup>

<sup>f</sup>Reported monetary amounts were converted to CAD using OECD purchasing price parity rates<sup>9</sup> for the respective currency year and then inflated to 2024 CAD using the Bank of Canada inflation calculator.<sup>10</sup> [Appendix 1, Table 5](#) details the PPP and inflation rates used to adjust monetary amounts to 2024 Canadian dollars.

**Table 7: Quality Appraisal Results**

Author, year	Critical appraisal: Joanna Briggs Institute checklist <sup>a</sup>											Total criteria met
	1	2	3	4	5	6	7	8	9	10	11	
<b>Peer-reviewed studies, broad population</b>												
Choi et al., 2018 <sup>11</sup>	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	6
Heo et al., 2017 <sup>12</sup>	Yes	Yes	Yes	No	No	No	Yes	Yes	No	No	No	5
Shami et al., 2020 <sup>15</sup>	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	No	5
Smith et al., 2013 <sup>16</sup>	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	No	5
<b>Peer-reviewed studies, narrow population</b>												
Ishigami et al., 2019 <sup>13</sup>	No	No	Unsure	No	No	No	Yes	Yes	Yes	No	No	3
Rodriguez Gonzalez-Moro et al., <sup>14</sup> 2016 <sup>b</sup>	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	6

NA = not applicable.

Note: This table has not been copy-edited.

<sup>a</sup>Questions:

1Is there a well-defined question?

2Is there a comprehensive description of alternatives?

3Are all important and relevant costs and outcomes for each alternative identified?

4Has clinical effectiveness been established?

5Are costs and outcomes measured accurately?

6Are costs and outcomes valued credibly?

7Are costs and outcomes adjusted for differential timing?

8Is there an incremental analysis of costs and consequences?

9Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?

10Do study results include all issues of concern to users?

11Are the results generalizable to the setting of interest in the review?

**Table 8: Key Clinical Parameters of Included Peer-Reviewed Studies of Adults at Least 18 Years to 64 Years**

Parameter	Author, year	Choi et al., 2018 <sup>11</sup>	Shami et al., 2020 <sup>15</sup>	Smith et al., 2013 <sup>16</sup>
Source of Clinical Efficacy	Vaccine uptake	100%	PCV13 + PPSV23: 10% PPSV23: 0%	33.9%
	Indirect Effects	Yes (relative reduction in IPD incidence)	No	Yes (relative reduction in PD incidence)
	PCV13	Moderate-risk: Expert panel High-risk: RCT investigating the VE of PCV9 in infants <sup>21</sup>	CAPiTA clinical trial <sup>20</sup>	Expert panel
	PPSV23	Moderate-risk: Expert panel and assumption High-risk: Expert panel and assumption	Assumption	Assumption

Parameter	Author, year	Choi et al., 2018 <sup>11</sup>	Shami et al., 2020 <sup>15</sup>	Smith et al., 2013 <sup>16</sup>
VE: IPD	PCV13	Moderate-risk: 63.8% High-risk: 58.5%	75.8%	Year 1: 50% Year 3: 45% Year 5: 35% Year 10: 25% Year 15: 5%
	PPSV23	Moderate-risk: 65.6% High-Risk: 20.0%	NR	50% of base IPD VE for PCV13
VE: Pneumonia	PCV13	<b>Adults aged 18 to 49</b> Moderate-risk: 5.6% <sup>a</sup> High-risk: 3.7% <sup>a</sup> <b>Adults aged 50 to 54</b> Moderate-risk: 5.4% <sup>a</sup> High-risk: 3.5% <sup>a</sup>	41.1% <sup>b</sup>	Year 1: 35% <sup>d</sup> Year 3: 32% <sup>d</sup> Year 5: 25% <sup>d</sup> Year 10: 18% <sup>d</sup> Year 15: 4% <sup>d</sup>
	PPSV23	0% <sup>a</sup>	0% <sup>c</sup>	0% <sup>b</sup>
Serotype coverage	PCV13	IPD: 35.1% NPP: 35.2%	Adults aged 20 to 64: 65%	Adults aged 19 to 49: 51.9% Adults aged 50 to 59: 48.3%
	PPSV23	IPD: 59.5% NPP: 49.8%	Adults aged 20 to 64: 76%	Adults aged 19 to 49: 78.0% Adults aged 50 to 59: 73.3%
	PCV13 + PPSV23	NR	NA	NR

IPD = invasive pneumococcal disease; NA = not applicable; NBP = nonbacteremic pneumonia; NR = not reported; NPP = nonbacteremic pneumococcal pneumonia; PCV13 = pneumococcal conjugate 13-valent; PD = pneumococcal disease; PPSV23 = pneumococcal polysaccharide 23-valent; RCT = randomized controlled trial; VE = vaccine effectiveness.

Notes: only inputs specific to the at-risk population, as defined by [Table 2](#), are reported (i.e., inputs pertaining to adults 65 and older or adults who are not at high risk are not reported).

Note: This table has not been copy-edited.

<sup>a</sup>Rate is specific to all-cause pneumonia.

<sup>b</sup>Rate is specific to NBP.

<sup>c</sup>Rate is specific to all-cause NBP.

<sup>d</sup>Rate is specific to NPP.

**Table 9: Key Clinical Parameters of Included Peer-Reviewed Studies of Adults 50 to 64 Years**

Parameter	Author, year	Heo et al., 2017 <sup>12</sup>	Ishigami et al., 2019 <sup>13</sup>	Rodriguez Gonzalez-Moro et al., 2016 <sup>14</sup>
Source of Clinical Efficacy	Vaccine uptake	60%	With clinical indication: 28.5% Without clinical indication: 9.7%	41%
	Indirect Effects	Yes (relative reduction in IPD and NPP incidence)	No	Yes (relative reduction in IPD and NBP incidence)

Parameter	Author, year	Heo et al., 2017 <sup>12</sup>	Ishigami et al., 2019 <sup>13</sup>	Rodriguez Gonzalez-Moro et al., 2016 <sup>14</sup>
	PCV13	CAPiTA clinical trial <sup>20</sup> and RCT investigating the VE of PCV9 in infants <sup>21</sup>	CAPiTA clinical trial <sup>20</sup>	CAPiTA clinical trial <sup>20</sup>
	PPSV23	Cochrane meta-analysis, <sup>22</sup> expert survey, and assumption	NA	Cochrane meta-analysis, <sup>22</sup> an observational study in adults ≥ 65, <sup>23</sup> and assumption
VE: IPD	PCV13	Year 1: 79.4% Year 3: 70.6% Year 5: 61.8% Year 7: 52.9% Year 10: 44.1% Year 15: 39.7%	51.8%	Year 0: 82.0% Years 1 to 5: 82.9% Years 6 to 10: 53.3% Years 11 to 15: 21.0% Years 15+: 19.3%
	PPSV23	Year 1: 95.3% Year 3: 91.2% Year 5: 87.2% Year 7: 61.5% Year 10: 20.5% Year 15: 0.0%	NA	Year 0: 87.3% Years 1 to 5: 69.0% Years 6 to 10: 22.8% Years 11 to 15: 2.7% Years 15+: 0.7%
VE: Pneumonia	PCV13	Year 1: 52.0% <sup>a</sup> Year 3: 46.6% <sup>a</sup> Year 5: 39.9% <sup>a</sup> Year 7: 32.4% <sup>a</sup> Year 10: 28.6% <sup>a</sup> Year 15: 25.9% <sup>a</sup>	30.6% <sup>b</sup>	Year 0: 9.5% <sup>c</sup> Years 1 to 5: 9.4% <sup>c</sup> Years 6 to 10: 6.2% <sup>c</sup> Years 11 to 15: 2.4% <sup>c</sup> Years 15+: 2.2% <sup>c</sup>
	PPSV23	0% <sup>a</sup>	NA	0% <sup>c</sup>
Serotype coverage	PCV13	IPD: 35.1% NPP: 35.2%	NR	IPD: 70.0% NBP: 19.4%
	PPSV23	IPD: 59.5% NPP: 49.8%	NR	IPD: 76.5% NBP: NR
	PCV13 + PPSV23	IPD: 60.8% NPP: 53.4%	NA	NA

IPD = invasive pneumococcal disease; NA = not applicable; NBP = nonbacteremic pneumonia; NR = not reported; NPP = nonbacteremic pneumococcal pneumonia; PCV13 = pneumococcal conjugate 13-valent; PPSV23 = pneumococcal polysaccharide 23-valent; RCT = randomized controlled trial; VE = vaccine effectiveness.

Notes: only inputs specific to the at-risk population, as defined by [Table 2](#), are reported (i.e., inputs pertaining to adults 65 and older or adults who are not at high risk are not reported). Shami et al. report the results for the population aged 50 to 64; parameters are presented in [Table 8](#).

Note: This table has not been copy-edited.

<sup>a</sup>Rate is specific to NPP.

<sup>b</sup>Rate is specific to noninvasive pneumococcal pneumonia.

<sup>c</sup>Rate is specific to NBP.

**Table 10: Original ICERs of Included Peer-Reviewed Studies of Adults at Least 18 Years to 64 Years**

Author, year	Country, currency	Population	Original ICER (monies/QALY)				
			PCV13 vs. no vaccination	2 doses PCV13 vs. PCV13 + 2 doses PPSV23	PCV13 + PPSV23 vs. no vaccination	PCV13 + 2 doses PPSV23 vs. PCV13	PCV13 + PPSV23 vs. PPSV23
Choi et al., 2018 <sup>11</sup>	South Korea, 2015 USD	18 to 64 and at risk <sup>a</sup>	NA	NA	6,643	NA	3,629
Shami et al., 2020 <sup>15</sup>	Hong Kong, 2017 USD	20 to 49 with chronic conditions <sup>b</sup>	NA	NA	NA	NA	26,677 <sup>c</sup>
		20 to 49 and immunocompromised <sup>d</sup>	NA	NA	NA	NA	Dominant <sup>c</sup>
		20 to 49 and high risk <sup>e</sup>	NA	NA	NA	NA	16,700 <sup>c</sup>
Smith et al., 2013 <sup>16</sup>	US, 2006 USD	19 to 64 and Immunocompromised <sup>f,g</sup>	70,937	Dominated	NA	136,724	NA
		19 to 64 and HIV positive <sup>g</sup>	44,316	Dominated	NA	89,391	NA

HIV = HIV; ICER = incremental cost-effectiveness ratio; NA = not applicable; PCV13 = pneumococcal conjugate 13-valent; PPSV23 = pneumococcal polysaccharide 23-valent; QALY = quality-adjusted life-year; USD = US dollar.

Notes: ICERs assume 1 dose per vaccine unless otherwise specified.

Note: This table has not been copy-edited.

<sup>a</sup>As defined by the authors, individuals at-risk have one or more of the following “chronic heart disease, chronic liver disease, chronic respiratory disease, diabetes, asthma, alcohol abuse and smoking...chronic renal disease, nephrotic syndrome, malignant tumour (hematologic malignancy, solid tumour), and immune deficiency (HIV, organ or bone marrow transplant, low immunoglobulin, asplenia, sickle cell disease, or immunosuppressive therapy)”.<sup>11</sup>

<sup>b</sup>As defined by the authors, chronic conditions include chronic cardiac, pulmonary, liver or renal disease, diabetes mellitus, or CSF leakage.<sup>15</sup>

<sup>c</sup>While Shami et al. assert that the sequential strategy is being compared to PPSV23, as uptake of PPSV23 is 0% among adults less than 65, it is likely more appropriate to state that the sequential strategy is being compared to no vaccination in adults 20 to 49 years of age.<sup>15</sup>

<sup>d</sup>As defined by the authors,<sup>15</sup> immunocompromised individuals include those with asplenia, HIV/AIDS, primary immunodeficiency, immunodeficiencies related to malignancy and transplant, immunodeficiencies related to the use of immunosuppressive drugs/systemic steroids.<sup>39</sup>

<sup>e</sup>As defined by the authors,<sup>15</sup> high-risk individuals have a history of invasive pneumococcal diseases, immunocompromised conditions (asplenia, HIV/AIDS, primary immunodeficiency, immunodeficiencies related to malignancy and transplant, immunodeficiencies related to use of immunosuppressive drugs/systemic steroid), chronic diseases (chronic cardiac, pulmonary, liver or renal disease, diabetes mellitus, or CSF leakage), or cochlear implants.<sup>39</sup>

<sup>f</sup>As defined by the authors, immunocompromised individuals include those with any of the following: HIV infection, Hodgkin disease, leukemia, lymphoma, myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, solid organ or bone marrow transplant, immunoglobulin deficiency, asplenia, sickle cell disease, or current immunosuppressive therapy (including radiation, systemic steroids, or chemotherapy).<sup>16</sup>

<sup>g</sup>In both the immunocompromised and HIV-positive populations, 2 doses of PCV13 was dominated by PCV13 plus 2 doses of PPSV23.<sup>16</sup> Additionally, both PPSV23 and 2 doses of PPSV23 were subject to extended dominance through no vaccination and PCV13.<sup>16</sup>

**Table 11: Original ICERs of Included Peer-Reviewed Studies of Adults 50 to 64 Years**

Author, year	Country, currency	Population	Original ICER (currency/QALY)		
			PCV13 vs. no vaccination	PCV13 vs. PPSV23	PCV13 + PPSV23 vs. PPSV23
Heo et al., 2017 <sup>12</sup>	South Korea, 2015 USD	Moderate-risk <sup>a</sup>	16,782	10,545	NA
		High-risk <sup>b</sup>	7,188	3,761	NA
Ishigami et al., 2019 <sup>13</sup>	US, 2018 USD	Moderate-risk <sup>c</sup> CDK	25,000	NA	NA
		High-risk <sup>d</sup> CKD	17,000	NA	NA
		Kidney failure or nephrotic-range UACR <sup>e</sup>	1,000	NA	NA
Rodriguez Gonzalez-Moro et al., 2016 <sup>14</sup>	Spain, 2015 Euros	COPD	NA	9,800	NA
Shami et al., 2020 <sup>15</sup>	Hong Kong, 2017 USD	Chronic conditions <sup>f</sup>	NA	NA	Dominant <sup>g</sup>
		Immunocompromised <sup>h</sup>	NA	NA	Dominant <sup>g</sup>
		High risk <sup>i</sup>	NA	NA	Dominant <sup>g</sup>

CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; ICER = incremental cost-effectiveness ratio; NA = not applicable; PCV13 = pneumococcal conjugate 13-valent; PPSV23 = pneumococcal polysaccharide 23-valent; QALY = quality-adjusted life-year; UACR = urinary albumin-creatinine ratio; USD = US dollar.

Notes: ICERs assume 1 dose per vaccine unless otherwise specified.

Note: This table has not been copy-edited.

<sup>a</sup>As defined by the authors, individuals must have at least one of the following: diabetes mellitus, chronic liver disease, chronic pulmonary disease, or chronic cardiovascular or other chronic conditions affecting cardiac function.<sup>12</sup>

<sup>b</sup>As defined by the authors, individuals must have at least one of the following: splenic dysfunction including postsplenectomy status, hematologic malignancy, a condition affecting the bone marrow or lymphatic system, solid organ or stem cell transplant, chronic renal disease, HIV infection, high-dose corticosteroid use ( $\geq 20$  mg/day of prednisone or an equivalent) lasting 2 or more weeks, or treatment with a recombinant human immunomodulator.<sup>12</sup>

<sup>c</sup>CKD with moderate-risk is defined by the authors as having an "eGFR of 45 to 59 mL/min/1.73 m<sup>2</sup> and UACR < 30 mg/g or eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> and UACR of 30 to 299 mg/g."<sup>13</sup>

<sup>d</sup>CKD with high-risk is defined by the authors as having an "eGFR of 15 to 44 mL/min/1.73 m<sup>2</sup> regardless of UACR, eGFR of 45 to 59 mL/min/1.73 m<sup>2</sup> and UACR of 30 to 299 mg/g, or UACR of 300 to 1,999 mg/g regardless of eGFR."<sup>13</sup>

<sup>e</sup>Kidney failure or nephrotic-range UACR is defined by the authors as having an "eGFR < 15 mL/min/1.73 m<sup>2</sup> and nephrotic-range albuminuria was UACR  $\geq 2,000$  mg/g."<sup>13</sup>

<sup>f</sup>As defined by the authors, chronic conditions include chronic cardiac, pulmonary, liver or renal disease, diabetes mellitus, or CSF leakage.<sup>15</sup>

<sup>g</sup>While Shami et al. assert that the sequential strategy is being compared to PPSV23, as uptake of PPSV23 is 0% among adults less than 65, it is likely more appropriate to state that the sequential strategy is being compared to no vaccination in adults 20 to 49 years of age.<sup>15</sup>

<sup>h</sup>As defined by the authors,<sup>15</sup> immunocompromised individuals include those with asplenia, HIV/AIDS, primary immunodeficiency, immunodeficiencies related to malignancy and transplant, immunodeficiencies related to the use of immunosuppressive drugs/systemic steroids.<sup>39</sup>

<sup>i</sup>As defined by the authors,<sup>15</sup> high-risk individuals have a history of invasive pneumococcal diseases, immunocompromised conditions (asplenia, HIV/AIDS, primary immunodeficiency, immunodeficiencies related to malignancy and transplant, immunodeficiencies related to use of immunosuppressive drugs/systemic steroid), chronic diseases (chronic cardiac, pulmonary, liver or renal disease, diabetes mellitus, or CSF leakage), or cochlear implants.<sup>39</sup>

**Table 12: ICERs (2024 \$CA) of Included Peer-Reviewed Studies of Adults at Least 18 Years to 64 Years**

Author, year	Country, currency	Population	ICER (2024 \$CA/QALY)				
			PCV13 vs. no vaccination	2 doses PCV13 vs. PCV13 + 2 doses PPSV23	PCV13 + PPSV23 vs. no vaccination	PCV13 + 2 doses PPSV23 vs. PCV13	PCV13 + PPSV23 vs. PPSV23
Choi et al., 2018 <sup>11</sup>	South Korea, 2015 USD	18 to 64 and at risk <sup>a</sup>	NA	NA	10,499	NA	5,735
Shami et al., 2020 <sup>15</sup>	Hong Kong, 2017 USD	20 to 49 with chronic conditions <sup>b</sup>	NA	NA	NA	NA	39,597 <sup>c</sup>
		20 to 49 and immunocompromised <sup>d</sup>	NA	NA	NA	NA	Dominant <sup>c</sup>
		20 to 49 and high risk <sup>e</sup>	NA	NA	NA	NA	24,788 <sup>c</sup>
Smith et al., 2013 <sup>16</sup>	US, 2006 USD	19 to 64 and Immunocompromised <sup>f,g</sup>	125,724	Dominated	NA	242,320	NA
		19 to 64 and HIV positive <sup>g</sup>	78,543	Dominated	NA	158,431	NA

HIV = HIV; ICER = incremental cost-effectiveness ratio; NA = not applicable; PCV13 = pneumococcal conjugate 13-valent; PPSV23 = pneumococcal polysaccharide 23-valent; QALY = quality-adjusted life-year; USD = US dollar.

Note: ICERs assume 1 dose per vaccine unless otherwise specified. Reported USD amounts were converted to CAD using OECD purchasing price parity rates<sup>9</sup> for the respective currency year and then inflated to 2024 CAD using the Bank of Canada inflation calculator.<sup>10</sup> [Appendix 1, Table 5](#) details the PPP and inflation rates used to adjust monetary amounts to 2024 Canadian dollars.

Note: This table has not been copy-edited.

<sup>a</sup>As defined by the authors, individuals at-risk have one or more of the following “chronic heart disease, chronic liver disease, chronic respiratory disease, diabetes, asthma, alcohol abuse and smoking...chronic renal disease, nephrotic syndrome, malignant tumour (hematologic malignancy, solid tumour), and immune deficiency (HIV, organ or bone marrow transplant, low immunoglobulin, asplenia, sickle cell disease, or immunosuppressive therapy)”.<sup>11</sup>

<sup>b</sup>As defined by the authors, chronic conditions includes chronic cardiac, pulmonary, liver or renal disease, diabetes mellitus, or CSF leakage.<sup>15</sup>

<sup>c</sup>While Shami et al. assert that the sequential strategy is being compared to PPSV23, as uptake of PPSV23 is 0% among adults less than 65, it is likely more appropriate to state that the sequential strategy is being compared to no vaccination in adults 20 to 49 years of age.<sup>15</sup>

<sup>d</sup>As defined by the authors,<sup>15</sup> immunocompromised individuals include those with asplenia, HIV/AIDS, primary immunodeficiency, immunodeficiencies related to malignancy and transplant, immunodeficiencies related to the use of immunosuppressive drugs/systemic steroids.<sup>39</sup>

<sup>e</sup>As defined by the authors,<sup>15</sup> high-risk individuals have a history of invasive pneumococcal diseases, immunocompromised conditions (asplenia, HIV/AIDS, primary immunodeficiency, immunodeficiencies related to malignancy and transplant, immunodeficiencies related to use of immunosuppressive drugs/systemic steroid), chronic diseases (chronic cardiac, pulmonary, liver or renal disease, diabetes mellitus, or CSF leakage), or cochlear implants.<sup>39</sup>

<sup>f</sup>As defined by the authors, immunocompromised individuals include those with any of the following: HIV infection, Hodgkin disease, leukemia, lymphoma, myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, solid organ or bone marrow transplant, immunoglobulin deficiency, asplenia, sickle cell disease, or current immunosuppressive therapy (including radiation, systemic steroids, or chemotherapy).<sup>16</sup>

<sup>g</sup>In both the immunocompromised and HIV-positive populations, 2 doses of PCV13 was dominated by PCV13 + 2 doses of PPSV23.<sup>16</sup> Additionally, both PPSV23 and 2 doses of PPSV23 were subject to extended dominance through no vaccination and PCV13.<sup>16</sup>



**Table 13: ICERs (2024 \$CA) of Included Peer-Reviewed Studies of Adults 50 to 64 Years**

Author, year	Country, currency	Population	ICER (2024 \$CA/QALY)		
			PCV13 vs. no vaccination	PCV13 vs. PPSV23	PCV13 + PPSV23 vs. PPSV23
Heo et al., 2017 <sup>12</sup>	South Korea, 2015 USD	Moderate risk <sup>a</sup>	26,523	16,666	NA
		High risk <sup>b</sup>	11,360	5,944	NA
Ishigami et al., 2019 <sup>13</sup>	US, 2018 USD	Moderate risk <sup>c</sup> CKD	36,150	NA	NA
		High risk <sup>d</sup> CKD	24,582	NA	NA
		Kidney failure or nephrotic-range UACR <sup>e</sup>	1,446	NA	NA
Rodriguez Gonzalez-Moro et al., 2016 <sup>14</sup>	Spain, 2015 Euros	COPD	NA	23,300	NA
Shami et al., 2020 <sup>15</sup>	Hong Kong, 2017 USD	Chronic conditions <sup>f</sup>	NA	NA	Dominant <sup>g</sup>
		Immunocompromised <sup>h</sup>	NA	NA	Dominant <sup>g</sup>
		High risk <sup>i</sup>	NA	NA	Dominant <sup>g</sup>

CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; ICER = incremental cost-effectiveness ratio; NA = not applicable; PCV13 = pneumococcal conjugate 13-valent; PPSV23 = pneumococcal polysaccharide 23-valent; QALY = quality-adjusted life-year; UACR = urinary albumin-creatinine ratio; USD = US dollar.

Note: ICERs assume 1 dose per vaccine unless otherwise specified. Reported monetary amounts were converted to CAD using OECD purchasing price parity rates<sup>9</sup> for the respective currency year and then inflated to 2024 CAD using the Bank of Canada inflation calculator.<sup>10</sup> [Appendix 1, Table 5](#) details the PPP and inflation rates used to adjust monetary amounts to 2024 Canadian dollars.

Note: This table has not been copy-edited.

<sup>a</sup>As defined by the authors, individuals must have at least one of the following: diabetes mellitus, chronic liver disease, chronic pulmonary disease, or chronic cardiovascular or other chronic conditions affecting cardiac function.<sup>12</sup>

<sup>b</sup>As defined by the authors, individuals must have at least one of the following: splenic dysfunction including postsplenectomy status, hematologic malignancy, a condition affecting the bone marrow or lymphatic system, solid organ or stem cell transplant, chronic renal disease, HIV infection, high-dose corticosteroid use ( $\geq 20$  mg/day of prednisone or an equivalent) lasting 2 or more weeks, or treatment with a recombinant human immunomodulator.<sup>12</sup>

<sup>c</sup>CKD with moderate-risk is defined by the authors as having an "eGFR of 45 to 59 mL/min/1.73 m<sup>2</sup> and UACR < 30 mg/g or eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> and UACR of 30 to 299 mg/g."<sup>13</sup>

<sup>d</sup>CKD with high-risk is defined by the authors as having an "eGFR of 15 to 44 mL/min/1.73 m<sup>2</sup> regardless of UACR, eGFR of 45 to 59 mL/min/1.73 m<sup>2</sup> and UACR of 30 to 299 mg/g, or UACR of 300 to 1,999 mg/g regardless of eGFR."<sup>13</sup>

<sup>e</sup>Kidney failure or nephrotic-range UACR is defined by the authors as having an "eGFR < 15 mL/min/1.73 m<sup>2</sup> and nephrotic-range albuminuria was UACR  $\geq 2,000$  mg/g."<sup>13</sup>

<sup>f</sup>As defined by the authors, chronic conditions include chronic cardiac, pulmonary, liver or renal disease, diabetes mellitus, or CSF leakage.<sup>15</sup>

<sup>g</sup>While Shami et al. assert that the sequential strategy is being compared to PPSV23, as uptake of PPSV23 is 0% among adults less than 65, it is likely more appropriate to state that the sequential strategy is being compared to no vaccination in adults 20 to 49 years of age.<sup>15</sup>

<sup>h</sup>As defined by the authors,<sup>15</sup> immunocompromised individuals include those with asplenia, HIV/AIDS, primary immunodeficiency, immunodeficiencies related to malignancy and transplant, immunodeficiencies related to the use of immunosuppressive drugs/systemic steroids.<sup>39</sup>

<sup>i</sup>As defined by the authors,<sup>15</sup> high-risk individuals have a history of invasive pneumococcal diseases, immunocompromised conditions (asplenia, HIV/AIDS, primary immunodeficiency, immunodeficiencies related to malignancy and transplant, immunodeficiencies related to use of immunosuppressive drugs/systemic steroid), chronic diseases (chronic cardiac, pulmonary, liver or renal disease, diabetes mellitus, or CSF leakage), or cochlear implants.<sup>39</sup>

## Appendix 3: Included Grey Literature Economic Evaluations

Note that this appendix has not been copy-edited.

**Table 14: Characteristics of Included Grey Literature Economic Evaluations**

Author, year	Kobayashi et al., 2023 <sup>17</sup> (Merck model)	Kobayashi et al., 2023 <sup>17</sup> (Pfizer model)
Country	US	US
Perspective	Societal	Health care payer and societal <sup>a</sup> perspective
Modelling approach	Multicohort model	Multicohort model
Time horizon	Lifetime	Lifetime
Discount rate	NR	NR
Study population	Adults aged 19 to 64 with certain risk conditions <sup>b</sup>	Adults aged 42 years (age selected to represent adults aged 19 to 64 years) with certain risk conditions <sup>b</sup>
Relevant population	Aligned with study population	Aligned with study population
Relevant intervention(s)	<ul style="list-style-type: none"> <li>• Single dose of PCV20</li> <li>• PCV15 + PPSV23</li> </ul>	Single dose of PCV20
Comparator	Previous CDC recommendation <sup>c</sup>	Previous CDC recommendation <sup>c</sup>
Cost per dose	NR	NR
Source of clinical efficacy	NR	NR
Industry funding	Merck <sup>d</sup>	Pfizer <sup>d</sup>

CDC = US Centers for Disease Control and Prevention; NR = not reported; PCV15 = pneumococcal 15-valent conjugate vaccine; PCV20 = pneumococcal 20-valent conjugate vaccine; PPSV23 = pneumococcal polysaccharide 23-valent vaccine.

Note: Limited details were provided in Kobayashi et al. regarding modelling inputs and assumptions. The models are described in greater detail elsewhere.<sup>7</sup>

<sup>a</sup>The report does not specify the perspective from which the presented results are reported.

<sup>b</sup>As defined by the CDC, risk conditions includes any of the following: alcoholism or cigarette smoking, CSF leak, chronic heart disease, including congestive heart failure and cardiomyopathies, excluding hypertension, chronic liver disease, chronic lung disease, including COPD, emphysema, and asthma, cochlear implant, decreased immune function from disease or drugs (i.e., immunocompromising conditions), diabetes mellitus, chronic renal failure or nephrotic syndrome, congenital or acquired asplenia, or splenic dysfunction, congenital or acquired immunodeficiency (includes B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders [excluding chronic granulomatous disease]), diseases or conditions treated with immunosuppressive drugs or radiation therapy (includes Hodgkin disease, leukemias, lymphomas, malignant neoplasms, and solid organ transplant), HIV infection, sickle cell disease, or other hemoglobinopathies).<sup>40</sup>

<sup>c</sup>The previous CDC recommendation pneumococcal vaccination strategy was defined by the authors as “PPSV23 only for adults aged 19–64 years with chronic medical conditions; PPSV23 with an option to receive PCV13 on the basis of shared clinical decision-making for adults aged ≥ 65 years without an immunocompromising condition, a CSF leak, or a cochlear implant; and both PCV13 and PPSV23 for adults with an immunocompromising condition, a CSF leak, or a cochlear implant.”<sup>17</sup>

<sup>d</sup>Conflict of interest statements are provided in Leidner et al.<sup>18</sup>

**Table 15: ICERs of Included Grey Literature Economic Evaluations**

Author, year	Country, currency <sup>a</sup>	Population	Original ICER (US\$/QALY)		ICER (2024 \$CA/QALY)	
			PCV15 + PPSV23 vs. PR	PCV20 vs. PR	PCV15 + PPSV23 vs. PR	PCV20 vs. PR
Kobayashi et al., 2023 <sup>17</sup> (Merck model)	US, 2022 USD	At-risk adults aged 19 to 64	\$274,000 to \$342,000	\$63,000 to \$201,000	\$345,161 to \$430,821	\$79,362 to \$253,202
Kobayashi et al., 2023 <sup>17</sup> (Pfizer model)		Adults aged 42 years (age selected to represent adults aged 19 to 64 years)	NA	\$13,000	NA	\$16,376

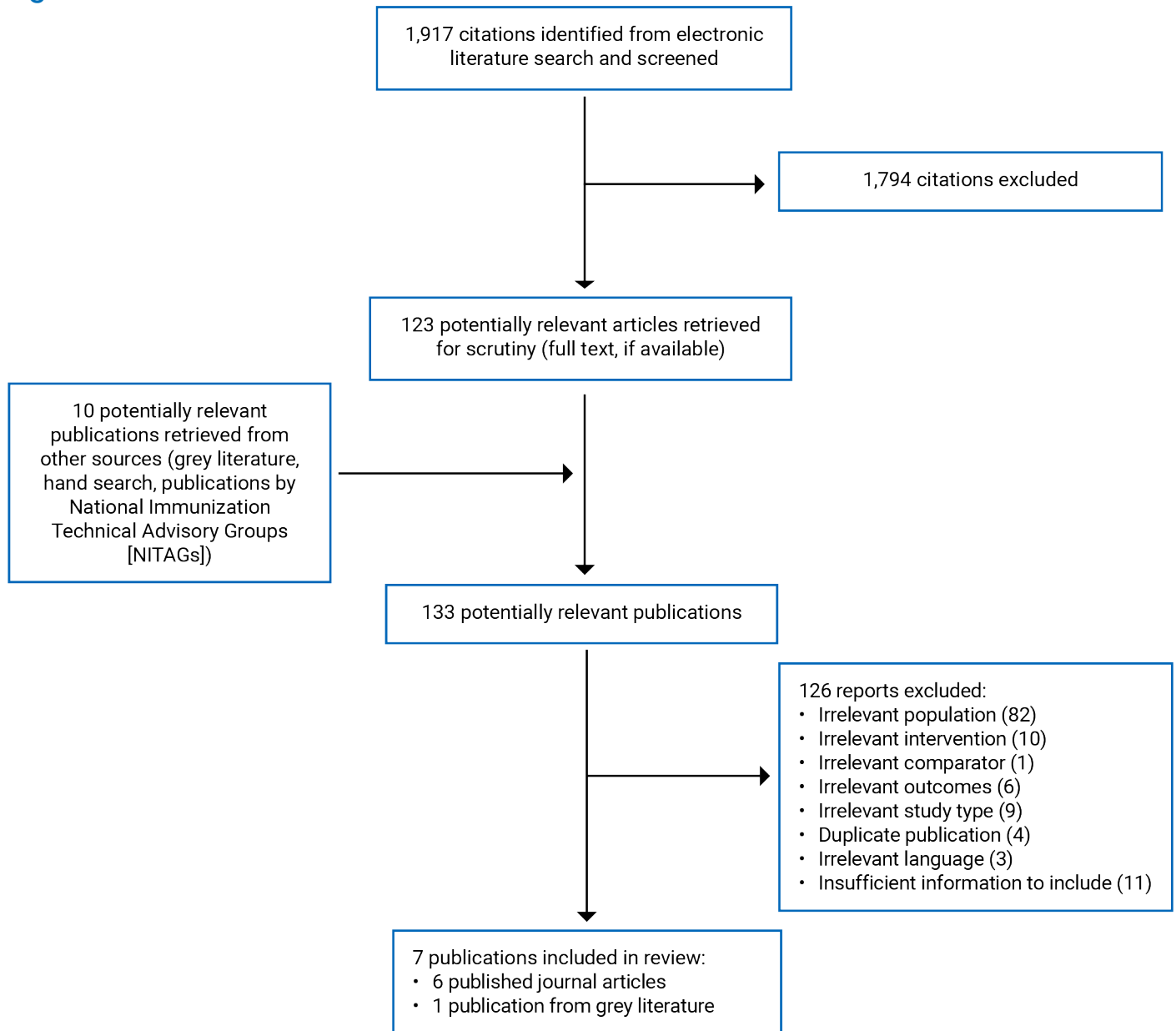
ICER = incremental cost-effectiveness ratio; NA = not applicable; PCV15 = pneumococcal conjugate 15-valent; PCV20 = pneumococcal conjugate 20-valent; PPSV23 = pneumococcal polysaccharide 23-valent; PR = previous recommendation; QALY = quality-adjusted life-year; USD = US dollar.

Note: all ICERs are presented relative to the previous CDC recommendation pneumococcal vaccination strategy, defined by the authors as "PPSV23 only for adults aged 19–64 years with chronic medical conditions; PPSV23 with an option to receive PCV13 on the basis of shared clinical decision-making for adults aged ≥ 65 years without an immunocompromising condition, a CSF leak, or a cochlear implant; and both PCV13 and PPSV23 for adults with an immunocompromising condition, a CSF leak, or a cochlear implant."<sup>17</sup> The reported ranges for the Merck model cover encompass 2 scenarios: one with indirect effects considered, and one without indirect effects considered. Reported USD amounts were converted to CAD using OECD purchasing price parity rates<sup>9</sup> for 2022 (1.164518) and then inflated to 2024 CAD using the Bank of Canada inflation calculator (inflation rate = 1.0817439).<sup>10</sup>

## Appendix 4: Literature Search Strategy

Note that this appendix has not been copy-edited.

Figure 1: Selection of Included Studies



## Economic Literature Search

### Overview

Interface: Ovid

### Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database.

Date of search: February 22, 2024

Alerts: Bi-weekly search updates until project completion (May 13, 2024)

Search filters applied: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; economic evaluations; and costs and cost analysis studies.

### Limits:

- Publication date limit: 2011-present
- Language limit: English- and French-language

### Table 16: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
Exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.pt	Publication type
.mp	Mapped term
.jw	Journal title word (MEDLINE)
freq = #	Requires terms to occur # number of times in the specified fields
Medal	Ovid database code: MEDLINE All, 1946 to present, updated daily

Syntax	Description
Omezd	Ovid database code; Embase, 1974 to present, updated daily

### Multi-Database Strategy

1. exp Pneumococcal Vaccines/
2. (Vaccines/ or Vaccines, Conjugate/) and Pneumococcal Infections/
3. (PCV13 or PCV15 or PCV20 or PCV21 or PPV23 or PPSV23 or PPSV 23 or PNEU-C-15 or PNEU-P-23 or Pneu23 or Prevnar\* or Prevenar\* or PncOMPC or MnCC or PCV7 or PNCRM7 or pneumovax\* or pneumorix\* or Vaxneuvance\* or synflorix\* or pne immune or pneu immune or pne imune or pneimmune or pneimunne or pneimune or apexnar\* or moniarix\* or pneumopur\* or streptopur\* or streptorix\* or 13 vpnc or 13vpnc or 20 vpnc or 20vpnc or SIIP-PCV or PHiD-CV or pneumo 23).ti,ab,kf.
4. ((Pneumoco\* or pneumonia\* or Streptococc\* or strep or PCV 13 or PCV 15 or PCV 20 or PCV 21 or PPV 23 or V116 or v 116 or v 110 or v 114 or v110 or v114) adj5 (vaccin\* or immunis\* or immuniz\*)).ti,ab,kf.
5. ((Pneumoco\* or pneumonia\* or Streptococc\* or strep or PCV 13 or PCV 15 or PCV 20 or PCV 21 or PPV 23 or V116 or v 116 or v 110 or v 114 or v110 or v114) and (vaccin\* or immunis\* or immuniz\*)).ti.
6. ((Pneumoco\* or pneumonia\* or Streptococc\* or strep) and (13-valent or 15 valent or 20 valent or 21 valent or 23 valent or PCV21 or PCV 13 or PCV 15 or PCV 20 or PCV 21 or PPV 23)).ti,ab,kf.
7. 1 or 2 or 3 or 4 or 5 or 6
8. (Adolescent/ or exp Child/ or exp Infant/ or Pediatrics/ or (child or children or childhood or infant or infants or baby or babies or newborn or newborns or neonate or neonatal or neonates or premie or premies or infancy or paediatric or pediatric or girl or girls or boy or boys or kid or kids or teen or teens or teenage or teenager or teenagers or youngster or youngsters or youth or youths or adolescent or adolescents or adolescence or preadolescent or preadolescence or pre adolescent or pre adolescence or preschooler or school age or school aged or schoolchildren).ti,ab.) not (exp Adult/ or (adult or adults or adulthood or middle age or middle aged or elderly or senior or seniors or man or men or woman or women).ti,ab.)
9. 7 not 8
10. (afghan\* or albania\* or algeria\* or angola\* or argentin\* or armenia\* or aruba\* or azerbaijan\* or bahrain\* or bangladesh\* or bengal\* or bangal\* or bayan or bajans or belarus\* or belorus\* or byelarus\* or byelorus\* or belize\* or benin\* or dahomey or bhutan\* or bolivia\* or bosnia\* or herzegovin\* or botswan\* or batswan\* or bechuanaland\* or brazil\* or brasil\* or bulgaria\* or burkina\* or burkinese\* or upper volta\* or burundi\* or urundi\* or cabo verde\* or cape verde\* or cambodia\* or kampuchea\* or khmer\* or cameroon\* or cameroun\* or ubangi shari\* or chad or Chadian or (china\* not (China National Infrastructure or China National Knowledge Infrastructure)) or beijing or shanghai or colombia\* or comoro\* or comore\* or comorian\* or mayotte\* or congo\* or zaire\* or costa rica\* or "cote d'ivoir\*" or "cote d'ivoir\*" or cote divoir\* or cote d ivoir\* or ivory coast\* or ivorian\* or cuba or

cuban or cubans or "cuba's" or djibouti\* or french somaliland\* or dominica\* or ecuador\* or egypt\* or united arab republic\* or el salvador\* or salvadoran\* or guinea\* or equatoguinea\* or eritrea\* or eswatini\* or swaziland\* or swazi\* or swati\* or ethiopia\* or fiji\* or gabon\* or gabonese\* or gabonaise\* or gambia\* or ghana\* or grenada\* or grenadian\* or guatemala\* or haiti\* or hispaniola\* or hondura\* or ((india or indian or indians) not american india\*) or delhi or indonesia\* or iran\* or iraq\* or jamaica\* or jordan\* or kazakh\* or kenya\* or karabati\* or kosovo\* or kosova\* or kyrgyz\* or kirgiz\* or kirghiz\* or laos or lao or laotian\* or lebanon\* or lebanese\* or lesotho\* or lesothan\* or lesothonian\* or basutoland\* or mosotho\* or basotho\* or liberia\* or libya\* or jamahiriya\* or macedonia\* or madagascar\* or malagasy\* or malawi\* or niasaland\* or malaysia\* or malay\* federation or maldives\* or maldivian\* or mali or malian\* or "mali's" or micronesia\* or marshallese\* or kiribati\* or marshall island\* or nauru or nauran or nauruans or "naurian's" or mariana or marianas or palau or paluan\* or tuvalu\* or mauritania\* or mauritan\* or mauritius\* or mexico\* or mexican\* or moldova\* or moldovia\* or mongol\* or montenegr\* or morocco\* or moroccan\* or ifni or mozambique\* or mozambican\* or myanmar\* or burma\* or burmese or namibia\* or nepal\* or netherlands antill\* or nicaragua\* or niger\* or pakistan\* or palestin\* or gaza\* or west bank\* or paraguay\* or peru or peruvian\* or "peru's" or philippine\* or philipine\* or phillipine\* or phillippine\* or filipino\* or filipina\* or russia\* or ussr\* or soviet\* or rwanda\* or rwandese or ruanda\* or ruandese or samoa\* or navigator island\* or polynesia\* or sao tome\* or santomean\* or senegal\* or serbia\* or sierra leone\* or melanesia\* or solomon island\* or norfolk island\* or somali\* or south africa\* or sri lanka\* or ceylon\* or saint lucia\* or st lucia\* or saint vincent\* or st vincent\* or vincentian\* or grenadine\* or sudan\* or surinam\* or syria\* or tajik\* or tadjik\* or tadzhik\* or tanzania\* or tanganyika\* or thai\* or timor leste\* or east timor\* or timorese\* or togo or togoles\* or "togo's" or tonga\* or tunisia\* or turkiy\* or turkey\* or turk or turks or turkish or turkmen\* or uganda\* or ukrain\* or uzbek\* or vanuatu\* or new hebrides\* or venezuela\* or vietnam\* or viet nam\* or yemen\* or yugoslav\* or zambia\* or zimbabwe\* or rhodesia\* or global south or sahara\* or subsahara\* or magreb\* or maghrib\*).ti,ab,hw,kf.

11. (developing countr\* or developing nation\* or developing world or less developed countr\* or less developed nation\* or less developed world or lesser developed countr\* or lesser developed nation\* or lesser developed world or under developed countr\* or under developed nation\* or under developed world or underdeveloped countr\* or underdeveloped nation\* or underdeveloped world or middle income countr\* or middle income nation\* or low income countr\* or low income nation\* or lower income countr\* or lower income nation\* or underserved countr\* or underserved nation\* or under served nation\* or deprived countr\* or high burden countr\* or high burden nation\* or countdown countr\* or countdown nation\* or poor countr\* or poor nation\* or poor world or poorer countr\* or poorer nation\* or poorer world or developing econom\* or less developed econom\* or underdeveloped econom\* or under developed econom\* or middle income econom\* or low income econom\* or lower income econom\* or low gdp or low gnp or low gross domestic or low gross national or lower gdp or lower gnp or lower gross domestic or lower gross national or lmic or lmic's or third world or lami countr\* or transitional countr\* or emerging econom\* or emerging nation\*).ti.
12. ("Georgia (Republic)"/ or (georgia or georgian or georgians).ti,ab,kf.) not (Georgia/ or (atlanta or california or florida).ti,ab,kf.)

13. 10 or 11 or 12
14. (American Samoa or Andorra\* or Antigua\* or Aruba\* or Australia\* or Austria\* or Baham\* or Barbuda\* or Bahrain\* or Barbad\* or Belgium or Belgian or Bermud\* or Brunei or Darussalam or Canad\* or Cayman Islands or Channel Islands or Chile or Chilean\* or Croatia\* or Curacao or Cyprus or cypriot\* or Czech\* or Denmark or Danish or Estonia\* or Faroe Islands or Finland or Finnish or France or French or Guyan\* or guiana\* or guyanese\* or German\* or Gibraltar or Greece or Greek\* or grecian\* or Greenland\* or Guam or Hong Kong or Hungar\* or Iceland\* or Ireland or Irish or "Isle of Man" or Israel\* or Ital\* or Japan\* or Korea\* or Kuwait\* or Latvia\* or Liechtenstein or Lithuania\* or Luxembourg or Macao or Malta or Maltese or "malta's" or Monaco or Nauru or Netherland\* or Dutch or New Caledonia\* or New Zealand\* or Northern Mariana Islands or Norway or Norwegian\* or oman or omani or omanis or "oman's" or Panam\* or Poland or Polish or Portug\* or Puerto Ric\* or Qatar or Romania\* or San Marino or Saudi Arabia\* or Saudis or Seychelles or Singapor\* or Sint Maarten or Slovak\* or Slovenia\* or Spain or Spanish or "St Kitts and Nevis" or saint kitts or st kitts or kittian\* or nevisian\* or St Martin or Swed\* or Switzerland or Swiss or Taiwan\* or Trinidad\* or Tobago or "Turks and Caicos" or United Arab Emirates or UAE or United Kingdom or UK or England or Wales or Welsh or Scotland or Scottish or Great Britain or British or US or USA or "the us" or Uruguay\* or Virgin Islands or high income or higher income or industrialized or industrialised or developed countr\* or british columbia\* or alberta\* or saskatchewan\* or manitoba\* or ontario\* or quebec\* or new brunswick\* or prince edward island\* or nova scotia\* or labrador\* or newfoundland\* or nunavut\* or northwest territor\* or yukon\* or toronto\* or montreal\* or vancouver\* or ottawa\* or calgary\* or edmonton\* or winnipeg\* or Appalachia\* or great lakes or midwestern-us\* or Midwest-us\* or great plains or northeastern-us\* or northeast-us\* or pacific northwest or northwestern-us\* or northwest-us\* or southeast-us\* or southeastern-us\* or southern-us\* or southwest-us\* or southwestern-us\* or "district of Columbia" or Washington dc or Alabama\* or Alaska\* or Arizona\* or Arkansas or California\* or Colorad\* or Connecticut or Delaware or Florid\* or Hawaii\* or Hawai'i\* or Idaho or Illinois or Indiana\* or Iowa\* or Kansas or Kansan or Kentucky or Louisiana\* or Maine or Maryland or Massachusetts or Michigan or Minnesota\* or Mississippi\* or Montana\* or Nebraska\* or Nevada\* or New Hampshire or New Jersey or New Mexico or New York or North Carolin\* or Dakota\* or Ohio or Ohian or Oklahoma\* or Oregon\* or Pennsylvania\* or Rhode Island\* or South Carolin\* or Tennessee\* or Texas or Texan or Utah or Vermont or Virginia or West Virginia\* or Wisconsin or Wyoming).ti,ab,hw,kf.
15. 13 not 14
16. 9 not 15
17. Economics/
18. exp "Costs and Cost Analysis"/
19. Economics, Nursing/
20. Economics, Medical/
21. Economics, Pharmaceutical/
22. exp Economics, Hospital/



23. Economics, Dental/
24. exp "Fees and Charges"/
25. exp Budgets/
26. budget\*.ti,ab,kf.
27. (economic\* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\* or pharmaco-economic\* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
28. (economic\* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\* or pharmaco-economic\* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
29. (cost\* adj2 (effective\* or utilit\* or benefit\* or minimi\* or analy\* or outcome or outcomes)).ab,kf.
30. (value adj2 (money or monetary)).ti,ab,kf.
31. exp models, economic/
32. economic model\*.ab,kf.
33. markov chains/
34. markov.ti,ab,kf.
35. monte carlo method/
36. monte carlo.ti,ab,kf.
37. exp Decision Theory/
38. (decision\* adj2 (tree\* or analy\* or model\*)).ti,ab,kf.
39. or/17-38
40. (systematic review or meta-analysis).pt.
41. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
42. ((systematic\* adj3 (review\* or overview\*)) or (methodologic\* adj3 (review\* or overview\*))).ti,ab,kf.
43. ((quantitative adj3 (review\* or overview\* or synthes\*)) or (research adj3 (integrati\* or overview\*))).ti,ab,kf.
44. ((integrative adj3 (review\* or overview\*)) or (collaborative adj3 (review\* or overview\*)) or (pool\* adj3 analy\*)).ti,ab,kf.
45. (data synthes\* or data extraction\* or data abstraction\*).ti,ab,kf.
46. (handsearch\* or hand search\*).ti,ab,kf.
47. (mantel haenszel or peto or der simonian or dersimonian or fixed effect\* or latin square\*).ti,ab,kf.
48. (met analy\* or metanaly\* or technology assessment\* or HTA or HTAs or technology overview\* or technology appraisal\*).ti,ab,kf.

49. (meta regression\* or metaregression\*).ti,ab,kf.
50. (meta-analy\* or metaanaly\* or systematic review\* or biomedical technology assessment\* or biomedical technology assessment\*).mp,hw.
51. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
52. (cochrane or (health adj2 technology assessment) or evidence report).jw.
53. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
54. (outcomes research or relative effectiveness).ti,ab,kf.
55. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison\*).ti,ab,kf.
56. (multi\* adj3 treatment adj3 comparison\*).ti,ab,kf.
57. (mixed adj3 treatment adj3 (meta-analy\* or metaanaly\*)).ti,ab,kf.
58. umbrella review\*.ti,ab,kf.
59. (multi\* adj2 paramet\* adj2 evidence adj2 synthesis).ti,ab,kf.
60. (multiparamet\* adj2 evidence adj2 synthesis).ti,ab,kf.
61. (multi-paramet\* adj2 evidence adj2 synthesis).ti,ab,kf.
62. or/40-61
63. 39 or 62
64. 16 and 63
65. 64 use medall
66. \*Pneumococcus vaccine/
67. (PCV13 or PCV15 or PCV20 or PCV21 or PPV23 or PPSV23 or PPSV 23 or PNEU-C-15 or PNEU-P-23 or Pneu23 or Prevnar\* or Prevenar\* or PncOMPC or MnCC or PCV7 or PNCRM7 or pneumovax\* or pneumorix\* or Vaxneuvance\* or synflorix\* or pne immune or pneu immune or pne imune or pneimmune or pneimunne or pneimune or apexxnar\* or moniarix\* or pneumopur\* or streptopur\* or streptorix\* or 13 vpnc or 13vpnc or 20 vpnc or 20vpnc or SIIPL-PCV or PHiD-CV or pneumo 23 or pneumo23).ti,ab,kf.
68. ((Pneumoco\* or pneumonia\* or Streptococc\* or strep or PCV 13 or PCV 15 or PCV 20 or PCV 21 or PPV 23 or V116 or v 116 or v 110 or v 114 or v110 or v114) adj5 (vaccin\* or immunis\* or immuniz\*)).ti,ab,kf.
69. ((Pneumoco\* or pneumonia\* or Streptococc\* or strep or PCV 13 or PCV 15 or PCV 20 or PCV 21 or PPV 23 or V116 or v 116 or v 110 or v 114 or v110 or v114) and (vaccin\* or immunis\* or immuniz\*)).ti. 20055
70. ((Pneumoco\* or pneumonia\* or Streptococc\* or strep) and (13-valent or 15 valent or 20 valent or 21 valent or 23 valent or PCV21 or PCV 13 or PCV 15 or PCV 20 or PCV 21 or PPV 23)).ti,ab,kf.
71. 66 or 67 or 68 or 69 or 70

72. (exp \*Adolescent/ or exp \*Child/ or exp \*Infant/ or exp \*Pediatrics/ or (child or children or childhood or infant or infants or baby or babies or newborn or newborns or neonate or neonatal or neonates or premie or preemies or infancy or paediatric or pediatric or girl or girls or boy or boys or kid or kids or teen or teens or teenage or teenager or teenagers or youngster or youngsters or youth or youths or adolescent or adolescents or adolescence or preadolescent or preadolescence or pre adolescent or pre adolescence or preschooler or school age or school aged or schoolchildren).ti.) not (exp Adult/ or (adult or adults or adulthood or middle age or middle aged or elderly or senior or seniors or man or men or woman or women).ti,ab.)
73. 71 not 72
74. (afghan\* or albania\* or algeria\* or angola\* or argentin\* or armenia\* or aruba\* or azerbaijan\* or bahrain\* or bangladesh\* or bengal\* or bangal\* or bajan or bajans or belarus\* or belorus\* or byelarus\* or byelorus\* or belize\* or benin\* or dahomey or bhutan\* or bolivia\* or bosnia\* or herzegovin\* or botswan\* or batswan\* or bechuanaland\* or brazil\* or brasil\* or bulgaria\* or burkina\* or burkinese\* or upper volta\* or burundi\* or urundi\* or cabo verde\* or cape verde\* or cambodia\* or kampuchea\* or khmer\* or cameroon\* or cameroun\* or ubangi shari\* or chad or Chadian or (china\* not (China National Infrastructure or China National Knowledge Infrastructure)) or beijing or shanghai or colombia\* or comoro\* or comore\* or comorian\* or mayotte\* or congo\* or zaire\* or costa rica\* or "cote d'ivoir\*" or "cote d'ivoir\*" or cote divoir\* or cote d ivoir\* or ivory coast\* or ivorian\* or cuba or cuban or cubans or "cuba's" or djibouti\* or french somaliland\* or dominica\* or ecuador\* or egypt\* or united arab republic\* or el salvador\* or salvadoran\* or guinea\* or equatoguinea\* or eritrea\* or eswatini\* or swaziland\* or swazi\* or swati\* or ethiopia\* or fiji\* or gabon\* or gabonese\* or gabonaise\* or gambia\* or ghana\* or grenada\* or grenadian\* or guatemala\* or haiti\* or hispaniola\* or hondura\* or ((india or indian or indians) not american india\*) or delhi or indonesia\* or iran\* or iraq\* or jamaica\* or jordan\* or kazakh\* or kenya\* or karabati\* or kosovo\* or kosova\* or kyrgyz\* or kirgiz\* or kirghiz\* or laos or lao or laotian\* or lebanon\* or lebanese\* or lesotho\* or lesothan\* or lesothonian\* or basutoland\* or mosotho\* or basotho\* or liberia\* or libya\* or jamahiriya\* or macedonia\* or madagascar\* or malagasy\* or malawi\* or nyasaland\* or malaysia\* or malay\* federation or maldives\* or maldivian\* or mali or malian\* or "mali's" or micronesia\* or marshallese\* or kiribati\* or marshall island\* or nauru or nauran or nauruans or "naurian's" or mariana or marianas or palau or paluan\* or tuvalu\* or mauritania\* or mauritan\* or mauritius\* or mexico\* or mexican\* or moldova\* or moldovia\* or mongol\* or montenegr\* or morocco\* or moroccan\* or ifni or mozambique\* or mozambican\* or myanmar\* or burma\* or burmese or namibia\* or nepal\* or netherlands antill\* or nicaragua\* or niger\* or pakistan\* or palestin\* or gaza\* or west bank\* or paraguay\* or peru or peruvian\* or "peru's" or philippine\* or philipine\* or phillipine\* or phillippine\* or filipino\* or filipina\* or russia\* or ussr\* or soviet\* or rwanda\* or rwandese or ruanda\* or ruandese or samoa\* or navigator island\* or polynesia\* or sao tome\* or santomean\* or senegal\* or serbia\* or sierra leone\* or melanesia\* or solomon island\* or norfolk island\* or somali\* or south africa\* or sri lanka\* or ceylon\* or saint lucia\* or st lucia\* or saint vincent\* or st vincent\* or vincentian\* or grenadine\* or sudan\* or surinam\* or syria\* or tajik\* or tadjik\* or tadjik\* or tanzania\* or tanganyika\* or thai\* or timor leste\* or east timor\* or timorese\* or togo or togoles\* or "togo's" or tonga\* or tunisia\* or turkiy\* or turkey\* or turk or turks or turkish or turkmen\* or

uganda\* or ukrain\* or uzbek\* or vanuatu\* or new hebrides\* or venezuela\* or vietnam\* or viet nam\* or yemen\* or yugoslav\* or zambia\* or zimbabwe\* or rhodesia\* or global south or sahara\* or subsahara\* or magreb\* or maghrib\*).ti,ab,hw,kf.

75. (developing countr\* or developing nation\* or developing world or less developed countr\* or less developed nation\* or less developed world or lesser developed countr\* or lesser developed nation\* or lesser developed world or under developed countr\* or under developed nation\* or under developed world or underdeveloped countr\* or underdeveloped nation\* or underdeveloped world or middle income countr\* or middle income nation\* or low income countr\* or low income nation\* or lower income countr\* or lower income nation\* or underserved countr\* or underserved nation\* or under served nation\* or deprived countr\* or high burden countr\* or high burden nation\* or countdown countr\* or countdown nation\* or poor countr\* or poor nation\* or poor world or poorer countr\* or poorer nation\* or poorer world or developing econom\* or less developed econom\* or underdeveloped econom\* or under developed econom\* or middle income econom\* or low income econom\* or lower income econom\* or low gdp or low gnp or low gross domestic or low gross national or lower gdp or lower gnp or lower gross domestic or lower gross national or lmic or lmic's or third world or lami countr\* or transitional countr\* or emerging econom\* or emerging nation\*).ti.
76. ("Georgia (Republic)"/ or (georgia or georgian or georgians).ti,ab,kf.) not (atlanta or california or florida).ti,ab,kf.
77. 74 or 75 or 76
78. (American Samoa or Andorra\* or Antigua\* or Aruba\* or Australia\* or Austria\* or Baham\* or Barbuda\* or Bahrain\* or Barbud\* or Belgium or Belgian or Bermud\* or Brunei or Darussalam or Canad\* or Cayman Islands or Channel Islands or Chile or Chilean\* or Croatia\* or Curacao or Cyprus or cypriot\* or Czech\* or Denmark or Danish or Estonia\* or Faroe Islands or Finland or Finnish or France or French or Guyan\* or guiana\* or guyanese\* or German\* or Gibraltar or Greece or Greek\* or grecian\* or Greenland\* or Guam or Hong Kong or Hungar\* or Iceland\* or Ireland or Irish or "Isle of Man" or Israel\* or Ital\* or Japan\* or Korea\* or Kuwait\* or Latvia\* or Liechtenstein or Lithuania\* or Luxembourg or Macao or Malta or Maltese or "malta's" or Monaco or Nauru or Netherland\* or Dutch or New Caledonia\* or New Zealand\* or Northern Mariana Islands or Norway or Norwegian\* or oman or omani or omanis or "oman's" or Panam\* or Poland or Polish or Portug\* or Puerto Ric\* or Qatar or Romania\* or San Marino or Saudi Arabia\* or Saudis or Seychelles or Singapor\* or Sint Maarten or Slovak\* or Slovenia\* or Spain or Spanish or "St Kitts and Nevis" or saint kitts or st kitts or kittian\* or nevisian\* or St Martin or Swed\* or Switzerland or Swiss or Taiwan\* or Trinidad\* or Tobago or "Turks and Caicos" or United Arab Emirates or UAE or United Kingdom or UK or England or Wales or Welsh or Scotland or Scottish or Great Britain or British or United States or USA or "the us" or Uruguay\* or Virgin Islands or high income or higher income or industrialized or industrialised or developed countr\* or british columbia\* or alberta\* or saskatchewan\* or manitoba\* or ontario\* or quebec\* or new brunswick\* or prince edward island\* or nova scotia\* or labrador\* or newfoundland\* or nunavut\* or northwest territor\* or yukon\* or toronto\* or montreal\* or vancouver\* or ottawa\* or calgary\* or edmonton\* or winnipeg\* or Appalachia\* or great lakes or midwestern-us\* or Midwest-us\* or great plains or

northeastern-us\* or northeast-us\* or pacific northwest or northwestern-us\* or northwest-us\* or southeast-us\* or southeastern-us\* or southern-us\* or southwest-us\* or southwestern-us\* or "district of Columbia" or Washington dc or Alabama\* or Alaska\* or Arizona\* or Arkansas or California\* or Colorad\* or Connecticut or Delaware or Florid\* or Hawaii\* or Hawai'i\* or Idaho or Illinois or Indiana\* or iowa\* or Kansas or Kansan or Kentucky or Louisiana\* or Maine or Maryland or Massachusetts or Michigan or Minnesota\* or Mississippi\* or Montana\* or Nebraska\* or Nevada\* or New Hampshire or New Jersey or New Mexico or New York or North Carolin\* or Dakota\* or Ohio or Ohian or Oklahoma\* or Oregon\* or Pennsylvania\* or Rhode Island\* or South Carolin\* or Tennessee\* or Texas or Texan or Utah or Vermont or Virginia or West Virginia\* or Wisconsin or Wyoming).ti,ab,hw,kf.

79. 77 not 78
80. 73 not 79
81. Economics/
82. Cost/
83. exp Health Economics/
84. Budget/
85. budget\*.ti,ab,kf.
86. (economic\* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\* or pharmaco-economic\* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
87. (economic\* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\* or pharmaco-economic\* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
88. (cost\* adj2 (effective\* or utilit\* or benefit\* or minimi\* or analy\* or outcome or outcomes)).ab,kf.
89. (value adj2 (money or monetary)).ti,ab,kf.
90. Statistical Model/
91. exp economic model/
92. economic model\*.ab,kf.
93. Probability/
94. markov.ti,ab,kf.
95. monte carlo method/
96. monte carlo.ti,ab,kf.
97. Decision Theory/
98. Decision Tree/
99. (decision\* adj2 (tree\* or analy\* or model\*)).ti,ab,kf.
100. or/81-99

101. 62 or 100
102. 80 and 101
103. 102 use oomezd
104. 65 or 103
105. exp animals/
106. exp animal experimentation/ or exp animal experiment/
107. exp models animal/
108. nonhuman/
109. exp vertebrate/ or exp vertebrates/
110. or/105-109
111. exp humans/
112. exp human experimentation/ or exp human experiment/
113. or/111-112
114. 110 not 113
115. 104 not 114
116. limit 115 to (english or french)
117. limit 116 to yr="2011 -Current"
118. 117 use medall
119. \*Pneumococcus vaccine/
120. (PCV13 or PCV15 or PCV20 or PCV21 or PPV23 or PPSV23 or PPSV 23 or PNEU-C-15 or PNEU-P-23 or Pneu23 or Prevnar\* or Prevenar\* or PncOMPc or MnCC or PCV7 or PNCrM7 or pneumovax\* or pneumorix\* or Vaxneuvance\* or synflorix\* or pneu immune or pneu immune or pneu imune or pneuimmune or pneuimunne or pneumune or apexxnar\* or moniarix\* or pneumopur\* or streptopur\* or streptorix\* or 13 vpnc or 13vpnc or 20 vpnc or 20vpnc or SIIPL-PCV or PHiD-CV or pneumo 23 or pneumo23).ti,ab,kf.
121. ((Pneumoco\* or pneumonia\* or Streptococc\* or strep or PCV 13 or PCV 15 or PCV 20 or PCV 21 or PPV 23 or V116 or v 116 or v 110 or v 114 or v110 or v114) adj5 (vaccin\* or immunis\* or immuniz\*)).ti,ab,kf.
122. ((Pneumoco\* or pneumonia\* or Streptococc\* or strep or PCV 13 or PCV 15 or PCV 20 or PCV 21 or PPV 23 or V116 or v 116 or v 110 or v 114 or v110 or v114) and (vaccin\* or immunis\* or immuniz\*)).ti.
123. ((Pneumoco\* or pneumonia\* or Streptococc\* or strep) and (13-valent or 15 valent or 20 valent or 21 valent or 23 valent or PCV21 or PCV 13 or PCV 15 or PCV 20 or PCV 21 or PPV 23)).ti,ab,kf.
124. 119 or 120 or 121 or 122 or 123
125. (exp \*Adolescent/ or exp \*Child/ or exp \*Infant/ or exp \*Pediatrics/ or (child or children or childhood or infant or infants or baby or babies or newborn or newborns or neonate or neonatal or neonates or

preemie or preemies or infancy or paediatric or pediatric or girl or girls or boy or boys or kid or kids or teen or teens or teenage or teenager or teenagers or youngster or youngsters or youth or youths or adolescent or adolescents or adolescence or preadolescent or preadolescence or pre adolescent or pre adolescence or preschooler or school age or school aged or schoolchildren).ti.) not (exp Adult/ or (adult or adults or adulthood or middle age or middle aged or elderly or senior or seniors or man or men or woman or women).ti,ab.)

126. 124 not 125

127. (afghan\* or albania\* or algeria\* or angola\* or argentin\* or armenia\* or aruba\* or azerbaijan\* or bahrain\* or bangladesh\* or bengal\* or bangal\* or bayan or bajans or belarus\* or belorus\* or byelarus\* or byelorus\* or belize\* or benin\* or dahomey or bhutan\* or bolivia\* or bosnia\* or herzegovin\* or botswan\* or batswan\* or bechuanaland\* or brazil\* or brasil\* or bulgaria\* or burkina\* or burkinese\* or upper volta\* or burundi\* or urundi\* or cabo verde\* or cape verde\* or cambodia\* or kampuchea\* or khmer\* or cameroon\* or cameroun\* or ubangi shari\* or chad or Chadian or (china\* not (China National Infrastructure or China National Knowledge Infrastructure)) or beijing or shanghai or colombia\* or comoro\* or comore\* or comorian\* or mayotte\* or congo\* or zaire\* or costa rica\* or "cote d'ivoir\*" or "cote d'ivoir\*" or cote divoir\* or cote d ivoir\* or ivory coast\* or ivorian\* or cuba or cuban or cubans or "cuba's" or djibouti\* or french somaliland\* or dominica\* or ecuador\* or egypt\* or united arab republic\* or el salvador\* or salvadoran\* or guinea\* or equatoguinea\* or eritrea\* or eswatini\* or swaziland\* or swazi\* or swati\* or ethiopia\* or fiji\* or gabon\* or gabonese\* or gabonaise\* or gambia\* or ghana\* or grenada\* or grenadian\* or guatemala\* or haiti\* or hispaniola\* or hondura\* or ((india or indian or indians) not american india\*) or delhi or indonesia\* or iran\* or iraq\* or jamaica\* or jordan\* or kazakh\* or kenya\* or karabati\* or kosovo\* or kosova\* or kyrgyz\* or kirgiz\* or kirghiz\* or laos or lao or laotian\* or lebanon\* or lebanese\* or lesotho\* or lesothan\* or lesothonian\* or basutoland\* or mosotho\* or basotho\* or liberia\* or libya\* or jamahiriya\* or macedonia\* or madagasca\* or malagasy\* or malawi\* or nyasaland\* or malaysia\* or malay\* federation or maldives\* or maldivian\* or mali or malian\* or "mali's" or micronesia\* or marshallese\* or kiribati\* or marshall island\* or nauru or nauran or nauruans or "naurian's" or mariana or marianas or palau or paluan\* or tuvalu\* or mauritania\* or mauritan\* or mauritius\* or mexico\* or mexican\* or moldova\* or moldovia\* or mongol\* or montenegr\* or morocco\* or moroccan\* or ifni or mozambique\* or mozambican\* or myanmar\* or burma\* or burmese or namibia\* or nepal\* or netherlands antill\* or nicaragua\* or niger\* or pakistan\* or palestin\* or gaza\* or west bank\* or paraguay\* or peru or peruvian\* or "peru's" or philippine\* or philipine\* or phillipine\* or phillippine\* or filipino\* or filipina\* or russia\* or ussr\* or soviet\* or rwanda\* or rwandese or ruanda\* or ruandese or samoa\* or navigator island\* or polynesia\* or sao tome\* or santomean\* or senegal\* or serbia\* or sierra leone\* or melanesia\* or solomon island\* or norfolk island\* or somali\* or south africa\* or sri lanka\* or ceylon\* or saint lucia\* or st lucia\* or saint vincent\* or st vincent\* or vincentian\* or grenadine\* or sudan\* or surinam\* or syria\* or tajik\* or tadjik\* or tadjhik\* or tanzania\* or tanganyika\* or thai\* or timor leste\* or east timor\* or timorese\* or togo or togoles\* or "togo's" or tonga\* or tunisia\* or turkiy\* or turkey\* or turk or turks or turkish or turkmen\* or uganda\* or ukrain\* or uzbek\* or vanuatu\* or new hebrides\* or venezuela\* or vietnam\* or viet nam\* or

- yemen\* or yugoslav\* or zambia\* or zimbabwe\* or rhodesia\* or global south or sahara\* or subsahara\* or magreb\* or maghrib\*).ti,ab,hw,kf.
128. (developing countr\* or developing nation\* or developing world or less developed countr\* or less developed nation\* or less developed world or lesser developed countr\* or lesser developed nation\* or lesser developed world or under developed countr\* or under developed nation\* or under developed world or underdeveloped countr\* or underdeveloped nation\* or underdeveloped world or middle income countr\* or middle income nation\* or low income countr\* or low income nation\* or lower income countr\* or lower income nation\* or underserved countr\* or underserved nation\* or under served nation\* or deprived countr\* or high burden countr\* or high burden nation\* or countdown countr\* or countdown nation\* or poor countr\* or poor nation\* or poor world or poorer countr\* or poorer nation\* or poorer world or developing econom\* or less developed econom\* or underdeveloped econom\* or under developed econom\* or middle income econom\* or low income econom\* or lower income econom\* or low gdp or low gnp or low gross domestic or low gross national or lower gdp or lower gnp or lower gross domestic or lower gross national or lmic or lmic's or third world or lami countr\* or transitional countr\* or emerging econom\* or emerging nation\*).ti.
129. ("Georgia (Republic)"/ or (georgia or georgian or georgians).ti,ab,kf.) not (atlanta or california or florida).ti,ab,kf.
130. 127 or 128 or 129
131. (American Samoa or Andorra\* or Antigua\* or Aruba\* or Australia\* or Austria\* or Baham\* or Barbuda\* or Bahrain\* or Barbad\* or Belgium or Belgian or Bermud\* or Brunei or Darussalam or Canad\* or Cayman Islands or Channel Islands or Chile or Chilean\* or Croatia\* or Curacao or Cyprus or cyriot\* or Czech\* or Denmark or Danish or Estonia\* or Faroe Islands or Finland or Finnish or France or French or Guyan\* or guiana\* or guyanese\* or German\* or Gibraltar or Greece or Greek\* or grecian\* or Greenland\* or Guam or Hong Kong or Hungar\* or Iceland\* or Ireland or Irish or "Isle of Man" or Israel\* or Ital\* or Japan\* or Korea\* or Kuwait\* or Latvia\* or Liechtenstein or Lithuania\* or Luxembourg or Macao or Malta or Maltese or "malta's" or Monaco or Nauru or Netherland\* or Dutch or New Caledonia\* or New Zealand\* or Northern Mariana Islands or Norway or Norwegian\* or oman or omani or omanis or "oman's" or Panam\* or Poland or Polish or Portug\* or Puerto Ric\* or Qatar or Romania\* or San Marino or Saudi Arabia\* or Saudis or Seychelles or Singapor\* or Sint Maarten or Slovak\* or Slovenia\* or Spain or Spanish or "St Kitts and Nevis" or saint kitts or st kitts or kittian\* or nevisian\* or St Martin or Swed\* or Switzerland or Swiss or Taiwan\* or Trinidad\* or Tobago or "Turks and Caicos" or United Arab Emirates or UAE or United Kingdom or UK or England or Wales or Welsh or Scotland or Scottish or Great Britain or British or United States or USA or "the us" or Uruguay\* or Virgin Islands or high income or higher income or industrialized or industrialised or developed countr\* or british columbia\* or alberta\* or saskatchewan\* or manitoba\* or ontario\* or quebec\* or new brunswick\* or prince edward island\* or nova scotia\* or labrador\* or newfoundland\* or nunavut\* or northwest territor\* or yukon\* or toronto\* or montreal\* or vancouver\* or ottawa\* or calgary\* or edmonton\* or winnipeg\* or Appalachia\* or great lakes or midwestern-us\* or Midwest-us\* or great plains or northeastern-us\* or northeast-us\* or pacific northwest or northwestern-us\* or northwest-us\* or



southeast-us\* or southeastern-us\* or southern-us\* or southwest-us\* or southwestern-us\* or “district of Columbia” or Washington dc or Alabama\* or Alaska\* or Arizona\* or Arkansas or California\* or Colorad\* or Connecticut or Delaware or Florid\* or Hawaii\* or Hawai’i\* or Idaho or Illinois or Indiana\* or Iowa\* or Kansas or Kansan or Kentucky or Louisiana\* or Maine or Maryland or Massachusetts or Michigan or Minnesota\* or Mississippi\* or Montana\* or Nebraska\* or Nevada\* or New Hampshire or New Jersey or New Mexico or New York or North Carolin\* or Dakota\* or Ohio or Ohian or Oklahoma\* or Oregon\* or Pennsylvania\* or Rhode Island\* or South Carolin\* or Tennessee\* or Texas or Texan or Utah or Vermont or Virginia or West Virginia\* or Wisconsin or Wyoming).ti,ab,hw,kf.

132. 130 not 131
133. 126 not 132
134. (systematic review or meta-analysis).pt.
135. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or “meta analysis (topic)”/ or “systematic review (topic)”/ or exp technology assessment, biomedical/ or network meta-analysis/
136. ((systematic\* adj3 (review\* or overview\*)) or (methodologic\* adj3 (review\* or overview\*))).ti,ab,kf.
137. ((quantitative adj3 (review\* or overview\* or syntheses\*) or (research adj3 (integrati\* or overview\*))).ti,ab,kf.
138. ((integrative adj3 (review\* or overview\*)) or (collaborative adj3 (review\* or overview\*)) or (pool\* adj3 analy\*)).ti,ab,kf.
139. (data syntheses\* or data extraction\* or data abstraction\*).ti,ab,kf.
140. (handsearch\* or hand search\*).ti,ab,kf.
141. (mantel haenszel or peto or der simonian or dersimonian or fixed effect\* or latin square\*).ti,ab,kf.
142. (met analy\* or metanaly\* or technology assessment\* or HTA or HTAs or technology overview\* or technology appraisal\*).ti,ab,kf.
143. (meta regression\* or metaregression\*).ti,ab,kf.
144. (meta-analy\* or metaanaly\* or systematic review\* or biomedical technology assessment\* or bio-medical technology assessment\*).mp,hw.
145. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
146. (cochrane or (health adj2 technology assessment) or evidence report).jw.
147. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
148. (outcomes research or relative effectiveness).ti,ab,kf.
149. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison\*).ti,ab,kf.
150. (multi\* adj3 treatment adj3 comparison\*).ti,ab,kf.
151. (mixed adj3 treatment adj3 (meta-analy\* or metaanaly\*)).ti,ab,kf.
152. umbrella review\*.ti,ab,kf.
153. (multi\* adj2 paramet\* adj2 evidence adj2 synthesis).ti,ab,kf.

154. (multiparamet\* adj2 evidence adj2 synthesis).ti,ab,kf.
155. (multi-paramet\* adj2 evidence adj2 synthesis).ti,ab,kf.
156. or/134-155
157. Economics/
158. Cost/
159. exp Health Economics/
160. Budget/
161. budget\*.ti,ab,kf.
162. (economic\* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\* or pharmaco-economic\* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
163. (economic\* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\* or pharmaco-economic\* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
164. (cost\* adj2 (effective\* or utilit\* or benefit\* or minimi\* or analy\* or outcome or outcomes)).ab,kf.
165. (value adj2 (money or monetary)).ti,ab,kf.
166. Statistical Model/
167. exp economic model/
168. economic model\*.ab,kf.
169. Probability/
170. markov.ti,ab,kf.
171. monte carlo method/
172. monte carlo.ti,ab,kf.
173. Decision Theory/
174. Decision Tree/
175. (decision\* adj2 (tree\* or analy\* or model\*)).ti,ab,kf.
176. or/157-175
177. 156 or 176
178. 133 and 177
179. exp animals/
180. exp animal experimentation/ or exp animal experiment/
181. exp models animal/
182. nonhuman/
183. exp vertebrate/ or exp vertebrates/

184. or/179-183
185. exp humans/
186. exp human experimentation/ or exp human experiment/
187. or/185-186
188. 184 not 187
189. 178 not 188
190. limit 189 to (english or french)
191. limit 190 to yr="2011 -Current"
192. 191 use oemezd

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