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RESEARCH

Streptococcus pneumoniae bacteremia: comparison of incidence, epidemiology, and clinical outcome in a pre- and post-COVID-19 period

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Abstract

Objectives *Streptococcus pneumoniae* is a leading cause of severe bacterial infections, including pneumonia, meningitis, and bacteremia. We aimed to evaluate the differences in clinical, epidemiological and outcome manifestations of patients admitted with *S. pneumoniae* bacteremia (SPB) in the pre- and post-COVID-19 period.

Methods The study analyzed all patients admitted in Province of Modena, Italy, during two time-periods: pre-COVID-19 (Jan 2018- Feb 2020) and post-COVID-19 (Mar 2020- Jun 2022) period. The data were compared using univariate and multivariate analysis.

Results A total of 150 patients with SPB were included, 109 and 41 patients in the pre- and post-COVID-19, respectively. We observed a decrease in SPB incidence from March 2020, after the implementation of the restrictive measures for the COVID-19 pandemic, and a new increase since Jun 2021, when lockdown measures were fully lifted. SPB was associated with pneumonia in 128 patients (85.3%), meningitis in 25 (16.7%) and otitis-mastoiditis in 14 (9.3%). The proportion of patients presenting with multi-lobar pneumonia significantly increased during the post-COVID-19 period (39.0% vs. 16.5%, $p=0.008$). Thirty-day mortality rate resulted higher in the post-COVID-19 period (24.4% vs. 11.9%, $p=0.075$), and multivariate analysis identified an age≥80 years (OR 4.45, 95% CI 1.12–17.61, $p=0.033$), multi-lobar pneumonia (OR 4.34, 95% CI 1.56–12.07, $p=0.005$), and central nervous system disease (OR 3.63, 95% CI 1.08–12.20, $p=0.036$) as independent risk factors for 30-day mortality. The rate of pneumococcal vaccination in the at-risk population was low (9.3%), but in the pandemic period the rate increased by 26.7%, driven by the anti-SARS-CoV-2 vaccination campaign.

Conclusions The COVID-19 pandemic has impacted the epidemiology and clinical severity of SPB. In our study, less than 10% of the high-risk population was vaccinated, while the older population (age≥80 years) had a significantly higher 30-day mortality risk. It would be necessary for Institutions to increase awareness campaigns for pneumococcal vaccination.

Keywords Invasive pneumococcal disease · COVID-19 · Bloodstream infection · Vaccine · Lockdown measures · Serotype · Pandemic · Pneumonia · Pneumococcal vaccination

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Introduction

Streptococcus pneumoniae bacteremia ranks among the top 10 most common bloodstream infection (BSI) and is associated with high morbidity and mortality worldwide [1, 2]. *S. pneumoniae* is typically a cause of respiratory infections such as community-acquired pneumonia but can also cause non- respiratory infections such as peritonitis, infective endocarditis, and meningitis [3]. Pneumococci usually colonize the human respiratory tract, especially during winter and early spring, spreading by air, via Flügge particles [4]. During the COVID-19 pandemic, the implementation of non- pharmaceutical interventions (NPIs), such as mask wearing, stay-at-home orders and physical distancing were adopted as strategies of prevention of SARS-CoV-2 spreading. In Italy, these NPIs were adopted until 28th June 2021. Introduction of NPIs has been associated with a decreased diffusion of other respiratory pathogens, including influenza virus, respiratory syncytial virus (RSV), and *S. pneumoniae* [5–7]. It has been proposed that a lower incidence of IPD may be due to reduced pneumococcal transmission [6, 7]. This study aims to compare the incidence, epidemiology, and clinical outcomes of *S. pneumoniae* bacteremia (SPB) before and after the onset of the COVID-19 pandemic.

Materials and methods

A retrospective study was conducted with the aim of investigating the impact of the SARS-CoV-2 pandemic on the epidemiology, clinical manifestations, and outcome of patients hospitalized for *Streptococcus pneumoniae* bacteremia (SPB). We compared two time periods: pre-COVID-19 period (January 2018-February 2020) and post-COVID-19 period (March 2020-June 2022). We included all adult patients admitted in the Province of Modena with positive blood cultures for *S. pneumoniae.* Demographic and microbiological data, underlying diseases, clinical aspects, vaccination status were collected through hospital medical files. The 30-day and 60-day mortality rates were obtained by consulting the medical records for patients who had been hospitalized for ≤2 months and by consulting the regional electronic health records for those discharged after two months. The cohort was divided into tertiles based on age (51 patients in 18–63 year-old group, 50 patients in 64–79 year-old, and 49 in the last group between 80 and 98 years). Underlying diseases were selected as those conditions affecting our study population at the time of hospital admission and identified as known risk factors for severe pneumococcal disease (cardiovascular disease, neurological disorders, splenectomy, chronic respiratory diseases, renal insufficiency, diabetes mellitus, solid-hematological neoplasms, chronic hepatopathy, immunodepression). *S. pneumoniae* was identified on blood samples through MALDI-TOF. Sites of infection were recorded and described. We included 'multiple sites of infection' as a dummy variable when more than one site was diagnosed. Antimicrobial susceptibility testing was performed through Vitek® 2, bioMérieux Italia, and pathogen MICs were interpreted according to EUCAST. The antimicrobials for which susceptibility testing was performed were: cefotaxime, ceftriaxone, imipenem, erythromycin, tetracycline, trimethoprim-sulfamethoxazole, levofloxacin, moxifloxacin, rifampin, vancomycin and chloramphenicol. SARS-CoV-2 infection, during the post-COVID-19 era, was detected through antigenic testing of symptomatic patients, according to the protocols of the provincial hospitals of Modena. We compared the incidence, clinical course and mortality rates of SPB between the two designated time periods, investing also potential risk factors correlated to 30-day mortality.

Ethics

The study was approved by local ethics committee (Prot. AOU 0007576/24, 13 March 2024) and conducted in compliance with the Italian legislation and the principles of the Declaration of Helsinki.

Statistical analyses

Statistical analyses were performed with IBM SPSS V.28 software version and R Stats Package. We compared incidence rates of SPB between patients admitted during the study period using P per trend analysis (Mantel-Haenszel linear-by-linear association chi-squared test). Descriptive statistics were presented as frequency and percentages for categorical variables, and medians with interquartile range (IQR) for continuous variables. Categorical variables were compared using Chi-square test in parametric conditions. Student's t test and Mann Whitney U test were used in the comparison of continuous variables for normally distributed and non-normally distributed data, respectively. Univariate logistic regression analysis was performed to investigate unadjusted associated factors with 30-days. A p-value of ≤0.05 was considered statistically significant and different multivariable logistic regression models were conducted: goodness of fitness post-estimation tests was performed to evaluate best model for associated factors with mortality (only selected model was shown in Results section).

Results

Between January 2018 and June 2022, 150 episodes of SPB were observed in 150 patients (109 and 41 in the pre- and post-COVID-19, respectively). Ninety-one (60.7%) patients were male, and the median age was 71.5 years (IQR 58–83 years). The incidence of SPB was regular until February 2020 (Fig. 1. A), with higher rates during the winter and spring months (Fig. 1. B). Thereafter, the annual incidence decreased from 8.5 cases/100,000 population in 2018 to 3 and 2.5 cases/100,000 population in 2020 and 2021, respectively. Finally, a trend toward a new increase in incidence was observed since June 2021, when lockdown measures were fully lifted in Italy (Fig. 2.A).

SPB was associated with pneumonia in 128 patients (85.3%), meningitis in 25 (16.7%) and otitis-mastoiditis in 14 (9.3%). Among patients with pneumonia, multi-lobar involvement and pleural effusion were present in 34 (22.7%) and 48 (37.5%) patients, respectively. Three patients were affected by complex clinical syndromes, with multi-site involvement, comprehending both lung and central nervous system (CNS). At the onset of SPB, the patients were in an emergency department in 75 (50.0%) cases, medical wards in 53 (35.3%), intensive care unit in 13 (8.7%), and onco-hematological ward in 9 (5.8%).

Urinary pneumococcal antigen test was performed in 68 patients (45.3%), proving positive in 46 (67.6%) patients. No significant differences were found between the site of infection (pneumonia, meningitis, otitis-mastoiditis, multiple-site of infection) and pneumococcal antigen positivity.

The main comorbidities of the patients were cardiovascular diseases ($n=64$; 42.7%), arterial hypertension ($n=59$; 39.3%), chronic renal failure ($n=32$; 21.3%), oncological pathology ($n=27$; 16.7%), diabetes mellitus ($n=26$; 17.3%). In 148 cases (98.6%), pneumococcal bacteremia occurred within the first 24 h of admission, representing the reason for hospitalization.

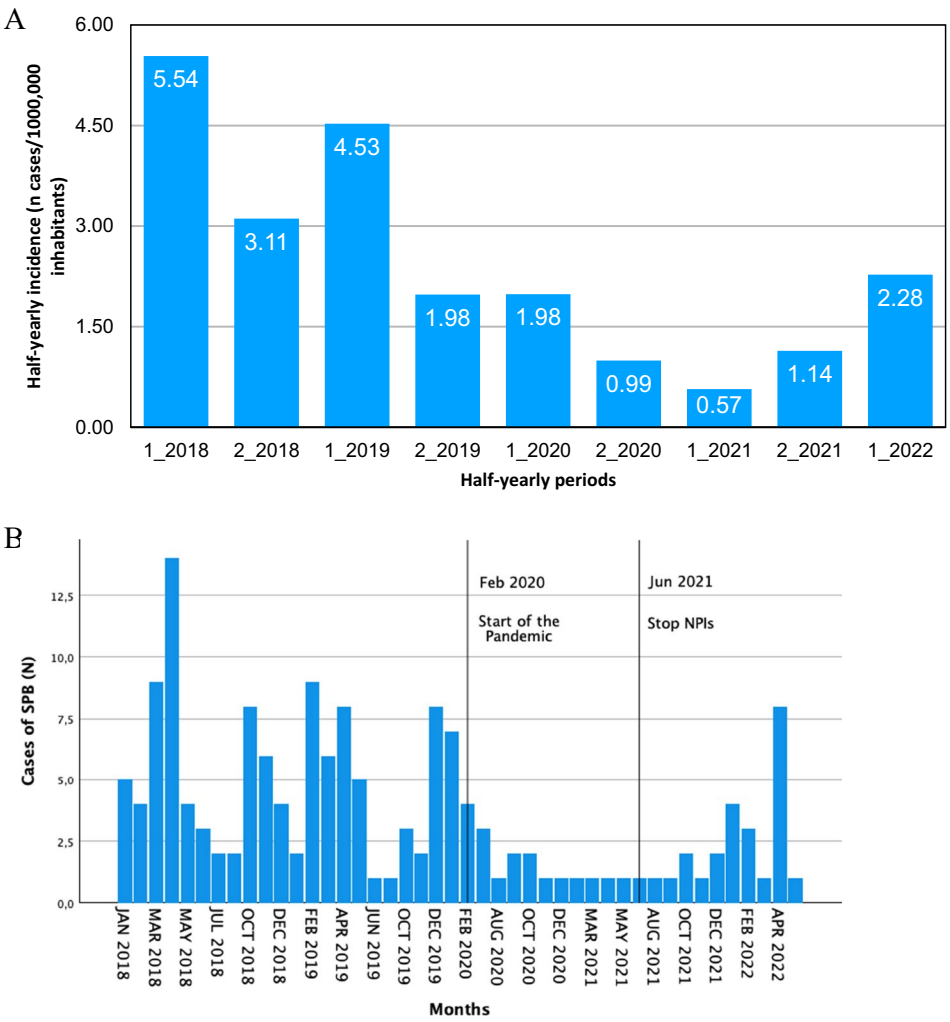

Fig. 1 (**A**) Half-yearly incidence of SPB - Province of Modena, Italy, (Jan 2018 - June 2022). (**B**) Monthly distribution of SPB cases in the Province of Modena, highlighting the start of the COVID-19 pandemic (February 2020) and the end of NPIs (June 2021) * NPIs: non-pharmaceutical interventions

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Demographic and clinical characteristics of patients with SPB, according to pre- and post-COVID-19 onset period, are shown in Table 1. In comparison with the pre-pandemic era, during the post-pandemic period patients were older (71.1 vs. 64.8 y, $p=0.063$), with a higher frequency of multi-lobular pneumonia (38.1% vs. 8.7%; $p=0.006$) and diabetes mellitus (28.5% vs. 13.1%; $p=0.027$). In addition, we observed a higher frequency of multi-lobar pneumonia in patients who had SPB and SARS -CoV-2 co-infection (OR 5.075; 95% CI: 1.079–23.872; $p=0.040$).

Anti-pneumococcal vaccination

Considering or patients with age≥65 years, immunocompromised and splenectomized, there were 106 (70.6%) patients in our study who were candidates for pneumococcal vaccination. Despite this, only 14 (9.33%) received it (8 patients with at least PCV13, and 6 patients fully vaccinated with both PCV13 and PPSV23). Interesting, during the post-COVID-19 period the percentage of vaccinated patients increased from 7.9 to 26.7% ($p=0.022$).

Table 1 Comparison of the main demographic and clinical characteristics of adult patients with *S. pneumoniae* bacteremia according to pre- or post-COVID-19 period of onset

Variable	All Episodes ($n=150$)	pre-COVID-19 period (Jan 18- Feb 20) ($n=109$)	post-COVID-19 period (Mar 20 – Jun 22) ($n=41$)	*P* Value
Demographics				
Male sex, N (%)	91 (60.7)	65 (59.6)	26 (63.4)	0.711
Age, median (IQR), y	71.5 (58–83)	70 (54–82)	74 (63–84)	0.154
Age tertiles	51 (34.0)	40 (36.7)	11 (26.8)	0.383
18–63	50 (33.3)	33 (30.3)	17 (41.5)	
64-79	49 (32.7)	36 (33.0)	13 (31.7)	
80–98				
Hospital wards stay at the time of bacteremia onset, N (%)				
Emergency department	75 (50.0)	55 (50.4)	20 (48.8)	0.349
Internal medicine ward	53 (35.3)	39 (35.8)	14 (34.1)	
Intensive care unit	13 (8.7)	7 (6.4)	6 (14.6)	
Onco-haematology unit	9 (6.0)	8 (7.3)	1 (2.4)	
LOS, median (IQR), days	15.7 (17.8)	14.9 (18.7)	17.0 (14.0)	0.115
Site of infection, N (%)				
Pneumonia	128 (85.3)	93 (85.3)	35 (85.4)	1.000
Multi-lobar pneumonia	34 (22.7)	18 (16.5)	16 (39.0)	**0.008**
Meningitis	25 (16.7)	18 (16.5)	7 (17.1)	1.000
Oto-mastoiditis	14 (9.3)	12 (11.0)	2 (4.9)	0.352
Multiple site of infection	17 (11.3)	14 (12.8)	3 (7.3)	0.404
Underlying conditions, N (%)				
Arterial hypertension	59 (39.3)	42 (38.5)	17 (41.4)	0.851
Cardiovascular disease	64 (42.7)	43 (39.4)	21 (51.2)	0.201
Hypercholesterolemia	16 (10.6)	10 (9.2)	6 (14.6)	0.377
Neurological disease	19 (12.7)	11 (10.1)	8 (19.5)	0.166
Gastrointestinal disease	21 (14.0)	15 (13.7)	6 (14.6)	1.000
Diabetes mellitus	26 (17.3)	14 (12.8)	12 (29.3)	**0.028**
Chronic lung disease	21 (14.0)	15 (13.7)	6 (14.6)	1.000
Chronic kidney failure	32 (21.3)	25 (22.9)	7 (17.1)	0.508
Chronic liver disease	11 (7.3)	9 (8.3)	2 (4.9)	0.728
Solid-hematological malignancy	27 (18.0)	19 (17.4)	8 (19.5)	0.813
Immunodepression	24 (16.0)	14 (12.8)	10 (24.4)	0.131
Splenectomy	2 (1.3)	1 (0.9)	1 (2.4)	0.473
Obesity	10 (6.7)	7 (6.4)	3 (7.3)	1.000
Smoke	25 (16.7)	18 (16.5)	7 (17.1)	1.000
Depression	16 (10.7)	15 (13.7)	1 (2.4)	0.071
Septic shock	11 (7.3)	9 (8.3)	2 (4.9)	0.728
Mortality, N (%)				
Death within 30 days	23 (15.3)	13 (11.9)	10 (24.4)	0.075
Death within 60 days	30 (20.0)	17 (15.6)	13 (31.7)	**0.039**

Abbreviations: *BC*, blood culture, *SD*, standard deviation. a. P values refer to pairwise comparisons based on Fisher exact test or Mann-Whitney U test, as appropriate

Serotype distribution

The distribution of *S. pneumoniae* serotypes is reported in Fig. 2, distinguishing pre- and post- COVID-19. Of the 150 strains, serotyping was performed in only 112 (74.6%): in 36 (24.0%) cases the strain was not sent to the Hub Laboratory for serotyping, in 5 (3.3%) cases the strain was not viable, and in 3 (2.0%) the sample was contaminated. The 4 most commonly detected serotypes in our population were serotype 8 in 33.9%, serotype 3 in 8.9%, serotype 12 F in 8.0%, and serotype 20 in 5.4%. Of the 14 vaccinated patients, none fully vaccinated developed SPB caused by a serotype that was included in the vaccine administered. Overall, no significant changes in the prevalence of the different serotypes were observed during the 2 study periods. We did not find any significant correlation between serotypes and severe clinical manifestations of pneumococcal disease, such as meningitis, septic shock, or multiple focus pneumonia (data not shown).

Antimicrobial susceptibility

It was not possible to test all antimicrobials on all isolates. Cefotaxime, ceftriaxone, imipenem, rifampin and vancomycin showed full activity towards the isolates (resistance rate 0.0%), and the MIC90 was ≤0.06, ≤0.06, 0.03 and 1 µg/ml, respectively. Only one (0.6%) isolate resulted resistant to levofloxacin, but 42 (26.9%) showed intermediate sensitivity (MIC = 0.5 µg/ml) to this antibiotic. Resistance was observed to erythromycin in 20/104 (16.1%) isolates, trimethoprim–sulfamethoxazole in 7/129 (5.4%), penicillin G in 12/155 (7.7%), tetracycline in 18/128 (14.0%), moxifloxacin in 1/129 (0.7%), and chloramphenicol in 3/129 (2.3%). No differences in antimicrobial resistance were observed between the pre- and post-COVID-19 period.

Mortality

The 30 and 60-day mortality rate were 15.3% (23 patients) and 20% (30 patients), respectively. The first-one increased from 11.9 to 24.4% in the post COVID-19 period ($p = 0.0075$); when we considered the 60-day mortality rate, the increase resulted statistically significant (from 15.6 to 31.7%, $p = 0.039$). Table 2 shows the univariate and multivariate analysis of risk factors related to 30-day mortality. At univariate analysis, an age ≥ 80 years (OR: 7.06; 95%CI: 1.89–26.29; $p = 0.004$), SARS-CoV-2 coinfection (OR:4.83; 95%CI: 1.00-23.23; $p = 0.049$), multi-lobar pneumonia (OR: 5.21; 95%CI: 2.03–13.31; $p = 0.001$), renal failure (OR: 2.90; 95%CI: 1.12–7.52; $p = 0.028$), and CNS diseases other than meningitis (OR: 4.19; 95%CI: 1.44–12.21; $p = 0.009$) resulted associated with higher mortality rate. Multivariate analysis confirmed that an age ≥ 80 years (OR: 4.45; 95%CI: 1.12–17.61; $p = 0.033$), multi-lobar pneumonia (OR: 4.11;

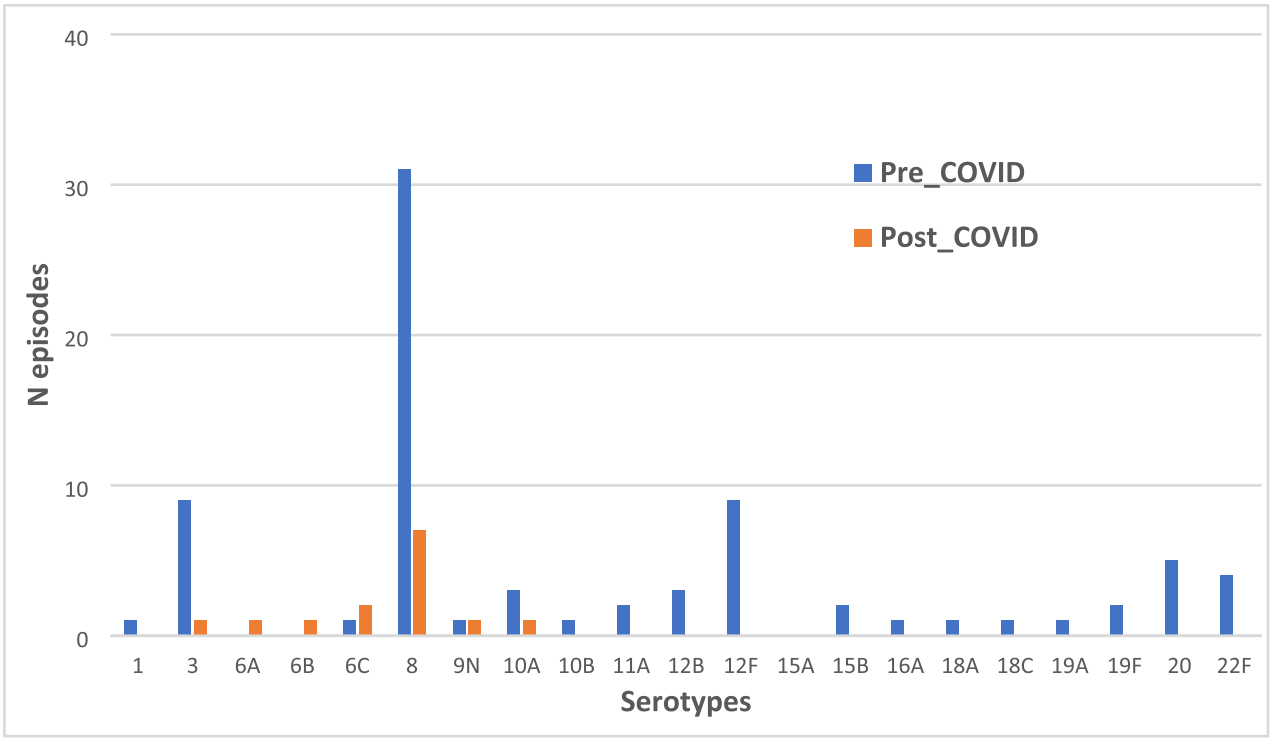

Fig. 2 Distribution of serotypes before (blue) and after (orange) COVID-19 pandemic

Table 2 Univariate and multivariate analysis of risk factors for death within 30 days from *S. pneumoniae* bacteremia

Variable (*N*=150)	Deaths (*N*=23, %)	Unadjusted cause-specific OR (95% CI)	*P*	Adjusted cause-specific OR (95% CI)	*P*
Demographic characteristics (*N*)					
Sex male (91)	14 (15.3)	1.01 (0.41–2.51)	0.983	-	-
Age tertile	3 (5.8)	1 (ref.)	-	1 (ref.)	-
18–63 (51)	5 (10.0)	1.77 (0.40–7.87)	0.449	1.40 (0.30–6.49)	0.667
64–79 (50)	15 (30.6)	7.06 (1.89–26.29)	**0.004**	4.45 (1.12–17.61)	**0.033**
80–98 (49)					
Clinical presentation					
SARS-CoV-2 pneumonia (7)	3 (42.8)	4.83 (1.00-23.23)	**0.049**	4.17 (0.70-24.67)	0.115
Multiple site of infection (17)	2 (11.7)	0.71 (0.15–3.34)	0.666	-	-
Multi-lobar pneumonia (34)	12 (35.2)	5.21 (2.03–13.31)	**0.001**	4.11 (1.47–11.49)	**0.007**
Pneumonia (128)	21(16.4)	1.96 (0.42–9.03)	0.387	-	-
Meningitis (25)	4 (16.0)	1.06 (0.33–3.44)	0.919	-	-
Otomastoiditis (14)	1 (7.1)	0.40 (0.05–3.20)	0.387	-	-
Comorbidity					
Immunodepression (24)	5 (20.8)	1.58 (0.52–4.76)	0.418	-	-
Shock (11)	2 (18.1)	1.24 (0.252–6.19)	0.786		
Hypertension (59)	10 (16.9)	1.22 (0.50–3.01)	0.659	-	-
Cardiovascular diseases (64)	11 (17.1)	1.28 (0.52–3.12)	0.587	-	-
Hypercholesterolemia (16)	2 (12.5)	0.76 (0.16–3.63)	0.740	-	-
Renal failure (32)	9 (28.1)	2.90 (1.12–7.52)	**0.028**	1.44 (0.48–4.34)	0.551
Solid/hematological cancer (27)	6 (22.2)	1.78 (0.63–5.05)	0.277	-	-
Diabetes (26)	5 (19.2)	1.40 (0.47–4.19)	0.546	-	-
Smoke (25)	1 (4.0)	0.19 (0.02–1.52)	0.119	-	-
COPD (21)	1 (4.7)	0.24 (0.03–1.91)	0.179	-	-
Gastro-intestinal disease (21)	3 (14.2)	0.91 (0.24–3.37)	0.886	-	-
CNS diseases (19)	7 (36.8)	4.19 (1.44–12.21)	**0.009**	3.22 (1.00–10.35)	**0.049**
Depression (16)	1 (6.2)	0.34 (0.04–2.70)	0.307	-	-
Other					
Resistance to ≥1 antimicrobial (23)	4 (17.3)	1.26 (0.38–4.12)	0.699	-	-
Post-COVID-19 period (41)	10 (24.3)	2.38 (0.95–5.97)	0.064	-	-

95%CI: 1.47–11.49; $p=0.007$), and CNS diseases (OR: 3.22; 95%CI: 1.09–10.35; $p=0.049$) as independent factors associated to a higher mortality rate. We also evaluated the impact of antimicrobial resistance on the outcome of patients with SPB: it was observed that strains with resistance to erythromycin, trimethoprim-sulfamethoxazole, or tetracycline were not related to a higher 30-day mortality rate (Table 2), or a higher frequency of more severe clinical manifestations.

Discussion

In this retrospective study, we evaluated the epidemiological trend of SPB between January 2018 and June 2022. The progressive reduction in SPB incidence that we have observed since March 2020 can certainly be related to the stringent measures implemented in our country to contain the SARS-Cov2 pandemic. In fact, the natural niche of *S. pneumoniae* is the human nasopharynx, and carriage is a prerequisite for human-to-human transmission and disease development [8]. In our study, an increasing trend of SPB cases has been recorded since the first half of 2022 (Fig. 2.A), specifically in the second quarter of 2022. The same trend was also observed by the National Surveillance System for Invasive Bacterial Diseases [9]. Other authors demonstrated a reduction in pneumococcal respiratory infections and SPB cases after the implementation of the SARS-CoV-2 pandemic containment measures. Angela B. Brueggemann et al. observed a significant and sustained decline of invasive diseases due to *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* in early 2020 (Jan 1 to May 31, 2020), coinciding with the introduction of COVID-19 containment measures in each country. The incidence of reported *S. pneumoniae* infections decreased by 68% at 4 weeks (incidence rate ratio 0·32 [95% CI 0·27–0·37]) and 82% at 8 weeks (0·18 [0·14–0·23]) following the introduction of preventive strategies [6]. Oster Y et al. observed a decline in overall respiratory tests and positivity rate during the first months of the SARS-CoV-2 pandemic. Respiratory isolations of *H. influenzae* and *S. pneumoniae* were significantly affected and returned to their monthly average by November 2020, despite a parallel surge

in COVID-19 activity, while *Mycoplasma pneumoniae* was almost erased from the respiratory pathogens' scene [10]. ML Nation et al. went further, attempting to quantify the impact of NPIs on the prevalence and density of pneumococcal carriage in 2,106 children over 24 months in Vietnam. The authors detected a decrease of pneumococcal carriage density up to 91.5% after the introduction of NPIs compared with pre-COVID-19, mainly due to capsular pneumococci. Only a minor effect on carriage prevalence was observed. Because respiratory viruses are known to increase pneumococcal carriage density, transmission, and disease, this study suggests that interventions targeting respiratory viruses may have the added benefit of reducing invasive pneumococcal disease, thus explaining the reductions observed after NPIs implementation [11].

Regarding the clinical manifestations of our study population, most SPB cases were associated with community acquired pneumonia, consistently with data from existing literature [12]. Clinical pictures were comparable between the pre- and post-COVID- 19 period, excepting for multilobar pneumonia which occurred more frequently during post-COVID-19 era. This can only partly be explained by concomitant SARS-CoV-2 infection, because only 1 quarter of patients with a multi-lobar pattern were SARS-CoV-2 co-infected. Noteworthy, during post-COVID-19 era we observed a tendency towards elderly age; this aspect may have had an impact on clinical manifestations of pneumococcal pneumonia, explaining a higher percentage of multilobar lung involvement.

The higher prevalence of diabetes in the post-COVID-19 period is not easy to interpret. One hypothesis could be related to the use of steroid therapy that all patients hospitalized for SARS-CoV-2 pneumonia received, even though only 7/41 patients in the post-COVID-19 period had a co-infection.

The prevalent serotype in both the pre- and post-COVID-19 period was serotype 8. Since this serotype is included in the 20- and 23-valent polysaccharide vaccine, both of which are recommended for the adult population, this prevalence may indicate suboptimal adherence of the at-risk population to the pneumococcal vaccine campaign, in our area.

Considering antimicrobial susceptibility testing, our study showed that the *S. pneumoniae* strains were fully susceptible to cefotaxime and ceftriaxone (100.0%), but less susceptible to erythromycin (85.9%) and tetracycline (86.0%). Despite this reduced susceptibility, the erythromycin data are encouraging: in fact, in comparison with the resistance rates in Emilia Romagna in 2019 [13], the resistance rate observed in our study is lower (45.4% vs. 14.1%, respectively), and probably indicates a more appropriate use of this class of antibiotics in our province. In addition, resistance to ≥1 antimicrobial had no impact on 30-day mortality, in our population.

In our study, we observed 30- and 60-day mortality rates of 15.3% and 20.0%, respectively. These results reflect the literature data: depending on the case series, the mortality rate of invasive pneumococcal disease varies from 10 to 20%, with higher rates among people aged≥65 years [14]. Moreover, in comparison with the pre-pandemic period, in the post-COVD-19 period, we observed an increase in mortality, both at 30 and 60 days. In particular, the 60-day mortality increased significantly from 24.4 to 31.7% ($p=0.039$). This finding indicates that patients with SPB had a worse prognosis in the pandemic period, and this could be related to SARS-CoV-2 co-infection. Other studies have also observed this increased mortality attributable to SARS-CoV-2 co-infection [15, 16].

In our case series only 7/41 (17%) patients were co-infected with SARS-Cov-2, so other hypotheses should be considered. It is possible that patients hospitalized with a severe disease such as SPB may have suffered more from hospital overcrowding due to the outbreak of the pandemic. Especially in the early months of the pandemic, both ordinary wards and intensive care units were overcrowded, and healthcare staff were often unable to meet the demand for healthcare. This critical situation may have led, in some cases, to delays in the diagnosis of bacteraemia (e.g. inability to perform blood cultures correctly), or made it difficult to administer antibiotic therapy within the prescribed time frame, or to quickly modify an empirical therapy with targeted therapy. Liechti et al. investigated the risk factors and clinical characteristics of pneumococcal meningitis episodes occurring during the COVID-19 pandemic, comparing them with those from baseline and the time afterwards [17]. During the COVID-19 pandemic, they observed worse outcomes in patients with pneumococcal meningitis; the authors assumed that this may be explained by differing adherence to restrictions according to risk groups or by reduced health care quality. However, no errors of this type were found in the medical records of our population, so other hypotheses should be considered. Multivariate analysis conducted in our study confirmed that an age≥80 years, multi-lobar pneumonia, and CNS diseases were independent factors associated with an increased 30-day mortality rate. Mannu et al., in their systematic review and metanalysis, showed how multi-lobar pneumonia resulted to be an independent risk factor for mortality in community acquired pneumonia [18]. Although they did not undertake any specific sub-analysis of the microorganisms involved, the authors observed that *S. pneumoniae* was frequently present in the sputum of patients with multi-lobar pneumonia. Multilobar lung involvement was also found to be an independent risk factor for early death (within 48 hours of admission) in hospitalized patients with community-acquired pneumonia in a Spanish prospective study [19]. Regarding advanced

age, numerous studies have shown its correlation with poor prognosis in both pneumococcal pneumonia and invasive pneumococcal disease [2, 12, 20, 21]. This is one of the reasons why pneumococcal vaccination is recommended for individuals older than 65 years of age.

Analyzing the data from our population, we can see that the target vaccination rate proposed for high-risk patients is still a long way off. In fact, only 13.2% of vaccination candidates had been vaccinated against *S. pneumoniae*. In our country, the National vaccination plan 2017–2019 set the following goals: reaching a vaccine coverage of 95% in newborn infants and of 75% in citizens aged≥65 years old [22]. National surveillance data during the period 2019–2022 showed significantly higher percentages of anti-pneumococcal vaccine rate among newborn infants, ranging between 70 and 95% [23]. Similar data are founded in the Pneumococcal Vaccination Atlas, which documents pneumococcal vaccination coverage and recommendations across Europe [24]. It should be noted that only a minority of European countries recommend pneumococcal vaccine in all three risk groups listed above; moreover, not all national health systems provide it free of charge, especially for categories other than infants. These aspects might indicate low awareness among citizens, especially those of advanced age, about the risks associated with pneumococcal infection. In our study, the vaccination rate during the post-COVID-19 period increased to 26.7%, among vaccination candidate patients. This result could be a consequence of the massive commitment to the anti-SARS-CoV-2 vaccination campaign and in general to the prevention of other serious respiratory infectious diseases. Despite this increase, the adherence rate is still too low to ensure effective protection in the population.

Conclusions

S. pneumoniae still represents a significant public health threat, affecting various age groups and vulnerable individuals. The SARS-CoV-2 pandemic has altered the circulation of respiratory pathogens: it is now clear that limiting the spread of respiratory viruses can help reduce the transmission of *S. pneumoniae* and its ability to cause severe infections. However, this is not feasible in everyday life, making vaccination the most effective prevention strategy. In our study, less than 10% of the high-risk population was vaccinated, while the older population (age≥80 years) had a significantly higher 30-day mortality risk. We believe that government institutions should increase awareness campaigns for pneumococcal vaccination, as already recommended by the World Health Organization.

Limitations

Our study is subject to several limitations. The retrospective design may introduce selection and information biases. Additionally, was not possible to collect some clinical and laboratory parameters (e.g., severity of fever, neurological symptoms, time of onset of symptoms) useful for better understanding the differences between the two groups of patients. Finally, we believe that it would have been more accurate to divide the study period into three phases (pre-COVID-19, pandemic period, and period following the discontinuation of NPIs, starting in June 2021). However, given the small sample size and the impossibility of performing relevant statistical analyses, we preferred to keep the study divided into only two periods, pre- and post-COVID-19.

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Declarations

Human ethics and consent to participate Not applicable. Given the retrospective nature of the study, it was not possible to obtain written informed consent from the subjects enrolled due to organizational reasons.

Conflict of interest No potential conflict of interest was reported by the author(s).

Competing interests The authors declare no competing interests.

Clinical trial number Not applicable.

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