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Streptococcus pneumoniae infections in an adult intensive care unit: A retrospective study from a tertiary Center in Portugal

Ana Catarina Rodrigues Gonçalves [a,1,*], Diogo Costa Oliveira [b,1], Rita Jorge [c], José Chen-Xu [d], Matilde Couto [e], Isabel Campos [f], José Artur Paiva [f,g]

[a] *Serviço de Doenças Infeciosas do Hospital de Curry Cabral, Unidade Local de Saúde de São José, Lisboa, Portugal*
[b] *Serviço de Medicina Intensiva, Unidade Local de Saúde de Trás-os-Montes e Alto Douro, Vila Real, Portugal*
[c] *Serviço de Medicina Intensiva, Hospital Beatriz Ângelo, Unidade Local de Saúde de Loures/Odivelas, Lisboa, Portugal*
[d] *Comprehensive Health Research Center (CHRC), Public Health Research Center, LA-REAL, National School of Public Health, NOVA University of Lisbon, Lisbon, Portugal*
[e] *Serviço de Medicina Interna do Hospital Vila Franca de Xira, Unidade Local de Saúde do Estuário do Tejo, Portugal*
[f] *Serviço de Medicina Intensiva, Unidade Local de Saúde de São João, Porto, Portugal*
[g] *Departamento de Medicina, Faculdade de Medicina da Universidade do Porto, Porto, Portugal*

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ABSTRACT

Introduction: Streptococcus pneumoniae (SP) infections and invasive pneumococcal diseases (IPD) are major contributors to morbidity and mortality in Europe. Vaccination is one of the most effective methods in preventing IPD. It is important to understand the impact of vaccination on patients admitted to the intensive care unit (ICU) with pneumococcal disease and to evaluate if further populational studies are necessary to guarantee better clinical outcomes.

Objective: This study aimed to assess vaccination status in adults (≥ 18 years old) ICU patients with SP infection and evaluate risk factors, mortality, and outcomes related to pneumococcal disease. Subgroup analysis focused on patients with IPD.

Methods: A retrospective study was conducted on adult ICU patients with SP infection in a Portuguese tertiary hospital from August 2018 to August 2023. Data on serotypes, antimicrobial susceptibility, and vaccination status were analysed using statistical methods.

Results: During the study period, 105 patients with confirmed SP infection were included, with a mean age of 62.5 years and a predominance of males (67.6 %). Arterial hypertension (52.4 %) and type 2 diabetes (23.8 %) were the most common comorbidities. In-hospital mortality was 13.3%, and 35.2 % of patients required invasive mechanical ventilation. Immunosuppression was significantly associated with both higher in-hospital mortality ($p = 0.028$) and the development of IPD ($p = 0.012$). Vaccination was associated with a reduced need for invasive mechanical ventilation ($p = 0.043$). Despite 94.8 % of patients meeting vaccination criteria, the overall vaccination rate was low (21.9 %).

Discussion and conclusion: Immunocompromised patients face a significantly higher risk of invasive pneumococcal disease and in-hospital mortality, highlighting the need for more effective vaccination strategies. Despite established national guidelines, vaccination coverage remains inadequate, emphasizing the necessity of targeted interventions. Vaccination was significantly associated with a reduced need for invasive mechanical ventilation. Additionally, our findings suggest that the complete PCV13 + PPSV23 vaccination scheme may be linked to lower mortality rates; however, the sample size was insufficient to establish a significant correlation. Enhanced surveillance and serotype studies are essential for addressing the burden of pneumococcal disease more effectively.

* Corresponding author.
[1] These authors have contributed equally to this work and should be considered first authors.

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1. Introduction/Background

Streptococcus pneumoniae (SP) infections and invasive pneumococcal diseases (IPD) significantly contribute to communicable disease-related morbidity and mortality, particularly in Europe. Risk factors for IPD include anatomical or functional asplenia, immunocompromised status and chronic illnesses such as chronic pulmonary/respiratory disease, heart disease, and type 2 diabetes, engaging in high-risk behaviors (such as alcoholism and smoking), and low socioeconomic status [1] Due to their high morbidity and mortality, SP infections, especially IPD, may need intensive care unit (ICU) admission.

A substantial proportion of IPD cases are preventable through vaccination [2]. The incidence of IPD in Europe has fluctuated over time and across different countries, influenced by factors such as the introduction of pneumococcal conjugate vaccines and serotype replacement [3]. Identifying the responsible serotype for invasive pneumococcal infections is crucial for shaping vaccine strategies and assessing their effectiveness **(**[4,5] **).**

For adults, vaccination aims to reduce IPD occurrence, preventing complications, long-term effects, and societal repercussions. This involves tailoring vaccination efforts to high-risk individuals and establishing a vaccination scheme based on risk stratification. Several countries have recently updated their guidelines regarding the vaccination schedules, namely United States of America where the vaccines are recommended among adults above 50 years **(** [6]**).**

In Portugal, adult vaccination against SP infections for high-risk individuals started in 2015 with the 13-valent pneumococcal conjugate vaccine (PCV13). National recommendations were updated in 2021 – risk-groups were extended (Supplementary Table 1) and 23-valent polysaccharide pneumococcal vaccine (PPSV23) became a funded vaccine for high-risk patients and adults above 64 years old [7] PPSV23 contains capsular polysaccharides of 23 serotypes, inducing immunity via a T cell-independent mechanism that lacks memory B cell generation. In contrast, PCV13, conjugating thirteen capsular serotypes to a non-toxic protein, has been shown to induce memory B cells.

Besides PPSV23 and PCV13, the 20-valent pneumococcal conjugate vaccine (PCV20) was recently approved for use in Portugal [8] though not yet part of the national vaccination program. PCV20 offers advantages by including capsular polysaccharide conjugates for seven additional serotypes not covered by PCV13, potentially expanding protection against vaccine-preventable pneumococcal disease [7].

1.1. Objective

Our main objective was to study the status of vaccination against SP in patients admitted to the ICU with the diagnosis of pneumococcal disease. Secondary outcomes included an evaluation of risk factors, mortality, and factors related to poor outcomes in these patients. A subgroup of patients with invasive pneumococcal disease was then further analysed for the same factors.

2. Methods

2.1. Study design and sample

In this retrospective observational study, the electronic medical records of all patients at least 18 years old, admitted to the ICU of a Portuguese tertiary hospital from August 2018 to August 2023, with *Streptococcus pneumoniae* infection were analysed.

All *Streptococcus pneumoniae* isolates using standard hospital clinical microbiology laboratory methods were identified. Confirmed cases were defined as all patients with clinical evidence of infection and positive microbiological results for *Streptococcus pneumoniae* in urine antigen, blood, cerebrospinal fluid (CSF), pleural or peritoneal fluid, and sputum. Data on serotypes were obtained from institutional laboratory reports. Invasive pneumococcal infection (IPD), defined by the European Centre for Disease Prevention and Control (ECDC), includes invasive pneumococcal infections with the microbiological isolation of SP in sterile sites.

Antimicrobial susceptibility of isolates was assessed using disk diffusion tests, automated systems, *E*-tests, and microdilution tests. *Streptococcus pneumoniae* was considered susceptible to penicillin if the minimum inhibitory concentration (MIC) was 0.06 μg/mL or less and resistant if the MIC was more than 0.06 μg/mL. According to criteria from the European Committee on Antimicrobial Susceptibility Testing (EUCAST), isolates were considered susceptible to third-generation cephalosporin if the cefotaxime or ceftriaxone MIC was $\leq$ 0.5 μg/mL [9] **.**

Procedures were followed according to the updated 2013 World Medical Association Declaration of Helsinki and the STROBE guidelines, with the approval of our institution's ethics committee (approval number: CES 317/23).

2.2. Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics, version 29 software. For descriptive analysis, the normal distribution of quantitative variables was initially assessed, reporting mean and standard deviation. Absolute and relative frequencies were used to describe qualitative variables. In the inferential analysis, 95% confidence intervals (CI) were estimated for proportions, with quantitative variables being converted to binary outcomes by defining cut-off values according to the mean. Chi-square and Fisher's Exact test were used to analyse the difference of variables according to previous vaccination status.

Bivariable and multivariable logistic regression models were then conducted to assess associations. A significance level was considered when p-value <0.05. Results were reported with p-value and Odds Ratio (OR) in the case of bivariable regressions, and adjusted Odds Ratio (adjOR) in multivariable models. Hosmer-Lemeshow tests were conducted to analyse the fitness of the multivariable logistic models.

3. Results

3.1. General results

During the selected period, a total of 105 patients were included with confirmed SP infection, according to the criteria stated above. The mean age of the patients was 62.5 (±12.1) years old (Supplementary Fig. 1). There was a predominance of male patients in the sample (n = 71, 67.6%).

Among the analysed comorbidities, arterial hypertension (n = 55, 52.4%) and type 2 diabetes (n = 25, 23.8 %) were the most frequent. Table 1 provides details about the patients' characteristics.

At ICU admission, patients presented a mean APACHE II score of 20, mean SAPS II score of 42.7 (mean predicted in-hospital mortality of 36.2%). The number of measured in-hospital mortality was 14 (13.3%). Invasive mechanical ventilation was required in 37 patients (35.2%). Further details of the ICU admission of these patients can be found below (Table 2).

Regarding microbiological diagnostic tests, the majority of patients had a positive urinary antigen test (n = 88, 83.8 %), while only 15.2% (n = 16) tested positive for bronchial secretions. Blood cultures were positive in 50.5% (n = 53) of cases. Antibiotic susceptibility testing (AST) was performed on all positive samples (n = 67). The prevalence of penicillin non-wild-type *Streptococcus pneumoniae* (SP)—including isolates with increased exposure (I) or resistance (R) to penicillin (MIC >0.06 mg/L)—was 14.9%. Resistance rates to macrolides and third-generation cephalosporins were 8.9% and 4.5%, respectively. Additionally, 8.9% of isolates exhibited both penicillin non-wild-type status and macrolide resistance. Further details are provided in Supplementary Table 2.

Table 1
- Comorbidities of the population.

Variable	n (%)	Variable	n (%)
Age (mean, standard deviation)	**65.2 (12.1)**		
Sex		**Immunocompromised**	**26 (24.8)**
Female	34 (32.4)	Asplenia	9 (8.6)
Male	71 (67.6)	Active cancer	11 (10.5)
Lifestyle factors	**43 (41.0)**	Human immunodeficiency virus (HIV)	4 (3.8)
Alcohol abuse	17 (16.2)	Active chemotherapy	9 (8.6)
Smoking	40 (38.1)	Systemic corticotherapy use	8 (7.6)
Substance abuse	9 (8.6)	Biologic drugs	3 (2.9)
Comorbidities		**Pulmonary Diseases**	**40 (38.1)**
Cardiovascular risk factors	**65 (61.9)**	COPD	18 (17.1)
Arterial Hypertension	55 (52.4)	Non-stratified pulmonary disease	18 (17.1)
Obesity	7 (6.7)	Asthma	10 (9. [5])
Diabetes mellitus	25 (23.8)	Interstitial pulmonary disease	2 (1.9)
Cardiac diseases	**15 (14.3)**	Bronchiectasis	2 (1.9)
Congestive heart failure	10 (9.5)	Home oxygen therapy	6 (5.7)
Ischemic Cardiopathy	7 (6.7)	**Others**	**12 (11.5)**
Cardiomyopathy	3 (2.9)	Chronic liver disease	8 (7.6)
		Chronic renal disease	2 (1.9)
		Neuromuscular disease	2 (1.9)

Legend: COPD: Chronic obstructive pulmonary disease.

Table 2
- Characteristics of ICU admission.

Variable	n (%)	Variable	n (%)
APACHE II at admission (mean, sd)	20.0 (8.3)	**Invasive mechanical ventilation**	37 (35.2)
SAPS II at admission (mean, sd)	42.7 (15.1)	**Corticotherapy treatment in ICU**	53 (50.5)
SAPS II predicted mortality (mean)	36.2% 14		
In-hospital mortality	([13.3)		
ICU Length of stay			
<3 days	25 (23.8)		
3-5 days	26 (24.8)		
6–10 days	28 (26.7)		
11-15 days	9 (8.6)		
>15 days	17 (16.2)		

Legend: APACHE II: Acute Physiology And Chronic Health Evaluation II; SAPS II: The Simplified Acute Physiology Score; ICU: Intensive care unit.

3.2. Vaccination status

With respect to vaccination status, 89 patients (94.8%) presented criteria for vaccination against SP, but only 23 (21.9%) were effectively vaccinated. After ICU hospitalization, 21 patients (20%) were vaccinated within the first year after discharge. There was a significant association between the absence of vaccination and the need for invasive mechanical ventilation ($p = 0.043$), as shown in Table 3.

3.3. ICU length of stay

The bivariable models showed that immunosuppression status (OR = 0.15, 95% CI 0.05–0.43, $p < 0.001$), invasive disease (OR = 0.43, 95% CI 0.20–0.96, p-value = 0.039) and having criteria for vaccination (OR = 0.30, 95% CI 0.09–1.00, $p = 0.049$) were negatively associated with that outcome. The multivariable model did not confirm these associations. The model presented a good fit with a p-value of 0.917. These can be found in Supplementary Table 3.

Table 3
- Associations found regarding SP vaccination status.

Variable	Vaccinated	Unvaccinated	p-value
Invasive pneumococcal Disease	11 (19.3 %)	46 (80.7 %)	0.482
Corticotherapy treatment in ICU	10 (18.9 %)	43 (81.1 %)	0.448
Length of stay in ICU > 5 days	9 (16.7 %)	45 (83.3 %)	0.182
Invasive mechanical ventilation	**4 (10.8 %)**	**33 (89.2 %)**	**0.043**
Mortality	2 (8.7 %)	12 (6.14%)	0.052

Legend: ICU: Intensive care unit.

3.4. In-hospital mortality

Immunosuppression status (OR = 3.79, 95% CI 1.18-12.13, p-value = 0.025), ambulatory use of systemic corticotherapy (OR = 8.70, 95% CI 1.88–40.29, p-value = 0.006) and use of corticotherapy while in the ICU (OR = 4.28, 95% CI 1.12- 16.36, p-value = 0.034) were positively associated with in-hospital mortality in the bivariable model (Table 4). The multivariable model confirmed the association with immunosuppression status, with an adjusted OR of 5.83 (95% CI 1.21–28.22, p = 0.028). The model showed a goodness of fit with a p-value of 0.761.

3.5. Invasive pneumococcal disease

According to the ECDC criteria, IPD was diagnosed in 57 patients (54.3 %). Bivariable regressions showed positive relations between IPD and immunosuppression status (OR = 3.78, 95% CI 1.37–10.43, p = 0.01), whereas a negative association was found for age ≥ 65 years old (OR = 0.39, 95% CI 0.18–0.87, p-value = 0.022) (Table 5). The multivariable models confirmed the association for immunosuppression (adjOR = 4.08, 95% CI 1.36–12.21, $p = 0.012$). This model presented a good fit to the data, with a p-value of 0.505.

3.6. Serotypes

SP serotype was only analysed in 11 of the 57 IPD patients (19,3 %) with a vaccination rate of 36,4 % (4/11). Six patients (55.5 %) presented a serotype covered by the recommended national vaccination (3, 22F, 23F) and in five patients (45.5 %) the serotype was not covered (reported as negative for first and second lines).

Clinical characteristics, vaccination rate and outcomes according to SP serotype identification can be found in Supplementary Table 4.

4. Discussion and conclusion

IPD remains a major cause of morbidity and mortality [10]. Although much of IPD is preventable through vaccination, uptake remains low, particularly within special risk programs (e.g., those targeting individuals based on IPD risk factors). In our study, 89 patients (94.8%) met the criteria for pneumococcal vaccination, only 23 patients (21.9%) were vaccinated upon admission, reflecting a vaccination rate below 25 %. Furthermore, even after hospitalization, only 20 % of previously unvaccinated patients received the vaccine within 12 months post-discharge.

These findings highlight the urgent need for a multifaceted approach to improve vaccination coverage. Strategies should include tailored interventions such as education, reminders, incentives, and policy changes to enhance vaccine uptake among at-risk populations [11]. Expanding publicly funded vaccination programs to cover all high-risk groups or reconsidering the overall population-based vaccination strategy could help address the low vaccination rates observed in our population.

Our findings demonstrate a significant statistical association

Table 4
- Logistic regression for the association with in-hospital mortality.

Variable	OR	95 %CI		p-value	adjOR	95 %CI		p-value
		LL	HL			LL	HL	
Age ≥ 65	0.56	0.16	1.91	0.353				
Female Sex	1.19	0.37	3.86	0.775				
Having criteria for vaccination (*)	2.57	0.31	21.12	0.381				
Vaccination	0.54	0.14	2.12	0.378				
Lifestyle factors	1.10	0.35	3.42	0.876				
Cardiovascular risk factors	0.57	0.18	1.76	0.329				
Heart Disease	0.42	0.05	3.50	0.425				
Pulmonary Disease	0.61	0.18	2.10	0.434				
Immunosuppression status	**3.79**	**1.18**	**12.** 13	**0.025**	**5.83**	**1.21**	**28.22**	**0.028**
Systemic corticotherapy in ambulatory	**8.70**	**1.88**	**40.29**	**0.006**				
Use of systemic corticotherapy in ICU	**4.28**	**1.12**	**16.36**	**0.034**	3.61	0.82	15.89	0.09
ICU LOS								
<3 days (ref)	1.00				1.00			
3-5 days	0.16	0.02	1.48	0.107	0.11	0.01	1. 13	0.063
6–10 days	0.48	0.10	2.26	0.353	0.69	0.11	4.53	0.699
11-15 days	1.14	0.18	7.28	0.888	2.43	0.24	24.22	0.451
>15 days	0.86	0.18	4.19	0.849	1.07	0.15	7.87	0.946
Invasive Mechanical Ventilation	2.85	0.91	8.97	0.073				

Legend: ICU - Intensive care unit, LOS - Length of stay; OR - odds ratio; adjOR - adjusted odds ratio; LL - lower limit; HL - higher limit; CI - confidence interval. (*) Criteria as stated in Supplementary Table 1.

Table 5
- Logistic regression analysing the association between patients' characteristics and Invasive Pneumococcal Disease.

Variable	OR	95 %CI		p-value	adjOR	95 %CI		p-value
		LL	HL			LL	HL	
Age ≥ 65	**0.39**	**0.18**	**0.87**	**0.022**	0.43	0.17	1.11	0.082
Female Sex	0.92	0.41	2.10	0.848				
Having criteria for vaccination (*)	0.49	0.16	1.51	0.213				
Vaccination	0.72	0.28	1.81	0.483				
Lifestyle factors	1.53	0.70	3.36	0.291	1.36	0.51	3.64	0.535
Cardiovascular risk factors	0.69	0.31	1.53	0.357	1.74	0.62	4.90	0.293
Heart Disease	0.37	0.12	1.16	0.087	0.43	0.12	1.53	0.190
Pulmonary Disease	0.47	0.19	1.17	0.104	0.54	0.19	1.50	0.237
Immunosuppression status	**3.78**	**1.37**	**10.43**	**0.010**	**4.08**	**1.36**	**12.21**	**0.012**
Systemic corticotherapy in ambulatory	1.44	0.33	6.37	0.629				
Use of systemic corticotherapy in ICU	1.93	0.88	4.19	0.099				
ICU LOS								
<3 days (ref)	1.00							
3-5days	3.08	0.92	10.25	0.067				
6-10 days	0.80	0.27	2.36	0.686				
11-15 days	1.15	0.25	5.34	0.855				
>15 days	0.50	0. 14	1.79	0.288				
Invasive Mechanical Ventilation	0.99	0.44	2.20	0.972				

Legend: OR -odds ratio; adjOR - adjusted odds ratio; LL - lower limit; HL - higher limit; CI - confidence interval; ICU - Intensive Care United; LOS - Lenght of stay. (*) Criteria as stated in Supplementary Table 1.

between IPD and people with immunosuppression status (*p*-value 0.014), likely due to changes in immune response and immunosuppression caused by comorbidities [12]. Although arterial hypertension ($n = 55$, 52.4%) and type 2 diabetes ($n = 25$, 23.8%) were prevalent among our study population, no significant associations were found between those comorbidities and IPD risk.

Notwithstanding the fact that lifestyle factors, namely high-risk behaviors (i.e., excessive alcohol consumption, drug use, and active smoking), as well as obesity, are well-recognized risk factors for IPD [13], our national recommendations do not account for these factors in individuals without other comorbidities. In our study, 5.2% of patients who developed IPD were not covered by current vaccination criteria but would have been if these risk factors had been included as independent risk factors. Therefore, we advocate for future recommendations to incorporate these factors to ensure protection for all high-risk individuals, particularly if national data reflect a similar epidemiological panorama.

Serotypes were identified in only 11 IPD patients (19.3%), limiting our ability to assess serotype mismatch between the vaccine and circulating strains due to the small sample size. Comprehensive epidemiological surveillance integrating clinical, epidemiological, and serological data is essential to better understand serotype distribution and vaccine impact. Given its broad serotype coverage, cost-effectiveness, safety, and immunogenicity, PCV20 should be considered for inclusion in national immunization recommendations. Changes in vaccination strategies and serotype coverage of available PCVs will likely influence the epidemiology of *S. pneumoniae*, potentially altering age-specific incidence and contributing to serotype replacement.

Understanding serotype distribution is crucial for deciphering antimicrobial resistance patterns, as specific serotypes may exhibit higher antibiotic resistance likelihoods. Our study's prevalence of penicillin non-wild-type *S. pneumoniae* (14.9%) was similar to the values reported in European surveillance. [14] The EU/EEA population-weighted mean percentage for combined penicillin non-wild-type and resistance to macrolides was 9.9 % in 2021. In our study the prevalence was lower (8.9%). [14].

In our sample, the majority of patients with IPD (83.8%) tested positive for pneumococcal infection via urinary antigen testing, with

subsequent confirmation through microbiological isolation from sterile sites. While urinary antigen testing for *Streptococcus pneumoniae* has several limitations—including reduced specificity due to colonization, prolonged antigen persistence after infection, inability to determine serotype, lower sensitivity in certain populations, and lack of antibiotic susceptibility data—it demonstrated a sensitivity of 83.9% in confirmed IPD cases. Therefore, in some instances, it may facilitate earlier targeted therapy, given the low resistance rate shown previously, supporting antimicrobial stewardship principles by optimizing antibiotic use [15].

In-hospital mortality was 13.3%, aligning with European rates of 15% [14]. Our analysis identified a statistically significant association between prior immunosuppression and both mortality and the development of IPD, highlighting the crucial role of immune function in disease progression and outcomes. A key reason for this association is the immune system's role in fighting bacterial infections. Immunosuppressed individuals—whether due to cancer, chronic diseases, or immunosuppressive treatments—have a weaker ability to defend against *S. pneumoniae*. This makes it easier for the bacteria to spread, leading to a higher risk of severe disease and worse outcomes. Additionally, a slower or less effective immune response can delay bacterial clearance, prolonging infection and increasing the risk of complications and death [15]. .

Our study was unable to directly confirm a protective effect of vaccination against IPD, likely due to the small sample size, which may have limited the detection of a significant association. Additionally, immunocompromised patients may have had weaker immune responses, potentially reducing the vaccine's effectiveness. However, vaccination appeared to offer protection against severe disease, as shown by a lower need for invasive mechanical ventilation among vaccinated individuals ($p = 0.043$).

This is a retrospective design and reliance on registry-based data introduce potential reporting biases. Additionally, as the data were collected from a single institution, they may not be representative of the national or global context, necessitating caution in interpreting and generalizing our findings. Future research should prioritize multicenter studies, which could provide more comprehensive and representative insights. Another limitation is the lack of data on ICU costs. However, given the structure of the national health system, determining the exact cost of an individual patient's hospitalization remains challenging.

In conclusion, our study highlights the urgent need for improved strategies to enhance both access to and motivation for vaccination, particularly among immunocompromised patients, who face a significantly higher risk of invasive pneumococcal disease (IPD) and related mortality. Despite established national vaccination guidelines, coverage remains suboptimal, emphasizing the need for more targeted interventions.

While our findings demonstrated a protective effect of vaccination against severe pneumococcal disease—evidenced by a reduced need for invasive mechanical ventilation—the protective effect on mortality only showed a tendency, underscoring the need for further research. From our data patients who received the complete vaccination scheme (PCV13 + PCV23) appeared to have lower mortality rates, when compared with the incomplete vaccination scheme, but our sample size was not large enough to establish a significant correlation. With the recent approval of PCV20 in Portugal, it will be interesting to see how PCV20 compares to the PCV13 + PCV23 scheme in terms of immunogenicity and real-world effectiveness, especially with PCV21 also in the pipeline. Future efforts should prioritize behavioural intervention that may sucessfully improve vaccine uptake and policy changes to address the suboptimal vaccination coverage in immunocompromised patients.

CRediT authorship contribution statement

Ana Catarina Gonçalves: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Diogo Costa Oliveira:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rita Jorge:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **José Chen-Xu:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Matilde Couto:** Conceptualization, Writing – review & editing. **Isabel Campos:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **José Artur Paiva:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2025.100627.

Data availability

The data that has been used is confidential.

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