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Efficacy and effectiveness of pneumococcal vaccination in elderly – an update of the literature

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Preface

This work is a collaboration between colleagues at the Norwegian, Swedish and Danish Public Health Institutes based on a common need for an updated knowledgebase to inform national guidelines for pneumococcal vaccination in medical risk groups and adults. We agreed on key questions for systematic literature searches, which were later divided into three separate review questions. This report is based on the first review and is related to effectiveness of pneumococcal vaccines in elderly.

At the outset of the work, we systematically searched for relevant published reviews and meta-analyses in PubMed and COCHRANE, and published protocols in PROSPERO and COCHRANE. Several reviews and meta-analyses were identified. Two were conducted for the same purpose as the current report: a Health Technology Assessment from the Belgian Knowledge Centre, and a German review, which serves as basis for the STIKO (Standing Committee on Vaccination) recommendations for pneumococcal vaccination in elderly. Both were independent from the industry, covered the outcomes of interest and were comprehensive and updated up until 2015. Against this backdrop we decided to update these reviews with publications from 2016 and onwards, rather than to repeat previous work.

We systematically searched for publications on the efficacy or effectiveness of pneumococcal conjugate- and polysaccharide vaccines of any valence and schedule against invasive pneumococcal disease and pneumococcal pneumonia from 01.01.2016 up until August 2018. The search was later updated until April 2019. The search included RCTs and observational studies. This systematic review is submitted for publication separately.

Thus, the current report is based on three separate reviews; the Health Technology Assessment from the Belgian Knowledge Centre, the German background paper serving as base for the STIKO recommendations for pneumococcal vaccination in elderly, and our own recently updated review.

The Norwegian, Swedish and Danish Public Health Institutes have funded the work in full.

Oslo December 20th, 2019

Key messages

- *S. pneumonia* is a major cause of morbidity and mortality, specifically at the extremes of age and in individuals with immunocompromising medical conditions. Two different vaccines, a 23-valent polysaccharide vaccine (PPV23) and a 13-valent pneumococcal conjugate vaccine (PCV13) are available to prevent pneumococcal disease in adults.
- No studies compare vaccine effectiveness of PPV23 and PCV13 head-to-head.
- Direct comparison between the two vaccines are difficult due to differences in populations, time since vaccination and study designs.
- Whereas the evidence for PCV13 is dominated by one large trial with overall healthy elderly, the evidence for PPV23 VE is based on several trials of moderate quality and several observational studies.
- Results obtained from RCTs and those obtained from various observational designs are inconsistent, making it difficult to summarize available evidence into single quantitative measures.
- Higher vaccine effectiveness seen in clinical trials may reflect shorter follow-up time compared with observational studies, where waning immunity is likely to play a role.
- Both PPV23 and PCV13 are comparably effective for the prevention of all-type invasive pneumococcal disease (IPD) in the broader adult population, across study designs and settings.
- PCV13 seems to provide better protection than PPV23 against vaccine type IPD (for serotypes common to PCV13 and PPV23).
- The overall body of evidence shows PPV23 VE at a level comparable to PCV13.
- Both vaccines showed generally lower VE with increasing age, but data are limited for PCV13.
- Both vaccines showed generally lower VE in groups with comorbidities compared with groups without known risk.
- With one exception from a case-control study with overall high VE estimates, both vaccines failed to show significant VE in immunocompromised groups.

Summary

Introduction

Young children, elderly and persons with weakened immune systems are at high risk of acquiring invasive pneumococcal disease and pneumococcal pneumonia. Two different vaccines are available for the prevention of pneumococcal disease in adults; a 23-valent polysaccharide vaccine (PPV23), and a 13-valent conjugated vaccine (PCV13). The updated review will serve as a bases to inform national recommendations for use of pneumococcal vaccines in elderly in Norway, Sweden and Denmark.

Methods

The report covers publications on PCV13 and PPV23 efficacy and effectiveness from 2000 until April 2019 from randomized controlled trials and observational studies. Outcomes include invasive pneumococcal disease and pneumococcal pneumonia.

Results

A total of 27 publications are included; 18 publications on PPV23 effectiveness and nine publications on PCV13 effectiveness. No study compared the effectiveness of PPV23 and PCV13 directly. One large trial with overall healthy elderly dominates the evidence for PCV13 efficacy and effectiveness. The evidence for PPV23 vaccine effectiveness, on the other hand, is based on trials of moderate quality and several observational studies. Differences in populations, study designs and time since vaccination makes it difficult to summarize available evidence into single quantitative measures.

The vaccine effectiveness of PPV23 in preventing invasive pneumococcal disease was consistent with past systematic reviews and similar to the estimates that have been reported for PCV13 efficacy and effectiveness. Consistent effects were reported across observational studies and ecological studies of surveillance data for the general elderly population. PCV13 seems to provide better protection than PPV23 against vaccine-type invasive pneumococcal disease (for serotypes common to PCV13 and PPV23).

We found both PPV23 and PCV13 to be effective in preventing pneumococcal pneumonia in elderly at comparable levels. The PPV23 vaccine effectiveness was higher in clinical trials than observational studies, possibly reflecting a shorter follow-up time and a more limited impact of waning immunity.

Both PPV23 and PCV13 showed generally lower effectiveness with increasing age for all outcomes and in groups with immunocompromising conditions. Overall, significant VE was not shown for immunocompromised groups.

Conclusion

This report shows that both PCV13 and PPV23 provide prevention for invasive disease and pneumococcal pneumonia in the elderly. The overall body of evidence shows PPV23 effectiveness at a level comparable to PCV13. This finding is of paramount importance for public health due to the high pneumococcal pneumonia disease burden. The serotype distribution in carriage and disease is important to consider for the impact of vaccination. The currently low proportion of patients falling ill with serotypes included in PCV13 suggests limited potential for prevention from adult PCV13 vaccination. Well-designed and serotype specific randomized controlled trials are important to improve evidence.

Abbreviations

ACIP	The Advisory Committee on Immunization Practices in the United States
CAP	Community Acquired Pneumonia
CAPITA	Community-Acquired Pneumonia Immunization Trial
CDC	Center for Disease Control and Prevention, USA
CI	Confidence Intervals
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HAP	Hospital Acquired Pneumonia
HR	Hazard Ratio
Ig	Immunoglobulin
IPD	Invasive pneumococcal disease
mITT	modified Intention-To-Treat analysis
OPA	Opsonophagocytic Assay
OR	Odds Ratio
PCV	Pneumococcal Conjugate Vaccine
PICO	Population, Intervention, Comparator and Outcome
PP	Per-Protocol analysis
PPV	Pneumococcal Polysaccharide Vaccine
RCT	Randomized Controlled Trial
RR	Relative Risk ratio
STIKO	Standing Committee on Vaccination, Germany
TND	Test-Negative Design
VE	Vaccine Efficacy or Effectiveness
VT	Vaccine-Type, i.e. refers to serotypes covered by the different vaccines

Glossary

GRADE	Grading of Recommendations, Assessment, Development and Evaluations. A methodology to assess the reliability of studies and to rank them according to level of evidence.
Indirect cohort	Serotype distributions (VT and non-VT serotypes) is compared in vaccinated and unvaccinated IPD cases. This is also referred to as Broome method.
Intention-to-treat analysis	A comparison of treatment groups that includes all patients as originally allocated after randomization.
Invasive pneumococcal disease	Detection of *S. penumoniae* (culture, antigen or PCR) from a normally sterile site.
Per-protocol analysis	A comparison of treatment groups that includes only those who completed the treatment originally allocated.
PICO	Framework to define and specify research questions. PICO's include a population, an intervention, a control group and outcome to meet the study question.
Test negative design (TSD)	All cases are ill (pneumonia); then etiology (*S. pneumoniae* and other etiologies) are compared in vaccinated and unvaccinated pneumonia patients.
Vaccine effectiveness	Ability of a vaccine to prevent disease in a real world setting, usually outside of a RCT. The measure commonly used to evaluate the impact of a vaccination programme at population level.
Vaccine efficacy	Percentage reduction in disease incidence in a vaccinated group compared to an unvaccinated group under optimal conditions.

Overview of tables and figures included in the report

Figures

1 Background

Pneumococcal infection is associated with significant morbidity and mortality in older adults. *Streptococcus pneumoniae (*pneumococcus) is a gram positive bacterium with more than 95 different serotypes identified.[1] The most severe form of pneumococcal disease is invasive pneumococcal disease (IPD). Additionally, *S. pneumoniae* causes non-invasive disease such as pneumonia, sinusitis and otitis media.[2,3] *S. pneumoniae* is the most common etiology in community acquired pneumonia (CAP) and is responsible for around 20% of all adult CAP-cases in Europe.[4] Non-invasive pneumonia is three times more frequent than invasive pneumonia in adults who are hospitalized with pneumonia.[5] Elderly and persons with underlying comorbidities are at higher risk of acquiring severe forms of pneumococcal disease.

Two different pneumococcal vaccines are currently available to prevent pneumococcal disease in adults; a 23-valent polysaccharide vaccine (PPV23, Pneumovax 23, MSD) and a 13-valent conjugate vaccine (PCV13, Prevenar13, Pfizer). The two vaccines can be used separately or in combination and recommendations vary across settings.

The polysaccharide vaccine has been available since the 1970s and has gradually changed from 14-valent until a 23-valent vaccine. The 23-valent polysaccharide vaccine, Pneumovax 23, is indicated for prevention of pneumococcal infections in individuals from 2 years of age. This vaccine has been available in the Scandinavian countries since the first half of the 1980's and has been recommended for use in elderly and individuals with higher risk of pneumococcal disease due to medical conditions.

The conjugated pneumococcal vaccine, Prevenar13, is indicated for the prevention of invasive disease and pneumonia caused by *S. pneumoniae* in children and adults ≥18 years of age. The European Commission approved PCV13 for the prevention of IPD in adults in October 2011 and pneumococcal pneumonia in adults in March 2015.[6] The first European authorization was based on immunological correlates of protection, i.e. immunoglobulin (Ig) and opsonophagocytic assay (OPA), and no efficacy estimates were available at the time.[6]

Two pneumococcal conjugate vaccines (PCV15 (Merck) and PCV20 (Pfizer)) are currently in adult Phase III trials with projected completion by the end of 2020 and 2019 respectively. Both products are working towards licensure in adults first, table 1.

Table 1, Serotypes included in current and future pneumococcal vaccines for use in adults

Status	Vaccine	Serotypes included
Currently available vaccines	PPV23	1, **2**, 3, 4, 5, 6B, 7F, **8**, **9N**, 9V, **10A**, **11A**, **12F**, 14, **15B**, **17F**, 18C, 19F, 19A, **20**, **22F**, 23F, and **33F**
	PCV13	1, 3, 4, 5, **6A**, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
Vaccines Phase III trials	PCV15	PCV13 + 22F and 33F
	PCV20	PCV13 + 8, 10A, 11A, 12F, 15B, 22F and 33F

Serotypes in bold (PCV13, PPV23) are not shared by the other currently available vaccine.

In addition, a 10-valent conjugate vaccine is available for use in children (PCV10, Synflorix, GSK), but is not licensed for use in adults. This vaccine covers the same serotypes as Prevenar13 except for serotypes 3, 6A and 19A.

1.1 Pneumococcal vaccination in adults

The optimal recommendation for adult pneumococcal vaccination has been debated in many countries. The direct effect of vaccination depends on both host-and vaccine related factors. Individuals at highest risk of severe disease may also be the ones who benefit least from vaccination, either due to age-related immunosenescence or due to comorbidities.[7-10] Further, the use of pneumococcal conjugate vaccines (PCVs) in childhood vaccination programs have had major impact on nasopharyngeal carriage of vaccine-type (VT) pneumococci, with a subsequent reduction in pneumococcal disease in all age-groups. Decision-making on pneumococcal vaccination in older adults and risk groups must take the indirect effects of childhood PCV programmes into account.[11]

Several literature reviews have been published in recent years, and one update is submitted for publication.[12-20] Two earlier reviews, one Cochrane review by Moberley et al.,[17] and one WHO commissioned review by Huss et al.,[19] pooled data from studies using pneumococcal vaccines of lower valences and with different quantities of antigens than more recent vaccines.[21] The relevance of these reviews are therefore less useful today. None of the more recent reviews were updated after 2015. An overview is provided in table 2. Against this backdrop we decided to update available evidence with a systematic search for publications from 2016 and onwards. The review is submitted for publication separately, and the results are included in the report. We did not search systematically for studies on pneumococcal VE by age, comorbidity-status, or the duration of effect. However, this information was extracted whenever available in the included publications.

1.2 Objective

The primary objective of this review was to provide updated knowledge on the efficacy and effectiveness of pneumococcal vaccination in elderly for the prevention of IPD, VT- IPD, pneumococcal pneumonia (PnPn) and VT-PnPn. Secondary objectives were to assess the effectiveness by age-group, by presence or absence of comorbidities and by time since vaccination.

1.3 Clinical outcomes

We selected IPD and PnPn as clinical outcomes. These were further classified into all serotypes and VT-pneumococcal disease. Pneumonia was considered as community acquired, unless otherwise reported.

2 Sources and Methods

2.1 Data sources

This report synthesizes data from the three separate reviews,[12-14] in which one was conducted as part of this report.[12] Their characteristics and differences are presented in table 3. The Belgian evaluation[13] limited their literature search to Pubmed and publications from non-US Western countries, mostly Europe. The German review[14] used the 2013 Cochrane review as their starting point and updated searches from 01.01.2011. The German review was limited to PPV23, whereas the Belgian and Scandinavian reviews included both PPV23 and PCV13 from 2000-2016 and 2016-2019 respectively. We hand searched reference-lists of other reviews to ensure that we captured relevant publications. In addition, we included expert opinions from Norway, Sweden and Denmark. All three reviews included RCTs and observational studies and the main outcomes IPD and PnPn.

2.2 Quality assessment

We used the Cochrane Collaboration's tool for assessing risk of bias in randomized controlled trials[22] and checklists from the Ottawa Non-Randomized Studies Workshop for quality assessment of observational studies.[23] The latter is based on a scoring system for case-control and cohort studies. Each study can achieve a maximum of nine stars within three separate domains: (i) the *selection* of the study groups (4 stars), (ii) *comparability* of groups (2 stars), and (iii) *ascertainment of exposure* in case-control studies and *outcome* in cohort studies (3 stars). We applied accepted thresholds for converting the Newcastle-Ottawa scales[23] to categorized standards from Agency for Healthcare Research and Quality.[24-26] Good quality studies were assigned 3-4 stars for *selection* AND 1-2 stars for *comparability* AND 2-3 stars for *ascertainment of exposure*. Fair quality studies were assigned 2 stars for *selection* AND 1-2 stars for *comparability* AND 2-3 stars for *ascertainment of exposure.* Poor quality studies were those assigned 0 or 1 star for *selection* OR 0 stars for comparability OR 0 -1 stars for *ascertainment of exposure*. On comparability, studies earned one star if they adjusted for age and comorbidities, and two stars if adjustment also included separate adjustments for immunocompetent and immunosuppressive conditions.

We applied the GRADE criteria (Grading of Recommendations, Assessment, Development and Evaluations) to rate the quality of evidence on outcome level.[27, 28] GRADE has four levels of quality of evidence: very low, low, moderate and high, box 1.

Box 1, Levels of quality as defined by GRADE

Grade	Definition
High	Confident that the true effect lies close to that of the estimate of the effect
Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	The true effect may be substantially different from the estimate of the effect
Very Low	The true effect is likely to be substantially different from the estimate of the effect

Evidence from RCTs starts at high quality of evidence, whereas observational studies starts at low quality of evidence due to the risk of residual confounding. The quality of evidence may then be upgraded or downgraded based on key indicators.[28] Evidence from observational studies may provide complementary information to evidence from RCTs or may provide a higher evidence

level than RCTs. To support our decision-making on criteria for up- or downgrading of the evidence, we followed the recommendations in the U.S. Advisory Committee on Immunization Practices (ACIP) handbook for developing evidence-based guidelines.[29]

2.3 Effect measures

We present results as odds ratios (OR), where OR < 1 favors vaccination. Vaccine effectiveness (VE) was calculated as (1-aOR)*100 with 95% CI. Consistent with previous reviews we used 5 years since vaccination as time-period for vaccination. We stratified results by vaccine used (PPV23 and PCV13), by outcome (all type and VT-IPD and pneumonia) study design (RCTs and observational designs), and by age and the presence or absence of medical risk factors.

2.4 Statistical analyses

We obtained risk ratios (RR) and odds ratios (OR) with corresponding 95% confidence intervals (95% CI). Subgroup data were extracted from the original publications. We calculated the log of each odds ratio and its corresponding standard error if this was not available from the reviews.

We used Review Manager (version 5.3, Cochrane collaboration) for meta-analyses. Inverse variance-weighted meta-analysis of extracted event count data was performed on the log odds ratio scale using a random effects model (half-counts were added to zero counts). We explored reasons for statistical heterogeneity through subgroup analysis. The inverse variance method enables pooling of adjusted effect estimates (e.g. adjusted ORs for observational studies) and was used in the German review on PPV23 VE. For this reason, we continued with the use of this method, despite low case-numbers in some analyses. This decision was based on a sensitivity analysis in the German review, which found the inverse-variance and the Mantel-Haenzel methods to produce identical results.[14] We restricted meta-analyses to subgroups only, due to differences in design, settings and year of study.

3 Results

3.1 Identified publications and amendments from previous reviews

We identified 36 publications from the three previous reviews; 25 publications reported efficacy or effectiveness of PPV23 and 11 publications reported efficacy or effectiveness of PCV13 (Appendix 1).

We made the following amendments:

- All cause pneumonia was not included as an outcome in the German review and this was also excluded as outcome from this report. Four studies identified in the most recent review reported only all-cause pneumonia and were not included.[30-33]
- We excluded one PCV13 conference abstract[34] which was included in the Belgian report as these data were later published in full in a publication captured by the most recent review.[35]
- We excluded one large Finnish trial on PPV23 effectiveness due to poor randomization procedure.[36] The allocation procedure was based on even or odd year of birth, and participants were allowed to change groups upon request. The study did not control for potentially confounding factors and could not be alternatively included as an observational study. A Cochrane review from 2013 excluded this trial for the same reason.[17]
- We excluded the data on pneumococcal pneumonia as outcome in the trial by Örtqvist.[37] In this trial, the diagnosis of pneumococcal pneumonia was based on detection of pneumolysin antibodies in serum (Ply-serum) and in circulating immune complexes (Ply-IC). Pneumolysin is a cholesterol-dependent cytotoxin produced by almost all strains of *S. pneumoniae* [38, 39] The authors have later concluded that the assays were not valid for analytical epidemiological studies or vaccine efficacy studies.[40] Low specificity is a main concern as this may bias the observed effect towards null.[40, 41] The German review excluded the pneumococcal pneumonia data in their review for the same reason.[14]
- Finally, we identified population overlaps in studies reported from the same research group in Terragona, Spain. Vila-Corcoles et al., published PPV23 clinical effectiveness data in 2006[42], 2009,[43] 2010[44] and 2012,[45] first as cohort and later as case-control designs (see details in Appendix 2). The 2006, 2009 and 2010 populations were all included in the EPIVAC study. Although they differ somehow in age cut-offs, observation years and outcomes, the populations and outcomes overlap.[42-44] The authors have previously confirmed overlap in the 2006 and 2009 publications,[17] and the population in the 2009 and 2010 publications is similar. We did not include data from the 2010 publication for the overall vaccine-effectiveness, but subgroup data were included for outcomes by comorbidity. For the overall vaccine effectiveness estimates, we only selected data from the 2009 publication.

A flow chart of inclusion of publications is presented in Appendix 3. A total of 27 publications were included; 18 publications on PPV23 effectiveness and nine publications on PCV13 effectiveness. In addition, we included data from Vila-Corcoles et al., 2010[44] for subgroups. No studies compared the performance of the vaccines head-to-head, and no new RCTs were identified in the most recent review.

The 18 PPV23 publications included three RCTs and 15 observational studies. Ten of the PPV23 publications were included in both the German and the Belgian evaluation (Appendix 1). The three RCTs included 2292 individuals,[37, 46, 47] the observational studies included four cohorts with 549 881 individuals, [48-51] four case-control studies with 3628 individuals,[43, 52-54] and seven studies with an indirect cohort or test negative design (TND) including 14 914 individuals.[1, 55-60] These are forms of case-control studies. In TND vaccine status is compared between pneumococcal test-positive and pneumococcal test-negative ill patients seeking medical care.[61,62] A similar approach is used in the 'indirect cohort' or 'Broome' method in which vaccine status is compared between cases with VT or nonVT-IPD.[63-65]

The nine PCV13 publications included one primary publication and five post-hoc analyses reporting from the Community-Acquired Pneumonia Immunization Trial (CAPITA),[66-71] and three observational studies (Table 5).[35, 72, 73] CAPITA was a parallel-group, double blind, randomized, placebo-controlled trial including 84 496 adults aged 65 years or older. The trial was conducted in the Netherlands 2008-2013, and the primary outcomes were PCV13 vaccine efficacy against VT community acquired pneumonia (VT-CAP), non-bacteremic VT-CAP (nb VT-CAP) and vaccine–type IPD (VT-IPD) in elderly. We present all CAPITA results, but overall effectiveness data were obtained only from the primary CAPITA publication from 2015.[66] A complete overview of the CAPITA publications is provided in table 6. This table is amended from the Belgian report. The observational studies included one cohort study with 2 025730 individuals[73] and two TND studies with 2216 individuals[35, 72], table 5.

The quality assessment of the individual studies are presented in full in Appendix 4, and the quality of individual observational studies are presented as good, fair or poor in table 4 (see Methods section on quality assessment). GRADE evidence profiles by outcomes are presented in Appendices 5a-c.

Table 2, Overview of previously completed systematic reviews on the effectiveness of pneumococcal vaccines in prevention of pneumococcal disease

Author, year	Vaccine	Study designs included	Age-groups	Studyperiod	IPD	PnCAP	All-cause CAP	Funding
Falkenhorst, 2016[14]	PPV23	RCT+OBS	≥60	01.01.2011-02.07.2016	Yes	yes		Other[a]
Kraicer-Melamed, 2016[16]	PPV23	RCT+OBS	≥60	[†]until Aug 2015	Yes	Yes		Other[b]
Schiffner-Rohe, 2016[18]	PPV23	RCT	≥60	2012-Oct 2014		Yes	Yes	Industry[l]
Diao, 2016[20]	PPV23	RCT	adults ≥18	[†]until April 2015		Yes	Yes	Other[c]
Htar, 2017[15]	PPV23+PCV13	OBS	adults ≥16	01.01.1980-30.10.2015		Yes	Yes	Industry[l]
Blommaert, 2016[13]*	PPV23+PCV13	RCT+OBS	adults	01.01.2000 – 01.03.2015	Yes	Yes	Yes	Other[d]
Berild, 2019[12]	PPV23+PCV13	RCT+OBS	adults	01.01.2016-18.04.2019	Yes	Yes	Yes	Other[e]

*Health Technology Assessment (HTA) report
[†] From the incipient date of the included databases.
Sponsor other: [a]Robert Koch Institute, Germany; [b]McGill University, Canada, Quebec Institute of Public Health (3 authors received research funding from GSK and Pfizer for unrelated projects); [c]Peking University Third Hospital; [d]Belgian Health Care Knowledge Center; [e]Norwegian Institute of Public Health
Sponsor Industry: [l] Pfizer

Table 3, Overview of PICO's and search criteria for included reviews on the efficacy and effectiveness of pneumococcal vaccines in elderly

Criteria	Berild et al. [12]	Falkenhorst et al. [14]	Blommaert et al. [13]
Population	Adults	Adults ≥60 y	Adults ≥65 y
Intervention	PPV23/PCV	PPV23	PPV23/PCV
Comparator	No vaccine/placebo	No vaccine/placebo	No vaccines/placebo
Outcome (efficacy/ effectiveness)	IPD (all IPD, VT-IPD) and Pneumonia (all Pn, PnPn, VT-PnPn)	IPD (all IPD) PnPn	IPD (all IPD, VT-IPD) and CAP (PnCAP, VT-PnCAP)
Search criteria			
Sources	Pubmed, Embase, Cinahl, Web of Science, Epistemonikos and Cochrane for publications and conference abstracts/PROSPERO and Cochrane for protocols/and reference lists of included studies	Medline, Embase, Cochrane/Cochrane for protocols	Pubmed
Publication years	01.01.2016 – 15.04.2019	01.01.2011 - 02.07.2016	01.01.2000 – 01.03.2015
Designs	RCTs/observational studies	RCTs/observational studies adjusted for at least age and comorbidities	RCTs/observational studies adjusted for the main confounding factors and with a minimum of 100 cases
Setting	All countries	-	Non-US, Western countries (mostly Europe)
Publication language	Scandinavian, English, French, German, Spanish or Dutch	All languages	-
Exclusion criteria	Case-studies, case-series, animal studies, modelling studies, health economic evaluations, carriage studies	Animal studies	Studies based on ICD codes only without revision of medical files/studies with all cause CAP as outcome/studies based on the screening method/observational studies in settings where PCV7 has been widely used (>50% uptake)

3.2 Study characteristics

The characteristics of studies included on the efficacy/effectiveness of PPV23 for prevention of pneumococcal disease is presented in table 4. This includes an overall score for the quality of the individual studies.

Table 4, Characteristics of studies included on the efficacy/effectiveness of PPV23 on pneumococcal disease by study design

Author, years	Design	Country	Study period	Study population	Age (y)	Vaccinated/non-vaccinated subjects (n)	Observation time since vaccination (y)	Outcome	Study quality[&]	Sponsor
Örtqvist, 1998 [37]	RCT	Sweden	1991-1995	former CAP patients	50-85	339/352	2.4 y	IPD	Good	Industry[i]
Alfageme, 2006 [46]	RCT	Spain	1999-2004	COPD patients	61-73	298/298	2.7 y	PnCAP	Good	Other[a]
Maruyama, 2010 [47]	RCT	Japan	2006-2009	nursing home residents	55-105	502/504	2.3 y	IPD PnPn	Good	Other[b]
Jackson, 2003 [51]	cohort	USA	1998-2001	residents	≥65	84203/42977 (PY)	Variable, (81%:5 to 8y)	IPD	Good	Other[c]
Hechter, 2012 [49]	cohort	USA	2002-2009	male residents	≥60	7718/9232	6.4 y (mean)	IPD	Good	Industry[ii]
Ochoa-Gondar, 2014 [50]	cohort	Spain	2008-2011	Residents	≥60	29065/46968(PY)	Up to 5 y	IPD[¤] PnCAP	Good	Other[d]
Tsai, 2015 [48]	cohort	Taiwan	2008-2009	residents	≥75	229181/229181	1 y	IPD	Fair	Other[e]
Dominguez, 2005[54]	case-control	Spain	2001-2002	IPD cases/controls	≥65	149/447	2 to 3 y	IPD VT-IPD	Poor	Other[f]
Vila-Corcoles, 2009 [43]	case-control	Spain	2002-2007	PnPn cases/controls	≥50	304/608	Up to 7.5 y	IPD VT-IPD PnPn	Good	Other[d]
Leventer-Roberts, 2015 [53]	case-control	Israel	2008-2010	IPD cases/controls	≥65	212/848	Up to 5 y	IPD	Good	Industry[iii]
Kim, 2019 [52]	case-control	South Korea	2013-2015	IPD & PnPn cases/controls	≥65	148/295 557/557	Up to 5 y	IPD VT-IPD PnPn VT-Pn	Good	Other[g]

Author, years	Design	Country	Study period	Study population	Age (y)	Vaccinated/non-vaccinated subjects (n)	Observation time since vaccination (y)	Outcome	Study quality[&]	Sponsor
Andrews, 2012 [55]	Indirect cohort	England & Wales	2003-2010	IPD cases	≥65	444/369 [§]	Up to 5 y	VT-IPD	Good	Other[h]
Djennad, 2018 [1]	Indirect cohort	England & Wales	2012-2016	IPD cases	≥65	4423/1822[§]	PPV given at any time	VT-IPD	Good	Other[j]
Rudnick, 2013 [56]	Indirect cohort	Canada	1995-2011	IPD cases	≥65	1138/240 [§]	Up to 5 y	VT-IPD	Good	Industry[iv]
Wright, 2013 [57]	Indirect cohort	England	2006-2012	IPD cases	≥65	555/106 [§]	Up to 9 y	VT-IPD	Good	Industry[v]
Gutierrez, 2014 [58]	Indirect cohort	Spain	2008-2011	IPD cases	≥60	588/211 [§]	Up to 5 y	VT-IPD	Good	No info
Wiemken, 2014 [59]	TND	Internat	2001-2012	CAP cases	≥65	279/2409 ^	PPV given at any time	PnCAP	Good	None
Suzuki, 2017 [60]	TND	Japan	2011-2014	CAP cases	≥65	419/1617 ^	Up to 5 y	PnPn VT-Pn	Good	Industry[vi]

RCT: Randomized Controlled Trial, indirect cohort: serotype distributions (VT and non-VT serotypes) is compared in vaccinated and unvaccinated IPD cases; TND: test-negative design: *S. pneumoniae* and other etiologies are compared in vaccinated and unvaccinated pneumonia patients; y: years; PY: person years

CAP: Community Acquired Pneumonia, PnCAP: pneumococcal CAP, PnPn: pneumococcal pneumonia, VTPnPn: vaccine-type pneumococcal pneumonia, IPD: invasive pneumococcal disease, VT-IPD: vaccine-type IPD

[&] Details on quality assessment is presented in Appendix 4. This is based on the Cochrane Collaboration's tool for assessing risk of bias in RCTs and checklists from the Ottawa Non-Randomized Studies Workshop for quality assessment of observational studies. We applied accepted thresholds for converting the Newcastle-Ottawa scales to categorized (good, fair, poor) standards from Agency for Healthcare Research and Quality

^ Hospitalized PnCAP/ Hospitalized non-PnCAP

[§] Hospitalized IPD cases caused by vaccine serotypes/ Hospitalized IPD cases caused by non-vaccine serotypes

Sponsor other: [a]Spanish Pneumology Society, Andalusian Health Service; [b]Japanese Ministry of Education, Culture, Sports, Science, and Technology; [c] CDC (USA); [d] Primary Care Service of Tarragona-Valls, Spain; [e]Taiwan CDC; [f]Directorate of Public Health, Catalonia, Department of Public Health, University of Barcelona, Spain; [g]Korea University college of Medicine, Korea University Anam Hospital; [h]Health Protection Agency, UK; [j]European Union's Horizon 2020

Sponsor industry: [i]Pasteur-Mérieux MSD, Swedish Heart-Lung Foundation, Karolinska Institutet; [ii]Kaiser Permanente Southern California; [iii]Calite Research Institute, Tel Aviv Israel and Pfizer; [iv]Canadian Institutes for Health Research, CDC USA, Ontario Thoracic Society, Abbott Laboratories, Bayer Healthcare, GlaxoSmithKline, Pfizer; [v]Health Protection Agency, Sanofi Pasteur MSD; [vi]Pfizer and Nagasaki University

The characteristics of studies included on the efficacy/effectiveness of PCV13 for prevention of pneumococcal disease is presented in table 5 and 6.

Table 5, Characteristics of studies included on the efficacy/effectiveness of PCV13 on pneumococcal disease by study design

Author, years	Country	Study period	Study population	Age (y)	Vaccinated/ non-vaccinated (n)	Obs time (y)	Outcomes	Study quality[&]	Sponsor
RCTs									
Bonten, 2015 [66]	The Netherlands (CAPITA)	2008 -2013	residents	≥65	42,240/42256	m 3.97 y	See table 6	Good	Industry [i]
***Gessner, 2018** [67]					42,240(167487PY) / 42,256(167748PY)	Variable		na[&]	
***Huijts, 2017** [68]					-	m 3.97 y			
***Patterson, 2016** [69]					42,240/42,256	m 3.97 y			
***Suaya, 2018** [71]					42,019/42,045	m 3.97 y			
***Webber, 2017** [70]					42,240/42,256	m 3.97 y			
Cohorts									
Vila-Corcoles, 2018 [73]	Spain	2005-2015	residents	≥50	6912/1983789 (PY)	1 y	PnPn		Other [a]
Test Negative Design									
McLaughlin, 2018 [72]	USA	2016-2016	CAP cases	≥65	68/1966	Up to 5 y	VT-CAP	Good	Industry [i]
Prato, 2018 [35]	Italy	2013-2015	CAP cases	≥65	59/123	Unclear	PnCAP VT-CAP	Poor	Industry [i]

RCT: Randomized Controlled Trial; CAP: community acquired pneumonia; PnCAP: pneumococcal CAP; VT-CAP: vaccine-type CAP; Pn: pneumonia; PnPn: pneumococcal pneumonia; Obs: observation; y: years; Incl: included

*Post-hoc analyses

[&] Details on quality assessment is presented in Appendix 4. This is based on the Cochrane Collaboration's tool for assessing risk of bias in RCTs and checklists from the Ottawa Non-Randomized Studies Workshop for quality assessment of observational studies. We applied accepted thresholds for converting the Newcastle-Ottawa scales to categorized (good, fair, poor) standards from Agency for Healthcare Research and Quality. No separate quality assessment is conducted for the post-hoc-analyses

Sponsor other: [a] Spanish Ministry of Science, Innovation and Universities

Sponsor industry: [i] Pfizer

Table 6, Overview of publications in CAPITA (clinical endpoints), amended from KCE report

Study characteristics, CAPITA	**Community-Acquired Immunization Trial in Adults**				
Region, country	The Netherlands				
Design	Parallel-group, double blind, randomized, placebo-controlled trial				
Study period	2008-2013, enrollment 2008-2010				
Population	Adults ≥65 years with no previous pneumococcal vaccination, no immunosuppression or immunodeficiency, no known hypersensitivity to vaccination and not living in nursing homes or other long-term care facilities. Included 84 496 participants, mean age 72.8, ± 5.7 years				
Intervention	PCV13				
Comparator	Placebo				
Outcome	Primary and secondary outcomes: First episode of VT-CAP, NI NB VT-CAP and VT-IPD Post-hoc analyses on pre-specified exploratory outcomes				
Primary and secondary outcomes	Per protocol (PP)		modified Intention To Treat (mITT)		Author, year
	vacc/non-vacc	VE % (95% CI)	vacc/non-vacc	VE % (95% CI)	
Or first episode of disease					
Any IPD	27/56	52 (22 to 71)	34/66	49 (21 to 67)	Bonten et al., 2015
VT-IPD	7/28	75 (41 to 91)	8/33	76 (47 to 90)	
All cause CAP[I]	-	-	747/787[I]	5 (-5 to 14)	
PnCAP	100/144	31 (10 to 47)	135/174	22 (2 to 39)	
VT-CAP	49/90	46 (22 to 63)	66/106	38 (14 to 55)	
NI NB CAP	66/87	24 (-6 to 46)	90/109	17 (-10 to 38)	
NI NB VT-CAP	33/60	45 (14 to 65)	43/73	41 (13 to 61)	
For any episode of disease					
VT-CAP	53/92	42 (18 to 60)	70/112	38 (15 to 54)	Bonten et al., 2015
Post-hoc analyses (pre-specified, exploratory outcomes)					
Clinical PnCAP (all episodes)[II]	-	-	1375/1495	8 (1 to 15)	Gessner et al., 2018
Culture confirmed PnCAP[III]	20/41	51 (15 to 73)	24/48	50 (17 to 71)	Webber et al., 2017
Culture confirmed VT-CAP[III]	5/20	75 (31 to 93)	5/23	74 (34 to 91)	
Culture confirmed nonVT-CAP[III]	50/53	6 (-42 to 37)	60/67	-3 (-46 to 28)	

mITT: modified intention to treat analysis (all confirmed IPD, including subjects who became immunodeficient or immunosuppressed before disease onset); VE: vaccine efficacy; CAP: community acquired pneumonia: Pn: pneumococcal; VT: vaccine serotypes; nonVT: non-vaccine serotypes; NI: non-invasive; NB: non-bacteremic

[I] *CAP cases met both clinical and radiological protocol-specified criteria*

[II] *Clinical PnCAP: a subset of suspected CAP for patients with at least two of seven symptoms. The outcome was included as a pre-requisite for adjudicated CAP*

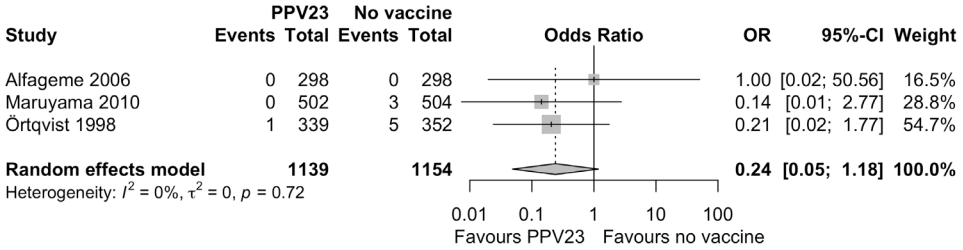
[III] *First episodes of culture confirmed pneumococcal disease*

3.3 Efficacy and effectiveness of 23-valent pneumococcal polysaccharide vaccine in adults

3.3.1 PPV23 VE for prevention of IPD, all serotypes

Evidence of PPV23 effectiveness for the prevention of IPD of any serotype is based on three RCTs[37, 46, 47] including 2293 individuals (Figure 1).

Figure 1. Forest plot for the comparison of PPV23 vs no vaccine for the prevention of invasive pneumococcal disease, all serotypes (any IPD) – RCTs



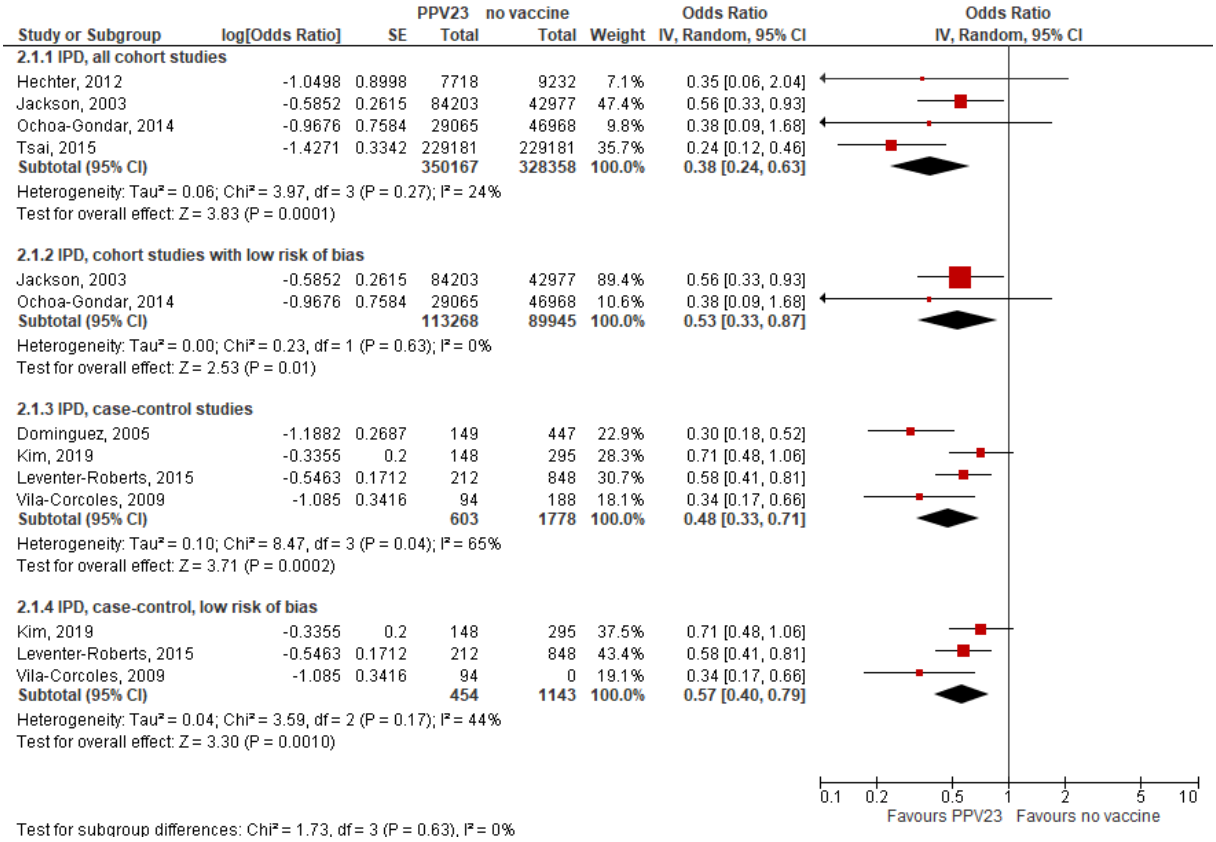
The pooled VE of 76% (-18 to 95), I^2=0% was non-significant. The confidence intervals were wide due to low case numbers. The trial by Alfageme et al.,[46] had no IPD cases reported. All cases in the trial by Örtqvist[37] were caused by vaccine serotypes, no serotype information was provided in the trial by Maruyama.[47] The two European trials[37, 46] were conducted in the pre-PCV era.

Observational studies

Pooled VE estimates from cohort and case-control studies with low risk of bias were fairly similar, and lower than results from RCTs. In four cohort studies,[48-51] including 532 708 individuals, the pooled PPV23 VE for the prevention of IPD was 62% (95% CI: 37 to 76), I^2=24% (Figure 2). However, two of the studies had methodological limitations. Hechter et al., included only men who voluntarily participated in a longitudinal study on mens health (risk of selection bias). In Tsai et al., there is a risk of healthy vaccinee bias since the vaccinated group was younger and had lower medical costs than the unvaccinated group, the study had limited follow-up time after vaccination (which may have overestimated the VE) and the study also reported an unexpectedly low all-cause mortality rate. The VE decreased to 47% (13 to 67), I^2=0% (n=57 396) with no heterogeneity if the pooled analyses was restricted to cohort studies with low risk of bias.[50, 51]

In four case-control studies including 2381 individuals,[42, 52-54] the pooled VE was 52% (29 to 67), I^2=65% (Figure 2). There is a risk of selection bias in the study by Dominguez et al.,[54] as the percentage of elderly with comorbidities was very high and the vaccine coverage was lower than normal in the region. After excluding this study from the pooled analysis (n=1597), the VE remained significant at 43% (21 to 60). The heterogeneity remained moderately high at 44%.[52,53] The study by Vila-Corcoles et al., included adults 50 years and older (26% were aged 50-64 years), which may explain the higher VE in this study. It was not possible to extract IPD data limited to adults 65 years or older from the publication.

Figure 2, Forest plot for the comparison of PPV23 vs no vaccine for the prevention of invasive pneumococcal disease, all serotypes (any IPD) – observational studies[1]



Quality of evidence

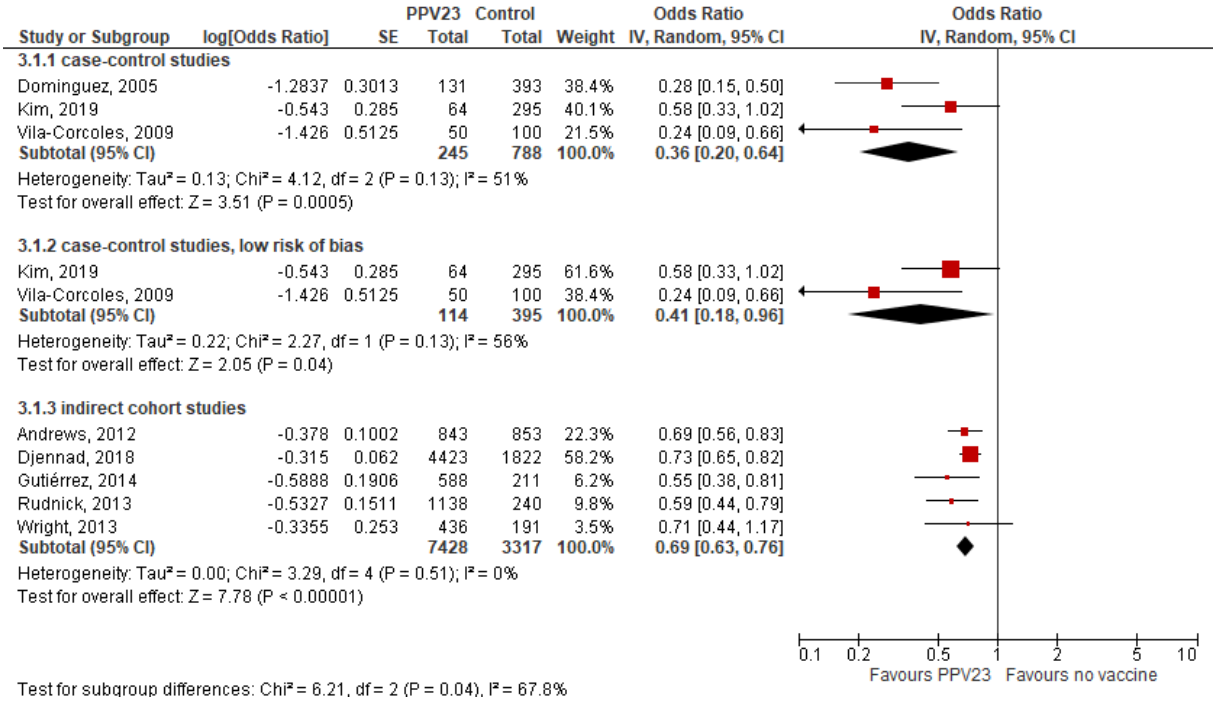
The quality of evidence from RCTs was downgraded to moderate quality due to imprecision as there were few IPD cases included with corresponding wide CIs. In two of the trials the study population was not completely representative of the general elderly population, as participants were nursing home residents or patients recently hospitalized with pneumonia. The effect of this potentially more frail population would be to underestimate rather than overestimate VE. However, the studies reported high VE and for this reason we did not downgrade the evidence for indirectness, evidence profile in Appendix 5a. Observational studies starts at low quality of evidence due to the risk of residual confounding. No factors were relevant to upgrade or downgrade the overall evidence from the observational studies.

3.3.2 PPV23 VE for prevention of vaccine-type IPD (VT-IPD)

VE against VT-IPD was reported in three case-control studies (n=1033)[52-54] and in five TND studies (n=10745)[1, 55-58] (Figure 3).

[1] In Figure 2, number of cases and controls for Ochoa-Gondar et al and Jackson et al., reflects person-years and not number of individuals

Figure 3, Forest plot for the comparison of PPV23 vs no vaccine for the prevention of vaccine-type invasive pneumocccal disease (VT-IPD) - observational studies



The pooled VE from the case-control studies was 64% (36 to 80), I^2=51%. The study by Dominguez et al., was excluded from the pooled estimate for the same reasons as described above for IPD. The pooled VE yielded a fairly similar estimate (VE 59% [4-82], I^2=56%) after exclusion of the study. The heterogeneity increased to 56%. The age-group in Vila-Corcoles et al., was younger than in the study by Kim et al., (≥50 vs ≥65 years). The study by Kim et al.,[52] was conducted in South Korea in 2013-2015. The study followed optional use of PCV7 in the childhood vaccination program since 2003, with coverage reaching 75% in 2013, whereas the study by Vila-Corcoles et al.,[43] was conducted in Spain in at a time where PCV7 was recommended only for at-risk infants. In both studies PPV23 coverage in elderly was high (>50%).

The five test negative studies yielded a precise VE estimate with pooled VE 31% (24 to 37), I^2=0%. Two of the studies covered data from the pre- *and* post PCV-period,[55 56] whereas three reported only from the post-PCV period.[57, 58] In the publication by Djennad et al., adjusted VE estimate was not available for vaccines given within the last five years.[1] Thus, the adjusted VE in the forest plot refers to PPV23 given at any time.

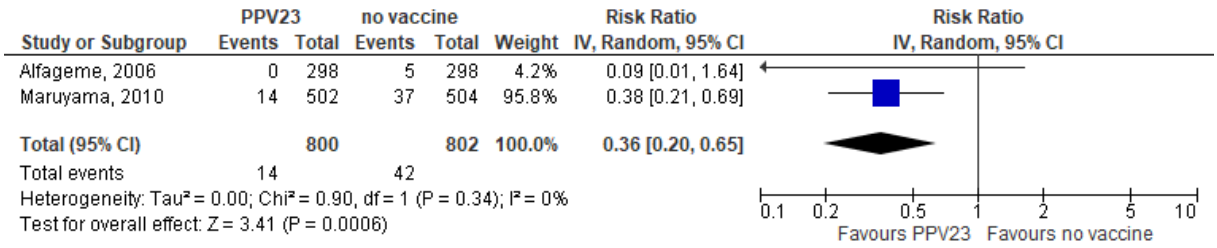
Quality of evidence

No RCT data were available for this outcome and no factors were relevant to upgrade or downgrade the overall evidence for the observational studies, evidence profile in Appendix 5b. The indirect cohort/Broome method is considered a robust type of observational study for evaluating VE for respiratory infectious diseases and studies using this design were consistent in their VE estimates. Strengths include the strong matching of controls and low risk of selection bias and reporting bias.

3.3.3 PPV23 VE for prevention of pneumococcal pneumonia, all serotypes

Evidence from RCTs for the prevention of pneumococcal pneumonia includes data from two trials including 1602 individuals (Figure 4).[46, 47]

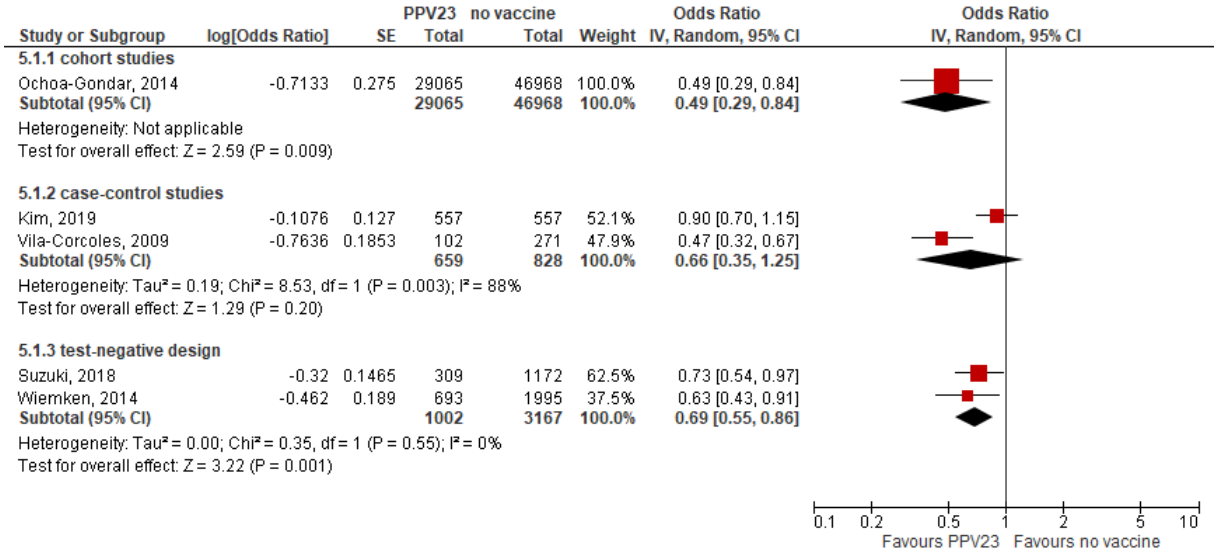
Figure 4, Forest plot for the comparison of PPV23 vs no vaccine for the prevention of pneumococcal pneumonia (PnPn) – RCTs



The pooled VE was 64% (95% CI: 35 to 80), I^2=0% (Figure 4). The pooled estimate is largely driven by the trial by Maruyama et al.,[47] The study was conducted in Japan and included nursing-home residents with low uptake of PPV23 and about 20 times higher incidence of pneumococcal pneumonia than the elderly community dwelling population (40.7/1000 versus 2/1000 per year). The smaller trial by Alfageme et al., included only five cases of pneumonia, all in the unvaccinated group.

One cohort study reported on pneumococcal pneumonia in adults. Ochoa-Gonder et al,[50] (n=58 662) found significant VE at 51 % (16 to 71) (Figure 5). The pooled analysis from the two case-control studies,[43, 52] showed high heterogeneity I^2=88%. There was considerable variation in point estimates and minimal overlap of confidence intervals.

Figure 5, Forest plot for the comparison of PPV23 vs no vaccine for the prevention pneumococcal pneumonia (PnPn) - observational studies



The study by Kim et al.,[52] (VE 10% [-15 to 30]) included only non-bacteremic pneumococcal pneumonia, whereas Vila-Corcoles et al.,[43] (VE 53% [33 to 68]) reported all pneumonia in the age-group ≥65 years, including bacteremic cases. The proportion bacteremic cases among pneumonia cases was high (31%) in the overall study population (age ≥50 years). The proportion bacteremic cases in elderly ≥65 years was not available.

Pooled VE from two TND studies including 4169 individuals,[59, 60] was significant at 31% (15 to 45), I^2=0%.

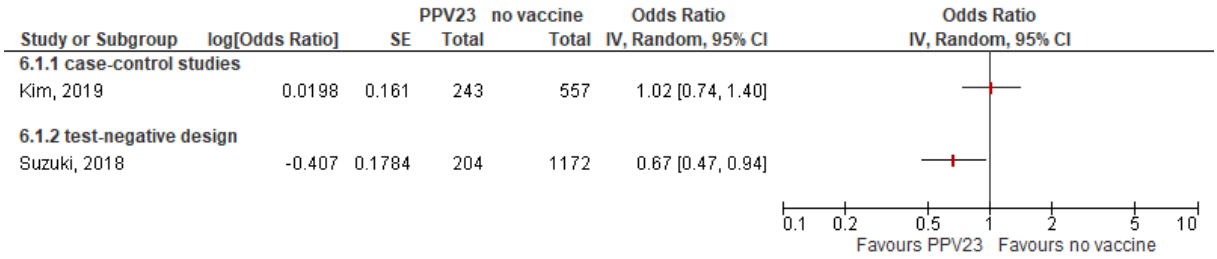
Quality of evidence

We downgraded the quality of evidence from RCTs for indirectness, since the population in the trial by Maruyama et al., included nursing home residents, which may not be completely representative for the general adult population. The confidence intervals include both substantially reduced risk and increased risk of pneumonia, and the study by Alfageme et al., was small and reported no cases in the vaccinated group. We did not find this sufficient to downgrade for inconsistency. The quality of evidence from the two case-control studies was downgraded to very low quality of evidence due to imprecision. Point estimates differed and CIs did not overlap. No factors were relevant for upgrading or downgrading the overall evidence for other observational studies and the overall quality remained low, evidence profile in Appendix 5c.

3.3.4 PPV23 VE for prevention of vaccine-type pneumococcal pneumonia (VT-PnPn)

Two observational studies reported VE for the prevention of VT-PnPn, the case-control study by Kim et al.,[52] (VE -2, [-40 to 26]), and the TND study by Suzuki et al., (VE 33%, [6 to 53])[60] (Figure 6).

Figure 6, Forest plot for the comparison of PPV23 vs no vaccine for the prevention vaccine-type pneumococcal pneumonia (VT-PnPn) - observational studies



Quality of evidence

A complete evidence profile table is not provided for this outcome since only two single studies are available. The overall quality of the evidence was low for both outcomes due to their observational design and there were no relevant factors identified to upgrade or downgrade the overall evidence.

3.4 Efficacy and effectiveness of the 13-valent conjugate pneumococcal vaccine in adults

The CAPITA trial is to date the only trial assessing the VE of PCV13 in adults. The study included 84 496 individuals. VE was 52% (22 to 71) for all type IPD and 75% (41 to 91) for VT-IPD in per-protocol (PP) analyses of first-episode of disease (excluding individuals who became immunocompromised during the study period) (Table 6).[66] Based on modified intention-to-treat (mITT) analysis, the VE estimates remained fairly similar to the PP analysis, 49% (21 to 67) and 76 (47 to 90) for all-type first episode IPD and first episode VT-IPD, respectively. For the main study outcome, first episode VT-CAP, VE was 46% (22 to 63) in PP analyses and 38% (14 to 55) in mITT analysis. VE for non-invasive VT-CAP was 45 (14 to 65) and 41 (13 to 61) in PP and mITT analyses respectively. A comprehensive overview of VE, including a range of post-hoc

analyses reported from the CAPITA trial, is presented in table 6. This table is updated from the KCE-report.[13] No other PCV13 studies have reported VE for the prevention of IPD or VT-IPD.

Several post-hoc publications from the CAPITA trial are available.[67-71] Webber et al., reported VE for 23 exploratory endpoints in CAPITA, confirming the significant VE from the primary analysis for prevention of all episodes PnCAP and IPD.[70] In CAPITA, the presence of underlying risk conditions at study entry was based on self-report and immunocompromised individuals were excluded from enrollment. Suaya et al.,[71] and Huijts et al.,[68] reported on PCV13 VE in the subgroup of elderly with underlying medical conditions, the first based their analyses on self-reported comorbidity, whereas the latter was based on comorbidities documented in medical records. Huijts et al., reviewed medical records for the 139 VT-cases in CAPITA and verified this information through a register-linkage for a larger sample. Diabetes mellitus (DM) was found to cause significant effect modification yielding higher VE in those with DM (VE 90% [66 to 97]) compared to those without DM (VE 25% [-10 to 50]). Gessner et al., presented a public health framework for analysis of clinical trial data and reported substantial reduction in the burden of pneumonia and IPD outcomes following adult PCV13 vaccination in a setting with high coverage of PCV in children and no use of PPV23.[67] Patterson et al., performed a time-to-event analysis for primary and secondary trial outcomes and found PCV13 to be effective with no waning of immunity over the 5-year duration of the study.[69]

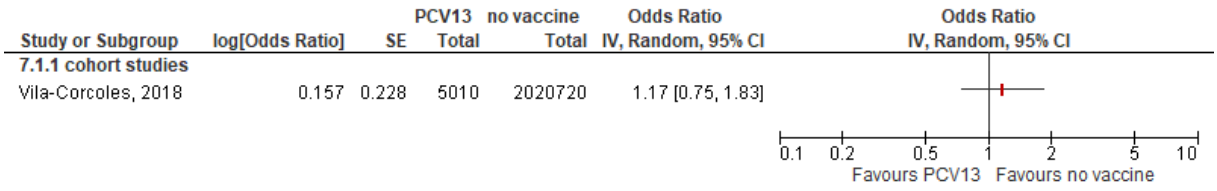
Quality of evidence

A complete evidence profile table is not provided for PCV13 PPV VE for IPD and VT-IPD, since the CAPITA trial is the only study available for these outcomes. The study population in CAPITA was younger than the target population for vaccination. The majority of study participants (58 %) were healthy (without comorbidities), and the remainder (42 %) had stable comorbidities.[66] It has been questioned whether this could lead to overestimation of VE compared to the general population. We do not judge this sufficient for downgrading for indirectness. The overall quality of evidence is high for all primary outcomes in CAPITA. We have not assessed the quality of the post-hoc analyses.

3.4.1 PCV13 VE for prevention of pneumococcal pneumonia, all serotypes

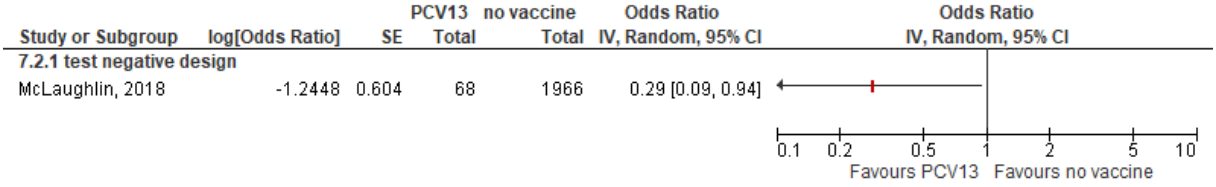
One Spanish cohort study including 2 020 720 individuals reported negative and non-significant VE -17% (-83 to 25) for pneumococcal pneumonia (Figure 7).[73] The study included administrative and clinical data from electronic records in primary health care centers. Although the study population is large, less than 1% of the study population were PCV13 vaccinated and the follow-up time was limited to the year 2015.

Figure 7, Forest plot for the comparison of PCV13 vs no vaccine for the prevention of pneumococcal pneumonia (PnPn) - observational studies



VE for the prevention of all VT-CAP was assessed in two TND studies.[35 72] However, Prato et al.,[35] reported only crude VE and the estimate is not included in the forest plots for this reason. The reported VE was 33% (95%CI -107% to 82%) for the prevention of all type PnCAP and 38% (-132 to 89) for VT-CAP. The study by McLaughlin et al., a population-based surveillance study of adults in the US, reported 71% VE (6-91) for VT-CAP (Figure 8).

Figure 8, Forest plot for the comparison of PCV13 vs no vaccine for the prevention of vaccine-type community acquired pneumococcal pneumonia (VT-CAP) - observational studies



Quality of evidence

The quality of evidence for CAPITA outcomes are graded as high as previously discussed. A complete evidence profile table is not provided for additional PCV13 VE studies, since only single studies are available for the different outcomes. There are limitations in the large study by Vila-Corcoles et al., as very few participants were vaccinated and outcome was observed over a limited period. PCV13 vaccination was recommended for high-risk individuals and the authors suggest that the higher prevalence of underlying conditions in the vaccinated group may have contributed to the low VE estimates. The study by Prato et al., only presented crude estimates and were not considered for pooled analyses for this reason. In the TND study by McLaughlin et al., eight percent of the CAP cases were bacteremic, which may overestimate VE. Cases were less likely to be immunocompromised and overweight or obese compared to controls. No relevant factors were identified to upgrade the quality of any of the single studies, which remained low or very low.

3.5 Effect of age on efficacy and effectiveness of pneumococcal vaccines in adults

Vaccine effectiveness estimates by age are presented in table 7 for PPV23 and in table 8 for PCV13. Overall, the vaccine effectiveness tended to be lower with higher age irrespective of vaccine used, study design or outcome. However, the magnitude of the reduction differed and was highest for the oldest age-group. Confidence intervals were broad for most estimates, due to low number of cases.

3.5.1 Vaccine effectiveness by age, PPV23

The only studies that provided sufficiently similar data for pooled estimates by age-groups were four of the indirect cohort studies measuring VE by Broome method (n=9367).[1, 55, 57, 58] The pooled VE for prevention of VT-IPD was significant and fairly similar at 33% (21 to 43), I^2=0%, 25% (9 to 38), I^2=20% and 28% (15 to 39), I^2=0% for the age-groups 65-74 years, 75-84 years and ≥85 years respectively. A forest plot for the comparison is included in Appendix 6. It should be noted that the study by Gutierrez et al.,[60] had slightly different age cut-offs; 60-69, 70-79 and 80 years and older respectively. Two case-control studies[52, 53] and one cohort study[51] reported PPV23 VE for the prevention of IPD. They found significant VE for individuals younger than 75 years of age, whereas VE was non-significant and low or even negative for the oldest age-groups.

3.5.2 Vaccine effectiveness by age, PCV13

The original report from the CAPITA trial[66] reported a decrease in PCV13 VE by age-group for the main outcome VT-CAP, ranging from 53% (24 to71) and 46% (-4 to 74) for age-groups 65-74 years and 75-84 years respectively, and negative effect for individuals 85 years or older -100% (-1156 to 58), table 8. The confidence intervals for the negative efficacy in the oldest age-groups are broad due to the low number of cases. A later CAPITA post-hoc modeling study[74] reported similar observed VE against VT-CAP or IPD based on modified intention-to-treat analysis: VE 49% (26 to 67), 41% (3 to 66) and -100 % (-1000 to 29) for the age-groups 65-74, 75-84 and 85 years and older respectively. When modeled, the VT-CAP VE showed a significant decline with increasing age; 65% in 65 years, 40% in 75 years and 0% in 85 years.

Table 7, PPV23 vaccine effectiveness (VE % [95% CI]) against pneumococcal disease outcomes by age-group

Author, year	Country	Design	Outcome	N	All	65-74 (y)	75-84 (y)	85+ (y)
Wright, 2013	England	ind cohort	VT-IPD	534	29 (-17 to 57)	44 (-27 to 75)	21 (-75 to 65)	8 (-159 to 67)
Guiterrez, 2014[II]	Spain	ind cohort	VT-IPD	588	45 (19 to 62)	54 (15 to 75)	54 (19 to 74)	26 (-23 to 55)
Andrews, 2012	England & Wales	ind cohort	VT-IPD	1270	24 (10 to 36)	28 (1 to 47)	25 (3 to 43)	18 (-11 to 39)
Djennad, 2018	England & Wales	ind cohort	VT-IPD	6245	27 (17 to 35)	31 (16 to 44)	17 (-3 to 32)	34 (17 to 47)
Jackson, 2003	USA	cohort	IPD	61	44 (7 to 67)	54 (13 to 76)		22 (-87 to 68)
Leventer-Roberts, 2015	Israel	case-control	IPD	1060	42 (19 to 59)	46 (10 to 68)	20 (-22 to 47)	
Kim, 2019	South Korea	case-control	IPD	443	29 (-6 to 52)	57 (19 to 78)	7 (-74 to 50)	
			PnPn[§]	1114	10 (-15 to 18)	35 (2 to 57)	-13 (-56 to 18)	
Vila-Corcoles, 2009	Spain	case-control	PnPn	304	53 (33 to 68)	48 (19 to 67)	--	56 (16 to 77)
Suzuki, 2017	Japan	TND	PnPn[¤]	419	27 (3 to 46)	32 (-21 to 62)	24 (-6 to 46)	
			VT-Pn[¤]	272	34 (6 to 53)	40 (-16 to 69)	28 (-9 to 53)	

N: number of cases; ind cohort: indirect cohort, i.e. serotype distributions (VT and non-VT serotypes) is compared in vaccinated and unvaccinated IPD cases; TND: test-negative design, i.e. *S.pneumoniae* and other etiologies are compared in vaccinated and unvaccinated pneumonia patients; y: years; IPD: invasive pneumococcal disease; VT-IPD: vaccine.type IPD, PnPn: pneumococcal pneumonia; VT-Pn: vaccine-type pneumococcal pneumonia, CAP: community acquired pneumonia

[II] *It should be noted that the study by Gutierrez et al., had slightly different age cut-offs: 60-69, 70-79 and 80 years and older respectively.*

[¤] *Includes CAP and hospital acquired pneumonia* [§] *Only non-bacteremic PnCAP*

Table 8, PCV13 vaccine effectiveness (VE % [95% CI]) against pneumococcal disease outcomes by age-group

Author, year	Country	Design	Outcome	N	All	65-74 (y)	75-84 (y)	85+ (y)
Bonten, 2015	Netherlands	RCT	VT-CAP[#]	139	46 (22 to 62)	53 (24 to 71)	46 (-4 to 74)	-100 (-1156 to 58)
Vila-Corcoles, 2018	Spain	cohort	PnPn	1648	-17 (-83 to 25)	-32 (-118 to 19)		

N: number of cases; VT: vaccine-type disease; CAP: community acquired pneumonia; Pneu: pneumonia; pnPn: pneumococcal pneumonia; vtPn: vaccine-type pn pneumonia; y: years

[#] *Per protocol analysis, first episode (table S3, Bonten et al.)*

3.6 Effect of comorbidities on efficacy and effectiveness of pneumococcal vaccines in adults

Vaccine effectiveness estimates by presence or absence of underlying medical conditions or immunosuppression are presented in tables 9 and table 10 for PPV23 and in table 11 for PCV13. Most studies categorized medical risk consistent with criteria in the CDC Advisory Committee on Immunization Practices (ACIP) for PPV23 immunization among adults.[75] For both vaccines, the VE tended to be lower in groups with underlying medical conditions and lowest in groups with immunocompromising conditions.

3.6.1 Vaccine effectiveness by medical risk factors, PPV23

Five out of six PPV23 VE studies evaluating VE against VT-IPD, yielded non-significantly higher VE in healthy adults compared with immunocompetent high-risk individuals, with a difference in point estimates ranging 6-22% (Table 10). In immunocompromised patients, four studies utilizing the Broome method, measured VE against PPV23 serotypes, which was never significant and had large CI (Table 10). This applied even to the largest study involving 1164 cases and 534 controls in immunocompromised subjects. The three UK studies[1, 55, 57] also stratified VE by age *and* risk group (data not shown). The study by Djennad et al.,[1, 55] reported a gradient of effectiveness with VE 48% (2 to 73) in 65-74 years with no risk. However, VE estimates were inconsistent across strata and with wide 95% CI due to small numbers. This overview has been updated from the Belgian report.[13]

Two case-controls studies[44 54] found high, and in the study by Vila-Corcoles[44] even significant VE of PPV23 against all type IPD in immunocompromised participants. Both studies included low numbers of cases with immunosuppression (29 and 39 respectively). In Vila-Corcoles[44] VE was higher in the immunocompetent and immunosuppressed high-risk groups compared with those without known medical risk, table 10. Only 18 case-control sets contributed to the analysis in the no-risk group. In the group assigned with a high-risk condition, few patients actually had severe immunosuppression.[44] The same study group reported a similar pattern with highest VE in the immunosuppressed group, also for PnCAP as outcome.[43] These are the only studies reporting significant VE in the immunocompromised population.

3.6.2 Vaccine effectiveness by medical risk factors, PCV13

In CAPITA, comorbidities were self-reported at baseline and were not verified by medical record review. Individuals with immunocompromising conditions were excluded from enrollment. Therefore, the immunocompromised group in CAPITA is small and only includes those who became immunocompromised after enrollment (n=82), table 11. Participants with recent immunosuppression may be different from those with known and potentially well-controlled conditions. For all main outcomes, VE estimates were significant and higher in immunocompetent than in immunocompromised high risk individuals, table 11. Confidence intervals for the immunosuppressed group were wide due to low case numbers.

Table 9, PPV23 vaccine effectiveness (VE % [95% CI]) against pneumococcal disease outcomes in individuals with and without chronic respiratory disease

Author, year	Country	Design	Outcome	N	All	With chronic respiratory disease	Without chronic respiratory disease
Suzuki, 2017	Japan	TND	PnPn*	419	27 (3 to 46)	27 (-19 to 55)	26 (-6 to 49)
			VT-Pn*	272	34 (6 to 53)	35 (-21 to 65)	32 (-4 to 56)

N: number of cases; TND: test negative design; PnPn: pneumococcal pneumonia; VT-Pn: vaccine-type pneumococcal pneumonia,
**Includes community and hospital acquired pneumonia*

Table 10, PPV23 vaccine effectiveness (VE % [95% CI]) against pneumococcal disease outcomes in no risk, high risk immunocompetent and high risk immunosuppressed individuals

Author, year	Country	Design	Outcome	N	VE all	VE No risk	VE HR immunocompetent	VE HR immunosuppressed
Jackson, 2003	USA	cohort	IPD	61	44 (7 to 67)	54 (13 to 76)		22 (-87 to 68)
Leventer-Roberts, 2015	Israel	case-control	IPD	212	42 (19 to 59)	37 (-33 to 70)	30 (1.0-51)	
Vila-Corcoles, 2010	Spain	case-control	IPD	88	72 (46 to 85)	60 (-89 to 91)	71 (21 to 89)	88 (47 to 97)
Dominguez, 2005	Spain	case-control	IPD	131	70 (48 to 82)	83 (-62 to 98)	75 (47 to 86)	50 (-44 to 82)
			VT-IPD	118	72 (50 to 85)	83 (-62 to 98)	77 (45 to 90)	46 (-54 to 81)
Andrews, 2012	England & Wales	ind cohort	VT-IPD	1270	24 (10 to 36)	34 (12 to 50)	20 (-9 to 41)	22 (-5 to 42)
Djennad, 2018	England & Wales	ind cohort	VT-IPD	6245	27 (17 to 35)	45 (27 to 59)	25 (11 to 37)	13 (-9 to 30)
Rudnick, 2013	Canada	ind cohort	VT-IPD	1311	39 (20 to 53)	69 (33 to 85)	47 (23 to 63)	-6.5 (-67 to 32)
Wright, 2013	England	ind cohort	VT-IPD	534	29 (-17 to 57)	-16 (-188 to 53)	32 (-36 to 66)	33 (-65 to 73)
Gutierrez, 2014	Spain	ind cohort	VT-IPD	588	45 (19 to 62)	60 (33 to 76)	32 (-2 to 54)	
Vila-Corcoles, 2009	Spain	case-control	PnCAP	304	53 (33 to 68)	61 (-2 to 85)	41 (10 to 61)	71 (34 to 89)
Alfageme, 2006	Spain	RCT	PnCAP	5	91 (-64 to 99)	-	NA (5 vs 0 cases)	-

VE: vaccine effectiveness %; N: number of cases; HR: high-risk; RCT: Randomized Controlled Trial; ind cohort: indirect cohort; IPD: invasive pneumococcal disease; VT-IPD: vaccine-type IPD; CAP: community acquired pneumonia; PnPn: pneumococcal pneumonia; vtPn: vaccine-type pneumococcal pneumonia; CAP: community acquired pneumonia

Table 11, PCV13 vaccine effectiveness (VE % [95% CI]) against pneumococcal disease outcomes high risk immunocompetent and high risk immunosuppressed individuals[§]

Author, year	Country	Design	Outcome	N	HR immunocompetent participants		HR immunosuppressed participants	
					Vacc/ non-vacc	VE % (95% CI)	Vacc/ non-vacc	VE % (95% CI)
Bonten, 2015	Netherlands	RCT (CAPITA)	VT-IPD	39	7/28	75 (41 to 91)	1/3	67 (-315 to 99)
			PnCAP	172	51/93	45 (22 to 62)	14/11	-27 (-212 to 47)
			NI NB VT-CAP	196	35/63	44 (14 to 65)	7/10	30 (-105.5 to 78)

VE: vaccine effectiveness; N: number of cases; HR: high-risk; RCT: randomized controlled study; PnCAP: community acquired pneumococcal pneumonia; VT-IPD: vaccine-type invasive pneumococcal disease, NI NB VT-CAP: non-invasive, non-bacteremic vaccine-type CAP
§ For total CAPITA population outcome, see table 6

Table 12, PCV13 vaccine effectiveness (VE % [95% CI]) against pneumococcal disease outcomes in individuals with and without comorbidities§

Author, year	Country	Design	Outcome	N	VE without comorbidity	VE with comorbidity
Hujits, 2017	Netherlands	RCT (CAPITA)	VT-CAP	139	47 (-26 to 77)	45 (20 to 63)
Suaya, 2018	Netherlands	RCT (CAPITA)	VT-CAP	169	64 (15 to 86)	33 (4 to 53)
Gessner, 2018	Netherlands	RCT (CAPITA)	PnCAP	322	31 (-19 to 60)	23 (0.3 to 40)
			VT-CAP	179	65 (20 to 87)	32 (4 to 52)
			IPD	99	47 (-34 to 80)	51 (19 to 71)
			VT-IPD	41	72 (-50 to 97)	77 (43 to 92)
Prato, 2018[II]	Italy	TND	PnCAP	51	Not reported	34 (-105 to 83)
			VT-CAP	34	Not reported	40 (-128 to 89)

VE: vaccine effectiveness; N: number of cases; RCT: randomized controlled study; TND: Test-negative design; IPD: invasive pneumococcal disease; VT-IPD: vaccine-type IPD, CAP: community acquired pneumonia, PnCAP pneumococcal CAP; VT-CAP: vaccine-type pneumococcal CAP
§ For total CAPITA population outcome, see table 6, II Prato, total VE PnCAP: 33 (-107-82), VT-CAP: 38 (-132-89)

In post-hoc analyses, Suaya et al.,[71] and Gessner et al.,[67] published additional VE in individuals with and without comorbidities (excluding those with immunosuppression, asplenia or missing medical information). Suaya et al., reported VE for VT-CAP using the CAPITA self-reported data with VE 64% versus 33% for the group without- or with comorbidity respectively, table 12. Gessner et al.,[67] complemented previous CAPITA publications, by adding additional outcome definitions and outcome measures using the same self-report medical data, table 12. VE was generally higher for specific etiology confirmed outcomes, but the difference in estimated VE for in participants with and without comorbidities were not as consistent in this report. Hujits et al,[68] retrospectively obtained information on comorbidities from medical records (from GPs, hospitals) for participants who were identified with VT-CAP (n=139), and from ICPC codes from general practitioners for 40427 CAPITA participants. The number of individuals with comorbidities was higher when data were obtained from medical records than from self-report. Hujits et al., reported VE 45% (20 to 54) in participants with comorbidities versus 47% (-26 to -77) for those without comorbidities.

Prato et al,[35] is the only other publication reporting PCV13 VE in individuals with comorbidities. This test-negative study reported non-significant VE 34% (-105 to 83) and 40% (-128 to 89) for pneumococcal CAP and VT-CAP respectively.

3.7 Effect of time since vaccination

3.7.1 Vaccine effectiveness by time since vaccination, PPV23

Six studies[1, 55-58, 60] reported PPV23 VE against by time since vaccination, table 13. Five were indirect cohorts reporting on VE for VT-IPD, and one was a TND study reporting on VE for pneumococcal and VT-pneumococcal pneumonia.

Table 13, Vaccine effectiveness (VE % [95% CI]) against pneumococcal disease outcomes by time since vaccination for PPV23

Author (y)	Outcome	VE by time since vaccination (y)			
		< 2 y	2 to < 5 y	5 to < 10 y	>= 10 y
Suzuki, 2017	PnPn	32 (2 to 51)	26 (-12 to 51)	0.2 (-77 to 27)	
	VT-PnPn	38 (5 to 59)	35 (-7 to 60)	26 (-56 to 65)	
Andrews, 2012	VT-IPD	48 (32 to 60)	21 (3 to 60)	15 (-3 to 30)	
Djennad, 2019	VT-IPD	41 (23 to 54)	34 (16 to 48)	23 (12 to 32)	
Gutierrez, 2014*	VT-IPD	45 (19 to 62)		33 (-6 to 57)	
Rudnick, 2013	VT-IPD	41 (20 to 57)		34 (6 to 54)	
Wright, 2013	VT-IPD	-9 (-119 to 43)		38 (-6 to 64)	-21 (-137 to 35)

*included individuals >= 60 years

Point estimates are similar across studies and shows declining VE with time since vaccination. The inconsistent results in the study by Wright et al., may arise from the low number of nonVT cases (only 15 patients contributed in the nonVT group for VE <5 years after vaccination). Only the two largest indirect cohort studies, including 6245 and 1378 participants respectively, reported significant VE five years after vaccination.[1 56] Djennad et al., explored the long-term decline through a spine model which indicated an initial drop in VE for VT-IPD from about 50% the first two years to a plateau at 20-25% more than five years after vaccination (figure in the publication[1]).

The cohort study by Ochoa-Gondar et al., conducted a sensitivity analysis to assess the duration of protection. They classified participants as *ever* vaccinated, i.e. at any time and as vaccinated within the last five years, i.e. excluding those with PPV23 vaccination more than 5 years ago. No significant protection appeared in the analyses including participants *ever* vaccinated, implying low or no VE ≥5 years after vaccination.[50]

Table 14, Vaccine effectiveness (VE % [95% CI]) against pneumococcal disease outcomes by age and time since vaccination for PPV23

Time after vaccination	VE by age and time since vaccination		
	65 to 74 (y)	75 to 84 (y)	85+ (y)
Andrews et al., 2012			
VE < 2 y	58 (32 to 73)	56 (32 to 71)	12 (-51 to 49)
VE 2 to < 5 y	4 (-42 to 35)	30 (2 to 50)	26 (-10 to 50)
VE ≥ 5y	25 (-11 to 49)	8 (-24 to 32)	14 (-20 to 39)
Djennad et al., 2018			
VE < 2 y	43 (17 to 61)	38 (1 to 62)	26 (-36 to 60)
VE 2 to < 5 y	35 (11 to 53)	39 (0-63)	6 (-81 to 52)
VE ≥ 5y	18 (-3 to 36)	15 (-6 to 31)	35 (18 to 49)

Two of the studies reported VE estimates based on surveillance data from England and Wales from subsequent time-periods. The studies stratified VE by time since vaccination and age-group.[1 55] In these populations, the majority had their pneumococcal vaccination more than five years prior to IPD diagnosis. In the study by Djennad et al., 90% of those >= 85 years were vaccinated more than 5 years prior to IPD diagnosis. VE was non-significant after 5 years in all other groups, and non-significant in general for the population >= 85 years.

3.7.2 Vaccine effectiveness by time since vaccination, PCV13

In CAPITA post-hoc analyses,[69, 71] in which they plotted the cumulative number of disease episodes against the time from vaccination, the authors concluded that efficacy occurred soon after vaccination and persisted throughout the duration of the trial (almost 4 years). However, case-numbers the fourth year was low and potentially insufficient to demonstrate a waning effect. CAPITA has not reported non-cumulative VE by time since vaccination, i.e. < 2 years, 2 to < 5 years.

4 Discussion

No study compares VE of PCV13 and PPV23 head-to-head and no new RCTs were published since the previous reviews. We found that both PPV23 and PCV13 are effective for the prevention of all type and VT-IPD in the broader adult population across study designs and settings. Further, we found PCV13 and PPV23 to be effective in preventing pneumococcal pneumonia in elderly, supporting the conclusions from Falkenhorst et al. However, results obtained from RCTs and those obtained from various observational designs are inconsistent, making it difficult to summarize available evidence into single quantitative measures. It is likely that the higher VE seen in PPV23 clinical trials may reflect shorter follow-up time compared with CAPITA and observational studies, where waning immunity is likely to play a role. VE estimates for PCV13 are almost exclusively based on data from CAPITA, with only a few additional observational studies. There are more data available for PPV23, although the overall quality remains more questionable. Both vaccines showed generally lower VE with increasing age and in medical high-risk groups.

The vaccine effectiveness of PPV23 in preventing IPD was consistent with past systematic reviews and fairly similar to the estimates that have been reported for PCV13 efficacy and effectiveness. Consistent benefits were also reported across observational studies and ecological studies of surveillance data for the general elderly population.

To measure VE for the prevention of pneumococcal pneumonia is difficult, due to lack of standardized diagnostic tools. Differences in test sensitivity and specificity might influence the number of pneumonia cases reported. CAPITA used an experimental serotype specific urinary antigen-detection assay (SSUAD) from Pfizer for diagnosis of non-bacteremic pneumococcal pneumonia. The assay, which depends on monoclonal antibody against capsule polysaccharides for the serotypes included in PCV13,[76] is currently only available for research purposes. The SSUAD assay is >95% sensitive and specific for identifying PCV13 serotypes in patients with bacteremic or non-bacteremic radiographically confirmed CAP, when validated against bacteremic pneumonia.[77-79] Although restricted to the PCV13 serotypes, the SSUAD have substantially increased the detection of pneumococcal pneumonia.[77] The two PCV13 TND studies reported overlapping confidence intervals with those in CAPITA. Prato et al.,[35] reported non-significant VE for PnCAP and VT-CAP. This study had low inclusion rate, stopped before planned time, and only presented crude VE. Yet, VE estimates were consistent with other reports. The US prospective population-based surveillance study by McLaughlin et al.,[72] reported significant and surprisingly high PCV13 VE against VT-CAP. The percentage of cases with bacteremic disease was 8% and when the authors restricted the analysis to non-bacteremic CAP (nbCAP) the VE was lower and no longer statistically significant. No VE estimates were provided for invasive disease, probably due to the low number of cases. Further, the follow-up time was only 157 days, which may also play a role.[72] Except for this US TND study, little evidence other than CAPITA is available to inform PCV13 VE.

The controversy of test sensitivity and specificity for the diagnosis of non-invasive pneumococcal pneumonia is more pronounced for PPV23 VE estimates. In addition, there is a continuing discussion on whether the study populations are sufficiently representative for the target population for pneumococcal vaccination. For these reasons, review authors have applied different inclusion and exclusion criteria, and none of the five systematic reviews from 2016 or 2017 included the same PPV23 RCT data and no new RCTs are available. In the trials by Honkanen[36] and Örtqvist[37], the diagnosis of pneumococcal pneumonia was based on detection of antibodies against pneumolysin, a cholesterol dependent cytotoxin produced by many

pneumococcal strains. Later studies have questioned the validity of this method, as it does not reliably distinguish between colonization and disease.[40 41] The main concern is low specificity, which may bias the VE towards no effect. Falkenhorst et al.,[14] extensively discussed this weakness in their review, and in a sensitivity analysis they demonstrated a markedly lower PPV23 VE when data from the two studies using pneumolysin-dependent diagnosis were included.[14] Schiffner-Rohe et al., on the other hand, included the trials by Honkanen and Örtqvist, arguing that the control groups in the original- and validation studies were not comparable and that the coating antigen used to capture anti-PLY IgGs in the validation study was different from the original study. We excluded the two studies in which the diagnosis of pneumonia was based on pneumolysin antibodies, in line with the German review. The validity of the diagnosis remain questionable, the assay has never been in clinical use and Örtqvist, the main author of the trial publication, supported the exclusion of trial data on pneumococcal pneumonia (personal communication). We excluded the trial by Honkanen et al., from all outcomes, due to the insufficient randomization procedure. This study was included in the review by Falkenhorst et al., for all type IPD. Pooled VE for all-type IPD after exclusion of Honkanen et al., remained fairly similar to the pooled estimate reported by Falkenhorst et al., (76% versus 73%). However, lower case-numbers broadened the CIs and the pooled VE estimate was no longer significant.

The trial by Maruyama et al.,[47] included nursing-home residents in Japan with low uptake of PPV23 and higher incidence of pneumococcal pneumonia than the general elderly population. The representativeness of the study population has been questioned, and the trial was excluded from the reviews by Schiffner-Rohe and Kraicer-Melamed for this reason. This is the only trial showing significant PPV23 VE for the protection of pneumococcal pneumonia. Although the reported VE is higher than expected in this population, we identified no clear flaws in the trial conduct. The inclusion of frail and older participants would rather underestimate than overestimate VE and the reported VE was high. This would also hold for the population in the trial by Örtqvist as these had recently been hospitalized for pneumonia. Bottom line is that the evidence for PPV23 VE from RCTs for the prevention of pneumococcal pneumonia includes a wide range of VE estimates (range no effect to 64% VE).

Although randomized controlled trials are powerful for showing vaccine efficacy, current knowledge about the PPV23 effectiveness for the prevention of pneumococcal pneumonia in elderly includes a number of case-control and cohort studies. Observational studies have reported PPV23 VE (range 10% to 51%) in different populations, although not all yielded statistically significant results. The 2009 case-control study by Vila-Corcoles et al.,[45] consistently showed high VE with corresponding heterogeneity when study data were included in pooled analyses. In the 2009 publication, Vila-Corcoles et al., reported outcomes for adults ≥50 years, which may overestimate VE. It was not possible to extract data for participants 65 years and older. For pneumococcal pneumonia outcome, the authors reported VE for the age-group 65 years or older. However, for this outcome they did not differentiate between bacteremic and non-bacteremic pneumonia. In their total study group, one third of pneumococcal pneumonia cases were bacteremic. Thus, VE are likely to be overestimated for all outcomes, either due to a younger population or the inclusion of bacteremic CAP. The hospital-based study by Kim et al.,[52] followed implementation of PPV23 in a national Immunization programme in 2013, reaching almost 60% uptake in 2015 and with high PCV coverage in children. The study showed high VE (>90%) for PPV23 unique serotypes.[52] However, this was based on a very small sample.

Test negative design (TND) and indirect cohorts (Broome method) are forms of case-control studies that are commonly used in VE studies. A major strength is that controls are drawn from the same source population as the cases. Thus, bias related to health-care seeking behavior and

ascertainment of vaccination status is reduced. The validity of using TND has been demonstrated by re-analyzing data from RCTs as TND in which VE estimates were found to be similar to the original RCT analysis.[61 80] The Broome method has logistical and cost advantages since cases and controls can be recruited from within a single surveillance system. PPV23 VE for the prevention of VT-IPD were consistent when measured by the Broome method. Only one TND study reported serotype-specific PPV23 VE for the protection of VT-CAP in elderly.[60] This study was conducted in Japan in 2011 to 2014 and used sputum PCR to define pneumococcal pneumonia. Positive samples were examined for 50 serotypes by a nanofluidic real-time PCR assay.[81] There is a chance that sputum positive samples represents carriage rather than disease. Low test specificity may cause underestimation of VE, and the VE estimates should therefore be regarded as minimum.[60] The study found low to moderate VE against all type pneumococcal pneumonia and VT-pneumonia in elderly and VE differed by vaccine serotype. Although no significant differences between subgroups were seen, VE was higher in some subgroups. The study reported PPV23 VE against PCV13 serotypes at 40% (10-60) which is not substantially different from that of PCV13 in the CAPITA trial.

No waning of protection was found for PCV13, although data are limited and only obtained from cumulative plots from CAPITA. PPV23 studies show waning of effect with time since vaccination and with questionable effect more than 5 years following vaccination, but confidence intervals are wide. More data are needed to establish the duration of clinical effectiveness for both vaccines.

All Scandinavian countries have well-established childhood PCV programs with considerable indirect effects on PCV serotypes in all age-groups. A substantial and increasing proportion of pneumococcal disease due to the additional PPV23 serotypes suggests that advantage of PPV23 over PCV13 in terms of serotypes covered may increase over time in older adults.[11] Although the exact VE for PPV23 for the prevention of IPD and pneumococcal pneumonia is difficult to estimate, the overall evidence from this synthesis shows protection. This is an important finding provided the current epidemiological situation.

Limitations in this report includes that the Belgian report restricted their search to non-US western countries. Relevant PCV13 publications from the US or other countries may have been missed for this reason. No studies compared the two vaccines directly and available studies are not completely comparable. The evidence of PCV13 VE is dominated by the large CAPITA trial which is a controlled trial under ideal conditions, whereas PPV23 studies were older RCTs or observational studies with higher risk of bias. Many were underpowered with corresponding wide confidence intervals. Time since vaccination was reported inconsistently across studies, which may impact on the comparability of reported VE. We stratified this to within the last five years whenever the information was available. Further, not all studies distinguished bacteremic from non-bacteremic pneumococcal pneumonia.

5 Conclusion

This review shows that both PCV13 and PPV23 provide prevention for IPD and pneumococcal pneumonia in the elderly. Although evidence from PPV23 RCTs for protection of pneumococcal pneumonia are inconsistent, the overall body of evidence shows PPV23 VE at a level comparable to PCV13. Although the exact size of the VE is difficult to estimate, the VE seems to be sufficiently high to provide both individual protection and public health importance given the disease burden of pneumococcal pneumonia. This will have to be determined in future studies. Decision-making on pneumococcal vaccination in older adults must also take into account the potential benefit of PCV13 vaccination in older adults. The serotype distribution in carriage and disease is important to consider for the impact of vaccination. Well-designed and serotype specific RCTs are important to improve evidence.

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7 Contributions

Brita Askeland Winje (BAW) was leading the project, responsible for development of the protocol and for writing the report. Jacob Dag Berild (JDB) and Jann Storsæter (JS) systematically screened publications by title and abstract. BAW, JDB, JS and Eva Denison (ED) extracted and analyzed data, assessed the quality of included publications and applied GRADE criteria for the overall confidence of the estimates. Adam Roth (AR), Didrik Frimann Vestrheim (DFV), Palle Valentiner-Branth (PVB), Tiia Lepp (TL) and Hans-Christian Slotved (HCS) has contributed in discussions and reviewed the final version of the report.

References

1. Djennad A, Ramsay ME, Pebody R, et al. Effectiveness of 23-Valent Polysaccharide Pneumococcal Vaccine and Changes in Invasive Pneumococcal Disease Incidence from 2000 to 2017 in Those Aged 65 and Over in England and Wales. EClinicalMedicine 2018;6:42-50. doi: 10.1016/j.eclinm.2018.12.007 [published Online First: 2019/06/14]

2. Ardanuy C, Marimon JM, Calatayud L, et al. Epidemiology of invasive pneumococcal disease in older people in Spain (2007-2009): implications for future vaccination strategies. *PLoS One* 2012;7(8):e43619. doi: 10.1371/journal.pone.0043619

3. Benfield T, Skovgaard M, Schønheyder HC, et al. Serotype Distribution in Non-Bacteremic Pneumococcal Pneumonia: Association with Disease Severity and Implications for Pneumococcal Conjugate Vaccines. *PLoS ONE* 2013;8(8):e72743. doi: 10.1371/journal.pone.0072743

4. Rozenbaum MH, Pechlivanoglou P, van der Werf TS, et al. The role of Streptococcus pneumoniae in community-acquired pneumonia among adults in Europe: a meta-analysis. *Eur J Clin Microbiol Infect Dis* 2013;32(3):305-16. doi: 10.1007/s10096-012-1778-4

5. Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PLoS One* 2013;8(4):e60273. doi: 10.1371/journal.pone.0060273

6. European Medicines agency (EMA). European public assessment report (EPAR) for Prevenar 13. Summary of product characteristics. In: (EMA). EMa, ed. London, 2015.

7. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *Journal of the American Medical Association* 2006;295(19):2275-85. doi: 295/19/2275 [pii];10.1001/jama.295.19.2275

8. Lujan M, Burgos J, Gallego M, et al. Effects of immunocompromise and comorbidities on pneumococcal serotypes causing invasive respiratory infection in adults: implications for vaccine strategies. *Clin Infect Dis* 2013;57(12):1722-30. doi: 10.1093/cid/cit640

9. Shigayeva A, Rudnick W, Green K, et al. Invasive Pneumococcal Disease Among Immunocompromised Persons: Implications for Vaccination Programs. *Clin Infect Dis* 2016;62(2):139-47. doi: 10.1093/cid/civ803

10. Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analyses. *Journal of Epidemiology & Community Health* 2012;66(12):1177-81. doi: jech-2011-200168 [pii];10.1136/jech-2011-200168

11. Hanquet G, Krizova P, Valentiner-Branth P, et al. Effect of childhood pneumococcal conjugate vaccination on invasive disease in older adults of 10 European countries: implications for adult vaccination. *Thorax* 2019;74(5):473-82. doi: 10.1136/thoraxjnl-2018-211767

12. Berild JD, Storsæter J, Vestrheim DF, et al. A systematic review of the effectiveness of pneumococcal vaccines for the prevention of pneumococcal disease 2016-2019. *under submission* 2019

13. Blommaert A, Hanquet G, Lander W, et al. Use of pneumococcal vaccines in the elderly: an economic evaluation. In: Centre BHCK, ed. Health Technology Assessment, KCE Report 274. Brussels: Belgian Health Care Knowledge Centre, 2016.

14. Falkenhorst G, Remschmidt C, Harder T, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (ppv23) against pneumococcal disease in the elderly: Systematic review and meta-analysis. *PLoS ONE* 2017;12 (1) (no pagination)(e0169368) doi: http://dx.doi.org/10.1371/journal.pone.0169368

15. Htar MTT, Stuurman AL, Ferreira G, et al. Effectiveness of pneumococcal vaccines in preventing pneumonia in adults, a systematic review and meta-analyses of observational studies. *PLoS ONE* 2017;12 (5) (no pagination)(e0177985) doi: http://dx.doi.org/10.1371/journal.pone.0177985

16. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. *Vaccine* 2016;34(13):1540-50. doi: 10.1016/j.vaccine.2016.02.024 [published Online First: 2016/02/24]

17. Moberley S, Holden J, Tatham DP, et al. Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev* 2013(1):CD000422. doi: 10.1002/14651858.CD000422.pub3

18. Schiffner-Rohe J, Witt A, Hemmerling J, et al. Efficacy of PPV23 in preventing pneumococcal pneumonia in adults at increased risk - A systematic review and meta-analysis. *PLoS ONE* 2016;11 (1) (no pagination)(e0146338) doi: http://dx.doi.org/10.1371/journal.pone.0146338

19. Huss A, Scott P, Stuck AE, et al. Efficacy of pneumococcal vaccination in adults: a meta-analysis. *CMAJ* 2009;180(1):48-58. doi: 10.1503/cmaj.080734

20. Diao WQ, Shen N, Yu PX, et al. Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: A systematic review and meta-analysis of randomized trials. *Vaccine* 2016;34(13):1496-503. doi: http://dx.doi.org/10.1016/j.vaccine.2016.02.023

21. Fedson DS, Liss C. Precise answers to the wrong question: prospective clinical trials and the meta-analyses of pneumococcal vaccine in elderly and high-risk adults. *Vaccine* 2004;22(8):927-46. doi: 10.1016/j.vaccine.2003.09.027

22. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi: 10.1136/bmj.d5928 [published Online First: 2011/10/20]

23. Wells G, Shea, B., Higgins, J.P.T., Sterne, J., Tugwell, P., Reeves, B.C. Checklists of methodological issues for review authors to consider when including non-randomized studies in systematic reviews. *Res Syn Meth* 2013;4:63-77.

24. Effective Health Care Program. Nitrous Oxide for the Management of Labor Pain, AHRQ Publication No. 12-EHC071-EF. Comparative Effectiveness Review. Maryland, USA: Agency for Healthcare Research and Quality, 2012.

25. Sons JWa, ed. Comparison of Newcastle Ottawa scale (NOS) and Agency for Health Research and Quality (AHRQ) as risk of bias assessment tools for cohort studies. Filtering the information overload for better decisions. 23rd Cochrane Colloquium; 2015; Vienna, Austria.

26. Hipwell AE, Kahn LG, Factor-Litvak P, et al. Exposure to non-persistent chemicals in consumer products and fecundability: a systematic review. *Hum Reprod Update* 2019;25(1):51-71. doi: 10.1093/humupd/dmy032

27. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011;64(4):401-6. doi: 10.1016/j.jclinepi.2010.07.015 [published Online First: 2011/01/07]

28. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026 [published Online First: 2011/01/05]

29. Ahmed F. U.S. Advisory Committee on Immunization Practices Handbook for Developing Evidence-based Recommendations Work Group. *Centers for Disease Control and Prevention, Atlanta,* 2013;Version 1.2.

30. Dominguez A, Ciruela P, Hernandez S, et al. Effectiveness of the 13-valent pneumococcal conjugate vaccine in preventing invasive pneumococcal disease in children aged 7-59 months. A matched case-control study. *Plos One* 2017;12(8):15. doi: 10.1371/journal.pone.0183191

31. Kolditz M, Schmitt J, Pletz MW, et al. Impact of pneumococcal polysaccharide vaccine on incidence and mortality after pneumonia in adults aged >=60 years-a population-based retrospective cohort study. *Clinical Microbiology and Infection* 2018;24(5):500-04. doi: http://dx.doi.org/10.1016/j.cmi.2017.08.010

32. Kondo K, Suzuki K, Washio M, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccine and seasonal influenza vaccine for pneumonia among the elderly - Selection of controls in a case-control study. *Vaccine* 2017;35(36):4806-10. doi: http://dx.doi.org/10.1016/j.vaccine.2017.07.005

33. Kolditz M, Schmitt J, Pletz MW, et al. Impact of the 13-Valent Pneumococcal Conjugate Vaccine on the Incidence of All-cause Pneumonia in Adults Aged >/=60 Years: A Population-based, Retrospective Cohort Study. *Clin Infect Dis* 2019;68(12):2117-19. doi: 10.1093/cid/ciy993

34. Martinelli D, Fortunato F, Cappelli M, et al. Effectiveness of PCV13 in the prevention of pneumococcal pneumonia among older adults: results from a test-negative design study in Italy, January 2013 - January 2015 - Conference Proceedings. *ECCMID 2015* 2015

35. Prato R, Fortunato F, Cappelli MG, et al. Effectiveness of the 13-valent pneumococcal conjugate vaccine against adult pneumonia in Italy: a case-control study in a 2-year prospective cohort. *BMJ Open* 2018;8(3):e019034. doi: 10.1136/bmjopen-2017-019034 [published Online First: 2018/03/28]

36. Honkanen PO, Keistinen T, Miettinen L, et al. Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. *Vaccine* 1999;17(20-21):2493-500.

37. Örtqvist A, Hedlund J, Burman LA, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. Swedish Pneumococcal Vaccination Study Group. *Lancet* 1998;351(9100):399-403.

38. Jalonen E, Paton JC, Koskela M, et al. Measurement of antibody responses to pneumolysin--a promising method for the presumptive aetiological diagnosis of pneumococcal pneumonia. *J Infect* 1989;19(2):127-34.

39. Leinonen M, Syrjälä H, Jalonen E, et al. Demonstration of pneumolysin antibodies in circulating immune complexes - a new diagnostic method for pneumococcal pneumonia. *Serodiagnosis and Immunotherapy in Infectious Disease* 1990;4(6):451-8.

40. Scott JA, Hall AJ, Leinonen M. Validation of immune-complex enzyme immunoassays for diagnosis of pneumococcal pneumonia among adults in Kenya. *Clin Diagn Lab Immunol* 2000;7(1):64-7. doi: 10.1128/cdli.7.1.64-67.2000

41. Musher DM, Mediwala R, Phan HM, et al. Nonspecificity of assaying for IgG antibody to pneumolysin in circulating immune complexes as a means to diagnose pneumococcal pneumonia. *Clin Infect Dis* 2001;32(4):534-8. doi: 10.1086/318709

42. Vila-Corcoles A, Ochoa-Gondar O, Hospital I, et al. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. *Clin Infect Dis* 2006;43(7):860-8. doi: 10.1086/507340

43. Vila-Corcoles A, Salsench E, Rodriguez-Blanco T, et al. Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in middle-aged and older adults: a matched case-control study. *Vaccine* 2009;27(10):1504-10. doi: 10.1016/j.vaccine.2009.01.013

44. Vila-Corcoles A, Ochoa-Gondar O, Guzman JA, et al. Effectiveness of the 23-valent polysaccharide pneumococcal vaccine against invasive pneumococcal disease in people 60 years or older. *BMC Infect Dis* 2010;10:73. doi: 10.1186/1471-2334-10-73 [published Online First: 2010/03/20]

45. Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, et al. Clinical effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumonia in patients with chronic pulmonary diseases: a matched case-control study. *Hum Vaccin Immunother* 2012;8(5):639-44. doi: 10.4161/hv.19466 [published Online First: 2012/05/29]

46. Alfageme I, Vazquez R, Reyes N, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax* 2006;61(3):189-95. doi: 10.1136/thx.2005.043323

47. Maruyama T, Taguchi O, Niederman MS, et al. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. *BMJ* 2010;340:c1004. doi: 10.1136/bmj.c1004

48. Tsai YH, Hsieh MJ, Chang CJ, et al. The 23-valent pneumococcal polysaccharide vaccine is effective in elderly adults over 75 years old--Taiwan's PPV vaccination program. *Vaccine* 2015;33(25):2897-902. doi: 10.1016/j.vaccine.2015.04.068 [published Online First: 2015/05/06]

49. Hechter RC, Chao C, Jacobsen SJ, et al. Clinical effectiveness of pneumococcal polysaccharide vaccine in men: California Men's Health Study. *Vaccine* 2012;30(38):5625-30. doi: 10.1016/j.vaccine.2012.06.085 [published Online First: 2012/07/14]

50. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against community-acquired pneumonia in the general population aged >/= 60 years: 3 years of follow-up in the CAPAMIS study. *Clin Infect Dis* 2014;58(7):909-17. doi: 10.1093/cid/ciu002

51. Jackson LA, Neuzil KM, Yu O, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med* 2003;348(18):1747-55. doi: 10.1056/NEJMoa022678 [published Online First: 2003/05/02]

52. Kim JH, Chun BC, Song JY, et al. Direct effectiveness of pneumococcal polysaccharide vaccine against invasive pneumococcal disease and non-bacteremic pneumococcal pneumonia in elderly population in the era of pneumococcal conjugate vaccine: A case-control study. *Vaccine* 2019;37(21):2797-804. doi: 10.1016/j.vaccine.2019.04.017

53. Leventer-Roberts M, Feldman BS, Brufman I, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive disease and hospital-treated pneumonia among people aged >/=65 years: a retrospective case-control study. *Clin Infect Dis* 2015;60(10):1472-80. doi: 10.1093/cid/civ096 [published Online First: 2015/02/12]

54. Dominguez A, Salleras L, Fedson DS, et al. Effectiveness of pneumococcal vaccination for elderly people in Catalonia, Spain: a case-control study. *Clin Infect Dis* 2005;40(9):1250-7. doi: 10.1086/429236 [published Online First: 2005/04/13]

55. Andrews NJ, Waight PA, George RC, et al. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. *Vaccine* 2012;30(48):6802-8. doi: 10.1016/j.vaccine.2012.09.019 [published Online First: 2012/09/25]

56. Rudnick W, Liu Z, Shigayeva A, et al. Pneumococcal vaccination programs and the burden of invasive pneumococcal disease in Ontario, Canada, 1995-2011. *Vaccine* 2013;31(49):5863-71. doi: 10.1016/j.vaccine.2013.09.049 [published Online First: 2013/10/09]

57. Wright LB, Hughes GJ, Chapman KE, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in people aged 65 years and over in the North East of England, April 2006–July 2012. *Trials in Vaccinology* 2013;2:45-48. doi: https://doi.org/10.1016/j.trivac.2013.09.004

58. Gutierrez Rodriguez MA, Ordobas Gavin MA, Garcia-Comas L, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccine in adults aged 60 years and over in the Region of Madrid, Spain, 2008-2011. *Euro Surveill* 2014;19(40):20922. [published Online First: 2014/10/18]

59. Wiemken TL, Carrico RM, Klein SL, et al. The effectiveness of the polysaccharide pneumococcal vaccine for the prevention of hospitalizations due to Streptococcus pneumoniae community-acquired pneumonia in the elderly differs between the sexes: Results from the Community-Acquired Pneumonia Organization (CAPO) international cohort study. *Vaccine* 2014;32(19):2198-203. https://doi.org/10.1016/j.vaccine.2014.02.048

60. Suzuki MD, B. G.: Ishifuji, T.: Yasunami, M.: Yaegashi, M.: Asoh, N.: Ishida, M.: Hamaguchi, S.: Aoshima, M.: Ariyoshi, K.: Morimoto, K.: Adult Pneumonia Study, Group-Japan. Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study. *Lancet Infect Dis* 2017;17(3):313-21. doi: 10.1016/S1473-3099(17)30049-X [published Online First: 2017/01/28]

61. de Serres G, Skowronski XW, Ambrose CS. AmbroseThe test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. *Euro surveillance* 2013;18(37):2165-68.

62. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine* 2013;31(17):2165-8. doi: 10.1016/j.vaccine.2013.02.053

63. Andrews N, Waight PA, Borrow R, et al. Using the indirect cohort design to estimate the effectiveness of the seven valent pneumococcal conjugate vaccine in England and Wales. *PLoS One* 2011;6(12):e28435. doi: 10.1371/journal.pone.0028435

64. Broome CV, Facklam RR, Fraser DW. Pneumococcal disease after pneumococcal vaccination: an alternative method to estimate the efficacy of pneumococcal vaccine. *N Engl J Med* 1980;303(10):549-52. doi: 10.1056/NEJM198009043031003

65. Ruckinger S, van der Linden M, Reinert RR, et al. Efficacy of 7-valent pneumococcal conjugate vaccination in Germany: An analysis using the indirect cohort method. *Vaccine* 2010;28(31):5012-6. doi: 10.1016/j.vaccine.2010.05.021

66. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med* 2015;372(12):1114-25. doi: 10.1056/NEJMoa1408544

67. Gessner BD, Jiang Q, Van Werkhoven CH, et al. A public health evaluation of 13-valent pneumococcal conjugate vaccine impact on adult disease outcomes from a randomized clinical trial in the Netherlands. *Vaccine* 2018 doi: http://dx.doi.org/10.1016/j.vaccine.2018.05.097

68. Huijts SM, van Werkhoven CH, Bolkenbaas M, et al. Post-hoc analysis of a randomized controlled trial: Diabetes mellitus modifies the efficacy of the 13-valent pneumococcal conjugate vaccine in elderly. *Vaccine* 2017;35(34):4444-49. doi: http://dx.doi.org/10.1016/j.vaccine.2017.01.071

69. Patterson S, Webber C, Patton M, et al. A post hoc assessment of duration of protection in CAPiTA (Community Acquired Pneumonia immunization Trial in Adults). *Trials in Vaccinology* 2016;5:92-96. doi: http://dx.doi.org/10.1016/j.trivac.2016.04.004

70. Webber C, Patton M, Patterson S, et al. Exploratory efficacy endpoints in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA). *Vaccine* 2017;35(9):1266-72. doi: http://dx.doi.org/10.1016/j.vaccine.2017.01.032

71. Suaya JA, Jiang Q, Scott DA, et al. Post hoc analysis of the efficacy of the 13-valent pneumococcal conjugate vaccine against vaccine-type community-acquired pneumonia in at-risk older adults. *Vaccine* 2018;36(11):1477-83. doi: http://dx.doi.org/10.1016/j.vaccine.2018.01.049

72. McLaughlin JMJ, Q.: Isturiz, R. E.: Sings, H. L.: Swerdlow, D. L.: Gessner, B. D.: Carrico, R. M.: Peyrani, P.: Wiemken, T. L.: Mattingly, W. A.: Ramirez, J. A.: Jodar, L. Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Hospitalization for Community-Acquired Pneumonia in Older US Adults: A Test-Negative Design. *Clin Infect Dis* 2018 doi: 10.1093/cid/ciy312 [published Online First: 2018/05/24]

73. Vila-Corcoles AO-G, O.: de Diego, C.: Satue, E.: Aragon, M.: Vila-Rovira, A.: Gomez-Bertomeu, F.: Magarolas, R.: Figuerola-Massana, E.: Raga, X.: Perez, M. O.: Ballester, F. Evaluating clinical effectiveness of 13-valent pneumococcal conjugate vaccination against pneumonia among middle-aged and older adults in Catalonia: results from the EPIVAC cohort study. *BMC Infect Dis* 2018;18(1):196. doi: 10.1186/s12879-018-3096-7 [published Online First: 2018/04/28]

74. van Werkhoven CH, Hollingsworth RC, Huijts SM, et al. Pneumococcal conjugate vaccine herd effects on non-invasive pneumococcal pneumonia in elderly. *Vaccine* 2016;34(28):3275-82. doi: http://dx.doi.org/10.1016/j.vaccine.2016.05.002

75. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practice (ACIP). MMWR Morb Mortal Wkly Rep. Atlanta, 1997.

76. Sinclair A, Xie X, Teltscher M, et al. Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by Streptococcus pneumoniae. *J Clin Microbiol* 2013;51(7):2303-10. doi: 10.1128/JCM.00137-13 [published Online First: 2013/05/17]

77. Wunderink RG, Self WH, Anderson EJ, et al. Pneumococcal Community-Acquired Pneumonia Detected by Serotype-Specific Urinary Antigen Detection Assays. *Clin Infect Dis* 2018;66(10):1504-10. doi: 10.1093/cid/cix1066 [published Online First: 2018/01/18]

78. Pride MW, Jansen KU. Reevaluation of Positivity Cutoff Values for the Pneumococcal Urinary Antigen Detection Assay. *Clin Vaccine Immunol* 2017;24(11) doi: 10.1128/CVI.00239-17 [published Online First: 2017/11/08]

79. Pride MW, Huijts SM, Wu K, et al. Validation of an immunodiagnostic assay for detection of 13 Streptococcus pneumoniae serotype-specific polysaccharides in human urine. *Clin Vaccine Immunol* 2012;19(8):1131-41. doi: 10.1128/CVI.00064-12 [published Online First: 2012/06/08]

80. Schwartz LM, Halloran ME, Rowhani-Rahbar A, et al. Rotavirus vaccine effectiveness in low-income settings: An evaluation of the test-negative design. *Vaccine* 2017;35(1):184-90. doi: 10.1016/j.vaccine.2016.10.077 [published Online First: 2016/11/24]

81. Dhoubhadel BG, Yasunami M, Yoshida LM, et al. A novel high-throughput method for molecular serotyping and serotype-specific quantification of Streptococcus pneumoniae using a nanofluidic real-time PCR system. *J Med Microbiol* 2014;63(Pt 4):528-39. doi: 10.1099/jmm.0.071464-0 [published Online First: 2014/01/28]

Appendices

Appendix 1: Overview of studies identified in the three separate reviews with references

Appendix 2: Overview over potential overlap in publications by Vila Corcoles et al.

Appendix 3: Flow chart of included studies

Appendix 4 a-c: Quality assessment of included studies

Appendix 5 a-c: Evidence profiles for separate outcomes

Appendix 6: PPV23 VE for the prevention of VT-IPD by age, indirect cohort studies

Appendix 1: Overview of studies identified in the three separate reviews

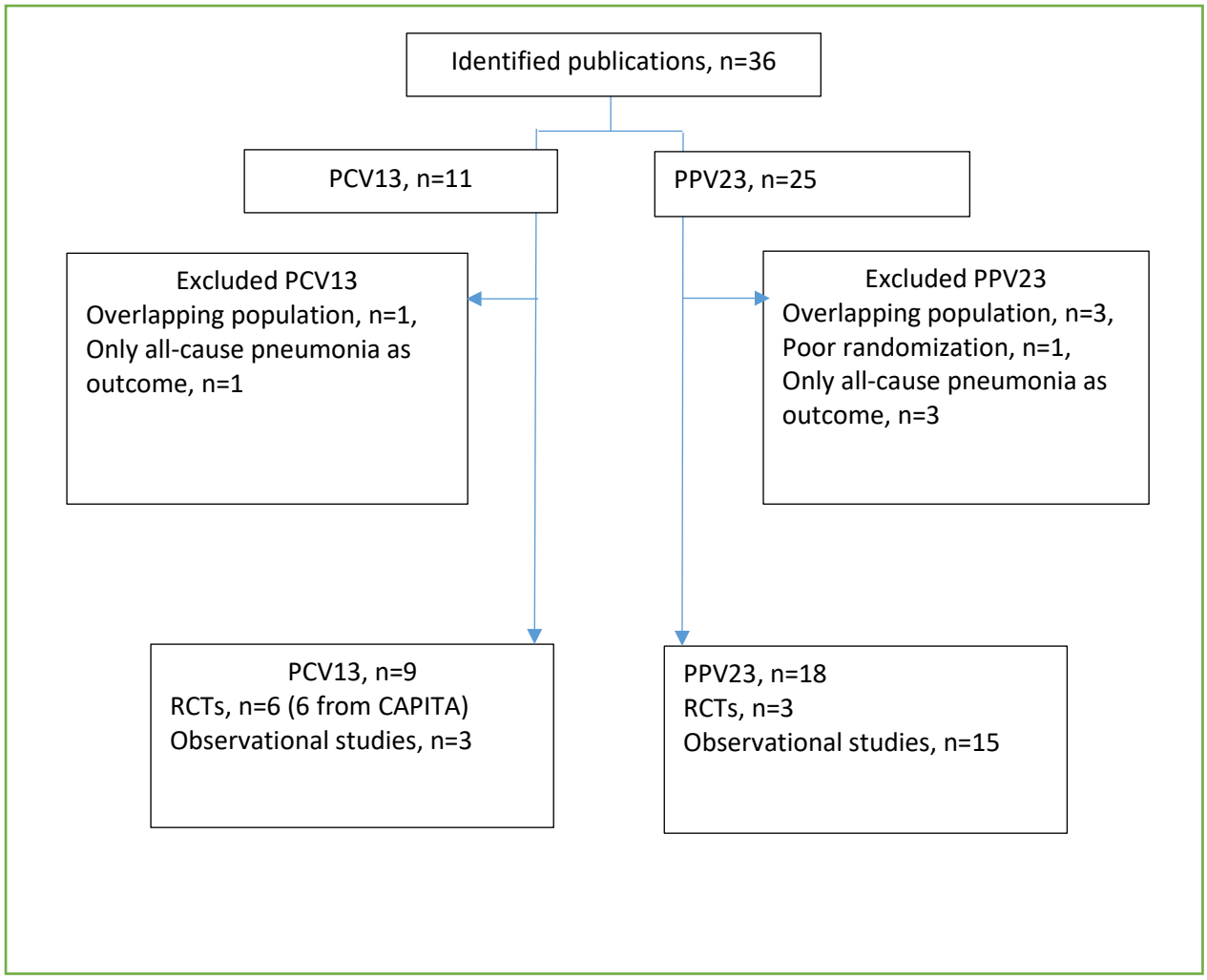
	Berild et al. (PPV and PCV)	Falkenhorst et al. (PPV only)	Blommaert et al. (PCV and PPV)
PCV13	Gessner 2018 (CAPITA)		
	Hujits 2017 (CAPITA)		
	Patterson 2016 (CAPITA)		
	Suaya 2018 (CAPITA)		
	Webber 2017 (CAPITA)		
	Vila-Corcoles 2018		
	MchLaughlin 2018		
	Prato 2018		
			Bonten 2015 (CAPITA)
			*Martinelli 2015
	*Kolditz 2018		
PPV23	Kim 2019		
	Djennad 2018		
	Suzuki 2017		
	*Dominguez 2017		
	*Kondo 2017		
	*Kolditz 2018		
		Jackson 2003	Jackson 2003
		Dominguez 2005	Dominguez 2005
		Alfageme 2006	Alfageme 2006
		Andrews 2012	Andrews 2012
		Wright 2013	Wright 2013
		Rudnick 2013	Rudnick 2013
		Gutierrez 2014	Gutierrez 2014
		Wiemken 2014	Wiemken 2014
		Vila-Corcoles 2009	Vila-Corcoles 2009
		Ochoa-Gondar 2014	Ochoa-Gondar 2014
		Örtqvist 1998	
		*Honkanen 1999	
		Maruyama 2010	
		*Vila-Corcoles 2006	
		Tsai 2015	
		Leventer-Roberts 2015	
		Hechter 2012	
			Vila Corcoles 2010
			*Vila-Corcoles 2012

*Publications in bold are excluded from this report. See rationale in 3.1. *Identified publications and amendments from previous reviews*

Appendix 2: Overview over potential overlap in publications by Vila Corcoles et al.

Publication year	Vaccine	Study	Age	Design	Outcomes
2006	PPV23	EVAN	>65	cohort	IPD, pneumococcal pneumonia
2009	PPV23	EPIVAC	>50	c/c	invasive pneumonia, vaccine-type invasive pneumonia, non-invasive pneumococcal pneumonia
2010	PPV23	EPIVAC	>60	c/c	IPD, vaccine-type IPD
2012	PPV23	EPIVAC	>50	c/c	invasive pneumonia, vaccine-type invasive pneumonia, non-invasive pneumococcal pneumonia
2018	PCV13	EPIVAC	>50	cohort	pneumococcal pneumonia

Appendix 3: Flowchart for included studies



Appendix 4: Quality assessment of included studies

4a Randomized Controlled Trials

Author, year	Vaccine	Selection bias (I)	Selection bias (II)	Performance bias	Detection bias	Attrition bias	Reporting bias
Örtqvist, 1998	PPV23	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Alfageme, 2006	PPV23	Low risk	Unclear risk	High risk	Low risk	Low risk	Unclear risk
Maruyama, 2010	PPV23	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Bonten, 2015	PCV13	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Selection bias (I): Random sequence generation, Selection bias (II): Allocation concealment, Performance bias: Blinding of participants and personnel, Detection bias: Blinding of outcome assessment, Attrition bias: Incomplete outcome data, Reporting bias: Selective reporting

Observational studies

Threshold for classification of quality of observational studies: *High:* 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. *Fair*: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. *Poor*: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

4b Cohort studies

Author, year	Vaccine	Selection (/4)	Comparability (/2)	Outcome (/3)	Total (/9)	Quality
Jackson, 2003	PPV23	4	2	3	9	Good
Hechter, 2003	PPV23	3	2	2	7	Good
Ochoa-Gondar, 2014	PPV23	4	2	3	9	Good
Tsai, 2015	PPV23	2	2	2	6	Fair
Vila-Corcoles 2018	PCV13	3	2	2	7	Good

Selection; Representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration of outcome not present at enrolment, Comparability; study controls for most important factors, Outcome; assessment of outcome, was follow-up long enough for outcomes to occur, adequacy of follow-up of cohorts, ascertainment of comorbidities.

4c Case-control, test-negative and indirect cohort studies

Author, year Case-control design	Vaccine	Selection (/4)	Comparability (/2)	Exposure (/3)	Total (/9)	Quality
Dominguez, 2005	PPV23	3	2	1	6	Poor
Vila-Corcoles, 2009	PPV23	3	2	2	7	Good
Leventer-Roberts, 2015	PPV23	4	2	3	9	Good
Kim, 2019	PPV23	3	2	3	7	Good
Andrews, 2012*	PPV23	3	2	2	7	Good
Djennad, 2018*	PPV23	3	2	2	7	Good
Rudnick, 2013*	PPV23	4	2	3	9	Good
Wright, 2013*	PPV23	4	2	2	8	Good
Gutierrez, 2014*	PPV23	4	2	3	9	Good
Wiemken, 2014**	PPV23	4	2	2	8	Good
Suzuki, 2017**	PPV23	4	2	3	9	Good
McLaughlin, 2018**	PCV13	4	2	3	9	Good
Prato, 2018**	PCV13	2	0	3	5	Poor

Selection; is the case definition adequate, representativeness of the cases, selection of controls, definition of controls, *Comparability*; study controls for most important factors, *Exposure*; ascertainment of exposure, same method of ascertainment for cases and controls, non-response rate, ascertainment of comorbidities.
*Indirect cohort/Broome method, **Test-negative design

Appendix 5: Evidence profiles for separate outcomes

5a. Evidence profile, PPV23 VE for prevention of IPD, all serotypes

Bibliography: Alfageme 2006, Maruyama 2010, Örtqvist, 1998, Jackson 2003, Hechter 2012, Ochoa-Gonder 2014, Tsai 2015, Dominguez 2005, Leventer-Roberts 2015, Vila-Corcoles 2009, Kim 2019

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	23-valent pneumococcal polysaccharide vaccine	Control	Relative (95% CI)	Absolute		
RCT												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1/1139 (0.09%)	8/1154 (0.69%)	OR 0.24 (0.05 to 1.18)	5 fewer per 1000 (from 7 fewer to 1 more)	⊕⊕⊕O MODERATE	CRITICAL
OBSERVATIONAL cohort studies												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/113268 (0.03%)[2]	43/89945 (0.05%)[2]	OR 0.53 (0.33 to 0.87)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	CRITICAL
OBSERVATIONAL case-control studies												
3	observational studies	no serious risk of bias[3]	no serious inconsistency [4]	no serious indirectness	no serious imprecision	none	454 cases 1143 controls		OR 0.57 (0.40 to 0.79)	-	⊕⊕OO LOW	CRITICAL

[1] Confidence intervals indicate both substantially reduced risk and increased risk. The study by Alfageme et al., did not include any IPD cases

[2] Refers to person-years

[3] The study by Kim et al., used hospital controls rather than controls from the community. We did not find this sufficient to downgrade the quality of the pooled estimate.

[4]The effect size is uncertain, although all point estimates favor vaccination. The I^2 of 44%, non-significant p-value and Tau value of 0.04 may represent moderate heterogeneity. We did not find this sufficient to downgrade for inconsistency.

5b. Evidence profile, PPV23 VE for prevention of vaccine-type IPD

Bibliography: Dominguez 2005, Kim 2019, Vila-Corcoles 2009, Andrews 2012, Djennad 2019, Gutierrez 2014, Rudnick 2013, Wright 2013

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	23-valent pneumococcal polysaccharide vaccine	Control	Relative (95% CI)	Absolute		
OBSERVATIONAL case-control studies												
2	observational studies	no serious risk of bias	no serious inconsistency[1]	no serious indirectness	no serious imprecision	none	114 cases, 395 controls		OR 0.41 (0.18 to 0.96)		⊕⊕OO LOW	CRITICAL
OBSERVATIONAL Broome method												
5	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	3005 VT-IPD (cases), 1495 nonVT-IPD (controls)		OR 0.69 (0.63 to 0.76)		⊕⊕OO LOW	CRITICAL

[1]*The pooled estimate includes only two studies. There is possibly high heterogeneity, I^2=56%, p=0.13 and Tau= 0.22. We found this insufficient to downgrade for inconsistency.*

5c. Evidence profile, PPV23 VE for prevention of pneumococcal pneumonia

Bibliography: Alfageme 2006, Maruyama 2010, Ochoa-Gondar 2014, Kim 2019, Vila-Corcoles 2009, Suzuki 2018, Wiemken 2014

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	23-valent pneumocccal polysaccharide vaccine	Control	Relative (95% CI)	Absolute		
RCT												
2	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	14/800 (1.8%)	42/802 (5.2%)	RR 0.36 (0.2 to 0.65)	34 fewer per 1000 (from 18 fewer to 42 fewer)	⊕⊕⊕O MODERATE	CRITICAL
OBSERVATIONAL cohort studies												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/29065 (0.01%)[2]	12/46968 (0.03%)[2]	OR 0.49 (0.29 to 0.84)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	CRITICAL
OBSERVATIONAL case control studies												
2	observational studies	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	659 cases 828 controls		OR 0.66 (0.35 to 1.25)	-	⊕OOO VERY LOW	CRITICAL
OBSERVATIONAL test negative design												
2	observational studies	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1002 with pneumococcal pneumonia (cases), 3167 with pneumonia of other etiology (controls)		OR 0.69 (0.55 to 0.86)	-	⊕⊕OO LOW	CRITICAL

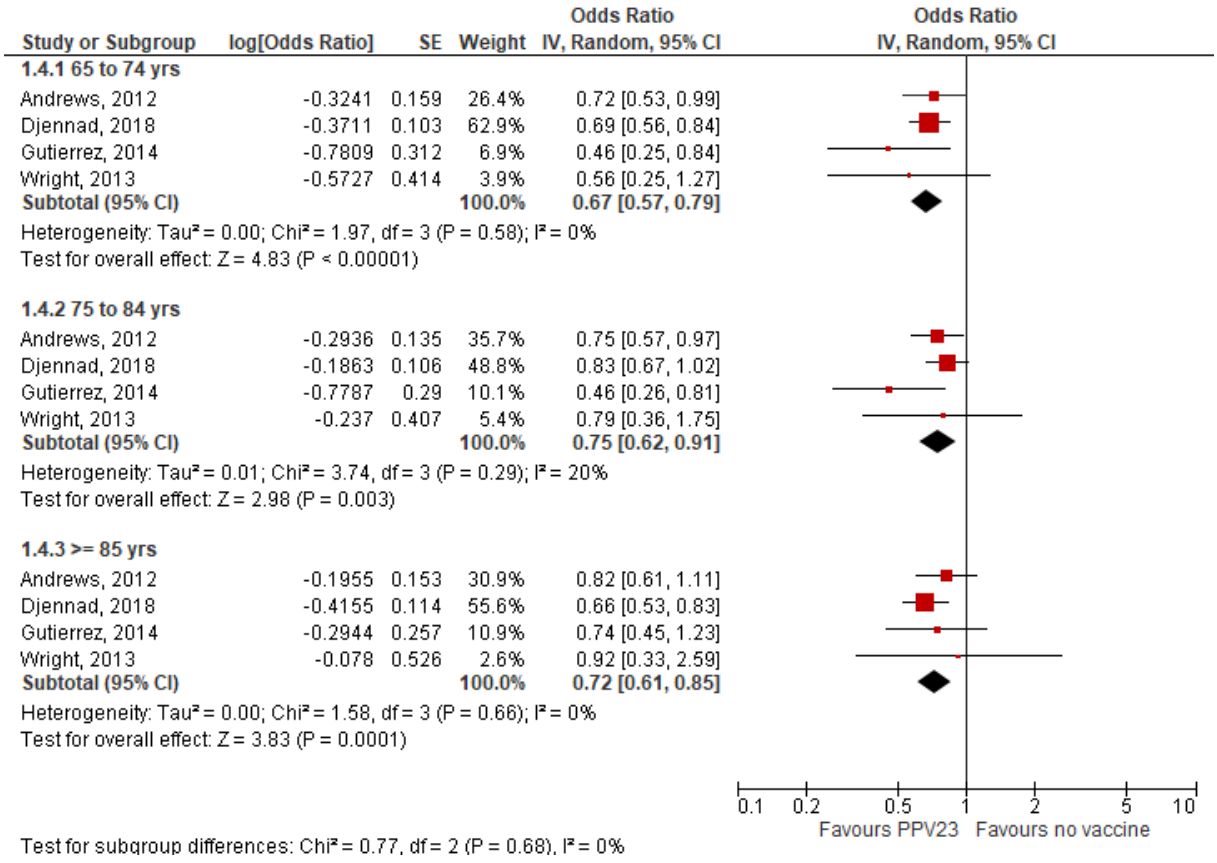
[1] We downgraded the overall quality for indirectness. The pooled estimate was largely based on the trial by Maruyama et al., in which the study population was immunocompetent nursing home resident in Japan with low uptake of PPV23 and about 20 times higher incidence of pneumococcal pneumonia than the elderly community dwelling population (40.7/1000 versus 2/1000 per year).

[2] Number refers to person-years.

[3] We downgraded for inconsistency. Pooled analyses show possibly high heterogeneity (I^2=88%, p=0.003 and Tau=0.19) and confidence intervals do not overlap.

[4] In the study by Wiemken, the participants were selected from a prospective cohort study. There is no compelling reason to believe that this should introduce substantial bias

Appendix 6: PPV23 VE for the prevention of VT-IPD by age, indirect cohort studies



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