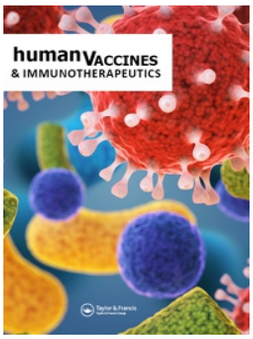

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Serotype 3 invasive pneumococcal disease in Tuscany across the eras of conjugate vaccines (2005–2024) and anthropic-driven respiratory virus fluctuations

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ABSTRACT

Serotype 3 Streptococcus pneumoniae (ser3) has emerged as a leading cause of invasive pneumococcal disease (IPD) despite targeted vaccination efforts. Preliminary evidence reported a differential impact of anti-ser3-pneumococcal-conjugate-vaccines (PCVser3) on different clinical presentations of ser3-IPD. Recently, a temporal association between respiratory syncytial virus (RSV) and IPD was observed in children, supporting a role of RSV in driving IPD dynamics. Ser3 IPD cases occurred in Tuscany from November 2005 to March 2024 were included. Comparisons of different clinical presentations (bacteremic pneumonias and osteomyelitis versus sepsis and meningitis) were made between younger and older patients and between vaccinated and unvaccinated ones. The temporal correlation between ser3 IPD, RSV and influenza was qualitatively described from 2015/2016 to 2023/2024. Among 160 ser3 IPD recorded cases, fully-immunized patients showed a significantly lower proportion of sepsis and meningitis compared to non-immunized patients (all ages: 7.5% versus 58.5%, $p < .0001$; aged 14-years and younger: 0% versus 31.3%, $p = .0019$). Ser3 IPD showed a strong temporal association with influenza virus outbreak but not with isolated RSV outbreak. Nearly two decades of molecular surveillance of ser3 in Tuscany suggest that the most severe IPD presentations, such as sepsis and meningitis, are significantly lower in individuals who received PCVser3 immunization. Ser3 IPD incidence is temporally associated with influenza outbreaks but not with RSV.

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Invasive pneumococcal disease; serotype 3; PCV; pneumococcal conjugate vaccine; sepsis; meningitis; children; immunization

Introduction

Invasive pneumococcal disease (IPD) represents the most common cause of invasive bacterial disease subject to active surveillance in Italy.[1] In the last years, serotype 3 *Streptococcus pneumoniae* (ser3) has emerged as one of the most common serotype responsible for IPD in the majority of western countries.[1–4] Its relative representation increased significantly compared to the other pneumococcal serotypes after the introduction of polyvalent anti-pneumococcal conjugate vaccines (PCV) and persisted even after the introduction of vaccines specifically targeting ser3 (PCVser3).[2,5] Real-world evidence has shown massive effectiveness of PCV in the overall reduction of IPD incidence but limited effectiveness against ser3.[2–6] This phenomenon is partially explained by the specific synthetic mechanisms of the capsular polysaccharide (CPS) that in ser3 is synthase-dependent and does not covalently link the CPS to the peptidoglycan of the bacterial cell wall, resulting in a thicker capsule and in the release of free CPS which hinders immune response by saturating anti-ser3 antibodies, thereby reducing opsonophagocytic killing and neutralization.[7,8] Previously published data provided preliminary evidence that the 13-valent pneumococcal conjugate vaccine (PCV13), although failing in the prevention of ser3 bacteremic pneumonia, could contribute to a significant degree of protection against the more invasive forms of ser3 IPD like sepsis and meningitis.[9]

Recently, a group from Quebec provided evidence of temporal association between post-pandemic respiratory syncytial virus (RSV) resurgence and IPD, theorizing a new role of RSV in driving IPD dynamics in children.[10]

The present report depicts the results of almost 20 years (2005–2024) of molecular surveillance of ser3 IPD in the Italian region of Tuscany, including the COVID-pandemic and post-pandemic periods where viral circulation was subject to anthropic-driven fluctuations due to social distancing measures. In order to further explore the above-mentioned preliminary observations, a specific focus has been granted to PCV impact on ser3 IPD clinical presentation and on the seasonal evolution of RSV and influenza virus with respect to ser3 IPD in pediatric patients.

Methods

Study design

All cases of ser3 IPD occurred in the Italian region of Tuscany between November 2005 and March 2024 were retrospectively

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retrieved from the regional molecular surveillance register (MSR) for invasive bacterial diseases. Cases were grouped for age and anti-pneumococcal vaccine status at the moment of infection, clinical presentation and epidemic season. A depiction of ser3 IPD throughout the epidemic seasons included in the study period is provided. The representation of more severe (sepsis and meningitis) and less severe (bacteremic pneumonia and osteomyelitis) forms of IPDs was compared in patients aged 14 and younger *versus (vs)* patients older than 14 years of age. A similar comparison, regarding the severity of clinical presentation, was carried out in fully-vaccinated *vs* unvaccinated patients throughout the whole study group and limited to patients younger than 14 years of age. The median time between the completion of full immunization schedule, as appropriate for age, and the development of IPD was extrapolated.

In order to qualitatively evaluate the seasonal dynamics of ser3 IPD, RSV and influenza virus infections in pediatric patients, the study period was restricted to the four seasons before and after the SARS-CoV-2 pandemic (2015/2016 to 2023/2024) where pneumococcal surveillance was stable in terms of samples received by the referral laboratory. The seasonal variations of ser3 IPD occurred in patients under 14 years of age from all Tuscany relative to the total number of cases occurred in the above-mentioned time frame were calculated. These very same relative variations were retrieved also for RSV and influenza virus cases recorded in the major pediatric hospital of Tuscany (Meyer Children's Hospital IRCCS, Florence, Italy) in the same seasons and in the same age population.

Case definition and clinical classification

IPD was operatively defined by the isolation of *Streptococcus pneumoniae* or the detection of pneumococcal DNA by polymerase chain reaction (PCR) from a normally sterile body site.[6] IPD cases in which ser3 was identified through real-time PCR (RT-PCR) performed directly on the biological sample or on culture isolates were considered ser3 IPDs. According to the European Centre for Disease Prevention and Control (ECDC), IPDs included sepsis or bacteremia, meningitis and osteomyelitis.[11] Pneumonia with documented bacteremia in the absence of clinical criteria of sepsis was considered an IPD[12] and classified as complicated in the presence of para-pneumonic effusion, empyema, necrotizing radiological features or whether requiring surgical lobectomy.[13,14] The presence of clinical criteria of sepsis[15] and the concomitant positivity of ser3 on blood allowed classification of the case as sepsis regardless of the primary site of infection. Similarly, cases with neurological symptoms and culture or PCR positivity for ser3 on cerebrospinal fluid (CSF) were classified as meningitis regardless of the presence of septic involvement and the isolation of the pathogen in the blood.[16] Sepsis and meningitis were regarded as severe systemic infections as opposed to bacteremic pneumonias and osteomyelitis that were considered as less severe forms of IPD. Influenza and RSV infection cases were defined by the positivity of the molecular specific testing from samples obtained from patients presenting with influenza-like-illness symptoms.

Data collection

Cases were included in the MSR only if at least one biological sample or a culture isolate obtained from a sterile body site was tested using RT-PCR at the regional referral laboratory for the molecular diagnosis of invasive bacterial disease. All pneumococcal cases suspected or detected in the whole region of Tuscany have to be centralized for molecular confirmation and serotyping to the regional referral laboratory as per regional law.[9] Samples collection and management and the laboratory analysis for the detection of *Streptococcus pneumoniae* and its subsequent serotyping, with RT-PCR using, respectively, *lytA* and *cpsA* genes were performed as previously reported by this study group.[9,17–19] Clinical and laboratory data, including the results of culture performed on the same and on other samples from the same patients during the same clinical episode, were recorded. Patients were considered pediatric when aged 14 or younger in accordance with the vast majority of IPDs literature.[6] Clinical and routine laboratory information of each ser3 IPD case was obtained by the referent physician through the completion of a standardized questionnaire including sex, age, vaccination status at the moment of sample collection and medical conditions predisposing to invasive bacterial infections.

Vaccination

Immunization status at the moment of infection was confirmed at the inclusion in the MSR through the Collective Prevention Health Information System of Tuscany Region. Data on both anti-pneumococcal polysaccharide (PPV23: pneumococcal polysaccharide vaccine) and conjugate vaccines (PCV: pneumococcal conjugate vaccine −7, −13, −15 and −20 valent) were recorded. The patient was considered fully vaccinated against ser3 when the completion of the age-appropriate vaccination schedule with a vaccine including ser3 antigen was completed at least 30 days before the IPD occurred. All patients that at the moment of IPD were partially vaccinated with PCV13, PCV15 or PCV20 and those who had received PCV7 (that does not include ser3 antigen) were considered non-immunized against ser3.

In Tuscany, during the study period 2005–2024, PPV23 was offered only to elder population over-65 and to the pediatric population with medical conditions that expose to a higher risk of capsulate bacterial infections (asplenia, complement deficiencies, etc.). In Tuscany PCV7 was offered to all subjects born after January 2002 without catch-up strategy until the introduction of PCV13, which subsequently replaced it. PCV13, the first conjugate anti-pneumococcal vaccine including ser3 antigen available in Tuscany, was included in the vaccination schedule in the last quarter of 2010. No catch-up strategy was implemented in Tuscany for those who were born before 2011, so that all patients that presented IPD over the age of 14 at the time of this study had not received a pneumococcal conjugate vaccine other than under special circumstances. In March 2023, PCV13 was replaced by PCV15 all over Tuscany. Both vaccines were administered in three doses during the first year of life (three, five and 11–13 month of life). PCV20 was made available free of charge upon individual request for the population aged 65 and older, following its licensure in Italy in May 2022.

Statistical analysis

Statistical analyses were performed using SPSS (version 29.0.1.0, IBM Corp, Endicott, New York). Data were reported as median and interquartile ranges (IQR) for continuous variables and as fraction and percentage for categorical variables. We compared the categorical variables using the Chi-squared or Fisher's exact test, depending on the number of observations. Two-sided p-values <0.05 were considered statistically significant.

Ethics

The present study was approved by the local Ethical Committee board in November 2021 with the code SEMBAI. All data were anonymized at the moment of inclusion in the MSR and collected retrospectively after March 2021. Clinical and laboratory data were obtained as part of the routine clinical practice standard of care.

Results

Demographic data

A total of 160 subjects (99 male-assigned-at-birth, 61.9%; median age: 64.0 years, IQR: 5.25–78) were hospitalized for a serotype 3 IPD in the Italian region of Tuscany (resident population on January 1st, 2024: 3,664,798 inhabitants) from November 2005 to March 2024.

Overall, about one-third of cases (53/160, 33.2%) occurred in patients under 14 years of age at the moment of hospitalization with the majority of them clustering between 24 and 59 months of age (22/53, 41.5%; median age 41.2 months, IQR: 30.9–50.8). No cases in patients younger than one year of age were recorded. Age-related case distribution per epidemic season is detailed in Figure 1.

Clinical presentation and vaccination status

Bacteremic pneumonia was the most common clinical presentation of ser3 IPD in our cohort (78/160, 48.7%). The 25.6% of pneumonias (20/78) displayed a complicated course with 9/78 (11.5%) presenting empyema, 7/78 (8.9%) necrotizing radiological features and 4/78 (5.1%) requiring surgical lobectomy. Ser3 otomastoiditis was 8/160 (5%). No bone infections in body sites other than the mastoid were recorded. A total of 55/160 cases (34.4%) were clinically classified as sepsis without meningeal involvement and 19/160 as meningitis (11.9%). Only one fatality was recorded in a 48-years-old unvaccinated patient of whom eventual presence of risk factors could not be retrieved. The patient developed a bacteremic pneumonia that evolved to septic shock. Overall, 86/160 (53.8%) patients presented with bacteremic pneumonia or

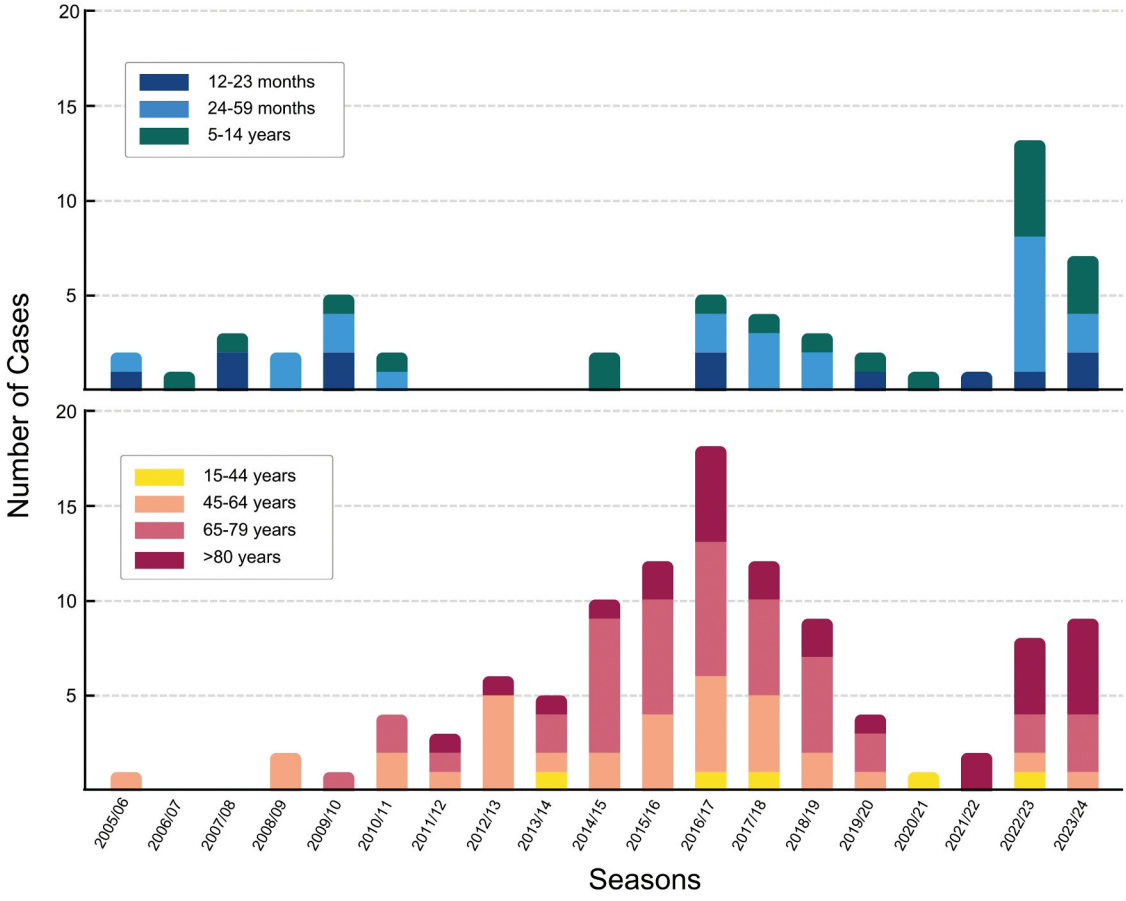

Figure 1. Number of cases of serotype 3 invasive pneumococcal disease recorded in Tuscany from November 2005 to March 2024 divided per epidemic season and age group (Upper panel: subjects aged 14 and younger; Lower panel: subjects older than 14 years of age).

otomastoiditis, regarded as less severe forms of IPD, and 74/160 (46.2%) with more invasive clinical presentations represented by sepsis and meningitis. Age distribution divided per different epidemic season and per clinical presentation is depicted in Table S1 and Table S2, respectively. Seasonal evolution of ser3 IPD cases divided per clinical manifestation is presented in Figure S1.

As a result of the vaccination strategy implemented in Tuscany, the patients in our cohort presenting with ser3 IPD before 14 years of age (53 cases) had a higher chance of being vaccinated with PCV13. In this group, the proportion of sepsis and meningitis (5/53, 9.4%) was significantly lower compared to the same proportion in patients older than 14 years of age (69/107, 64.5%; $p < .0001$; Figure 2a). Alongside, the proportion of pneumonia and otomastoiditis occurred in patients under 14 years of age (48/53, 90.5%), was significantly higher when compared to the same clinical presentation in patients equal or older than 14 years of age (38/107, 35.5%; $p < .0001$).

Vaccination status data at the moment of infection was available for 158/160 total cases as the information could not be retrieved for two cases occurred in patients under 14 years of age (51/53). The overall rate of PCV13-full-immunization was of 40/158 (25.3%). Only 5/107 (4.7%) patients equal or older than 14 years had received a PCV13 full immunization or other PCVs (Figure 2b). Among the PCV13-vaccinated patients, 37/40 (92.5%) presented with pneumonia or otomastoiditis. Among patients who had not received PCV13-full-immunization at the moment of infection, only 49/118 (41.5%) presented a pneumonia or otomastoiditis (p-value <.0001; Figure 2c). No patients had received PPV23 vaccination.

When considering only patients under 14 year of age, 35/51 (68.6%) were fully immunized with PCV13. Among the remaining 16/51 (31.4%) cases, seven (7/16; 43.8%) were unvaccinated; three (3/16; 18.7%) were partially vaccinated and six (6/16, 37.5%) had received the PCV7 which does not include the ser3 antigen. Of the 35 PCV13-fully-vaccinated cases under 14 years of age no one presented meningitis or sepsis: 32/35 (91.4%) developed bacteremic or complicated pneumonia and 3/35 (8.6%) otomastoiditis. Of the 16 PCV13-unvaccinated cases, 10 (10/16, 62.5%) presented with bacteremic or complicated pneumonia, one (1/16, 6.3%) with otomastoiditis, three with meningitis (3/16, 18.7%) and two with sepsis (2/16, 12.5%). Overall, in patients under 14 years of age the rate of sepsis and meningitis was significantly lower in the vaccinated group (0%) compared to the unvaccinated group (31.3%; $p = .0019$; Figure 2d).

The median time between with the completion of PCV13 immunization and the development of IPD was 31.5 months (IQR: 11.75–53; min-max: 7–116 months). Zero cases of ser3-IPD were recorded in patients vaccinated with PCV15. Details of the distribution of IPD per age, according to their vaccination status, are presented in Figure 2.

Ser 3, influenza and RSV

The absolute numbers of ser3 IPD, Influenza virus and RSV and recorded per season in pediatric patients (0–14 years), respectively, from all over Tuscany (ser3 IPD) and from the major pediatric regional Hospital (Influenza and RSV) during the four epidemic seasons prior to the first Sars-CoV-2 pandemic season (2019/2020) and in the four subsequent seasons are presented graphically in Figure 3. The percentages of RSV, influenza and ser3 IPD cases per season relative to the total number of cases in the four pre- and post-pandemic seasons are reported in Table S3.

During the 2020/2021 season, when stringent social distancing measures for the containment of the SARS-CoV-2 pandemic were implemented all across Italy, almost no pediatric cases of Influenza, RSV or Ser3 infections were recorded. RSV infections resurged in the 2021/2022 season with a number of recorded cases 4.1 times higher than the average of the four pre-pandemic seasons and slowly decreased in the subsequent seasons. In 2021/2022, during the RSV peak, Influenza and Ser3 IPD cases were nearly absent. Influenza infections reemerged with significant burden only in the 2022/2023 season with 8.8 times increase compared to the average of the pre-pandemic seasons. This resurgence of influenza was paralleled by 4.3 times rise of ser3 IPD cases. Notably, while RSV, Influenza, and Ser3 IPD were nearly absent during the 2020/2021 season, the resurgence of RSV in 2021/2022, in the absence of Influenza, was not followed by a corresponding increase in Ser3 IPD cases. Instead, Ser3 IPD cases peaked in 2022/2023, following the seasonal Influenza outbreak.

Discussion

Ser3 persists as a prominent cause of IPD in Tuscany despite targeted immunization efforts. This is particularly evident in children born after 2011, who were the primary recipients of the PCV13 vaccination strategy. This observation aligns with findings from other epidemiological settings worldwide.[2–6] The absolute increase in the annual number of cases observed after 2015 may relate with the progressive improvement of the molecular surveillance system, documented by the increase in the number of samples tested for pneumococcus by the regional reference laboratory, operationally stable since approximately 2015 (data not shown, available upon request). Older adults and pediatric subjects, especially those aged two to five, but not infants, confirmed to be the most affected age groups.[3,6] However, clinical presentation differs significantly when stratified by age (Figure 2a). Adult subjects presented with more severe infections like sepsis and meningitis in more than 60% of cases compared to less than 10% in subjects under 14 years of age (Figure 2b). The significantly higher representation of more severe ser3 IPD cases in the adult population could be ascribed to the immunological and physiological differences embedded in the very nature of these two age groups (e.g. higher comorbidity rates in the elderlies or different ability to respond to polysaccharide or conjugated antigens). Moreover, in adult patients, etiologic and molecular diagnostics may have been reserved for the most severe cases, thus influencing the results. However, it cannot be overlooked that only less than 5% of adult patients with ser3 IPD were fully immunized with a PCV containing the ser3 antigen (PCVser3) compared to an immunization rate of nearly 70% among cases occurred in subject aged 14 years or younger (Figure 2c). Overall, only 7% of PCVser3-vaccinated individuals developed a severe IPD, compared to the 60% of severe presentations recorded among unvaccinated ones (Figure 2d). This finding holds even when limiting the

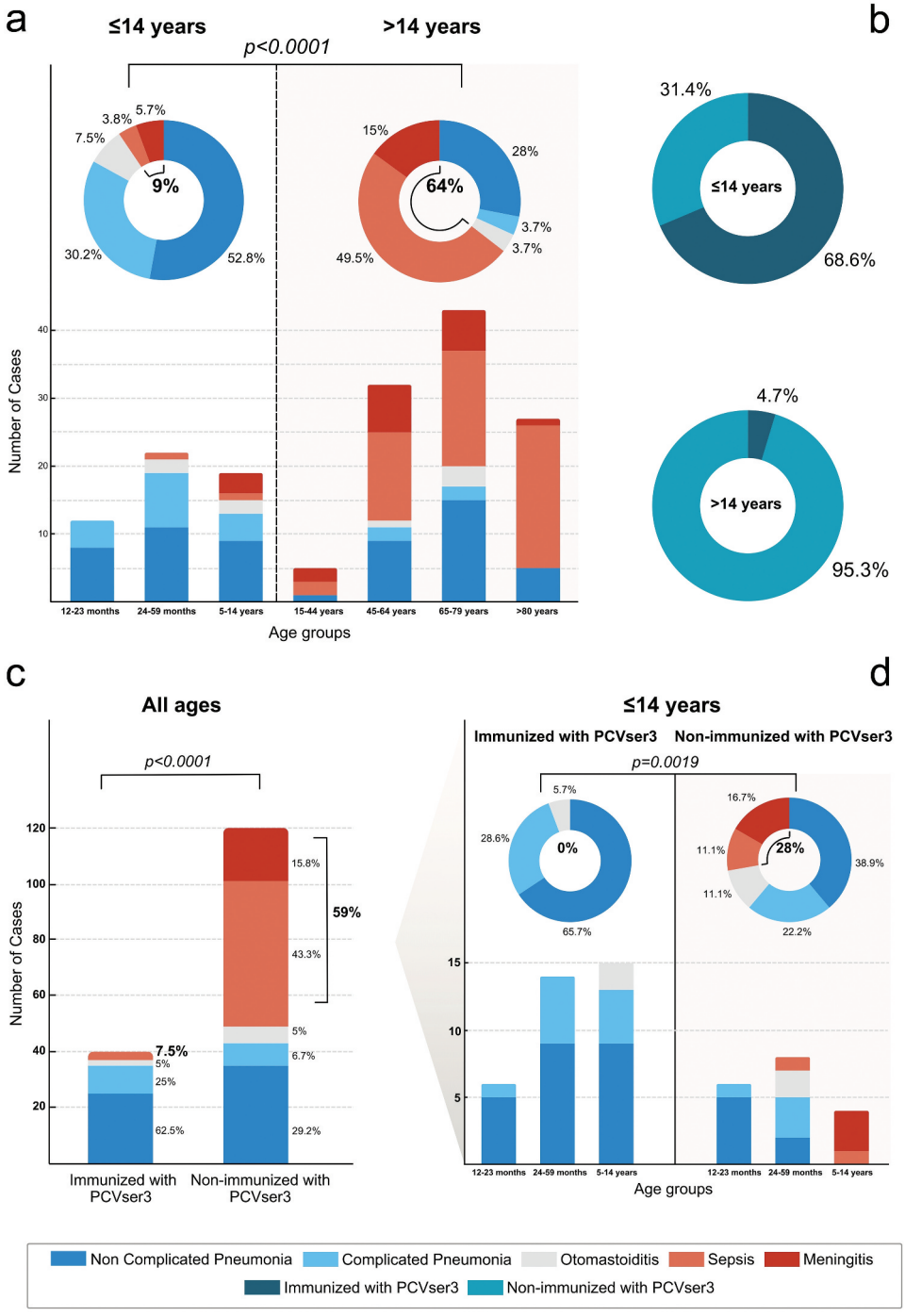

Figure 2. (a) The column chart depicts the number of cases of serotype 3 invasive pneumococcal disease (ser3 IPD) recorded in Tuscany from November 2005 to March 2024 divided per age groups and clinical presentation. The pie charts depict the percentage representation of the different clinical presentations of ser3 IPD in subjects aged 14 and younger and in subjects older than 14 years of age. (b) Percentage of full immunization with a pneumococcal conjugate vaccine containing the ser3 antigen (PCVser3) in subjects aged 14 and younger and in subjects older than 14 years of age. (c) Percentage representation of the different clinical presentations of ser3 IPD in PCVser3-immunized and non-immunized subjects of all ages. (d) Absolute numbers of cases of ser3 IPD dived per age and clinical presentation (column charts) and percentage representation of the different clinical presentation (pie charts) in PCVser3-immunized and non-immunized subjects aged 14 and younger. Color legend refers to all panels. P stands for *p*-value obtained with the Chi-squared or Fisher's exact test, depending on the number of observations.

analysis to pediatric subjects, where no cases of sepsis or meningitis were recorded among PCVser3-immunized individuals, against a rate of over 30% in unvaccinated children. These data corroborate our previous observation that in children under 8, the incidence of sepsis and meningitis was almost 12 times lower in the post-PCV13 cohort compared to the pre-PCV13 cohort.[9] These observations might be explained by the fact that PCV13 elicits anti-ser3 antibody titers sufficient to prevent more disseminated IPD but suboptimal for the prevention of bacteremic pneumonia and otomastoiditis.[20–22] In our cohort, the median time between the completion of PCV13 immunization and the development of IPD was 32 months. This suggests that shortly after immunization, the antibody titers may reach levels sufficient to prevent even less systemic

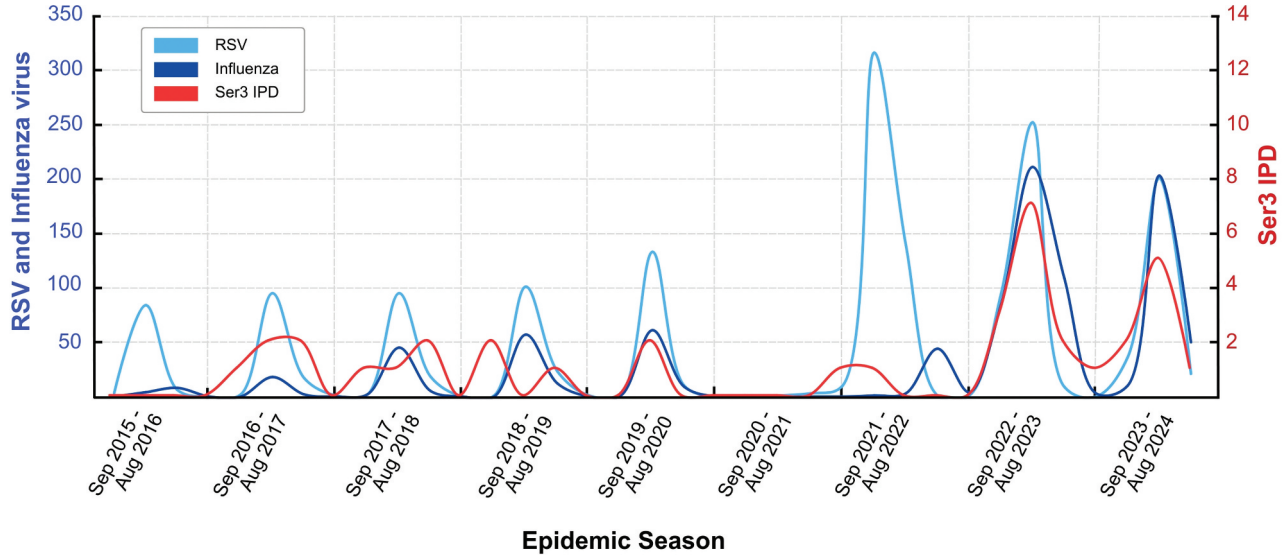

Figure 3. Absolute number of cases of serotype 3 invasive pneumococcal disease (ser3 IPD, red line), influenza virus (influenza, blue line) and respiratory syncytial virus (RSV, light blue line) infection recorded per year from the 2015/2016 to the 2023/2024 epidemic season in subject aged 14 years and younger. Ser3 IPD cases were recorded all over Tuscany. RSV and influenza cases were recorded in the major pediatric hospital of Tuscany region. RSV and influenza virus recorded case scale is presented on the left side (blue) while ser3 IPD recorded case scale is presented on the right side (red).

infections such as bacteremic pneumonias and otomastoiditis. However, as titers decline over time, the risk of ser3 IPD progressively increases, with PCV13 offering a short-lived protection against ser3 as already observed in Canada and in antibody persistence studies.[9,23–25] Based on this hypothesis, it is possible to speculate that PCV15, which in immunogenicity pre-license studies has demonstrated higher anti-ser3 titers compared to PCV13,[26–28] may offer more durable protection even against pneumonia. Although the observation period is relatively short, no cases of ser3 IPD have been recorded in PCV15-vaccinated subjects in our cohort. If these data should be confirmed, it might open to the opportunity of considering a booster dose of PCVser3 to grant transient protection in pediatric age groups most at risk for developing ser3 bacteremic pneumonia, especially in light of newly emerging immunization schedules with a reduced number of doses in the first year of life.[6,29] More strikingly, presented data underscore the urgency of implementing PCV-based immunizations strategies that are effective against ser3 in the elderly population.

In Tuscany, the PCV13 coverage rate at 24 months in 2021 (most recent data available) was approximately 90%.[30] However, due to the almost absent influence of PCV on ser3 carrier status and the restricted age group targeted by the vaccination program, a herd-effect was unlikely to have influenced ser3 IPD occurrence.[25]

Social distancing measures implemented for the containment of SARS-CoV-2 pandemic brought about an almost complete seasonal cessation of RSV, influenza virus, and ser3 IPD cases, with a stepwise reemergence of the respiratory viruses and ser3 IPD in subsequent seasons.[31] This scenario has offered a unique opportunity to gain a deeper insight into the role of respiratory viruses in driving IPD dynamics.[32] Ouldali et al. reported an increase in IPD cases among children during the first post-pandemic season which was temporally associated with the unusual surge of RSV cases observed that year in Quebec, Canada.[10] An analogous phenomenon was identified in southern Israel.[32] A similar observation cannot be confirmed in our setting, where during the extraordinary post-pandemic RSV outbreak, ser3 IPD cases remained virtually absent in the pediatric population and reemerged significantly in the following season coinciding with the enhanced circulation of influenza virus observed that year and absent in the previous season. The number of RSV and influenza testing performed remained similar all along the epidemic seasons analyzed in the Central Lab being routinely administered to all patients admitted with respiratory infections symptoms in our setting and paralleled a nation-wide surge of RSV infections and related pediatric admission in the reported seasons.[33–35] This suggests that influenza virus, but not RSV, may influence ser3 IPD dynamics in the pediatric population.[36,37] The recent introduction of Nirsevimab in new preventive strategies and its expected reduction in RSV cases could provide further elements on this regard in the near future. It cannot definitively be established a causal link between respiratory viruses and IPD dynamics, although the timing of an Influenza outbreak followed by an IPD resurge suggests a connection. The data is limited to ser3 and is specific to Tuscany region and may not be applicable elsewhere. Moreover, the observational nature of the study does not allow the formal establishment of a causal relation between respiratory viruses and ser3 IPD but provides an interesting observation which contrast with those acquired in other settings and needs to be further investigated.

Conclusion

Nearly two decades of molecular surveillance of ser3 in Tuscany indicate that the most severe IPD presentations, such as sepsis and meningitis, are significantly lower in individuals who received PCVser3 immunization. Data from four pre- and post-pandemic seasons demonstrate that in the pediatric population, ser3 IPD is temporally correlated with influenza virus outbreaks but not RSV.

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Methodology was checked by LL, FC, SR and CA. Project administration was performed by SR and CA. Supervision was performed by LL, FC, WMS, MG, MV, FL, CP, CC, SR and CA. Formal analysis was performed by LL and FC. Software was provided by LL and FC. Resources were provided by LL, FC, WMS, MG, MV, FL, CP, CC, SR and CA. Writing of the original draft was performed by LL and FC. Reviewing and editing of the manuscript was performed by LL, FC, WMS, SR and CA. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors attest they meet the ICMJE criteria for authorship. MG reports personal fees from Sanofi, Thermo Fisher Scientific.

Disclosure statement

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Notes on contributor

Silvia Ricci holds a specialization in Pediatrics from the University of Florence, where she graduated with highest honors in February 2017. She earned her medical degree in 2010, also with distinction. Her thesis, focusing on *Streptococcus pneumoniae*, highlighted her research interest in invasive infectious diseases, a key area of her ongoing work.

Currently, Dr. Ricci is a Researcher Type B at the Department of Health Sciences, University of Florence. Her clinical activities include the diagnosis, management, and follow-up of children with inborn errors of immunity, as well as the development of vaccination strategies for high-risk pediatric populations. Additionally, she specializes in the molecular diagnosis of invasive and viral pediatric infections and oversees newborn screening programs for primary immunodeficiencies.

Dr. Ricci has authored 119 indexed publications, 20 in Italian journals, and contributed to numerous textbooks and international conferences. Her clinical expertise is grounded in extensive experience with both observational and interventional studies. Notably, she has served as a visiting researcher at the Imagine Institute and Hôpital Necker-Enfants Malades in Paris. Dr. Ricci holds a national scientific qualification as an associate professor in pediatrics and child neuropsychiatry, valid through February 2033.

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Ethical statement

The present study was approved by the local Ethical Committee board in November 2021 with the code SEMBAI. All data were anonymized at the moment of inclusion in the MSR and collected retrospectively after March 2021. Clinical and laboratory data were obtained as part of the routine clinical practice standard of care.

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