HEALTH-ECORE

Systematic literature review to identify vaccinations for chronic respiratory diseases (CRDs)

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Executive summary

Individuals with chronic respiratory diseases (CRDs) are at a higher risk of developing respiratory infections. This systematic literature review aimed to identify the relevant evidence regarding the use of pneumococcal, respiratory syncytial virus (RSV), *Haemophilus influenzae*, pertussis and group B streptococcus (GBS) vaccines in patients with CRDs. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to determine the certainty of evidence.

A total of 4,356 articles were screened by title and abstract, with 32 articles ultimately included for data extraction. The majority of these were observational studies (n=25), followed by randomized control trials (n=6), and one cost-effectiveness study. Of the 32 articles, 31 focused on the pneumococcal vaccine (PV), while one article studied non-typeable *Haemophilus influenzae* (NTHi) vaccine. The pneumococcal polysaccharide 23-valent vaccine (PPV23) was the most studied among pneumococcal vaccines. A variety of interventions were identified, including comparing PPV23 with no vaccine, pneumococcal conjugate vaccines (PCV7 or PCV13) versus no vaccine, comparing between PPV23 and PCV7 or PCV13, and PV in combination with influenza vaccine (IV).

The studies reported a broad range of outcomes, such as mortality, hospitalization and pneumonia, with varying effects of PV, ranging from protective to increasing the risk. The certainty of evidence for each outcome was generally low or very low, primarily due to large confidence interval across different studies. However, some conclusions can be drawn with low degree of certainty:

1. Vaccination with pneumococcal vaccine may reduce the hospitalization and exacerbation rate. While the impact of PPV23 reduces after one year, PCV13 had a more persistent effect beyond one year.
2. Generally, the studies reported a non-significant to no effect of pneumococcal vaccine (any type) on all-cause mortality.
3. Combination of PV and IV improved the protective effect on hospitalization and exacerbation compared to IV alone or placebo.

1 Introduction

The diseases related to airways and other structures of the lung are categorized as chronic respiratory diseases (CRDs) (1). Asthma and chronic obstructive pulmonary disease (COPD) are the most common forms of CRDs (2). Other conditions within this category include for example bronchiectasis, interstitial lung disease (ILD), and pulmonary sarcoidosis (2). CRDs were the third leading cause of death in the Netherlands, accounting for 7% of all fatalities (3). Respiratory infections, including pneumococcus, RSV and pertussis, contribute significantly to the exacerbation of CRDs, and conversely, CRDs increases the risk of such infections (4). Lung disease is also associated with group B streptococcus (GBS) (5). *Haemophilus influenzae* is an important contributor to lower respiratory tract infections, which can lead to COPD exacerbations (6).

1.1 Main disease areas

1.1.1 Pneumococcal disease

Pneumonia is a major contributor to morbidity, mortality and healthcare costs worldwide (7). It is responsible for the majority of deaths related to lower respiratory infections, accounting for 55.4% of such deaths globally in 2015 (8). *Streptococcus pneumoniae* is the main bacterial cause of community-acquired pneumonia (CAP) (7). Individuals with underlying chronic conditions are at a higher risk of developing invasive pneumococcal diseases (IPD) – culture of *Streptococcus pneumoniae* from normal sterile site, i.e. pneumococcal bacteremia – compared to healthy individuals (9). IPD is a leading cause of death and morbidity in adults under 65 years old who have chronic or immunocompromising conditions (10). The relative risk of IPD is estimated to be 2.1 for individuals with COPD and 1.8 for those with asthma, compared to healthy individuals (11). The incidence of pneumococcal pneumonia has been estimated to be 535 per 100,000 persons in the Netherlands among general population older than 50 years old (12).

1.1.2 RSV

RSV is a key cause of illness among adults (13). It is estimated that 158,229 RSV-related hospitalizations occur annually among adults in the European Union (14). In the Netherlands, the annual RSV-related hospitalizations were estimated to be 3,896, with 89% of these cases involving individuals aged 65 and older (14). A meta-analysis found that comorbidities, including COPD and asthma, can increase the likelihood of RSV-related acute respiratory infection by up to 4.1 times (15). A recent study in Denmark and Scotland showed that adults with COPD, ischemic heart disease, stroke or diabetes have a 2 to 4 times higher risk of RSV-related hospitalization, while those with asthma face a 1.5 to 3 times higher risk (16).

1.1.3 Pertussis

Pertussis is a highly contagious respiratory disease, and the immunity reduces 4 to 12 years after vaccination (17). A retrospective study in the United States showed that between 2007 and 2019, adults with COPD and asthma had a higher risk of pertussis compared to general population, with rate ratios of 1.83 and ≥ 2.79, respectively (18). Likewise, a study in Australia among individuals aged 50 or older showed that individuals with COPD or asthma had a higher risk of pertussis, with odds ratios of 2.01 and 2.46, respectively (19).

1.1.4 Haemophilus influenzae

There are two types of *Haemophilus influenzae*; typable and non-typeable strains (20). Serotype b (Hib) is the most prominent typeable *Haemophilus influenzae* (20). In the Netherlands, the incidence of invasive Hib was lower than 0.5 cases per 100,00 persons among individuals older than 20 years old, the incidence of invasive NTHi was 0.75 and 3.0 cases per 100,000 persons among adults aged 20 to 64 and 65 years or older in 2022, respectively (21). Between 13 to 50% of COPD exacerbations are caused by *Haemophlilus influenzae* (22).

1.1.5 Group B streptococcus

Pneumonia and empyema are among the clinical presentation of invasive GBS (23). A systematic review and meta-analysis estimated that the pooled incidence of invasive GBS among individuals older than 15 years old is 2.86 per 100,000 individuals. However, the incidence is higher among older adults with 9.13 and 19.4 cases per 100,000 persons among individuals ≥ 50 and ≥ 65 years old, respectively (23). Lung disease is among the comorbidities that is associated with invasive GBS (5).

Individuals with COPD who experience CAP usually undergo a sudden and persistent decline in health-related quality of life (24). CAP can lead to an acute exacerbation in individuals with COPD (24), which have a considerable impact on the quality of life (25). Respiratory infections increase the risk of cardiac events and a COPD exacerbation, particularly when caused by an infection, may also be linked to a higher risk of cardiac complications (26). Pneumonia caused by any pathogen and/ or exacerbation of CRD is associated with loss of quality of life and increased morbidity.

1.2 Objectives of current study

One of the most effective methods to prevent diseases is vaccination (27). In the Netherlands, the annual influenza vaccine is estimated to have prevented 13% of infections, 24% of hospitalizations and 35% of deaths between 2003 and 2015 (28). A systematic review and meta-analysis by Ferrar et al. 2023 showed that 23-valent pneumococcal polysaccharide vaccines (PPV23) and 13-valent pneumococcal conjugate

vaccine (PCV13) provide protection against vaccine type IPD and pneumococcal pneumonia among adults aged 16 or older (29).

Currently, the influenza and COVID-19 vaccines are recommended for CRDs in the Netherlands (30,31). Additionally, the pneumococcal vaccine is advised and reimbursed for medical risk groups, including CRDs (32,33).

Recent studies have highlighted the importance of vaccination in individuals with CRDs. For instance, a recent published review advocates several vaccines for individuals with COPD, including those for influenza, SARS-CoV-2, pneumococcus, pertussis, RSV, and varicella-zoster virus (27).

Given the continuous development and availability of new vaccines tailored to CRDs, there is a need for updated recommendations based on the state-of-the-art scientific literature. These recommendations can support optimizing vaccination strategies and enhancing the protection of vulnerable populations against respiratory infections.

The objectives of this systematic literature review were as follows:

1. Identifying the scientific evidence related to vaccines targeted at CRD patients.
2. Assessing the quality of the evidence related to vaccines for the CRD population.

2 Methods

This systematic literature review was performed in accordance with PRISMA 2020 statement reporting guideline (34).

2.1 Eligibility criteria

2.1.1 Population

CRD is a broad term referring to various lung diseases. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) is a comprehensive study to quantify levels and trends in health (35). The GBD study includes 369 diseases and injuries, including CRDs (2). In that study, CRDs were defined based on the International Classification of Diseases (ICD)-9 and ICD-10 codes. We mapped the ICD-10 codes into ICD-11 codes. We consulted experts to include other relevant ICD-11 codes and exclude the population not relevant for this research, mainly acute respiratory diseases. Asthma, COPD and ILD are the main included categories of CRDs (2). Table S1 in the Supplementary Materials shows a complete overview of the included and excluded CRDs. In addition, patients with lung cancer were included after a meeting with the LAN working group.

2.1.2 Interventions (vaccines)

To identify the relevant vaccines, three steps were taken as follows:

1- Identifying the vaccinations in Dutch and international guidelines.
2- Identifying additional potentially relevant vaccines by consulting major vaccine manufacturers.
3- Consulting experts to include the relevant vaccines.

The following vaccines were selected as interventions following a consensus meeting of the LAN working group:

- Pneumococcal vaccine
- Respiratory syncytial virus (RSV) vaccine
- *Haemophilus influenzae* vaccine
- Pertussis vaccine (including Tdap [Tetanus, Diphtheria, Pertussis])
- Group B streptococcus (GBS) vaccine

The influenza and COVID-19 vaccines have already been implemented for CRDs in the Netherlands (30,31), and there currently is a positive advice from the Dutch Health Council (*Gezondheidsraad*) to implement the herpes zoster vaccine for elderly aged 60 and over (36). As a result, the influenza, COVID-19 and herpes zoster vaccines were excluded from this review. The list of included and excluded vaccines are presented in Table S2 in Supplementary Material.

2.1.3 Comparators

The main comparator was no vaccine or placebo or studies comparing different vaccines.

2.1.4 Outcomes

A broad range of outcomes was included. The outcomes of interest included hospitalization (all-cause, due to disease, and pneumonia), mortality (all-cause and due to disease), early and late exacerbation, primary care visits, outpatient pneumonia, laboratory-confirmed cases, and unplanned visits (including emergency visits). Due to disease in this context means that the event can be related to the vaccine, e.g., an RSV-related hospitalization in case of a study about the RSV vaccine.

2.1.5 Type of studies, language and study period

The following study types were included in this review: observational studies (prospective or retrospective, before-after), randomized control trials (RCTs), cohort studies, cross-sectional studies, case-control studies, registry studies, hospital records analysis and cost-effectiveness/benefit/modelling studies. The language was restricted to English or Dutch. We included the studies published in 2000 or afterward. However, the evidence for pertussis vaccine was deemed insufficient during a meeting with the LAN working group, thus the inclusion for pertussis vaccine was expanded to 1970 and later.

2.1.6 Exclusion criteria

The studies that did not include a vaccine were excluded. In addition, phase I or II studies were not included. The complete list of exclusion criteria has been presented in Table S3 in Supplementary Material.

2.2 Electronic sources

We searched PubMed, Embase and Web of Science.

2.2.1 Search strategy (search terms)

Broad search terms were applied to identify the relevant articles. In the first step, various search terms were used based on different types of CRDs. Then, the terms for the vaccines were included. Finally, we restricted the search to human studies, the desired types of studies and search date (after 2000, and 1970 for pertussis vaccine).

2.3 Study records

The PITTS online platform for systematic literature reviews (37) was used to detect duplicates. After removing duplications, the study selection process started.

The study selection process consisted of two steps. In the first step, titles and abstracts were screened which were performed independently by two reviewers (SE and BS). The disagreements were discussed among reviewers to reach a consensus. Any unresolved disagreements were discussed with the third independent reviewer (SvdP). The second step was full-text screening which was performed for the selected articles in the first step. The selection process for full-text screening was the same as the process of title and abstracts screening. The reason for exclusion was documented in the full-text screening step.

Using the PITTS application, the following data were extracted:

- Main details
    - Title
    - Authors
    - Year of publication
    - Journal
    - Funding source
    - Conflicts of interest
- Design
    - Study objectives
    - Study country/countries
    - Period of conducting the study
    - Study design
    - Interventions and comparators
    - Study population
    - Included subgroups
- Results
    - Population characteristics (age, sex, body mass index, smoking status, comorbidities and sample size)
    - Outcomes (see table S3 for complete list), if relevant for the various subgroups
    - Follow-up duration

Data extraction was conducted by two reviewers (SE and BS). Prior to performing data extraction, ten articles were selected randomly and the two reviewers independently performed data extraction in duplicate. Any disagreements were discussed for these ten articles to prevent further disagreement on the rest of included articles. Subsequently, the data extraction for all included articles was carried out, with each reviewer responsible for extracting data from 50% of the included articles. To ensure

consistency, 10% of the articles were randomly selected to assess the discrepancies among two reviewers. If serious discrepancies emerge, such as differing values for reported outcomes, each reviewer cross-checked the data extraction performed by other reviewer.

2.3.1 Considerations for pneumococcal vaccines

PCV7 was introduced in 2001 (38) and was recommended for children (39). PCV10 and PCV13 were introduced in 2009 (40). PCV10 was recommended only in children while PCV13 was recommended for all ages from six weeks old (41). Therefore, if articles did not report the specific type of pneumococcal vaccine, it was assumed the vaccine was PPV23 if the following conditions were met:

1. The study period started in 2011 or earlier.
2. The study design was observational and the recommended pneumococcal vaccination was PPV23 in the country of the study.

2.4 Risk of bias (quality) assessment

For RCT studies, we used the Cochrane Risk of Bias-2 tool (42). For non-RCT studies, we used the checklists developed by National Heart, Lung and Blood Institute (43). The appropriate checklist was applied depending on the type of study (e.g. observational studies, case-control studies). In addition, we followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence (44). The summary of finding (SoF) were created for all outcomes with four level of certainty (high, moderate, low and very low).

2.5 Data synthesis

We qualitatively synthesized the extracted data. We presented the evidence of vaccinations based on ICD-11 codes.

3 Results

3.1 Prisma diagram

Figure 1 shows the PRISMA diagram. After removing the duplications, and title and abstract screening, 462 articles were selected for full-text screening. The main reasons for excluding the articles were as follow: disease burden studies (n = 85), not reporting specific results for the interested population (n = 84) and review articles (n = 80). Thirty-two articles were included for data extraction.

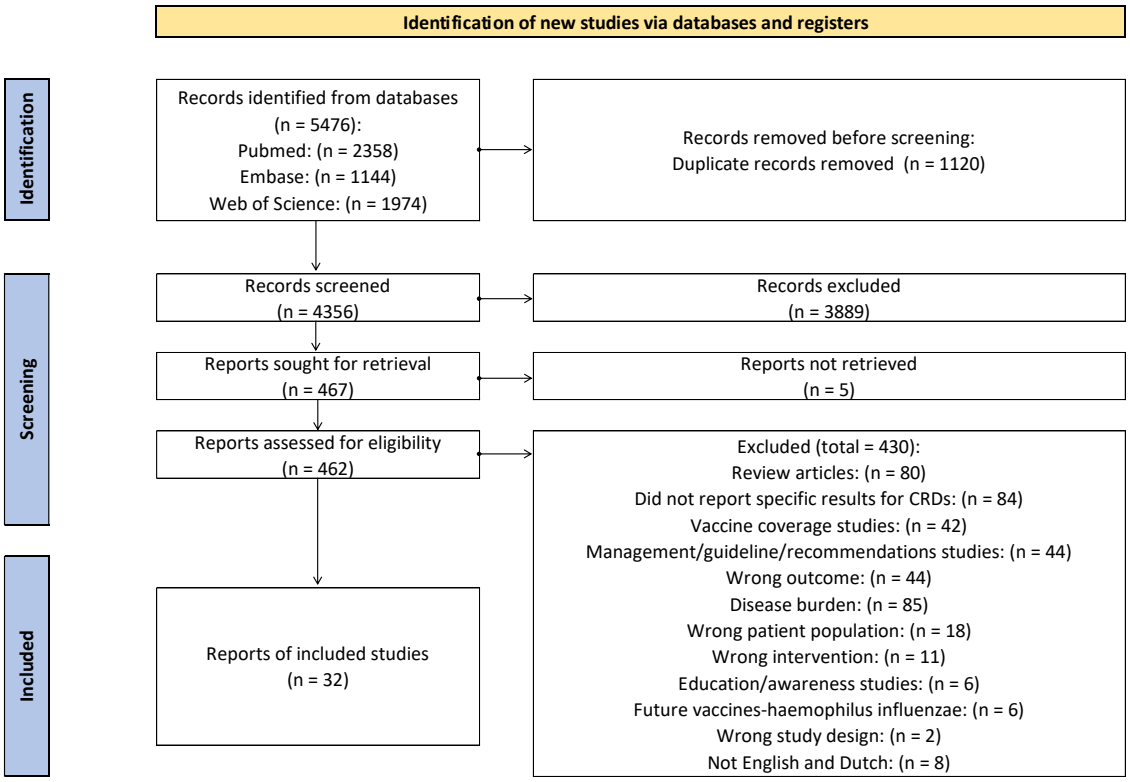

Figure 1: PRISMA flow diagram
CRDs: chronic respiratory diseases

3.2 Study characteristics, such as baseline characteristics

Table 1 shows the baseline characteristics of the included articles. Pneumococcal vaccine was the intervention in all studies except for one study which was non-typeable *Haemophilus influenzae* (NTHi).

3.3 Pneumococcal vaccines

Among the different types of pneumococcal vaccines, PPV23 was the vaccine that studied more than other pneumococcal vaccines, followed by PCV13. In four studies the

type of pneumococcal vaccine was not mentioned. The outcomes are shown in Table 2 to Table 6 based on the type of pneumococcal vaccine and the comparator.

Table 2 shows the main outcomes of comparing PPV23 to placebo (16 studies). In the studies by Schembri, 2009 (45) (in the UK, the recommended PV was PPV23 during the study period (46)), Zichen Ji, 2020 (in the Spain, the recommended PV was PPV23 during the study period (47)) (48) and Lee, 2007 (49) (in the US, the recommended PV was PPV23 during the study period (50)) the type of pneumococcal vaccine was not specified. We assumed the vaccine was PPV23 as the study period started on 2011 or earlier. The study by Alfageme et al. 2006 (51) was the only RCT study (with low risk of bias) and the rest were observational studies with poor to fair overall quality. The studies reported various outcomes such as all-cause mortality, hospitalization and exacerbation. Two studies with lung cancer population reported a protective impact of PPV23 on all-cause mortality. For the COPD, asthma and CRD populations, the reported protective impact of PPV23 differed by study.

Table 3 shows the main outcomes of comparing PCV13 to placebo (5 studies). The population of these studies was COPD. These studies reported a protective effect of PCV13 on hospitalization and exacerbation, though in some studies it was not statistically significant. The impact of PCV13 on mortality was not significant. It should be noted that two studies (Figueira-Gonçalves et al. 2017 (52) and Figueira-Gonçalves et al. 2020 (53)) had the same population. The latter study explored the impact of diabetes in the COPD population, therefore, we did not present the outcomes of the latter study.

Four studies compared an undefined pneumococcal vaccine with placebo. In these studies, the type of pneumococcal vaccine has not been mentioned. Table 4 shows the main outcomes of those studies. Most of the studies reported a protective impact of pneumococcal vaccine on hospitalization or exacerbation in COPD and bronchiectasis population. However, the impact of pneumococcal vaccine on mortality was less certain. The study by Lee et al. 2007 (49) reported that the impact of pneumococcal vaccine for asthma patients was uncertain.

Table 5 shows the studies comparing PPV23 and PCV13 or PCV7. The study by Ignatova et al. 2021 (54) showed that after five years, individuals with COPD who received PCV13 had a much lower hospitalization rate (due to pneumonia or due to COPD exacerbation) compared to PPV23 group. Dransfield et al. 2012 (55) performed an RCT to compare PPV23 with PCV7. Individuals in PCV7 group had a lower all-cause mortality and exacerbation rate than PPV23, although the results were not significant. Rodríguez González-Moro et al. 2016 (56) performed a cost-effectiveness study to compare PPV23 and PCV13 in COPD patients $\geq$ 50 years old over a lifetime horizon. PCV 13 led to 3.8% and 2.17% less invasive pneumococcal disease and disease-related mortality compared to PPV23.

Table 6 shows the outcomes for comparing pneumococcal vaccine plus influenza vaccine (IV) versus IV and PV + IV versus placebo. Overall these studies demonstrated an additional benefit of PV to IV compared to IV alone or placebo.

3.4 NTHi vaccine

Only one study was included to assess NTHi vaccine compared to placebo in a COPD population (Table 7). That study reported no protective effect of NTHi in the total study population, however in the individual younger than 65 years the rate of exacerbation was lower. We excluded the study by Teo et al. 2017 (57), since it was a systematic review (please see section 3.9 and Table S18).

Table 1: Baseline characteristics of the included studies

Author, year	Population	Inclusion and exclusion criteria	Arm name	Sample size	Age (mean or median)	Gender (%.male)	BMI	Current smoker (%)	Former Smoker (%)	Follow-up duration (months)
Rosario Menéndez, 2017[1] (58)	bronchiectasis	*Inclusion*: Adult bronchiectasis patients with chronic sputum production and/or frequent respiratory infections with CT scan *Exclusion*: Severe immunosuppression Active tuberculosis Cystic fibrosis Pulmonary interstitial disease	PCV13 and PPV23	123	70.0	40.0%	NR	47.0%	NR	12
			Placebo	142	70.0	40.0%	NR	47.0%	NR	
Alessandra M Lanz, 2022 (59)	Asthma	*Inclusion*: History of cough-variant asthma and ≥2 exacerbations needing systemic steroids or antibiotics in the past year. *Exclusion*: Uncontrolled gastroesophageal reflux disease, smoking history, ACE-inhibitor use, or chronic peripheral edema.	PPV23	65	NR	NR	NR	NR	NR	12
			Placebo	65	NR	NR	NR	NR	NR	

Olga Ochoa-Gondar, 2008 (60)	CRD (chronic bronchitis, emphysema and asthma)	*Inclusion*: Individuals aged 65 years with chronic bronchitis, emphysema and asthma *Exclusion*: NR	PPV23	886	76.5	73.0%	NR	15.7%	NR	40
			Placebo	412	74.2	75.0%	NR	23.5%	NR	
Sumitani, 2008 (61)	CRD (COPD, bronchial asthma, bronchiectasis)	*Inclusion*: Patients with chronic respiratory disease who were on regular ambulatory treatment *Exclusion*: NR	PPV23 + IV	105	74.0	60.0%	NR	34.3%	31.4%	24
			IV	105	74.0	60.0%	NR	34.3%	31.4%	
Angel Vila-Corcoles, 2012[1] (62)	CRD (chronic bronchitis, emphysema and/or asthma)	*Inclusion:* Chronic pulmonary disease Patients aged 50+ with pneumococcal pneumonia. *Exclusion:* Immunodeficiency (including AIDS), asplenia, cancer (solid or hematological), chronic nephropathy (e.g., renal failure, dialysis), or long-term corticosteroid therapy (≥20 mg/day prednisone or equivalent).	PPV23	176	73.0	83.3%	NR	28.1%	NR	64
			Placebo	112	73.0	83.3%	NR	28.1%	NR	
Kwok WC, 2024 (63)	CRD (asthma, bronchiectasis, COPD)	*Inclusion:* Adults (18+) with asthma, bronchiectasis, or COPD, previously vaccinated	PPSV23	133	75.1	77.4%	NR	NR	NR	NR

		against seasonal influenza, and hospitalized with laboratory-confirmed influenza. *Exclusion:* Patients with viral co-infection	PCV13	1091	78.0	72.5%	NR	NR	NR	
			Both PPSV23/PCV13	321	72.4	77.9%	NR	NR	NR	
			Placebo	1521	75.7	66.3%	NR	NR	NR	
Rosalyn J Singleton, 2007[1,2] (64)	CRD (COPD, bronchiectasis, or pulmonary fibrosis [not asthma])	*Inclusion:* Cases of IPD occurring in Alaska Native adults aged 20 years and older during 1986–2000 *Exclusion:* NR	PPV23	36	45.0	55.1%	NR	60.8%	NR	180
			Placebo	47	45.0	55.1%	NR	60.8%	NR	
Satoshi Inoue, 2011 (65)	CRD (Bronchial asthma, chronic pulmonary emphysema, old tuberculosis, chronic bronchitis)	*Inclusion:* outpatients ≥ 60 years of age with chronic pulmonary disease (bronchial asthma, chronic pulmonary emphysema, old tuberculosis, chronic bronchitis, bronchiectasis, non-tuberculous mycobacteria) *Exclusion:* Patients who presented with a fever (≥37.5°C)	PPV23	646	NR	NR	NR	NR	NR	24
			Placebo	728	NR	NR	NR	NR	NR	

Alfageme, 2006 (51)	COPD	*Inclusion:* A spirometric diagnosis of COPD *Exclusion:* Patients who were pregnant, were immunosuppressed, or had known neoplasia, renal insufficiency in dialysis, HIV infection, hypogammaglobulinaemia, or anatomical or functional asplenia.	PPV23	298	69.0	96.6%	NR	22.0%	NR	32.4
			Placebo	298	68.0	93.3%	NR	26.0%	NR	
R L Clancy, 2016 (66)	COPD	*Inclusion:* Ages 40–85, with moderate–severe COPD (post-bronchodilator FEV1 <60% predicted and FEV1/FVC <0.7) and at least one moderate–severe exacerbation in the past 12 months. *Exclusion:* Post/planned lung surgery, corticosteroids in excess of 10 mg/day, antibiotics within 4 weeks of study onset, other concomitant lung disease, new/altered therapy within 4 weeks of study, pregnancy and other significant medical	NTHi	160	71.2	66.9%	25.3	11.6%	85.5%	9
			Placebo	160	67.9	58.1%	26.7	19.6%	79.2%	

		disease as determined by each site's clinician.								
Dransfield, 2012 (55)	COPD	*Inclusion:* Men and women over 40 with a 10+ pack-year smoking history and moderate to very severe COPD (post-bronchodilator FEV1/FVC <70% and FEV1 <70% predicted). *Exclusion:* Asthma diagnosis, use of immunosuppressants (except corticosteroids), conditions affecting pneumococcal vaccine response, or recent illness requiring antibiotics or systemic steroids within the past month.	PCV7	91	63.0	65.0%	NR	36.0%	NR	24
			PPV23	90	64.0	58.0%	NR	36.0%	NR	
Figueira-Gonçalves[1], 2020 (53)	COPD	*Inclusion:* COPD patients aged over 40, active or former smoker with a 10+ pack-year history or prolonged exposure to harmful agents; post-bronchodilator FEV1/FVC <70% and FEV1 ≤65% predicted. *Exclusion:* Exacerbations that were identified as community	PCV13	44	72.0	86.8%	28.3	21.5%	76.9%	18
			No vaccination	77	72.0	86.8%	28.3	21.5%	76.9%	

		acquired pneumonia were excluded								
Figueira-Gonçalves, 2017[1] (52)	COPD	*Inclusion:* COPD patients aged over 40, active or former smoker with a 10+ pack-year history or prolonged exposure to harmful agents; post-bronchodilator FEV1/FVC <70% and FEV1 ≤65% predicted. *Exclusion:* Exacerbations that were identified as community acquired pneumonia were excluded	PCV13	44	72.0	86.8%	28.3	21.5%	76.9%	18
			No vaccination	77	72.0	86.8%	28.3	21.5%	76.9%	
Akitsugu Furumoto, 2008 (67)	COPD	*Inclusion:* Patients aged 40–80 with chronic lung disease (CLD) and a history of acute exacerbations, able to attend monthly clinical visits. *Exclusion:* Patients who were pregnant, immunocompromised (e.g., active cancer, dialysis-dependent renal insufficiency, HIV, hypogammaglobulinemia, asplenia), or previously	PPV23 + IV	87	69.0	63.5%	NR	NR	NR	24
			IV	80	70.1	57.5%	NR	NR	NR	

		received the 23-valent PV vaccine.								
Gómez-Junyent, 2014[1] (68)	COPD	*Inclusion:* Non-severely immunosuppressed adults hospitalized with pneumonia. *Exclusion:* Patients with neutropenia, solid organ transplants, chemotherapy, AIDS, or chronic corticosteroid therapy (≥20 mg prednisone/day for at least two months).	PPV23	226	74.0	90.5%	NR	25.8%	54.8%	200
			No vaccine	757	74.0	90.5%	NR	25.8%	54.8%	
Ignatova, 2021 (54)	COPD	*Inclusion:* Men aged 45 or older with a clinical COPD diagnosis and a smoking history of 10+ pack-years. *Exclusion:* Asthma, tuberculosis, bronchiectasis, other lung diseases, severe comorbidities, malignancies, daily oxygen therapy (>12 hours/day), or recent systemic corticosteroid use (within 3 months).	PPV23	32	60.0	100.0%	21.0	NR	NR	60
			PCV13	123	61.0	100.0%	21.0	NR	NR	
			No vaccination	147	63.0	100.0%	21.0	NR	NR	

Arda Kiani, 2023[1] (69)	COPD	*Inclusion:* 1) Respiratory symptoms consistent with COPD (dyspnea, exertional dyspnea, and productive cough) for over 3 months in the past 2 years with no other causes found, 2) significant exposure to toxic particles, especially a smoking history of ≥10 pack-years, and 3) spirometry showing post-bronchodilator FEV1/FVC <70%. *Exclusion:* Asthma-COPD overlap, allergies/hypersensitivity, autoimmune diseases, or current use of systemic corticosteroids.	Unspecified PV	482	63.7	78.5%	29.1	75.9%	5.3%	24
			Placebo	491	63.7	78.5%	29.1	75.9%	5.3%	
Yan Li, 2022 (70)	COPD	*Inclusion:* Patients diagnosed with COPD and a post-bronchodilator FEV1/FVC ratio <0.70. *Exclusion:* Patients who received the influenza vaccine (September–October 2018) or PPSV23 in the past 5 years, had a vaccine allergy, refused	PPV23	69	66.0	75.3%	NR	37.7%	NR	24
			Placebo	69	66.0	75.3%	NR	37.7%	NR	

		vaccination, or were unwilling to attend follow-up visits.								
Mao, 2022[1] (71)	COPD	*Inclusion:* COPD patients with no exacerbation or respiratory tract infection for at least one month before enrollment. *Exclusion:* Subjects who were pregnant or breastfeeding or had chronic unstable diseases of other systems or malignancies.	Unspecified PV	109	71.8	72.2%	22.7	11.0%	48.9%	18
			Placebo	539	71.8	72.2%	22.7	11.0%	48.9%	
Rodríguez González-Moro, 2016 (56)	COPD	*Inclusion:* Individuals with COPD aged 50 years or older *Exclusion:* NR	PCV13	629727	≥ 50	NR	NR	NR	NR	Lifetime horizon
			PPV23	629727	≥ 50	NR	NR	NR	NR	
Schembri, 2009 (45)	COPD	*Inclusion:* Patients over 40, registered in the THIN database with a diagnosis of COPD, chronic obstructive airway disease (COAD), chronic bronchitis, or emphysema. *Exclusion:* Patients with any history of lung fibrosis, sarcoidosis, lung cancer or lung surgery were excluded.	PPV23[3]	5635	NR	42.3%	NR	NR	NR	81.6
			Placebo	31062	NR	42.8%	NR	NR	NR	

Steentoft, 2006 (72)	COPD	*Inclusion:* COPD was defined according to the GOLD-guideline, i.e., FEV1/FVC <70%, FEV1 reversibility-test <200 ml. *Exclusion:* NR	PPV23	37	69.1	54.1%	NR	45.9%	54.1%	6
			Placebo	12	67.5	58.3%	NR	58.3%	41.7%	
Görkem Vayiso Şahin, 2022 (73)	COPD	*Inclusion:* Adults (>18 years) with COPD (post-bronchodilator FEV1/FVC <70%). *Exclusion:* Lung cancer, interstitial lung disease, asthma, bronchiectasis, or missing medical records.	PCV13	108	65.7	83.3%	23.6	35.4%	61.9%	12
			Placebo	108	65.7	83.3%	23.6	35.4%	61.9%	
Rajesh Venkitakrishnan, 2023 (74)	COPD	*Inclusion:* 1) COPD diagnosis per GOLD criteria. 2) Hospitalization for acute COPD exacerbation during the study period. Both criteria must be met. *Exclusion:* 1) Unclear vaccination status. 2) Overlapping chronic lung diseases (e.g., asthma, interstitial lung diseases, bronchiectasis). 3) Immunocompromised states (e.g., active HIV, malignancies, primary	PCV13	60	74.4	61.7%	NR	41.6%	NR	12
			Placebo	60	70.4	90.0%	NR	41.6%	NR	

		immunodeficiencies, regular systemic steroid use). 4) Patients who declined active management during hospitalization.								
Hua, J. L., 2024 (75)	COPD	*Inclusion:* 1) Adults aged 18–80. 2) COPD diagnosis per GOLD 2019 (post-bronchodilator FEV1/FVC <0.70). 3) Moderate-to-very severe airflow limitation (post-bronchodilator FEV1 <80% predicted). 4) History of at least two COPD exacerbations in the past 12 months requiring systemic glucocorticoids or antibiotics. 5) Stable COPD. *Exclusion:* 1) Significant chronic hepatic, renal, gastrointestinal issues, or malignant tumors (excluding lung cancer). 2) Patients who are in critical condition. 3) Recent COPD exacerbation or other acute illness (antibiotics/systemic corticosteroids) in the past 4 weeks. 4) Concomitant	PPV23 + IV	31	68.4	87.1%	22.8	87.1%	NR	12
			Conventional treatment	30	66.0	86.7%	22.7	73.3%	NR	

		pulmonary diseases (e.g., bronchiectasis, interstitial lung disease, asthma). 5) Likely to be lost to follow-up. 6) Pregnant or nursing women. 7) Recent influenza vaccination or pneumococcal vaccination within 5 years, or vaccination contraindications. 8) Allergy to amikacin or other aminoglycosides. 9) Recent participation in interventional clinical trials (last 3 months). 10) Mental or cognitive disorders affecting treatment and follow-up. 11) Long-term oral corticosteroid use. 12) α-1 antitrypsin deficiency.								
Zichen Ji, 2020 (48)	COPD	*Inclusion:* COPD patients aged over 40 with a smoking history of ≥10 pack-years and an FEV1 <70% predicted, who underwent spirometry between January and June 2011. *Exclusion:* Patients with nonobstructive chronic respiratory diseases or	PPV23[3]	164	NR	NR	NR	NR	NR	68
			No vaccine	109	NR	NR	NR	NR	NR	

		those participating in clinical trials.								
Raúl H Sansores, 2022[1] (76)	COPD	*Inclusion:* COPD patients with daily wood smoke exposure and tobacco smoking history of >10 pack-years.	Unspecified PV + IV	65	71.2	55.7%	NR	31.5%	NR	12
		Exclusion: Exposure to both biomass and tobacco, or a history of other chronic pulmonary conditions (e.g., asthma, tuberculosis, bronchiectasis).	No vaccine	84	71.2	55.7%	NR	31.5%	NR	
Kurashima, 2016[1] (77)	COPD, Asthma	*Inclusion:* COPD patients with or without medical history of asthma, a post bronchodilator increase in FEV1 of >12%	PPV23	158	68.1	89.6%	21.7	NR	NR	66
		Exclusion: Doctor-diagnosed aspiration pneumonia	Placebo	662	68.1	89.6%	21.7	NR	NR	
Lee, 2007[1] (49)	COPD, Asthma	*Inclusion:* Inclusion in the COPD or asthma cohorts was based on presence of diagnostic codes in FY1998.	PPV23[3]	18820	65.8	97.8%	NR	NR	NR	30.8
		Exclusion: Patients with codes for both COPD and asthma, or if FY1997 diagnosis codes	Placebo	15373	65.8	97.8%	NR	NR	NR	

		did not match the FY1998 group.								
El-Bardissy, 2019 (78)	COPD or Asthma	*Inclusion:* Adults (18+) admitted to the medical ward who received PCV-13 or PPV-23 upon discharge.	PCV13 and/or PPV23	72	≥ 18	NR	NR	NR	NR	24
		Exclusion: Pregnant women, patients on dialysis, or those with organ transplants (kidney or liver) on regular immunosuppressants.	Placebo	72	≥ 18	NR	NR	NR	NR	
Chiou, 2015 (79)	Lung cancer	*Inclusion:* Older than 75 years old	PPV23	157	80.2	76.4%	NR	NR	NR	48
		Exclusion: Lung cancer patients diagnosed before 2007	No intervention	628	80.2	76.4%	NR	NR	NR	
Akshay J Patel, 2020[1] (80)	Lung cancer	*Inclusion:* NR	PPV23	147	71.9	56.7%	NR	14.5%	54.1%	27
		Exclusion: NR	Placebo	308	71.9	56.7%	NR	14.5%	54.1%	

Abbreviations: AIDS = acquired immunodeficiency syndrome; CLD = chronic lung disease; COAD = chronic obstructive airway disease; COPD = chronic obstructive pulmonary disease; CRD = chronic respiratory disease; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; GOLD = Global Initiative on Obstructive Lung Disease; HIV = human immunodeficiency virus; IPD = invasive pneumococcal disease; IV = influenza vaccine; NR = not reported; NTHi = Non-Typeable Heamophilus influenza; PCV13 = pneumococcal conjugate vaccine 13-valent; PP(S)V23 = pneumococcal polysaccharide vaccine 23-valent; PV = pneumococcal vaccine; THIN (database) = The Health Improvement Network

[1]The baseline characteristics were not reported per arm.

[2]The number of people with CRD who received vaccine, was not reported.

[3]The type of pneumococcal vaccine was not specified. We assumed the vaccine is PPV23, since the study was started in 2011 or earlier.

Table 2: Outcomes for PPV23 versus placebo (16 studies)

Author, year	Population	Study design	Main outcomes[1]	Study conclusion	Quality assessment/ main concerns
Alessandra M Lanz, 2022 (59)	Asthma	Before-After design (Pre- and post-12-month vaccination questionnaires)	54% reported decrease in respiratory exacerbations and use of systemic steroids/antibiotics in the year following PPSV23 vaccination (no P-value or CI provided)	These data reveal a subset of asthma in younger adults, <65 years, with significantly decreased S. pneumoniae antibody titers with less CC symptoms and asthma medication use for exacerbations after PPSV-23 vaccination.	Low No statistical analysis for the outcome (exacerbation) was performed.
Olga Ochoa-Gondar, 2008 (60)	CRD (chronic bronchitis, emphysema and asthma)	Observational study (Prospective cohort)	Multivariable HR for all-cause mortality: 1.20 (0.91 to 1.59, P=0.202) Multivariable HR for CAP mortality: 0.87 (0.33 to 2.28, P=0.783) Multivariable HR for overall hospitalized CAP: 0.70 (0.48 to 1.00, P=0.052)	The effectiveness of the vaccine on the combined endpoint of pneumococcal and unknown organism infections reached 34% (HR: 0.66; 95% CI: 0.43—1.01; *p* = 0.059). Although our findings suggest moderate benefits from the vaccination, the evidence of clinical effectiveness appears limited.	Fair The baseline characteristics were not presented per arm. In addition the impact of PPV23 with and without IV was not presented.
Angel Vila-Corcoles, 2012 (62)	CRD (chronic bronchitis, emphysema and/or asthma)	Observational study (A population-based case-control)	Adjusted OR for overall PP: 0.71 (0.37 to 1.39, P=0.320) Adjusted OR for overall PP for 50–74 years old: 1.48 (0.62 to 3.56, P=0.379)	The effectiveness of the PPV-23 in preventing pneumonia among patients with chronic pulmonary disease is uncertain. Our results point to PPV-23 having little or null effect against pneumococcal pneumonia in such patients,	Fair The follow-up duration was not reported.

			Adjusted OR for overall PP for ≥ 75 years old: 0.45 (0.16 to 1.27, P=0.130)	but definitive conclusions cannot be established based on our data.	
Rosalyn J Singleton, 2007 (64)	CRD (COPD, bronchiectasis, or pulmonary fibrosis [not asthma])	Observational study (Retrospective)	Vaccine effectiveness (preventing the infection caused by PPV23 serotypes defined as 1 - OR): 0.74 (<0 to 100, P=0.321)	Alaska Native adults experience high rates of IPD. The majority of IPD cases occurred in persons with underlying conditions and behaviors associated with increased risk of IPD in other populations. PPV-23 vaccine effectiveness was confirmed in younger Alaska Native adults but not among adults ≥55 years.	Poor The baseline characteristics for vaccinated and unvaccinated population were not reported. The impact of pneumococcal vaccine was not reported on the population that did not receive influenza vaccine. In addition, the confounders were not controlled.
Satoshi Inoue, 2011 (65)	CRD (Bronchial asthma, chronic pulmonary emphysema, old tuberculosis, chronic bronchitis)	Observational study (Prospective)	HR for the all-cause mortality: 0.795 (0.499 to 1.264, P=0.332) HR for the first episode of pulmonary infection (pneumonia, acute bronchitis or exacerbation of chronic bronchitis): 1.096 (0.848 to 1.416, P=0.396)	The efficacy of PPV23 against pulmonary infection and death of any cause might be unachievable if pulmonary infection occurs during the pre-vaccine period. PPV23 needs to be given to older patients with chronic pulmonary disease at an earlier time in which infectious complications in the lung have not yet occurred.	Fair The baseline characteristics for vaccinated and unvaccinated population were not reported.
Chiou, 2015 (79)	Lung cancer	Observational study (A nationwide population-based cohort study	Adjusted inpatient CAP: IRR 0.74 (P = 0.0339, no CI provided)	For elderly lung cancer patients aged ≥ 75 years, PPSV23 inoculated during anti-	Fair A higher percentage of unvaccinated population were

		diagnosed elderly lung cancer patients receiving PPSV23)	Two-year cumulative CAP hospitalization rates and overall survival rates were 37.1% vs. 55.4%, and 46.6% vs. 26.2%, respectively, for lung cancer patients with and without PPSV23 (both P< 0.001, no CI provided).	cancer treatment period could reduce CAP hospitalizations and improve survival.	on cancer treatment compared to vaccinated population. In addition, vaccinated people had a high healthy awareness and take care for aspiration pneumonia or other infections. Thus, the effectiveness of vaccine may be overestimated.
Akshay J Patel, 2020 (80)	Lung cancer	Observational study (Retrospective observational analysis)	OR for in-hospital mortality: 0.16 (0.077 to 0.366, P<0.0001) OR for in-hospital mortality for the Pn sub-group: 0.269 (0.102 to 0.713, P=0.008)	Vigilance for infection, optimizing vaccination, judicious use of antibiotics particularly in the era of immunotherapy, patient education, early diagnosis with adequate assessment and efforts to identify a culprit organism should be a priority in both the inpatient and outpatient setting to improve outcome in NSCLC and reduce the incidence of hospital admission.	Fair The baseline characteristics were not reported per arm.
Alfageme, 2006 (51)	COPD	RCT	All-cause mortality: 19.1% vs 19.5% (PPV23 vs placebo, P=0.92, no CI provided) Mortality due to pneumonia: 2% vs 2% (PPV23 vs placebo, P=1.00, no CI provided) Vaccine efficacy for preventing pneumonia All patients: 24% (-24 to 54%, P=0.333)	PPV is effective in preventing CAP in patients with COPD aged less than 65 years and in those with severe airflow obstruction. No differences were found among the other groups of patients with COPD.	Low risk of bias

			PP: 0 in vaccinated arm (out of 298) and 5 in non-vaccinated arm (out of 289) (P = 0.061) Age < 65 years old: 76% (20 to 93%, P=0.013) Age ≥ 65 years old: -14% (-107 to 38%, P=0.801)		
Gómez-Junyent, 2014 (68)	COPD	Observational study (Prospective)	OR for mortality in patients with COPD and pneumonia: 0.232 (0.072 to 0.754, P=0.015)	CAP in patients with COPD presents specific characteristics and risk factors for mortality. Prior pneumococcal vaccine has a beneficial effect on outcomes. P. aeruginosa pneumonia is associated with low FEV1 values and poor prognosis.	Fair The baseline characteristics were not reported per arm. In addition the impact of PPV23 with and without influenza vaccine was not reported.
Yan Li, 2022 (70)	COPD	Before-After design (A self-controlled, one year before-and-after vaccination)	HR of PPV23 for preventing the following outcomes: AECOPD: 0.46 (0.29 to 0.74, P=0.001) Pneumonia: 0.47 (0.24 to 0.92, P=0.03) Related hospitalization: 0.54 (0.31 to 0.92, P=0.02)	Influenza vaccination and PPSV23 vaccination, separately and together, can effectively reduce the risk of AECOPD, pneumonia and related hospitalization. Effectiveness for preventing AECOPD was the greatest.	Fair The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed.
Steentoft, 2006 (72)	COPD	RCT	Exacerbation: 81% (30 out 37) in vaccinated arm and 75% (9 out of 12) in placebo arm (no P-value or CI provided)	We conclude that a rise in antibody level after pneumococcal vaccination can be expected in patients with COPD despite of the use of systemic steroids. The clinical effect of vaccination is debatable.	Some concerns The sample size was small. In addition the follow-up period was relatively short (six months).

			Hospitalization: 49% (18 out 37) in vaccinated arm and 50% (6 out of 12) in placebo arm (no P-value or CI provided) Pneumonia: 30% (11 out 37) in vaccinated arm and 42% (5 out of 12) in placebo arm (no P-value or CI provided)		
Kurashima, 2016 (77)	COPD, Asthma (62% with COPD, 38% with asthma-COPD overlap syndrome)	Observational study (Retrospective)	Mortality due to pneumonia: 0% (0 out of 158) in vaccinated arm and 1.1% (7 out of 662) in unvaccinated arm (P = 0.222, no CI provided) Frequency of pneumonia 28.4 cases vs 62.4 cases per 1000 patient-years (p=0.151, no CI provided) for vaccinated and unvaccinated Incidence rate ratio for frequency of pneumonia: 0.48 (0.23 to N.D, P = 0.01)	The index of multidimensional risk factors is useful to predict the frequency of pneumonia in patients with chronic airflow obstruction. The pneumococcal vaccination was associated with significantly lower incidence of pneumonia.	Fair Vaccination status was self-reported. No baseline characteristics for vaccinated and unvaccinated were reported.
Ignatova, 2021 (54)	COPD	Observational study (Prospective)	Pneumonia rate after one year: 6.3% in PPV23 and 15% in placebo (P=0.707, no CI provided)	Although both vaccines have comparable clinical effects during the first year after vaccination, only PCV13 is characterized by persistent clinical effectiveness during the	Fair The PPV23 arm had a significantly lower sample size.

	Pneumonia rate after five years: 47% in PPV23 and 23.1% in placebo (P=0.027, no CI provided) COPD exacerbation rate after one year: ±15% in PPV23 and ±70.0% in placebo (no P-value or CI provided, values were not presented in the text, values were read from the figures) COPD exacerbation rate after five years: ±80% in PPV23 and ±90.0% in placebo (P>0.999, no CI provided, values were not presented in the text, values were read from the figures) Hospitalization due to pneumonia after one year: ~1% in PPV23 and ~10% in placebo (no P-value or CI provided, values were not presented in the text, values were read from the figures) Hospitalization due to pneumonia after five year: ±47% in PPV23 and ±21% in	5-year follow-up period. Patients older than 55 years who received PPV23 have significantly higher risks of having pneumonia episodes more frequently during the long-term follow-up.	Moreover, in order to minimize the risk of bias associated with the non-randomized study design, they employed PSM method. However, PSM (propensity score matching) method was not explained.

			placebo (P=0.018, no CI provided, values were not presented in the text, values were read from the figures)		
Schembri, 2009[3] (45)	COPD	Observational study (Retrospective analysis)	Adjusted RR for all-cause mortality: December to March period: 1.68 (1.58 to 1.78, P-value not provided) April to November period: 1.28 (1.20 to 1.36, P-value not provided)	Influenza but not pneumococcal vaccination was associated with a reduced risk of all-cause mortality in COPD.	Fair Little baseline characteristics reported. Besides, there might be some bias due to unrecorded factors: it may be true that patients with good health behavior seek vaccination more frequently than those with poor health behavior
Zichen Ji, 2020[3] (48)	COPD	Observational study (Prospective)	HR for all-cause mortality: 0.92 (0.58 to 1.45, P=0.720)	Pneumonia is associated with worse prognosis in COPD patients. It is important to take into account this comorbidity for a comprehensive care of these patients.[2]	Poor The baseline characteristics for vaccinated and unvaccinated population did not reported. Furthermore, very little is written down about the impact of the vaccination
Lee, 2007[3] (49)	COPD, Asthma	Observational study (Retrospective study)	COPD population (crude rates per 100 person-year), post- vs pre-vaccination: Pneumococcal pneumonia only: 0.37 vs 0.47 (no P-value or CI provided)	This study supports the value of vaccinating COPD patients; however, the value of vaccination for asthma patients is less certain.	Good

	Pneumococcal and unspecified pneumonias: 5.90 vs 4.83 (no P-value or CI provided) Any pneumonia: 7.07 vs 5.77 (no P-value or CI provided) All-cause hospitalization: 45.64 vs 64.71 (no P-value or CI provided) Asthma population (Crude rates per 100 person-year), post- vs pre-vaccination: Pneumococcal pneumonia only: 0.03 vs 0.09 (no P-value or CI provided) Pneumococcal and unspecified pneumonias: 0.99 vs 1.11 (no P-value or CI provided) Any pneumonia: 1.11 vs 1.27 (no P-value or CI provided) All-cause hospitalization: 17.75 vs 49.59 (no P-value or CI provided)	

Abbreviations: AECOPD = acute exacerbations of chronic obstructive pulmonary disease; CAP = community-acquired pneumonia; CC = chronic cough; COPD = chronic obstructive pulmonary disease; CRD = chronic respiratory disease; FEV1 = forced expiratory volume in one second; HR = hazard ratio; IPD = invasive pneumococcal disease; IRR = incidence rate ratio; OR = odds ratio; NSCLC = non-small cell lung cancer; PCV13 = pneumococcal conjugate vaccine 13-valent; Pn = pneumonia; PP = pneumococcal pneumonia; PP(S)V23 = pneumococcal polysaccharide vaccine 23-valent; PSM = propensity score matching; RCT = randomized control trial

[1]Comparing vaccine with placebo, unless otherwise stated. Values in the parenthesis are 95% confidence interval, unless otherwise stated.

[2]The impact of vaccination on mortality was reported in that study. However, vaccination was not included in the conclusion of that study because the aim of that study was to assess influence of pneumonia on the survival of COPD patients.
[3]The type of pneumococcal vaccine was not specified. We assumed the vaccine is PPV23, since the study was started in 2011 or earlier.

Table 3: Outcomes for PCV13 vs placebo (5 studies)

Author, year	Population	Study design	Main outcomes[1]	Study conclusion	Quality assessment/ main concerns
Figueira-Gonçalves, 2017 (52)	COPD	Observational study (Prospective)	All-cause mortality: 25% (11 out of 44) in vaccinated arm and 21% (16 out of 77) in unvaccinated arm (P = 0.592, no CI provided) Exacerbation: 61.4% (27 out of 44) in vaccinated arm and 68.8% (53 out of 77) in unvaccinated arm (P = 0.404, no CI provided) Hospitalization: 18.2% (8 out of 44) in vaccinated arm and 32.2% (25 out of 77) in unvaccinated arm (P = 0.067, no CI provided) OR for the risk of hospital admission: 2.77 (1.03 to 7.50, P=0.044) among non-	Not vaccinating with PCV13 almost triples the risk of hospitalization in patients with COPD.	Fair The baseline characteristics were not reported per arm. In addition the impact of PCV13 with and without influenza vaccine was not reported. The sample size was small as well.

			vaccinated patients compared to vaccinated ones		
Figueira-Gonçalves, 2020 (53)	COPD	Observational study (Prospective)	OR for the risk of hospitalization: 0.307 (0.11 to 0.80, P=0.02)	The risk of hospital admission in the course of exacerbation seems to be higher in COPD/+T2DM patients than in COPD/−T2DM subjects.[2]	Fair The baseline characteristics were not reported per arm. In addition the impact of PCV13 with and without influenza vaccine was not reported. The sample size was small as well.
Görkem Vayiso Şahin, 2022 (73)	COPD	Before-After design (within one year before and after vaccination)	Mean pneumonia: after vaccination 0.7±1.1, before vaccination 1.1±1.3 (P=0.004) Mean exacerbation: after vaccination 1.6±1.7, before vaccination 2.0±1.9 (P=0.005)	This study revealed that PCV13 provides a significant decrease in both exacerbation and pneumonia episodes in COPD patients. On the other hand, the use of ICSs and the types of ICSs were not found to have adverse effects on pneumonia and acute exacerbations in vaccinated COPD patients.	Fair The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed.
Ignatova, 2021 (54)	COPD	Observational study (Prospective)	Pneumonia rate after one year: 4.9% in PCV13 and 15% in placebo (P=0.024, no CI provided) Pneumonia rate after five years: ±5% in PCV13 and 23.1% in placebo (P<0.001, no CI provided, values were not presented in the text, values were read from the figures)	Although both vaccines have comparable clinical effects during the first year after vaccination, only PCV13 is characterized by persistent clinical effectiveness during the 5-year follow-up period. Patients older than 55 years who received PPV23 have significantly higher risks of having pneumonia episodes more frequently during the long-term follow-up.	Fair The PPV23 arm had a significantly lower sample size. Moreover, in order to minimize the risk of bias associated with the non-randomized study design, they employed propensity score matching, but did not explain this further.

		COPD exacerbation rate after one year: ±25% in PCV13 and ±70% in placebo (no P-value or CI provided, values were not presented in the text, values were read from the figures) COPD exacerbation rate after five years: ±25% in PCV13 and ±90% in placebo (P<0.001, no CI provided, values were not presented in the text, values were read from the figures) Hospitalization due to pneumonia after one year: ±5% in PCV13 and ±10% in placebo (no P-value or CI provided, values were not presented in the text, values were read from the figures) Hospitalization due to pneumonia after five year: ±4% in PCV13 and ±21% in placebo (P<0.0001, no CI provided, values were not presented in the text, values were read from the figures)

Rajesh Venkitakrishnan, 2023 (74)	COPD	Observational study (Prospective)	In-hospital mortality: 0% (0 out of 60) for vaccinated arm and 1.7% (2 out of 60) for unvaccinated arm (P = 0.13, no CI provided)	COPD patients who have received prior pneumococcal vaccination have better outcomes when they are hospitalized for an acute exacerbation. Pneumococcal vaccination may be recommended for all patients with COPD who are at risk of hospitalization with acute exacerbation.	Fair The confounding factors were not adjusted. In addition, the presence of medical comorbidities was higher in the vaccinated group (significant), this might have biased the results

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; OR = odds ratio; PCV13 = pneumococcal conjugate vaccine 13-valent; PPV23 = pneumococcal polysaccharide vaccine 23-valent; PSM = propensity score matching; T2DM = type-2 diabetes mellitus

[1]Comparing vaccine with placebo, unless otherwise stated. Values in the parenthesis are 95% confidence interval, unless otherwise stated.

[2]This study was a sub-analysis of a previous study by Figueira-Gonçalves et al. 2017 (52) (please see the first row of Table 3) and the main aim was to assess the impact of diabetes.

Table 4: Outcomes for unspecified pneumococcal vaccine vs placebo (4 studies)

Author, year	Population	Study design	Main outcomes[1]	Study conclusion	Quality assessment/ main concerns
Arda Kiani, 2023[2] (69)	COPD	Observational study (Prospective)	Adjusted HR of the risk of annual exacerbation for not receiving PV: 1.44 (1.21 to 2.26, P=0.01)	Eosinophilia upon COPD diagnosis is a factor of recurrent AECOPDs. To reduce the risk of AECOPDs and the burden of disease, clinicians may consider inhaler corticosteroids and domiciliary oxygen with a lower threshold for eosinophilic-COPD patients regardless of their clinical status.[3]	Fair The baseline characteristics were not reported per arm. In addition the impact of pneumococcal vaccine with and without influenza vaccine was not reported.
Mao, 2022[2] (71)	COPD	Observational study (Cross-sectional)	Acute exacerbation (RR - 1): -47.92% (-66.01 to -20.22%, P=0.003)	Both influenza and pneumococcal vaccinations had a protective effect on COPD patients.	Fair The baseline characteristics for vaccinated and unvaccinated population did not reported. The impact of pneumococcal vaccine was not reported on the population that did not receive influenza vaccine.
El-Bardissy, 2019[4] (78)	COPD or Asthma	Observational study (Retrospective, 2 years before and after vaccination)	Hospitalization due to pneumonia: 36.1% vs 75.0% for post- and pre-vaccination (P < 0.001, no CI provided)	The pneumococcal vaccine is effective in reducing hospital admission amongst diabetic, hypertensive and COPD/Asthma patients; however, the clinical significance of pneumococcal vaccines in decreasing hospital and ICU admissions as well as the age-specific concomitant comorbidities that will highly benefit from the vaccine and the	Fair The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed.

				timing of the booster doses must be determined in more extensive long-term clinical trials in the future.	
Rosario Menéndez, 2017[5] (58)	bronchiectasis	Observational study (Prospective)	OR for hospitalization due to exacerbation with multivariable analysis: 0.37 (0.19 to 0.70, P=0.003)	Previous hospitalization, use of proton pump inhibitors, heart failure along with BSI or FACED scores is associated factors for developing exacerbations that require hospitalization. Pneumococcal vaccination was protective. This information may be useful for the design of preventive strategies and more intensive follow-up plans.	Fair The baseline characteristics for vaccinated and unvaccinated population were not reported.

Abbreviations: AECOPD = acute exacerbations of chronic obstructive pulmonary disease; BSI = bronchiectasis severity index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; ICU = intensive care unit; OR = odds ratio; PV = pneumococcal vaccine; RR = relative risk

[1]Comparing vaccine with placebo, unless otherwise stated. Values in the parenthesis are 95% confidence interval, unless otherwise stated.

[2]The type of pneumococcal vaccine has not been specified.

[3]The impact of vaccination on exacerbation was reported in that study. However, vaccination was not included in the conclusion of that study because the aim of that study was to assess the relationship between blood eosinophil count and COPD exacerbation.

[4]PPV23 and/or PCV13, the rate for each vaccine was not specified.

[5]38.5% received PPV23 and 7.9% PCV13

Table 5: Outcomes for PPV23 in comparison to PCV7 or PCV13 (3 studies)

Author, year	Population	Study design	Main outcomes[1]	Study conclusion	Quality assessment/ main concerns
Ignatova, 2021 (54)	COPD	Observational study (Prospective)	Pneumonia rate after one year: 4.9% in PCV13 and 6.3% in PPV23 (no P-value or CI provided)	Although both vaccines have comparable clinical effects during the first year after vaccination, only PCV13 is characterized by persistent clinical effectiveness during the 5-year follow-up period. Patients older than 55	Fair The PPV23 arm had a significantly lower sample size. Moreover, in order to minimize

	Pneumonia rate after five years: ±5% in PCV13 and 47% in PPV23 (P<0.0001, no CI provided, values were not presented in the text, values were read from the figures) COPD exacerbation rate after one year: ±25% in PCV13 and ±15% in PPV23 (no P-value or CI provided, values were not presented in the text, values were read from the figures) COPD exacerbation rate after five years: ±25% in PCV13 and ±80% PPV23 (P<0.0001, no CI provided, values were not presented in the text, values were read from the figures) Hospitalization due to pneumonia after one year: ±5% in PCV13 and ±1% in PPV23 (no P-value or CI provided, values were not presented in the text, values were read from the figures) Hospitalization due to pneumonia after five year: ±4% in PCV13 and ±47% in	years who received PPV23 have significantly higher risks of having pneumonia episodes more frequently during the long-term follow-up.	the risk of bias associated with the non-randomized study design, they employed PSM method. However, PSM (propensity score matching) method was not explained.

			PPV23 (P<0.0001, no CI provided, values were not presented in the text, values were read from the figures)		
Dransfield, 2012 (55)	COPD	RCT (open-label)	HR for acute exacerbation for PCV7 compared to PPV23: 0.91 (P = 0.66) (no CI provided) All-cause mortality: 4.4% (4 out of 91) in PCV7 compared to 7.8% (7 out of 90) in PPV23 (the study was not powered to detect differences between groups) (no P-value or CI provided)	PCV7 induces a greater functional antibody response than PPSV23 in patients with COPD that persists for 2 years after vaccination. This superior functional response supports testing of conjugate vaccination in studies examining clinical end points.	Some concerns One of the eligible criteria was the participants had never received PPSV23 or if it was administered >5 years before randomization. However, the assessors did rely in part on self-reported vaccination, and thus, it is possible that some participants were misclassified as vaccine naive or previously vaccinated or were enrolled <5 years after previous PPSV23.
Rodríguez González-Moro, 2016 (56)	COPD	Cost-effectiveness model (Markov)	Incremental cost-effectiveness ratio: €1518 per quality-adjusted life-year (QALY) gained for PCV13 versus PPV23	At the commonly accepted willingness-to-pay threshold of €30,000/QALY gained, PCV13 vaccination in COPD patients aged ≥ 50 years was a cost-effective strategy compared with CVP (PPV23) from 5 years to lifetime horizon in Spain.	Not applicable

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVP = current vaccination policy; HR = hazard ratio; PCV7 = pneumococcal conjugate vaccine 7-valent; PCV13 = pneumococcal conjugate vaccine 13-valent; PP(S)V23 = pneumococcal polysaccharide vaccine 23-valent; PSM = propensity score matching; QALY = quality-adjusted life-years

[1]Comparing vaccine with placebo, unless otherwise stated. Values in the parenthesis are 95% confidence interval, unless otherwise stated.

Table 6: Outcomes for pneumococcal vaccine in combination with influenza vaccine (7 studies)

Author, year	Population	Study design	Main outcomes[1]	Study conclusion	Quality assessment/ main concerns
PPV23/PCV13 + IV vs IV					
Sumitani, 2008 (61)	CRD (COPD, bronchial asthma, bronchiectasis)	Before-After design (Retrospective study, 2 years before and after PPV23 inoculation)	Hospitalization due to pneumonia: 18 vs 40 for post PPV23 versus pre PPV23 (no P-value or CI provided) All-cause hospitalization: 42 vs 77 for post PV versus pre PPV23 (P=0.001, no CI provided)	The additive inoculation of IV and PV in Japanese patients with chronic respiratory disease prevented the development of bacterial respiratory infections and warrants further study in patients with respiratory disease.	Fair The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed. Limited information on how the statistical analysis was performed.
Akitsugu Furumoto, 2008 (67)	COPD	RCT (open-label)	All-cause mortality: 8.0% (7 out of 87) in PPV23+IV vs 8.8% (7 out of 80) in IV (P = 0.87, no CI provided) HR for the following outcomes in the first year: Pneumonia: 0.70 (0.31 to 1.60, P=0.402) Acute exacerbation, infectious: 0.58 (0.37 to 0.91, P=0.019) Acute exacerbation, non-infectious: 1.40 (0.50 to 3.94, P=0.522)	An additive effect of PV with IV on infectious acute exacerbation was found during the first year after vaccination (P = 0.019), but not during the second year (P = 0.342), and was associated with serotype-specific immune response in sera of these patients who used PV during the same period.	Some concerns The assessors were not blinded and there might be some bias for assessing the outcomes.

			HR for the following outcomes in the second year: Pneumonia: 0.54 (0.13 to 2.25, P=0.397) Acute exacerbation, infectious: 0.65 (0.26 to 1.59, P=0.342) Acute exacerbation, non-infectious: 0.99 (0.28 to 3.51, P=0.987)		
Kwok WC, 2024 (63)	CRD (69.2% COPD, 33.8% asthma and 16.9% bronchiectasis)	Observational study (Retrospective)	Adjusted OR for all-cause mortality: PCV23+IV compared to IV: 1.19 (0.55 to 2.56, P-value not provided) PCV13+IV compared to IV: 0.53 (0.34 to 0.83, P=0.005) PPV23 and PCV13 +IV compared to IV: 0.12 (0.03 to 0.53, P=0.005) Adjusted OR for respiratory mortality: PCV23+IV compared to IV: 1.18 (0.46 to 2.56, no P-value provided) PCV13+IV compared to IV: 0.61 (0.38 to 0.97, P=0.036) PPV23 and PCV13 +IV compared to IV: 0.04 (0.00 to 0.27, P=0.0038)	Completed pneumococcal vaccination with PSV23/PCV13 conferred protection against secondary bacterial pneumonia, all-cause mortality, and respiratory cause of mortality with adjusted odds ratios of 0.74 (95% CI = 0.57–0.95, p = 0.019), 0.12 (95% CI = 0.03–0.53, p = 0.005), and 0.04 (95% CI = 0.00–0.527, p = 0.0038), respectively.	Fair Not reported how long follow-up timeframe was. In addition, The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed (only was discussed for IPD).
PV + IV vs placebo					
Hua, J. L., 2024 (75)	COPD	RCT (Multi-center, parallel)	Frequency of moderate-to-severe exacerbations: 0.53±0.79 in PPV23+IV vs 0.84±0.91 in placebo (no P-value provided)	The influenza-*S. pneumoniae* vaccine and long-term oral probiotic LGG can significantly delay the next moderate-to-severe AECOPD. Periodically amikacin	Low risk of bias The sample size was relatively small.

				inhalation seems to work in symptomatic patients. The findings in the current study warrants validation in future studies with microbiome investigation.	
Raúl H Sansores, 2022 (76)	COPD	Observational study (Prospective) (unspecified PV)	All-cause hospitalization: OR for non-vaccination 1.48 (1.30 to 4.61, P=0.005)	Clinical characteristics, inflammatory markers, and microbiological isolates were similar in both groups but biomass exposure-related COPD (BE-COPD) show a tendency to present higher inflammatory Th2 cells and low requirement mechanical ventilation (MV) compared with tobacco exposure-related COPD (TE-COPD).[2]	Poor The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed. The baseline characteristics for vaccinated and unvaccinated population were not reported. The vaccinated group contained individuals with at least PV or IV, so the percentage of participants that received both PV and IV was not mentioned.
Schembri, 2009 (45)	COPD	Observational study	Adjusted RR for all-cause mortality (vaccinated with IV and PV):	Influenza but not pneumococcal vaccination was associated with a	Fair

		(Retrospective analysis) (PPV23)	December to March period: 0.53 (0.51 to 0.56, no P-value provided) April to November period: 0.88 (0.85 to 0.91, no P-value provided)	reduced risk of all-cause mortality in COPD.	Little baseline characteristics reported. Besides, there might be some bias due to unrecorded factors: it may be true that patients with good health behavior seek vaccination more frequently than those with poor health behavior
Yan Li, 2022 (70)	COPD	Before-After design (A self-controlled, one year before-and-after vaccination)	HR of PPV23+TIV vs placebo for preventing the following outcomes: AECOPD: 0.28 (0.21 to 0.38, P<0.01) Pneumonia: 0.27 (0.17 to 0.42, P<0.01) Related hospitalization: 0.31 (0.23 to 0.43, P<0.01)	Influenza vaccination and PPSV23 vaccination, separately and together, can effectively reduce the risk of AECOPD, pneumonia and related hospitalization. Effectiveness for preventing AECOPD was the greatest.	Fair The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed.

Abbreviations: AECOPD = acute exacerbations of chronic obstructive pulmonary disease; BE-COPD = biomass exposure-related chronic obstructive pulmonary disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CRD = chronic respiratory disease; HR = hazard ratio; IPD = invasive pneumococcal disease; IV = influenza vaccine; LGG = *Lactobacillus rhamnosus* GG; OR = odds ratio; PCV13 = pneumococcal conjugate vaccine 13-valent; PP(S)V23 = pneumococcal polysaccharide vaccine 23-valent; PV = pneumococcal vaccine; RCT = randomized control trial; RR = relative risk; TE-COPD = tobacco exposure-related chronic obstructive pulmonary disease; TIV = trivalent seasonal influenza vaccine

[1]Comparing vaccine with placebo, unless otherwise stated. Values in the parenthesis are 95% confidence interval, unless otherwise stated.

[2]The impact of vaccination on hospitalization was reported in that study. However, vaccination was not included in the conclusion of that study because the aim of that study was to describe clinical characteristics and biomarkers of inflammation during a COPD exacerbation, comparing BE-COPD to TE-COPD.

Table 7: Outcomes for non-typeable *Haemophilus influenzae* (NTHi) versus placebo (1 study)

Author, year	Population	Study design	Main outcomes[1]	Study conclusion	Quality assessment/ main concerns
Clancy, 2016 (66)	COPD	RCT (Multi-center, randomized, double-blind, placebo-controlled, parallel group study)	All-cause mortality for the total population: 2.5% (4 out of 158) in vaccinated arm vs 1.3% (2 out of 159 in placebo arm (P-value not significant) Exacerbation rate for total population: 1.1±1.32 in vaccinated arm vs 1.1±1.24 in placebo arm (P-value not significant) Exacerbation rate for < 65 years old: 0.6±0.85 in vaccinated arm vs 1.3±1.32 in placebo arm (P=0.0009)	The exploratory analysis of the patients <65 years of age suggests that this group of patients benefited from the treatment, but this needs to be confirmed in future studies. Further studies are also needed to clarify the optimal target population for oral NTHi immunization and to test strategies, such as using a higher immunizing dose to increase efficacy in older patients.	Low risk of bias

Abbrevations: COPD = chronic obstructive pulmonary disease; NTHi = Non-Typeable *Haemophilus influenzae*; RCT = randomized control trial
[1]Comparing vaccine with placebo, unless otherwise stated. Values in the parenthesis are 95% confidence interval, unless otherwise stated.

3.5 Risk of bias (RCTs)

Table S7 shows the risk of bias assessment for the RCTs that were included in the review. Three out of six RCT studies had a low risk of bias. The concerns for other three studies were recall bias, assessors were not blinded, short follow-up duration and small sample size.

3.6 Quality assessment (observational)

The observational studies were distinguished between cohort studies with control group and the studies with before-after design (no control group), Table S8 and Table S9 shows the quality assessment these two types of studies, respectively.

The overall quality of most of the observational studies was fair. The most common concern was not reporting or difference in baseline characteristics between vaccinated and non-vaccinated groups. Other concerns were small sample size, not reporting the impact of PV with and without influenza vaccine and not adjusting for confounders. Similarly, the overall quality of most of the before-after studies were fair. The common concern was that the studies did not report the required sample size.

3.7 GRADE

Tables S10 to S16 show the summary of findings per intervention for reported outcomes. The certainty of evidence in all of the reported outcomes were low or very low. The first reason was that the impact of vaccines was not statistically significant and in some outcomes the vaccine had a negative impact. Second, in some outcomes the sample size was small with only one study. Third, the baseline characteristics for vaccinated and non-vaccinated either were not reported or there were significant differences between them.

3.8 Studies on RSV and *Haemophilus influenzae* vaccines

Table S17 shows the studies on RSV and NTHi vaccines that were excluded during full-text screening. The main reason for excluding NTHi was that these studies concerned phase 1 or phase 2 trials. Similarly, RSV vaccine studies were excluded because they were either phase 2 trial or they did not report the outcomes for our population of interest. For instance the study by Feldman et al. 2024 (81) reported vaccine efficacy of 94.6% (95% CI: 65.9 to 99.99%) and 81.0% (95% CI: 58.9 to 92.3%) for preventing RSV related lower respiratory tract disease and RSV related acute respiratory illness, respectively in older adults (≥ 60 years old) with at least one cardiorespiratory conditions. In that study, the outcomes specifically for CRDs were not reported and hence, were excluded from the current review.

4 Discussion

In this systematic literature review, we searched for evidence on the effectiveness of vaccines (pneumococcal, RSV, NTHi, pertussis and GBS vaccines) in individuals with chronic respiratory diseases.

We included 32 studies, with all but one focusing on pneumococcal vaccines; showing that among the vaccines included in the analysis, the pneumococcal vaccine has been studied more frequently than others, both in the general population and among individuals with CRDs. Several articles have examined RSV vaccines in the general population, with or without underlying medical conditions (aged ≥ 60 years) (81–85). We excluded these studies as the outcomes were not reported specifically for the CRD population. Few studies have explored the efficacy of *Haemophilus influenzae* and pertussis vaccines in adults. Among these, we included only the study by Clancy et al. 2016 (66), which focuses on the efficacy of the NTHi vaccine in the COPD population. We were unable to find any relevant studies on the GBS vaccine.

The pneumococcal vaccine studies reported a variety of outcomes, sometimes with conflicting results. For instance, Schembri et al. 2009 (45) reported an increased relative risk for all-cause mortality in COPD patients for vaccinated with PV versus non vaccinated people (OR in December to March period: 1.68, 95%CI: 1.58 to 1.78 and April to November period: 1.28 95% CI:1.20 to 1.36). This effect may be explained by channeling bias (i.e. patients with worse health conditions may be more likely to be vaccinated), misdiagnosis of COPD patients and some unidentified confounding (45). In contrast, Gómez-Junyent et al. 2014 (68) reported a lower odds ratio in the vaccinated COPD population (OR: 0.232, 95% CI: 0.072 to 0.754). These discrepancies may be due to the differences in observational design of the studies, which could result in variations in follow-up duration and baseline characteristics.

Two studies reported a significant protective impact of PPV23 on mortality in lung cancer patients. In the study by Chiou et al. 2015 (79), a lower percentage of the vaccinated group were on active chemotherapy and the rate influenza vaccine were higher in the PPV23 vaccinated group. These differences may overestimated the impact of PPV23. Similarly, Patel et al. 2020 reported a significant protective impact of PPV23 on mortality in non-small cell lung cancer patients (80). The main concern regarding this article was that the baseline characteristics of vaccinated and non-vaccinated were not reported.

Few studies compared between PPV23 and PCV13. Among them, Ignatova et al. 2021 (54), with a relatively long follow-up (five years), found that PCV13 had a more persistent effect over a five year follow-up period. Interestingly, the pneumonia rate for PPV23 was higher than in the unvaccinated population after five years. Gonzalez-Moro et al. 2016 (56) concluded that PCV13 was more cost-effective than PPV23 in a population of COPD

patients aged 50 years and older, using a threshold of €30,000 per quality-adjusted life year gained.

A common concern across the studies with pneumococcal vaccination was the lack of reporting on IV status or the impact of PV with and without IV. The reported IV rate in those studies varied from 4.4% (69) to 71.4% (68). Studies that compared pneumococcal vaccines (of any type) in combination with IV compared to IV alone or placebo generally reported favourable outcomes, although the number of studies and sample size were small.

Clancy et al. 2016 (66) reported that NTHi did not impact all-cause mortality and exacerbation rates compared to the unvaccinated group for the total population. However, for the COPD population younger than 65 years old, NHTi vaccination significantly reduced exacerbation rates. A systematic review by Teo et al. 2017 (57) concluded that there is insufficient evidence to recommend NTHi vaccination for the COPD population.

Goldstein et al. 2015 (86) reported that RSV had a significant contribution to respiratory hospitalization among older adults (≥ 75 years old) in New York City from 2003 to 2011. Similar studies in Germany and England also reported a significant burden of RSV among older adults (13,87). Considering the protective impact of RSV vaccine on preventing the RSV lower respiratory tract disease and acute respiratory illness for older adults with and without cardiorespiratory conditions (81), RSV vaccine is expected to have a protective effect in individuals with CRDs .

No relevant studies were found for the Tdap and GBS vaccines. The study by Pearce et al. 2024 (19) reported a not significant protective impact of pertussis vaccine on pertussis (OR: 0.77, 95% CI: 0.48 to 1.24, P=0.28) among adults ≥ 50 years old during 2015 to 2019 in Australia. In addition, they reported a greater burden of pertussis in individuals with COPD and asthma (19). Another study by Naeger et al. 2024 (18) highlighted the increased risk of pertussis in the individuals with COPD or asthma compared the general population, suggested that pertussis vaccine could reduce the disease burden among these population. Individuals with asthma and pertussis can have 4.3 and 3.1 times more emergency visits and general practitioner (GP)/nurse visits, compared to individuals with asthma and without pertussis (88).

The certainty of evidence for each outcome was generally low or very low, primarily due to large confidence interval across different studies. However, some conclusions can be drawn with low degree of certainty:

1. Vaccination with pneumococcal may reduce the hospitalization and exacerbation rate. While the impact of PPV23 reduces after one year, PCV13 had a more persistent effect beyond one year.

2. Generally, the studies reported a non-significant to no effect of pneumococcal (any type) on all-cause mortality.
3. Combination of PV and IV improved the protective effect on hospitalization and exacerbation compared to IV alone or placebo.

A review of the selected international guidelines suggests that PCV with 13 or more valent are preferred over PPV23. In the current review we only identified studies focusing on PCV13. Since 2018/2019, approximately 60% of IPDs in European adults is caused by serotypes covered by PCV20 (89). This suggests that PCV20 is likely to prevent more pneumococcal disease compared to other PCVs (89). Additionally, most guidelines recommend pertussis vaccine for all adults, with booster doses every 10 years in the US and Germany and a single booster in Belgium. There are no recommendations for *Haemophilus influenzae* and GBS vaccines. RSV vaccination is recommended for patients with CRDs from the age of 60 in Germany, Belgium and the US.

5 Preliminary conclusions

The evidence supporting pneumococcal vaccination—particularly for PPV23—remains uncertain in patients with chronic respiratory disease. Nevertheless, factors such as the burden of pneumococcal pneumonia and invasive pneumococcal disease in this population (e.g., incidence and hospitalization rates), along with the demonstrated efficacy and effectiveness of PPV23 and PCVs in the general population, should be considered when developing recommendations.

Based on the conclusions of this review, no recommendation can be drafted for RSV vaccination for the CRD population. If evidence from a broader population, namely patients with cardiopulmonary conditions, can be transferred to the more specific CRD population, vaccination may be considered for patients aged 60 and over. This would be in line with the recommendations for Germany and Belgium.

No recommendation can be drawn for the pertussis vaccine, NTHi and GBS based on the current review.

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Supplementary Material

Table S1: ICD-10 and 11 codes for CRDs based on Global Burden of Disease (GBD) 2023 (2)

Category	ICD-10 codes (GBD 2023)	ICD-11 codes	Include/exclude	Reason(s) to exclude
	J41 Simple and mucopurulent chronic bronchitis	**CA20** Bronchitis **CA20.1** Chronic bronchitis	Include	
	J42 Unspecified chronic bronchitis (tracheitis, tracheobronchitis)	**CA20.1Y** Other specified chronic bronchitis (Chronic tracheitis, Chronic tracheal infection, Chronic bronchorrhoea, Chronic laryngotracheobronchitis, Chronic pharyngotracheitis and Chronic tracheopharyngitis) **CA27** Tracheobronchitis (Tracheobronchopathia osteochondroplastica, Tracheobronchomegaly, Mounier-Kuhn syndrome)	Include: chronic tracheitis, chronic tracheal infection, chronic bronchorrhoea, chronic laryngotracheobronchitis, chronic tracheopharyngitis, tracheobronchopathia osteochondroplastica, tracheobronchomegaly, Mounier-Kuhn syndrome Exclude: chronic pharyngotracheitis, chronic tracheopharyngitis	Chronic pharyngotracheitis, Chronic tracheopharyngitis (URT)
	J43 Emphysema (including MacLeod syndrome)	**CA21** Emphysema (including MacLeod syndrome, Swyer-James syndrome,	Include	

		Unilateral transparency of lung, hyperlucent lung)		
Certain lower respiratory tract diseases	**J44** Other chronic obstructive pulmonary disease (Chronic obstructive airway disease and Chronic obstructive lung disease)	**CA22** Chronic obstructive pulmonary disease (other terms: Chronic obstructive airway disease and Chronic obstructive lung disease)	Include	
	J45 Asthma	**CA23** Asthma (including bronchospasm)	Include: asthma and bronchospasm	
	J46 Status asthmaticus		Exclude: status asthmatic	Status asthmatic (it is an acute exacerbation of asthma)
		CA24 Bronchiectasis *(not in GBD, J47 in ICD-10, was removed in GBD)*	Include	
		CA25 Cystic fibrosis (lung, *not in GBD*)	Include (terms: cystic fibrosis and lung fibrosis)	
		CA26 Chronic bronchiolitis (including diffuse panbronchiolitis)	Include	

		CA05.1 Acute tracheitis	Exclude	It is an outcome.
		1C12 *Whooping cough (not in GBD)*	Exclude	It is an outcome.
		MD12 *Chronic cough (not in GBD)*	Include	
Lung infections		***CA40*** *Pneumonia (not in GBD)*	Exclude	It is an outcome.
		CA43 *Abscess of lung or mediastinum (including Gangrene or necrosis of lung, Abscess of mediastinum, not in GBD)*	Exclude	It is an outcome.
		CA44 *Pyothorax (not in GBD)*	Exclude	It is an outcome.
	J82 Pulmonary eosinophilia, not elsewhere classified (Eosinophilic asthma, Löffler pneumonia, Tropical (pulmonary) eosinophilia NOS)	**CB02** Pulmonary eosinophilia	Include	
	J84.0 Alveolar and parietoalveolar conditions (Alveolar proteinosis, Pulmonary alveolar microlithiasis)	**CB04.31** Pulmonary alveolar proteinosis **CB06** Pulmonary alveolar microlithiasis	Include	Include

Respiratory diseases principally affecting the lung interstitium	**J84.1** Other interstitial pulmonary diseases with fibrosis (Diffuse pulmonary fibrosis, Fibrosing alveolitis (cryptogenic), Hamman-Rich syndrome, Idiopathic pulmonary fibrosis, Usual interstitial pneumonia)	**CB03.4** Idiopathic pulmonary fibrosis (interstitial pulmonary fibrosis, idiopathic lung fibrosis, fibrosing lung disease, pulmonary fibrosis NOS, fibrosing pneumonitis, fibrosing alveolitis)	Include (main terms: interstitial lung diseases and pulmonary fibrosis)	
		CB03.0 Acute interstitial pneumonitis (Hamman-Rich syndrome)	Exclude	No CRD
	J84.8 Other specified interstitial pulmonary diseases	**CB0Y** Other specified respiratory diseases principally affecting the lung interstitium (Dendriform pulmonary ossification)	Include	
	84.9 Interstitial pulmonary disease, unspecified	**CB0Z** Respiratory diseases principally affecting the lung interstitium, unspecified (diffuse parenchymal lung disease)	Include	
	J60 Coalworker pneumoconiosis	**CA60.1** Coal worker pneumoconiosis	Include	
	J61 Pneumoconiosis due to asbestos and other mineral fibres	**CA60.2** Pneumoconiosis due to mineral fibres including asbestos	Include	

	J62 Pneumoconiosis due to dust containing silica (silicotic fibrosis (massive) of lung)	**CA60.0** Pneumoconiosis due to dust containing silica (talc dust)	Include	
	(**J63** Pneumoconiosis due to other inorganic dusts) **J63.0** Aluminosis (of lung)	(**CA60** Pneumoconiosis) **CA60.4** Aluminosis of lung	Include	
	J63.1 Bauxite fibrosis (of lung)	**CA60.5** Bauxite fibrosis of lung	Include	
	J63.2 Berylliosis	**CA60.6** Berylliosis	Include	
Lung diseases due to external agents	**J63.3** Graphite fibrosis (of lung)	**CA60.7** Graphite fibrosis of lung	Include	
	J63.4 Siderosis	**CA60.8** Siderosis	Include	
	J63.5 Stannosis	**CA60.9** Stannosis	Include	
	J63.8 Pneumoconiosis due to other specified inorganic dusts	**CA60.Y** Other specified pneumoconiosis	NA	NA

J65 Pneumoconiosis associated with tuberculosis	**CA60.3** Pneumoconiosis associated with tuberculosis	Include
(J66 Airway disease due to specific organic dust) **J66.0** Byssinosis (Airway disease due to cotton dust)	**(CA80** Airway disease due to specific organic dust) **CA80.0** Byssinosis due to exposure to cotton (it has 14 other names such as brown lung disease and carders' asthma)	Include
J66.1 Flax-dresser disease	**CA80.1** Byssinosis due to exposure to flax (also called flax dressers)	Include
J66.2 Cannabinosis	**CA80.2** Byssinosis due to exposure to cannabis (also due to hemp)	Include
J66.8 Airway disease due to other specific organic dusts	**CA80.Y** Other specified airway disease due to specific organic dust (Byssinosis due to exposure to jute, Byssinosis due to exposure to sisal)	Include
J67 Hypersensitivity pneumonitis due to organic dust (Farmer lung, Bagassosis, Bird fancier lung,	**CA70** Hypersensitivity pneumonitis due to organic dust (Farmer lung, Bagassosis, Bird fancier lung, Suberosis,	Include

Suberosis, Malt worker lung, Mushroom worker lung, Maple bark stripper lung, Air conditioner or humidifier lung)	Malt worker lung, Mushroom worker lung, Maple bark stripper lung, Air conditioner or humidifier lung)		
J68 Respiratory conditions due to inhalation of chemicals, gases, fumes and vapours (Pulmonary oedema, Pulmonary fibrosis)	**CA81** Respiratory conditions due to inhalation of chemicals, gases, fumes or vapours (Bronchitis or pneumonitis, Pulmonary oedema)	Include	
J70 Respiratory conditions due to other external agents (Radiation pneumonitis, pulmonary manifestations due to radiation, Acute/chronic drug-induced interstitial lung disorders)	**CA82** Respiratory conditions due to other external agents (Radiation pneumonitis, pulmonary manifestations due to radiation, Acute/chronic drug-induced interstitial lung disorders)	Include	
J30 Vasomotor and allergic rhinitis	**CA08** Vasomotor or allergic rhinitis	Exclude	URT
J31 Chronic rhinitis, nasopharyngitis and pharyngitis	**CA09** Chronic rhinitis, nasopharyngitis or pharyngitis	Exclude	URT
J32 Chronic sinusitis	**CA0A** Chronic rhinosinusitis	Exclude	URT
J33 Nasal polyp	**CA0J** Nasal polyp	Exclude	URT

Upper respiratory tract disorders	**J34** Other disorders of nose and nasal sinuses (Cyst and mucocele of nose and nasal sinus, Deviated nasal septum, Hypertrophy of nasal turbinates, Other specified disorders of nose and nasal sinuses)	**CA0Z** Upper respiratory tract disorders, unspecified	Exclude	URT
	J35 Chronic diseases of tonsils and adenoids	**CA0F** Chronic diseases of tonsils or adenoids	Exclude	URT
	J37 Chronic laryngitis and laryngotracheitis	**CA0G** Chronic laryngitis or laryngotracheitis	Exclude	URT
	J38 Diseases of vocal cords and larynx, not elsewhere classified	**CA0H** Diseases of vocal cords or larynx, not elsewhere classified	Exclude	URT
	J39 Other diseases of upper respiratory tract	**CA0Y** Other specified upper respiratory tract disorders	Exclude	URT
	D86.0 Sarcoidosis of lung	**4B20.0** Sarcoidosis of lung	Include	
	D86.1 Sarcoidosis of lymph nodes	**4B20.1** Sarcoidosis of lymph nodes	Include	

	D86.2 Sarcoidosis of lung with sarcoidosis of lymph nodes	**4B20.Y** Other specified sarcoidosis	Include	
Other CRDs	**D86.9** Sarcoidosis, unspecified	**4B20.Z** Sarcoidosis, unspecified (Besnier-Boeck-Schaumann disease, Boeck's disease, Boeck's sarcoid, Schaumann's disease or syndrome, Hutchinson-Boeck disease or syndrome)	Include	
	G47.3 Sleep apnoea (central and obstructive)	**7A40** Central sleep apnoeas **7A41** Obstructive sleep apnoea	Exclude	URT
	J91 Pleural effusion in conditions classified elsewhere	**CB27** Pleural effusion	Include	
	J92 Pleural plaque (Pleural plaque with presence of asbestos, Pleural plaque without asbestos)	**CB20** Pleural plaque (pleural plaques with or without asbestos, Pleural plaque with presence of asbestos)	Exclude	Not relevant for vaccination
Lung cancer	**-**	**-**	Include	

URT: upper tract respiratory

Table S2: List of vaccines

Vaccine	Types (examples, inclusion is based on the main group of vaccines)	Source of recommendation*	Include/exclude	Reason to exclude
Pneumococcal	Pneumococcal conjugate vaccine (PCV) 7, 10, 13, 20	ERS (27), CDC (90)	Include	
	Pneumococcal polysaccharide vaccine 23 (PPSV23)			
Respiratory syncytial virus (RSV)	Arexvy (GSK)	ERS (27), CDC (90)	Include	
	Abrysvo (Pfizer)			
	Beyfortus (nirsevimab, AstraZeneca and Sanofi)			
Td and Tdap	-	ERS (27), CDC (90)	Include	
Haemophilus influenzae	*Haemophilus influenzae* type B (Hib) vaccine	ERS (27)	Include	
	Non-typable *Haemophilus influenzae* and Moraxella			

	catarrhalis (NTHi-Mcat, GSK)			
Group B streptococcus (GBS)	GBS6 by Pfizer	Expert opinion	Include	
	GBS-NN/NN2 by MinervaX			
Influenza	Inactivated trivalent or quadrivalent	*Gezondheidsraad* (30), ERS (27), CDC (90)	Exclude	Influenza vaccine has been already recommended for CRDs .
	Live attenuated influenza vaccine (LAIV)			
	Recombinant hemagglutinin (HA)			
Herpes zoster (shingles)	Zoster vaccine	ERS (27), CDC (90)	Exclude	There is an advice from the *Gezondheidsraad* already (36).
COVID-19	mRNA	*Gezondheidsraad* (31), ERS (27), CDC (91)	Exclude	COVID-19 vaccine has been already recommended for CRDs (31).
	Subunit Protein Vaccine			

Bacillus Calmette–Guérin (BCG)	-	Recommended for tuberculosis (92,93)	Exclude	Not relevant for the Dutch context

*A vaccine was included if it was recommended for one or more chronic respiratory diseases
ERS, European respiratory society; CDC, centers for disease control and prevention

Table S3: List of inclusion ad exclusion criteria

Criterion	Inclusions	Exclusions
Population	• Adults with CRDs (≥ 18 years old)	• Studies that did not include CRDs patients.
Intervention	Following vaccines (Table S2 for more details): • Pneumococcal • RSV • Td and Tdap • HiB • NTHi • GBS	• Influenza vaccine • Herpes zoster vaccine • BCG • COVID-19
Comparator	• No vaccine (placebo) • Comparison between vaccines	
Outcomes	Studies that reported at least one of the following outcomes: • Hospitalization (all-cause, due to disease, and pneumonia) • Mortality (all-cause and due to disease) • Early and late exacerbation • Primary care visits • Outpatient pneumonia • Laboratory confirmed cases • Unplanned visits (including emergency visits)	• Studies that did not report relevant outcomes.
Study design	• Observational studies (prospective or retrospective) • Randomized control trials • Clinical trials phase III, phase IV • Cohort studies • Cross-sectional studies • Case-control studies • Registry studies • Consensus statements about using vaccines • Cost-effectiveness/benefit/modelling studies	• Animal studies • Preclinical studies • Phase I or II studies • Case reports • Diagnostics studies • Editorials or commentaries or preprints • Lab-based /in-vitro studies (e.g. biochemistry,

		immunological or molecular studies) • Systematic literature reviews* • Targeted literature reviews* • Meta-analysis*
Language	• English and Dutch	Other than Dutch and English
Date	• Published articles including and after 2000**	Published articles before 2000

*Will not be included in the current SLR, however, they will be presented in the SLR report.
**Restriction can be relaxed to 1980 if the included articles do not provide sufficient evidence as decided by the independent advisory board.

Table S4: PubMed search, date: 31/07/2024

No	Block	Search terms	Results
#1	**Certain lower respiratory tract diseases**	"Bronchitis"[Mesh] OR bronch*[Title/Abstract] OR "Tracheitis"[MeSH Terms] OR chronic tracheitis[Title/Abstract] OR "Trachea"[MeSH Terms] OR chronic tracheal infection[Title/Abstract] OR chronic bronchorrhoea[Title/Abstract] OR chronic laryngotracheobronchitis[Title/Abstract] OR chronic tracheopharyngitis[Title/Abstract] OR tracheobronchopathia[Title/Abstract] OR "Tracheobronchomegaly"[Mesh] OR tracheobronchomegaly[Title/Abstract] OR Mounier-Kuhn syndrome[Title/Abstract] OR "Emphysema"[Mesh] OR "Pulmonary Emphysema"[Mesh] OR Emphysema[Title/Abstract] OR MacLeod syndrome, Swyer-James syndrome[Title/Abstract] OR Unilateral transparency of lung[Title/Abstract] OR	749,069

		hyperlucent lung[Title/Abstract] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Lung Diseases, Obstructive"[Mesh] OR chronic obstructive pulmonary disease*[Title/Abstract] OR chronic obstructive airway disease*[Title/Abstract] OR chronic obstructive lung disease*[Title/Abstract] OR COPD[Title/Abstract] OR COAD[Title/Abstract] OR COLD[Title/Abstract] OR chronic lung disease[Title/Abstract] OR chronic lung diseases[Title/Abstract] OR "Asthma"[Mesh] OR Asthma[Title/Abstract] OR "Bronchiectasis"[Mesh] OR diffuse panbronchiolitis[Title/Abstract] OR "Cystic Fibrosis"[Mesh] OR "Chronic Cough"[Mesh] OR chronic cough[Title/Abstract] OR lower respiratory tract disease*[Title/Abstract] OR LRTD[Title/Abstract]	
#2	**Respiratory diseases principally affecting the lung interstitium**	"Pulmonary Eosinophilia"[Mesh] OR pulmonary eosinophilia[Title/Abstract] OR "Pulmonary Alveolar Proteinosis"[Mesh] OR pulmonary alveolar proteinosis[Title/Abstract] OR pulmonary alveolar microlithiasis[Title/Abstract] OR "Lung Diseases, Interstitial"[Mesh] OR interstitial lung disease*[Title/Abstract] OR	107,716

		"Pulmonary Fibrosis"[Mesh] OR pulmonary fibrosis[Title/Abstract] OR fibrosing lung disease[Title/Abstract] OR fibrosing alveolitis[Title/Abstract] OR diffuse parenchymal lung disease[Title/Abstract] OR Dendriform pulmonary ossification[Title/Abstract]	
#3	**Lung diseases due to external agents**	"Pneumoconiosis"[Mesh] OR pneumoconiosis[Title/Abstract] OR Aluminosis[Title/Abstract] OR Bauxite*[Title/Abstract] OR Berylliosis[Title/Abstract] OR Siderosis[Title/Abstract] OR Stannosis[Title/Abstract] OR (Pneumoconiosis[Title/Abstract] AND tuberculosis[Title/Abstract]) OR "Pulmonary Edema"[Mesh] OR Pulmonary Edema[Title/Abstract] OR Pulmonary oedema[Title/Abstract] OR Byssinosis[Title/Abstract]	52,859
#4	**Other CRDs**	"Sarcoidosis"[Mesh] OR Sarcoidosis[Title/Abstract] OR Besnier-Boeck-Schaumann disease[Title/Abstract] OR Boeck's disease[Title/Abstract] OR Boeck's sarcoid[Title/Abstract] OR Schaumann's disease[Title/Abstract] OR Schaumann's syndrome[Title/Abstract] OR Hutchinson-Boeck disease[Title/Abstract] OR Hutchinson-Boeck syndrome[Title/Abstract] OR "Pleural Effusion"[Mesh] OR Pleural effusion[Title/Abstract]	69,908

#5	**Lung cancer**	"Lung Neoplasms"[Mesh] OR "Small Cell Lung Carcinoma"[Mesh] OR "Carcinoma, Non-Small-Cell Lung"[Mesh] OR (Adenocarcinoma[Title/Abstract] AND lung[Title/Abstract]) OR ((lung[Title/Abstract] OR trachea*[Title/Abstract] OR bronchus[Title/Abstract]) AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR malignan*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract]))	429,721
#6	**Vaccines**	"Pneumococcal Vaccines"[MeSH Terms] OR "Respiratory Syncytial Virus Vaccines"[MeSH Terms] OR "Diphtheria-Tetanus-Pertussis Vaccine"[MeSH Terms] OR "Pertussis Vaccine"[MeSH Terms] OR "Haemophilus influenzae type b polysaccharide vaccine"[Supplementary Concept] OR "Haemophilus influenzae type b-polysaccharide vaccine-diphtheria toxoid conjugate"[Supplementary Concept] OR ((pneumococcal[Title/Abstract] OR pneumococcal conjugate[Title/Abstract] OR respiratory syncytial virus[Title/Abstract] OR rsv[Title/Abstract] OR Pertussis[Title/Abstract] OR DTP[Title/Abstract] OR DPT[Title/Abstract] OR DTAP[Title/Abstract] OR haemophilus influenz*[Title/Abstract] OR hemophilus influenz[Title/Abstract] OR h.influenzae[Title/Abstract] OR nthi[Title/Abstract] OR	43,923

		Group B streptococcus[Title/Abstract] OR GBS[Title/Abstract]) AND ("Vaccines" [Mesh] OR "Immunization"[Mesh] OR "Immunotherapy" [Mesh] OR vaccin*[Title/Abstract] OR immune[Title/Abstract]))	
#7	**Human**	"Animals"[Mesh] NOT "Humans"[Mesh]	5,220,148
#8	**Type of studies**	"Comment"[Publication Type] OR "Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Case Reports"[Publication Type] OR "case report*"[Title] OR "case stud*"[Title] OR "case series"[Title] OR "case histor*"[Title]	4,536,600
#9	**(#1 OR #2 OR #3 OR #4 OR #5) AND #6 NOT (#7 OR #8)**	After 2000 Language (Dutch and English)	**2,356**
#10	**Vaccination for chronic cough before 2000**	("Pneumococcal Vaccines"[MeSH Terms] OR "Respiratory Syncytial Virus Vaccines"[MeSH Terms] OR "Diphtheria-Tetanus-Pertussis Vaccine"[MeSH Terms] OR "Pertussis Vaccine"[MeSH Terms] OR "Haemophilus influenzae type b polysaccharide vaccine"[Supplementary Concept] OR "Haemophilus influenzae type b-polysaccharide vaccine-diphtheria toxoid conjugate"[Supplementary Concept] OR (("pneumococcal"[Title/Abstract] OR "pneumococcal conjugate"[Title/Abstract] OR "respiratory syncytial virus"[Title/Abstract] OR "rsv"[Title/Abstract] OR "Pertussis"[Title/Abstract] OR "DTP"[Title/Abstract] OR "DPT"[Title/Abstract] OR "DTAP"[Title/Abstract] OR "haemophilus influenz*"[Title/Abstract] OR (("haemophilus"[All Fields] OR "haemophilus"[MeSH Terms] OR "hemophilus"[All Fields]) AND "influenz"[Title/Abstract]) OR "h.influenzae"[Title/Abstract] OR "nthi"[Title/Abstract] OR "group b streptococcus"[Title/Abstract] OR "GBS"[Title/Abstract]) AND ("Vaccines"[MeSH Terms] OR "Immunization"[MeSH Terms] OR "Immunotherapy"[MeSH Terms] OR "vaccin*"[Title/Abstract] OR "immune"[Title/Abstract]))) AND ("Chronic Cough"[MeSH Terms] OR "Chronic Cough"[Title/Abstract]) AND 1979/01/01:2000/12/31[Date - Publication] Filters: from 1979 - 1999	**2**

#11			**2358**

Table S5: Embase search, date: 31/07/2024

No	Block	Search terms	Results
#1	**Certain lower respiratory tract diseases**	'bronchitis'/exp OR 'bronch*':ti,ab,kw OR 'tracheitis'/exp OR 'chronic tracheitis':ti,ab,kw OR 'trachea'/exp OR 'chronic tracheal infection':ti,ab,kw OR 'chronic bronchorrhoea':ti,ab,kw OR 'chronic laryngotracheobronchitis':ti,ab,kw OR 'chronic tracheopharyngitis':ti,ab,kw OR 'tracheobronchopathia':ti,ab,kw OR 'tracheobronchomegaly'/exp OR 'tracheobronchomegaly':ti,ab,kw OR 'mounier-kuhn syndrome':ti,ab,kw OR 'emphysema'/exp OR 'lung emphysema'/exp OR 'emphysema':ti,ab,kw OR 'macleod syndrome, swyer-james syndrome':ti,ab,kw OR 'unilateral transparency of lung':ti,ab,kw OR 'hyperlucent lung':ti,ab,kw OR 'chronic obstructive lung disease'/exp OR 'obstructive lung disease'/exp OR 'chronic obstructive pulmonary disease*':ti,ab,kw OR 'chronic obstructive airway disease*':ti,ab,kw OR 'chronic obstructive lung disease*':ti,ab,kw OR 'copd':ti,ab,kw OR 'coad':ti,ab,kw OR 'cold':ti,ab,kw OR 'chronic lung disease':ti,ab,kw OR 'chronic lung diseases':ti,ab,kw OR 'asthma'/exp OR 'asthma':ti,ab,kw OR 'bronchiectasis'/exp OR 'diffuse panbronchiolitis':ti,ab,kw OR 'cystic fibrosis'/exp OR 'chronic cough'/exp OR 'chronic cough':ti,ab,kw OR 'lower respiratory tract disease*':ti,ab,kw OR 'lrtd':ti,ab,kw	1,203,131
#2	**Respiratory diseases principally affecting the lung interstitium**	'pulmonary eosinophilia'/exp OR 'pulmonary eosinophilia':ti,ab,kw OR 'lung alveolus proteinosis'/exp OR 'pulmonary alveolar proteinosis':ti,ab,kw OR 'pulmonary alveolar microlithiasis':ti,ab,kw OR 'interstitial lung disease'/exp OR 'interstitial lung disease*':ti,ab,kw OR 'lung fibrosis'/exp OR 'pulmonary fibrosis':ti,ab,kw OR 'fibrosing lung disease':ti,ab,kw OR 'fibrosing alveolitis':ti,ab,kw OR 'diffuse parenchymal lung disease':ti,ab,kw OR 'dendriform pulmonary ossification':ti,ab,kw	213,869
#3	**Lung diseases due to external agents**	'pneumoconiosis'/exp OR 'pneumoconiosis':ti,ab,kw OR 'aluminosis':ti,ab,kw OR 'bauxite*':ti,ab,kw OR 'berylliosis':ti,ab,kw OR 'siderosis':ti,ab,kw OR 'stannosis':ti,ab,kw OR ('pneumoconiosis':ti,ab,kw AND 'tuberculosis':ti,ab,kw) OR 'lung edema'/exp OR 'pulmonary edema':ti,ab,kw OR 'pulmonary oedema':ti,ab,kw OR 'byssinosis':ti,ab,kw	77,776

#4	**Other CRDs**	'sarcoidosis'/exp OR 'sarcoidosis':ti,ab,kw OR 'besnier-boeck-schaumann disease':ti,ab,kw OR 'boeck`s disease':ti,ab,kw OR 'boeck`s sarcoid':ti,ab,kw OR 'schaumann`s disease':ti,ab,kw OR 'schaumann`s syndrome':ti,ab,kw OR 'hutchinson-boeck disease':ti,ab,kw OR 'hutchinson-boeck syndrome':ti,ab,kw OR 'pleura effusion'/exp OR 'pleural effusion':ti,ab,kw	173,745
#5	**Lung cancer**	'lung tumor'/exp OR 'small cell lung cancer'/exp OR 'non small cell lung cancer'/exp OR ('adenocarcinoma':ti,ab,kw AND 'lung':ti,ab,kw) OR (('lung':ti,ab,kw OR 'trachea*':ti,ab,kw OR 'bronchus':ti,ab,kw) AND ('cancer*':ti,ab,kw OR 'neoplasm*':ti,ab,kw OR 'carcinoma*':ti,ab,kw OR 'malignan*':ti,ab,kw OR 'tumor*':ti,ab,kw OR 'tumour*':ti,ab,kw))	749,066
#6	**Vaccines**	'Pneumococcus vaccine'/exp OR 'respiratory syncytial virus vaccine'/exp OR 'diphtheria pertussis tetanus vaccine'/exp OR 'pertussis vaccine'/exp OR 'haemophilus influenzae type b polysaccharide vaccine' OR 'haemophilus influenzae type b-polysaccharide vaccine-diphtheria toxoid conjugate' OR (('pneumococcal':ti,ab,kw OR 'pneumococcal conjugate':ti,ab,kw OR 'respiratory syncytial virus':ti,ab,kw OR 'rsv':ti,ab,kw OR 'pertussis':ti,ab,kw OR 'dtp':ti,ab,kw OR 'dpt':ti,ab,kw OR 'dtap':ti,ab,kw OR 'haemophilus influenz*':ti,ab,kw OR 'hemophilus influenz':ti,ab,kw OR 'h.influenzae':ti,ab,kw OR 'nthi':ti,ab,kw OR 'group b streptococcus':ti,ab,kw OR 'gbs':ti,ab,kw) AND ('vaccine'/exp OR 'immunization'/exp OR 'immunotherapy'/exp OR 'vaccin*':ti,ab,kw OR 'immune':ti,ab,kw))	70,800
#7	**Human**	'animal'/de NOT 'human'/de	1,631,516
#8	**Type of studies**	'comment':it OR 'letter':it OR 'editorial':it OR 'case reports':it OR 'case report*':ti OR 'case stud*':ti OR 'case series':ti OR 'case histor*':ti	2,690,137
#9	**(#1 OR #2 OR #3 OR #4 OR #5) AND #6 NOT (#7 OR #8)**		8,848

#10	**Filter for adults, language and publications after 2000**		2,163
#11	**Applying filter on publication types (article, article in press)**		**1,141**
#12	**Vaccination for chronic cough before 2000**		3
#13	**#11 OR #12**		**1144**

Table S6: Web of science, date: 31/07/2024

No	Block	Search terms	Results
#1	**Certain lower respiratory tract diseases**	TS=(bronchitis OR bronch*) OR TS=("chronic tracheitis" OR chronic tracheitis) OR TS=("chronic tracheal infection" OR chronic tracheal infection) OR TS=("chronic bronchorrhoea" OR chronic bronchorrhoea) OR TS=("chronic laryngotracheobronchitis" OR chronic laryngotracheobronchitis) OR TS=("chronic tracheopharyngitis" OR chronic tracheopharyngitis) OR TS=("tracheobronchopathia" OR tracheobronchopathia) OR TS=("tracheobronchomegaly" OR tracheobronchomegaly) OR TS=("Mounier-Kuhn syndrome" OR Mounier-Kuhn syndrome) OR TS=("emphysema" OR pulmonary emphysema OR emphysema) OR TS=("MacLeod syndrome" OR "Swyer-James syndrome" OR "unilateral transparency of lung" OR "hyperlucent lung") OR	1,080,940

		TS=("chronic obstructive pulmonary disease*" OR "chronic obstructive airway disease*" OR "chronic obstructive lung disease*" OR COPD OR COAD OR COLD OR "chronic lung disease" OR "chronic lung diseases") OR TS=(asthma) OR TS=(bronchiectasis OR "diffuse panbronchiolitis") OR TS=("cystic fibrosis") OR TS=("chronic cough" OR chronic cough) OR TS=("lower respiratory tract disease*" OR LRTD)	
#2	**Respiratory diseases principally affecting the lung interstitium**	TS=("pulmonary eosinophilia") OR TS=("pulmonary alveolar proteinosis" OR "pulmonary alveolar microlithiasis") OR TS=("interstitial lung disease*" OR "lung diseases, interstitial") OR TS=("pulmonary fibrosis" OR "fibrosing lung disease" OR "fibrosing alveolitis" OR "diffuse parenchymal lung disease" OR "dendriform pulmonary ossification")	60,422

#3	**Lung diseases due to external agents**	TS=("pneumoconiosis") OR TS=("aluminosis") OR TS=("bauxite*") OR TS=("berylliosis") OR TS=("siderosis") OR TS=("stannosis") OR TS=("pneumoconiosis" AND "tuberculosis") OR TS=("pulmonary edema" OR "pulmonary oedema") OR TS=("byssinosis")	34,938
#4	**Other CRDs**	TS=("sarcoidosis" OR "Besnier-Boeck-Schaumann disease" OR "Boeck's disease" OR "Boeck's sarcoid" OR "Schaumann's disease" OR "Schaumann's syndrome" OR "Hutchinson-Boeck disease" OR "Hutchinson-Boeck syndrome") OR TS=("pleural effusion")	52,252
#5	**Lung cancer**	TS=("lung neoplasms" OR "small cell lung carcinoma" OR "carcinoma, non-small-cell lung") OR TS=(adenocarcinoma AND lung) OR TS=((lung OR trachea* OR bronchus) AND	529,130

		(cancer* OR neoplasm* OR carcinoma* OR malignan* OR tumor* OR tumour*))	
#6	**Vaccines**	TS=("pneumococcal vaccines" OR "respiratory syncytial virus vaccines" OR "diphtheria-tetanus-pertussis vaccine" OR "pertussis vaccine" OR "haemophilus influenzae type b polysaccharide vaccine" OR "haemophilus influenzae type b-polysaccharide vaccine-diphtheria toxoid conjugate") OR (TS=(pneumococcal OR "pneumococcal conjugate" OR "respiratory syncytial virus" OR rsv OR Pertussis OR DTP OR DPT OR DTAP OR "haemophilus influenza" OR "hemophilus influenz" OR h.influenzae OR nthi OR "Group B streptococcus" OR GBS) AND TS=("vaccines" OR "immunization" OR "immunotherapy" OR vaccin* OR immune))	45,010
#7	**Human**	TS=(animals NOT humans)	1,185,452
#8	**Type of studies**	TI=("case report*" OR "case stud*" OR "case series" OR "case histor*") OR TS=("Comment" OR "Letter" OR "Editorial" OR "Case Report" OR "Case Study" OR "Case Series" OR "Case History")	1,477,742
#9	**Infants**	TS=(infants OR newborns OR neonates OR "young children" OR "early childhood")	**804,602**
#10	**Vaccination for chronic cough before 2000 and after 1970**		**8**

#11	**(#1 OR #2 OR #3 OR #4 OR #5) AND #6 NOT (#7 OR #8 OR #9),**		**4,110**
#12	**Applying filters for language, publication year and publication type**		**1,966**
#13	**#10 OR #12**		**1,974**

Table S7: Risk of bias assessment for RCTs (6 studies)

Author	Randomization process	Deviations interventions	Missing outcome	Measurement of the outcome	Selection of the reported result	Overall bias	What is the overall predicted direction of bias for this outcome? (optional)
Alfageme, 2006 (51)	Low	Low	Low	Low	Low	Low	
R L Clancy, 2016 (66)	Low	Low	Low	Low	Low	Low	
Dransfield, 2012 (55)	Low	Low	Low	Some concerns	Low	Some concerns	One of the eligible criteria was the participants had never received PPSV23 or if it was administered >5 years before randomization. However, the assessors did rely in part on self-reported vaccination, and thus, it is possible that some participants were misclassified as vaccine naive or previously vaccinated or were enrolled <5 years after previous PPSV23.
Akitsugu Furumoto, 2008 (67)	Low	Low	Low	Some concerns	Low	Some concerns	The assessors were not blinded and there might be some bias for assessing the outcomes.
Steentoft, 2006 (72)	Low	Low	Low	Low	Low	Some concerns	The sample size was small. In addition the follow-up period was relatively short (six months).
Hua, J. L., 2023 (75)	Low	Low	Low	Low	Low	Low	The sample size was relatively small.

Table S8: Quality assessment of observational studies with control group (20 studies)

Author	1. Research question	2. Study population	3. Participation rate	4. Recruited site	5. Sample size	6. measuring the exposure(s)	7. Sufficient timeframe	8. Different levels of the exposure	9. Exposure measures	10. Exposure(s) assessments	11. Outcome measures	12. Blinding	13. loss to follow-up	14. Confounding	15. Overall quality	Overall quality (description)
Chiou, 2015 (79)	Yes	Yes	NA	Yes	No	No	Yes	NA		NA	Yes	CD	CD	Yes	Fair	A higher percentage of unvaccinated population were on cancer treatment compared to vaccinated population. Hence, the vaccinated people. In addition, vaccinated people have high healthy awareness and take care for aspiration pneumonia or other infections. Thus, the effectiveness of vaccine may be overestimated.
Figueira-Gonçalves, 2017 (52)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	CD	Yes	Yes	Fair	The baseline characteristics were not reported per arm. In addition the impact of PCV13 with and without influenza vaccine was not reported. The sample size was small as well.
Figueira-Gonçalves, 2020 (53)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	CD	Yes	Yes	Fair	The baseline characteristics were not reported per arm. In addition the impact of PCV13 with and without influenza vaccine was not reported. The sample size was small as well.
Gómez-Junyent, 2014 (68)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	CD	CD	CD	Fair	The baseline characteristics were not reported per arm. In addition the impact of PPV23 with and without influenza vaccine was not reported. The sample size was small as well.
Ignatova, 2021 (54)	Yes	Yes	CD	Yes	No		Yes	NA	Yes	NA	Yes	No	CD	No	Fair	The PPV23 arm had a significantly lower sample size. Moreover, n order to minimize the risk of bias associated with the non-randomized study design,

																they employed PSM method. However, PSM method was not explained.
Arda Kiani, 2023 (69)	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	NA	CD	CD	Yes	Yes	Fair	The baseline characteristics were not reported per arm. In addition the impact of pneumococcal vaccine with and without influenza vaccine was not reported.
Kurashima, 2016 (77)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	No	NA	Yes	CD	CD	Yes	Fair	Vaccination status was self-reported. No baseline characteristics for vaccinated and unvaccinated.
Lee, 2007 (49)	Yes	Yes	CD	Yes	Yes	Yes	Yes	NA	Yes	NA	Yes	CD	CD	Yes	Good	By solely focusing on patients vaccinated, they removed concerns about selection bias, and they also matched all patients with similar controls in the same time period, accounting for secular trends related to infection
Mao, 2022 (71)	Yes	Yes	CD	Yes	No	No	No	NA	Yes	NA	Yes	CD	CD	Yes	Fair	The baseline characteristics for vaccinated and unvaccinated population did not reported. The impact of pneumococcal vaccine was not reported on the population that did not receive influenza vaccine.
Rosario Menéndez, 2017 (58)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	CD	NA	Yes	CD	CD	Yes	Fair	The baseline characteristics for vaccinated and unvaccinated population was not reported
Olga Ochoa-Gondar, 2008 (60)	Yes	Yes	CD	No	No	Yes	Yes	NA	Yes	NA	Yes	CD	CD	Yes	Fair	It must be noted that the results of the study tended to vary with the method of analyses.'
Akshay J Patel, 2020 (80)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	CD	CD	Yes	Fair	The baseline characteristics were not reported per arm.
Schembri, 2009 (45)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	CD	CD	Yes	Fair	Little baseline characteristics reported. Besides, there might be some bias due to unrecorded factors: it may be true that patients with good health behaviour seek vaccination more frequently than those with poor health behaviour
Rosalyn J Singleton, 2007 (64)	Yes	Yes	NA	Yes	No	Yes	No	NA	Yes	NA	Yes	CD	CD	No	Poor	The baseline characteristics for vaccinated and unvaccinated population were not reported. The impact of pneumococcal vaccine was not reported on

																the population that did not receive influenza vaccine. In addition, the confounders were not controlled.
Rajesh Venkitakrishnan, 2023 (74)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	No	CD	No	Fair	They did not adjust for confounding factors, also the presence of medical comorbidities was much higher in the vaccinated group (significant), this might have biased the results
Angel Vila-Corcoles, 2012 (62)	Yes	Yes	CD	Yes	Yes	Yes	CD	NA	Yes	NA	Yes	CD	No	Yes	Fair	The follow-up duration was not reported.
Satoshi Inoue, 2011 (65)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	Yes	NA	Yes	No	CD	Yes	Fair	The baseline characteristics for vaccinated and unvaccinated population were not reported.
Zichen Ji, 2020 (48)	Yes	Yes	CD	Yes	No	Yes	Yes	NA	No	NA	Yes	No	CD	CD	Poor	Not reported baseline characteristics of control and vaccination group. Furthermore, very little is written down about the impact of the vaccination
Kwok WC, 2024 (63)	Yes	Yes	NA	Yes	No	Yes	CD	NA	Yes	NA	Yes	No	CD	Yes	Fair	Not reported how long follow-up timeframe was. In addition, The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed (only was discussed for IPD).
Raúl H Sansores, 2022 (76)	Yes	Yes	No	Yes	No	Yes	Yes	NA	Yes	NA	Yes	CD	CD	Yes	Poor	The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed. The baseline characteristics for vaccinated and unvaccinated population were not reported. The vaccinated group contained individuals with at least PV or IV, so the percentage of participants that received both PV and IV was not mentioned.

Abbreviations: CD = cannot determine; NA= not applicable

Table S9: Quality assessment of observational studies with before-after design without control group (5 studies)

Author	1. Research question	2. Study population	3. Representative of the general population	4. Participants enrolment	5. Sample size	6. Intervention description	7. Prespecified measurements of outcome	8. Blinding	9. Loss to follow-up	10. Statistical analyses	11. Outcome measurements	12. Use of individual-level data	13. Overall quality	Overall quality (description)
Yan Li, 2022 (70)	Yes	Yes	Yes	Yes	CD	Yes	Yes	CD	Yes	Yes	NA	NA	Fair	It should be noted that the follow-up time was one year. The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed.
Sumitani, 2008 (61)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	Yes	NA	NA	Fair	The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed. Limited information on how the statistical analysis was performed.
Görkem Vayiso Şahin, 2022 (73)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	Yes	NA	NA	Fair	It should be noted that the follow-up time was one year. The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed.

El-Bardissy, 2019 (78)	Yes	Yes	Yes	CD	No	Yes	Yes	No	CD	Yes	NA	CD	Fair	The sample size needed to detect a hypothesized difference in outcomes and a discussion on statistical power were not discussed.
Alessandra M Lanz, 2022 (59)	No	No	Yes	CD	No	Yes	No	No	No	No	NA	CD	Poor	No statistical analysis for the outcome (exacerbation) was performed.

Abbreviations: CD = cannot determine; NA= not applicable

Table S10: Summary of findings (GRADE) for PPV23 compared to Placebo for CRDs and lung cancer

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
All-cause mortality follow-up: range 24 months to 81.6 months	The impact of PPV23 on all-cause mortality was mixed. One study reorted increased HR in vaccinated poeple. Another study reported increases RR for vaccinated people. The other five studies reported a protective impact of PPV23, however in three studies the impact was not statistically significant (two studies reported that PPV23 had a significant protective impact on all-cause mortality in lung cancer patients).	41478 (6 non-randomised studies and 1 RCT)	⊕◯◯◯ Very low[a,b]
Mortality due to pneumonia follow-up: range 27 months to 200 months	Most of the studies reported a protective impact of PPV23, however in three studies (out of five) the impact was not statistically significant.	4152 (4 non-randomised studies and 1 RCT)	⊕◯◯◯ Very low[a,b]
All-cause hospitalization follow-up: range 6 months to 24 months	One study reported a significant protective impact of PPV23 on all-cause hospitalization while another study reported no difference.	187 (1 non-randomised study and 1 RCT)	⊕◯◯◯ Very low[b,c]
Hospitalization due to pneumonia follow-up: range 40 months to 60 months	Two studies reported a protective impact on hospitalization due to pneumonia (CAP), however one study was statistically significant and another not. One study showed a lower rate of pneumonia in first year (confidence interval or P-value were not provided) and higher after five years (statistically significant) for PPV23 compared to non-vaccinated group.	36455 (3 non-randomised studies)	⊕◯◯◯ Very low[a,b]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Exacerbation follow-up: range 6 months to 60 months	Three studies reported reduction in exacerbation in the PPV23 arm (one study did not provide confidence interval or P-value, in the other study the decrease was not significant and in the last study there was a significant reduction). Conversely, two studies reported increase in exacerbation (not statistically significant).	1870 (5 non-randomised studies)	⨁◯◯◯ Very low[a,b]
Pneumonia follow-up: range 24 months to 180 months	Five studies reported a reduction in pneumonia in PPV23 arm (in two studies the reduction was significant and in three studies it was not significant). One study reported a not significant reduction in first year and a statistically significant after five years.	2104 (6 non-randomised studies and 1 RCT)	⨁◯◯◯ Very low[a,b]

a. Not reporting or different in baseline characteristics for vaccinated and non-vaccinated population

b. Wide range of reported confidence intervals or not statistically significant

c. Small sample size

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table S11: Summary of findings (GRADE) for PCV13 compared to Placebo for CRDs

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
All-cause mortality follow-up: range 12 months to 18 months	The impact of PCV13 on all-cause mortality was mixed. One study reported higher mortality rate in vaccinated group while another one reported lower mortality rate in the vaccinated group (both not significant).	241 (2 non-randomised studies)	⊕◯◯◯ Very low[a,b]
All-cause hospitalization follow-up: range 18 months to 18 months	One study reported a protective impact of PCV13 on all-cause hospitalization (not statistically significant).	165 (1 non-randomised study)	⊕◯◯◯ Very low[a,c]
Exacerbation follow-up: range 12 months to 60 months	Vaccinated people with PCV13 had a lower rate of exacerbation, in two studies the impact was statistically significant and in another one not.	607 (3 non-randomised studies)	⊕◯◯◯ Very low[a,b]
Pneumonia follow-up: range 12 months to 60 months	Two studies reported lower rate of pneumonia (statistically significant).	486 (2 non-randomised studies)	⊕◯◯◯ Very low[c]
Hospitalization due to pneumonia follow-up: range 60 months to 60 months	One study reported a statistically significant reduction in hospitalization rate due to pneumonia in the people vaccinated with PCV13.	270 (1 non-randomised study)	⊕◯◯◯ Very low[c]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)

a. Not reporting or different in baseline characteristics for vaccinated and non-vaccinated population

b. Wide range of reported confidence intervals or not statistically significant

c. Small sample size

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table S12: Summary of findings (GRADE) for unspecified pneumococcal vaccine (PV) compared to placebo for CRDs

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Hospitalization due to exacerbation	One reported a lower rate of all-cause hospitalization in people vaccinated with PV (statistically significant).	265 (1 non-randomised studies)	⊕◯◯◯ Very low[c]
Hospitalization due to pneumonia	One study reported a significant reduction in hospitalization due to pneumonia.	144 (1 non-randomised study)	⊕◯◯◯ Very low[c]
Exacerbation follow-up: range 18 months to 24 months	Two studies reported a protective impact of PV on exacerbation (statistically significant).	1621 (2 non-randomised studies)	⊕◯◯◯ Very low[a]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)

a. Not reporting or different in baseline characteristics for vaccinated and non-vaccinated population

c. Small sample size

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table S13: Summary of findings (GRADE) for PPV23 compared to PCV13 or PCV7 for CRDs

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
All-cause mortality follow-up: range 24 months to 24 months	One study reported lower rate of all-cause mortality for PCV7 compared to PPV23 (statistical test was not provided).	181 (1 RCT)	⊕⊕◯◯ Low[a,b]
Hospitalization due to pneumonia follow-up: range 60 months to 60 months	One study reported a statistically significant lower rate of hospitalization due to pneumonia in PCV13 compared to PPV23.	155 (1 non-randomised study)	⊕◯◯◯ Very low[a]
Exacerbation follow-up: range 24 months to 60 months	One study reported not statistically significant protective effect of PCV7 compared to PPV23 and one study reported statistically significant lower rate of exacerbation in PCV13 compared to PPV23.	336 (1 non-randomised study and 1 RCT)	⊕◯◯◯ Very low[a,b]
Pneumonia	One study reported a statistically significant lower rate of pneumonia in PCV13 compared to PPV23.	155 (1 non-randomised study)	⊕◯◯◯ Very low[a]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)

a. Small sample size

b. Wide range of reported confidence intervals or not statistically significant

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table S14: Summary of findings (GRADE) for PPV23/PCV13 + influenza vaccine (IV) compared to IV for CRDs

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
All-cause mortality (PPV23+IV vs IV) follow-up: range 24 months to 24 months	One study reported increased rate while another study reported decreased rate of all-cause mortality (both not statistically significant).	1711 (1 non-randomised study and 1 RCT)	⨁◯◯◯ Very low[a,b]
All-cause mortality (PCV13+IV vs IV)	One study reported a protective effect (statistically significant).	2612 (1 non-randomised study)	⨁◯◯◯ Very low[a]
All-cause mortality (PPV23 and PCV13+IV vs IV)	One study reported a protective effect (statistically significant).	2612 (1 non-randomised study)	⨁◯◯◯ Very low[a]
All-cause hospitalization follow-up: range 24 months to 24 months	One study reported decrease in all-cause hospitalization after vaccination with PPV23 (statistically significant).	210 (1 non-randomised study)	⨁◯◯◯ Very low[a]
Hospitalization due to pneumonia	One study reported decrease in hospitalization due to pneumonia after vaccination with PPV23 (statistical test was not reported) .	210 (1 non-randomised study)	⨁◯◯◯ Very low[a,b]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Exacerbation follow-up: range 24 months to 24 months	One study reported decrease in exacerbation for PPV23+IV compared to IV (in the first year was statistically significant while not in the second year).	167 (1 RCT)	⨁⨁◯◯ Very low[a,b]
Pneumonia follow-up: range 24 months to 24 months	One study reported decrease in pneumonia for PPV23+IV compared to IV (not statistically significant).	167 (1 RCT)	⨁⨁◯◯ Very low[a,b]

a. Small sample size

b. Wide range of reported confidence intervals or not statistically significant

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table S15: Summary of findings (GRADE) for pneumococcal vaccine (PV) + influenza vaccine (IV) compared to Placebo for CRDs

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
All-cause mortality	One study reported decrease in all-cause mortality (statistically significant).	36697 (1 non-randomised study)	⊕◯◯◯ Very low[a]
All-cause hospitalization follow-up: range 12 months to 24 months	Two studies reported a statistical significant protective effect on all-cause hospitalization (one study with PPV23 and one study did not specify PV).	642 (2 non-randomised studies)	⊕◯◯◯ Very low[a,b]
Exacerbation follow-up: range 12 months to 24 months	Two studies reported decrease in exacerbation (in one study it was statistically significant, in another study the statistical test was not provided).	653 (1 non-randomised study and 1 RCT)	⊕⊕◯◯ Low
Pneumonia	One study reported a decrease in pneumonia (statistically significant).	592 (1 non-randomised study)	⊕◯◯◯ Very low[b]

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)

a. Not reporting or different in baseline characteristics for vaccinated and non-vaccinated population

b. Small sample size

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table S16: Summary of findings (GRADE) for NTHi compared to placebo for COPD

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
All-cause mortality follow-up: range 9 months to 9 months	The vaccinated individuals had a higher all-cause mortality (not statistically significant).	320 (1 RCT)	⨁⨁◯◯ Low[a,b]
Exacerbation follow-up: range 9 months to 9 months	The exacerbation rate was the same for both vaccinated and non-vaccinated groups for the total population. However, the people aged younger than 65 had a statistically significant lower exacerbation rate in vaccinated arm compared to non-vaccinated arm.	320 (1 RCT)	⨁⨁◯◯ Low[a,b]

a. Small sample size

b. Wide range of reported confidence intervals or not statistically significant

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table S17: Excluded RSV and NTHi vaccine studies

Author, year	Population	Study design	Study conclusion	Reason to exclude
NTHi vaccine				
Smedt, 2021 (94)	Healthy adults 18 to 71 years old	RCT, Phase 1	Immune responses against NTHi antigens persisted for 4 years after two-dose vaccination with the investigational NTHi-Mcat vaccine. There was no persistent response against the Mcat antigen. No safety concerns were identified during the long-term follow-up.	Phase 1
Andreas, 2022 (95)	COPD	RCT, Phase 2b	NTHi–Mcat vaccine administered to patients with COPD did not show efficacy in reducing the yearly rate of moderate or severe exacerbations. No safety concerns were identified.	Phase 2
Galgani, 2023 (96)	COPD	RCT, Phase 2b	In conclusion, the study demonstrated immunological non-inferiority of sequential administration of the NTHi-Mcat vaccine following RZV administration versus administration of the NTHi-Mcat vaccine alone. No specific time window was required between the two vaccines, which contain the same AS01 components in different quantities.	Phase 2
Arora, 2022 (97)	COPD	RCT, Phase 2b	Results suggest potential efficacy with the NTHi-Mcat vaccine against severe exacerbations in certain patients with COPD, in particular those who have frequent exacerbations and use inhaled corticosteroids. This potential signal requires confirmation in an appropriately designed prospective clinical trial.	Phase 2
Wilkinson, 2019 (98)	COPD	RCT, Phase 2	The NTHi vaccine had an acceptable safety and reactogenicity profile and good immunogenicity in adults with COPD.	Phase 2
RSV vaccine				
Curran, 2024 (99)	Adults ≥ 60 years of age	RCT, Phase 3	The RSVPreF3 OA vaccine, in addition to preventing infection, attenuated the severity of RSV-associated symptoms in breakthrough infections, with trends of reduced impact on PF and health utility.	The outcomes were not reported for CRDs.

Eto, 2024 (100)	Adults ≥ 60 years of age	RCT, Phase 1	A single dose of Ad26.RSV.preF/RSV preF protein vaccine had an acceptable safety and tolerability profile and induced RSV-specific humoral immunity in Japanese healthy adults.	Phase 1 study
Falsey, 2024 (101)	Adults ≥ 60 years of age	RCT, phase 2b (CYPRESS)	Ad26.RSV.preF–RSV preF protein maintained high efficacy against RSV LRTD in older adults across three RSV seasons.	Phase 2 study
Falsey, 2008 (102)	Adults ≥ 65 years of age with cardiopulmonary diseases	RCT	Although the safety and immunogenicity data of these RSV vaccines are encouraging, low rates of infection make it challenging to design efficacy trials.	The outcomes were not reported for CRDs.
Leroux-Roels, 2023 (103)	Healthy women, aged 18–45 years	RCT, Phase 1	V-306 was safe and well-tolerated. Future modifications of the vaccine and assay conditions will likely improve the results of vaccination.	Phase 1 study
Schmoele-Thoma, 2022 (104)	Healthy adults (18 to 50 years of age)	RCT, Phase 2a	preF vaccine was effective against symptomatic RSV infection and viral shedding. No evident safety concerns were identified. These findings provide support for further evaluation of RSVpreF vaccine in a phase 3 efficacy study.	Phase 2a study
Walsh, 2023 (83)	Adults ≥ 60 years of age	RCT, Phase 3	RSVpreF vaccine prevented RSV-associated lower respiratory tract illness and RSV-associated acute respiratory illness in adults (≥60 years of age), without evident safety concerns.	The outcomes were not reported for CRDs.
Ison, 2024 (82)	Adults ≥ 60 years of age	RCT, Phase 3	One RSVPreF3 OA dose was efficacious against RSV-LRTD over 2 RSV seasons in ≥60-year-olds. Revaccination 1 year post–dose 1 was well tolerated but did not seem to provide additional efficacy benefit in the overall study population.	The outcomes were not reported for CRDs.
Feldman, 2024 (81)	Older Adults (≥ 60) With Underlying Medical Conditions	RCT, Phase 3	RSVPreF3 OA was efficacious against RSV-LRTD and RSV-ARI in older adults with coexisting medical conditions associated with an increased risk of severe RSV disease.	The outcomes for cardiopulmonary conditions were reported and not separately for CRDs.

Abbreviations: COPD = chronic obstructive pulmonary disease; CRD = chronic respiratory disease; LRTD = lower respiratory tract disease; NTHi = Non-Typeable *Haemophilus influenzae*; RCT = randomized control trial; RSV = respiratory syncytial virus; RZV = recombinant zoster vaccine

Relevant review/recommendation articles

Table S18 shows the selected reviews or recommendation that were found in full-text screening. The Cochrane review by Teo et al. 2017 (57) concluded that the evidence for advocating NTHi in COPD population is limited. A review by Simon et al. 2023 (27) advocates pneumococcal and pertussis for COPD population. There are also recommendations for pneumococcal vaccine in idiopathic pulmonary fibrosis, bronchiectasis and the population with a high risk of IPD and immunocompetent (105–107).

Table S18: Relevant review/recommendation studies found in the full-text screening

Author, year	Population	Vaccine(s)	Conclusion/recommendation	Remarks
Simon, 2023 (27)	COPD	Pneumococcal	A single-dose PCV20	European respiratory society
		Pertussis	With the tetanus/diphtheria vaccine recommended every 10 years for other reasons, a triple vaccine (including pertussis booster) or even a quadruple vaccine (plus polio) should be preferred.	
Teo, 2017 (57)	COPD	*Haemophilus influenzae*	Evidence was mixed, and the individual trials that showed a significant benefit of the vaccine are too small to advocate widespread oral vaccination of people with COPD.	Cochrane review
Cottin, 2023 (105)	Idiopathic pulmonary fibrosis	Pneumococcal	Despite the absence of evidence, pneumococcal vaccination may be given using the 13-valent pneumococcal polysaccharide conjugate vaccine (Prevenar 13^{TM}) supplemented two months later with the 23-valent pneumococcal polysaccharide vaccine (Pneumo 23^{TM}).	French practical guidelines

Hill, 2018 (106)	Bronchiectasis	Pneumococcal	Offer polysaccharide pneumococcal vaccination to all patients with bronchiectasis (D). Consider use of 13 valent protein conjugate pneumococcal vaccine in patients with bronchiectasis who do not have an appropriate serological response to standard polysaccharide vaccine (23 valent carbohydrate pneumococcal vaccine).	British Thoracic Society guideline
Agraw, 2019 (108)	COPD	Pneumococcal	The pneumococcal PPSV23 is recommended in younger patients with COPD and FEV1 than 40% of predicted (Evidence B). The pneumococcal PCV13 vaccination is recommended in all patients 65 and older as the evidence has shown that it reduces the risk of bacteremia and serious invasive pneumococcal disease (Evidence B).	
Gemmill, 2015 (107)	High risk of IPD and immunocompetent	Pneumococcal	NACI recommends vaccination with an age-appropriate pneumococcal vaccine for individuals who required medical attention for asthma in the past 12 months. Individuals with medical conditions putting them at high risk of IPD should receive one lifetime booster dose of Pneu-P-23 5 years after the previous one, regardless of age at first dose. One dose of pneumococcal polysaccharide (Pneu-P-23) vaccine is recommended for all adults 65 years of age and older as long as 5 years has passed since any previous Pneu-P-23 dose, and for immunocompetent adults less than 65 years of age in long-term care facilities, or who have conditions putting them at increased risk of pneumococcal disease. All individuals who have previously received Pneu-P-23 vaccine and require reimmunization with pneumococcal conjugate (Pneu-C-13) vaccine should receive Pneu-C-13 vaccine no sooner than five years after the most recent dose of Pneu-P-23.	Canadian Immunization Guide

			Pneu-C-13 should be administered to adults with immunocompromising conditions, followed by Pneu-P-23 at least eight weeks after—if not already administered.	
Riccò, 2024 (109)	Older Adults	RSV	In conclusion, adult RSV vaccination was quite effective in preventing LRTD in older adults, but the overall efficacy rapidly decreased in the second season after the delivery of the vaccine. Because of the heterogenous design of the parent studies, further analyses are required before tailoring specific public health interventions.	Systematic Review and Meta-Analysis of Randomized Controlled Trials

Abbreviations: COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; IPD = invasive pneumococcal disease; LRTD = lower respiratory tract disease; NACI = National Advisory Committee on Immunization (Canada); PCV13 = pneumococcal conjugate vaccine 13-valent; PCV20 = pneumococcal conjugate vaccine 20-valent; PP(S)V23 = pneumococcal polysaccharide vaccine 23-valent

Reviewing the guidelines from selected countries

Table S19 shows the recommendations by the United States (US), the United Kingdom (UK), Germany, Belgium, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the Global Initiative for Asthma (GINA). For PV, all recommended PCV20 with the expectation from the UK which is PCV13 or PCV15. While all recommended pertussis vaccine for all adults, none had a commendation for *Haemophilus influenzae* vaccine. For RSV, Germany, Belgium and the US recommended for the individuals with CRDs at age 60 or above. The UK does not have a recommendation specific for CRDs. The GOLD recommendations were based on the Centers for Disease Control and Prevention (CDC) recommendations (110). The GINA recommended to follow local immunization schedule (111).

Table S19: Vaccine recommendations for selected countries/associations

Country/association	Vaccine	Population	Recommendation
United States	Pneumococcal (112)	Chronic lung disease, including chronic obstructive pulmonary disease, emphysema, and asthma (adults 19–64 years)	*No prior vaccination or vaccination with PCV7:* PCV20 (option A) or PCV15 and ≥1 year then PPV23 (option B) *Prior vaccination with PPV23 only:* ≥1 year then PCV20 (option A) or PCV15 (option B) *Prior vaccination with PCV13 only:* ≥1 year then PCV20 (option A) or PPV23 (option B) *Prior vaccination with PCV13 and PPV23:* No vaccines until 65 years old
	Haemophilus influenzae (113)	-	No recommendation for CRDs

	RSV (114)	Chronic lung disease	Ages 60 to 74 (recommended for all adults aged 75 and older)
	Pertussis (115)	-	No recommendations for CRDs (CDC recommends whooping cough (pertussis) vaccination for everyone: one Tdap shot if they have never received. All adults should receive a Td or Tdap shot every 10 years.)
	GBS	-	No recommendations for CRDs
United Kingdom	Pneumococcal (116)	Chronic respiratory disease (chronic respiratory disease refers to chronic lower respiratory tract disease)	One PCV13 or PCV15 dose PPV23 at 2 years, at least 8 weeks after last PCV dose
	Haemophilus influenzae (117)	-	No recommendations for CRDs
	RSV (118)	-	No recommendations for CRDs (recommended for all adults aged 75 to 79 years)
	Pertussis (119)	-	No recommendations for CRDs (Currently routine immunization against pertussis is not recommended for those aged ten years and over, except for pregnant women (see below) or as part of outbreak control.

			Note: Individuals aged ten years or over who have only had three doses of pertussis vaccine do not need further doses of pertussis-containing vaccine, except in pregnancy, for occupational vaccination of specific healthcare workers or as part of outbreak control.)
	GBS	-	No recommendations for CRDs
Germany	Pneumococcal (120)	Respiratory system diseases (such as COPD, bronchial asthma and pulmonary emphysema)	*No prior vaccination or vaccination with PCV7:* PCV20 *Prior vaccination with a sequential vaccination (PCV13 + PPSV23):* PCV20 at least 6 years after the PPSV23 vaccination PCV20 at least 1 years after the PPSV23 vaccination, in the case of a pronounced immunodeficiency
	Haemophilus influenzae (120)	-	No recommendations for CRDs
	RSV (121)	Chronic respiratory diseases	≥ 60 years old (recommended for all adults aged ≥ 75)
	Pertussis (120)	-	No recommendations for CRDs (Td booster vaccination every 10 years. Next due Td vaccination requires one dose as a Tdap or, in the case of a respective indication, as a Tdap-IPV combination vaccination for all adults ≥18 years old.)
	GBS	-	No recommendations for CRDs

	Pneumococcal (122)	Chronic lung disease of smokers	**Age 50 to 85 years old:** *No prior vaccination:* PCV20 is Preferred. The alternative is PCV15 followed by PPV23 after at least 8 weeks. Revaccination after 5 years with PPV23. *Prior vaccination only with PPV23:* One vaccination with PCV20 at least 1 year after last PPV23. Revaccination with one PPV23 five years after PCV20. *Prior vaccination with PCV13:* First revaccination with PPV23 after at least 8 weeks and then one PPV23 after 5 years All adults older than 85 years: *No prior vaccination:* PCV20 is Preferred. The alternative is PCV15 followed by PPV23 after at least 1 year Alternative: PCV15 followed by PPV23 after at least 1 year *Prior vaccination only with PPV23:* Single vaccination with PCV20 at least 1 year after the last PPV23 *Prior vaccination with PCV13:* Single PPV23 at least 1 year after PCV13 Vaccination with PPV23 is the second choice for primary vaccination
Belgium	*Haemophilus influenzae*	-	No recommendations for CRDs

	RSV (123)	Chronic Respiratory Diseases (COPD, asthma, bronchiectasis, interstitial lung diseases, chronic respiratory failure)	≥ 60 years old
	Pertussis (124)	-	No recommendations for CRDs (one dose for all adults ≥18 years old, booster every 10 years was not recommended)
	GBS	-	No recommendations for CRDs
GOLD (110)	Pneumococcal		
	Haemophilus influenzae		
	RSV	Chronic obstructive pulmonary disease	Based on CDC recommendations for all vaccines
	Pertussis		
	GBS		
GINA (111)	Pneumococcal		
	Haemophilus influenzae		

RSV	Asthma	Follow local immunization schedule
Pertussis		
GBS		

Abbreviations: CDC = Center for Disease Control and Prevention; CRD = chronic respiratory disease; GBS = Group B streptococcus; GINA = Global Initiative for Asthma; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PCV7 = pneumococcal conjugate vaccine 7-valent; PCV15 = pneumococcal conjugate vaccine 15-valent; PCV20 = pneumococcal conjugate vaccine 20-valent; PP(S)V23 = pneumococcal polysaccharide vaccine 23-valent; RSV = respiratory syncytial virus; Tdap = tetanus, diphtheria and pertussis vaccine