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RESEARCH ARTICLE

Recent changes to adult national immunization programs for pneumococcal vaccination in Europe and how they impact coverage: A systematic review of published and grey literature

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ABSTRACT

Despite widespread use of pneumococcal vaccines throughout Europe, the burden of pneumococcal disease (PD) in adults is considerable. To mitigate this burden, National Immunization Technical Advisory Groups (NITAGs) and Health Technology Assessment (HTA) agencies assess the value of different vaccine schedules for protecting against PD. The aim of this review was to assess the evidence and rationales used by NITAGs/HTA agencies, when considering recent changes to National Immunization Programs (NIPs) for adults, and how identified changes affected vaccine coverage rates (VCRs). A systematic review was conducted of published literature from PubMed® and Embase®, and gray literature from HTA/NITAG websites from the last 5 y, covering 31 European countries. Evidence related to NIP recommendations, epidemiology (invasive PD, pneumonia), health economic assessments and VCRs were collected and synthesized. Eighty-four records providing data for 26 countries were identified. Of these, eight described explicit changes to NIPs for adults in seven countries. Despite data gaps, some trends were observed; first, there appears to be a convergence of NIP recommendations in many countries toward sequential vaccination, with a pneumococcal conjugate vaccine (PCV), followed by pneumococcal polysaccharide vaccine 23. Second, reducing economic or healthcare burden were common rationales for implementing changes. Third, most health economic analyses assessing higher-valency PCVs for adults found its inclusion in NIPs cost-effective. Finally, higher coverage rates were seen in most cases where countries had expanded their NIPs to cover at-risk populations. The findings can encourage agencies to improve surveillance systems and work to reach the NIP's target populations more effectively.

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Introduction

Pneumococcal disease (PD) includes a set of symptomatic infections caused by the bacteria *Streptococcus Pneumoniae* (*S. Pneumoniae*) and is a major cause of morbidity and mortality in both children and adults worldwide. PD can be divided into noninvasive and invasive forms of the disease. The most burdensome manifestations of invasive pneumococcal disease (IPD) are pneumococcal meningitis, bacteremic pneumonia, and pneumococcal bacteremia.[1] Though anyone can contract PD, children under 5 y of age, the elderly, and immunocompromised people are at the greatest risk.[2,3] In adults, noninvasive pneumococcal community-acquired pneumonia (CAP) is the most common expression of pneumococcal disease[4] and it is the leading cause of mortality in adults and children around the world.[5]

For European countries, the burden of PD in adults has been explored previously in the literature.[3,4,6,7] Worldwide, the most common cause of CAP is S. *Pneumoniae*.[8] Though the microbiologic diagnostic data is limited, and their estimates vary, CAP is often used as a surrogate for pneumococcal pneumonia. A 2013 estimate for annual incidence of all-cause CAP in European adults ranged between 1.07 and 1.2 per 1000 person-years and increased with age (14 per 1000 person-years in adults aged 65 y). A separate study estimated that all-cause CAP in adults costs the European economy about €10.1 billion (2012 Euros) annually, with €3.6 billion of that value related to productivity loss.[9]

A large part of the burden associated with PD can be mitigated through pneumococcal vaccination. *S. pneumoniae* produces a polysaccharide capsule essential for its pathogenicity, serving as a virulence factor that hampers host immune clearance mechanisms.[3,10] Currently, there are more than 100 recognized polysaccharide serotypes.[11,12] Pneumococcal conjugate vaccines (PCVs) and pneumococcal polysaccharide vaccines (PPVs) have successfully targeted several of them, thus reducing the risk of infection by conferring protection against the specific serotypes selected for those vaccines. All the available pneumococcal vaccines were designed to elicit antibodies against the capsule polysaccharides of the pneumococcal isolates commonly causing disease at the time of development. Therefore, the antibodies only provide protection against the pneumococcus expressing the vaccine-targeted capsules (i.e., against the serotypes chosen for the vaccine), and are not intended to provide protection against non-vaccine serotypes.[12] Pneumococcal vaccines provide protection from IPD as well as noninvasive pneumococcal infection, and decrease vaccine-type nasopharyngeal colonization, thus reducing transmission to unvaccinated individuals.[4]

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In 1983, the first PPV developed, PPV23, was approved for use on children aged two or older and adults,[13] and is still in circulation today. Following the introduction of PCV7, the first pneumococcal conjugate vaccine, widespread inoculation of children throughout Europe substantially decreased most vaccine-type disease, and reduced the overall prevalence of the seven most common serotypes of *S. Pneumoniae* [14] and provided additional protection for adults by mitigating the spread across the population.[15] However, the residual burden associated with the increased prevalence of non-vaccine serotypes[16] encouraged the development of higher-valency PCVs.[15] The European Medicines Agency approved PCV10 and PCV13 in 2009, which improved overall serotype coverage.[17] As a result, these higher valency pneumococcal vaccinations have been introduced into NIPs for children, adults, or both, in certain European countries at varying timepoints over the past 13 y. The continued partial coverage of the newer PCVs have further encouraged the development and introduction of two PCVs with higher valency: PCV15 and PCV20.[18] In addition, recent studies in Europe have encouraged the use of sequential vaccination in adults and elderly, to improve coverage for at-risk individuals.[19,20]

Figure 1 provides the European Centre for Disease Prevention and Control's (ECDC) overview of the current recommendations for pneumococcal vaccination in adults, by European country.

Variations in vaccine introduction and use stem from recommendations made by Health Technology Assessment (HTAs) or by National Immunization Technical Advisory Groups (NITAGs). These multidisciplinary expert panels are appointed by each country to assess the value of adding different vaccines to their NIPs. They do so by reviewing epidemiological evidence (incidence, prevalence, unmet need, etc.), as well as health-economic evidence (cost-effectiveness, budget impact, etc.), among other aspects. A study from 10 y ago determined that 85% of the 27 European countries who responded to their survey had formed a NITAG to help determine NIP policy,[22] a number which has grown since then.

The recent emergence of the COVID-19 pandemic has sparked further interest in vaccination for PD in adults.[23]

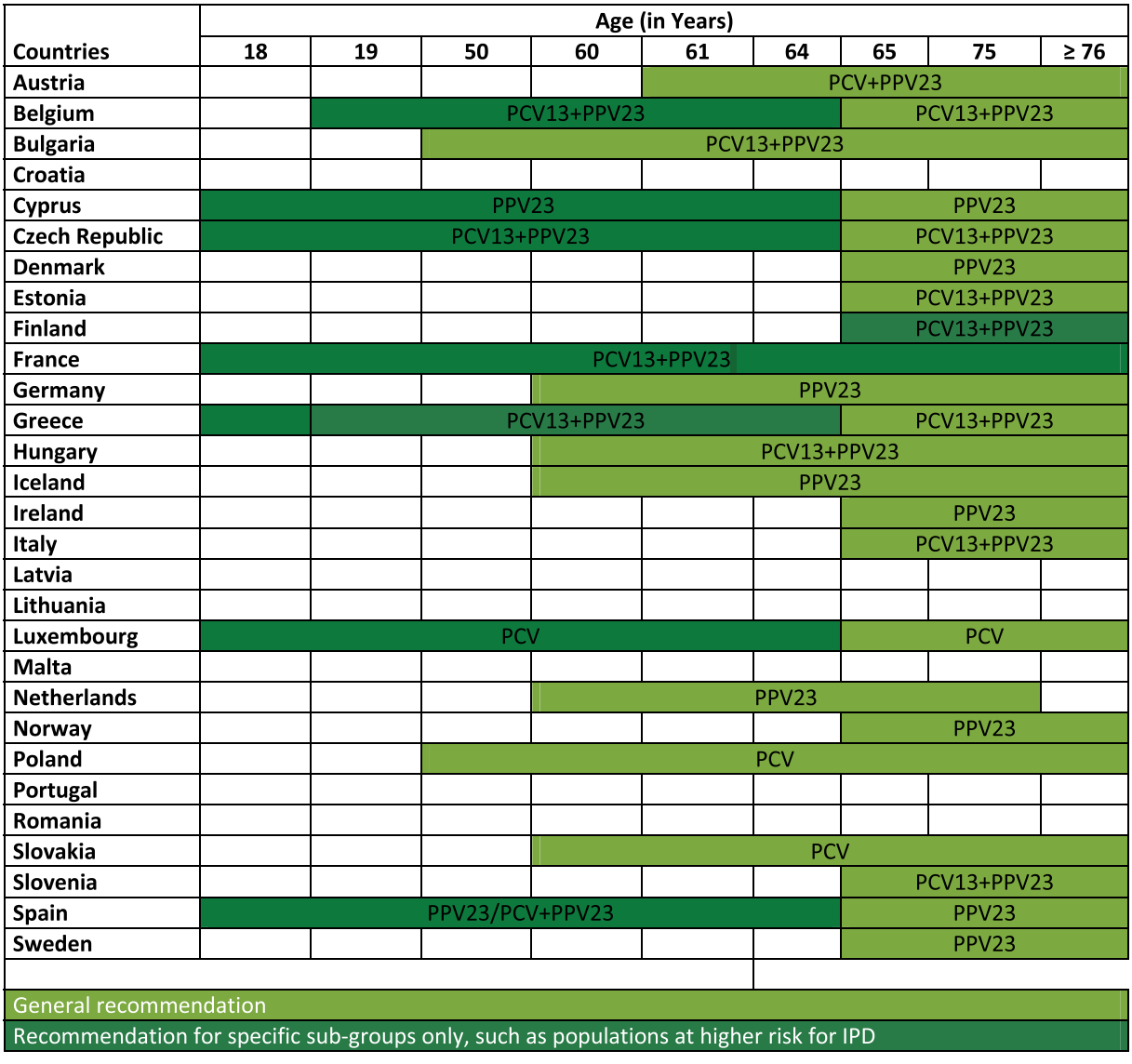

Figure 1. Recommended pneumococcal vaccinations for adults in 2022, by country (ECDC)[21].

New studies assessing the relationship between SARS-CoV-2 and *S. Pneumoniae* have posited increased lethality of coinfection with both pathogens,[24] as well as reduced antibiotic susceptibility in non-vaccine serotypes coinciding with the emergence of COVID-19.[25] Given that PD is an issue in both the young and the old, different factors need to be considered by NITAGs for these separate populations. The use of pneumococcal vaccines in NIPs for children is well documented, and previous literature has assessed the epidemiological and health economic evidence reviewed by NITAGs in their decision-making processes.[26] However, to our knowledge, there is a lack of literature assessing the decisions European NITAGs make about including adult pneumococcal vaccines in their NIPs, particularly in recent years.

Understanding more about how NITAGs make these recommendations can provide academic, public, and private stakeholders with more information on why certain countries choose to include adult pneumococcal vaccines in their NIPs. Furthermore, it highlights how the decisions can potentially impact access for the population and the disease burden within that country. Despite widespread use of pneumococcal vaccines in children and adults, the burden of PD persists,[27,28] meaning that these decisions can affect the lives of thousands of people.

The present study aimed to systematically review and collect information on the consideration of changes to NIPs for adults by European HTAs or NITAGs, in 27 EU countries, as well as Iceland, Norway, Switzerland, and the United Kingdom (UK). If changes had been considered by a particular agency, associated records from gray and published literature were reviewed and the available epidemiological and health economic evidence on burden of IPD and CAP, used by those agencies in their decision-making processes was collected. Finally, an attempt was made to map any changes in NIPs for adults to the vaccine coverage rates (VCRs) in the respective country, after that NIP change.

Methods

This systematic literature review (SLR) involved a structured and pragmatic process for finding, collecting, synthesizing, and reporting the relevant content from records identified within the pre-specified project parameters. The SLR was carried out in line with the Centre for Reviews and Dissemination's (CRD) guidance for undertaking reviews in health care,[29] which included using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and a four-phase flow diagram.[30] All methods implemented in this review were pre-specified in the study protocol.

The eligibility criteria are provided in detail in supplementary Table S1. In brief, published articles and gray literature containing information for the chosen countries about pneumococcal NIP recommendations for adults, epidemiological evidence for IPD/pneumonia in adults, and health economic evidence related to pneumococcal vaccines for adults were included. Relevant record types included technology appraisal guidance, appraisal reports, recommendation extensions, NITAG reports with relevant data, and published literature reporting on pneumococcal vaccine recommendations for adults. The countries included in the review were as follows: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Republic of Malta, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, the UK.

The following literature sources were used:

- Grey literature (HTA and NITAG websites)
- PubMed®, PubMed® in-process from January 1st, 2017 – May 20th, 2022
- EMBASE® from January 1st, 2017 – May 20th 2022

The HTA agencies and NITAG websites outlined in supplementary Table S2 were searched for relevant evidence. The agency website list was developed and merged based on information from several sources including the Global NITAG Network website,[31] and the publicly available lists of HTA and advisory agencies from the International Network of Agencies for Health Technology Assessment (INAHTA)[32] and European Network for Health Technology Assessment (EUNetHTA).[33] All identified recommendation and/or vaccine coverage reports, and other relevant outcomes that fulfilled the criteria in supplementary Table S1 were included in the review. English websites and records were considered as a first choice, however, in case the website and/or subsequent relevant material was not available in English, that text was translated to English using Google Translate and included in the review with this limitation.

In addition to the agency website search, PubMed® and Embase® were searched to identify additional relevant HTA and advisory reports. Search strings can be found in supplementary Table S3 and Table S4, respectively.

The methods for selecting records mimic the recommendations found in the PRISMA guidelines for conducting systematic reviews.[30] Study selection followed a two-step process; in step one, identified literature were screened by title and abstract (or equivalent text) and categorized as 'include,' 'unsure' and 'exclude,' by two independent reviewers based on eligibility criteria. In step two, two reviewers independently reviewed the full texts of the records in the 'included' and 'unsure' categories against the eligibility criteria. Reasons for rejections and exclusions of studies were recorded for all records reviewed at the full-text stage. All relevant data from the included full text reports were extracted into a prespecified data extraction grid, developed during the protocol phase. Two reviewers extracted data independently. At all stages, discrepancies between reviewers were resolved by consensus and unresolved discrepancies were referred to a third arbitrator who was a senior advisor, and a consensus was reached.

The data extraction grid contained the following outcome categories:

- Metadata: Author, year, title, country, etc.
- General information: HTA/NITAG agency(s), population, recommendation, considered changes
- Epidemiological evidence: Context, incidence, prevalence, mortality, etc.

- Serotype data: Distribution, antibiotic resistance/susceptibility
- Economic evidence: HE models used, major assumptions, major inputs, outcomes, conclusion

For the synthesis process, information related to recommendation decisions and evidence used did not require the use of effect measures. VCRs were recorded as percentages, with confidence intervals included, where reported. As the majority of records were expected to be gray literature, and the expected study types would vary considerably, it was deemed impractical at the protocol stage to conduct a risk of bias assessment that would allow the quality of records to be assessed and compared.

This study employed a narrative synthesis of the results; no meta-analysis of the extracted data was performed. No methods were used to assess reporting bias. The potential reporting bias from missing results in the synthesis is examined in the discussion section. It was deemed unnecessary to assess certainty and/or confidence beyond the methods reported in the individual studies. However, the limitations of the body of evidence are considered in the discussion section.

Results

Figure 2 is a PRISMA flow chart, visualizing the record selection process. A total of 460 unique records were identified across the bibliographic database (PubMed® and Embase®) and gray literature searches. The records were then screened and assessed for eligibility according to the methods described above, with the reasons for exclusion recorded at the full text review stage (provided in Figure 2). In total, 84 (52 + 32) records were included for the final data extraction.[34–118]

The 84 records included evidence for 26 of the 31 chosen countries, with no data identified for Bulgaria, Cyprus, Czech Republic, Latvia, and Malta. Some of the included studies provided data for multiple countries and/or multiple outcome categories (recommendation data, coverage rates, etc.). The countries with the greatest number of records containing relevant data were Netherlands (10 records), Italy, Germany, France, and Denmark (8 records each). A total of 42 records provided data related to adult, pneumococcal NIP recommendations, 41 records contained data on VCR, 22 records contained economic evidence and 22 records included epidemiological evidence for IPD or pneumonia. However, the authors were only able to identify data in all four outcome categories for seven of the included countries (Belgium, Denmark, France, Germany, Italy, Portugal, and Netherlands), meaning that for the other chosen countries, the included records did not include data for one or more of the outcome categories.

The supplementary material contains the results of the individual studies, organized into tables for each of the outcome categories: recommendation data (Table S5), epidemiology data (Table S7), health economic data (Table S8), and vaccine coverage (Table S9).

Pneumococcal NIP recommendations for adults

There were 42 records containing information on pneumococcal NIP recommendations. Of those, 32 (76%) were identified through NITAG/HTA websites, while 10 (24%) were from PubMed® and Embase®. Most of these records focused on describing existing recommendations, with 40 of the 42 records expressing positive decisions. The remaining two records just discussed the recommendations for adults.

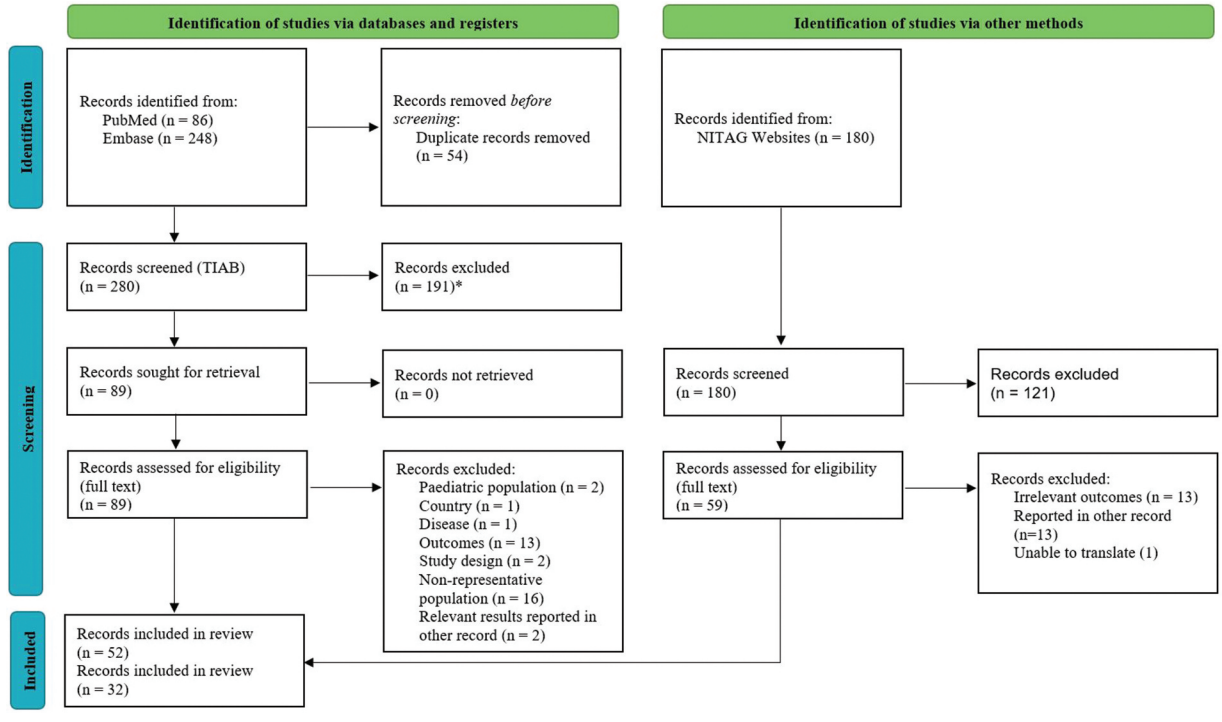

Figure 2. PRIMSA flow chart depicting the record selection process.

Figure 3 provides a breakdown of the number of records recommending each pneumococcal vaccination, by country. The most common pneumococcal recommendations for adults were sequential vaccination with PCV13 and then PPV23 (21 records, across 12 countries) and PPV23 alone (17 records, across 10 countries). Eleven records established that 10 countries recommended use of PCV13 alone. Two records each were identified with recommendations for the use of PCV20 (Belgium and Denmark) and PCV10 (Greece and Ireland), while one record in Belgium recommended the alternative use of PCV15 in tandem with PPV23 for adults. For further details about the recommendation information, see Table S5.

Eight of the records with recommendation information explicitly expressed interest in changing their pneumococcal NIP recommendations. Table S6 provides an overview of the discussions in these records. There are differences in the considerations and evidence that NITAGs employ when assessing the value of including adult pneumococcal vaccinations in their NIPs. A recommendation record for the UK described a panel discussion where the participants considered a change to their NIP.[65] The topics included in this discussion were the introduction of new conjugate vaccines, PCV15 and PCV20, the relationship between COVID-19 and PD, trends in the incidence of PD, the relative effectiveness of PCV13 and PPV23 for adults, indirect protection from childhood immunization programs, and other. The committee concluded that it would be useful to have a model assessing the impact of introducing the newer high-valency PCVs into NIPs for adults.

A recommendation document for Portugal described a change in their NIP for adults to include PPV23 in addition to PCV13.[51] They also extended coverage to provide free PPV23 for select at-risk groups (in addition to PCV13) and expanded the risk groups included in the recommendation. The justifications for this change focused mainly on the shift in residual burden of serotypes not covered by the currently recommended vaccinations as well as the responsibility of the state to bear this cost to reduce societal burden.

Despite these variations in evidence and recommendations, the evidence collected appears to show a convergence in NIP recommendations among the included European countries, toward similar strategies for vaccination. The predominant update to recommendations was a change from single vaccine (e.g., PPV23, PCV13) to sequential vaccination with a higher-valency PCV (PCV13, PCV15, or PCV20), followed by PPV23 for older and/or immunocompromised adults, with the intention of improving both effectiveness and serotype coverage. There are a few other trends present as well; many of the

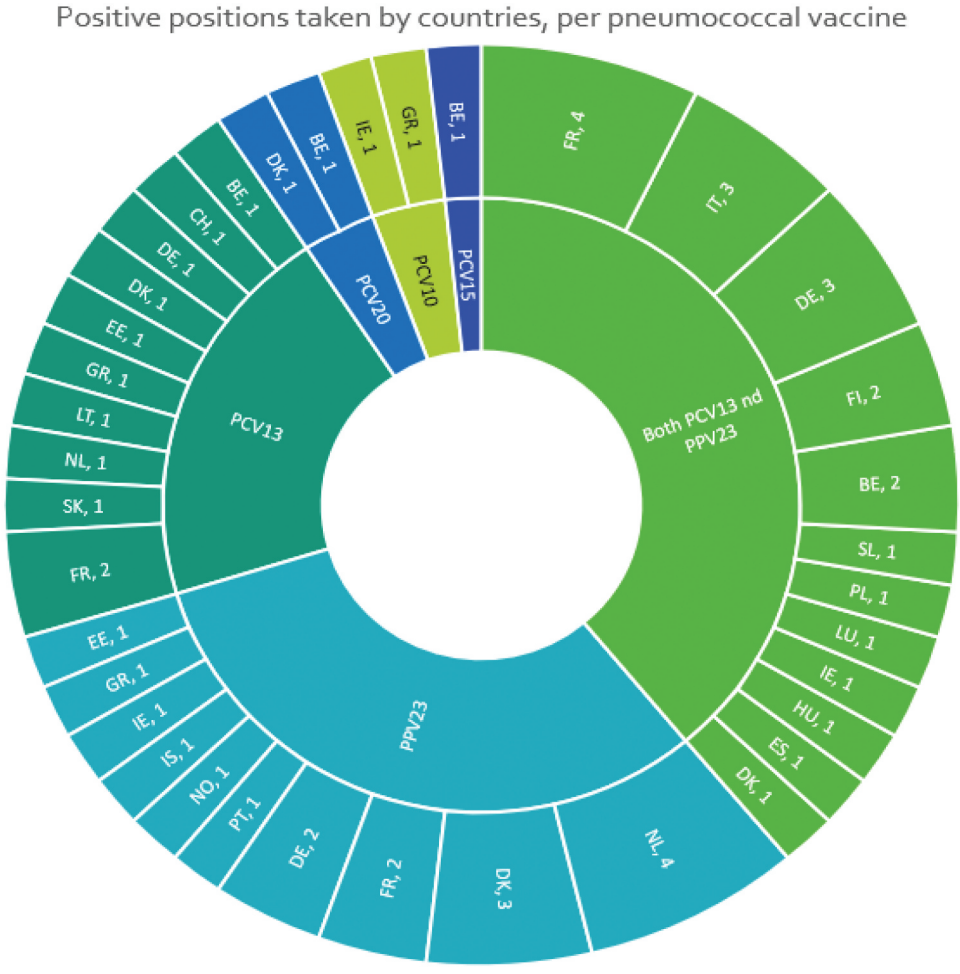

Figure 3. Number of records per country providing a recommendation, per pneumococcal vaccination (as of 2022).
Abbreviations: BE: Belgium, CH: Switzerland, DE: Germany, DK: Denmark, EE: Estonia, ES: Spain; FI: Finland, FR: France, GR: Greece, HU: Hungary, IE: Ireland, IS: Iceland, IT: Italy, LT: Lithuania, LU: Luxembourg, NL: Netherlands, NO: Norway, PL: Poland, PT: Portugal, SK: Slovakia, SI: Slovenia

recommendations involve an expansion of coverage to additional risk groups in adults. The available rationales for these changes commonly focus on reducing either healthcare or economic burden, with some even mentioning the COVID-19 pandemic and the subsequent risk of co-infection. The available rationales are provided in more detail in Table S6. Some of the included records also discuss partial or total reimbursement for vaccination, to reduce economic burden for at-risk individuals.

However, there are some countries, such as Netherlands, who continue to maintain, or have reverted to individual PPV23 vaccination, citing cost benefit, or herd immunity achieved from childhood vaccination as a rationale.

Epidemiological evidence

There were 22 records with epidemiologic evidence provided in the context of PV use for adults. Fourteen records (63.6%) were from PubMed® and Embase®, and eight (36.4%) were from HTA/NITAG reports. The types of data examined by countries, where data were identified are summarized in Table 1, color coded by the source of data. Supplementary Table S7 provides the details of the data available in the identified records. The most common types of evidence assessed across countries were incidence and serotype distribution data for IPD, and incidence and mortality data for pneumonia. Incidence data can provide decision makers with a clear picture of the annual burden of pneumococcal disease in adults. Serotype distribution data can aid in discussions of the extent of coverage that different pneumococcal vaccines can provide (i.e., whether the common serotypes expressed in the public are covered by certain pneumococcal vaccines). The interest in mortality data for pneumonia is also understandable, given that all-cause CAP is the leading cause of pneumonia mortality in the world.[5]

Of the 22 identified records, 11 (50%) expressed positive recommendations for their NIPs, e.g., with either a new recommendation or simply by retaining or amending the existing dosing scheme at that time. The remaining 11 records did not discuss recommendations. Some countries furthermore referenced European-level data, and/or data sourced at the national and subnational level, though the majority of data were identified from published literature. It was also interesting to note that most of the records (21/22, 95%) were either economic assessments or recommendation records, which also reported epidemiological data in the background for their assessments.

Many of the records provided data stratified by age groups above 50, suggesting the importance of agespecific data for determining which groups to include in the recommendations. The only record which provided time-trend data was from Finland, which indicated an increase in the incidence of hospital-treated primary pneumonia for all adult age groups except the oldest (ages 75+ y).

Health economic evidence

Of the 22 identified records reporting health economic evidence, 20 (91%) were published papers from PubMed® and Embase®, while two (9%) were HTA/NITAG reports. The summary of the available data in the records can be found in supplementary Table S8. Sixteen of the 22 records performed cost-effectiveness analyses (CEA), and 12 of those CEAs were cost-utility analyses (CUA). Four studies performed budget impact models (BIM) and three performed cost analyses (CA). A summary of the key study features is provided in Table 2. Of the health economic analyses identified, the majority (17/22, 77.2%) assessed the impact of including PCV13 for adults in the NIP for their respective country. Ten records assessed the impact of introducing PCV13 versus the following comparators: PPV23 or no vaccine (4/10, 40% each), PCV13 +PPV23 sequentially or just PPV23 (1/10, 10%), and remaining record did not report the comparator (1/10, 10%). In three records, sequential vaccination with PCV13 and PPV23 (both)

Table 1. Summary of epidemiology data types included in records for each country.

Type of data	IPD				Pneumonia			
Countries	Inc.	Mor.	StD.	% S.	Inc.	Mor.	StD.	% S.
Austria	Pub Lit		Pub Lit					
Belgium			Pub Lit		Pub Lit Natl		Pub Lit	
Denmark	Pub Lit	Pub Lit	Pub Lit		Pub Lit	Pub Lit	Pub Lit	
Finland	Natl		Natl		Natl			
France	Natl	Natl	Natl		Natl	Natl		
Germany	Pub Lit	Pub Lit			Pub Lit Subnatl	Pub Lit		Pub Lit
Ireland	Natl							
Italy			Pub Lit		Pub Lit		Pub Lit	Pub Lit
Poland	Natl							
Portugal	Pub Lit	Pub Lit			Pub Lit	Pub Lit		
Slovakia	Natl				Natl	Natl		Natl
Sweden	Pub Lit				Pub Lit			
Netherlands	Pub Lit	Pub Lit			Pub Lit	Pub Lit		Pub Lit

Color coding:
Pub Lit = Published literature
Natl = National data
Subnatl = Subnational data

Abbreviations: Inc. = incidence; Mor. = mortality; StD. = Serotype distribution; %S. = Percent of cases attributable to *S. Pneumoniae*.

Table 2. Key features of the health economic assessment records.

Country	Author (Ref.)	Analysis type	Intervention	Comparator	Assessment
Austria	Walter et al.[110]	BIM	PCV13 or PPV23	None	Positive
Belgium	Marbaix et al.[71]	CUA	PCV13	None	Positive
Belgium	Willem et al.[112]	CUA	PPV23	PCV13+PPV23	Positive
Denmark	Sevilla et al.[95]	CA	PCV13	NR	Positive
Denmark	Birck et al.[41]	CEA	PPV23	None	Positive
EU*	Esposito et al.[52]	CA	NR	NR	Positive
Finland	THL[103]	CEA	NR	NR	NR
France	HCSP[59]	CUA	PCV13+PPV23	PPV23	Positive
Germany	Kuchenbecker et al.[67]	CEA	PCV13+PPV23	PCV13+PPV23	Positive
Germany	Kuhlmann[36]	CUA	PCV13	PCV13+PPV23 or PPV23	Positive
Germany	Storch et al.[100]	CA	PCV13 or PPV23	None	Positive
Italy	Boccalini et al.[42]	BIM	PCV13	None	Positive
Italy	Sanduzzi et al.[93]	BIM	PCV13	None	Positive
Portugal	Gouveia et al.[56]	CUA	PCV13 or PPV23	None or PPV23	Positive
Spain	Gomez et al.[55]	CUA	PPV23	PCV13+PPV23	Negative
Sweden	Wolff et al.[113]	CUA	PSV13	PPV23	Subpop.
Netherlands	Zorginstituut[117]	CEA	PCV13 or PPV23	None	Positive
Netherlands	Rozenbaum[90]	CUA	PCV13+PPV23	PPV23	Positive
Netherlands	de Vries et al.[50]	CUA	PCV13	None	Negative
Netherlands	Thorrington et al.[105]	CUA & BIM	PCV13	PPV23	Negative
Netherlands	Zeevat et al.[116]	CUA	PCV13	PPV23	Positive
Netherlands	Rozenbaum[91]	CUA	PCV13	PPV23	Positive

Abbreviations: BIM = budget impact model; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; CA = cost analysis; EU=Europe; Ref. = reference; Subpop. = subpopulation.

*The review record did not specify which EU countries are included in their synthesis, but cites specific examples and discusses economic rationales for PV use in adults.

was compared to either PPV23 alone (2/3, 66.7%) or in separate dosing schemes for different subgroups (1/3, 33.3%).

For CEAs or CUAs assessing the inclusion of PCV13 (either alone or in combination with PPV23), the studies found PCV13 to be cost-effective in 76.9% (10/13) of assessments. Two studies in Netherlands found PCV13, not to be cost-effective; one study compared PCV13 alone to PPV23 alone, determining that the higher cost of PCV13 yielded too high of an incremental cost-effectiveness ratio (ICER) for people aged 70+ y.[105] The other study assessed the impact of including vaccinated adults' future costs on the cost-effectiveness of PCV13 versus no NIP for adults. The authors argued that extending the lifespan of those with comorbidities incurs higher future costs, thus reducing the cost-effectiveness of PCV13.[50]

The major point of concern in assessments comparing PCV13 to PPV23 was that of the relatively high price of PCV13.[105,113] However, adding a single dose of PCV13 for those with chronic medical conditions (moderate risk) and immunocompromising conditions (high risk) was shown to be highly cost-effective compared to vaccination with PPV23 alone (different records from Germany, Netherlands, and France).[59,67,90] A record from Spain also concluded that sequential vaccination of immunocompetent adults aged 60+ y with PCV13-PPV23 would improve the health outcomes, but at a higher cost, exceeding typical cost-effective benchmarks, compared to PPV23 alone,[55] indicating that these cost-effectiveness comparisons were dependent on other factors in addition to price.

Vaccine coverage rates

There were 41 records that included data on VCR, most of which (38, 92.6%) came from PubMed® and Embase®. The countries with the highest number of records reporting coverage rate data were France ($n = 7$), Germany ($n = 6$) and Belgium ($n = 4$). The most commonly reported rates were vaccine-specific; either for PPV23 alone (17 studies) or PCV13 alone (14 studies). Nine studies reported VCRs for adults vaccinated with PPV23 and/or PCV13, and five studies reported VCRs for adults vaccinated sequentially with both. Fourteen studies did not specify a vaccine type for their coverage rates. There were 13 studies that stratified estimates into sub-groups, based on age, risk group (e.g., comorbidity) or geography. Furthermore, five (12.2%) of these studies estimated coverage rates for the protection that a specific vaccine provides against the *S. pneumoniae* serotypes prevalent in that population (hereafter referred to as 'serotype coverage rates'), while remaining 36 (87.8%) studies estimated the shares of the population that has received one or more pneumococcal vaccines (VCRs). The details of the coverage rate data included in the identified records is presented by country in supplementary Table S9.

The estimates, target populations assessed, and reporting methods varied for all included records. However, some associations can be drawn between the VCR and the changes in recommendation presented above. Before the latest expansion of the German NIP in 2016 to include more coverage for elderly and at-risk individuals, two records estimated low overall VCRs with PCV13 in immunocompromised adults (4.4%)[94] and elderly people (3.2%).[100] However, after the change in NIP, more recent studies estimated a higher coverage rate for both sequential vaccination (9.9% who received PCV13 +PPV23) as well as for PPV23 vaccination (35.1%) in the at-risk population.[76] Similarly higher VCRs were estimated in older populations after the German change in NIP (PPV23: 39%,[76] 50% [[74]; PCV13: 38%;[74] overall: 30.3%[111]]. High PPV23

coverage rates were also reported in Dutch adults [(73%[87]] after the 2018 change to their NIP. In these cases, the VCR evidence confirms the impact of the NIP change.

Only three studies provided trends in VCRs over time, the details of which are provided in Table 3. An Austrian study estimated an increase in VCR over the past 5 y from 15% to 20%, in the population aged 50+ y, and at-risk with chronic disease.[110] A French study estimated about a 9% point increase in VCR in immunocompromised adults from 2014 to 2018, but about an 8% point decrease in the overall coverage rate of at-risk adults.[114] A separate French study estimated a small decrease in the number vaccinated patients diagnosed with chronic diseases between their control and study periods.[66]

Studies comparing PPV23 uptake in adults, ages 50+ y in Belgium[112] and Spain[109] estimated very different VCRs (Belgium, ages 65–74 in 2015: 2.48%; Spain, ages 65–79 in 2017: 63.1%). The differences between the two samples (e.g., ages included, year of estimation) likely does not explain all the variation in these rates; other influencing factors could include access to supplies, the date of introduction of NIP, differences in vaccine delivery infrastructure, the cost to the individual and more.

There were four records estimating serotype coverage rates for specific vaccines, with one study each providing estimates for Denmark[41] Poland,[75] Greece,[70] and Croatia.[43] Across the timeframes for the different estimates, there was more variation in the serotype coverage of PCV13 than PPV23. For PCV13, estimates ranges from 37.8% in Greece between 2009 and 2016, to 80.2% in Croatia between 2005 and 2019. Meanwhile, estimates for PPV23 ranged from 73% in Denmark in 2017 to 93.6% in Croatia between 2005 and 2019. The smaller variation in serotypes covered may in part be indicative of the additional serotypes included in PPV23 but variations in estimates for both imply changes to the composition of serotypes across European countries.

Discussion

This study sought to assess the recent changes and trends in adult pneumococcal vaccination programs across Europe, and to tie those decisions to both the evidence used and their impact on VCRs. Across the literature describing recommendations by NITAGs, there were several general trends that could be gleaned from the available data. In recent years, there appears to be a convergence of NIP recommendations toward sequential vaccination with a higher-valency PCV, followed by PPV23, for optimal coverage across serotypes. Also, most countries with new recommendations have expanded their NIPs to cover additional risk groups in adults, sometimes subsidizing the cost for vaccines for these groups as well. The rationales provided in the available data revealed common goals to reduce economic or healthcare burden, or

Table 3. Included VCR studies with data across time.

Country	Author (Ref.)	Description of population	Type of vaccine	Time period	Coverage rate (%)
Austria	Walter 2019 (110)	adults aged 50+ and at-risk with chronic disease	PPV23 ± PCV13	2018-2023	These are all estimates based on Austrian market research • Year 0 (2018): 15% • Year 1 (2019): 16% • Year 2 (2020): 17% • Year 3 (2021): 18% • Year 4 (2022): 19% • Year 5 (2023): 20%
France	Kopp 2021 (66)	Adults diagnosed with chronic disease (COPD, DM, CHF, and HIV)	PCV13 and PPV23, PPV23	Control period: 2012-2013 Study period: 2013-2017	Overall • 2012-2013: 6% • 2013-2017: 4% COPD: • 2012-2013: 7% • 2013-2017: 5% DM: • 2012-2013: 2% • 2013-2017: 2% CHF: • 2012-2013: 7% • 2013-2017: 4% HIV: • 2012-2013: 16% • 2013-2017: 12%
France	Wyplosz 2022 (114)	Adults at risk of pneumococcal diseases	NR	2014-2018	All adults at risk of PD • 2014: 464,376 (12.7%) • 2015: 365,011 (9.8%) • 2016: 354,740 (9.3%) • 2017: 337,480 (8.6%) • 2018: 182,730 (4.5%) Immunocompromised adults: • 2014: 50,298 (10.3%) • 2015: 53,132 (10.4%) • 2016: 57,130 (10.7%) • 2017: 77,405 (13.8%) • 2018: 106,977 (18.8%)

Abbreviations: COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; CHF = chronic heart failure; HIV = human immunodeficiency virus

both, as well as minimizing risk of co-infection. It was also evident from the data gathered that agencies reviewing epidemiological evidence found value in collecting estimates stratified by age.

This convergence of recommended vaccine schedules and the prevailing rationales in the data suggested that the majority of the countries where data were identified found that sequential vaccination with a high-valency PCV, followed by vaccination with PPV23 provided optimal protection and a minimization of economic burden, for their country's circumstances. The strategy of a high-valency PCV combined with PPV23 is also the current recommendation in both the USA[119] and Australia,[120] for adults with underlying risks. However, the recommendations for elderly populations differ; in the US, either PCV20 alone or a high-valency PCV combined with PPV23 is recommended for those age 65 or older, while in Australia, PCV13 alone is recommended for those age 70 or older. Meanwhile, Japan currently recommends the use of PPV23 alone for older people.[121] These differences imply that a multitude of factors (e.g., vaccine availability, vaccine recommendations for the pediatric population, age-specific considerations, risk of pneumococcal infection, costs, etc.) may influence policy maker's recommendations.

Health economic analyses predominantly studying the introduction of PCV13 to target adult populations were overwhelmingly positive, with the majority (76.9%) of studies determined that inclusion of PCV13 would be cost-effective at the chosen willingness-to-pay threshold. However, a few studies and/or recommendation records expressed concerns about the high cost associated with PCV13, ruling that the herd immunity granted by inoculating children combined with use of PPV23 provided adequate protection without the inclusion of PCV13. In addition, where VCR could be associated with changes in recommendations, higher coverage rates were seen in most cases where countries had expanded their NIPs to cover additional risk groups and include additional vaccines.

Changes to NIPs for adults in large European countries affect both access to treatment and PD burden for millions of people. For example, the Austrian record detailed in Table 3 involved a budget impact analysis of the current NIP for adults, which consists of sequential vaccination with PCV13 and PPV23 for all adults ages 50+ y.[110] A 2022 population pyramid of Austria showed that almost 42% of their population are 50+ y (about 3.7 million adults).[122] The record estimated that the VCR for this population increased by 5% points over the past 5 y, which suggests that the policy impacted the lives about 186,000 newly vaccinated people in Austria during that period.[110]

The included evidence was not without limitations. The density and format of the available information in the chosen countries was inconsistent despite reviewing both published and gray literature. For example, it was difficult to compare either VCRs or recent epidemiology data with the decisions made in the countries with available information. This made assessments of the impact of these decisions difficult to conduct. Data inconsistencies could be minimized by the implementation of surveillance systems and standardized methods for reporting. However, some patterns were identified; age-stratified epidemiological data indicated an interest in identifying the target age groups where vaccination would be beneficial. This age-specific interest was also expressed in health economic assessments like the CUA in Netherlands, which found too high of an ICER for people aged 70+ y.[105] A recent CUA in Belgium, assessing the impact of sequential vaccination with PCV13 and PPV23,[112] was succeeded by a change in the Belgian NIP for adults to include sequential vaccination with a high-valency PCV and PPV23.[47] Many of the included records discussed expansions of the risk groups included in the existing recommendations, providing further coverage for immunocompromised groups, which was then evident within reported data from Austria and France.[66,110,114] However, inconsistent trends in coverage implied that factors other than the implementation of new NIPs impact coverage.

There were also limitations of the review process, biggest of which was the issue of language and translation. The inability for the review team to review all records in their native languages, combined with the inconsistent accuracy of Google Translate made it more difficult to determine whether certain records were relevant, or whether they described a change in policy or continuation of existing policy. Furthermore, the review team chose not to include published literature in other languages than English, as there was a worry that Google Translate would be insufficient to translate peer-reviewed academic writing. Additionally, the project did not have the scope to contact each of the individual agencies to get direct guidance on their NIPs for pneumococcal disease, meaning that the grey literature search process was in part dependent on the navigability of government websites in each country.

Despite these limitations, it is clear throughout all records that despite widespread recommendation of high-valency pneumococcal vaccinations in both adults and children, the burden of PD is still high. This residual burden persists in-part through non-vaccine serotypes[123,124] and through vaccine serotypes, such as 19A and 3, which continue to be prevalent in populations where pneumococcal vaccines are available.[125] This shift has encouraged the development of vaccines covering additional serotypes.[27,126] However, other research points toward concerns over the waning benefits associated with the expansion of serotype coverage.[127,128] Additionally, despite improved NIP recommendations for adults, differences in reimbursement policy, availability, public awareness, and other factors mean that not all at-risk individuals follow these recommendations.

For these reasons it is important that HTAs, NITAGs, and policy makers understand the importance of collecting, reporting, and then considering all the available information, being transparent about their decision-making processes, and communicating those decisions to their target populations so that the maximum benefit of these inoculations can be realized. These actions can better be achieved through consistent reporting of the relevant information by academia and relevant agencies, to provide a solid foundation upon which to make these decisions.

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Author's contributions

AB and ET conceptualized the project and developed the design together with NN, PK, and SA. SA reviewed all publications, and together with NN extracted all data. NN and SA synthesized the results and wrote the manuscript, with support from PK and high-level input from both AB and ET. AB was chief advisor on the project. All authors discussed the results and contributed to the final manuscript.

Consent for publication

All authors approved the final version of the article, including the authorship list.

Data availability statement

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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