TECHNOLOGY REVIEW (MINI-HTA)

PNEUMOCOCCAL VACCINATION WITH 23-VALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPV23) FOR ELDERLY

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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EXECUTIVE SUMMARY

Background

Pneumococcal diseases are bacterial infections caused by *Streptococcus pneumoniae* which range from invasive pneumococcal disease (IPD) with severity level of moderate to severe including meningitis, septicaemia and pneumonia to non-invasive pneumococcal disease with milder infections such as sinusitis and otitis media**.** According to World Health Organization (WHO) estimate, about 1.6 million cases of fatal pneumococcal disease occurred worldwide every year, typically in infants and the elderly. The incidence and mortality rates are described in pneumonia and IPD which are notably higher in developing countries with the majority of deaths taking place in sub-Saharan Africa and Asia.

In Malaysia, pneumonia is the second leading cause of death after ischaemic heart disease with 12.2% of 109,164 medically certified death in 2019 and remains the leading cause of death for females, accounting for 13.2% of death in 2019, 12.8% of death in 2018 and 14.1% of deaths in 2017. It was also estimated that the community acquired pneumonia incidence was highest in the youngest and oldest age groups. Pneumonia is the most common pneumococcal disease in Malaysia. *Streptococcus pneumoniae* is a significant pathogen which is responsible for community acquired pneumonia in Kuala Lumpur and potentially in the nearby Klang Valley areas with about 13.2% was reported among adult patients with community-acquired pneumonia at a major urban-serving hospital in Kuala Lumpur.

Pneumococcal vaccine has been developed since early 1900 and has evolved with time. It has been used to prevent pneumococcal diseases for more than three decades. At present, two different kinds of pneumococcal vaccines are available on the market are: (i) the 23-valent polysaccharide vaccine (PPV23) that is available since the early 1980s and (ii) two conjugate vaccines that are available since 2009, the 10-valent (PCV10) and the 13-valent (PCV13).[8] World Health Organization (WHO) recommends the inclusion of PCVs in childhood immunisation programmes worldwide[8] and Centre for Disease Control and Prevention (CDC) recommends routine administration of PPV23 for all adults 65 years or older.[9]

Recently, in Malaysia, immunisation for children less than two years old with the pneumococcal conjugate vaccine PCV10 has been added into the National Immunisation Programme beginning December 2020 for infants born from January 2020. This decision is deemed crucial and timely for Malaysia in combatting the increased incidence of pneumococcal disease in children in recent years. However, there is yet a national programme to be established for pneumococcal vaccination with PPV23 targeting the elderly in Malaysia albeit their increased risk of morbidity and mortality related to invasive pneumococcal disease.

Hence, this technology review was conducted to review the current best scientific evidence on pneumococcal vaccination with PPV23 for the elderly before its implementation in Malaysia.

Objective/ aim

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of pneumococcal vaccination with PPV23 for elderly.

Results and conclusion

From a total of 1137 titles identified through the Ovid interface,16 studies were included in this review which were consisted of systematic reviews with meta-analysis (six), cohort study (one), retrospective cohort study (two), cross-sectional study (one), quasi-experimental study (one) and cost-utility analysis (five). The included articles were published between 2016 and 2020. Most of the studies were conducted in countries such as Japan, South Korea, US, Spain, Europe and UK followed by studies conducted in Sweden as well as Australia for cost-utility analysis.

Effectiveness

There was good level of retrievable evidence to suggest that pneumococcal vaccination with PPV23 in elderly population had low to moderate efficacy against invasive pneumococcal disease (IPD) and pneumococcal pneumonia. Evidence on effectiveness of PPV23 against all-cause pneumonia and mortality were not statistically significant.

Safety

There was no serious adverse events and safety issues reported in the included studies.

Cost/Cost-effectiveness

Cost analyses done in industrialised countries showed varying results depending on parameters and thresholds. The estimates of disease burden, vaccine effectiveness, cost assumptions and the effects of herd protection had the most influence on the results. For financial implication, assuming 100% coverage, introduction of pneumococcal vaccination with PPV23 for elderly ≥65 years old in Malaysia is estimated to have an economic implication of approximately RM 189 million to RM 345 million in the first year.

Organisational

Hospitalisation

Limited fair level of retrievable evidence to suggest that pneumococcal vaccination with PPV23 in elderly population reduced all-cause inpatient hospital stays.

Guidelines

Various international organisations from industrialised countries recommend pneumococcal vaccination with PPV23 for the elderly and other high-risk groups. However, WHO stated that in resource limited settings where there are many competing health priorities, a higher priority should be given to introducing and maintaining high coverage of infants with PCV vaccine given the substantial effects of herd immunity in adult age groups following routine infant immunisation.

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to December 2020), EBM Reviews-Cochrane Central Register of Controlled Trials (December 2020), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2020), EBM Reviews-Health Technology Assessment (1st Quarter 2020), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2020). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits were applied to the search. The last search was run on 8 December 2020. Additional articles were identified from reviewing the references of retrieved articles. One of the tools used to assess the risk of bias and methodological quality of all the articles retrieved is the Critical Appraisal Skills Programme (CASP) checklist. All full text articles were then graded based on guidelines from the U.S./Canadian Preventive Services Task Force.

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ABBREVIATION

ADL	Activities of daily living
AE	Adverse event
AEFI	Adverse event following immunisation
CAP	Community acquired pneumonia
CASP	Critical Appraisal Skills Programme
CDC	Centre for disease control and prevention
CI	Confidence Interval
ECDC	European Centre for disease control and prevention
ER	Emergency Room
GBD	Global Burden of Diseases, Injuries and Risk Factors
HR	Hazard Ratio
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
INAHTA	The International Network of Agencies for Health Technology Assessment
IPD	Invasive Pneumococcal Disease
LYG	Life year gained
NBPP	Non-bacteraemic pneumococcal pneumonia
NOS	Newcastle-Ottawa Scale
NIP	National Immunisation Programme
PCV	Pneumococcal Conjugate Vaccine
PCV7	7-valent Pneumococcal Conjugate Vaccine
PCV10	10-valent Pneumococcal Conjugate Vaccine
PCV13	13-valent Pneumococcal Conjugate Vaccine
PPV	Pneumococcal Polysaccharide Vaccine
PPV23	23-valent Pneumococcal Polysaccharide Vaccine
QALY	Quality adjusted life years
RCT	Randomised controlled trial
RR	Relative risk
SR	Systematic review
USFDA	United States Food and Drugs Administration
USA	United States of America
VE	Vaccine Effectiveness
VT	Vaccine-type
WHO	World Health Organization

1.0 BACKGROUND

Pneumococcal diseases are bacterial infections caused by *Streptococcus pneumoniae* which range from invasive pneumococcal disease (IPD) with severity level of moderate to severe including meningitis, septicaemia and pneumonia to non-invasive pneumococcal disease with milder infections such as sinusitis and otitis media.[1] The Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study 2016 reported that *Streptococcus pneumoniae* was the leading cause of lower respiratory infection morbidity and mortality globally, contributing to more deaths than all other aetiologies combined in 2016.[2] According to World Health Organization (WHO) estimate, about 1.6 million cases of fatal pneumococcal disease occurred worldwide every year, typically in infants and the elderly.[3] In developed countries, the annual incidence rate of IPD is about 8 to 34 per 100,000 population whereas in elderly aged more than 65 years, the incidence rate is approximately 24 to 85 cases per 100,000 population.[3] The mortality rates of pneumococcal bacteremia are reportedly 16% to 36% in all adults and about 20% to 40% in elderly.[4] The incidence and mortality rates of pneumonia and IPD are notably higher in developing countries with the majority of deaths taking place in sub-Saharan Africa and Asia.[1] Aside from the high incidence in children <2 years of age, the risk for pneumococcal disease is increased in the elderly >65 years of age, and in people who use tobacco or alcohol excessively as well as in individuals who suffer from chronic medical conditions.[1]

In Malaysia, pneumonia is the second leading cause of death after ischaemic heart disease with 12.2% of 109,164 medically certified death in 2019 and remains the leading cause of death for females, accounting for 13.2% of death in 2019, 12.8% of death in 2018 and 14.1% of deaths in 2017.[5,6] It was also estimated that the community acquired pneumonia incidence was highest in the youngest and oldest age groups, with 496 per 100 000 among children below 5 years of age, 64 per 100 000 for patients aged between 5 and 64 years, and 1305 per 100 000 for patients aged 65 years and older.[7] Pneumonia is the most common pneumococcal disease in Malaysia.[8] *Streptococcus pneumoniae* is a significant pathogen which is responsible for community acquired pneumonia in Kuala Lumpur and potentially in the nearby Klang Valley areas with about 13.2% was reported among adult patients with community-acquired pneumonia at a major urban-serving hospital in Kuala Lumpur.[8] It is estimated that one fifth of patients hospitalised due to pneumococcal infections are children <2 years old, and that the elderly are the second most commonly infected group with approximately 50% of the hospitalised cases were invasive pneumococcal disease.[8] Only a limited number of studies provided information on serotype distribution in Malaysia. Data on the trend in serotype distributions concluded that 19F, 14, 23F, 6B and 19A were the major serotypes responsible for various invasive and non-invasive pneumococcal diseases in Asia and this is similar in Malaysia, where serotype 19F was the most common serotype detected, irrespective of age groups and sites of isolation.[8]

Pneumococcal vaccine has been developed since early 1900 and has evolved with time. It has been used to prevent pneumococcal diseases for more than three decades. At present, two different kinds of pneumococcal vaccines are available on the market are: (i) the 23-valent polysaccharide vaccine (PPV23) that is available since the early 1980s and (ii) two conjugate vaccines that are available since 2009, the 10-valent (PCV10) and the 13-valent (PCV13).[8] An earlier pneumococcal conjugate vaccine called the 7-valent conjugate vaccine (PCV7) is gradually being removed from the market. World Health Organization (WHO)

recommends the inclusion of PCVs in childhood immunisation programmes worldwide[8] and Centre for Disease Control and Prevention (CDC) recommends routine administration of PPV23 for all adults 65 years or older.[9]

Recently, in Malaysia, immunisation for children less than two years old with the pneumococcal conjugate vaccine PCV10 has been added into the National Immunisation Programme beginning December 2020 for infants born from January 2020.[10] The pneumococcal vaccine will be given in three doses: two primer doses at age four months and six months, followed by a booster shot at age 15 months.[10] This decision is deemed crucial and timely for Malaysia in combatting the increased incidence of pneumococcal disease in children in recent years. However, there is yet a national programme to be established for pneumococcal vaccination with PPV23 targeting the elderly in Malaysia albeit their increased risk of morbidity and mortality related to invasive pneumococcal disease.

Hence, this technology review was conducted following a request from the Head of Geriatric Unit, Hospital Queen Elizabeth, Sabah to review the current best scientific evidence on pneumococcal vaccination with PPV23 for the elderly before its implementation in Malaysia.

2.0 OBJECTIVE / AIM

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of pneumococcal vaccination with PPV23 for elderly.

3.0 TECHNICAL FEATURES

Pneumococcal vaccines are characterised by the number of Streptococcus pneumoniae serotype antigens that they contain and whether or not these antigens are conjugated to a protein carrier. The older pneumococcal vaccines are unconjugated or known as polysaccharide vaccines (PPV) whilst the newer vaccines are conjugated or known as conjugated vaccines (PCV).[11]

3.1 Pneumococcal Polysaccharide Vaccine (PPV23)

Currently available PPV contain 23 purified capsular polysaccharide antigens of Streptococcus pneumoniae, serotypes.[11] Pneumococcal 23-valent vaccine consists of 25 µg of each capsular polysaccharide antigens from the following serotypes - 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.[11] The 23-valent polysaccharide vaccine (PPV23) represents pneumococcal serotypes that are responsible for 85–90% of invasive pneumococcal infections in United States of America (USA) and some other industrialised countries.[3] This vaccine is widely licensed for use in adults and children aged >2 years who have certain underlying medical conditions.[3] In many countries including USA, routine vaccination with PPV23 is recommended for elderly over 65 years of age.[1] For primary immunisation, PPV23 is administered as a single intramuscular dose or as a subcutaneous dose.[3]

Pneumococcal Polysaccharide Vaccine (PPV23) is considered safe. Most common adverse events reported include injection-site pain, local swelling or induration, headache, local

erythema, asthenia and fatigue and myalgia. Less than 1% developed fever or more severe local reactions. Typically, local reactions are resolved within five days following vaccination.[11]

National recommendations with regards to additional doses of PPV23 vary and the ideal timing, frequency and clinical effectiveness of these additional doses are poorly defined. However, on the basis of the data on the duration of vaccine-induced protection, WHO suggests one single revaccination >5 years after a first vaccination.[3]

3.2 Pneumococcal Conjugated Vaccine (PCV)

Pneumococcal conjugated vaccine (PCV) consists of protein-polysaccharide combinations and contain a variable number (7, 10 or 13) of capsular polysaccharides antigens bound to a protein carrier.[11] Available PCV vaccines in the market are the PCV10 and PCV13 while PCV7 is gradually taken out from the market.

Pneumococcal conjugate 7-valent vaccine is the earlier version of PCV which consists of 2-4 µg of capsular polysaccharide antigens from the following serotypes; 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to non-toxic diphtheria toxin (CRM197).

Pneumococcal conjugate 10-valent vaccine consists of 1 microgram of polysaccharide for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F, and 3 micrograms of serotypes 4, 18C and 19F.

Pneumococcal conjugate 13-valent vaccine – consisting of 2 – 4 µg polysaccharides of the capsular antigens of Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually conjugated to a nontoxic diphtheria CRM197).

The conjugated vaccines induce immunological memory in children less than 2 years of age.[11] World Health Organization (WHO) recommends PCVs to be included in national childhood immunisation programmes worldwide. According to WHO, both PCV10 and PCV13 have comparable safety and efficacy profiles and that the choice of PCV vaccine depends on factors such as the vaccine serotypes compared to serotypes prevalent in the locally identified target groups, vaccine supply, as well as cost-effectiveness considerations.[12]

4.0 METHODS

4.1 SEARCHING

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews – Cochrane Central Registered of Controlled Trials – December 2020
- EBM Reviews – Database of Abstracts of Review of Effects – 1st Quarter 2020
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to December 2020
- EBM Reviews – Health Technology Assessment – 1st Quarter 2020
- EBM Reviews - NHS Economic Evaluation Database - 1st Quarter 2020

Other databases:

- PubMed
- Horizon Scanning database (National Instutute of Health research (NIHR) Innovation Observatory, Euroscan International Network)
- Other websites: US FDA, INAHTA

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. The search was limited to articles on humans. There was no language limitation in the search. Appendix 1 showed the detailed search strategies. The last search was conducted on the 8th December 2020.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	General elderly patients, elderly more than 65 years old
Interventions	Pneumococcal vaccination, pneumococcal polysaccharide vaccine (PPV23)
Comparators	Other pneumococcal vaccines No comparator
Outcomes	Vaccine effectiveness, morbidity, mortality Adverse effects, complications, safety issues, Cost-effectiveness, cost-utility, cost-minimisation, cost-analysis and economic evaluation Organizational –guidelines, recommendations
Study design	Health Technology Assessment (HTA), Systematic reviews (SR), Randomised control trials (RCTs), observational studies
Type of publication	English, full text articles

Exclusion criteria

Study design	Case report, survey, anecdotal, animal studies
Type of publication	Non-English
Intervention	Influenza vaccine, other vaccines

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) checklist and evidence graded according to the US/Canadian Preventive Services Task Force (See Appendix 2). Data were extracted from included studies using a pre-designed data extraction form (evidence table as shown in Appendix 6) and presented qualitatively in narrative summaries. No meta-analysis was conducted for this review.

5.0 RESULTS

A total of 1137 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to December 2020), EBM Reviews-Cochrane Central Register of Controlled Trials (December 2020), EBM Reviews-Database of Abstracts of Review of Effects (1st Quarter 2020), EBM Reviews-Health Technology Assessment (1st Quarter 2020), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2020) and PubMed. The last search was run on 8 December 2020. Additional articles were identified from reviewing the references of retrieved articles.

Forty-five articles were identified from references of retrieved articles. After removal of 65 duplicates, 1117 titles were screened. A total of 1117 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 1019 abstracts were found to be irrelevant. Ninety-eight potentially relevant abstracts were retrieved in full text. After applying the inclusion and exclusion criteria and critical appraisal to the 98 full text articles, 16 full text articles were included and 82 full text articles were excluded. (Figure 3). The review included 16 studies which were consisted of systematic reviews with meta-analysis (six), cohort studies (one), retrospective cohort study (two), cross-sectional study (one), quasi-experimental study (one) and cost-utility analysis (five).

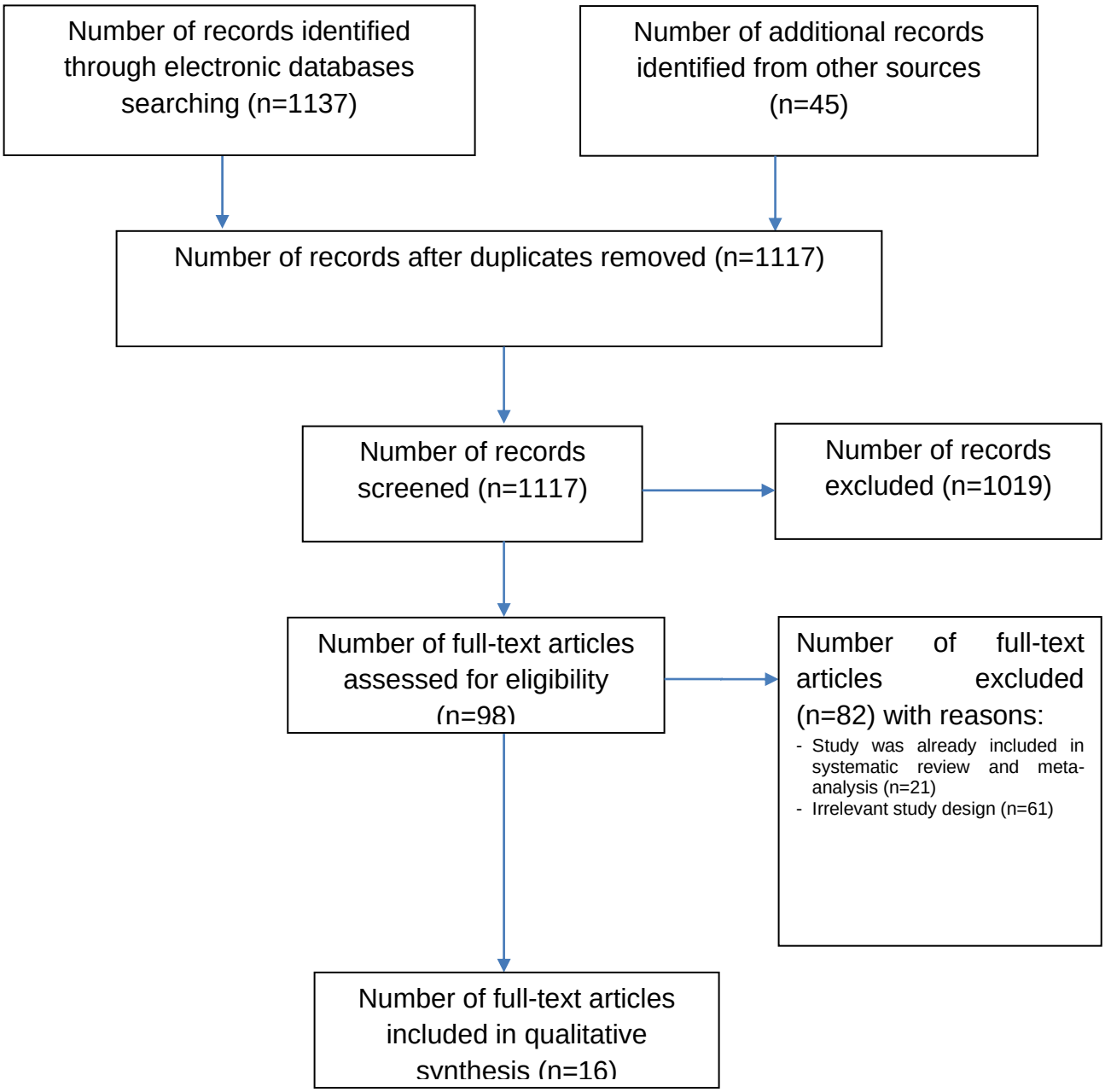

Figure 3: Flow chart of study selection

Of the 16 included articles in this review, seven studies were included in the effectiveness section, three studies were in the safety and six studies were in the cost-effectiveness section. The included articles were published between 2016 and 2020. Most of the studies were conducted in countries such as Japan, South Korea, US, Spain, Europe and UK followed by studies conducted in Sweden as well as Australia for cost-utility analysis.

5.1 RISK OF BIAS / QUALITY ASSESSMENT OF INCLUDED STUDIES

The tool used to assess the risk of bias or quality assessment for the included articles was the Critical Appraisal Skills Programme (CASP) checklist.[8] It is done by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates low risk of bias
?	indicates unclear risk of bias
-	Indicates high risk of bias

Assessment for Systematic Review (SR) Studies Using Critical Appraisal Skills Programme (CASP) Checklist

The risk of bias or quality assessment for Systematic Review studies was assessed using four domains based on CASP checklist. Six articles were included in this assessment. The risk of bias or quality assessment is shown in Figure 4a. There was no mention of quality assessment of the included studies in the SR by Nishikawa A M et al. (2018), thus was judged as 'unclear risk of bias' for that domain. The other five articles were of good quality as all were judged to have low risk of bias in all domains assessed.

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Berild J D et al. 2020 [13]	+	+	+	N/A
Falkenhorst G et al. (2016)[14]	+	+	+	+
Kraicer-Melamed H et al. (2016)[15]	+	+	+	+
Diao W et al. (2016)[19]	+	+	+	+
Vadlamudi N K et al. (2019)[20]	+	+	+	+
Nishikawa A M et al. (2018)[25]	+	+	?	+

Figure 4a: Assessment of risk of bias of systematic review (CASP)

Assessment for Cohort Study Using Critical Appraisal Skills Programme (CASP) Checklist

Figure 4b shows the risk of bias of one cohort study and two retrospective cohort studies based on five domains from the CASP checklist. Most studies were at low risk of bias for all five domains assessed. There was no mention of concomitant vaccines receipt by the participants in the study by Naito T et al. (2020) thus was judged as 'high risk of bias' for the domain assessing confounding factors.

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Naito T et al. (2020)[16]	+	+	+	-	+
Vila-Corcoles A et al. (2020)[17]	+	+	+	+	+
Tseng H F et al. (2018)[21]	+	+	+	+	+

Figure 4b: Quality assessment of cohort studies (CASP)

Quality Assessment of Economic Evaluation using Critical Appraisal Skills Programme (CASP) Checklist

Figure 4c shows the quality assessment of five cost-utility analysis based on the CASP checklist. All studies were of good quality for all nine domains assessed.

Criteria assessed	Wolff E et al. (2020)[23]	Wateska A R et al. (2020)[24]	Thorrington D et al. (2018)[26]	Chen C et al. (2018)[27]	Heo J Y et al. (2018)[28]
A well-define question posed?	+	+	+	+	+
Comprehensive description of competing alternative given?	+	+	+	+	+
Effectiveness established?	+	+	+	+	+
Effects of intervention identified, measured and valued appropriately?	+	+	+	+	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	+	+	+	+	+
Costs and consequences adjusted for different times at which they occurred (discounting)?	+	+	+	+	+
Results of the evaluation?	+	+	+	+	+

Incremental analysis of the consequences and costs of alternatives performed?	+	+	+	+	+
Sensitivity analysis performed?	+	+	+	+	+

Figure 4d: Assessment of risk of bias of economic evaluation (CASP)

5.2 EFFECTIVENESS

There were seven studies retrieved on the effectiveness of PPV23 for elderly consisted of three SR with meta-analysis, one SR, one cohort study, two retrospective cohort studies and one quasi-experimental study.

5.2.1 Vaccine Effectiveness against Pneumonia and Invasive Pneumococcal Disease

Berild J D et al. (2020) conducted a systematic review of studies published between the year of 2016 and 2019 on the effectiveness of pneumococcal vaccination on pneumonia and IPD in general elderly population. Systematic search was performed for eligible publications on vaccine effectiveness of the PCV13 or PPV23 in a general elderly population in Pubmed, Embase, Cinahl, Web of Science, Epistemonikos and Cochrane databases. Fifteen studies were included in this review which consisted of nine studies reported on vaccine effectiveness of PCV13 and six studies reported on vaccine effectiveness of PPV23. Some studies including the Italian test negative study on PCV13, the German cohort on PPV23, the Spanish case–control on PPV23 and the Japanese case–control study on PPV23 were judged to be of low quality while the other remaining studies were judged of high quality according to Newcastle–Ottawa Scale (NOS). Vaccine effectiveness (VE) was reported on the following outcomes: all-cause pneumonia, community-acquired pneumonia (CAP), non-bacteremic pneumococcal pneumonia (NBPP), vaccine-type (VT)-NBPP, pneumococcal pneumonia and VT-pneumonia, IPD and VT-IPD.[13 Level I]

Table 1. Description of the included studies for PPV23 and PCV13 in Berild J D et al. (2020)

Study	Study design	Country	Study period	Time between outcome and vaccination	Outcome	Quality
			PPV23			
Kolditz (2018)	Cohort >60 years old	Germany	2010-2011	Up to 5 years	• Pneumonia	Low
Suzuki (2017)	Case-control >65 years old	Japan	2011-2014	Up to 5 years	• Pn-Pneumonia • VT-Pneumonia	High
Djennad (2018)	Indirect cohort >65 years old	UK	2000-2016	Vaccine given at any time	• VT-IPD	High
Dominguez (2017)	Case-control >65 years old	Spain	2013-2015	Up to 5 years	• Pneumonia	Low
Kondo (2018)	Case-control >65 years old	Japan	2009-2014	Up to 5 years	• Pneumonia	Low
Kim (2019)	Case-control >65 years old	South Korea	2013-2015	Up to 5 years	• Pneumonia • Pn-Pneumonia • VT-Pneumonia	High
			PCV13			
Gessner (2018) Huijts (2017) Suaya (2018) Webber (2017) Patterson (2016)	Post hoc of RCT >65 years old	Netherlands	2008-2013	Up to 5 years	• Pneumonia • Pn-pneumonia, • VT-pneumonia, IPD • VT-IPD	NA
Vila-Corcoles (2018)	Cohort >50 years old	Spain	2015	Not stated	• Pneumonia • Pn-pneumonia	High
Kolditz (2018)	Cohort >60 years old	Germany	2014-2016	Up to 5 years	• Pneumonia	High
McLaughlin (2018)	Case-control >65 years old	US	2015-2016	Up to 5 years	• VT-pneumonia	High

PCV13: 13-valent pneumococcal conjugate vaccine, PPV23: 23-valent pneumococcal polysaccharide vaccine, RCT: randomised controlled trial, IPD: invasive pneumococcal disease, Pn: Pneumococcal, VT: Vaccine-type.

The review found that for PCV13, vaccine effectiveness (VE) in observational studies on PCV13 ranges from a negative VE (adjusted VE -69%) against all-cause pneumonia to a high protective VE of 71% against vaccine type- community acquired pneumonia (VT-CAP). All of these studies were conducted in the period 2014 to 2016, and in regions where PCV13 is a part of the routine childhood immunisation schedule. For PPV23, the VE ranged from 3% to 16% against all-cause pneumonia. For pneumococcal pneumonia, the VE ranged from 10% to 27%. For vaccine type pneumonia (VT-Pneumonia), the VE ranged from 2% to 34%. The South Korean case–control study (Kim et al.) found an adjusted overall VE of 10% (95% CI: -15 to 30) against non-bacteraemia pneumococcal pneumonia (NBPP) and 29% (95% CI: -6, 52) against IPD for all patients ≥65 years old. For VT-NBPP and VT-IPD the VE was -2% (95% CI: -40 to 26) and 42% (95% CI: -2 to 67), respectively. The UK study (Djennad et al.) reported a VE of 27% (95% CI: 17 to 35) against VT-IPD.[13] Level I

Table 2. Vaccine effectiveness (VE) percentage with 95% confidence interval by study, vaccine type and outcome.

Study	VE% Pneumonia	VE% Pn-Pneumonia	VE% VT-Pneumonia	VE% IPD	VE% VT-IPD
		PPV23			
Kolditz (2018)	3% (1% to 6%)				
Suzuki (2017)		27% (3% to 46%)	34% (6% to 53%)		
Djennad (2018)					27% (17% to 35%)
Dominguez (2017)	15% (-3% to 30%)				
Kondo (2018)	16% (-30% to 46%)	10% (-15% to 30%)			
Kim (2019)			2% (-39% to 26%)	29% (-6% to 52%)	42% (-2% to 67%)
		PCV13			
Vila-Corcoles (2018)	-69% (-94% to -48%)	-17% (-83% to 25%)			
Kolditz (2018)	11% (3% to 19%)				
McLaughlin (2018)			71% (6% to 91%)		
Prato (2018)		33% (-107%to 82%)	38% (-132% to 89%)		

PCV13: 13-valent pneumococcal conjugate vaccine, PPV23: 23-valent pneumococcal polysaccharide vaccine, RCT: randomised controlled trial, IPD: invasive pneumococcal disease, Pn: Pneumococcal, VT: Vaccine-type.

Five studies on PPV23 reported VE stratified by age groups. The South Korean case-control study (Kim et al.) found insignificant VE against NBPP or IPD for all patients 65 years and older, however when stratified by age, significant protection was found in patients aged 65 to 74 years old against both outcomes [VE 57.4% (95% CI:19.4, 77.5) against IPD and VE 35.0% (95% CI:2.3, 56.7) against NBPP]. For PPV23 there seems to be a decreasing VE with increasing age, and only one study reported a significant VE in the oldest age group (≥85 years). For PCV13, one study showed decreasing VE by age, while another did not find any difference.[13 Level I]

A systematic review and meta-analysis was conducted by Falkenhorst G et al. (2016) to assess the efficacy of PPV23 against pneumococcal pneumonia and invasive pneumococcal disease (IPD) in people aged >60 years living in industrialised countries. The review included four clinical trials and 13 observational studies. The three RCTs were conducted between 1991 and 2009 in Sweden, Spain, and Japan and included 596 to 1006 participants while the other trial was conducted in Finland and included almost 27,000 participants. Five cohort studies were conducted between 1998 and 2011 in Spain, United States (US), and Taiwan involving 34,000 to 458,000 person-years of follow-up. Risk of bias of individual studies was assessed using the Cochrane Risk of Bias tool for randomised controlled trials and the Newcastle-Ottawa Scale for observational studies. The three case-control studies were conducted between 2001 and 2010 in Spain and Israel. For the outcome IPD, the risk of bias was

rated as low for all the clinical trials. For the outcome pneumococcal pneumonia, two studies were judged to have a high risk of bias. Ten of 13 observational studies were judged to have low risk of bias. Meta-analyses of studies grouped by outcome and study design were done using random-effects models. Sensitivity analysis was performed excluding studies with high risk of bias.[14] Level I

The review found that pooled vaccine effectiveness (VE) against IPD (by any serotype) was 73% (95% CI: 10%, 92%) in four clinical trials, 45% (95%CI: 15%, 65%) in three cohort studies, and 59% (95%CI: 35%, 74%) in three case-control studies. After excluding studies with high risk of bias, pooled VE against pneumococcal pneumonia (by any serotype) was 64% (95%CI: 35%, 80%) in two clinical trials and 48% (95%CI: 25%, 63%) in two cohort studies.[14] Level I

Kraicer-Melamed H et al. (2016) conducted a systematic review and meta-analysis to review the evidence on vaccine effectiveness of PPV23, in preventing IPD and CAP in the general population of individuals over the age of 50. A total of 32 studies published between 1999 and 2015 were included in this review which was consisted of three trials, 11 cohort studies, 10 case–control studies, three ecological studies, and five case series/data from surveillance systems. The review found that the pooled VE for PPV23 in preventing IPD was 50% (95% CI: 21%, 69%) for cohort studies and 54% (95% CI: 32%, 69%) for case–control studies. The pooled VE estimates for CAP were 4% (95% CI: −26%, 26%) for trials, 17% (95% CI: −26%, 45%) for cohort studies, and 7% (95% CI: −10%, 21%) for case–control studies.[15] Level I

5.2.2 Mortality outcomes

Naito T et al. (2020) conducted a retrospective cohort study to assess the efficacy of national routine pneumococcal vaccination programme with PPV23 that has been implemented in elderly individuals more than 65 years old in Japan since 2014. Elderly patients' data between April 2014 and September 2018 were reviewed from the inpatient database of Juntendo University Hospital. A total of 1,355 patients who were ≥65 years old and had been treated by the Department of General Medicine at least once and hospitalised as inpatient were included in the study, consisting of 310 patients who had received pneumococcal vaccination and 1,045 patients who had not. Data retrieved from the database included age, vaccination survey answers, baseline comorbidities, smoking index, Barthel index for the activities of daily living (ADL), diagnosis of pneumonia-related conditions during hospital admission, transfer from the emergency room for pneumonia-related hospital admission, days of hospitalisation, and total health care expenditure during hospital stay. Primary outcome of this study was all-cause in-hospital mortality and secondary outcomes included confirmed diagnosis of pneumonia, pneumonia diagnosed at the emergency room (ER), total medical expenditure and the number of days as inpatient.[16] Level II-2 The study found that both groups had no significant differences in most of the demographic characteristics and comorbidities except that the Barthel index was higher in vaccinated group than in unvaccinated group (p = 0.039). Vaccinated patients had lower all-cause in hospital mortality rate (adjusted OR = 0.42, 95% CI: 0.22, 0.83) than unvaccinated patients.[16] Level II-2

Vila-Corcoles A et al. (2020) conducted a cohort study involving 2,025,730 middle-aged and older adults (aged 50 years and older) in Catalonia, Spain to evaluate clinical effectiveness for both PPV23 and PCV13 vaccines in preventing hospitalised pneumonia (pneumococcal, other microorganisms, unknown aetiology and all-cause), death from pneumonia (pneumococcal, other microorganism, unknown aetiology, all-cause) and death from any cause in the total study population at two-year follow-up. The PPV23 and PCV13 vaccination status were determined by a review of the electronic clinical records. Multivariable Cox regression models were used to estimate vaccination effectiveness adjusted for age and baseline-risk conditions. The study found that the cohort members were followed for 3,897,151 person-years of which 1,551,502 were PPV23 vaccinated and 17,496 were PCV13 vaccinated. Mean age of cohort members was 66-years-old. Vaccinated individuals were older (particularly PPV23 vaccinated), suffered more comorbidities/ risk conditions (particularly PCV13 vaccinated) and had higher proportion of influenza vaccination than unvaccinated subjects. There were 79,585 (4.0%) cohort members died and 51,175 (2.5%) moved or were lost subjects. Global incidence rates for pneumococcal pneumonia were 83.6 per 100,000 person-years (360.1 in PCV13 vaccinated, 144.6 in PPV23 vaccinated) and 617.9 per 100,000 person-years for all-cause pneumonia (3235.0 in PCV13 vaccinated, 1128.5 in PPV23 vaccinated). In the multivariable analyses, PPV23 did not significantly alter the risk of pneumococcal pneumonia (HR: 1.08; 95% CI: 0.98–1.19; $p = 0.132$) and slightly increased the risk of all-cause pneumonia (HR: 1.17; 95% CI: 1.13–1.21; $p < 0.001$). For pneumococcal pneumonia, overall case-fatality rate was 6.1% (200/3259), with 6.4% (4/63) in PCV13 vaccinated and 7.3% (164/2243) in PPV23 vaccinated ($p = 0.772$). For all-cause pneumonia, overall case-fatality rate was 9.1% (2196/24079), with 6.9% (39/566) in PCV13 vaccinated and 9.6% (1689/17508) in PPV23 vaccinated ($p = 0.028$). For all-cause death, mortality rate was 2042.1 per 100,000 person-years with 4795.4 per 100,000 in PCV13 vaccinated and 3725.0 per 100,000 in PPV23 vaccinated. In multivariable analyses pneumococcal vaccination with neither PCV13 nor PPV23 did not significantly alter the risk of death from pneumonia and/or death from any cause. In stratified analyses focused on specific target population subgroups including elderly people, at-risk and high-risk individuals, protective effects of vaccination were not seen either.[17] Level II-2

Jung S et al. (2018) conducted a quasi-experimental study in Japan to estimate the impact of pneumococcal vaccination with PPV23 on pneumonia mortality among the elderly ≥65 years old. Publicly available database on the cause-of-death in Japan from 2003 to 2017 were reviewed. Two types of mortality data were collected; the prefecture-dependent mortality and age– and gender-specific mortality data. Mortality due to malignant neoplasm and heart disease were used as control groups. The study showed that based on malignant neoplasm and heart disease as controls, the reduced pneumonia mortality in 2017 owing to pneumococcal vaccination was as large as 41.9 (95% CI:33.2, 50.6) and 31.2 (95% CI:23.8, 38.6) per 100,000 individuals, respectively. The largest mortality reduction was observed for the oldest group (aged ≥90 years), especially among men. The pneumonia mortality in elderly males aged ≥90 years was reduced every year from 2014 by 357.4 (95% CI :314.0, 400.7) or 276.3 (95% CI: 237.3, 315.2) per 100,000 individuals, respectively. The authors concluded that an abrupt decline in pneumonia mortality was seen from 2014 specifically the mortality was reduced by 20–40 per 100,000 individuals because of pneumococcal

vaccination, with the largest causal effect among the oldest group aged 90 years and older.[18 Level II-3]

Diao W et al. (2016) conducted a systematic review and meta-analysis of randomised trials to assess the efficacy of PPV23 in preventing CAP among immunocompetent adults and included seven RCTs involving 156,010 participants. Three studies were conducted in Western Europe, one in the US, and three in Japan. In the control group, three trials used a placebo, two trials used influenza vaccine and no vaccine was used in two trials. Five trials had the target population of persons aged over 65 years and adults at high risk of pneumonia due to chronic lung illness or living in a nursing home. Meanwhile, another two trials had healthy military trainees aged 17–20 years and subjects with a history of CAP. The study found that the pooled relative risk (RR) indicated that PPV23 reduced the incidence of all-cause pneumonia (RR 0.87, 95%CI: 0.76, 0.98). It also showed a trend of reducing the incidences of pneumococcal pneumonia (RR 0.54, 95%CI: 0.18, 1.65) and mortality from pneumonia (RR 0.67, 95%CI: 0.43, 1.04), but these results were not statistically significant possibly due to the small number of trials included. The PPV23 vaccine did not decrease all-cause mortality (RR 1.04, 95%CI: 0.87, 1.24). Sensitivity analyses were performed by excluding studies with risk of bias and it demonstrated that the results were stable. Analysis stratified for study population on data for all-cause pneumonia demonstrated that PPV23 protected target adults, which included those aged over 65 years and those aged 19 to 64 years at high risk of pneumonia (RR 0.72, 95%CI: 0.69, 0.94, p = 0.58, I^2= 0%); however, it did not protect young healthy military trainees aged 17 to 20 years or individuals with a history of CAP history (RR 1.00, 95%CI: 0.84, 1.19, p = 0.36, I^2= 0%). An analysis stratified for population age revealed that PPV23 was effective in elderly individuals aged more than 40 years (RR 0.80, 95%CI: 0.69, 0.94, p = 0.12, I^2= 42%) but not in young individuals aged less than 20 years (RR 0.96, 95%CI: 0.78, 1.18). Administration of PPV23 in combination with influenza vaccine had no additional protective effect over administration of PPV23 alone (RR 0.84, 95%CI: 0.64, 1.10, p = 0.62, I^2= 0%).[19 Level I]

5.3 SAFETY

There were one SR and meta-analysis, one retrospective cohort study and one cross-sectional study retrieved on the safety of PPV23 for elderly.

Vadlamudi N K et al. (2019) conducted a systematic review and meta-analysis of head to-head randomised controlled trials evaluating the immunogenicity and safety of a single dose of PCV13 and PPV23, in immunocompetent adults. Five RCTs were included in this review with 4561 subjects ranging from 50 to 95.5 years, with 51% females. Two studies were conducted in the United States, one was conducted in both the United States and Sweden with another in South Africa. Three out of five studies included pneumococcal vaccine-naive subjects while the other two studies included populations who were previously vaccinated with PPV23. All five studies enrolled immunocompetent subjects who had stable chronic conditions (i.e. cardiovascular, diabetes mellitus or renal or urinary disorders) for at least 12 weeks. Most of the studies were considered to have low risk of bias according to the Cochrane Risk of Bias Tool evaluation. The review reported that the risk for experiencing adverse effects

was comparable between the two vaccines with pooled RR for local and systemic reactions did not differ between PCV13 and PPV23; overall rate of local reactions was found to be 1.08 (95% CI: 0.95, 1.24), while the RR for overall systemic reactions was 0.97 (95% CI: 0.91, 1.04). Among pneumococcal naive subjects' local reactions were significantly higher in the PCV13 arm compared with PPV23 arm (RR: 1.15, 95%CI: 1.05–1.26, p = 0.0025). Overall local and systemic events were comparable when assessed by age (under and 65 years of age versus over 65 years of age), except fever and fatigue, which were significantly higher in those under 65 years of age (p < 0.05).[20 Level I]

Tseng H F et al. (2018) conducted a retrospective cohort study involving patients aged ≥65 years old in the US to assess for risk of adverse events (AE) requiring medical attention following vaccination with PCV13 as compared with vaccination with PPSV23. Patients aged 65 years and older who were vaccinated with either PPSV23 or PCV13 between January 1, 2011, and August 15, 2015 were included in this study. The prespecified AEs included cardiovascular events, Bell's palsy, Guillain-Barré syndrome, syncope, erythema multiforme, thrombocytopenia, cellulitis and infection, allergic reaction, and anaphylaxis. The study reported that a total of 313,136 doses of PCV13 and 232,591 doses of PPSV23 were included. The adjusted RRs comparing the incidence of AEs following PCV13 vs PPSV23 were all <1 except for anaphylaxis with RR 1.32 (95% CI: 0.3, 5.79) and were all insignificant.[21 Level II-2]

Yang T U et al. (2016) conducted a cross-sectional study in Korea to assess the performance of the national elderly pneumococcal vaccination programme with PPV23 vaccine in May 2013 in terms of coverage rate, and safety. Administrative data before and after the programme were reviewed. The study found that the adverse events following immunisation (AEFI) incidence rate was 4.98 per 100,000 doses from January 2012 to April 2013 and 5.11 per 100,000 doses from May 2013 to December 2014 (p = 0.9491). A total of 178 cases of AEFI were reported during the 20 months of the program, including six deaths, which were not related to the vaccine.[22 Level II-3]

5.4 COST / COST-EFFECTIVENESS ANALYSIS/ ECONOMIC IMPLICATION

There were one SR, one retrospective cohort study and five cost-utility analysis retrieved on the cost-effectiveness of PPV23 for elderly.

Nishikawa A M et al. (2018) conducted a systematic review of economic evaluations of PPV23 in adults aged >60 years published up to March 2016. There were 27 studies published from 1980 to 2016 included in this review. Thirteen studies involved cost-effectiveness analysis and another 13 studies involved cost-utility analysis while one conducted both. Most studies were conducted in Europe and the US while three studies were conducted in Latin America. Most studies compared the scenario of vaccination with the PPV23 to non-vaccination. In addition, three studies also compared PPV23 to pneumococcal conjugate 13-valent vaccine (PCV13). All studies used static models. Markov models were used in 12 studies whereas six studies used decision tree models, six were described as cohort studies, with no information regarding the type of model used and three did not mention which type of model was used. Most used a lifetime (44.4%) horizon or five to six years' time horizon (33.3%).

Only three studies considered herd protection from children immunization with PCV13 in the model. The discount rate for both costs and outcomes was 3% in 14 studies, 5% in nine studies, and 3.5% in one study. Another one study used discount rates of 6% for costs and 1.5% for outcomes. Two other studies used discount only for costs, at 3% and 4%. Most studies constructed the analysis from the perspective of society (12 studies). Four studies constructed the analysis from the perspective of the payer, two studies from the perspective of the health system, two studies from the perspective of the health care provider and two other studies from the perspectives of both society and the health system. Data on IPD incidence was obtained from local epidemiological data in most studies, except from four studies due to lack of local data. Seven (25.9%) studies considered NBPP, seven studies included pneumococcal pneumonia and three studies included CAP or all-cause pneumonia. Burden for pneumococcal pneumonia was estimated based on a proportion of all hospitalizations for CAP or a proportion of all CAP cases or based on a local database. Vaccine effectiveness (VE) for PPV23 varied significantly among the studies, depending on the age of the vaccinees, clinical syndrome considered, and time since vaccination. In the first year post vaccination, VE varied from 50% to 93% for IPD, from 45% to 80%, for pneumococcal pneumonia, from 21% to 39% for NBPP and from 10% to 21% for CAP. Most (74.1%) studies used VE estimates from the study published in 1991 by Shapiro et al. alone or in conjunction with other studies.[25]

The review found that vaccination at >60 years of age was considered cost-effective in 22 studies (81.5%) with ICER less than US$50,000 per LYG or QALY and cost-saving in five studies with results ranging from cost-saving to US$84,636/QALY. The estimates of disease burden, the efficacy/effectiveness of PPV23, and the effects of herd protection from childhood immunization had most influence on the results.[25]

A retrospective cohort study by Naito T et al. (2020) comparing vaccinated and unvaccinated elderly individuals with PPV23 in Japan reported that vaccinated patients had lower in hospital mortality rate, shorter length of hospital stay, and lower total medical expenditure (adjusted RR=0.76, 95% CI: 0.66, 0.87) compared with unvaccinated patients.[16 Level II-2] Over half of vaccinated patients (52.6%) and 40.8% of unvaccinated patients had total medical expenditure of less than ¥1,000,000 for the hospital stays. Median medical expenditure was ¥1,356,505 (IQR: ¥521,490 to ¥2,907,100) in the unvaccinated group and ¥917,130 (IQR: 379,390 to ¥2,146,878) in the vaccinated group.[16 Level II-2]

Wolff E et al. (2020) conducted a cost-utility analysis of including pneumococcal vaccination for elderly in a national vaccination programme in Sweden. Single-cohort deterministic decision-tree model was used to simulate the current burden of pneumococcal disease in Sweden. The model accounted for invasive pneumococcal disease (IPD) and pneumonia caused by pneumococci. Costs included in the analysis were those incurred when treating pneumococcal disease, and acquisition and administration of the vaccine. Health effects were measured as quality-adjusted life years (QALY). The time-horizon was set to five years, both effects and costs were discounted by 3% annually. Health-effects and costs were accumulated over the time-horizon and used to create an incremental cost-effectiveness ratio. The 23-valent polysaccharide vaccine (PPV23) was used in the base-case analysis. The 13-valent pneumococcal conjugate vaccine PCV13 was included in sensitivity analyses. The

vaccine effectiveness against IPD (approximately 50%) and CAP (approximately 28%) for the 65-year-old cohort have been derived from different studies.[23]

The analysis found that vaccination programme with PPV23 would significantly reduce the burden of pneumococcal related disease when vaccinating both 65-year-old cohort and 75-year-old cohort. For the 65-year-old cohort, a vaccination programme with a coverage of 75% would decrease the number of IPD-cases with 38%, and the number of primary care treated and hospitalised CAP with 21%, during the first year after implementation. For the 75-year-old cohort the corresponding figures were 29% for IPD and 29% for primary care and hospitalized CAP. Over the five-year time-horizon, vaccination would lead to a total decrease in the number of IPD cases by 30% among the 65-year-old cohort and by 29% for the 75-year-old cohort. The figures for CAP were 19% and 15%, respectively. The cost per QALY gained of vaccinating 65-year-olds with PPV23 in the base-case model was estimated to be EUR 94,000 compared to EUR 29,500 for 75-year-olds. The sensitivity analysis on the impact of the vaccine price indicated that, given a willingness to pay of EUR 50,000, the vaccine price of PPV23 would have to be reduced by approximately 55% for it to be cost-effective to vaccinate the 65-year-old cohort. With one dose PCV13 given instead of PPV23, the cost per gained QALY would increase for both cohorts, with a cost per gained QALY for 65-year-old cohort year-olds at approximately EUR 360,000 compared to EUR 200,000 for 75-year-old cohort. The authors concluded that introducing a vaccination programme against pneumococcal disease for 65-year-olds in Sweden is unlikely to be cost-effective, whereas for 75-year-olds and using PPV23, it can be considered good value for money. The model indicates that vaccine price needs to be reduced by 55% for vaccination of 65-year-olds to be cost-effective, given a threshold of EUR 50,000.[23]

Wateska A R et al. (2020) conducted a cost-utility analysis in the US to compare between; (1) the current recommendation (continuing PPV23 use in all older people, plus routine PCV13 for the immunocompromised and potential PCV13 use for the immunocompetent based on shared clinical decision making); (2) an alternative policy omitting age-based PCV13 use in immunocompetent older people due to the herd protection effects of childhood PCV13 use; and (3) adding intervention programs to these strategies to increase vaccination uptake in older people, with a particular emphasis on underserved minority populations, where pneumococcal illness risk is higher than in the general population, but pneumococcal vaccine uptake is lower. A Markov model was constructed and all strategies were examined in hypothetical cohorts of US adults, aged 65 years or older. Outcomes were estimated in both the black population and in the general population. Model outputs include public health outcomes (case frequency and mortality for IPD and NBPP) and cost-effectiveness analysis results. Costs were adjusted to 2014 US dollars, using the US Consumer Price Index. The analysis took a healthcare perspective, with future costs and effectiveness discounted by 3%over a lifetime horizon.[24]

The analysis showed that the current pneumococcal vaccination recommendation was the most effective strategy, but afforded slight public health benefits compared to an alternative (PPV23 for all older people plus PCV13 for the immunocompromised) and had an incremental cost-effectiveness ratio (ICER) of greater than $750 000 per quality adjusted life-year (QALY) gained in either population group with a vaccine

uptake improvement program in place. The alternative strategy was more economically favourable, but with ICER of greater than $100 000/QALY in either population, with or without an uptake intervention. Results were robust in sensitivity analyses; however, in black older people, the alternative strategy with an uptake program was most likely to be favoured in probabilistic sensitivity analyses at a $150 000/QALY gained threshold. The authors concluded that current pneumococcal vaccination recommendations for US older people are economically unfavourable compared to an alternative strategy omitting PCV13 in the immunocompetent.[24]

Thorrington D et al. (2018) conducted a cost-utility analysis in The Netherlands to investigate the impact and cost-effectiveness of vaccination with PPV23 or PCV13, among all those aged 60, 65 or 70 and/or in combination with replacing PCV10 with PCV13 in the infant vaccination programme. A static cost-effectiveness model quantifying the impact of different vaccination strategies from a health care provider's perspective was parameterised including projected trends for IPD and hospitalised CAP using surveillance data, literature values and expert opinion if no consistent information was available. The different strategies were evaluated using vaccine list prices and a 10-year time horizon. The costs of the vaccines per dose were set at €72.67 for PCV13 and €21.20 for PPV23 based on the list price, excluding additional administration costs. For IPD, VE was assumed to be 75% for PCV13 based on the phase 3 trial and 62% for PPV23 based on a meta-analysis of several trials and cohort studies at the start of first administration of the vaccine. For CAP, VE was estimated to be at 19.6%. Incremental cost-effectiveness ratios (ICER) were calculated with the current strategy (infant vaccination program with PCV10) as reference. The impact of vaccination was quantified by comparing the difference in future disease incidence, and subsequent mortality, costs and loss of quality of life, by projecting the future with the new vaccination strategy under study and comparing to the reference current strategy. The future costs and QALYs were discounted using a discount rate of 4.0% for costs and 1.5% for health benefits according to national guidelines. The sensitivity analysis tested the sensitivity of the ICER to assumptions on vaccine effectiveness, age at vaccination, mortality assumptions, cost assumptions, adding administration costs, QALY assumptions, discounting, time horizon and the level of herd protection generated by the infant programme.[26]

The analysis found that the largest impact on pneumococcal disease burden was projected with a combined use of PCV13 among infants and PPV23 at 60, 65 and 70 years, preventing 1,635 cases of IPD and 914 cases of CAP. The most cost-effective strategy was vaccinating with PPV23 at 70 years only with ICER € 6,201 per QALY. Vaccinating with PPV23 at age 60 and 65 years old were also cost-effective with similar low ICERs. Vaccinating elderly with either PCV13 or PPV23 was dominated by PPV23 in all investigated scenarios, mainly due to the lower price of PPV23. Sensitivity analysis revealed that the ICER were most sensitive to changes in the mortality rate and the total costs of implementing the programme. The health care costs, discount rate for health effects, and the QALY weights for IPD and CAP did not have a large influence on the findings. The authors concluded that the best value for money is the use of PPV23 for elderly, with a single dose or at five-year increment between age 60 to age 70.[26]

Chen C et al. (2018) conducted a cost-utility analysis to evaluate the PPV23 programme in older adults in Australia from 2005 to 2015 with a focus on how the value for money may have changed over time as a result of herd protection effects from infant PCV7 and PCV13 programmes. A multi-cohort Markov model with a cycle length of one year was developed to retrospectively evaluate the cost-effectiveness of the PPV23 immunisation program from 2005 to 2015 and followed the whole Australian population with a background mortality rate from the Australian Bureau of Statistics. The analysis was performed from the healthcare system perspective with costs and quality-adjusted life years discounted at 5% annually. The incremental cost-effectiveness ratio (ICER) for PPV23 doses provided from 2005 to 2015 was calculated separately for each year when compared to no vaccination. Parameter uncertainty was explored using deterministic and probabilistic sensitivity analysis. The analysis showed that it was estimated that PPV23 doses given out over the 11-year period from 2005 to 2015 prevented 771 hospitalisations and 99 deaths from IPD in those aged over 65 years. However, the estimated IPD cases and deaths prevented by PPV23 declined by more than 50% over this period most likely driven by herd effects from infant PCV programs. The estimated ICER over the period 2005 to 2015 was approximately A$224,000/QALY gained compared to no vaccination. When examined per year, the ICER for each individual year increased from $140,000/QALY in 2005 to $238,000/QALY in 2011 to $286,000/QALY in 2015. The decrease in cost-effectiveness corresponded to the decline of PPV23 vaccine-type IPD incidence which was likely the result of herd impacts from the infant PCV7 and PCV13 programs in Australia. The authors concluded the PPV23 adult vaccination program in Australia is unlikely to have been cost-effective, unless PPV23 was effective against pneumococcal CAP and/or a low vaccine price was negotiated. [27]

Heo J Y et al. (2018) conducted a cost-utility analysis to assess the current vaccination strategy in Korea with a single-dose PPV23 vaccination compared to a single-dose PCV13 vaccination and sequential PCV13-PPV23 vaccinations in the elderly population aged ≥65 years. The National Immunisation Program (NIP), which provides free PPSV23 vaccination, was implemented in May of 2013 for all people aged 65 years or older in South Korea. By May of 2014, paediatric PCV10/PCV13 was also included in the NIP. A probabilistic Markov model was used to evaluate three pneumococcal vaccination strategies in Korean adults aged 65 years or older: (1) PPSV23 vaccination only, (2) PCV13 vaccination only, and (3) sequential PCV13-PPSV23 vaccination. The Markov model was constructed based on epidemiological data, vaccine effectiveness, and economic parameters according to a review of previous studies. Five health states were modelled, comprising health (without any pneumococcal disease), IPD, NBPP, neurological sequelae, and death. The Markov model was set at a cycle length of one year with a 15-year time horizon following vaccination in four age cohorts (19-49, 50-64, 65-74, ≥75 years). The transition probabilities, utility weights to estimate quality adjusted life year (QALY), and disease treatment costs were either calculated or cited from published data and the Health Insurance Review and Assessment Service. Costs and benefits were discounted at a rate of 5%, converting costs to US dollars based on the value of the dollar in 2015. Based on the Korean gross domestic product (GDP), a gain of $25,000/QALY (< 1 × GDP per capita) was considered highly cost-effective, and a gain of $38,000/QALY (< 1.5 × GDP per capita) was accepted as moderately cost-effective. One-way and

probabilistic sensitivity analyses comparing the PCV13 strategy with current PPV23 strategies in elderly subjects aged 65 years or older were performed.[28]

The analysis showed both PPV23 and PCV13 vaccination strategies in comparison with no vaccination were cost-effective with ICERs less than $38,000/QALY. Compared to no vaccination, the estimated ICERs of current PPSV23 vaccination strategy were $25,786 per QALY with a targeted vaccine uptake rate of 60% and $17,354 per QALY with a targeted vaccine uptake rate of 80%. The ICER was most sensitive to the incidence of NBPP and vaccine effectiveness against NBPP.[28]

There was no local economic evaluation on pneumococcal vaccination with PPV23 for elderly retrieved in the medical databases. There was one technical report by Farhana A et al. (2021) who conducted cost-effectiveness analysis of pneumococcal vaccination with PPV23 specifically for Malaysian Hajj pilgrims to determine the cost-effectiveness and budget impact of introducing the PPV23 to Malaysian Hajj pilgrims compared to the status quo of no vaccination. The analysis involved data from a total of 40,837 Malaysian pilgrims in the year 2017 and used decision tree model. Majority of the pilgrims aged ≥ 50 years old (74.6%). The report showed that the PPV23 vaccination program for Malaysian Hajj pilgrims was cost-effective with ICER of -MYR449.30 per disease case averted. The total medical savings would be RM9.1 million at a vaccine price of RM130.80 per dose. Sensitivity analysis showed changes in annual incidence and hospitalised cost of septicaemia and disease without vaccination had the major influence on the ICER. The authors concluded that the PPV23 vaccination program offers additional benefits to both the provider and community in reducing the burden of pneumococcal related-diseases and the healthcare cost. Nonetheless, the policymaker must judiciously consider the best options to execute this strategy; to ensure its feasibility and sustainability.[29]

Economic implication

The price for pneumococcal vaccination with one single dose of PPV23 in public and private sector in Malaysia ranges from RM82 to RM150. In 2020, the total population in Malaysia was estimated at 32.7 million.[30] Population of elderly ≥65 years old in Malaysia for the same year was estimated at 2.3million (7.0%).[30] Assuming 100% coverage, introduction of pneumococcal vaccination with PPV23 for elderly ≥65 years old in Malaysia is estimated to have an economic implication of approximately RM 189 million to RM 345 million in the first year. Assuming 70% coverage, the estimates range from RM 132 million to RM 241 million in the first year. These estimates will reduce in the subsequent years of implementation however, the estimation is limited by data unavailability on the total population of elderly aged 65 years old every year.

5.5 ORGANISATIONAL

5.5.1 Hospitalisation

Naito T et al. (2020) conducted a retrospective cohort study to assess the efficacy of national routine pneumococcal vaccination programme with PPV23 that has been implemented in elderly individuals more than 65 years old in Japan since 2014. A total of 1355 patients were retrospectively enrolled and comprised of 1045 unvaccinated and 315 vaccinated elderly individuals. The study found that the most common cause

of hospitalisation in the vaccinated and unvaccinated groups were similar, in which 3 of the top causes of hospitalisation were the same in both groups: malignancy in the colon (8.1 and 7.1%), polyp of colon (6.1 and 3.6%), and pneumonia (2.9 and 2.6%). Severity of pneumonia hospitalisations were also similar in both groups. There were 154 cases of pneumonia, and 127 of these cases were diagnosed at the ER. The proportions of patients diagnosed with pneumonia (11.4% unvaccinated group versus 11.3% vaccinated group) and pneumonia transferred from ER (9.2% in unvaccinated group and 10.0% in vaccinated group) were similar between vaccinated and unvaccinated group. Prior vaccination was found associated with all-cause shorter hospital stays (adjusted RR = 0.66, 95% CI: 0.57, 0.76). The authors concluded that the study demonstrated that implementation of national PPV23 vaccination program contributed to beneficial clinical outcomes. Significant effect on reducing all-cause inpatient hospital stays, mortality, and medical expenses was observed, in the elderly aged ≥65 years under the Japanese medical system. The findings support the utilisation of pneumococcal vaccination as a protective measure in the elderly, although the co-contribution from influenza vaccination and PCV requires further investigation.[16] Level II-2

5.5.2 Guidelines

World Health Organization (WHO)

In the WHO position paper on PPSV23 in 2008, WHO summarised evidence on PPV23 and concluded that the results of RCTs and meta-analyses of such trials are consistent with a protective effect against IPD and all-cause-pneumonia among healthy young adults as well as a lesser degree of protection against IPD in individuals aged >65 years. The RCTs have failed to demonstrate efficacy against IPD or all-cause pneumonia in individuals with immunocompromising conditions, regardless of age. Most observational studies suggest an effectiveness as high as 50–80% against IPD in healthy adults, and similar results have been reported in some high-risk populations. Many industrialised countries recommend PPV23 immunization of their elderly and other high-risk groups. In resource limited settings where there are many competing health priorities, the evidence does not support routine immunisation of the elderly and high-risk populations with PPV23. Given the substantial effects of herd immunity in adult age groups following routine infant immunization with PCV7, a higher priority should be given to introducing and maintaining high coverage of infants with PCV7. Countries considering introducing PPV23 to elderly or other high-risk populations will need to develop strategies for reaching these target populations.[31]

Centre of Disease Control and Prevention (CDC)

Pneumococcal Vaccination recommendations from CDC include routine administration of pneumococcal polysaccharide vaccine (PPSV23) for all adults 65 years or older. In addition, CDC recommends PCV13 based on shared clinical decision-making for adults 65 years or older who do not have an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant and have never received a dose of PCV13. Clinicians should consider discussing PCV13 vaccination with these patients to decide if vaccination might be appropriate.[32]

National Health Services (NHS), UK

In UK, NHS includes the administration of PPV23 to individuals from 65 years of age, and individuals from 2 years of age in a clinical risk group, in accordance with the national immunisation programme.[33]

Boonave C et al. (2019) conducted a review on pneumococcal vaccination to compare the national guidelines for pneumococcal immunization for adults in Europe. National guidelines on pneumococcal vaccination for adults of 31 European countries were obtained by Google search, the website of European Centre for Disease Prevention and Control (ECDC), and from public health officials. The analysis showed that in Europe, two vaccine types are used in adults for pneumococcal immunisation which are PPV23 and PCV13. In age-based guidelines, vaccination is mostly recommended in adults aged over 65 years using PPV23. Boosters are generally not recommended. An upper age limit for vaccination is reported in three countries. In the immunocompromised population, vaccination with both vaccines and administration of a booster is mostly recommended. In the population with chronic health conditions, there is more heterogeneity according vaccine type, sequence, and administration of boosters. Asplenia is the only comorbidity for which all countries recommend vaccination. The authors concluded that the great variability in European pneumococcal vaccination guidelines warrants European unification of the guidelines for better control of pneumococcal disease.[34]

5.6 LIMITATION

Our review has several limitations and these should be considered when interpreting the results. Although there was no restriction in language during the search, only the full text articles in English published in peer-reviewed journals were included in the review, which may have excluded some relevant articles and further limited the study numbers. One of the important limitations was the methodological quality of the included reviews and the limitations of the primary studies themselves. Included studies which had a high risk of bias in the systematic review may affect the methodological quality. We did not conduct a rigorous assessment of the concordance of the data reported in the SR with those stated in the primary studies. It is presumed that each review generally included the full available and eligible evidence that data extraction was accurate, and that analyses were scientifically sound.

6.0 CONCLUSION

There was good level of retrievable evidence to suggest that pneumococcal vaccination with PPV23 in elderly population had low to moderate efficacy against invasive pneumococcal disease (IPD) and pneumococcal pneumonia. Evidence on effectiveness of PPV23 against all-cause pneumonia and mortality were not statistically significant. There was no serious adverse events and safety issues reported in the included studies. Cost analyses done in industrialised countries showed varying results depending on parameters and thresholds. The estimates of disease burden, vaccine effectiveness, cost assumptions and the effects of herd protection had the most influence on the results. Introduction of pneumococcal vaccination with PPV23 for elderly in Malaysia is estimated to have major financial implication. Various international organisations from industrialised countries recommend pneumococcal vaccination with PPV23 for the elderly and other high-risk groups. However, WHO stated that in resource limited settings where there are many competing health priorities, a higher priority should be given to introducing and maintaining high coverage of infants with PCV vaccine given the substantial effects of herd immunity in adult age groups following routine infant immunisation.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: SEARCH STRATEGY

Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1946 to present

1 Aged/
2 aged.tw.
3 elderly.tw.
4 1 or 2 or 3
5 PNEUMOCOCCAL VACCINES/
6 ((pnu imune or pneumococcal polysaccharide) adj2 vaccine*).tw.
7 pneumovax.tw.
8 ((pnu-imune or pnuimune or pneumococcal) adj2 vaccine*).tw.
9 pneumococcal ppsv23 vaccine.tw.
10 pneumococcal ppv23 vaccine.tw.
11 5 or 6 or 7 or 8 or 9 or 10
12 4 and 11
13 limit 12 to (english language and "all aged (65 and over)")

OTHER DATABASES	
EBM Reviews – Cochrane Central Registered of Controlled Trials	Similar MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Database of Abstracts of Review of Effects	
EBM Reviews – Cochrane database of systematic reviews	
EBM Reviews – Health Technology Assessment	
NHS economic evaluation database	
PubMed	Similar MeSH, keywords, limits used as per MEDLINE search
INAHTA	
US FDA	

APPENDIX 3: EVIDENCE TABLE

Evidence Table : **Effectiveness**
Question : **Is pneumococcal vaccination effective for the elderly?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Berild JD, Winje BA, Vestrheim DF et al. A Systematic Review of Studies Published between 2016 and 2019 on the Effectiveness and Efficacy of Pneumococcal Vaccination on Pneumonia and Invasive Pneumococcal Disease in an Elderly Population. Pathogens. 2020;9(4):259.	Systematic Review **Aim:** To update the evidence base for vaccine efficacy and effectiveness of PPV23 and PCV13 against invasive pneumococcal disease and pneumonia among an unselected elderly population. **Methods:** -Systematic search was conducted for clinical trials and observational studies published between January 1, 2016 and April 17, 2019 in Pubmed, Embase, Cinahl,Web of Science, Epistemonikos and Cochrane databases. -Risk of bias was assessed using Cochrane Risk of Bias tool for and the Newcastle–Ottawa Scale. -Results were stratified by vaccine type and outcome. - Meta-analysis was not done due to different outcomes,	I	9 studies on PCV13 and 6 on PPV23 9 studies on PCV13 VE: -5 were post-hoc analyses based on CAPITA data -Besides the post-hoc studies, two cohort studies, one from Spain and one from Germany and two studies using test-negative design (TND), one from US and one from Italy -For PPV23 one cohort study from Germany, one TND study from Japan, one indirect cohort study from UK and 3 case–control studies from Spain, Japan and South Korea	PPV23 vaccine	PCV13 vaccine		**Results:** PCV13: -The Spanish cohort study did not find any protective VE on all-cause pneumonia or pneumococcal pneumonia -The German cohort study found an adjusted VE of 11% (95% CI: 3 to 19) against all-cause pneumonia. -The American TND study found an adjusted VE of 71% (95% CI: 6 to 91) against VT-CAP. -The Italian TND study found a crude VE of 33% (95% CI: -107 to 82) against pneumococcal CAP and a crude VE of 38% (95% CI: -132 to 89) against VT-CAP PPV23: -The German cohort study : adjusted (propensity score matched) VE of 3% (95% CI: 1 to 6) against all-cause pneumonia. -The Japanese TND study: an adjusted VE of 27% (95%CI: 3 to 46) against pneumococcal pneumonia and a VE of 34% (95% CI: 6 to 53) against VT-pneumonia. -The Spanish case–control study :an adjusted VE of 15% (95% CI: -3 to 30) against CAP.	

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Evidence Table : Effectiveness
Question : Is pneumococcal vaccination effective for the elderly?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. 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):e0169368.	Systematic review and meta-analysis **Aim:** To investigate the efficacy of PPV23 against the specific outcomes PP and IPD in people aged >60 years living in industrialized countries. **Methods:** -Systematic search was done for pertinent clinical trials and observational studies in databases MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. -Risk of bias of individual studies was assessed using the Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. -Overall quality of the evidence was rated by GRADE criteria. -Meta-analysis performed	I	17 studies included: 4 RCTs 5 cohort studies 3 case-control studies 5 case-case studies	Pneumococcal vaccination PPV23			**Results:** -Pooled VE against IPD (by any serotype) was 73% (95%CI: 10±92%) in four clinical trials, 45% (95%CI: 15±65%) in three cohort studies, and 59% (95%CI: 35±74%) in three case-control studies. -After excluding studies with high risk of bias, pooled VE against pneumococcal pneumonia (by any serotype) was 64% (95%CI: 35±80%) in two clinical trials and 48% (95%CI: 25±63%) in two cohort studies. -Higher VE estimates in trials (follow-up ~2.5 years) than in observational studies (follow-up ~5 years) may indicate waning protection. -Unlike previous meta analyses, we excluded two trials with high risk of bias regarding the outcome pneumococcal pneumonia, because diagnosis was based on serologic methods with insufficient specificity **Conclusion:** Meta-analysis revealed significant VE of PPV23 against both IPD and pneumococcal pneumonia *by any serotype* in the elderly, comparable to the efficacy of PCV13 against *vaccine-serotype* disease in a recent clinical trial in elderly people. Due to its broader serotype coverage and the decrease of PCV13 serotypes among adults	

Evidence Table : **Effectiveness**
Question : **Is pneumococcal vaccination effective for the elderly?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. 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):e0169368.	on studies, grouped by outcome and study design using random-effects models. -Sensitivity analysis was done excluding studies with high risk of bias.						resulting from routine infant immunization with PCV13, PPV23 continues to play an important role for protecting adults against IPD and pneumococcal pneumonia.	

Evidence Table : **Effectiveness**
Question : **Is pneumococcal vaccination effective for the elderly?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Kraicer-Melamed H, O'Donnell S, Quach C et al. 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):1540-1550.	Systematic Review and meta-analysis **Aim:** To evaluate and summarize the results from all studies reporting on the vaccine effectiveness of PPV23 in preventing invasive pneumococcal disease (IPD) and community-acquired pneumonia (CAP)in individuals over the age of 50. **Methods:** -Systematic database searches were completed in PubMed, Medline, Embase, CINAHL, Web of Science, and Cochrane. Google Scholar and hand searches of seminal articles and past systematic reviews were employed. -Studies were included if they independently evaluated the effect of PPV23 on IPD and/orCAP in adults (50+).	I	-A total of 32 studies were included in the present systematic review - 12 reported only on IPD, and 12reported only on CAP. -The included studies were trials (n = 3), cohort studies (n = 11), case–control studies (n = 10), ecological studies(n = 3), and data from surveillance systems (n = 5).	PPV23 vaccination			**Results:** -Meta-analyses were completed by study design (trials, case–control, and cohort studies) for both IPD and CAP. -The pooled VEs for IPD were 50% (95% CI: 21–69%) for cohort studies and 54% (95% CI: 32–69%) for case–control studies, which indicate a protective effect with 95% CIs that do not cross the null value. - The pooled effect estimates for preventing CAP were 4% (95% CI:−26% to 26%) for trials, 17% (95% CI: −26% to 45%) for cohort studies, and 7% (95% CI: −10% to 21%) for case–control studies and all estimates were not statistically significant. **Conclusion:** -The vaccine effectiveness of PPV23 in preventing IPD and all-cause CAP was consistent with past systematic reviews and similar to the estimates that were reported in the CAPiTA trial evaluating the vaccine effectiveness of PCV13. -Consistent benefits were also reported across ecological studies and reports of surveillance data for the general population 50 years and older. -The results suggests that the current practice of vaccinating the adults 65 years of age and older with PPV23 would have similar benefits to PCV13 in preventing potential cases of all-serotype IPD and all-cause CAP.	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Kraicer-Melamed H, O'Donnell S, Quach C et al. 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):1540-1550.	-Data extraction and quality assessment were both completed independently by two researchers. -Quality was assessed using the National Advisory Committee on Immunization methodology for quality assessment. -All conflicts were resolved by consensus.							

Evidence Table : Effectiveness
Question : Is pneumococcal vaccination effective for the elderly?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Naito T, Suzuki M, Kanazawa A, et al. Pneumococcal vaccination reduces in-hospital mortality, length of stay and medical expenditure in hospitalized elderly patients. J Infect Chemother. 2020;26(7):715-721.	Retrospective cohort study **Aim:** To determine whether prior pneumococcal vaccination contributed to better clinical outcomes, as well as the expenditure of all-cause hospital admissions in >65-year-old elders under the Japanese medical system. **Method:** -In-patient database Juntendo University Hospital were reviewed and elderly patients (>65 years-old) who had received in-patient care in general medicine department during 2014 to 2018 were selected. -The following data of retrospectively enrolled patients were retrieved from the in-patient database: age, vaccination survey answers, baseline comorbidities, smoking	II-2	Total of 1355 patients were retrospectively enrolled in the study, consisting of 310 patients who had received pneumococcal vaccination (vaccinated) and 1045 who had not (unvaccinated)	23-valent pneumococcal polysaccharide vaccine (PPV23)	No vaccination	Length of hospital stays (6-49days)	**Results:** -Most common cause of hospitalization (representing 1.9 to 8.1% of patients) in the vaccinated and unvaccinated groups were similar, in which 3 of the top causes of hospitalization were the same in both groups: malignancy in the colon (8.1 and 7.1%), polyp of colon (6.1 and 3.6%), and pneumonia (2.9 and 2.6%) - Severity of pneumonia hospitalizations were similar between the two groups - The proportions of patients with pneumonia diagnosis were similar between vaccinated and unvaccinated group (n = 119, 11.4% of the unvaccinated group; n =35, 11.3% of the vaccinated group), as well as of pneumonia transferred from the emergence department (9.2% in unvaccinated group and 10.0% in vaccinated group). -In contrast, vaccinated patients had lower all-cause in hospital mortality rate than unvaccinated patients (3.9% vs. 8.2%, p = 0.008). - In addition, the LOS was significantly shorter and the total medical expenditure lower in the vaccinated group compared with the unvaccinated group (both p < 0.001).	

Evidence Table : Effectiveness
Question : Is pneumococcal vaccination effective for the elderly?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Naito T, Suzuki M, Kanazawa A, et al. Pneumococcal vaccination reduces in-hospital mortality, length of stay and medical expenditure in hospitalized elderly patients. J Infect Chemother. 2020;26(7):715-721.	index, the index for activities of daily living (ADL), diagnosis of pneumonia-related conditions during hospital admittance, transfer from the emergency room (ER) for pneumonia-related hospital admittance, days of hospitalization, total health care expenditure during the stay. - Primary clinical outcome was all-cause in-hospital mortality. -Secondary outcomes included: a. Confirmed diagnosis of pneumonia, b. Pneumonia diagnosed at the ER, c. Total medical expenditure, d. Number of days as in-patient.						-Over half of vaccinated patients (52.6%) and 40.8% of unvaccinated patients had total medical expenditure of less than ¥1,000,000 for the hospital stays, respectively. -Median medical expenditure was ¥1,356,505 (IQR ¼ ¥521,490 to ¥2,907,100) in the unvaccinated group and ¥917,130 (IQR ¼ 379,390 to ¥2,146,878) in the vaccinated group -Vaccinated patients had lower all-cause in hospital mortality rate (adjusted OR = 0.42, 95% CI: 0.22 to 0.83), shorter LOS (adjusted RR = 0.66, 95% CI: 0.57 to 0.76), and lower total medical expenditure (adjusted RR = 0.76, 95% CI: 0.66 to 0.87) compared with unvaccinated patients. **Authors conclusion:** Current study demonstrated that implementation of national PPV23 vaccination program contributed to beneficial clinical outcomes. Significant effect on reducing all-cause inpatient hospital stays, mortality, and medical expenses was observed, in the elderly aged >65 years under the Japanese medical system. The findings support the utilization of pneumococcal vaccination as a protective measure in the elderly, although the co-contribution from influenza vaccination and PCV requires further investigation	

Evidence Table : **Effectiveness**
Question : **Is pneumococcal vaccination effective for the elderly?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Vila-Corcoles A, Hospital I, Ochoa-Gondar O et al. Clinical effectiveness of 13-valent and 23-valent pneumococcal vaccination in middle-aged and older adults: The EPIVAC cohort study, 2015-2016. Vaccine. 2020;38(5):1170-1180.	Cohort study **Aim:** To investigate clinical effectiveness for both PPsV23 and PCV13 in preventing pneumonia among middle-aged and older adults **Methods:** -Closed population-based prospective cohort study involving 2,025,730 middle-aged and older adults in Catalonia Spain. - Cohort members were followed from the beginning of the study until the occurrence of any event, disenrollment from the PHCC, death, or until the end of the two-years follow-up (31/12/2016). - Primary outcomes were hospitalisation from pneumococcal or all-cause pneumonia and main explanatory variable was PCV13/PPsV23 vaccination status.	II-2	-2,025,730 cohort members were observed for a total of 3,897,151 person-years, of which 1,551,502 were PPsV23 vaccinated and 17,496 were PCV13 vaccinated - Mean age of cohort members was 66 years-old (SD:11.5), being 932,072 (46%) men and 1,093,658 (54%) women. - vaccinated subjects older (especially PPsV23 vaccinated), more comorbidities/ risk conditions (especially PCV13 vaccinated) and had higher proportion	PPsV23	PCV13		**Results:** During the two-year study period, 79,585 (4.0%) cohort members died and 51,175 (2.5%) moved or were lost subjects. -Cohort members were followed for 3,897,151 person-years (17,496 PCV13 vaccinated and 1,551,502 PPsV23 vaccinated), observing 3259 pneumococcal pneumonias (63 in PCV13 vaccinated, 2243 in PPsV23 vaccinated) and 24,079 all-cause pneumonias (566 in PCV13 vaccinated, 17,508 in PPsV23 vaccinated). -Global incidence rates (per 100,000 person-years) were 83.6 for pneumococcal pneumonia (360.1 in PCV13 vaccinated, 144.6 in PPsV23 vaccinated) and 617.9 for all-cause pneumonia (3235.0 in PCV13 vaccinated, 1128.5 in PPsV23 vaccinated). -In the multivariable analyses, the PCV13 appeared significantly associated with an increased risk of pneumococcal pneumonia (hazard ratio [HR]: 1.52; 95% confidence interval [CI]: 1.17–1.97; p = 0.002) and all-cause pneumonia (HR: 1.76; 95% CI: 1.61–1.92; p < 0.001) whereas the PPsV23 did not alter the risk of pneumococcal pneumonia (HR: 1.08; 95% CI: 0.98–1.19; p = 0.132) and	

Evidence Table : **Effectiveness**
Question : **Is pneumococcal vaccination effective for the elderly?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Vila-Corcoles A, Hospital I, Ochoa-Gondar O et al. Clinical effectiveness of 13-valent and 23-valent pneumococcal vaccination in middle-aged and older adults: The EPIVAC cohort study, 2015-2016. Vaccine. 2020;38(5):1170-1180.			of influenza vaccination than unvaccinated subjects				slightly increased the risk of all-cause pneumonia (HR: 1.17; 95% CI: 1.13–1.21; p < 0.001). -In stratified analyses focused on specific target population subgroups (i.e., elderly people, at-risk and high-risk individuals), protective effects of vaccination did not emerge either. **Conclusion:** Data does not support clinical benefits from pneumococcal vaccination (nor PCV13 neither PPsV23) against pneumonia among Catalonian adults in the current era of universal PCV's childhood immunisation.	

Evidence Table : **Effectiveness**
Question : **Is pneumococcal vaccination effective for the elderly?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
6. Jung SM, Lee H, Nishiura H. The impact of pneumococcal vaccination on pneumonia mortality among the elderly in Japan: a difference-in-difference study. PeerJ. 2018;6:e6085.	Quasi-experimental study **Aim:** To estimate the causal effect of this vaccination on pneumonia mortality, using the available cause-of-death data and employing a difference-in-difference (DID) design. **Methods:** -Study was conducted using publicly available datasets on the cause-of-death in Japan from 2003 to 2017 -mortality trends of only three major causes of death, namely, malignant neoplasm, heart disease, and pneumonia were analysed -Two types of mortality data, that is, prefecture-dependent and age- and gender-specific mortality data, from 2003 to 2017 were retrieved. We used mortality due to malignant neoplasm and heart disease as control groups and employed a DID design with an assumed	II-3	Mortality data from 2003-2017	Pneumococcal vaccination starts in 2014 PPV23 among elderly >65 years old	control disease selected either from malignant neoplasm or heart disease,		**Results:** -Estimation based on malignant neoplasm and heart disease as controls indicated that the reduced pneumonia mortality in 2017 owing to pneumococcal vaccination was as large as 41.9 (33.2, 50.6) and 31.2 (23.8, 38.6) per 100,000 individuals, respectively. -The largest mortality reduction was observed for the oldest group (aged >90 years), especially among men **Conclusion:** The pneumococcal vaccination program, perhaps mainly represented by high vaccination coverage of PCV13 among children and partly by PPV23 administration with low coverage among the elderly in Japan, was shown to have reduced the pneumonia mortality in the elderly at the population level.	

Evidence Table : Effectiveness
Question : Is pneumococcal vaccination effective for the elderly?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
6. Jung SM, Lee H, Nishiura H. The impact of pneumococcal vaccination on pneumonia mortality among the elderly in Japan: a difference-in-difference study. PeerJ. 2018;6:e6085.	parallel mortality trend between pneumonia and control group mortality since 2013 to estimate the causal effect of pneumococcal vaccination from 2014. - In 2013, pneumococcal conjugate vaccine 13 (PCV13) replaced PCV7, and the vaccination with PCV13 became a part of routine immunization program. Regardless of PCV7 or PCV13, the first, second and third doses were given at 2 months old, 4 months old, and 6 month old, respectively, with an optional supplementary dose at 12–15 months old.							

Evidence Table : Effectiveness
Question : Is pneumococcal vaccination effective for the elderly?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
7. 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):1496-1503.	Systematic review and meta-analysis **Aim:** To independently assess the efficacy of PPV-23 specifically, rather than all PPVs, in preventing CAP. **Methods:** -Systematic search was conducted in PUBMED, EMBASE, and Cochrane Library databases for randomized trials. -Overall relative risks (RRs) with 95% confidential intervals (CIs) were calculated, and the Cochrane Q test(p, I2) was performed. -Outcomes were assessed by the GRADE framework.	I	Seven randomized trials involving 156,010 participants were included in this meta-analysis.	PPV23 vaccination			**Results:** -High-quality evidence according to the GRADE framework revealed that PPV-23 administration was weakly associated with the prevention of all-cause pneumonia, especially among target adults, including those aged over 65 years and those aged 19–64 years at high risk of pneumonia, the elder group (>40 years) and Japanese individuals. -Analysis stratified for study population demonstrated that PPV-23 protected target adults, which included those aged over 65 years and those aged 19–64 years at high risk of pneumonia ([RR] 0.72, [95%CI] 0.69–0.94, p = 0.58, I2= 0%); however, it did not protect young healthy military trainees aged 17–20 years or individuals with a history of CAP history ([RR] 1.00, [95%CI]0.84–1.19, p = 0.36, I2= 0%). -An analysis stratified for population age revealed that PPV23 was effective in elderly individuals aged more than 40 years ([RR] 0.80, [95%CI] 0.69–0.94, p = 0.12, I2= 42%) but not in young individuals aged less than 20 years ([RR] 0.96, [95%CI]0.78–1.18). -Administration of PPV-23 in combination with IV had no additional protective effect over administration of PPV-23 alone([RR] 0.84, [95%CI] 0.64–1.10, p = 0.62, I2= 0%).	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
7. 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):1496-1503.							**Conclusion:** PPV-23 provided weak protection against all-cause pneumonia in an immunocompetent population, especially among the target population. The additional benefit of PPV-23 in preventing CAP further supports its application in the target population.	

Evidence Table : **Safety**
Question : **Is pneumococcal vaccination safe for the elderly?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Vadlamudi NK, Parhar K, Altre Malana KL et al. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine compared to 23-valent pneumococcal polysaccharide in immunocompetent adults: A systematic review and meta-analysis. Vaccine. 2019;37(8):1021-1029.	Systematic review and meta-analysis **Aim:** To perform a meta-analysis of head to-head randomized controlled trials evaluating the immunogenicity and safety of a single dose of PCV13 and PPV23, in immunocompetent adults in order to provide decision makers with details for future policy changes. **Methods:** -Systematic search was done for publications until January 2018 from PubMed, Embase, MEDLINE, and CENTRAL. -Inclusion criteria were (i) randomized control trial, (ii) adult population 18 years of age and over, (iii) a single dose of PCV13 compared with PPV23.	I	Five randomized trials were included with 4561 subjects ranging from 50–95.5 years, with 51% females. -Two studies were conducted in the United States, one was conducted in both the United States and Sweden, with another in South Africa, and Japan. -Of the five studies selected, four were randomized, modified double-blind experiments, whereas Jeurgens et al., was a randomized, open-label experiment	PPV23	PCV13		**Results:** -Overall, pooled risk ratios (RR) for local and systemic reactions did not differ between PCV13 and PPV23. -Pneumococcal naïve subjects experienced significantly higher local reactions in the PCV13 arm compared with the PPV23 arm (RR: 1.15, 95%CI: 1.05–1.26, p = 0.0025).	

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1. Vadlamudi NK, Parhar K, Altre Malana KL et al. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine compared to 23-valent pneumococcal polysaccharide in immunocompetent adults: A systematic review and meta-analysis. Vaccine. 2019;37(8):1021-1029.	-Randomized controlled trials evaluating immunogenicity of a single dose of PCV13 and PPV23 in adults by the opsonophagocytic assay (OPA) geometric mean titer (GMT) response at 1-month postvaccination were considered for inclusion. -Quality of each randomized control trial was assessed using Cochrane risk of bias tool							

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Tseng HF, Sy LS, Qian L et al. Pneumococcal Conjugate Vaccine Safety in Elderly Adults. Open Forum Infect Dis. 2018;5(6):ofy100	Retrospective cohort study **Aim:** To examine adults ≥65 years for risk of adverse events (AEs) requiring medical attention following vaccination with PCV13 as compared with vaccination with PPSV23 **Methods:** - The exposed person-time included follow-up time of the first PCV13 received by subjects age ≥65 years from January 1 to August 15, 2015. -The comparator person-time included follow-up time after the first PPSV23 received by subjects of the same age during Jan 1 to August 15 of each year of 2011–2015. -The prespecified AEs included cardiovascular events, Bell's palsy, Guillain-Barré syndrome, syncope, erythema multiforme, thrombocytopenia, cellulitis and infection, allergic reaction, and anaphylaxis.	II-2	A total of 313 136 doses of PCV13 and 232 591 doses of PPSV23 were included.	PCV13	PPV23	Follow-up time of the first PCV13 received by subjects age ≥65 years from January 1 to August 15, 2015	**Results:** -The adjusted RRs comparing the incidence of AEs following PCV13 vs PPSV23 were all <1, except for anaphylaxis, which was insignificant with an RR of 1.32 (95% confidence interval, 0.30–5.79). -Only 1 patient who received PCV13 and 4 other vaccines concomitantly was confirmed by medical chart review as having experienced anaphylaxis after vaccination.	

Evidence Table : **Safety**
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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Tseng HF, Sy LS, Qian L et al. Pneumococcal Conjugate Vaccine Safety in Elderly Adults. Open Forum Infect Dis. 2018;5(6):ofy100	-Inverse probability of treatment weighting–adjusted Poisson regression models was used to estimate the relative risk (RR) of each AE.							

Evidence Table : **Cost-effectiveness**
Question : **Is pneumococcal vaccination cost-effective for the elderly?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Wolff E, Storsaeter J, Örtqvist Å et al. Cost-effectiveness of pneumococcal vaccination for elderly in Sweden. Vaccine. 2020;38(32):4988-4995.	Cost-effectiveness study **Aim:** To assess cost-effectiveness of including pneumococcal vaccination for elderly in a national vaccination programme in Sweden, comparing health-effects and costs of pneumococcal related diseases with a vaccination programme versus no vaccination. **Methods:** -A single-cohort deterministic decision-tree model was used to simulate the current burden of pneumococcal disease in Sweden. -The model accounted for invasive pneumococcal disease (IPD) and pneumonia caused by pneumococci. -Costs included in the analysis were those incurred when treating pneumococcal disease, and acquisition and administration of the vaccine.			PPV23 vaccination	PCV13 vaccination		**Results:** -A vaccination programme using PPV23 would reduce the burden of pneumococcal related disease significantly, both when vaccinating a 65-year-old cohort and a 75-year-old cohort. -IPD would decrease by 30% in the 65-year-old cohort, and by 29% in the 75-year-old cohort. -The corresponding figures for CAP (communicable acquired pneumonia) are 19% and 15%. -The cost per gained QALY was estimated to EUR 94,000 for vaccinating 65-year-olds and EUR 29,500 for 75-year-olds. -With one dose PCV13 given instead of PPV23, the cost per gained QALY would increase by around 400% for both cohorts. The results were robust in sensitivity analyses **Conclusion:** Introducing a vaccination programme against pneumococcal disease for 65-year-olds in Sweden is unlikely to be cost-effective, whereas it for 75 year olds and using PPV23 can be considered good value for money. The model indicates that vaccine price needs to be reduced by 55% for vaccination of 65-year-olds to be cost-effective, given a threshold of EUR 50,000.	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Wolff E, Storsaeter J, Örtqvist Å et al. Cost-effectiveness of pneumococcal vaccination for elderly in Sweden. Vaccine. 2020;38(32):4988-4995.	-Health effects were measured as quality-adjusted life years (QALY). -The time-horizon was set to five years, both effects and costs were discounted by 3% annually. -Health-effects and costs were accumulated over the time-horizon and used to create an incremental cost-effectiveness ratio. -The 23-valent polysaccharide vaccine (PPV23) was used in the base-case analysis. -The 13-valent pneumococcal conjugate vaccine PCV13 was included in sensitivity analyses.							

Evidence Table : **Cost-effectiveness**
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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Wateska AR, Nowalk MP, Lin CJ et al. Pneumococcal Vaccination in Adults Aged ≥65 Years: Cost-Effectiveness and Health Impact in U.S. Populations. Am J Prev Med. 2020;58(4):487-495.	Cost-effectiveness analysis **Aim:** To estimate public health impact and cost-effectiveness of using both vaccines in all adults aged ≥65 years compared with an alternative strategy (omitting pneumococcal conjugate vaccine in the non-immunocompromised) and with the newly revised recommendation (giving or omitting conjugate vaccine based on patient−physician shared decision making). **Methods:** -Strategies were examined in hypothetical U.S. 65-year-old population cohorts and segmented into health states based on age- and population-specific data in a Markov state-transition model with a lifetime time horizon from a healthcare perspective.		1. No vaccination; 2. The prior CDC recommendation where all individuals aged ≥65 years receive PCV13 and PPSV23 1 year apart (both vaccines); 3. The recent ACIP recommendation, where all seniors receive PPSV23 and PCV13 is added for all immunocompromised patients and for non-immunocompromised patients based on shared decision making (current ACIP recommendation); and 4. All people aged ≥65 years receive PPSV23 and immunocompromised individuals receive both PCV13 and PPSV23 (alternative strategy).	Pneumococcal vaccination			**Results:** -Giving both vaccines, either routinely or with shared decision making, was most effective, reducing pneumococcal disease incidence compared with no vaccination, but costing $765,000−$2.18 million/quality-adjusted life year gained. -Depending on examined population and scenario, the alternative strategy cost $65,700−$226,700/quality-adjusted life year gained (less in black populations) and reduced cases and deaths by 0.3%−0.9%. **Conclusion:** A vaccination strategy that omits pneumococcal conjugate vaccine in immunocompetent U.S. seniors may be economically reasonable, particularly for black seniors. Use of both pneumococcal vaccines was more effective but substantially more expensive.	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Wateska AR, Nowalk MP, Lin CJ et al. Pneumococcal Vaccination in Adults Aged ≥65 Years: Cost-Effectiveness and Health Impact in U.S. Populations. Am J Prev Med. 2020;58(4):487-495.	-Black population cohorts were examined separately given greater illness risk and lower vaccine uptake. -Model parameters came from the Centers for Disease Control Active Core Bacterial Surveillance network, National Health Interview Survey, and Nationwide Inpatient Sample data. -Outcomes included incremental costs per quality-adjusted life year gained and pneumococcal disease outcomes for each strategy. -Data were gathered and analysis performed in 2018.							

Evidence Table : Cost-effectiveness
Question : Is pneumococcal vaccination cost-effective for the elderly?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Wateska AR, Nowalk MP, Lin CJ et al. Cost-Effectiveness of Pneumococcal Vaccination Policies and Uptake Programs in US Older Populations. J Am Geriatr Soc. 2020;68(6):1271-1278.	Cost-utility analysis **Aim:** To compare cost-effectiveness of revised vaccination recommendations for US adults, aged 65 years and older, include both 23-valent pneumococcal polysaccharide vaccine (PPSV23) and 13-valent pneumococcal conjugate vaccine (PCV13), with PCV13 now recommended for immunocompetent older people based on shared decision making. **Methods:** -Markov model was constructed -Public health impact and cost-effectiveness of the following pneumococcal vaccination strategies were estimated: (1) no vaccination; (2) all adults, aged 65 years or older, receive PPSV23, the		-All strategies were examined in hypothetical cohorts of US adults, aged 65 years or older. -Outcomes were estimated in both the black population and in the general population	Pneumococcal vaccination -Current pneumococcal vaccination recommendation for US older people,	Different strategies -alternative policy omitting PCV13 in immunocompetent older people, and vaccine uptake improvement programs.		**Results:** -The current pneumococcal vaccination recommendation was the most effective strategy, but afforded slight public health benefits compared to an alternative (PPSV23 for all older people plus PCV13 for the immunocompromised) and cost greater than $750 000 per quality adjusted life-year (QALY) gained in either population group with a vaccine uptake improvement program (absolute uptake increase = 12.3%; cost = $1.78/eligible patient) in place. -The alternative strategy was more economically favourable, but cost greater than $100 000/QALY in either population, with or without an uptake intervention. -Results were robust in sensitivity analyses; however, in black older people, the alternative strategy with an uptake program was most likely to be favoured in probabilistic sensitivity analyses at a $150 000/QALY gained threshold.	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Wateska AR, Nowalk MP, Lin CJ et al. Cost-Effectiveness of Pneumococcal Vaccination Policies and Uptake Programs in US Older Populations. J Am Geriatr Soc. 2020;68(6):1271-1278.	immunocompromised receive PCV13, with all others receiving PCV13 based on shared decision making (hereafter referred to as current recommendation); (3) the current recommendation strategy with an intervention program to increase vaccine uptake; (4) an alternative strategy, where all adults, aged 65 years and older, receive PPSV23 with the immunocompromised also receiving PCV13 (ie, no PCV13 for the immunocompetent, hereafter referred to as “alternative strategy”); and (5) the alternative strategy with an intervention program to improve vaccine uptake. - Model outputs include public health outcomes (case frequency and mortality for invasive pneumococcal disease [IPD] and nonbacteremic pneumococcal pneumonia						**Conclusion:** Current pneumococcal vaccination recommendations for US older people are economically unfavourable compared to an alternative strategy omitting PCV13 in the immunocompetent. The alternative recommendation with an uptake improvement program may be economically reasonable in black population analyses and could be worth considering as a population-wide recommendation if mitigating racial disparities is a priority.	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Wateska AR, Nowalk MP, Lin CJ et al. Cost-Effectiveness of Pneumococcal Vaccination Policies and Uptake Programs in US Older Populations. J Am Geriatr Soc. 2020;68(6):1271-1278.	[NBP]) and cost-effectiveness analysis results. - All IPD cases were assumed to be hospitalized, while NBP cases could be either inpatient or outpatient, based on assumptions described below. -Cost-effectiveness analysis results are expressed as the incremental cost-effectiveness ratio (ICER) (ie, a cost per quality-adjusted life-year [QALY] gained). -Costs were adjusted to 2014 US dollars, using the US Consumer Price Index. -The analysis took a healthcare perspective, with future costs and effectiveness discounted by 3% over a lifetime horizon.							

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Nishikawa AM, Sartori AMC, Mainardi GM et al. Systematic review of economic evaluations of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in individuals 60 years of age or older. Vaccine. 2018;36(19): 2510-2522.	Systematic Review **Aim:** To systematically review the published economic evaluations of PPV23 in adults aged >60 years to inform the development of local studies through the discussion of parameters and assumptions that influence the results of the analyses. **Methods:** MEDLINE, Excerpta Medica, Cochrane Library, Latin-American and Caribbean Health Sciences Literature (LILACS), Brazilian Regional Library of Medicine, National Health Service Economic Evaluation, and Centre for Reviews and Dissemination—as well as the Scopus citation index and the Web of Science for full economic evaluations of PPV23 published up to March 2016.	I	-Twenty-seven studies published from 1980 to 2016 were reviewed. -Most studies were conducted in Europe and the USA; three studies were conducted in Latin America (Brazil, 2; Colombia, 1). -In addition to the scenario comparing the vaccination with the PPV23 to non-vaccination, three studies also compared PPV23 to pneumococcal conjugate 13-valent vaccine (PCV13). -All studies used static models. -Most used a lifetime (44.4%) or 5–6 year's time horizon (33.3%).	PPV23 vaccination	-No vaccination -PCV13 vaccination		**Results:** -Most studies considered PPV23 cost effective (less than US$50,000 per LYG or QALY) and sometimes cost-saving (results ranging from cost saving to US$84,636/QALY). -The estimates of disease burden, the efficacy/effectiveness of PPV23, and the effects of herd protection from childhood immunization had most influence on the results. **Conclusion:** Well-designed cost-effectiveness studies of PPV23 that represent the current epidemiological scenario and reduce uncertainty related to efficacy/effectiveness are extremely relevant to informing the decision-making process.	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Nishikawa AM, Sartori AMC, Mainardi GM et al. Systematic review of economic evaluations of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in individuals 60 years of age or older. Vaccine. 2018;36(19): 2510-2522.	-Two independent reviewers screened the articles for relevance and extracted the data. -Main study characteristics and methods (clinical and epidemiological data, cost and incremental cost-effectiveness ratios (ICERs) were extracted and compared. -Costs were updated to 2016 international dollars.		-Only three studies considered herd protection from children immunization with PCV13 in the model.					

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Thorrington D, van Rossum L, Knol M et al. Impact and cost-effectiveness of different vaccination strategies to reduce the burden of pneumococcal disease among elderly in the Netherlands. PLoS One. 2018;13(2):e0192640.	Cost-effectiveness analysis **Aim:** To estimate the potential impact of vaccinating different cohorts in terms of health-related quality of life and the economic burden caused by both IPD and hospitalised CAP from a health care provider's perspective. **Methods:** -A static cost-effectiveness model quantifying the impact of different vaccination strategies from a health care provider's perspective was parameterized using surveillance data, literature values and expert opinion in case no consistent information was available. -The different strategies were evaluated using vaccine list prices and a 10-year time horizon.		Elderly aged 60, 65 or 70	Vaccination with 23-valent pneumococcal polysaccharide vaccine (PPV23) or 13-valent PCV (PCV13) among all those aged 60, 65 or 70 and/or in combination with replacing PCV10 with PCV13 in the infant vaccination programme.	Different strategies		**Resuts:** -Compared to the reference, the largest impact on pneumococcal disease burden was projected with a combined use of PCV13 among infants and PPV23 at 60, 65 and 70 years, preventing 1,635 cases of IPD and 914 cases of CAP. -The most cost-effective strategy was vaccinating with PPV23 at 70 years only with similar low ICERs at age 60 and 65. -The impact of the use of PCV13 among infants depends strongly on the projected herd-immunity effect on serotype 19A. -Vaccinating elderly with either PCV13 or PPV23 was dominated by PPV23 in all investigated scenarios, mainly due to the lower price of PPV23. **Conclusion:** Under the current assumptions, the best value for money is the use of PPV23 for elderly, with a single dose or at five-year increment between age 60 to age 70.	

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5. Thorrington D, van Rossum L, Knol M et al. Impact and cost-effectiveness of different vaccination strategies to reduce the burden of pneumococcal disease among elderly in the Netherlands. PLoS One. 2018;13(2):e0192640.	-Incremental cost-effectiveness ratios (ICER) were calculated with the current strategy (infant vaccination program with PCV10) as reference. - The future costs and QALYs were discounted using a discount rate of 4.0% for costs and 1.5% for health benefits according to national guidelines							

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Question : Is pneumococcal vaccination cost-effective for the elderly?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
6. Chen C, Beutels P, Wood J et al. Retrospective cost-effectiveness of the 23-valent pneumococcal polysaccharide vaccination program in Australia. Vaccine. 2018;36(42): 6307-6313.	Cost-utility analysis **Aim:** To evaluates the cost-effectiveness of the PPV23 programme in older adults in Australia from 2005 to 2015 with a focus on how the value for money may have changed over time as a result of herd protection effects from infant PCV7 and PCV13 programmes. **Methods:** -A multi-cohort Markov model with a cycle length of one year was developed to retrospectively evaluate the cost-effectiveness of the PPV23 immunisation program from 2005 to 2015. -The analysis was performed from the healthcare system perspective with costs and quality-adjusted life years discounted at 5% annually.		In older adults in Australia from 2005 to 2015	PPV23 vaccination programme	Herd protection effects from infant PCV7 and PCV13 programme		**Results:** -It was estimated that PPV23 doses given out over the 11-year period from 2005 to 2015 prevented 771 hospitalisations and 99 deaths from invasive pneumococcal disease (IPD). -However, the estimated IPD cases and deaths prevented by PPV23 declined by more than 50% over this period (e.g. from 12.9 deaths for doses given out in 2005 to 6.1 in 2015), likely driven by herd effects from infant PCV programs. -The estimated ICER over the period 2005 to 2015 was approximately A$224,000/QALY gained compared to no vaccination. -When examined per year, the ICER for each individual year worsened from $140,000/QALY in 2005 to $238,000/QALY in 2011 to $286,000/QALY in 2015. **Conclusion:** The cost-effectiveness of the PPV23 program in older Australians was estimated to have worsened over time. It is unlikely to have been cost-effective, unless PPV23 provided protection against non-invasive pneumococcal pneumonia and/or a low vaccine price was negotiated. A key policy priority should be to review of the future use of PPV23 in Australia, which is likely to be more cost-effective in certain high-risk	

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6. Chen C, Beutels P, Wood J et al. Retrospective cost-effectiveness of the 23-valent pneumococcal polysaccharide vaccination program in Australia. Vaccine. 2018;36(42): 6307-6313.	-The incremental cost-effectiveness ratio (ICER) for PPV23 doses provided from 2005 to 2015 was calculated separately for each year when compared to no vaccination. -Parameter uncertainty was explored using deterministic and probabilistic sensitivity analysis.						groups.	

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7.Heo JY, Seo YB, Choi WS et al. Cost-effectiveness of pneumococcal vaccination strategies for the elderly in Korea. PLoS One. 2017;12(5):e0177342.	Cost-utility analysis **Aim:** To evaluate the cost-effectiveness of the current vaccination strategy (a single-dose PPSV23 vaccination) compared to a single dose PCV13 vaccination and sequential PCV13-PPSV23 vaccinations in the elderly population aged ≥ 65 years. **Methods:** -Using a Markov model, the incremental cost-effectiveness ratios (ICERs) of three vaccination strategies: (1) PPSV23 vaccination only, (2) PCV13 vaccination only, and (3) sequential PCV13-PPSV23 vaccination. were assessed in a societal context. -The transition probabilities, utility weights to estimate quality adjusted life year (QALY),		Elderly population aged >65years	PPSV23 vaccination	PCV13 and sequential PCV13-PPSV23 vaccination		**Results:** -Current PPSV23 vaccination strategies were cost-effective (ICER, $25,786 per QALY). -Both PPV23 and PCV13 vaccination strategies in comparison with no vaccination were cost-effective with ICERs less than $38,000/QALY. -Compared to no vaccination, the estimated ICERs of current PPSV23 vaccination strategy were $25,786 per QALY with a targeted vaccine uptake rate of 60% and $17,354 per QALY with a targeted vaccine uptake rate of 80%. -The ICER was most sensitive to the incidence of NBPP and vaccine effectiveness against NBPP	

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7.Heo JY, Seo YB, Choi WS et al. Cost-effectiveness of pneumococcal vaccination strategies for the elderly in Korea. PLoS One. 2017;12(5):e0177342.	and disease treatment costs were either calculated or cited from published data and the Health Insurance Review and Assessment Service. -Simulations were performed in hypothetical cohorts of Korean adults aged >19 years. -The vaccine effectiveness of PPSV23 was cited from a Cochrane Review report, while PCV13 effectiveness data were gathered from the CAPiTA trial.							

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