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Shifts in invasive pneumococcal disease epidemiology following the SARS-CoV-2 pandemic in Madrid, Spain: insights from a six-year hospital-based study

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Abstract

Background Invasive pneumococcal disease (IPD) is influenced by vaccination strategies, circulating serotypes and respiratory viral activity. The COVID-19 pandemic substantially altered respiratory infection dynamics. The aim of the study was to evaluate temporal changes in IPD incidence, clinical characteristics and serotype distribution before, during and after the COVID-19 pandemic.

Methods We conducted a retrospective study of all IPD cases diagnosed between January 2018 and December 2023 at a tertiary hospital in Madrid, Spain. IPD was defined by isolation or molecular detection of *Streptococcus pneumoniae* from normally sterile sites. Demographic, clinical, microbiological and virological data were analysed, together with available respiratory viral testing results, although testing was not systematic and viral coinfections may have been underdetected. Incidence rates were calculated using the hospital catchment population. Temporal patterns of IPD and population-level respiratory virus detections were compared descriptively.

Results A total of 315 patients were identified, including 256 adults (81.3%) and 59 children (18.7%). Pneumonia was the most frequent clinical presentation (76.5%). Adults had a higher prevalence of comorbidities (78.1%) and mortality (11.3%), whereas children were generally healthy and more frequently required intensive care (67.8%), largely due to empyema-related management rather than increased disease severity. Overall, 68.6% of isolates were serotyped; serotypes 8 and 3 predominated. The annualized incidence of IPD decreased from 15.4 cases per 100,000 inhabitants (95% CI, 13.0–18.0) before the pandemic to 6.7 (95% CI, 5.5–8.2) during the pandemic period, followed by a partial recovery to 10.8 (95% CI, 7.4–15.1) in the post-pandemic period. Incidence calculations were restricted to patients residing within the hospital catchment area ($n=284$). Respiratory viral coinfection was documented in 18.4% of cases and was more frequent in children (39%). Serotype 11A showed the highest proportion of penicillin resistance.

Conclusion IPD incidence declined sharply during the pandemic and increased again thereafter, coinciding with substantial changes in respiratory virus circulation. The persistent circulation of serotype 3 and the emergence of non-vaccine serotypes underscore the need for continued surveillance and updated vaccination strategies.

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Introduction

Acute respiratory infections remain a leading cause of morbidity and mortality worldwide [1, 2]. Among bacterial pathogens, *Streptococcus pneumoniae* is a major cause of both mucosal and severe disease. Invasive pneumococcal disease (IPD), defined by organism detection in normally sterile sites, may present as bacteremia, meningitis or empyema and is associated with substantial mortality, particularly among older adults, immunocompromised individuals and those with chronic conditions [3].

More than 100 pneumococcal serotypes have been described, differing in invasiveness, virulence and vaccine susceptibility [4, 5]. The introduction of pneumococcal conjugate vaccines (PCVs) has substantially reduced disease caused by vaccine-included serotypes. However, this success has been accompanied by serotype replacement, with increasing contribution of non-vaccine serotypes and regional variation in distribution. In the post-PCV13 era, serotypes such as 3, 8, 9N, 12F and 22F are among the most frequently identified in both children and adults [6, 7]. In Europe, IPD incidence ranges from approximately 2 to 8 cases per 100,000 population, with higher rates among older adults [8].

Respiratory viral infections play an important role in pneumococcal pathogenesis by facilitating invasion from colonization [9, 10]. The COVID-19 pandemic profoundly altered the circulation of respiratory pathogens through non-pharmaceutical interventions and behavioural changes [11, 12]. Several surveillance studies reported declines in IPD during pandemic periods, followed by resurgence after relaxation of control measures [13, 14].

Understanding how pandemic-related disruptions influenced pneumococcal epidemiology is essential for interpreting recent trends and informing vaccination strategies. We therefore analyzed temporal patterns of IPD incidence, serotype distribution and clinical characteristics in a large tertiary hospital over a six-year period spanning pre-pandemic, pandemic and post-pandemic phases.

Materials and methods

Study design and setting

A retrospective study was conducted at Hospital Universitario 12 de Octubre, a tertiary-care facility located in southern Madrid, serving a reference population of approximately 460,000 inhabitants, including 95,000 children. All consecutive patients diagnosed with IPD between January 2018 and December 2023 were included. IPD was defined as the isolation of *Streptococcus pneumoniae* or its molecular detection in blood cultures, cerebrospinal fluid (CSF), pleural fluid, or other normally sterile sites. All patients with pneumococcal detection in CSF fulfilled clinical criteria for meningitis and were classified accordingly. For temporal analyses, the study period was categorized as pre-pandemic (January 2018–February 2020), pandemic (March 2020–April 2023), and post-pandemic (May–December 2023).

Clinical and microbiological data

Demographic characteristics, underlying comorbidities and clinical outcomes were collected for each patient. Respiratory viral coinfection was defined as the detection of one or more respiratory viruses by PCR within 7 days before or after the diagnosis of IPD. Respiratory viral testing was performed according to clinical criteria and was not systematically conducted in all patients with IPD, potentially leading to underdetection of viral coinfections. The viruses included in the analysis were influenza, respiratory syncytial virus (RSV), rhinovirus, adenovirus, human metapneumovirus, parainfluenza viruses, SARS-CoV-2, and seasonal coronaviruses.

S. pneumoniae identification was confirmed by the growth of α-haemolytic colonies on blood agar and optochin susceptibility, or by molecular detection in CSF samples using the BioFire FilmArray panel (bioMérieux, Marcy-l'Étoile, France) or in pleural fluid using an in-house PCR targeting exclusively the autolysin *lytA* gene

[15]. When isolates were available, antimicrobial susceptibility testing was performed and interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.

Serotyping

Viable *S. pneumoniae* isolates, or alternatively samples with positive molecular detection, were submitted to the Regional Public Health Laboratory of the Community of Madrid as part of the epidemiological surveillance program for serotyping. Serotype analyses were performed at the IPD episode level. Therefore, when pneumococcal detection was obtained from more than one sterile site during the same episode, the corresponding serotype was included only once in the analysis. Initial serogrouping was performed using latex agglutination (ImmuLex™ Pneumotest Kit, SSI Diagnostica), and serotype confirmation was carried out using the Quellung reaction with pooled and type-/subtype-specific antisera (SSI Diagnostica, Hillerød, Denmark). Clinical samples without bacterial growth but with positive molecular detection were directly serotyped by direct PCR-hybridization assay using the S. PneumoStrip® test (Operon S.A., Zaragoza, Spain).

Incidence and viral circulation analysis

Annualized IPD incidence rates were calculated for the predefined pre-pandemic, pandemic, and post-pandemic periods using only patients residing within the hospital catchment area; patients residing outside this area were excluded from incidence calculations. The estimated catchment population comprised 460,000 inhabitants (95,000 children and 365,000 adults) and was assumed to remain stable throughout the study period. Incidence rates were annualized according to the duration of each epidemiological period and expressed as cases per 100,000 inhabitants per year. Ninety-five percent confidence intervals (95% CIs) were calculated assuming a Poisson distribution.

Population-level respiratory virus circulation was assessed using monthly numbers of RT-PCR-confirmed influenza, RSV, and SARS-CoV-2 detections (Hologic Inc., San Diego, CA, USA) recorded within the hospital catchment area between 2018 and 2023. These data included patients evaluated in primary care and emergency departments and patients hospitalized with acute respiratory infection. Population-level viral surveillance data were independent of respiratory viral testing performed in individual patients with IPD.

Monthly IPD cases and population-level respiratory virus detections were plotted together to descriptively illustrate their temporal patterns across the study period. Because respiratory virus testing activity and testing indications may have varied over time, particularly during the COVID-19 pandemic, no inferential correlation or regression analyses were performed to assess an independent association between respiratory virus circulation and IPD incidence.

Statistical analysis and ethical considerations

Quantitative variables were described using medians and interquartile ranges, while qualitative variables were expressed as absolute or relative frequencies. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were analyzed using the Mann–Whitney U test or Student's t test, depending on data distribution. A two-sided p value < 0.05 was considered statistically significant. Given the exploratory nature of the study and the limited number of predefined comparisons, no correction for multiple comparisons was applied. Statistical analyses were performed using SPSS software version 15.0 (Chicago, IL, USA).

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the hospital Research Ethics Committee (CEIm) (reference number 25/262).

Results

Patient distribution and infection source

Between 2018 and 2023, a total of 315 patients were included, of whom 256 (81.3%) were adults and 59 (18.7%) were children.

Pneumococcal isolates were recovered from blood cultures ($n=248$), pleural fluid ($n=41$), and CSF ($n=12$). Additionally, simultaneous isolation from blood and CSF was documented in 13 patients, and from blood and pleural fluid in one patient. The primary focus of infection was pneumonia in 76.5% of cases ($n=241$), followed by meningitis ($n=30$; 9.5%) and primary bacteremia ($n=27$; 8.6%).

In patients with empyema, pleural fluid *S. pneumoniae* detection was mainly achieved by real-time PCR after negative conventional cultures. Of the 42 pleural fluid detections, only 10 (23.8%) were recovered by conventional culture.

Clinical characteristics of patients

Pediatric patients

Pediatric patients with IPD had a median age of 3 years [IQR: 1–5], with an even sex distribution (50.9% male). Only 10.2% had underlying comorbidities. One death was recorded in the pediatric cohort.

Despite the low prevalence of comorbidities, 67.8% of children required ICU admission. ICU admission was recorded in all 35 children with pleural empyema (100%), compared with 5 of 24 children (20.8%) presenting with other manifestations of IPD. By epidemiological period, ICU admission occurred in 13/13 (100%), 18/18 (100%), and 4/4 (100%) children with empyema during the pre-pandemic, pandemic, and post-pandemic periods, respectively, compared with 2/15 (13.3%), 2/8 (25.0%), and 1/1 (100%) children with other IPD presentations. ICU admission in children was mainly related to transthoracic drainage in pneumonia complicated by empyema, reflecting procedural management rather than necessarily greater disease severity. Most cases of pneumonia complicated by empyema occurred in the pediatric cohort, accounting for 35 of the 42 total cases (83.3%), a significantly higher proportion than that observed in adults ($p<0.0001$).

Adult patients

Among adults, the median age was 61.5 years [49–75.5], with a male predominance (56.6%). Overall, 78.1% had at least one underlying condition. During hospitalization, 21.9% required ICU admission and 11.3% died as a consequence of the infection.

Most cases of meningitis occurred in adults (26 of 30 cases), with a median age of 57 years [45–70] and a male predominance (65.4%; $n=17$). Among adults with meningitis, 61.5% ($n=16$) required ICU admission, a significantly higher proportion than that observed in adults with other IPD clinical syndromes (17.3%; 40 of 230 patients; $p<0.0001$). Four adult patients with meningitis died.

All clinical and demographic characteristics are summarized in Table 1.

Previous respiratory viral infection

Overall, detection of respiratory viruses within 7 days before or after the IPD episode was documented in 18.4% of cases. The most frequently detected viruses were RSV ($n=16$), influenza A ($n=14$), and rhinovirus ($n=8$). This proportion was significantly higher in pediatric patients, reaching 39% of cases.

Table 1 Descriptive clinical and demographic characteristics of patients with IPD

	Children (N = 59)	Adults (N = 256)
Age (years)[a]	3 [1–5]	61.5 [49–75.5]
Male sex[b]	30 (50.9)	145 (56.6)
Country of origin[b]		
Spain	54 (91.5)	188 (73.4)
Latin America	3 (5.1)	48 (18.8)
Eastern Europe	1 (1.7)	11 (4.3)
Underlying conditions[b]		
Diabetes mellitus	0	56 (21.9)
Coronary artery disease	0	65 (25.4)
Arterial hypertension	1 (1.7)	104 (40.6)
Dyslipidemia	0	53 (20.7)
Obesity	0	23 (9)
Chronic lung disease	0	64 (25)
Obstructive sleep apnea on CPAP	0	19 (7.4)
Chronic kidney disease	1 (1.7)	33 (12.9)
Chronic liver disease	0	12 (4.7)
Cancer	0	42 (16.4)
Hematologic disease	2 (3.4)	24 (9.4)
Solid organ transplantation	0	9 (3.5)
HIV infection	0	11 (4.3)
Immunosuppression	0	52 (20.3)
Any underlying condition	6 (10.2)	200 (78.1)
ICU admission[b]	40 (67.8)	56 (21.9)
Mortality[b]	40 (67.8)	29 (11.3)

[a]Median [interquartile range]; [b]n (%); ICU: intensive care unit; CPAP: continuous positive airway pressure

Data are presented separately for pediatric and adult patients. The table is intended as a descriptive summary of the study population; therefore, statistical comparisons between groups were not performed

In children, nearly all viruses included in the study were detected, in some cases as co-detections. RSV was the most frequently identified virus in this group ($n=6$). Among adults, ten cases of influenza A, ten of RSV, and six of SARS-CoV-2 infection were identified, the latter exclusively detected in this age group.

Respiratory viral screening was performed in 186 of 315 patients (59%), including 41 of 59 children (69.5%) and 145 of 256 adults (56.6%). Testing coverage varied substantially across the study period, ranging from 32.1% in 2019 to 90.9% in 2021. Annual viral-testing coverage stratified by age group is presented in Supplementary Table S1.

Pneumococcal serotypes in invasive disease

Of the 315 episodes, 68.6% ($n=216$) had available serotype data. The proportion of cases without available serotype data decreased from 49.3% in 2018 to 4.6% in 2023, reflecting a substantial improvement in serotyping coverage over time. Annual serotyping coverage stratified by age group is presented in Supplementary Table S1. A wide diversity of serotypes was identified, with serotypes 8 ($n=51$) and 3 ($n=49$) being the most frequent.

In children, serotype 3 predominated (46.5%), followed by serotypes 8, 15A and 19A (7% each). In adults, serotype 8 was the most frequent (27.2%), followed by serotype 3 (16.2%) and serotype 11A (5%). Serotype 3 was significantly more common in children, whereas serotype 8 predominated in adults ($p<0.0001$ and $p=0.0042$, respectively) (Fig. 1).

Differences in serotype distribution were observed according to sample type and patient age. In blood cultures, serotype 8 was the most prevalent ($n=48$; 25.8% of typed isolates from this source) (Fig. 2A). In contrast, serotype 3 predominated in pleural fluid samples ($n=20$), representing 69% of isolates characterized at this site, most of which were obtained from pediatric patients (Fig. 2B).

In meningitis cases, serotype 8 was also the most common; however, serotypes of serogroup 16 and serotypes 10A, 22F, and 23A showed a relatively higher representation compared with other clinical sources (Fig. 2C).

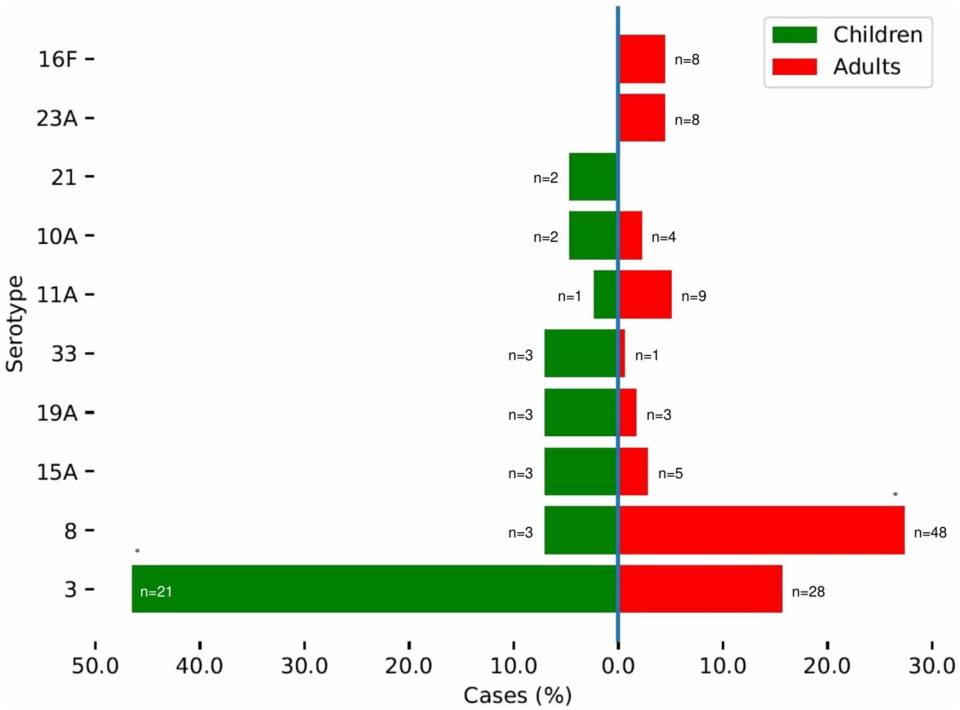


Fig. 1 Distribution of the most frequent pneumococcal serotypes among serotyped invasive pneumococcal disease cases, by age group. Only the most frequent serotypes are shown. Serotypes accounting for less than 4% of cases in both age groups were not displayed. Bars represent the percentage of isolates within each age group, and the numbers displayed at the ends of the bars indicate the corresponding absolute counts (n). An asterisk (*) indicates a statistically significant difference between pediatric and adult patients ($p < 0.05$)

A temporal analysis of serotype distribution revealed a marked increase in serotype 3 in 2022 and 2023, mainly driven by pleural fluid isolates from pediatric patients. An increase in serotype 22F was also observed in 2023. In a descriptive sensitivity analysis restricted to 2022–2023, when serotyping coverage reached 94.6%, serotype 3 was the most frequently identified (29.5%), followed by serotype 8 (17.1%), while serotype 11A accounted for 5.7% of serotyped cases. Thus, serotypes 3 and 8 remained the most frequent during the years with the highest serotyping coverage, although their relative frequencies differed from those observed in the overall study period.

Serotype distribution was also examined according to respiratory viral testing status. Among patients with available serotype data, 48 had a positive respiratory viral test, 100 had negative testing results, and 68 had not undergone respiratory viral testing. Serotype 3 accounted for 35.4%, 20.0%, and 17.6% of cases in these groups, respectively, whereas the corresponding proportions for serotype 8 were 10.4%, 28.0%, and 26.5%. The complete serotype distribution is presented in Supplementary Table S2.

Serotype-specific clinical impact was evaluated using case fatality as the outcome measure. Serotyping information was available for 19 of 30 fatal cases (63.3%). Among these, the most commonly identified serotypes were 3 ($n = 3$), followed by serotypes 8, 11A, 16F, and 23A ($n = 2$ each).

Although serotype 3 was among the most frequent causes of IPD, its case fatality rate was relatively low (6.1%; 95% CI, 1.3–16.9%), as was that of serotype 8 (3.9%; 95% CI, 0.5–13.5%). In contrast, less prevalent serotypes showed higher fatality rates, including serotype 16F (28.6%; 95% CI, 3.7–71.0%), serotype 23A (25.0%; 95% CI, 3.2–65.1%), and serotype 11A (20.0%; 95% CI, 2.5–55.6%) (Fig. 3). These findings indicate that higher prevalence does not necessarily correlate with higher mortality, although the low frequency of some serotypes limits interpretation.

Antimicrobial susceptibility

Antimicrobial susceptibility data were available for 251 isolates (79.7%); therefore, percentages were calculated using the number of isolates tested for each antibiotic. All 251 isolates were susceptible to cefotaxime/ceftriaxone, whereas six (2.4%) were resistant to penicillin. These penicillin-resistant isolates were not clustered within a specific time period.

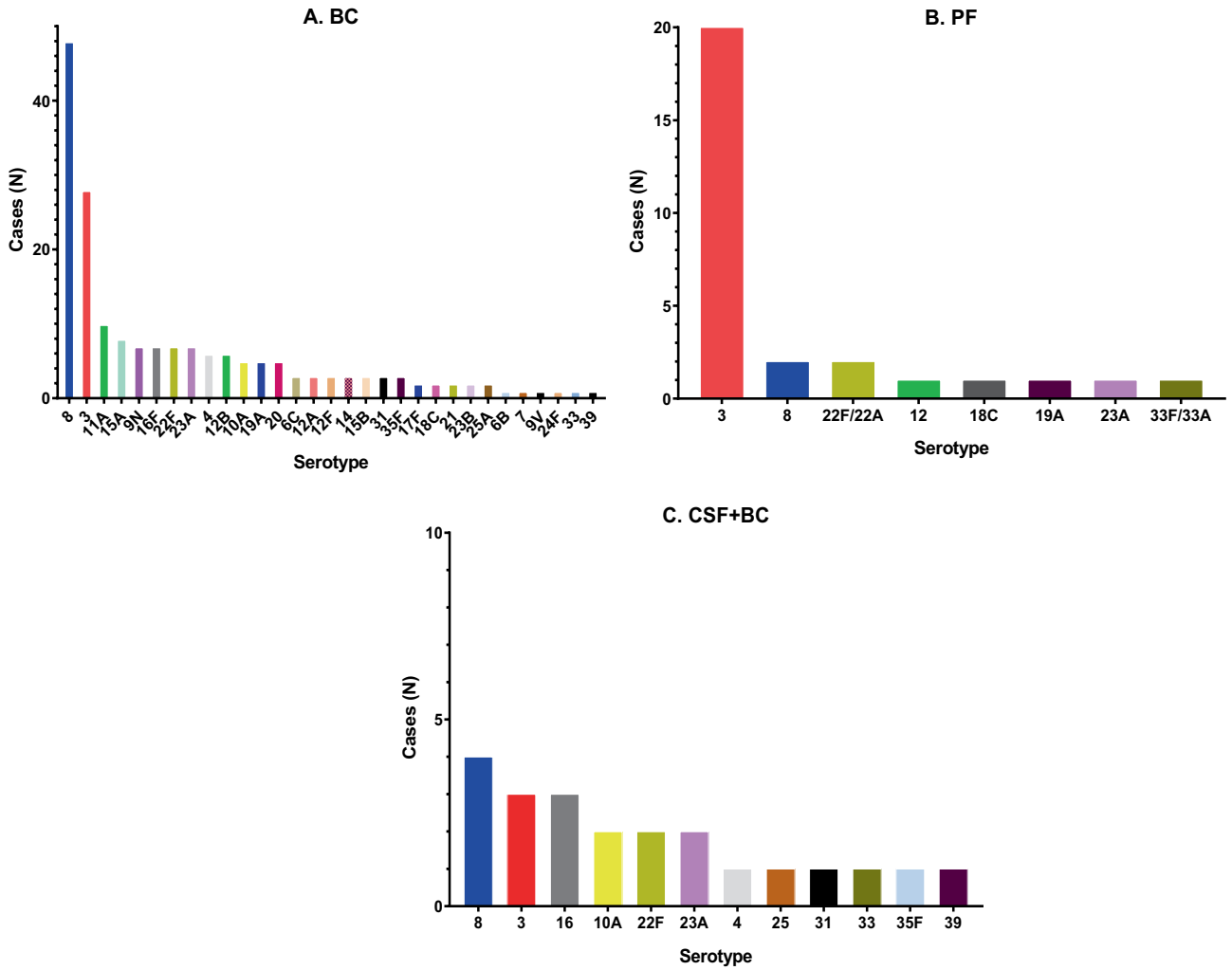


Fig. 2 Distribution of *Streptococcus pneumoniae* serotypes among major invasive disease presentations. (**A**) Serotype distribution among isolates detected in blood cultures. (**B**) Serotype distribution in pleural fluid samples from patients with pneumonia complicated by empyema. (**C**) Serotype distribution among meningitis episodes, including cases with pneumococcal detection in cerebrospinal fluid and/or blood cultures. Each episode was counted once regardless of the number of positive specimens. BC: blood culture; PF: pleural fluid; CSF: cerebrospinal fluid

Three isolates had penicillin mínimum inhibitory concentration (MIC) values < 1 mg/L but were classified as resistant because they were associated with meningitis, in accordance with EUCAST criteria. Penicillin resistance was particularly notable among serotype 11A isolates. Of the ten serotype 11A isolates identified in the study, nine had available antimicrobial susceptibility data, and three of these (33.3%) showed penicillin resistance, with MIC values > 1 mg/L. All three were obtained from blood cultures in adult patients (two with pneumonia and one with primary bacteremia). Among the six penicillin-resistant isolates, one was also resistant to erythromycin and clindamycin and another to trimethoprim–sulfamethoxazole.

Overall susceptibility was 87.1% (196/225) for erythromycin, 88.3% (212/240) for clindamycin, and 83.3% (200/240) for trimethoprim–sulfamethoxazole. Resistance to levofloxacin was detected in three isolates (1.3% of 240 tested), while no resistance to vancomycin was observed among the 235 isolates with available results.

When stratified by serotyping availability, resistance to erythromycin, clindamycin, and trimethoprim–sulfamethoxazole was more frequent among isolates without available serotype information than among serotyped isolates (21.6% vs. 8.6%, 20.3% vs. 7.8%, and 25.7% vs. 12.7%, respectively). Notably, most non-serotyped

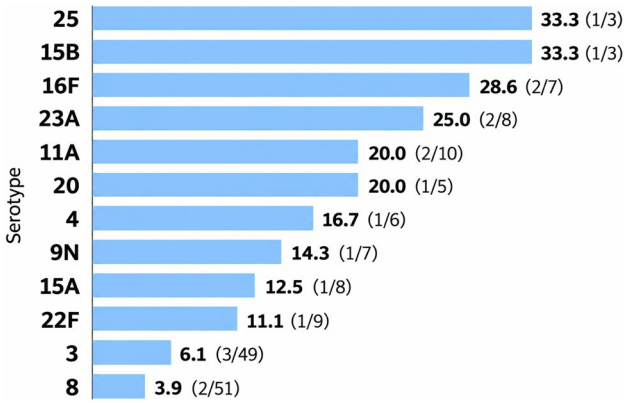


Fig. 3 Case fatality by *Streptococcus pneumoniae* serotype. Bars represent serotype-specific case fatality rates (%). Values in parentheses indicate the number of deaths relative to the total number of cases for each serotype (deaths/total cases). Serotype 6B ($n=1$) resulted in death (100% case fatality) and is not shown in the figure. Estimates for serotypes with a small number of cases should be interpreted with caution

isolates were collected during the earlier years of the study, when systematic serotyping had not yet been fully implemented. Among serotyped isolates, penicillin resistance was confined to serotype 11A, whereas resistance to other antimicrobial agents was distributed across several serotypes. In particular, resistance to erythromycin and clindamycin was observed among serotype 3 isolates, while trimethoprim–sulfamethoxazole resistance was also identified among serotypes 8 and 23A.

Regarding temporal trends, trimethoprim–sulfamethoxazole resistance decreased from 25.0% in 2018–2019 to 3.9% in 2022–2023. This reduction was also observed when the analysis was restricted to serotyped isolates (22.7% vs. 4.2%). No similarly consistent temporal pattern was observed for resistance to the other antimicrobial agents (Supplementary Table S3).

Temporal distribution and incidence rates of IPD

A marked decrease in IPD cases was observed following the onset of the COVID-19 pandemic, a trend that persisted until December 2021. During 2020 and 2021, only 34 and 23 cases were reported, respectively. Case numbers increased thereafter, reaching 47 cases in 2022 and 72 in 2023, returning to levels similar to those observed before the pandemic (Fig. 4).

The increase observed from 2022 onward was particularly notable in the pediatric population. No pediatric IPD cases were recorded from March 2020 through February 2022. Pediatric cases subsequently re-emerged, and between October 2022 and May 2023, 17 children with IPD presented with pneumonia complicated by pleural empyema, indicating that this clinical presentation contributed substantially to the pediatric resurgence.

Of the 315 patients included in the study, 284 (90.2%) resided within the hospital catchment area and were included in the incidence calculations. The remaining 31 patients (9.8%) were referred to our tertiary care hospital from other healthcare areas due to the severity of their clinical condition and were therefore excluded from incidence calculations. The annualized overall incidence decreased from 15.4 cases per 100,000 inhabitants per year (95% CI, 13.0–18.0) in the pre-pandemic period to 6.7 (95% CI, 5.5–8.2) during the pandemic, followed by a partial recovery to 10.8 (95% CI, 7.4–15.1) in the post-pandemic period. This pattern was particularly evident among adults, whereas pediatric incidence estimates should be interpreted cautiously because of the small number of cases and the marked temporal discontinuity in pediatric disease. Age-stratified incidence rates and corresponding 95% confidence intervals for the three epidemiological periods are presented in Table 2.

Temporal patterns of IPD and respiratory virus circulation

The temporal distribution of IPD cases was descriptively examined alongside population-level detections of SARS-CoV-2, influenza, and RSV between 2018 and 2023 (Fig. 5). A marked reduction in IPD cases was observed during 2020–2021, occurring concurrently with the marked increase in population-level SARS-CoV-2

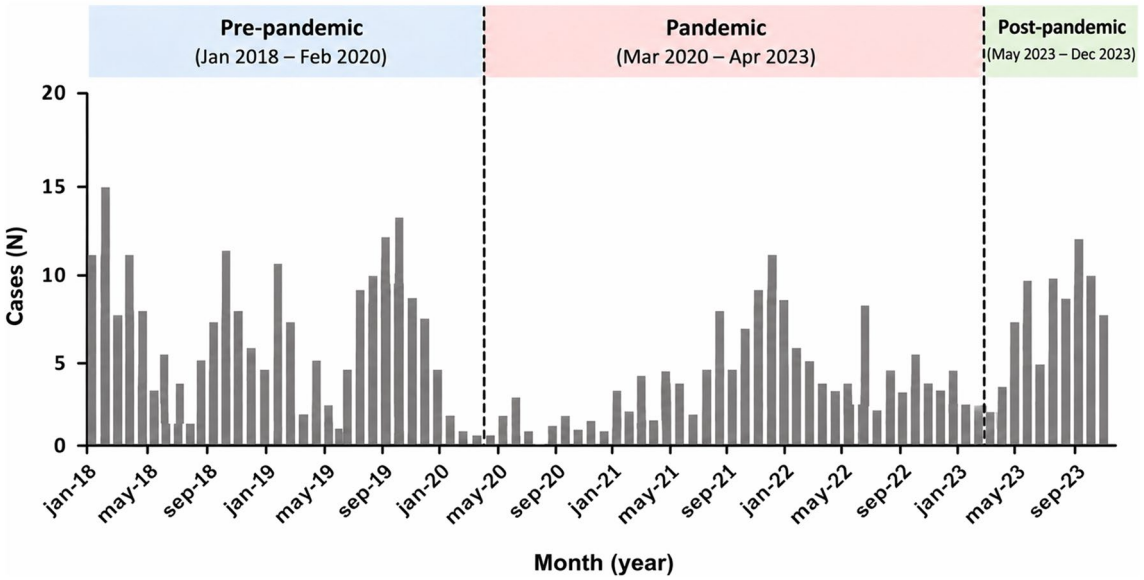


Fig. 4 Monthly distribution of invasive pneumococcal disease cases across the pre-pandemic, pandemic, and post-pandemic periods. Vertical dashed lines indicate the transitions between the predefined epidemiological periods: pre-pandemic (January 2018–February 2020), pandemic (March 2020–April 2023), and post-pandemic (may–December 2023)

Table 2 Annualized incidence of invasive pneumococcal disease by study period and age group

Period	Overall (n)	Incidence (95% CI)	Pediatric (n)	Incidence (95% CI)	Adult (n)	Incidence (95% CI)
Pre-pandemic (Jan 2018–Feb 2020)	153	15.4 (13.0–18.0)	16	7.8 (4.4–12.3)	137	17.3 (14.5–20.5)
Pandemic (Mar 2020–Apr 2023	98	6.7 (5.5–8.2)	13	4.3 (2.3–7.4)	85	7.4 (5.9–9.1)
Post-pandemic (May–Dec 2023)	33	10.8 (7.4–15.1)	3	4.7 (1.0–13.8)	30	12.3 (8.3–17.6)

Incidence rates were calculated using only patients residing within the hospital catchment area ($n=284$), excluding 31 patients from other healthcare areas. The estimated catchment population was assumed to remain stable throughout the study period (460,000 inhabitants, including 95,000 children and 365,000 adults). Rates were annualized according to the duration of each study period and expressed per 100,000 inhabitants per year. The 95% confidence intervals (CI) were calculated using the exact Poisson method

detections and reduced detections of influenza and RSV. From 2022 onward, the increase in IPD cases occurred concurrently with renewed influenza and RSV detections. These temporal patterns are presented descriptively and should not be interpreted as evidence of an independent or causal association between respiratory virus circulation and IPD incidence.

Discussion

Our study describes the temporal, clinical, and epidemiological evolution of IPD in Madrid during a period of particular relevance, namely the SARS-CoV-2 pandemic. Between 2018 and 2023, a total of 315 IPD cases were recorded, most of them occurring in adults, many of whom had underlying comorbidities. These findings are consistent with previous reports identifying older adults and patients with chronic conditions as populations at highest risk for severe pneumococcal disease [16, 17]. In contrast, only 10.2% of pediatric patients had underlying conditions, in line with prior studies showing that most cases of IPD in children occur in previously healthy individuals.

Significant differences in serotype distribution were observed. In adults, serotypes 8 and 3 predominated, followed by serotypes 11A, 23A, 16F, 9N and 22F. In the pediatric population, serotype 3 was clearly dominant (46.5% of cases), followed by serotypes 8, 15A, 19A and 33F. These findings should be interpreted in the context

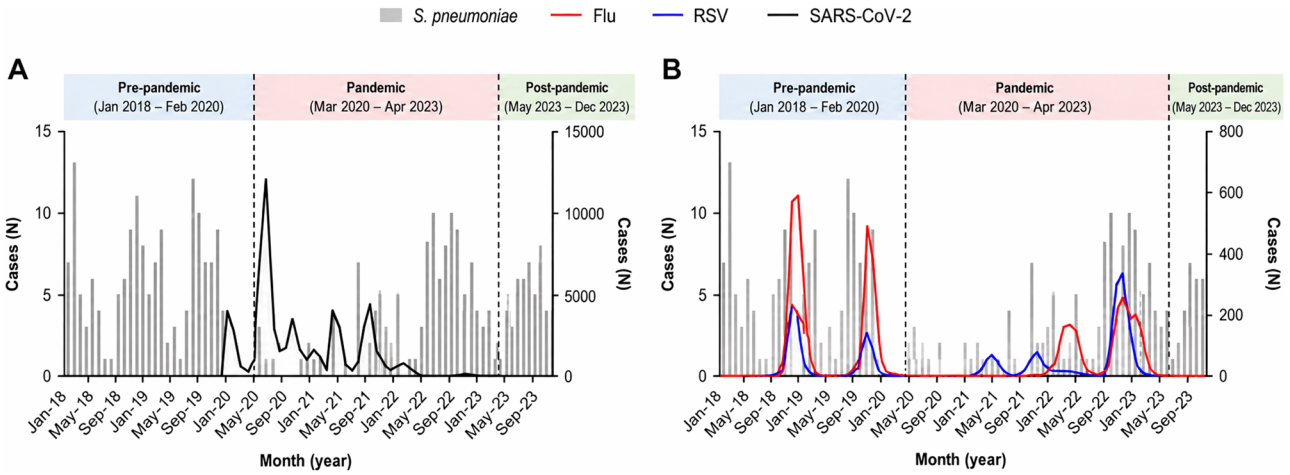


Fig. 5 Temporal distribution of invasive pneumococcal disease cases and population-level respiratory virus circulation during the study period. (**A**) Monthly number of IPD cases and RT-PCR-confirmed SARS-CoV-2 detections. (**B**) Monthly number of IPD cases and RT-PCR-confirmed influenza and RSV detections. Viral detections represent population-level surveillance data from patients evaluated in primary care, emergency departments, or hospitalized with acute respiratory infection and are independent of respiratory viral testing performed in patients with IPD. Vertical dashed lines indicate the transitions between the predefined pre-pandemic (January 2018–February 2020), pandemic (March 2020–April 2023), and post-pandemic (may–December 2023) periods. Because respiratory virus testing activity may have varied over time, viral circulation data are presented descriptively to illustrate temporal patterns and should not be interpreted as evidence of an independent or causal association with IPD incidence

of pneumococcal conjugate vaccine introduction, particularly PCV13, which has been included in the Spanish childhood immunisation schedule since 2016.

Despite systematic vaccination, some PCV13-included serotypes—most notably serotypes 3 and 19A—continue to circulate and cause invasive disease, reflecting suboptimal effectiveness against certain serotypes. This phenomenon has been widely documented [18], and serotype 3 has emerged as one of the leading causes of IPD in multiple European cohorts, particularly in pediatric empyema, as also observed in our study. Official data from the Community of Madrid show that pediatric pneumococcal primary vaccination coverage remained high throughout 2018–2023 (98.1–100%), including during the COVID-19 pandemic (100% in 2020 and 2021), while booster-dose coverage ranged from 92.0% to 100% [19]. Thus, the persistence of serotype 3 is unlikely to be explained solely by insufficient vaccine uptake and may also reflect the limited effectiveness of PCV13 against this serotype. In contrast, pneumococcal vaccination coverage among adults has historically been lower than in children and varies according to age and underlying risk conditions. Throughout most of the study period, pneumococcal vaccination was primarily recommended for older adults and individuals with specific risk conditions. However, the absence of individual vaccination and eligibility data in our cohort limits the interpretation of the potential influence of adult vaccination on the observed serotype distribution. In addition, the diagnostic approach used for pleural fluid samples should be taken into account. Conventional cultures are often negative in pediatric empyema, whereas PCR-based methods markedly improve detection [20]. Thus, the use of molecular techniques in our study likely increased case detection and contributed to the high proportion of serotype 3, while their absence may lead to underdiagnosis and biased serotype distribution.

The COVID-19 pandemic was accompanied by a marked change in IPD epidemiology, with a substantial decline in cases from March 2020 that persisted throughout 2021, coinciding with the implementation of non-pharmaceutical interventions and reduced circulation of respiratory viruses [21]. From 2022 onward, case numbers increased progressively, reaching levels in 2023 that exceeded those observed in the pre-pandemic period.

This pattern is consistent with national and international reports. In Spain, Pérez-García et al. documented a marked decline in IPD across all age groups in 2020 followed by a gradual rebound, with pediatric cases returning

to pre-pandemic levels by 2022 and adult incidence exceeding pre-pandemic levels in 2023 [14]. Complementarily, Brueggemann et al. reported substantial reductions in invasive bacterial diseases, including IPD, across multiple countries during the implementation of COVID-19 containment measures [12].

In addition to non-pharmaceutical interventions, changes in respiratory virus circulation may have contributed to the observed temporal patterns of IPD. Respiratory viral infections are known to facilitate pneumococcal invasion by disrupting mucosal barriers and modulating host immune responses [9, 10, 22]. In our study, the decline in IPD during 2020–2021 occurred concurrently with increased population-level SARS-CoV-2 detections and reduced influenza and RSV detections, whereas the subsequent increase in IPD coincided with renewed influenza and RSV detections. Although these temporal patterns do not establish an independent or causal relationship, they are compatible with the hypothesis that changes in respiratory virus circulation may contribute to variations in IPD incidence. Larger population-based studies using appropriate time-series approaches to account for seasonality, temporal dependence, and changes in viral-testing activity are needed to further investigate this relationship.

In our cohort, viral coinfection was documented in 18.4% of IPD cases, reaching 39% among pediatric patients. This proportion is likely underestimated, as many patients had a recent clinical history suggestive of viral respiratory infection without microbiological confirmation. Moreover, respiratory viral screening was not performed systematically and, when conducted, often relied on partial diagnostic panels, limiting complete viral detection.

The potential facilitating role of viral infections is further supported by studies analyzing nasopharyngeal colonization with *S. pneumoniae* in pre- and post-pandemic settings, which did not identify significant differences in carriage rates, particularly in children [23, 24]. These studies suggested that the reduction in IPD observed during 2020–2021 may not have been primarily attributable to decreased pneumococcal colonization, but rather to reduced circulation of concomitant respiratory virus that can act as triggers for progression from colonization to invasive disease.

Regarding clinical severity, our data show that meningitis was the invasive syndrome associated with the poorest outcomes. This observation is consistent with international literature [25], which highlights the high case fatality of pneumococcal meningitis regardless of vaccine coverage, and its strong association with advanced age, comorbidities, and poor prognosis.

Serotype-specific mortality showed marked heterogeneity. Consistent with our findings, De Miguel et al. reported low case fatality for serotype 8 (<10%), while serotype 3, despite intermediate mortality, contributed substantially to the overall disease burden due to its high incidence. The same study identified serotype 11A as one of the serotypes with the highest case fatality [26]. A recent meta-analysis by Darkwah et al. similarly associated serotypes 31, 11A, 3, 6A, 15A and 19F with increased mortality risk in IPD, particularly among immunocompromised patients [27]. These data emphasize the importance of monitoring not only serotype frequency but also serotype-specific mortality. However, the relatively small number of cases and deaths associated with several serotypes in our cohort limits the precision of these unadjusted estimates and precludes reliable adjustment for potential confounding factors, such as patient age and underlying comorbidities. Therefore, these observations should be considered exploratory and hypothesis-generating, as the observed differences in case fatality cannot be attributed to serotype independently of patient characteristics and warrant confirmation in larger studies.

Certain pneumococcal serotypes are also associated with antimicrobial resistance. Although PCVs have reduced the circulation of historically multidrug-resistant serotypes, serotype replacement has favoured the emergence of non-vaccine serotypes such as 11A, 24F, 23B and 8. In our cohort, serotype 11A was the serotype most frequently associated with penicillin resistance, in agreement with reports linking this serotype to reduced susceptibility and multidrug-resistant clones such as PMEN3 (Spain9V-ST156) [28–30].

In this context, the introduction of higher-valency pneumococcal conjugate vaccines, including PCV15 and PCV20, may further modify the epidemiology of IPD in the coming years. Several of the most prevalent serotypes identified in our cohort, including serotypes 8, 10A, 11A, 12F, 22F and 33F, are covered by PCV20 but not by PCV13. Continued surveillance will therefore be essential to assess the impact of these newer vaccines on serotype distribution, antimicrobial resistance patterns, and overall disease burden.

This study has several limitations. First, its retrospective and single-centre design may limit the generalizability of the findings to other settings. Second, serotyping was not available for all isolates, and in some cases, strains could only be characterized at the serogroup level. Molecular testing was limited to an in-house PCR assay targeting the *lytA* gene; additional assays targeting *wzg* or *ply* were not performed. Although *lytA* is commonly used for pneumococcal detection, potential cross-reactivity with closely related streptococcal species cannot be completely excluded. Furthermore, molecular serotyping of PCR-positive samples does not independently confirm species identification. Most non-serotyped isolates corresponded to cases from the early years of the study period, when systematic submission of isolates for serotyping was not yet fully implemented. Serotyping coverage increased substantially over time and was nearly complete during the final study years. This may have resulted in an underestimation of less prevalent serotypes and may have influenced the overall distribution of serotypes observed during the study period. Third, respiratory viral testing was not systematically performed, potentially leading to underdetection of viral coinfections. Although the same diagnostic methods were available throughout the study period, testing was requested according to clinical criteria rather than systematically, which may have introduced selection bias. Consequently, the reported frequency of viral coinfections should be interpreted as a minimum estimate and may not fully reflect the true burden of respiratory viral infections among patients with IPD. Individual vaccination status was also not consistently available, preventing assessment of vaccine effectiveness or the direct impact of specific pneumococcal conjugate vaccines at the patient level. Consequently, the influence of vaccination policies and eligibility criteria on the observed serotype distribution could only be interpreted indirectly. In addition, the relatively small number of cases and deaths for certain serotypes limited the precision of serotype-specific mortality estimates and precluded reliable adjustment for potential confounding factors, such as patient age and underlying comorbidities. Finally, although incidence calculations were restricted to patients residing within the hospital catchment area, a stable population denominator was assumed throughout the study period, which may not fully account for demographic changes over time. Furthermore, changes in healthcare-seeking behaviour, referral patterns, and diagnostic practices during the COVID-19 pandemic may have influenced case ascertainment and contributed to the observed differences in incidence between study periods. Overall, our findings highlight the dynamic epidemiology of IPD in the post-PCV13 and post-pandemic era. The marked decline during the COVID-19 pandemic followed by a rapid rebound, together with the persistence of serotype 3 and the emergence of non-vaccine serotypes such as 11A, underscores the importance of continuous epidemiological and microbiological surveillance to guide future vaccination strategies.

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Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate Patient rights were protected in accordance with the principles of the Declaration of Helsinki. The study was approved by the Research Ethics Committee with Medicines (CEIm) of Hospital Universitario 12 de Octubre, Madrid, Spain (reference number 25/262). Given the retrospective and observational design of the study, with no intervention on patients, the requirement for informed consent was formally waived by the Ethics Committee in accordance with applicable regulations and international ethical standards.

Consent for publication Not applicable.

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Competing interests The authors declare no competing interests.

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