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REVIEW

Burden of pneumococcal disease among adults in Southern Europe (Spain, Portugal, Italy, and Greece): a systematic review and meta-analysis

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ABSTRACT

The aim was to summarize pneumococcal disease burden data among adults in Southern Europe and the potential impact of vaccines on epidemiology. Of 4779 identified studies, 272 were selected. Invasive pneumococcal disease (IPD) incidence was 15.08 (95% CI 11.01–20.65) in Spain versus 2.56 (95% CI 1.54–4.24) per 100,000 population in Italy. Pneumococcal pneumonia incidence was 19.59 (95% CI 10.74–35.74) in Spain versus 2.19 (95% CI 1.36–3.54) per 100,000 population in Italy. Analysis of IPD incidence in Spain comparing pre-and post- PCV7 and PCV13 periods unveiled a declining trend in vaccine-type IPD incidence (larger and statistically significant for the elderly), suggesting indirect effects of childhood vaccination programme. Data from Portugal, Greece and, to a lesser extent, Italy were sparse, thus improved surveillance is needed. Pneumococcal vaccination uptake, particularly among the elderly and adults with chronic and immunosuppressing conditions, should be improved, including shift to a higher-valency pneumococcal conjugate vaccine when available.

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Introduction

Streptococcus pneumoniae infections are a leading cause of morbidity and mortality worldwide and pose a major threat to public health.[1] *S. pneumoniae* produces a polysaccharide capsule essential for its pathogenicity, serving as a virulence factor that hampers host immune clearance mechanisms.[2] Currently, there are up to 100 recognized polysaccharide serotypes.[3] Pneumococcal conjugate vaccines (PCVs) have successfully targeted several of them reducing the risk of infection by conferring serotype-specific protection.

Streptococcus pneumoniae causes a spectrum of invasive diseases, including sepsis, meningitis, and bacteremic pneumonia,[4] and is the most frequent causative agent identified in community-acquired pneumonia (CAP).[5] Children under 5 years of age, the elderly population, and people with respiratory disease, diabetes, human immunodeficiency virus (HIV) infection, and immunosuppression are at greater risk of pneumococcal disease.[6]

The true burden of pneumococcal disease remains undetermined in Europe. Despite the existence of a European enhanced surveillance of the invasive pneumococcal disease, notification rates vary markedly among countries. Apart from diverse population characteristics, the variations in the notification rate are most likely due to differences in medical and surveillance practices, and diverse implementation of pneumococcal vaccination (e.g., date of introduction, vaccine type, and vaccination schedules and policies).[7] These differences particularly relate to CAP, as prevalence estimates among adults differ across settings and are affected by under-detection.[8]

In 2001, the heptavalent pneumococcal conjugate vaccine (PCV7) was first authorized for its use in children in Europe, and the authorization was extended to the ten-, and thirteen-valent pneumococcal conjugate vaccines (PCV10/PCV13) in mid-2010. PCV13 was licensed in 2012 as the first pneumococcal conjugate vaccine for adults. In the Community-Acquired Pneumonia Immunization Trial (CAPiTA study), PCV13 showed an efficacy of 75% in preventing the first vaccine-type IPD episode, whereas efficacy against vaccine-type noninvasive pneumococcal pneumonia was estimated at 45%,[9] and at 70% in a real-world effectiveness study.[10]

Many of the European countries have issued national guidelines for pneumococcal vaccination in adults. Guidelines are either age-based or risk-based[11] with Southern European countries, such as Spain, Greece, and Italy implementing advanced age-based PCV13 recommendations at the national level or for many of their regions.[12–14] However, PCV13 uptake among adults is still modest in those countries.[15,16]

We conducted a systematic review and meta-analysis to summarize the evidence of the burden of pneumococcal disease among adults in Southern European countries (Spain, Portugal, Italy, and Greece).

Methods

This manuscript reports a systematic review of observational studies and was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] For the formulation of the PICO question (Population, Intervention, Comparator, Outcome), the CoCoPop (Condition, Context, Population) model was used.[18]

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Search strategy

A comprehensive search was performed in MEDLINE through OVID, EMBASE, SCOPUS, and SCIELO databases. To search for gray literature, Open Grey and OpenDOAR databases were included. Search terms were *("Streptococcus pneumoniae" OR pneumococcus OR pneumococcal infection) AND (meningitis OR pneumonia OR bacteremia OR "invasive pneumococcal disease") AND (epidemiolog* OR prevalence OR incidence) LIMITS ([1990– 2019] AND [Spain, Portugal, Greece, Italy])*. No language restrictions were applied to the search. Additional articles were identified and retrieved from references of found articles.

Inclusion and exclusion criteria

The review included observational studies (including prospective, retrospective, registry-, and population-based designs) according to the following criteria: (1) studies containing information about adult patients (≥18 years of age); (2) published between 1990 and 2019; (3) referring to settings located in Spain, Italy, Portugal or Greece; (4) studies containing information concerning invasive pneumococcal disease or CAP; and (5) articles reporting on pneumococcal disease prevalence, pneumococcal disease incidence, or vaccine-type related incidence [PCV7, PCV13 or the 23-valent pneumococcal polysaccharide vaccine (PPV23)].

It excluded studies that did not contain information on pneumococcal disease cases; that addressed pneumococcal disease cases having diagnostics other than pneumonia or isolation of *S. pneumoniae* from a normally sterile site; studies not including adult patients or outside the publication timeframe (1990–2019), or studies that did not have information on prevalence or incidence of pneumococcal disease.

Study selection and data extraction

After deduplication, titles and abstracts were screened by two independent reviewers using the selection criteria. Then, full-text article screening was carried out and the following data were extracted: age group of patients (adult or elderly), time frame of study, country of study, pneumococcal disease type, number of patients with condition and number of them being pneumococcal, incidence rates, number of cases attributed to any of the vaccine serotypes and conditions that might increase susceptibility to pneumococcal infection (i.e., cancer, diabetes, immunosuppression, HIV infection, chronic kidney disease, cirrhosis, COPD). Age cutoffs of either 60 or 65 years were used to define the "elderly" age group.[19]

Any disagreement between the two reviewers was resolved after discussion and reaching consensus based on the predefined selection criteria.

The quality of the articles was assessed using the Joanna Briggs Institute´s Critical Appraisal Tool for prevalence/incidence systematic reviews. This Critical Appraisal Tool provides a checklist that covers nine domains: appropriateness of sample frame, recruitment of participants, adequacy of sample size, description of study subjects and setting, coverage of identified samples, valid methods for identification of the condition, a standardized and reliable measurement of the condition, appropriateness of the statistical analysis, and adequacy of the response rate.[18,20]

Data analysis

A pooled analysis of the included papers was performed, and a quantitative synthesis and meta-analyses were undertaken. Prevalence was expressed as the percentage of cases attributed to pneumococcus among all the cases of the disease, and incidence was expressed as cases per 100,000 population. Meta-analyses of the values expressed as a proportion were conducted using the *metaprop* package in R software (v.3.6.1). Proportions were treated by double arcsin transformation.[21] Random effects models were fitted for the global effect size as significant heterogeneity across studies was detected.

Subgroup analyses were pre-specified for different conditions and countries and were included if enough data was available for the indicated subgroup. IPD incidence was also analyzed in subgroups to evaluate differences in reported serotypes causing disease. The year of marketing approval for each vaccine in the different countries was used as cutoff to compare incidence between the pre- (2001 for PCV7, and 2010 for PCV13), and post-vaccine introduction periods. If a manuscript contained values for different times of analysis but that occurred in the same segment respect to the cutoff (for example, both occurred after some vaccine introduction), duplicated labels can appear due to values coming from the same study but from different times of measurement.

To assess the impact of several covariates on estimates from the meta-analyses, a meta-regression method was utilized. Similar to a conventional regression, this method calculates a coefficient for each variable included in the analysis. This coefficient could be either positive, indicating that the estimate value increases as the predictor value increases, or negative, demonstrating a negative correlation, meaning that the estimate value decreases as the predictor value increases.

Results

Study characteristics

Of the 4779 screened studies, 272 were selected according to the eligibility criteria (Figure 1). From these, 232 records were obtained for prevalence analysis, with 182 containing information about pneumonia, 31 about bacteremia, 18 about meningitis and 1 about peritonitis; 108 records were retrieved for the incidence analysis, with 59 about IPD, 15 about pneumonia, 13 about bacteremia, 13 on meningitis and 8 related to other sites.

Information on prevalence were more frequently identified from studies carried out in hospital settings and incidence data were mostly provided by population-, or database-based studies. Most of the studies had an adequate level of quality, although in some studies there was a lack of representativeness of the sample or the information about methods used to diagnose the different conditions was missing.

Funnel plots to assess publication bias showed great variability, as expected from observational studies, with some deviation toward greater values.

The characteristics of the included studies are described in the online supplement (Supplemental material).[16,22–286]

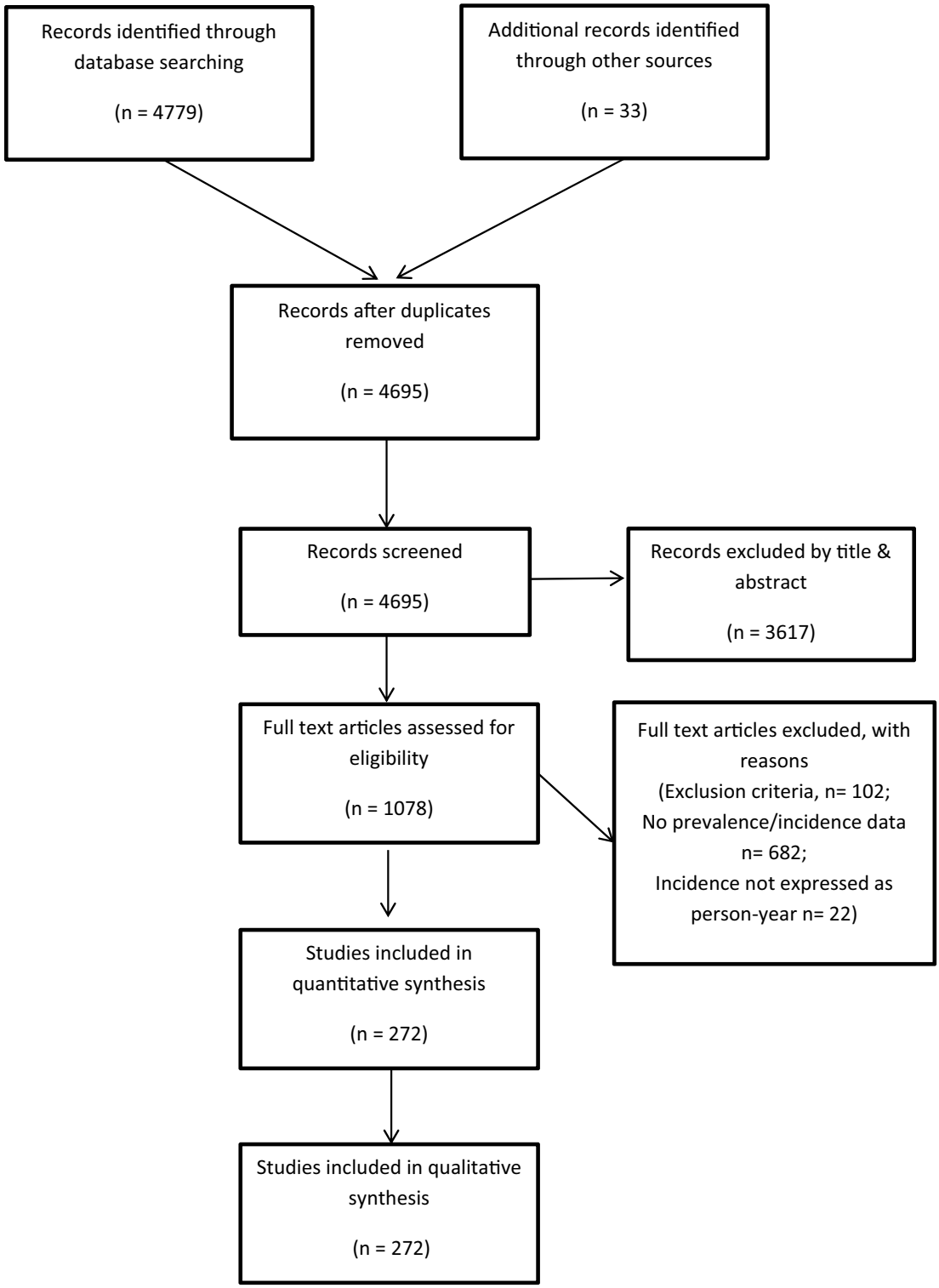

Figure 1. PRISMA flow diagram.

Prevalence and incidence of pneumococcal disease in Southern European countries

Invasive pneumococcal disease

Frequency of IPD infections was rarely reported as prevalence. Therefore, only IPD incidence data were analyzed. Incidence of IPD was only available for Spain and Italy (Table 1) and no articles were retrieved from Portugal or Greece. The pooled analysis showed significant differences between Spain and Italy, with an incidence of 15.08 per 100,000 population (95% CI 11.01–20.65) in Spain and 2.56 per 100,000 population (95% CI 1.54–4.24) in Italy. Italy contributed with fewer records, but its pooled estimate had a narrow confidence interval (Table 1).

Table 1. Summary values for incidence of pneumococcal disease in Southern European countries*.

Pneumococcal disease type	Country	Number of records	Incidence (cases per 100.000 person-years)	95% CI
IPD	Overall	59		
	Spain	50	15.08	11.01–20.65
	Italy	9	2.56	1.54–4.24
	Portugal	0	-	-
	Greece	0	-	-
Bacteremia	Overall	13	-	-
	Spain	13	4.13	2.38–7.20
	Italy	0	-	-
	Portugal	0	-	-
	Greece	0	-	-
Pneumonia	Overall	15		
	Spain	13	19.59	10.74–35.74
	Italy	2	2.19	1.36–3.54
	Portugal	0	-	-
	Greece	0	-	-
Meningitis	Overall	13		
	Spain	11	1.22	0.86–1.73
	Italy	2	2.12	0.58–7.71
	Portugal	0	-	-
	Greece	0	-	-

*Random effects summary estimates from meta-analyses.

Pneumococcal pneumonia

Spain had the highest prevalence of pneumococcal pneumonia with a prevalence of 19% (95% CI 17%-20%) (Table 2) followed by Portugal with 11% (95% CI 5%-18%), Italy with 8% (95% CI 7%-9%), and Greece with 5% (95% CI 2%-10%). Differences were only statistically significant for Spain compared to Italy and Greece, whereas the confidence intervals partially overlapped for Spain and Portugal (Table 2).

The analysis of the pneumococcal pneumonia incidence data showed an incidence of 19.59 per 100,000 population (95% CI 10.74–35.74) for Spain whereas Italy presented a lower incidence at 2.19 per 100,000 population (95% CI 1.36–3.54). The difference was statistically significant (Table 1). No information was retrieved on pneumococcal pneumonia incidence from Portugal or Greece.

Table 2. Summary values for prevalence of pneumococcal disease in Southern European countries*.

Pneumoccocal disease type	Country	Number of records	Prevalence	95%CI
Bacteremia	Overall	31	6%	4%-8%
	Spain	29	6%	4%-8%
	Italy	2	5%	0%-24%
	Portugal	0	-	-
	Greece	0	-	-
Pneumonia	Overall	182	16%	15%-18%
	Spain	140	19%	17%-20%
	Italy	26	8%	7%-9%
	Portugal	12	11%	5%-18%
	Greece	4	5%	2%-10%
Noninvasive pneumonia	Overall	31	64%	56%-71%
	Spain	28	64%	55%-71%
	Italy	2	77%	53%-95%
	Portugal	1	40%	21%-60%
Meningitis	Overall	18	25%	17%-35%
	Spain	11	21%	9%-35%
	Italy	6	33%	23%-42%
	Portugal	1	35%	29%-42%
	Greece	0	-	-

*Random effects summary estimates from meta-analyses.

Noninvasive pneumococcal pneumonia

Noninvasive pneumococcal pneumonia was defined as community-acquired pneumonia (CAP) for which the pneumococcus was isolated from sites other than normally sterile sites. The selected studies clearly stated that pneumonia was noninvasive.

Overall, 31 studies were selected, and prevalence was 64% (95% CI 55%-71%), 77% (95% CI 53%-95%), and 40% (95% CI 21%-60%) for Spain, Italy, and Portugal, respectively. Again, differences between any two of the four countries were not statistically significant.

Bacteremia

Portugal and Greece did not contribute records to the pneumococcal bacteremia prevalence pooled estimate whilst Spain had a prevalence of 6% (95% CI 4%-8%) and Italy of 5% (95% CI 0%-24%). Differences were not statistically significant and only two records for Italy were captured (Table 2), thus a higher number of records would be desirable for sound comparisons.

In relation to incidence, Spain was the only country with studies on pneumococcal bacteremia and it was estimated at 4.13 per 100,000 population (95% CI 2.38–7.20).

Meningitis

The summary values for pneumococcal meningitis prevalence were 35% (95% CI 29%-42%), 33% (95% CI 23–42%), and 21% (95% CI 9–35%) for Portugal, Italy, and Spain, respectively. Differences between countries were not statistically significant.

Pneumococcal meningitis incidence was 1.22 per 100,000 population (95% CI 0.86–1.73) for Spain, and 2.12 per 100,000 population (95% CI 0.58–7.71) for Italy with overlapping confidence intervals.

Incidence of invasive pneumococcal disease caused by vaccine serotypes

Data analysis about incidence of IPD stratified by vaccine type was only performed for Spain, as information from Portugal and Greece was not found and there was only one article from Italy. Information on other clinical presentations was very scarce and excluded from the analysis.

The pooled analysis was carried out for the general (≥18 years of age) and the elderly (≥60 years or ≥65 years of age) populations.

Among adults 18 years of age and older, the analysis showed a decrease in PCV7 type IPD incidence from the pre-vaccine introduction period to the post-vaccine introduction period: from 8.00 per 100,000 population (95% CI 3.73–17.18) to 2.85 per 100,000 population (95% CI 2.06–3.94), respectively, and nearly reached statistical significance (Table 3). In the same age group, a non-significant decrease in PCV13 type IPD incidence was observed between the pre-vaccine introduction period and the post-marketing period, from 10.45 per 100,000 population (95% CI 7.12–15.32) to 4.92 per 100,000 population (95% CI 3.17–7.64), respectively. Comparing the pre- and post-periods, non-PCV13 type (serotypes not

Table 3. Distribution of IPD incidence by vaccine type pre-, and post-marketing introduction among the general and elderly populations in Spain.

IPD vaccine type	Year of introduction of the vaccine	Period	Ns	Nr	Incidence (cases per 100.000)	95%CI
≥ 18 years						
PCV7	2001	Pre	4	6	8.00	3.73– 17.18
		Post	12	40	2.85	2.06– 3.94
PCV13	2010	Pre	7	14	10.45	7.12– 15.32
		Post	6	15	4.92	3.17– 7.64
Non-PCV13	2010	Pre	4	9	5.25	3.16– 8.74
		Post	5	13	6.79	4.15– 11.12
≥ 60 years or ≥ 65 years						
PCV7	2001	Pre	3	3	19.10	17.69– 20.62
		Post	10	21	5.50	3.84– 7.86
PCV13	2010	Pre	6	8	17.10	13.64– 22.96
		Post	6	8	9.55	6.97– 13.09
Non-PCV13	2010	Pre	4	5	9.63	7.18– 12.91
		Post	5	7	14.04	10.41– 18.94

PCV7: hepta-valent pneumococcal conjugate
PCV13: thirteen-valent pneumococcal conjugate
Non-PCV13: non-thirteen-valent pneumococcal conjugate vaccine type
Pre: pre-vaccine introduction period
Post: post-vaccine introduction period
Ns: number of studies; Nr: number of records

included in PCV13) IPD incidence increased from 5.25 per 100,000 population (95% CI 3.16–8.74) to 6.79 per 100,000 population (95% CI 4.15–11.12), although confidence intervals overlapped.

After age stratification, among the elderly group (≥60 years or ≥65 years of age), there was a significant decrease in PCV7 type IPD incidence from 19.10 per 100,000 population (95% CI 17.69–20.62) to 5.50 per 100,000 population (95% CI 3.84–-7.86) comparing the two time periods. PCV13 type IPD incidence also declined from 17.10 per 100,000 population (95% CI 13.64–22.96) to 9.55 per 100,000 population (95% CI 6.97–-13.09) (Table 3), reaching statistical significance. However, non-PCV13 type IPD incidence increased non-significantly from 9.63 per 100,000 population (95% CI 7.18–12.91) in the pre-vaccine introduction period to 14.04 per 100,000 population (95% CI 10.41–18.94) in the post-period.

Case fatality ratio

A total of 92 papers contained information that allowed the calculation of the case fatality ratio (CFR) among patients suffering from pneumococcal disease. Overall CFR was 11% (95% CI 10%-12%), 12% (95% CI 10%-14%), and 8% (95% CI 3%-16%) for Spain, Italy, and Portugal, respectively. Differences between countries were not statistically significant.

The CFR analysis by pneumococcal disease type showed statistically significant differences between IPD and pneumonia, at 15% (95% CI 12%-19%) and 8% (95% CI 6%-9%), respectively. CFR due to meningitis at 14% (95% CI 10%-18%) did not differ from bacteremia at 17% (95% CI 11%-23%).

Risk factors for pneumococcal disease

To identify the risk factors for pneumococcal pneumonia prevalence, a meta-regression model was fitted including the country of study, age group, PCV13 authorization period and PPV23 vaccination as covariates. Data coming from Italy and old age (≥60 years or ≥65 years of age) were found to be positive predictors, although non-significantly. PCV13 post-authorization period appeared as negative predictor (albeit non-significantly) whereas both PPV23-vaccinated and PPV23-non-vaccinated were also negative predictors. This apparent contradiction may relate to the fact that those PPV23 studies showed a low prevalence of pneumococcal pneumonia, independently of the vaccination status.

A meta-regression sub-analysis for meningitis prevalence in Spain, Portugal, Italy, and Greece indicated that HIV-positive status was a significant positive predictor, whereas immunosuppressed population, solid organ transplant patients, and data from Spain were negative predictors (the first two being significant).

A meta-regression of overall bacteremia prevalence indicated that mechanical ventilation was the only negative significant predictor. Other negative predictors were old age (≥60 years or ≥65 years of age), immunosuppressed patients, and solid organ transplant patients. The only positive predictor was HIV-positive status, being marginally non-significant.

Discussion

This systematic review highlights the high burden of pneumococcal disease among adults as well as the changes in the epidemiology of pneumococcal disease in Southern European countries. This review has revealed differences in the prevalence and incidence of pneumococcal disease between the Southern European countries. These differences have been previously identified, particularly in relation to the prevalence of CAP in adults, and hold true after adjusting for potential confounders, including patient characteristics, diagnostic tests, antimicrobial resistance, and healthcare setting.[8] Geographical variations in the epidemiology of pneumococcal disease have been reported as most likely due to selection of patients, or blood-culture practices,[287] but also the spread of resistant clones may have contributed to these differences.[288] Apart from clinical practices and patients characteristics, decreasing trends in the incidence of pneumococcal bacteremia or meningitis have been associated with improvement in socioeconomic factors (i.e., reduced crowding), the widespread use of antibiotics, and the introduction of the pneumococcal conjugate vaccines[289] in the European countries.[7] Records from Portugal, Greece and to some extent from Italy were scarce in this review and it may well correspond to incomplete

surveillance systems and not fully developed diagnostics and ascertainment strategies.[290–292]

This review unveiled significant differences in incidence of IPD between Spain and Italy, with Spain showing a larger disease burden. Divergence in IPD notification rates between both countries has remained constant since the inception of the European IPD surveillance programme.[293] The potential reasons have been profusely explained above. Similarly, pneumonia incidence among adults in Spain was significantly higher compared to Italy and consistent with that in other reports.[294]

A sub-analysis of noninvasive pneumococcal pneumonia revealed a high prevalence in Italy, Spain, and Portugal (77%, 64%, and 40%, respectively). The considerable high prevalence in Italy may reflect that there were only two records identified and the study included special populations, either injection drug users including HIV-positive patients[42] or a general HIV-positive cohort.[121] Papers from Spain mainly included elderly populations, and HIV or COPD patients.[49,263,276,278,279,282]

There were no differences in meningitis incidence between Spain and Italy and this was consistent with published figures.[295] Unfortunately, the selected articles did not contain enough information to assess pneumococcal serotype distribution before and after the different pneumococcal conjugate vaccines introduction.

Data on incidence of invasive pneumococcal disease from Spain allowed to analyze vaccine-type evolution comparing the pre-, and post-vaccine introduction periods. Among the overall adult population, PCV7 and PCV13 type IPD incidence declined non-significantly between the two periods. These differences were larger and statistically significant after stratifying by age (≥60 years or ≥65 years of age). In the context of recent introduction of PCV13 and a low PCV13 uptake among adults, this decrease may be attributed to indirect effects of the pediatric pneumococcal immunization programmes as reported for other settings.[152,296,297] A recent analysis points to the impact of pneumococcal childhood vaccination on the reduction of adult PCV13 type IPD in Spain before the implementation of adult vaccination programmes.[298] Regarding any potential impact of direct vaccination of adults with PPV23, we were not able to explore, because there was identified only one article referring to PPV23-specific serotypes, and we decided not to include it in this analysis. Conversely, several articles with information about disease caused by non-PCV13 serotypes were included in this analysis.

The analysis also identified an increasing trend in non-PCV13 type IPD incidence comparing the pre-, and post-vaccine introduction periods, both for the overall adult population and for the elderly. These epidemiological changes showing the emergence of non-vaccine serotypes have been attributed to the implementation of the pneumococcal conjugate vaccines, but this is a complex phenomenon and there are a number of other factors implicated, such as selective pressure of antibiotics and carriage and transmission dynamics. This holds true particularly among children, who are affected by pneumococcal carriage and transmission due to factors, such as child care attendance, crowding, or birth rate.[299] Whether the introduction of pneumococcal conjugate vaccines is the sole cause for serotype replacement remains unclear since there are regions with high serotype replacement rate but low vaccine uptake.[300] In addition, regional differences in the reporting systems and other non-vaccine environmental factors[295] may have contributed to this phenomenon.

Published data show that the case fatality ratio for pneumococcal disease overall has been estimated at 15% whereas it was as high as 10–30% among pneumococcal meningitis patients.[301] Results from our review allineate with those figures and do not differ among Spain, Italy, and Portugal at 11%, 12%, and 8%, respectively. As expected, CFR of invasive disease, either overall IPD, meningitis or bacteremia, was considerably higher compared to pneumonia CFR.

An assessment of the risk factors for pneumococcal pneumonia prevalence demonstrated that older age and articles from Italy correlated with higher prevalence. In the elderly, pneumococcal pneumonia is a key contributor to the burden of pneumococcal disease. The presence of underlying conditions and phenomena such as immunosenescence and inflammageing is associated with an increased risk for pneumococcal pneumonia in this age group.[302,303] The meta-regression of studies that contained information on PCV13 from the post-authorization period, showed an inverse correlation with pneumococcal pneumonia prevalence pointing to the ability of PCV13 to protect against vaccine-type pneumococcal pneumonia.

HIV-positive status correlated with higher prevalence of pneumococcal meningitis and bacteremia as already highlighted in a recent review.[304] In contrast, immunosuppressed patients and patients with solid organ transplant correlated inversely with pneumococcal bacteremia and meningitis. This aligns with some studies that have showed that patients using immunosuppressive treatment are less likely to present with typical characteristics of meningitis, have less alterations in their cerebrospinal fluid (CSF), and often their CFS culture predominantly yields atypical causative microorganisms.[305]

Previous studies have identified younger age as an independent risk factor for bacteremia in patients with community-acquired pneumonia[306,307]; although statistically non-significantly, our results are in agreement with this. The reasons for younger patients being at higher risk of bacteremia still need to be elucidated. Pneumococcal vaccination and serotype distribution may be partly responsible for it. The pneumococcal vaccines are recommended in the Southern European countries, depending on the regions, for adults aged ≥60 or ≥65 years to prevent invasive pneumococcal disease and pneumonia. Younger adults are not expected to be vaccinated against pneumococcal disease, except for those with certain at-risk conditions, likely putting them at a higher risk for pneumococcal bacteremia. Unfortunately, sparsity of data on serotype distribution among bacteremic cases did not allow an in-depth analysis of its impact on age distribution. Mechanical ventilation has been associated with pneumococcal bacteremic pneumonia.[306] Our data are not consistent with this finding since we found that mechanical ventilation negatively correlated with bacteremia. However, respiratory complications (including mechanical ventilation) have been associated to older age in bacteremic pneumococcal pneumonia.[308]

This review has strengths and limitations. One key strength of the review is that it consisted of a large number of records for Spain, Italy, Portugal, and Greece, including gray literature sources. One limitation of our study is the heterogeneity observed in the meta-analyses. We applied a quality appraisal tool, and fitted random effects models and subgroup analyses but among the research community, there is still no consensus on the optimal methodology for the conduct of systematic

reviews and meta-analyses for observational studies.[309,310] Additionally, data from Portugal, Greece, and Italy were scant which may have resulted in the underestimation of the true burden of pneumococcal disease in those countries.

Despite these limitations, this review aims to trigger awareness among policy and decision makers of the need to inform policies and strategies to tackle pneumococcal disease among adults in the Southern European countries.

Conclusions

Despite limitations, the results of this review point to a considerable pneumococcal disease burden and PCV13 type IPD burden among adults even with the indirect effects of the pediatric PCV13 vaccination programmes. It has also unveiled an increase in the incidence of non-PCV13 serotypes over time. Based on this review, we suggest it is worth considering the expansion of pneumococcal vaccination recommendations to the elderly and adults with chronic diseases, HIV-positive, and other immunosuppressing conditions.

Moreover, improving surveillance of pneumococcal disease and the harmonization of reporting systems are warranted among the Southern European countries to ensure close monitoring of changes in the epidemiology of the pneumococcal disease, and the impact of vaccines.

At present, next-generation pneumococcal conjugate vaccines with a wider serotype coverage are being developed. Therefore, switching to extended-valency pneumococcal conjugate vaccines when they become available would be advisable. At the same time, every effort should be made to take advantage of existing recommendations in the Southern European countries and to enhance pneumococcal vaccination uptake both in the elderly and in adults with comorbidities that put them at increased risk for pneumococcal disease.

Highlights

- Pneumococcal disease among adults poses a significant burden on Southern European countries
- Indirect effects of childhood pneumococcal vaccination are noted among adults in Spain
- Pneumococcal surveillance and reporting need improvement in Italy, Greece, and Portugal
- Changes in epidemiology suggest the need for higher-valency conjugate vaccines

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Contributors

A. Navarro-Torné designed, interpreted data, and drafted the manuscript; Eva Agostina Montuori, Vasiliki Kossyvaki, and Cristina Méndez critically revised the manuscript, contributed comments, and gave final approval to the manuscript.

Disclosure of potential conflicts of interest

All author(s) are Pfizer employees and may hold company stocks.

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